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IL-4 E IL-13 SON CITOQUINAS CLAVE EN LA INFLAMACIÓN TIPO 2 EN EL ASMA PERSISTENTE NO CONTROLADO[1-3]

IL-4 PARTICIPA EN LA PRODUCCIÓN DE IL-5 E IL-13[4]

- IL-5 promueve la activación, supervivencia y reclutamiento de los eosinófilos[5-8]
- IL-13 causa hipersecreción de moco, hiperreactividad de las vías respiratorias e hipertrofia del músculo liso[9]

IL-4 JUEGA UN PAPEL IMPORTANTE EN:

- Producción de citoquinas que regulan procesos posteriores en la cascada de señalización como IL-5, IL-9 e IL-13[4]
- Diferenciación de células Th2, reclutamiento de mastocitos, cambio de isotipo de células B para la producción de IgE[4]
- Reclutamiento de eosinófilos[5-8]

Descubre más en **www.AsmaTipo2.es**

Referencias: 1. Fulkerson PC, Rothenberg ME. Targeting eosinophils in allergy, inflammation and beyond. *Nat Rev Drug Discov.* 2013;12(2):1-23. **2.** Caruso M, Crisafulli E, Lizzio R, Polosa R. Biologic therapy for atopic asthma and beyond. *Curr Opin Allergy Clin Immunol.* 2013;13(6):677-85 **3.** Hammad H, Lambrecht BN. Dendritic cells and epithelial cells: linking innate and adaptive immunity in asthma. *Nat Rev Immunol.* 2008;8:193-204. **4.** Maes T, Joos GF, Brusselle GG. Targeting interleukin-4 in asthma: lost in translation? *Am J Respir Cell Mol Biol.* 2012;47(3):261-70. **5.** Berair R, Pavord ID. Rationale and clinical results if inhibiting interleukin-5 for the treatment of severe asthma. *Curr Allergy Asthma Rep*. 2013;13(5):469-76. **6.** Fahy J. Type 2 inflammation in asthma—present in most, absent in many. *Nat Rev Immunol.* 2015;15(1):57-65. **7.** Brusselle GG, Maes T, Bracke KR. Eosinophilic airway inflammation in nonallergic asthma. *Nat Med.* 2013;19(8):977-99. **8.** Toru H, Pawankar R, Ra C, Yata J, Nakahata T. Human mast cells produce IL-13 by high-affinity IgE receptor cross-linking: enhancing IL-13 production by IL-4-primed human mast cells. *J Allergy Clin Immunol.* 1998;102(3):491-502. **9.** Zhu Z, Homer RJ, Wang Z, *et al*. Pulmonary expression of interleukin-13 causes inflammation, mucus hypersecretion, subepithelial fibrosis, physiologic abnormalities and eotaxin production. *J Clin Invest.* 1999;103(6):779-88.

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Alergonorte Sociedad de Alergólogos del Norte

II EDICIÓN DEL PREMIO NACIONAL DE INVESTIGACIÓN EN DERMATITIS DE CONTACTO "DR. DANIEL MUÑOZ LEJARAZU"

La Sociedad de Alergólogos del Norte, Alergonorte, en agradecimiento a la labor desarrollada por el Dr. Daniel Muñoz Lejarazu convoca el premio que lleva su nombre y quiere premiar en esta convocatoria la investigación de relevancia en dermatitis de contacto.

OBJETIVO

Incentivar la publicación de artículos originales en el campo de la Alergia de Contacto en revistas internacionales por parte de Alergólogos.

BASES

- ✓ Su periodicidad será bianual.
- ✓ Se concederá un único premio, con una dotación de 2.500 euros, además de la invitación a la reunión anual de Alergonorte correspondiente.
- ✓ Optarán al premio todos los artículos originales publicados en las revistas indexadas en PubMed que traten temas relacionados con la alergia de contacto y que se presenten expresamente para su valoración.
- ✓ En esta segunda edición se valorarán los números de dichas revistas publicados entre el 1 de enero de 2018 hasta 31 diciembre 2019; en los cuales al menos un firmante sea Socio Numerario de la SEAIC.
- ✓ El premio va dirigido exclusivamente a Alergólogos miembros de SEAIC. Sólo se entregará un premio, valorándose para su concesión el orden de firma y el grado de participación en el trabajo.
- ✓ Es necesario que el autor envíe el trabajo para su evaluación a la dirección de correo: secretaria.alergorte@outlook.es.
- ✓ El autor no está obligado a aceptar el premio. La aceptación de este implica presentar un resumen del trabajo en la reunión anual de ALERGONORTE, en sección especial, durante la entrega del premio.
- ✓ El premio podrá quedar desierto si así lo considera el jurado.

JURADO

- Está compuesto por la Junta Directiva de Alergonorte, respetándose los cargos dePresidente y Secretario.
- El jurado se reserva la posibilidad de solicitar ayuda externa, en caso de necesidad, a expertos en el tema.
- Su decisión será inapelable.

ENTREGA DEL PREMIO

- La entrega efectiva del premio se realizará durante la Reunión Anual de ALERGONORTE, San Sebastián-Donostia, mayo de 2020.
- En caso de no poder acudir, el autor premiado podrá designar a la persona que recogerá el premio y presentará el resumen del trabajo.
- El designado para recoger el premio debe ser miembro numerario de SEAIC o miembro titular de ALERGONORTE.

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RETARD RAPID

Extracto alergénico nativo

La solución a medida para cada paciente

Inmunoterapia subcutánea
CON EXTRACTOS
ALERGÉNICOS NATIVOS

LETIPharma
desde 1919

EPITELIOS

- Caballo
- Gato
- Conejo
- Perro

DENOMINACIÓN DEL MEDICAMENTO: Retard Rapid®. COMPOSICIÓN CUALITATIVA Y CUANTITATIVA: Extractos alergénicos acuosos adsorbidos en hidróxido de aluminio, estandarizados biológicamente y cuya concentración se expresa en HEPL/ml. Se preparan en soluciones terapéuticas individuales de acuerdo con la composición especificada en la prescripción médica. La composición se indica en el envase. **FORMA FARMACÉUTICA:** Suspensión inyectable. **DATOS CLÍNICOS: Indicaciones terapéuticas:** Tratamiento hiposensibilizante (inmunoterapia específica con alérgenos) indicado en el tratamiento de enfermedades alérgicas respiratorias mediadas por IgE, tales como rinitis alérgica, conjuntivitis alérgica y/o rinoconjuntivitis alérgica con o sin asma bronquial alérgica. **Posología y forma de administración:** Retard Rapid® debe ser administrado por vía subcutánea. El extracto alergénico debe ser administrado siempre bajo supervisión médica y, en concreto, el inicio del tratamiento deber ser siempre administrado en unidades de inmunoterapia y bajo la supervisión de un médico especialista. El médico responsable del tratamiento fijará y adaptará la dosis y los intervalos según la tolerancia y la respuesta clínica del paciente. **Contraindicaciones:** Se consideran contraindicaciones las generales de la inmunoterapia específica con alérgenos, fundamentalmente: asma grave o no controlado o enfermedad crónica que afecte a los órganos diana (p. ej. enfisema, bronquiectasias). Presencia de enfermedad clínicamente relevante (p. ej. cardiovascular, renal, hepática, tiroidea, hematológica, sistema nervioso). Procesos infecciosos agudos, enfermedades inflamatorias graves, neoplasias malignas, enfermedades del sistema inmunológico clínicamente relevantes (p. ej. enfermedades autoinmunes, inmunodeficiencias incluyendo las secundarias a tratamiento con inmunosupresores o inmunomoduladores). Procesos patológicos en los que el paciente recibe betabloqueantes, incluidos los tópicos (o cualquier sustancia que pudiera disminuir la respuesta a adrenalina), o procesos patológicos en los que la adrenalina esté contraindicada. Pacientes en tratamiento con medicamentos que interfieran en el metabolismo de la adrenalina como los antidepresivos tricíclicos o inhibidores de la monoaminooxidasa. Trastornos mentales o psiquiátricos no controlados que puedan afectar la adherencia a la inmunoterapia. Hipersensibilidad a cualquiera de los excipientes. **Fertilidad, embarazo y lactancia:** El inicio de la inmunoterapia específica con alérgenos durante el embarazo está contraindicado. Si se produce el embarazo durante el tratamiento con Retard Rapid® se debe consultar al médico especialista, quien realizará una valoración clínica de la paciente para decidir la continuidad o la interrupción de la inmunoterapia. No hay datos clínicos sobre el uso de Retard Rapid® en el embarazo, ni durante periodo de lactancia, ni sobre un posible efecto sobre la fertilidad. **Advertencias y precauciones especiales de empleo:** • Es fundamental el seguimiento periódico del enfermo por el médico prescriptor, al cual incumbe realizar las modificaciones en el tratamiento que considere necesarias para el paciente. • El tratamiento debe ser iniciado en un período asintomático o con síntomas leves o controlados. • No administre el tratamiento al paciente durante un proceso agudo (fiebre, infección) o si presenta síntomas graves de alergia (p. ej. asma no controlado). • Comprobar la fecha de administración de la última dosis y la tolerancia a la misma, la fecha de caducidad del vial y la dosis. • Agitar suavemente el vial antes de extraer la dosis. • **Instruir al paciente en el reconocimiento de los síntomas asociados a una reacción adversa y cómo proceder (tratamiento necesario o cuándo acudir a un Servicio de Urgencias). · Se debe hacer especial hincapié en la instrucción relativa a las reacciones sistémicas que pueden aparecer de forma tardía.** • Administrar el extracto alergénico bajo supervisión médica. • Los extractos alergénicos sólo deben aplicarse si se dispone de medios inmediatamente accesibles que permitan proceder al tratamiento de un paciente que eventualmente sufra una reacción sistémica. Por eso, estos tratamientos deben realizarse en consultas médicas, Centros de Atención Primaria, Ambulatorios u Hospitales convenientemente dotados de medios para instaurar tratamiento inmediato ante un shock anafiláctico. No deben ser administrados en ningún caso en el domicilio del paciente. • Inyectar lentamente por **vía subcutánea**, en la cara posterolateral del brazo, aproximadamente en la zona comprendida desde el borde inferior del deltoides hasta 4 cm por encima del codo, evitando la penetración intravenosa. • El paciente debe permanecer bajo observación médica al menos 30 minutos después de cada inyección. • Alternar los brazos en cada administración. • No realizar ejercicios violentos ni tomar el sol, ni saunas unas horas antes y después de la inyección. • No aplicar ningún masaje o calor, ni rascarse sobre la zona inyectada. **Interacción con otros medicamentos y otras formas de interacción**. No se han realizado estudios de interacción. Los medicamentos que modifican la respuesta alérgica (p. ej. antihistamínicos, corticoides, estabilizadores de los mastocitos, antagonistas de los leucotrienos, etc.) o los broncodilatadores, aumentan el umbral de tolerancia del paciente a la inmunoterapia, si se administran antes de la misma. Pueden surgir reacciones adversas si el paciente olvida tomar su medicación habitual para el tratamiento de síntomas alérgicos antes de la administración de la inmunoterapia. La exposición adicional a alérgenos puede disminuir la tolerancia a la inmunoterapia. No se debe administrar inmunoterapia con alérgenos si se está recibiendo tratamiento con inmunosupresores. El tratamiento con betabloqueantes es un factor de riesgo para la aparición de reacciones sistémicas más graves y con mala respuesta a adrenalina, por tanto, el especialista debe valorar de forma individualizada el riesgo-beneficio de prescribir inmunoterapia en estos casos. No debe mezclarse este preparado con otra vacuna de extractos alergénicos: deben administrarse en inyecciones separadas. En caso de usar concomitantemente un producto Retard Rapid® y otra preparación de inmunoterapia con alérgenos, se recomienda administrarlos con un intervalo de 3-4 días entre inyecciones, en función de las características de los dos productos (composición y/o concentración). La administración de cualquier otro tipo de vacuna (inmunización profiláctica) debe realizarse durante la fase de mantenimiento, al menos una semana después de la última dosis de Retard Rapid®. Cualquier dosis de Retard Rapid® se administrará al menos 2 semanas después de la inmunización profiláctica (en caso de urgencia, valorar riesgo-beneficio). **Efectos sobre la capacidad para conducir y utilizar máquinas:** la aparición de un leve cansancio tras la inyección no es frecuente. **Reacciones adversas:** Pueden presentarse reacciones adversas locales y/o sistémicas, tanto inmediatas (en los primeros minutos siguientes a la inyección), como tardías (pasados los primeros minutos tras la inyección). Ante la aparición de cualquier reacción adversa, antes de proseguir el tratamiento, se deberá consultar con el médico prescriptor. **Reacción local:** eritema, picor, tumefacción y/o calor en el lugar de la inyección. De manera tardía pueden aparecer nódulos subcutáneos en el lugar de la inyección. **Reacción sistémica:** las reacciones sistémicas leves incluyen fatiga, urticaria localizada, rinitis o asma leve. Las reacciones sistémicas moderadas incluyen urticaria generalizada y/o asma moderada. Las reacciones sistémicas severas se engloban en el concepto de anafilaxia (pudiendo llegar al shock anafiláctico). Las reacciones anafilácticas consisten en la afectación simultánea de varios órganos con varios síntomas concurriendo simultáneamente, tales como: picor generalizado, calor generalizado, urticaria, angioedema, rinitis, conjuntivitis, sabor metálico, sensación de muerte inminente, malestar generalizado, debilidad, sudoración, tos, cefalea, disnea, sibilancias, broncoespasmo, estridor, afectación gastrointestinal con distensión, dolor, vómitos, retortijones, o diarrea, contracciones uterinas, metrorragia, mareo, hipotensión, ritmo cardíaco anormal, síncope, pérdida de control de esfínteres, colapso circulatorio, convulsiones y/o pérdida de consciencia. Ante cualquier indicio de reacción sistémica después de la inyección, y aunque fuera muy discreta en forma de leves molestias, debe aplicarse de inmediato el tratamiento indicado en estos casos: adrenalina, antihistamínicos, corticosteroides, etc. La severidad de una reacción sistémica suele correlacionarse con la rapidez de instauración de los síntomas tras la inyección, aunque también podrían aparecer reacciones sistémicas graves de forma tardía, que deben ser tratadas del mismo modo. **Pauta para la correcta administración de la adrenalina:** La adrenalina se administrará por vía intramuscular en una concentración al 1/1.000 a una dosis de 0,01 ml/kg de peso. Una pauta orientativa en caso de ser necesaria una actuación rápida puede ser la siguiente: Niños hasta los 6 años: 0,15 ml, niños de 6 a 12 años: 0,3 ml, niños mayores de 12 años y adultos: 0,5 ml (0,3 ml si el niño es prepuberal o de baja talla/peso). En caso de persistencia de la reacción sistémica, podrán ser repetidas dichas dosis cada 5-15 minutos, dependiendo de la respuesta del paciente. Ante una reacción anafiláctica se recomienda el traslado del paciente a un Servicio de Urgencia Hospitalario para su posterior observación y tratamiento. **Sobredosis:** La administración de una dosis superior a la dosis máxima recomendada y/o la utilización de una vía de administración distinta a la subcutánea pueden conducir a la aparición de reacciones adversas. **PROPIEDADES FARMACOLÓGICAS: Grupo farmacoterapéutico:** Extractos alergénicos. Código ATC V01AA. **DATOS FARMACÉUTICOS: Lista de excipientes:** Cloruro sódico, fenol, hidróxido de aluminio y agua para inyectables. Incompatibilidades: En ausencia de estudios de compatibilidad, este producto no debe ser mezclado con otros medicamentos. **Periodo de validez:** Observar la fecha de caducidad que consta en la etiqueta. **Precauciones especiales de conservación:** Almacenar en frigorífico (entre 2 °C y 8 °C). No congelar. **Naturaleza y contenido del envase:** Suspensión en viales de vidrio blanco de tipo I, con tapón de bromobutilo (sin látex) y cápsula de aluminio. **FECHA DE REVISIÓN DEL TEXTO:** Junio 2018.

Septiembre 2019

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Acertadamente PRECISO

Cupa 1 MOL

Un...
nuevo concepto
frente a la alergia
a cupresáceas

INMUNOTERAPIA MOLECULAR
la inmunización más precisa, a la dosis exacta

DIATER

FICHA TÉCNICA O RESUMEN DE LAS CARACTERÍSTICAS DEL PRODUCTO. Cup a 1 MOL. Suspensión inyectable. **1. NOMBRE DEL MEDICAMENTO.** Cup a 1 MOL 0,3 µg/mL suspensión inyectable. Cup a 1 MOL 3 µg/mL suspensión inyectable. **2. COMPOSICIÓN CUALITATIVA Y CUANTITATIVA.** La sustancia activa consiste en la proteína purificada y aislada de Cup a 1, alérgeno mayor de *Cupressus arizonica*, gimnosperma de la familia Cupressaceae. Cada vial A contiene 0,3 microgramos por mililitro de Cup a 1. Cada vial B contiene 3 microgramos por mililitro de Cup a 1. Para consultar la lista completa de excipientes, ver sección 6.1. **3. FORMA FARMACEÚTICA.** Suspensión inyectable. **4. DATOS CLÍNICOS. 4.1 Indicaciones terapéuticas.** Cup a 1 MOL es un producto de inmunoterapia específica individualizada (vacuna alergénica) para el tratamiento de pacientes alérgicos con rinitis, conjuntivitis, asma alérgico y otras patologías producidas por una hipersensibilidad de tipo I frente al polen de la familia Cupressaceae. **4.2 Posología y forma de administración.** Posología. La pauta general recomendada es (aunque el médico puede modifi carla según su criterio terapéutico): 1. **Inicio:** el objetivo es ir incrementando la dosis del medicamento gradualmente hasta que se alcance la dosis máxima tolerada, que será la dosis de mantenimiento o continuación. Debido a las diferencias de sensibilidad al alérgeno, el tratamiento para cada paciente debe ser controlado por su médico. La dosis debe aumentarse solamente en caso de que la dosis previa sea bien tolerada. 2. **Continuación:** consiste en la administración de la dosis máxima tolerada durante un periodo de 3-5 años. Es importante que Cup a 1 MOL sea usado de forma regular durante todo el periodo del tratamiento para que sea efectivo.Cup a 1 MOL es un tratamiento por vía subcutánea. Cup a 1 MOL se presenta en envases monodosis. Posteriormente a la administración de cada dosis desechar el vial para evitar confusiones.La pauta recomendada es una pauta clúster, en la cual se va aumentando progresivamente la concentración de alérgeno. Será a criterio médico la modificación de la pauta en función de la tolerabilidad y grado de sensibilización individual, la aparición de procesos intercurrentes en el transcurso de la inmunoterapia y/o el nivel de exposición al alérgeno. Estas pautas deben seguirse siempre excepto cuando el médico indique lo contrario: **Tratamiento de Inicio.** Compruebe que la presentación consta de dos viales A y cuatro viales B. Comience la administración del tratamiento siempre por el vial A que corresponde al de menor concentración del alérgeno Cup a 1. Las inyecciones deben administrarse una vez por semana excepto el último vial B que se espaciará un mes. **Tratamiento de Continuación.** Compruebe que la presentación consta de tres o seis viales B, según la prescripción del médico. Las inyecciones se administrarán mensualmente durante 3-5 años. *Población pediátrica.* La seguridad y eficacia de Cup a 1 MOL en la población pediátrica no se ha determinado. De cualquier modo, el tratamiento con inmunoterapia subcutánea en niños está ampliamente apoyado por publicaciones científicas (ver sección 5.1) si bien siguiendo las recomendaciones vigentes para el manejo de la inmunoterapia subcutánea, Cup a 1 MOL no debe emplearse en niños menores de 2 años y debe emplearse con precaución en niños de 2 a 5 años. Para el tratamiento en pacientes pediátricos, el médico debe tener experiencia en el tratamiento de enfermedades alérgicas en niños. La posología será determinada por el médico tras una cuidadosa consideración, teniendo en cuenta el nivel de eficacia esperado en ese grupo de edad (ver sección 5.1). *Pacientes de edad avanzada.* No se ha establecido todavía la seguridad y eficacia de Cup a 1 MOL en ancianos (mayores de 65 años). Forma de administración. Cup a 1 MOL está destinado a la administración por vía subcutánea. Es muy importante seguir las instrucciones antes de la utilización de Cup a 1 MOL: • Comenzar la administración del tratamiento siempre por el vial A que corresponde al de menor concentración. • Agitar el vial suavemente antes de cada extracción. • Proceder a extraer las dosis de tratamiento. • Asegurar que la vía de administración sea por vía subcutánea. Las inyecciones se realizarán en la cara dorsal superior del brazo, 20 cm por encima del codo, alternando de brazo en cada administración, asegurándose de no administrarlo por vía intravenosa. • Proceder de la misma forma a medida que corresponda con los viales siguientes. Después de la aplicación de cada una de las dosis, el paciente debe permanecer 30 minutos como mínimo en el centro donde se le haya administrado el medicamento. **4.3 Contraindicaciones.** Hipersensibilidad a alguno de los excipientes incluidos en la sección 6.1. El uso de Cup a 1 MOL se encuentra adicionalmente contraindicado en los siguientes casos: • Asma grave o mal controlada. • Enfermedades autoinmunes activas (sin respuesta al tratamiento). • Neoplasias malignas. • Niños menores de 2 años. • El tratamiento de inmunoterapia no debe iniciarse durante el embarazo. • SIDA. • Pirexia. **Referencias bibliográficas.** • Pitsios C. *et al.* (2015) Clinical contraindications to allergen immunotherapy: an EAACI position paper. Allergy; 70: 897–909. **4.4 Advertencias y precauciones especiales de empleo.** Siguiendo las recomendaciones vigentes, el uso de inmunoterapia con aeroalérgenos, incluido Cup a 1 MOL debe emplearse con precaución valorando el beneficio/riesgo de forma individual en los siguientes casos: - Pacientes con asma parcialmente controlada. Ante un paciente con asma parcialmente controlada se recomienda su estabilización previa al inicio de la inmunoterapia. - Niños de 2-5 años dada la limitada cooperación y la tolerabilidad del paciente ante un episodio de anafilaxia y al uso de adrenalina. - Enfermedad autoinmune en remisión. Se desconoce el efecto de la inmunoterapia en la enfermedad de base. - Inmunodeficiencias adquiridas o uso de inmunosupresores (diferentes a tratamientos anti-IgE) Se desconoce su impacto en la eficacia de la inmunoterapia. - Infecciones crónicas (p. ej. hepatitis B o C). - Trastornos psiquiátricos / mentales que interfieran en el buen cumplimiento y colaboración del paciente. El paciente debe, estar en cualquier caso, bien controlado antes del inicio de la inmunoterapia. - Historia de reacciones sistémicas graves a inmunoterapia previa dado el mayor riesgo de desarrollo de nuevas reacciones sistémicas. En general, la experiencia clínica con inmunoterapia en pacientes mayores de 65 años es limitada. En estos pacientes se deberá tener en cuenta la presencia de comorbilidades y medicaciones concomitantes previamente descritas. Como con otras inmunoterapias, existe un mayor riesgo potencial de reacciones adversas en etapas de mayor exposición al alérgeno. Se recomienda el inicio de tratamiento con inmunoterapia subcutánea, incluido Cup a 1 MOL, al menos dos meses antes de la estación polínica o cuando la exposición al alérgeno sea la más baja. En niños con asma concomitante e infección aguda del tracto respiratorio superior se debe suspender temporalmente el tratamiento con Cup a 1 MOL hasta que la infección haya desaparecido. No se recomienda la administración de Cup a 1 MOL el mismo día de la administración de otras inmunizaciones. Es aconsejable que entre las administraciones haya una diferencia de al menos 10 días (ver sección 4.5). En casos excepcionales, este tratamiento puede entrañar riesgo de reacciones generalizadas a veces graves (urticaria, asma, shock anafiláctico, etc.) por lo que deben seguirse durante toda la duración del mismo las siguientes normas: • Es de suma importancia que el personal sanitario lea atentamente los requisitos de administración antes de aplicar este medicamento. • Cup a 1 MOL debe ser administrado siempre bajo supervisión médica. • Cup a 1 MOL sólo debe aplicarse si se dispone de medios inmediatamente accesibles que permitan proceder al tratamient o de un paciente que eventualmente sufra una reacción generalizada (urticaria, asma, shock anafiláctico, etc.), tales como adrenalina por vía intramuscular u otros. Por eso este tratamiento debe realizarse en consultas médicas, centros de atención primaria, ambulatorios u hospitales convenientemente dotados. No debe administrarse en ningún caso en el domicilio del paciente. • Después de la aplicación de todas y cada una de las dosis, el paciente permanecerá 30 minutos como mínimo en el centro donde se le haya administrado el medicamento. • Ante la aparición de cualquier reacción adversa, antes de proseguir con el tratamiento, el riesgo debe ser evaluado por el médico. • Es esencial que el paciente esté controlado de forma regular por el médico prescriptor, que es el responsable de cualquier dilución del medicamento u otra alteración necesaria en el tratamiento. Cup a 1 MOL es un tratamiento por vía subcutánea, es preciso asegurarse de no administrarlo por vía intramuscular o intravenosa. El enrojecimiento en el lugar de la inyección es normal, siempre y cuando éste no exceda de 5 cm de diámetro (Malling & Weeke 1993). Si se presenta una reacción mayor, se deberán tomar las medidas necesarias a criterio del médico para dicha reacción. Este medicamento contiene menos de 1 mmol de sodio (23 mg) por dosis, por lo que se considera esencialmente "exento de sodio". **Referencias bibliográficas.** • Pitsios C. *et al.* (2015) Clinical contraindications to allergen immunotherapy: an EAACI position paper. Allergy; 70: 897–909. • Roberts G. *et al.* (2017) EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. Allergy; 1-34. • Malling H.J., Weeke, B. (1993) Position paper: immunotherapy. Allergy; 48:9–35. **4.5 Interacción con otros medicamentos y otras formas de interacción.** No se han realizado estudios de interacciones. El uso concomitante de medicamentos para el tratamiento sintomático de la alergia (p. ej. antihistamínicos, corticoides) puede incrementar la tolerancia a la inmunoterapia del paciente. El uso de betabloqueantes debe tenerse en cuenta, ya que en caso de anafilaxia puede verse comprometida la capacidad de respuesta a la medicación de emergencia y se incrementaría el riesgo de reacciones sistémicas más graves. Se recomienda sustituir los betablogueantes por otro tratamiento alternativo si es posible (Pitsios *et al.* 2015). No hay experiencia clínica respecto al tratamiento con Cup a 1 MOL y la vacunación profiláctica simultánea para enfermedades infecciosas (p. ej. gripe, tétanos…). **Referencias bibliográficas.** • Pitsios C. *et al.* (2015) Clinical contraindications to allergen immunotherapy: an EAACI position paper. Allergy; 70: 897–909. **4.6 Fertilidad, embarazo y lactancia.** Embarazo y lactancia. No se pueden excluir riesgos para el bebé/neonato. No se dispone de información sobre la seguridad del medicamento durante el embarazo o la lactancia. El inicio de una inmunoterapia con alérgenos, incluido Cup a 1 MOL, está contraindicado durante el embarazo. Fertilidad. No se dispone de información sobre la seguridad del medicamento para la fertilidad. **4.7 Efectos sobre la capacidad para conducir y utilizar máquinas.** No se han descrito efectos que afecten sobre la capacidad de conducción y el manejo de herramientas o máquinas, por lo que no se requieren precauciones especiales. **4.8 Reacciones adversas.** Resumen del perfil de seguridad. Las reacciones locales consisten en la aparición de prurito, urticaria, calor, dolor, edema o inflamación en el lugar/zona de inyección. Suelen presentarse entre los 10 y 60 minutos tras la administración y persistir varias horas, desapareciendo sin necesidad de tratamiento. La induración y/o eritema de la zona de inyección es normal, mientras no exceda los 5 cm de diámetro. En caso de una reacción local mayor se aconseja el uso de antihistamínicos orales y/o corticoides de uso tópico. Deberán seguirse las medidas y/o medicamentos indicados por el médico. En general, las reacciones sistémicas consisten en rinitis o (rino)rinoconjuntivitis alérgica, obstrucción o congestión nasal, rinorrea, estornudos, eritema, prurito, parestesia, (angio)edema, edema de labio o palpebral, sibilancia, disnea, tos, hipoventilación o dificultad respiratoria, disfagia, malestar torácico, hipotensión, mareo, pirexia, cefalea, malestar general, que pueden ocurrir entre 15 minutos y 4-6 horas tras la inyección subcutánea. En el caso de broncoespasmo se recomienda usar broncodilatadores. Excepcionalmente este medicamento puede producir asma , urticaria generalizada, anafilaxia, shock o reacción anafiláctica. Lista tabulada de reacciones adversas: La siguiente tabla de reacciones adversas está basada en datos de la experiencia poscomercialización de extractos alergénicos en suspensión, adsorbidos en hidróxido de aluminio. Dentro de la clasificación por órganos y sistemas, las reacciones adversas identificadas durante el periodo de comercialización están listadas por frecuencia (número de pacientes que se espera experimenten la reacción), utilizando la siguiente categoría: frecuencia no conocida (no puede estimarse a partir de los datos disponibles). Descripción de las reacciones adversas seleccionadas. Si el paciente experimenta reacciones adversas importantes a raíz del tratamiento, se debe considerar el uso de medicación antialérgica. Este medicamento puede producir reacciones anafilácticas graves, incluido el shock anafiláctico, considerándose un efecto de clase de la inmunoterapia. Por ello, como medida de precaución importante el tratamiento debe ser supervisado por un médico (ver sección 4.2 y 4.4). Se deberá contactar con un médico inmediatamente en caso de reacciones sistémicas severas. En estos casos, se debe suspender el tratamiento de forma permanente, o hasta que el médico lo recomiende. Población pediátrica. En general, la naturaleza de los efectos adversos observados en niños y adolescentes tratados con inmunoterapia subcutánea es similar a la observada en adultos. Notificación de sospechas de reacciones adversas. Es importante notificar sospechas de reacciones adversas al medicamento tras su autorización. Ello permite una supervisión continuada de la relación beneficio/riesgo del medicamento. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas a través del Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano www.notificaRAM.es. **4.9 Sobredosis.** Si la dosis suministrada es más alta que la dosis diaria recomendada, puede aumentar el riesgo de reacciones adversas, incluyendo el riesgo de reacciones sistémicas o reacciones locales severas. En estos casos, el tratamiento debe suspenderse de forma permanente o hasta que el médico lo recomiende. **5. PROPIEDADES FARMACOLÓGICAS. 5.1 Propiedades farmacodinámicas.** Grupo farmacoterapéutico: Grupo V (Varios), Código ATC: V01AA05. Polen de árbol. Mecanismo de acción. Existen pruebas recientes que proveen una explicación plausible para los múltiples mecanismos de la inmunoterapia con alérgenos (ITA), induciendo una rápida desensibilización y tolerancia inmune alérgeno-específica a largo plazo, así como la supresión de inflamación alérgica en el tejido afectado. El mecanismo descrito incluye la modificación de la presentación del alérgeno por las células dendríticas, las cuales por su parte modifican el fenotipo de los linfocitos T alérgeno-específicos, pasando de una respuesta tipo Th2, típica de la inflamación alérgica, a una respuesta tipo Th1. Los linfocitos alérgeno-específicos T reguladoras (Treg) juegan un papel importante, productores de citocinas supresoras como IL-10 y TGF-beta (Incorvaia 2013). La inducción e incremento de secreción de IL-10 debido a AIT aparentemente regula contra las IgEs alérgeno específicas y ello simultáneamente incrementa la producción de IgG4. En consecuencia, IL-10 no solo genera tolerancia en los linfocitos T sino que regula la formación de isotipos específicos e influye la respuesta IgE-específica a un fenotipo dominante IgG4 (Akdis & Akdis 2007). Las pruebas sugieren efectos biológicos importantes de IgG4 alérgeno específica. Estos efectos incluyen la capacidad IgG-dependiente del suero posinmunoterapia de inhibir la unión de complejos IgE-alérgeno con linfocitos B, bloqueando la subsecuente presentación del alérgeno facilitada por IgE y la activación de linfocitos T alérgeno específicos, y la prevención de la activación alérgeno-IgE dependiente de los basófilos periféricos. Cup a 1 MOL contiene solamente la proteína purificada y aislada Cup a 1, por lo tanto presenta menos epítopos al sistema inmunitario lo que permite la modulación de la respuesta inmune y la producción de IgG del tipo 4 (IgG4) específicos frente a solo un alérgeno. Eficacia clínica y seguridad. La Organización Mundial de la Salud (Bousquet *et al.* 1998) y la Academia Europea de Alergia e Inmunología Clínica (Burks *et al.* 2013; Roberts et al. 2017) consideran a la inmunoterapia con alérgenos un tratamiento efectivo frente a la rinoconjuntivitis y el asma alérgica. Las reacciones adversas se clasifican en locales y sistémicas. La gravedad de las reacciones sistémicas inducidas por la inmunoterapia subcutánea puede variar desde leves síntomas a anafilaxia. En un sondeo realizado durante 2007 y 2009 tras la administración de 8 millones de inyecciones por año, las reacciones sistémicas registradas fueron de 0,1% de las inyecciones, ninguna con desenlace fatal. La mayoría de estas reacciones sistémicas (86%) sucedieron dentro de los 30 minutos posteriores tras la administración de la inyección. En cuanto a las reacciones sistémicas retardadas la mayoría fueron leves, aunque también se observaron graves (Burks *et al.* 2013). El riesgo de reacciones sistémicas a inmunoterapia con alérgenos basado en protocolos convencionales de aumento de dosi s es de aproximadamente 0,2% por inyección (1 en 500) (Ravi & Rank 2013). Revisiones sistemáticas han mostrado que la inmunoterapia subcutánea (ITSC) es segura cuando se prescribe a pacientes seleccionados en una consulta de un especialista con unas instalaciones adecuadas y personal médico entrenado. ITSC puede producir reacciones adversas tanto locales como sistémicas; no obstante, en la mayoría de los casos estos síntomas son fácilmente reversibles si se reconocen a tiempo y con el tratamiento adecuado. Las reacciones adversas pueden darse con preparados de alérgenos tanto si son extractos estandarizados, alergoides o alérgenos recombinantes (Calderon *et al.* 2011). Población pediátrica. La inmunoterapia con alérgenos no es un tratamiento indicado para niños menores de 2 años. En niños de entre 2 y 5 años se deberá considerar su uso caso a caso y bajo completa supervisión de un médico con experiencia en la identificación y tratamiento de signos de anafilaxia en este grupo de edad (Wiley *et al.* 2006; Pitsios *et al.* 2015). Un estudio retrospectivo de inmunoterapia subcutánea en 239 niños menores de 5 años (8-59 meses de edad), que recibieron 6.689 inyecciones registró una reacción sistémica 90 minutos después de la administración en un niño de 3 años de edad. Un segundo estudio de inmunoterapia subcutánea para tratar el asma alérgica debida a ácaros, en 22 bebés, de los cuales cuatro eran menores de 3 años, se observó un broncoespasmo leve en 7/22 de los bebés como reacción adversa, aunque continuaron con el tratamiento (Pitsios *et al.* 2015). El inicio temprano del tratamiento de inmunoterapia apropiado en niños con rinoconjuntivitis alérgica con o sin asma es la mejor garantía de una correcta evolución de esta enfermedad, previniendo el empeoramiento durante la edad adulta (Jacobsen et al. 1996; Arède *et al.* 2013). La evaluación de los efectos diferenciales de la inmunoterapia basada en el estado de desarrollo de los niños y adolescentes puede ayudar a optimizar el tratamiento y a identificar la dosis óptima, frecuencia, duración y edad de inicio del tratamiento en niños (Kim *et al.* 2013). Otra revisión analiza 31 estudios sobre ITSC en niños de 3 a 18 años, y concluye que hay una evidencia aceptable de que la inmunoterapia subcutánea con polen de gramíneas, Alternaria alternata y ácaros del polvo es beneficiosa en niños alérgicos (Larenas-Linnemann *et al.* 2011). **Referencias bibliográficas.** • Incorvaia C. (2013) Preventive capacity of allergen immunotherapy on the natural history of allerg y. J Prev Med Hyg; 54(2): 71-74. • Akdis M., Akdis C. A. (2007) Mechanisms of allergen-specific immunotherapy. J Allergy Clin Immunol; 19(4): 780-791. • Frolán S., Pineda F., Rodríguez D. (2014) Caracterización del polimerizado de "Dermatophagoides pteronyssinus" modificado con glutaraldehído. Dianas; 3(1): e20140907. • Bousquet, Jean *et al.* (1998) Allergen immunotherapy: Therapeutic vaccines for allergic diseases A WHO position paper. Journal of Allergy and Clinical Immunology; 102(4): 558 - 562. • Burks A. 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Ann Allergy Asthma Immunol; 107:407-16. **5.2 Propiedades farmacocinéticas.** No se dispone de información sobre las propiedades farmacocinéticas de Cup a 1 MOL.No es posible llevar a cabo estudios farmacocinéticos de productos de inmunoterapia con alérgenos, debido a que la concentración de sustancia activa en el plasma es demasiada baja para ser determinada, debido a la naturaleza del producto (CHMP/EWP/18504/2006). **Referencias bibliográficas.** • Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases. CHMP/EWP/18504/2006. **5.3 Datos preclínicos sobre seguridad.** No se dispone de datos de estudios preclínicos que puedan mostrar riesgos especiales para los seres humanos según los estudios convencionales de farmacología de seguridad, toxicidad a dosis repetidas, genotoxicidad y de potencial carcinogénico. **6. DATOS FARMACEUTICOS. 6.1 Lista de excipientes.** Cloruro sódico. Hidróxido de aluminio. Agua para inyectables. **6.2 Incompatibilidades.** No se dispone de datos de estudios de compatibilidad. En ausencia de estudios de compatibilidad, este medicamento no debe mezclarse con otros. **6.3 Periodo de validez.** No utilice este medicamento después de la fecha de caducidad que aparece en el envase. **6.4 Precauciones especiales de conservación.** Conservar en nevera (entre 2 ºC y 8 ºC). No congelar. Cuando el intervalo entre dosis sea de 30 minutos, no desechar los viales y conservar en nevera (entre 2 ºC y 8 ºC). No congelar. En el resto de dosis, desechar los viales tras su administración para evitar confusiones. Conservar en el embalaje original. No utilice Cup a 1 MOL si observa pérdida de contenido de los viales o deterioro en el envase. **6.5 Naturaleza y contenido del envase.** Vial de vidrio (Tipo I), con tapón de goma (Tipo I) y cápsula de aluminio. Cup a 1 MOL está formado por dos presentaciones: tratamiento de inicio y continuación. **Envase para tratamiento de inicio.** Tratamiento de inicio contiene 2 unidades de vial A (etiqueta amarilla) que contiene 1 mL de solución que contiene 0,3 µg de Cup a 1, y 4 unidades de vial B (etiqueta roja) que contiene 1 mL de solución que contiene 3 µg de Cup a 1. **Envases para tratamiento de continuación.** Tratamiento de continuación que contiene 3 unidades de vial B (etiqueta roja) que contiene 1 mL de solución que contiene 3 µg de Cup a 1. Tratamiento de continuación que contiene 6 unidades de vial B (etiqueta roja) que contiene 1 mL de solución que contiene 3 µg de Cup a 1. Puede que solo estén comercializadas algunas de las presentaciones. **6.6 Precauciones especiales de eliminación y otras manipulaciones.** Ninguna especial. La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él se realizará de acuerdo con la normativa local. **7. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN.** DIATER Laboratorio de Diagnósticos y Aplicaciones Terapéuticas, S.A. Avenida Gregorio Peces Barba, nº 2. Parque Tecnológico de Leganés. 28918 Leganés (Madrid) España. Tel: +34 91 496 60 13. Fax: +34 91 460 60 12. e-mail: info@diater.com. **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN. 9. FECHA DE LA PRIMERA AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN. 10. FECHA DE LA REVISIÓN DEL TEXTO.** Septiembre 2019.

DÍA	VIAL	DOSIS RECOMENDADAS	INTERVALO ENTRE DOSIS	FRECUENCIA DE ADMINISTRACIÓN	FECHA
Día 1	A Etiqueta amarilla	1ª Dosis: 0,1 mL 2ª Dosis: 0,2 mL	30 minutos	semanal	
Día 8	A Etiqueta amarilla	1ª Dosis: 0,4 mL 2ª Dosis: 0,4 mL	30 minutos	semanal	
Día 15	B Etiqueta roja	1ª Dosis: 0,1 mL 2ª Dosis: 0,2 mL	30 minutos	semanal	
Día 22	B Etiqueta roja	1ª Dosis: 0,4 mL 2ª Dosis: 0,4 mL	30 minutos	semanal	
Día 37	B Etiqueta roja	0,8 mL	mensual		
Día 67	B Etiqueta roja	0,8 mL	mensual		

VIAL	DOSIS RECOMENDADAS	FRECUENCIA DE ADMINISTRACIÓN	FECHA
B Etiqueta roja	0,8 mL	mensual	
B Etiqueta roja	0,8 mL	mensual	
B Etiqueta roja	0,8 mL	mensual	

Clasificación por órganos y sistemas	Frecuencia	Reacción adversa al medicamento
Trastornos del sistema inmunológico	Frecuencia no conocida (no puede estimarse a partir de los datos disponibles)	Anafilaxia, reacción anafiláctica; shock anafiláctico
Trastornos respiratorios, torácicos y mediastínicos	Frecuencia no conocida	Disnea, tos, broncoespasmo, asma, sibilancia, rinitis alérgica, rinorrea, obstrucción o congestión nasal, estornudos, hipoventilación o dificultad respiratoria
Trastornos generales y alteraciones en el lugar de administración	Frecuencia no conocida	Reacciones en la zona de inyección/vacunación (incluyendo eritema, urticaria, prurito, calor, dolor, induración, edema o inflamación); edema o hinchazón periférico, malestar torácico, malestar general, pirexia
Trastornos oculares	Frecuencia no conocida	Edema palpebral, rinoconjuntivitis alérgica, conjuntivitis alérgica
Trastornos gastrointestinales	Frecuencia no conocida	Edema de labio, disfagia
Trastornos de la piel y tejido subcutáneo	Frecuencia no conocida	Urticaria, prurito, (angio)edema, eritema (incluso generalizados)
Trastorno del sistema nervioso	Frecuencia no conocida	Parestesia, mareo, cefalea
Trastornos vasculares	Frecuencia no conocida	Hipotensión

Therapeutic Strategy According to Differences in Response to Omalizumab in Patients With Chronic Spontaneous Urticaria

Giménez Arnau AM[1], Valero Santiago A[2], Bartra Tomás J[3], Jáuregui Presa I[4], Labrador-Horrillo M[5], Miquel Miquel FJ[6], Ortiz de Frutos J[7], Sastre J[8], Silvestre Salvador JF[9], Ferrer Puga M[10]

[1]Dermatology Department, Hospital del Mar, Institut Mar D´Investigacions Mèdiques, Universitat Autónoma de Barcelona, Barcelona, Spain
[2]Allergy Unit, Pneumology Department, Hospital Clínic, Institut d´Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain and RETIC de Asma, Reacciones adversas y Alérgicas (ARADYAL)
[3]Allergy Unit, Pneumology Department, Hospital Clínic, Barcelona, Institut d´Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain and RETIC de Asma, Reacciones adversas y Alérgicas (ARADYAL)
[4]Allergy Department, Hospital Universitario Basurto, Bilbao, Spain
[5]Allergology Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain and RETIC de Asma, Reacciones adversas y Alérgicas (ARADYAL)
[6]Dermatology Department, Hospital Arnau de Vilanova, Valencia, Spain
[7]Dermatology Department, Hospital Universitario 12 de Octubre, Madrid, Spain
[8]Allergology Department, Fundación Jiménez Díaz, Madrid, Spain
[9]Dermatology Department, Hospital General Universitario de Alicante, Alicante, Spain
[10]Department of Allergy and Immunology, Clínica Universidad de Navarra, Instituto de Investigación Sanitaria de Navarra (IdiSNA), RETIC de Asma, Reacciones adversas y Alérgicas (ARADYAL), Pamplona, Spain

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Abstract

Chronic spontaneous urticaria (CSU) is a heterogeneous condition that can severely impact quality of life. Consequently, rapid disease control is essential. First-line treatment of the symptoms of CSU is the licensed dose of second-generation H_1 antihistamines. For second-line treatment, this dose may be increased by up to 4 times. In patients who fail to respond to higher doses of H_1 antihistamines, omalizumab for up to 24 weeks is recommended to achieve disease control. After this 24-week period, the patient's response to omalizumab should be assessed in order to identify refractory patients. Optimal management of refractory patients has not been established. Therefore, the aim of the present consensus document, which was drafted by allergists and dermatologists with specific expertise in treating urticaria, was to define specific patient profiles based on differences in their response to omalizumab. We also developed a treatment algorithm based on the specific response profile. After a comprehensive literature review, a group meeting was held to discuss issues related to the therapeutic management of patients with CSU that had not been addressed in previous studies. The experts considered both the available evidence and their own clinical experience with omalizumab. We believe that implementation of the proposed algorithm will optimize management of CSU patients who are refractory to antihistamines, reduce disease-related costs, and improve quality of life.

Key words: Chronic urticaria. Antihistamines. Omalizumab. Algorithm. Treatment.

Resumen

La urticaria crónica espontánea (UCE) es una afección heterogénea que puede afectar gravemente la calidad de vida, por lo que el control rápido de la enfermedad es esencial. El tratamiento sintomático de primera línea de CSU es la dosis autorizada de antihistamínicos H1 de segunda generación. Para el tratamiento de segunda línea, esta dosis se puede aumentar hasta cuatro veces. En pacientes que no responden a estas dosis más altas de antihistamínicos H1, se recomienda el tratamiento con omalizumab (hasta 24 semanas) para lograr el control de la enfermedad. Después de este período de 24 semanas, se debe definir el perfil de respuesta del paciente a omalizumab para identificar a los pacientes refractarios. El enfoque de manejo óptimo para pacientes refractarios no ha sido establecido. En este contexto, el objetivo del presente estudio de consenso de expertos que involucró a un grupo de especialistas (alergólogos y dermatólogos) con experiencia específica en el tratamiento de la urticaria fue definir perfiles de pacientes específicos en función de sus diferentes respuestas a omalizumab. Otro objetivo fue desarrollar un algoritmo de tratamiento basado en el perfil de respuesta específico. Primero, se realizó una revisión exhaustiva de la literatura. Luego, se llevó a cabo una reunión grupal para discutir todos los temas relacionados con el manejo terapéutico de estos pacientes que no se habían abordado en ningún estudio previo. En todos los casos, los expertos consideraron tanto la evidencia disponible como su propia experiencia clínica con omalizumab. Creemos que la implementación de este algoritmo propuesto ayudará a optimizar la gestión de los pacientes con CSU que son refractarios al tratamiento con antihistamínicos, reduciendo los costos relacionados con la enfermedad y mejorando la calidad de vida de los pacientes.

Palabras clave: Urticaria crónica. Antihistamínicos. Omalizumab. Algoritmo. Tratamiento.

Introduction

Chronic spontaneous urticaria (CSU) is a heterogeneous condition that causes significant morbidity [1,2]. It is characterized by the sudden appearance of wheals and/or angioedema that persist for 6 weeks or longer [2]. In most cases, the average duration of CSU is from 1 to 5 years [3,4]. CSU is estimated to affect between 0.5% and 1% of the general population, with an annual frequency of 1.4% [5]. The annual prevalence of urticaria appears to have increased in recent years. In Italy, the prevalence increased from 0.02% in 2002 to 0.38% in 2013, with a current incidence rate of 0.10-1.50 per 1000 persons per year [6]. CSU imposes a significant economic burden and has a substantial negative impact on patient quality of life (QOL). Therefore, it is crucial to administer effective treatment as soon as possible [7-9].

The management of CSU consists of a 2-pronged approach based on avoiding the triggers (if known) and pharmacological treatment of the symptoms [3]. The current EAACI/GA$_2$LEN/EDF/WAO guidelines recommend second-generation H$_1$ antihistamines as first-line treatment of the symptoms of CSU [2,10]. However, given that approximately 70% of patients remain symptomatic despite the use of antihistamines at the licensed doses [11,12], the guidelines recommend increasing the licensed dose by up to 4 times for second-line treatment [2]. However, a recent systematic review and meta-analysis estimated that up to 36.8% of patients might be refractory to the maximum dose of H$_1$ antihistamines (4-fold the standard dose) [13]. Recent guidelines recommend adding omalizumab to treatment with antihistamines as a third-line treatment. Fourth-line treatment includes the use of cyclosporine A. For exacerbations, the guidelines recommend short courses of oral corticosteroids for no more than 10 days (Figure 1) [2,10].

Phase 3 trials have demonstrated the favorable efficacy and safety profile of omalizumab [3,14,15], which is substantially safer than cyclosporine, particularly with regard to renal toxicity [10]. An expert panel recently drew the same conclusions regarding the favorable safety and efficacy profile of omalizumab compared with cyclosporine [16]. In addition, a recent meta-analysis found that more than 50% of patients

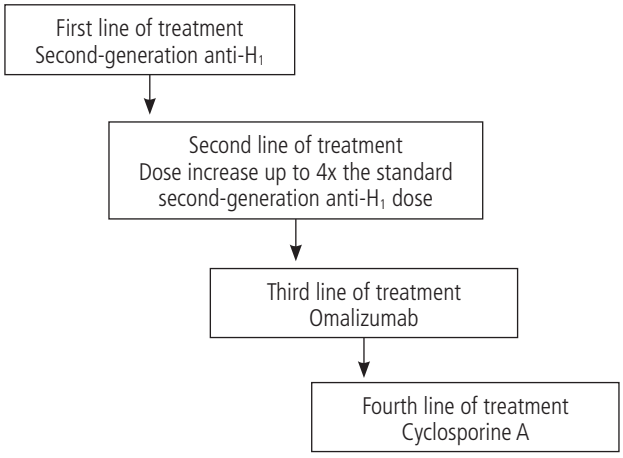


Figure 1. Treatment algorithm for chronic spontaneous urticaria.

who received cyclosporine at doses of 4-5 mg/kg/d presented adverse events [17].

Omalizumab selectively binds to human IgE, thus preventing binding of IgE to its high-affinity receptor (FcεRI) and reducing the amount of free IgE. This process affects the immunological cascade of urticaria on several levels (Figure 2) [18,19]. Both the European Medicines Agency and the United States Food and Drug Administration approved omalizumab for the treatment of CSU in 2014. The favorable efficacy and safety data for omalizumab obtained in clinical trials are further supported by results from real-world clinical studies [1,20,21]. Available evidence supports the use of omalizumab for up to 24 weeks as a third-line treatment for CSU [22]; however, the efficacy of this drug beyond 24 weeks is less well-established [23]. Although most patients respond well to omalizumab, the response profile is highly variable and unpredictable, with some responding quickly and others responding more slowly or not at all. To date, the different response profiles have not been well defined, even though clear

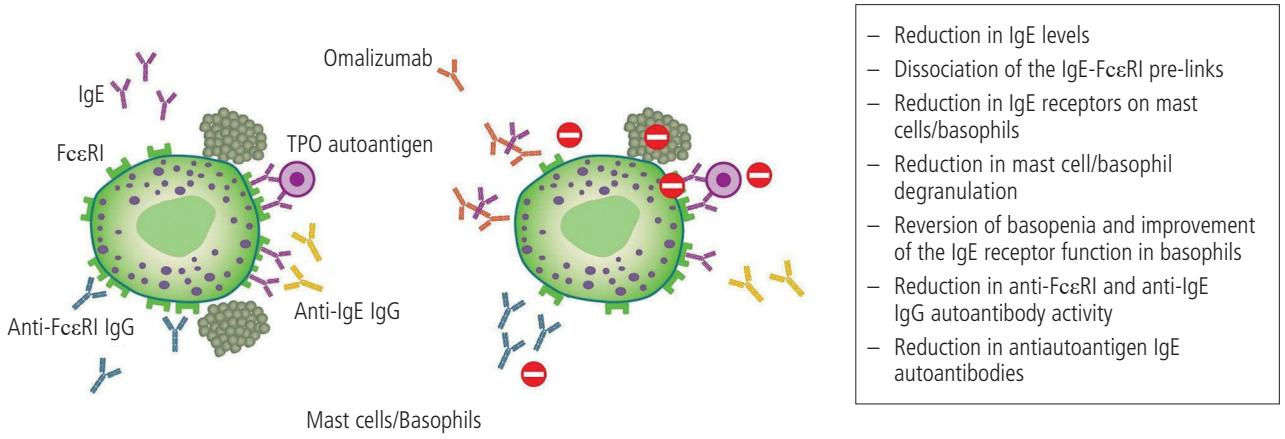


Figure 2. Mechanism of action of omalizumab.

definitions would help to guide the medical management of patients in accordance with their individual response profile.

In this context, an expert working group comprising specialists with broad experience in treating urticaria was convened to define CSU patient profiles depending on the varying responses to omalizumab. We describe these profiles and provide a clear, straightforward therapeutic algorithm to guide the management of patients with CSU according to their specific response to omalizumab.

Methods

We report the consensus opinions of a group of experts in urticaria treatment. The group comprised allergists and dermatologists in Spain with expertise in treating urticaria. This working group met 3 times from 2015 to 2016 to discuss the main unresolved issues regarding therapeutic management of CSU patients.

Initially, the group generated a series of unresolved questions about the optimal use of omalizumab for the treatment of CSU patients that commonly arise in routine clinical practice. The 3 main questions raised were as follows: (*1*) What criteria are taken into consideration when urticaria is "controlled"? (*2*) Can we identify specific patient profiles based on individual differences in the response to omalizumab? (*3*) What is the optimal therapeutic strategy for each of these profiles?

To answer these questions, we performed a bibliographic review of publications on urticaria in the MEDLINE database. Using the PubMed search engine, we searched for various combinations of the following key words in English: *Management, Disease, Urticaria, Chronic Spontaneous Urticaria, Guidelines, Prevalence, Treatment, Therapy, Omalizumab, Antihistamines, Refractory, Cyclosporine, Responders, Non-responders, Activity, UAS, UAS7, QoL, Control, Algorithms, Response predictors, Questionnaire*, and *Impact*.

Questions that were not fully addressed in the literature were addressed based on the extensive clinical experience of the team of experts. Prior to the meetings, the experts were asked to individually prepare their responses to the 3 main study questions in order to facilitate the group discussions. The therapeutic protocol and patient profiles defined in this document are based on available published scientific evidence in conjunction with the consensus expert option of this group of specialists. In addition, a consensus summary of the key points was also developed.

The discussions held to address the aforementioned unresolved issues also yielded several other omalizumab- and CSU-related questions. These issues are addressed in this document.

Discussion

Measurement of the Activity and Impact of CSU

In many cases, it is difficult to precisely assess CSU owing to the heterogeneous nature of the condition and the evanescence of the skin lesions. For this reason, clinical guidelines recommend the use of grading scales in routine clinical practice, and several validated tools are available to monitor disease activity and control and to assess the impact of the condition on patient QOL [2,10]. While it is important to use these scales for the initial assessment, they should also be used for follow-up purposes after initiation of treatment. The scales are particularly useful in patients with poor disease control despite good adherence to treatment. By contrast, these scales may be unnecessary in stable, well-controlled patients [2].

By measuring disease activity, control, and impact, the clinician can identify the patient's individual clinical profile and determine whether his/her CSU is under control. The resulting scores can be used to guide selection of treatment in accordance with the patient's disease status [2].

The Urticaria Activity Score (UAS), particularly the UAS7 version, is recommended for assessment of the symptoms of CSU [2,24]. The UAS7, which was validated in 2008 to measure urticaria symptoms, defines 5 "disease activity categories" according to the score obtained (Supplementary Material, Table 1) [25]. The Spanish versions of the UAS and UAS7 were both recently validated in the EVALUAS trial for use as diagnostic and follow-up tools for patients with CSU [26]. Note, however, that the UAS7 is not suitable for evaluating the activity of chronic inducible urticaria or angioedema. The Angioedema Activity Score is used to assess isolated or CSU-associated angioedema [27].

The consensus opinion of the present expert group is that the Urticaria Control Test (UCT) is the best currently available tool for quantification of disease control in all types of chronic urticaria (which includes both CSU and inducible forms of urticaria). The patient's current treatment should be considered when using these scales, otherwise the scores would not be comparable at different time points.

When evaluating the overall status of a patient with CSU, it is essential to assess the impact of the disease on QOL [2,10]. To date, the only questionnaire specifically developed to measure QOL in CSU patients is the Chronic Urticaria Quality of Life Questionnaire [28].

We recommend using the UAS7 to evaluate the activity of CSU, given that this instrument has proven its value in numerous clinical trials and studies; moreover, the members of this expert group have successfully used this tool for many years. The UAS7 questionnaire is a self-reported instrument that correlates well with the Dermatology Life Quality Index, which is commonly used to assess QOL in dermatology patients [29-31]. Ideally, the UAS7 should be administered weekly to monitor treatment response. It is advisable to use the UCT concomitantly with the UAS7 to ensure that patients have completed both of these instruments correctly during the consultation.

Definition of a Well-Controlled CSU Patient

To accurately determine disease control during follow-up, it is essential to first establish a clear definition of qualitative control to permit the specialist to evaluate response to treatment in daily clinical practice. Moreover, such a definition is important in order to facilitate reliable comparisons of clinical trials.

According to the EAACI/GA2LEN/EDF/WAO guidelines, the aim of treatment in CSU is to achieve complete control of signs and symptoms while ensuring patient safety and QOL [2]. Several scales are available to monitor the variations in different aspects of the disease (Table 1), and a "good" clinical course could be defined based on any of the following: UAS7 activity index <6; a decrease >90% on the UAS7: UCT score >12; or the clinical course based on the clinical criteria of the treating physician.

Given the lack of a specific recommendation regarding the optimal evaluation scale, we believe that a patient whose CSU activity is "well-controlled" should be defined as a stable UAS7 score ≤6 that is sustained over time. Importantly, a UAS7 score ≤6 is closely correlated with the QOL index [32,33].

No clinical trials have yet been performed to establish precisely how long the patient needs to maintain a UAS7 <6 to be considered in remission. Management is patient-specific, both in regard to the type and duration of treatment. Likewise, the best approach to treatment discontinuation (ie, sudden termination or gradual tapering) has not yet been determined.

Antihistamine-Refractory Patients

The activity of CSU may fluctuate between low- and high-activity periods, when the condition is considered severe. Even when the maximum accepted antihistamine dose is prescribed, this is insufficient to control the clinical manifestations of CSU in a substantial proportion of patients (63%) [11]. The UCREX trial [34] showed that more than 75% of CSU patients remain symptomatic even after 6 months of antihistamine treatment. Likewise, the REG-MAR trial [12], carried out in a cohort of 549 CSU patients, showed that 77.3% were refractory to H_1 antihistamines at the licensed dose. Importantly, antihistamine treatment can exacerbate urticaria, although this reaction is rare [35,36]. However, these data should be interpreted taking into account the fact that patients with CSU in these studies, who were seen mostly at tertiary centers, do not necessarily represent the general population of patients with the disease. Most CSU patients who respond properly to a second-generation antihistamine at a licensed dose prescribed by their family doctor probably do not attend specialized units in urticaria.

CSU has a major negative impact on QOL and health care costs [7,8]. The recent ASSURE-CSU trial [11] highlighted the financial burden and negative impact of CSU/chronic inducible urticaria on health-related QOL in refractory patients. The results of that study showed that not only did CSU interfere with QOL, but that it also had both direct (ie, health) costs and indirect (ie, social) costs.

The favorable safety profile of most second-generation antihistamines means that these drugs can be used as second-line therapy at doses higher than the licensed doses [2,37]. A recently published meta-analysis and systematic review [13] found that 63.3% of CSU patients who did not respond to the licensed dose of H_1 antihistamines responded well to higher doses. Furthermore, the increased dose significantly improved control of wheals and itching in the 49% of patients who required a dose increase.

Nevertheless, there is no effective method to predict whether an antihistamine will have a beneficial clinical effect or not. A recent study showed that measurement of the histamine-induced wheal can predict which patients will have a strong clinical response to antihistamines, although its utility for identifying nonresponders is limited [38].

The off-label indication for antihistamine dosing should be revised in light of the availability of new, highly effective treatments such as omalizumab and other emerging

Table 1. Activity, Control, and Quality of Life Scales for Urticaria and Angioedema Patients

Activity measure	UAS7 AAS	– Patients with wheals – Patients with wheals and angioedema – Patients with angioedema	– Exact clinical picture of the current frequency and severity of the CSU symptoms (daily evaluation, weekly score)	– Prospective PRO measure – Patient must complete daily (not always feasible) – Valid only for patients with CSU, not for patients with CIndU – Has been validated for use in adults only
Control measure	UCT	– Patients with wheals, angioedema, or both	– Retrospective PRO measure – Short and simple structure – Simple scoring system – Results available immediately after completion – Can be applied to all the forms of CU	– The information is not well explained
QOL measure	CU-Q2oL	– Patients with wheals or with wheals and angioedema	– Validated in many languages – Good validity and reliability level – Good sensitivity to change	– Slight variations among versions in different languages – Applicable to CSU but not to CindU – Comparatively complicated scoring system – Not perfectly adapted to CSU patients in whom angioedema predominates

Abbreviations: AAS, Angioedema Activity Score; CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; CU, chronic urticaria; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; PRO, patient-reported outcome; QOL, quality of life; UAS, Urticaria Activity Score; UAS7, Urticaria Activity Score 7; UCT, Urticaria Control Test.

biologics [39], although it is also important to consider their cost. In this context, data on the relative value of high-dose antihistamines compared with alternative treatments should be clear and rigorous. Given the proven efficacy and safety of omalizumab, it is our expert opinion that clinicians should consider using this medication to shorten and simplify the gradual treatment approach that is typically used in antihistamine-refractory CSU patients [13].

Omalizumab for Treatment of CSU

The efficacy and safety of omalizumab for the treatment of CSU has been demonstrated in several phase 3 pivotal trials, namely, ASTERIA I [14], ASTERIA II [3], and the GLACIAL trial [15,40] (Supplementary Material, Table 2). The improvements observed in all efficacy variables at week 12 were still present at week 24 in the ASTERIA I and GLACIAL trials [14,15]. Overall, the findings from these trials support the efficacy of omalizumab over 6 months.

Pivotal trials also confirm the favorable safety profile of omalizumab. The authors found that the incidence rate for adverse events, the severity of those events, and the incidence of serious adverse events were all similar in the treatment group (regardless of the omalizumab dose) and placebo group [3,14,15].

Importantly, in real-world observational studies, the efficacy and safety of omalizumab in CSU patients was similar or even better than in pivotal trials [20,21,41-43]. Of particular interest is the retrospective, descriptive analysis of 110 CSU patients treated with omalizumab at 9 Spanish hospitals [1]. The authors found that 81.8% of patients had a complete or significant response to treatment, with only 7.2% not responding to treatment. Moreover, 60% of the patients in that study remained asymptomatic while receiving omalizumab alone (that is, they were able to discontinue antihistamine therapy), and no serious adverse events were reported.

Predictors of Response to Omalizumab

It would clearly be beneficial, if possible, to identify the clinical predictors of response to omalizumab. Knowledge of these predictors would also enable physicians to provide patients with more accurate information about the expected course of the disease. The findings of the 3 aforementioned pivotal trials show that the response pattern is dose-dependent. Thus, the standard dose of 300 mg/4 wk results in a higher percentage of complete response (UAS=0) or good response (UAS≤6); moreover, higher doses resulted in faster response and more sustained disease control [44]. In the pooled analysis of the trials, disease control was good (UAS7 ≤6) or complete (UAS7=0) in 58% and 40% of patients, respectively, 12 weeks after administration of 3 × 300 mg doses of omalizumab [40]. However, disease control was not achieved in all patients over that period. An analysis of the 3 pivotal trials revealed that of the patients with uncontrolled urticaria (UAS7 ≤6) at week 12, 58% subsequently achieved disease control between weeks 13 and 24 [44]. The mean number of weeks necessary to obtain a score ≤6 or 0 on the UAS7 was, respectively, 6 weeks and 12-13 weeks. These data show that some patients respond quickly to omalizumab, whereas others respond more slowly. Patients who respond within 4-6 weeks could be classified as "fast responders" and those requiring 12-16 weeks of treatment could be considered "slow responders" [45] (Table 2).

Table 2. Patient Profile According to the Response to Omalizumab

Fast responder	Patient who responds in 4-6 weeks
Slow responder	Patient who responds in 12-16 weeks
Complete responder	– Sustained UAS7 score = 0 – Absence of symptoms – Absence of angioedema – Requires neither salvage medication nor H_1- antihistamines
Good responder	– Sustained UAS7 score = 1-6
Partial responder	– Partial improvement in baseline UAS7, with scores ranging from 7-15
Nonresponder	– No change in baseline UAS7 score and sustained scores >16

Abbreviations: UAS, Urticaria Activity Score; UAS7, Urticaria Activity Score 7.

According to a recent study [43], the predictors of a favorable response to omalizumab are as follows: (*1*) diagnosis of CSU with chronic inducible urticaria, (*2*) no prior treatment with immunosuppressive drugs, (*3*) older age, (*4*) shorter duration of symptoms, (*5*) absence of angioedema, and (*6*) negative histamine release test. Over 85% of patients who present these characteristics achieve a complete response to treatment. In addition, a negative histamine release test result and absence of angioedema both predict a good response to omalizumab and correlate with previous trial results showing that a positive autologous serum skin test (ASST) result is associated with a longer duration of and more severe CSU [46,47]. In addition, patients in whom angioedema is a significant component of urticaria tend to relapse faster after treatment is discontinued [10]. Neither the patient's gender nor their smoking habits have been shown to influence the efficacy of omalizumab [43]. A significant reduction in D-dimer values following treatment with omalizumab in patients with elevated baseline D-dimer levels has also been shown [48].

Deza et al [49] recently demonstrated the predictive value of baseline basophil expression of high-affinity IgE receptors (FcεRI) for response to omalizumab. The authors found that FcεRI expression levels in CSU patients are usually significantly higher than in healthy controls. Moreover, after the first treatment with omalizumab, FcεRI expression levels drop immediately, while UAS7 scores decrease and UCT scores rise. Deza et al observed that baseline FcεRI expression with a mean fluorescence intensity of less than 4743 in peripheral blood basophils is a significant predictor of nonresponse to omalizumab (100% sensitivity and 73.2% specificity). Another study showed that the baseline expression level of FcεRI was lower in slow responders than in fast responders [50]. Gericke et al [51] recently reported a slower response to omalizumab in patients with a positive result in the ASST or basophil histamine release assay, thus suggesting that patients presenting with anti-IgE or anti-FcεRI IgG respond more slowly than those presenting with IgE autoantibodies against autoantigens (eg, TPO, IL-24) [51].

Even though omalizumab generally provides an early benefit [3,14,15], some patients have a delayed response, often only after 12 weeks of treatment [14,44]. This finding suggests that if fewer than 3 treatments (300 mg/4 wk) are administered, the opportunity to achieve symptom control in a nonresponder (UAS7 ≤6) could be lost [44].

Prediction of symptom return after stopping omalizumab was recently addressed in a study that analyzed data from 2 clinical trials, including 642 patients [52]. The authors studied the predictive potential of 746 variables, which included baseline patient characteristics and disease measures (ie, start of treatment), such as IgE levels, weekly urticaria activity score (UAS7), and pre- and postbaseline medications.

Only 2, variables, UAS7 and the speed of response to treatment, predicted speed of symptom return. The results suggest that patients with worse symptoms before treatment (ie, higher UAS7 score) and a slow response to omalizumab have a higher probability of rapid symptom return after discontinuation of treatment. In contrast, those with a lower UAS7 score at baseline and fast response to omalizumab have a lower probability of rapid symptom return.

Therapeutic Strategy According to the Patient's Response Profile

Defining patient profiles according to the response to omalizumab would have 2 main benefits: first, it would facilitate medical management of the patient, and second, it would improve treatment selection, thus enabling the clinician to select the most appropriate therapeutic plan based on the individual's response profile. Unfortunately, to date, no such categorization has been reported in the published literature.

CSU patients can be either fast or slow responders to omalizumab [44,51]. Available evidence for slow responders indicates that omalizumab should be continued for 24 weeks to obtain a sustained favorable response (UAS7≤6) over time [44]. In patients with severe disease (ie, UAS7>28 with unbearable symptoms), the therapeutic schedule could be modified prior to administration of the sixth dose.

Based on our clinical experience and the literature review we conducted for this study, we recommend classifying patients into 1 of 4 different response profiles—nonresponders, partial responders, good responders, and complete responders—depending on their response to omalizumab (300 mg/4 wk) after the first 3 and 6 months of treatment [33]. Based on this classification system, we also propose a specific therapeutic approach for each response profile.

The 4 different approaches mainly involve modification of the omalizumab dose or a change in the treatment interval [33,45]. Dose increases or reductions should be stepwise. Thus, a standard dose of 300 mg/4 wk should be increased to 450 mg/4 wk [33,53-55] and then, if necessary, up to 600 mg/4 wk [33,56]. In cases requiring dose reduction, the dose would be reduced from 300 mg/4 wk to 150 mg/4 wk.

According to a study by Curto et al [12] involving 286 patients treated at 15 hospitals under conditions of routine clinical practice, 16% of patients required their dose to be increased to 450 mg/4 wk, while 4% required an increase to 600 mg/4 wk to achieve complete disease control. The authors found that 21% of patients required updosing; in addition, several factors—body mass index ≥30, age >57 years, and previous cyclosporine use—were strongly correlated with the need for updosing to ensure good disease control [12].

The standard dose of omalizumab is 300 mg administered every 4 weeks; this frequency could be increased to every 2 weeks at the same dose (300 mg) [3], according to the criteria of the attending physician. However, the dose interval should never be longer than 8 weeks, except in cases in which the medication is being discontinued [57].

If the aim of the therapeutic strategy is to increase the dose or to shorten the administration interval, the change must first be tailored to the patient. However, it should be noted that in most cases—such as in patients in whom the UAS7 score remains stable over the 4-week period—the recommended strategy is to increase the dose while maintaining the administration interval, given that this strategy is supported by the strongest scientific evidence [56,58]. By contrast, evidence to support an increase in the administration interval at the same dose is scant, and the samples in the few available studies are small [56]. Nonetheless, this strategy may be considered in certain cases: (*1*) when the usual strategy (ie, updosing) fails to produce an improvement; (*2*) when the symptoms recurrently worsen and the UAS7 score increases during the 2 weeks prior to receiving the following omalizumab dose; (*3*) when the pattern of response is better during the first 2 weeks after administration; and (*4*) when the patient expresses a clear preference for this strategy.

Although administration of omalizumab at >600 mg has proven to be safe and effective in asthmatic patients [59], we suggest that clinicians should not exceed the 600 mg/4 wk dose owing to the lack of clinical evidence to support this dose in CSU patients [56].

Likewise, therapeutic strategies based on dose reduction or shortening of the treatment interval may be combined successively (never simultaneously), as it is important that treatment be withdrawn or reduced gradually. Thus, for example, the dose can first be reduced by 1 step, and then—provided that the patient's condition remains stable—the same dose could be administered over longer intervals until the decision is made to discontinue treatment [3,60].

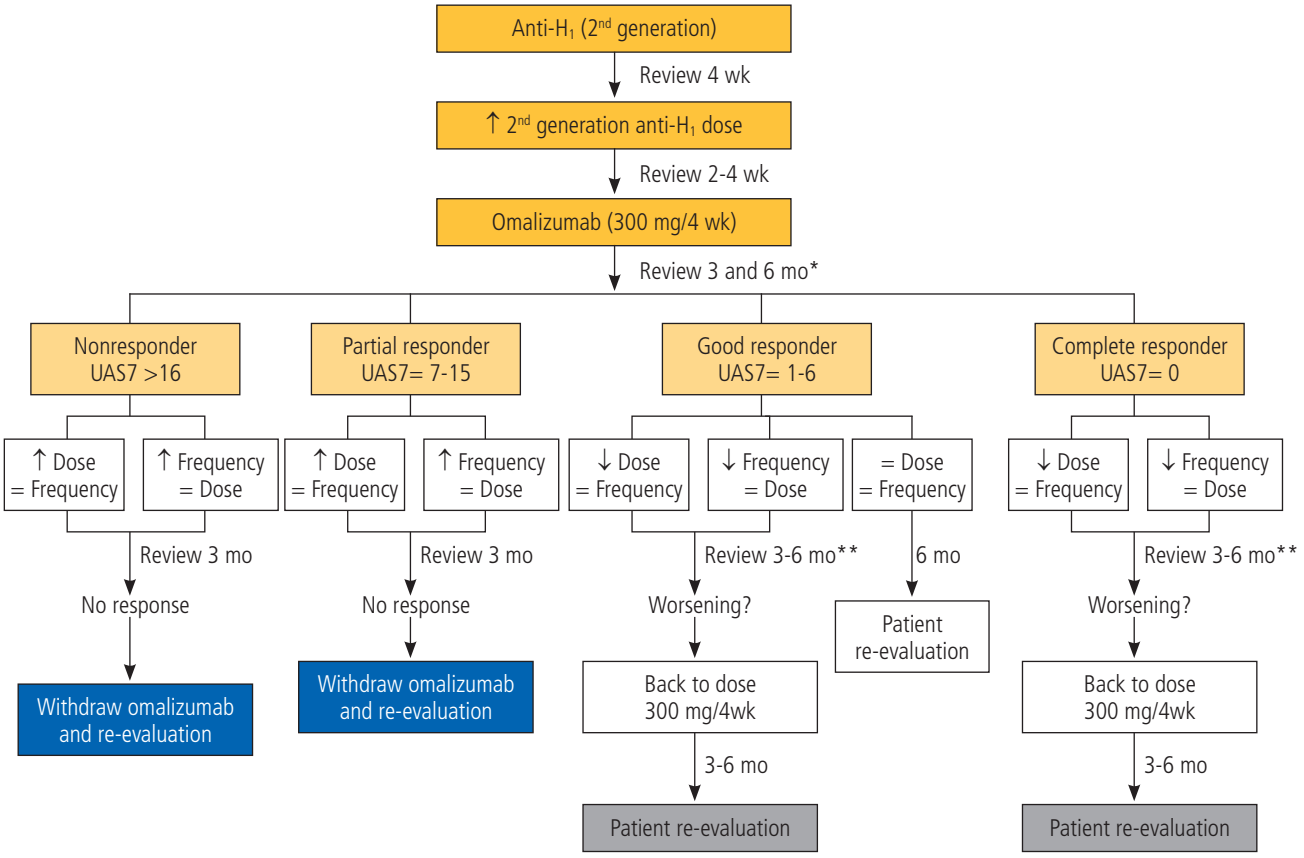
The 4 different patient profiles defined in this study, which are based on the individual response to omalizumab at the standard dose (300 mg/4 wk) after 6 months of treatment, are described in detail below. Figure 3 shows the recommended therapeutic approach according to the specific patient profile.

After careful consideration and much discussion about the advantages of using either the UCT and UAS7 scales or using the percentage decrease from baseline in the UAS7, we believe that the UAS7 should be used as the main, but not the only, indicator of response to omalizumab (Table 2).

4.1. Nonresponders

Patients classified as nonresponders to omalizumab are those whose baseline UAS7 score remains unchanged after treatment and who continue to present a UAS7 score >16 after 6 doses of omalizumab at 300 mg/4 wk (Table 2).

Given that some patients are late responders—that is, only achieving disease control between 13 and 24 weeks after



Short corticosteroid cycles are permitted in exacerbations
*Continue omalizumab up to 6 months, except in nonresponders with intolerable signs and symptoms, and in complete responders, in whom the therapeutic strategy could be adapted 3 months after initiation of omalizumab.
**In those cases in which a sustained response is achieved for ≥8 weeks, omalizumab can be discontinued to evaluate whether the patient continues in remission.

Figure 3. Therapeutic algorithm for the 4 different omalizumab response profiles.

initiation of treatment—our recommendation is to re-evaluate the patient after 6 months on omalizumab [45]. However, if the nonresponder shows symptoms of intolerance, therapy may be changed after 3 months of omalizumab instead of 6 months.

In nonresponders, there are 2 possible therapeutic strategies: increasing the omalizumab dose while maintaining the same treatment interval; and reducing the treatment interval while maintaining the original dose. The strategy selected will depend on the patient's weekly UAS7 scores over the 4-week period. Thus, if the UAS7 score remains >16 at all weekly assessments, then the dose should be increased. However, if the score is >16 only during 2 weeks after administration, then the treatment interval should be reduced.

In cases in which the therapeutic strategy is modified, it is advisable to re-evaluate the patient 3 months after changing the strategy; if the response does not improve, then we recommend withdrawing omalizumab and performing another medical evaluation to reassess the treatment approach.

4.2. Partial Responders

A partial responder to omalizumab is defined a patient whose UAS7 score partially improves over baseline but who maintains a UAS7 score of 7-15 (Table 2). In patients who demonstrate a partial response to the standard omalizumab dose, we recommend waiting 6 months before altering the treatment plan, although this will depend on the patient's symptoms or level of discomfort. If the UAS7 scores remain in the 7-15–point range after 6 months of standard treatment, we recommend modifying the regimen. As with nonresponders, the recommended modification is to either increase the dose while maintaining the same treatment interval or, conversely, to shorten the interval from 4 to 2 weeks while maintaining the original dose. The patient should be re-evaluated after 3 months, and if disease control remains poor, we suggest withdrawing omalizumab and reassessing the patient. However, it is important to consider the patient's opinion with regard to the efficacy of the drug before deciding to discontinue treatment.

4.3. Good Responders

Patients with a sustained UAS7 score ranging from 1 to 6 points are considered good responders (Table 2). In these patients, the standard dose and treatment frequency should continue until the 6-month follow-up assessment. If the disease remains controlled, then the strategy could be modified in an attempt to identify the minimum effective dose for good disease control. In these cases, the 3 possible strategies are as follows: (*1*) dose reduction at the same treatment interval, (*2*) increased treatment interval with the same dose, and (*3*) no change in dose or treatment interval.

If either the dose or the treatment interval is modified, then the patient should be re-evaluated after 3 and 6 months. If this assessment shows a deterioration in the patient's health, then the patient should be returned to the previous standard dose and frequency and re-evaluated after a further 3 and 6 months.

Similarly, when no change is made to standard therapy, the patient should be re-evaluated at a maximum of 6 months.

4.4. Complete Responders

Patients considered complete responders are those with sustained UAS7 scores of 0 and no signs or symptoms of urticaria while on the standard omalizumab dose.

Considering add-on treatment, the complete responder profile also includes patients who require neither H_1 antihistamines nor salvage medications (Table 2). In fact, we recommend reducing the dose or even complete withdrawal of H_1 antihistamines in these patients.

Prolongation of the standard prescription of omalizumab beyond 6 months is not recommended in complete responders. However, a change in the therapeutic approach may be considered 3 months after initiation of omalizumab in complete responders. In these cases, the change in strategy would involve a dose reduction while maintaining the treatment interval; alternatively, the treatment interval could be increased while maintaining the dose in order to find the minimum effective dose. If possible, treatment should be withdrawn.

If the patient's condition has worsened at the 3- or 6-month re-evaluation following the modification in strategy, a return to the standard dose and frequency (300 mg/4 wk) is recommended, followed by re-evaluation 3 to 6 months later. Discontinuation of omalizumab should be considered in patients who maintain a sustained response lasting ≥8 weeks to determine whether the patient has achieved disease remission.

Although implementation of the therapeutic strategies for omalizumab suggested may involve an increase in costs, these may be compensated by a decrease in concomitant medication use, improvement in patients' quality of life, and reduced disease-related health care costs [42].

5. Conclusion

European guidelines support the use of omalizumab as a third-line treatment for patients with CSU. Patients typically respond to omalizumab within the first 4-8 weeks of treatment, and the response is often evident within the first week. Importantly, even patients who do not initially respond to treatment (nonresponders) can obtain a significant reduction in disease activity and achieve "good control" (UAS7≤6) or "complete control" (UAS7=0) if treatment is continued for up to 24 weeks.

The therapeutic algorithm presented here is intended to facilitate the clinical management of omalizumab and to help clinicians determine the most appropriate therapeutic strategy based on the 4 different patient response profiles described in this study.

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Conflicts of Interest

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Antonio Valero belongs to the Spanish advisory group in chronic urticaria sponsored by Novartis. He has participated in several observational studies sponsored by Novartis involving chronic urticaria patients. He has also accepted invitations to international meetings and travel grants from Novartis and other companies.

Joan Bartra reports having served as a consultant to Novartis, FAES FARMA, Hal Allergy, and UCB and having been paid lecture fees by Novartis, Stallergenes, Hal Allergy, FAES FARMA, and Thermo Fisher.

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Ana María Giménez Arnau

Dermatology Department
Hospital del Mar
Passeig Maritim 25-26b
08003 Barcelona, Spain
E-mail: anamariagimenezarnau@gmail.com

Neuropathic Pain and Itch Mechanisms Underlying Allergic Conjunctivitis

Kuruvilla M, Kalangara J, Eun-Hyung Lee F

Emory University, Atlanta, USA

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Abstract

Objective: Among the constellation of symptoms that characterizes allergic conjunctivitis, many (eg, burning and stinging) can be attributed to chronic neuropathic pain. Cumulative data support that these hallmark symptoms might be linked to the effects of allergen-induced neuromodulation. This review investigates the key characteristics of neuropathic itch and pain in allergic conjunctivitis and their underlying pathogenic mechanisms.
Methods: A literature review was conducted using a PubMed search focusing on allergic conjunctivitis, neurogenic inflammation, neuropathic itch, and neuropathic pain. Articles were reviewed, and those discussing clinical course, pathophysiology, and neuronal regulation of chronic neuropathic symptoms as related to allergic disease were summarized.
Results: Recent evidence suggests that some symptoms of allergic conjunctivitis may be better represented as a chronic neuropathic disorder. We found that neurogenic mechanisms may have a significant role in chronic ocular surface inflammation from allergic inflammation. Manifestations may be associated with repeated ocular sensory nerve injury leading to an acute-to-chronic transition, which is in turn associated with neuropathologic changes (peripheral and central sensitization), neuronal dysfunction, and spontaneous ocular pain.
Conclusion: Current goals in the management of allergic conjunctivitis aim to minimize the inflammatory cascade associated with the allergic response in the initial stages of the pathogenic mechanism. Based on the mechanistic data reviewed herein, the recognition that neuronal inflammation explains many of the symptoms in allergic conjunctivitis opens new frontiers for drug discovery.

Key words: Allergic conjunctivitis. Neuropathic pain. Neuronal dysfunction. Dry eye. Sensitization. Transient receptor potential vanilloid 1 (TRPV1). Transient receptor potential ankyrin 1 (TRPA1). Substance P (SP). Nerve growth factor (NGF).

Resumen

Objetivo: Entre la constelación de síntomas que caracteriza la conjuntivitis alérgica, muchos, como la sensación de ardor y escozor, pueden ser fundamentados en el dolor neuropático crónico. Cada vez disponemos de más datos para respaldar que estos síntomas característicos podrían estar relacionados con los efectos de la neuromodulación inducida por alérgenos. En esta revisión se enfatizarán las características clave del dolor y el prurito neuropático en la conjuntivitis alérgica y sus mecanismos patológicos.
Métodos: Se realizó una revisión de la literatura realizando una búsqueda bibliográfica en la base PubMed utilizando, como palabras clave, conjuntivitis alérgica, inflamación neurogénica, prurito neuropático, dolor neuropático. Se revisaron los artículos y se resumieron aquellos que se centraban en el curso clínico, la fisiopatología y la regulación neuronal de los síntomas neuropáticos crónicos en relación con la enfermedad alérgica.
Resultados: La literatura científica reciente sugiere que algunos síntomas de la conjuntivitis alérgica se representan mejor como un trastorno neuropático crónico. Los mecanismos neurogénicos parecen tener un papel significativo en la inflamación crónica de la superficie ocular inducida por las reacciones alérgicas. Las manifestaciones pueden estar asociadas con la lesión del nervio sensorial ocular repetida que conlleva una transición de aguda a crónica y se asocia con cambios neuropatológicos (sensibilización periférica y central), disfunción neuronal y dolor ocular espontáneo.
Conclusión: Los objetivos actuales de manejo de la conjuntivitis alérgica se centran en minimizar la cascada inflamatoria asociada con la respuesta alérgica en los estadíos iniciales fisiopatológicos. Sin embargo, y en relación con los datos mecanísticos revisados en este documento, el reconocimiento de que la inflamación neuronal explica muchos de los síntomas en la conjuntivitis alérgica abre nuevas fronteras para el descubrimiento de nuevas opciones terapéuticas.

Palabras clave: Conjuntivitis alérgica. Dolor neuropático. Disfunción neuronal. Ojo seco. Sensibilización. Receptor de potencial transitorio vaniloide 1 (TRPV1). Receptor de potencial transitorio anquirina 1 (TRPA1). Sustancia P (SP). Factor de crecimiento neuronal (NGF).

Background

A recent hypothesis has implicated neuronal inflammation as a novel mechanism in the pathogenesis of allergy. Several allergy symptoms, including rhinorrhea, nasal congestion, and cough, are a direct consequence of nervous system alterations [1]. Allergic inflammation can trigger complex neurogenic signaling mechanisms to manifest as neuropathic itch. Neuropathic itch is a chronic condition caused by neuronal dysregulation that typically presents with pruritus but can also present with characteristic neuropathic pain symptoms such as burning and stinging. This differentiates it from classic itch in inflammatory skin diseases, as neuropathic itch is often described as burning in quality. Although pain is not typically considered a significant symptom in allergic conditions, it is a common feature of allergic conjunctivitis (AC). Sensations of irritation and pain of varying intensity frequently accompany AC, including burning, dryness, and grittiness. Neuronal mechanisms underlying these sensations of irritation, discomfort, and itch have yet to be investigated. Delineation of the molecular pathways underlying neuronal inflammation in AC may play a key role in identifying potential therapeutic targets.

Methods

A comprehensive literature review was performed using a PubMed search with the following terms (in order of relevance): *allergic conjunctivitis, neurogenic inflammation, neuropathic itch, neuropathic pain, substance P (SP), calcitonin-gene related peptide (CGRP), nerve growth factor (NGF), transient receptor potential vanilloid 1 (TRPV1), allergic rhinitis, asthma, chronic cough,* and *gabapentinoids*. All searches were conducted in English back to 2000. Articles were reviewed, and those discussing clinical course, pathophysiology, and neuronal regulation of ocular symptoms as related to chronic allergic conjunctivitis were summarized.

Epidemiologic, Pathophysiologic, and Clinical Aspects of AC

Prevalence and Impact

Epidemiological data on AC are scarce, likely due to underdiagnosis and the fact that this disease is often linked with allergic rhinitis (AR). It is estimated that 20% of the US population reports ocular symptoms consistent with AC [2], and approximately 70%-80% of seasonal AR patients have severe ocular symptoms [3]. Ocular symptoms were as severe or more severe than nasal symptoms in approximately 70% of over 500 hay fever patients in one study [4]. In another recent survey, over 50% of nasal allergy patients stated that AC symptoms were moderately to extremely bothersome, and for 15% of these patients, the ocular component of their reactions was the most troublesome [5]. The underlying mechanisms of AC warrant further investigation.

Seasonal AC and perennial AC, which are the most common forms and the benign end of the spectrum of ocular allergy, are increasing in prevalence [6]. Vernal keratoconjunctivitis and atopic keratoconjunctivitis represent only 2% of ocular allergy cases, yet are even more severe and have a greater impact on quality of life.

Pathophysiology

Since the discovery of 2 functionally distinct $CD4^+$ T-cell subpopulations (T_H1 and T_H2) about 30 years ago, it quickly became evident that T_H2 cells play a crucial role in the development of allergic airway inflammation. It has been commonly assumed that a T_H2 immune response and type I hypersensitivity form the basis of AC. The allergic response is elicited by ocular exposure to an allergen, such as pollen, that cross-links membrane-bound IgE and triggers mast cell degranulation. This releases a cascade of mediators including histamine, leukotrienes, proteases, prostaglandins, and cytokines. The main contributors to the severity of AC are thought to be the allergen load on the ocular surface and locally produced specific IgE. Furthermore, there is a highly significant correlation between the presence of allergen-specific IgE in tears and ocular allergy symptoms [7]. This continued histamine release, along with increasing allergen load, leads to an expanding population of resident mast cells in conjunctival tissue, thus perpetuating the allergic response [8].

With seasonal AC, the immediate response is predominantly mast cell–mediated. However, little is known about the pathogenesis of the late phase allergic reaction corresponding to the persistent clinical inflammation that typifies ocular signs and symptoms in chronic allergic diseases. Vernal keratoconjunctivitis and atopic keratoconjunctivitis in particular are characterized by a severe late-phase reaction comprising mucosal infiltration by eosinophils, neutrophils, basophils, and T lymphocytes. Mediators released by conjunctival mast cells during the early-phase reactions also contribute to the development of late-phase inflammation during IgE-mediated AC in vivo. There is a general correlation between the degree of cellular infiltration and the severity of disease. Moreover, products from infiltrating cells are known to promote conjunctival irritation. In addition, conjunctival and corneal epithelial cells and fibroblasts mount the allergic response by producing cytokines and other factors that maintain local inflammation and lead to tissue remodeling.

Clinical Manifestations

Ocular symptoms of AC are frequently underreported. The pathognomonic symptoms of ocular allergy include itching, tearing, and conjunctival and eyelid swelling and redness. These are reflected in the Total Ocular Symptom Score questionnaire, which is used to measure symptoms of AC. However, AC patients have multiple distinguishing symptoms beyond itch including grittiness, burning and stinging (65%), and soreness (75%) [9]. They may also complain of a foreign body sensation, blurring, and photophobia if there is corneal involvement. Conjunctival hyperemia and papillae on the tarsal conjunctiva may be observed on examination. Local symptoms are often

accompanied by irritability and fatigue [3] and patients with AC have a poor quality of life, irrespective of the severity of associated nasal symptoms [10].

Neuronal dysregulation is likely to be responsible for at least some of these symptoms. Exaggerated hyperreactivity to nonspecific stimuli such as temperature changes, strong odors, and irritants is known to be a manifestation of neuronal inflammation in nonallergic and mixed rhinitis [11]. This is akin to hyperreactivity to heat, sunlight, and wind during the active phase of vernal keratoconjunctivitis, which may be reflective of neural involvement [12], as is the nonspecific increase in reactivity in the conjunctival response to histamine in AC patients [13]. In addition, exposure to nonspecific environmental stimuli, pollutants, and cigarette smoke were reported to be triggers in a substantial proportion of AC patients [14] and may be similarly attributable to neural hypersensitivity. The term vasomotor conjunctivitis has been used to describe this phenomenon [15].

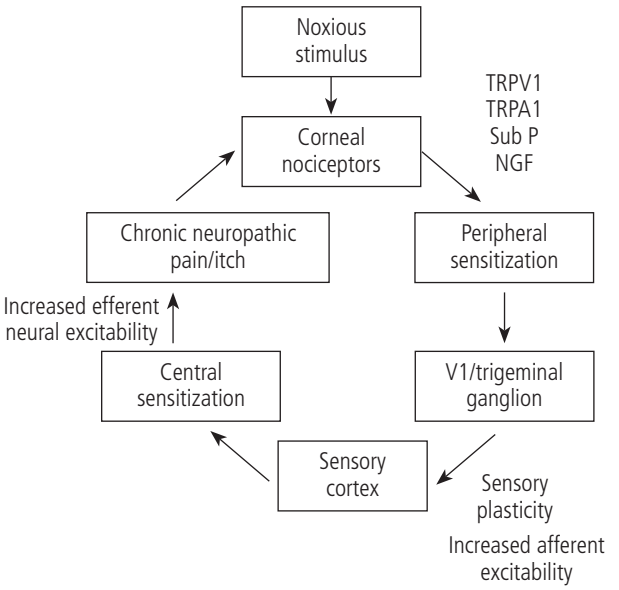

Figure 1. Schematic representation of neuropathic pain and itch in ocular surface disease.

Mechanisms of AC-Induced Neuropathic Pain

Sensory Nociceptive Innervation of the Ocular Surface

Peripheral origin: The ocular surface is innervated by primary sensory neurons located in the trigeminal ganglion, most of which (70%) are polymodal nociceptors [16]. The afferent C fibers express transient receptor potential (TRP) channels that play a role in many diseases. Pain and itch also employ largely overlapping transduction machinery. Transient receptor potential vanilloid 1 (TRPV1) and transient receptor potential ankyrin 1 (TRPA1) are 2 such TRP channels that appear to be important in allergic responses. TRPV1 is known as a capsaicin responder, but also reacts to a host of other proinflammatory exogenous and endogenous agents. In addition, it is stimulated by several mediators that are relevant to the allergic reaction, such as histamine and bradykinin. As with TRPV1, TRPA1 is activated by inflammatory mediators including those involved in allergic disease.

TRPV1/TRPA1 receptor activation in the eye induces the release of neuropeptides such as neurokinins, calcitonin gene-related peptide (CGRP), and substance P (SP). Furthermore, activated sensory neurons can themselves directly release proinflammatory peptides into surrounding tissue (antidromic release). Other molecules known as neurotrophins (eg, nerve growth factor [NGF]), act directly on peptidergic C fiber nociceptors to potentiate TRPV1 receptors and increase the expression of substance P and TRPV1. This ultimately translates into nociception and pain [16].

Central representation: The cell bodies of sensory neurons innervating the ocular surface are located in the trigeminal ganglion and terminate in the trigeminal brainstem complex. There, they establish contact with second-order ocular neurons that project to the somatosensory cortex, where the original noxious signal is perceived as pain.

A schematic representation of the pathogenesis of ocular pain and itch is outlined in Figure 1.

Allergen-Induced Neuromodulation of Sensory Nerves

Under pathological and chronic conditions, dysfunction of the nervous system itself can generate chronic neuropathic pain and itch. This is secondary to neural plastic changes in primary sensory neurons of the peripheral nervous system (peripheral sensitization) and spinal cord, brainstem, and cortical neurons in the central nervous system (central sensitization). A significant body of physiological data suggests that allergy symptoms may be significantly modulated by the nervous system. This neural plasticity may be responsible for symptoms of neuropathic pain and itch in AC. Reflex neural activity is upregulated in the presence of allergic inflammation and further amplifies the histamine-mediated immunopathological response in the conjunctiva.

Peripheral sensitization in allergic inflammation: During chronic inflammation, including allergic inflammation, long-lasting changes develop in the expression and function of stimulus-transducing ion channels such as TRPV1 and TRPA1. This results in abnormal hyperexcitability of neurons and may evoke chronic neuropathic pain.

TRPV1 is believed to be a major cause of neuropathic pain [17]. It also has a proven role in itch and, in particular, histamine-induced itch. Chronic allergic inflammation is known to mediate plasticity of TRPV1 in airway diseases. Inhalation of allergen by rats or guinea pigs leads to the expression of TRPV1 in Aδ cough nerves [18]. TRPV1 expression and substance P levels were found to be significantly higher in patients with nonallergic rhinitis [19] and asthma, especially refractory cases [20]. Furthermore, histamine sensitizes the nociceptor TRPV1 and has been shown to contribute to visceral hypersensitivity in animals [21]. In addition, other endogenous inflammatory allergy mediators such as prostaglandin E2 and bradykinin can markedly enhance the sensitivity of TRPV1 and lower its threshold for activation of sensory nerves [22].

Inhalation of allergen also upregulates the expression of genes involved in the production of substance P and CGRP, both of which act as itch sensation–enhancing neuropeptides [23,24]. Allergen exposure also enhances the release of substance P and CGRP from sensory nerve endings (antidromic pathway). Substance P and CGRP cause antidromic stimulation of nociceptive fibers, which results in C-fiber activation and synergistically augments the allergic inflammatory reaction [24,25]. In 2017, Azimi et al [26] described the role of substance P–mediated activation of MC receptors in inducing itching in a mouse model.

Allergic reactions can also lead directly to the release of neurotrophic factors, especially NGF, from mast cells and other cells, such as the airway epithelium [27]. NGF is a complex regulator of neural plasticity that further sensitizes afferent nerves. It has been found in eosinophils and peripheral nerves [25,28] and is upregulated by nasal allergen provocation. Endogenous NGF levels are elevated not only in certain chronic pain conditions, but NGF serum levels have also been found to be increased in allergic diseases and asthma [29], as well as in bronchioalveolar lavage and nasal lavage fluids from these patients.

All of these factors further stimulate the vascular endothelial cells or mast cells to release even more chemical mediators such as histamine, thus producing a vicious circle of disease exacerbation.

This concept of peripheral sensitization was supported by a guinea pig model of AC, which demonstrated a reduced threshold for activation of polymodal nociceptors, as well as an augmented response to noxious chemical stimuli. The authors suggested the operation of a comparable pathway in humans. The overall changes in firing of corneal sensory fibers correlate with the foreign body and itching sensations reported by AC patients [30], thus suggesting a possible TRPV1-dependent pathway in the sensitization stage. However, further studies must be performed to confirm this finding.

The sensitization of sensory nerves results in augmented pain sensations and may be responsible for the burning quality of AC symptoms. Chronic inflammation may also damage sensory nerve fibers of the ocular surface leading to formation of neuromas that spontaneously discharge and cause unpleasant sensations, such as pain, dryness, and grittiness [16].

Central sensitization in allergic inflammation: Neuropathic pain may also result from abnormal function of higher brain structures, from where ocular trigeminal ganglion neurons project. Amplification of responses occur in the central nervous system through sensitization of central pathways, failure of inhibitory control mechanisms, or both. Central sensitization can cause secondary hyperalgesia and allodynia, thus contributing to enhanced inflammatory pain.

Central neural mechanisms are also thought to be involved in allergic inflammation. Extended exposure to allergen in a primate model of allergic asthma causes phenotypic changes in the intrinsic membrane properties of central nervous system neurons, resulting in their increased excitability [31]. This is analogous to the increased excitability of spinal neurons during prolonged neuropathic or inflammatory pain.

Other consequences of central sensitization include changes in autonomic nerve activity. Allergic inflammation may enhance autonomic tone, which has been directly observed in an allergen-sensitized guinea pig model [32].

Loss of inhibitory synaptic transmission (disinhibition) in the spinal cord has also been attributed to both chronic pain and chronic itch. This disinhibition of the central nervous system and, therefore, hyperactivity of trigeminal nociceptive pathways can produce a much more intense response to irritants.

Taken together, the evidence supports a model in which allergic inflammation leads to the release of proinflammatory mediators that sensitize trigeminal sensory neurons (and their processes), resulting in a decreased pain/itch threshold. This may manifest as neuropathic pain and itch. Therefore, there is a putative positive feedback loop between allergic cells and neuronal inflammation in the development and maintenance of the pathophysiology of AC. These, in turn, modulate ocular responses to allergic and nonallergic stimuli, thus translating the degree of inflammation into severity of neural hyperreactivity.

Figure 2 outlines neural involvement in allergic conjunctivitis.

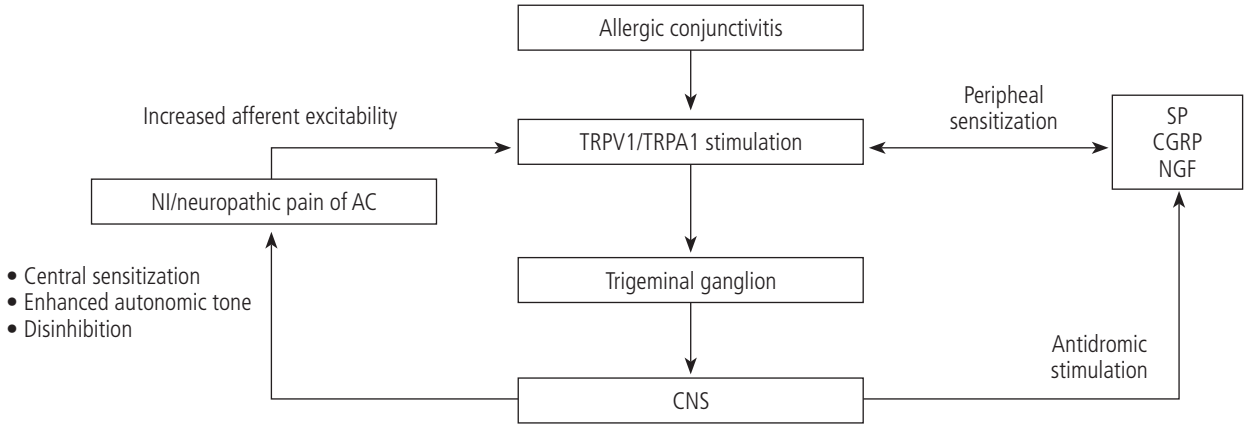

Figure 2. Schematic representation of neural sensitization in allergic conjunctivitis. AC indicates allergic conjunctivitis; TRPV, transient receptor potential vanilloid; TRPA, transient receptor potential ankyrin; SP, substance P; CGRP, calcitonin gene-related peptide; NGF, nerve growth factor.

Ocular Symptoms Deriving From Neurogenic Inflammation

The importance of neurogenic inflammation is suggested by the large trigeminal sensory innervation of the ocular surface. Mast cell activation in AC results in overt stimulation of polymodal nociceptors, which are responsible for burning and stinging eye pain. Nasal provocation studies in AR patients showed that TRPV1 and TRPA1 activators induced immediate and more prolonged pain; during the pollen season, provocations with TRPV1 activators induced itch as well as pain [33]. In fact, in a recent series, 80% of patients with symptomatic AC had no evidence of conjunctival inflammation, while over half had nasal inflammation only. It was postulated that neurogenic mediators could explain this disconnect between ocular symptoms (especially itching) and detectable inflammatory conjunctival infiltration [34].

Emerging evidence suggests that the underlying allergic and neural inflammatory pathways can interact. Histamine-induced itching via H1 receptors on conjunctival sensory nerve fibers requires activation of TRPV1. Histamine-independent pruritic pathways, as in IL-31–induced itch, also directly activate TRPV1/TRPA1 sensory nerves in mouse models of dermatitis [35]. Furthermore, leukotriene B4 (LTB4) can activate TRPV1 and induce itching via interaction with LTB4 receptors on sensory nerves [36].

The activation of TRPV1 causes the release of proinflammatory and pruritic mediators. It has been reported that substance P levels are increased in tears of patients with AC compared with healthy individuals, suggesting that substance P may contribute to the pathogenesis and severity of AC [37]. The concentration of substance P in tears has also been found to be elevated at baseline in patients with seasonal AC and vernal keratoconjunctivitis [38], with further increases in substance P and CGRP documented after conjunctival allergen challenge [39]. On the ocular surface, NGF has been hypothesized to influence the immune response in AC [40].

A strong relationship has long been recognized between AC and dry eye, with a large symptomatic crossover that may reflect interrelated mechanistic characteristics [41]. Tear film instability, a characteristic of dry eye, was also noted to be more pronounced in children with AC [42]. Increased inflammatory allergic cytokines are also associated with goblet cell loss and tear volume insufficiency. Recent evidence has further expanded the phenotypic spectrum of patients with dry eye syndrome and implicated neuropathic pain in dry eye pathogenesis. A significant body of physiological data suggests that dry eye symptoms may be significantly modulated by the nervous system [43]. However, our understanding of neuropathic pain in dry eye remains incomplete, largely because of limited access to tests that assess the function of the ocular sensory-nociceptive apparatus.

Neurogenic Mechanisms of AC: Implications for Management Approaches

The current mainstay of AC therapy includes topical mast cell stabilizers and antihistamines, with variable and limited clinical success possibly because factors other than mast cells and histamine play important roles in AC. Therefore, research into more effective treatments is necessary. The simultaneous targeting of multiple inflammatory signaling mediators might represent a more promising treatment modality.

Addressing the neurogenic component of allergic inflammation has been an active area of study. The hyperreactivity phenotype of allergic sensitization can be physiologically dissociated from the immune component, and neural sensitization has been targeted in animal models as well as in humans.

Murine models of allergic sensitization have provided evidence of the anti-inflammatory actions induced by the depletion of neuropeptides [25]. Mice that had undergone surgical denervation of cutaneous sensory nerves demonstrated dampened inflammatory responses after induction of anaphylaxis and mast cell activation. Similar responses were obtained following pretreatment with selective substance P and CGRP antagonists [44]. Recently, treatment with olopatadine and naphazoline hydrochloride was shown to reduce conjunctivitis in mice via effects on NGF [45].

A prominent candidate pathway is TRPV1, which has been described in several forms of allergic disease. Vagal sensory neurons in TRPV1 can dramatically affect airway hyperreactivity. Several trials have explored therapies that target TRPV1-expressing neurons as a strategy for the management of allergic diseases. This has been supported by murine models, where ablation of TRPV1 expressing vagal neurons abolishes airway hyperreactivity, even in the presence of a full lung inflammatory response [46]. In yet another mouse model, the use of a TRPV1 antagonist alleviated atopic dermatitis–like symptoms as evidenced by suppression of itch behavior and acceleration of skin barrier recovery [47]. In another murine model of AC, ocular itch was significantly attenuated in TRPA1 and TRPV1 knockout mice, implicating both TRPA1 and TRPV1 in the genesis of allergic ocular itch [48].

Clinical trials exploring the potential for neuronal-targeted therapies in patients with allergic inflammation are in their early stages. However, in subjects with allergic rhinitis, an intranasal TRPV1 antagonist alone or combined with fluticasone propionate did not improve allergen-induced symptoms [49]. Similarly, symptoms appearing after exposure to cold dry air in patients with nonallergic rhinitis did not Improve with this therapy [50].

These findings may indicate that TRPV1 may be a facilitating ion channel—but not a key mediator—for itch and other allergic symptoms, suggesting that other receptors expressed in C fibers, such as TRPA1, might be involved in their development.

On the other hand, a recent study of patients with nonallergic rhinitis revealed overexpression of TRPV1 in the nasal mucosa and increased substance P levels in nasal secretions at baseline, with reduced symptoms and reduced levels of nasal hyperreactivity following topical capsaicin treatment [19]. The authors suggest that the ablation of the TRPV1–substance P nociceptive signaling pathway

Table. Randomized Controlled Trials of Neuropathic Therapies for Allergic/Nonallergic Airway Inflammation

Drug	Mechanism	Disease Evaluated	Outcome Assessed	Efficacy
SB-705498	Intranasal TRPV1 antagonist	Allergic rhinitis	Total nasal symptom score (TNSS) - SB-705498 versus placebo, fluticasone propionate (FP), and SB-705498 + FP	No differences in allergen-induced mean TNSS between SB-705498 alone and placebo or between SB-705498 plus FP and FP alone [49]
SB-705498	Intranasal TRPV1 antagonist	Nonallergic rhinitis	Total symptom score (TSS), expressed as weighted mean over 60 minutes (WM0-60) or maximum TSS at 1 hour and 24 hours postdosing	No differences in or maximum TSS at 1 hour and 24 hours postdosing on days 1 or 14, relative to placebo [50]
Capsaicin	Intranasal TRPV1 agonist that ablates the TRPV1-SP signaling pathway	Idiopathic rhinitis	Visual analog scale (VAS) and therapeutic response evaluation (TRE) scores, and nasal hyperreactivity by means of cold dry air (CDA) provocation	Significant decrease in VAS and TRE scores, and abrogation of nasal hyperreactivity to CDA [19]
Capsaicin	Intranasal TRPV1 agonist that ablates the TRPV1-SP signaling pathway	Nonallergic rhinitis	Visual analog scale (VAS) scores, and nasal hyperreactivity by means of CDA provocation	Significant decrease in VAS scores, and abrogation of nasal hyperreactivity to CDA up to 9 months after treatment [53]
ICX72 (capsicum + eucalyptol)	Intranasal TRPV1 agonist that ablates the TRPV1-SP signaling pathway	Nonallergic rhinitis	Total nasal symptom scores (TNSS), individual symptom scores (ISS) over 2 weeks and average time to first relief	Significant improvements in TNSS and each ISS, and average time to first relief of 52.6 seconds [51]

by capsaicin in the nasal mucosa was responsible for this therapeutic effect. Several trials of topical capsaicin in patients with nonallergic rhinitis have demonstrated relief of symptoms and nasal hyperreactivity [51-53].

Systemic neuromodulating agents may constitute another approach to the management of neuropathic symptoms in allergic disease. With the recognition that chronic cough is similar to other hypersensitivity neuropathic syndromes such as chronic pain [54], gabapentin, a common treatment for neuropathic pain, has proven clearly efficacious for refractory cough [55]. The clinical relevance of neuroinflammation and sensitization has also been extrapolated to chronic itch. Cevikbas et al [56] described a synergistic role for γ-aminobutyric acid A and B agonists for addressing symptoms of itching in murine atopic dermatitis. The utility of gabapentin has also been demonstrated in this setting [57].

The Table summarizes trials examining neuromodulation to date for allergic and nonallergic upper airway diseases presumed to be related to neuroplasticity.

Future Directions

Despite substantial advances in our understanding of the pathophysiology of AC, the exact association between targeted therapy and successful responses remains controversial and prevents these findings being applied in clinical practice. However, targeting neuronal inflammation remains a potential novel strategy for the treatment of AC. The definition of these pain-relevant neural circuits may facilitate future development of targeted therapies.

Conclusions

Among the constellation of symptoms that characterizes AC, many, such as burning and stinging, can be attributed to chronic neuropathic pain. There is evidence to support that these hallmark symptoms might be linked to the effects of allergen-induced neuromodulation. Thus, neurogenic mechanisms may have a significant role in chronic ocular surface inflammation. Current management goals in allergic conjunctivitis aim to minimize the inflammatory cascade associated with allergic response in the early stages of the pathogenic mechanism. Based on the mechanistic data reviewed herein, the recognition that neuronal inflammation explains many of the symptoms in AC opens new frontiers for drug discovery.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Merin Elizabeth Kuruvilla

1365 Clifton Rd NE, Bldg A, 3rd Flr
Atlanta, GA-30322
USA
E-mail: merin.ek1@gmail.com

ORIGINAL ARTICLE

Epidemiological Data on Anaphylaxis in French Emergency Departments

Corriger J[1,2], Beaudouin E[1], Rothmann R[3], Penven E[4,5], Haumonte Q[1], Thomas H[1], Picaud J[1], Nguyen-Grosjean VM[1], Corriger-Ippolito J[5,6], Braun F[3], De Talancé M[7], Auburtin B[8], Atain-Kouadio P[6], Borsa-Dorion A[9], Baugnon D[10], De Carvalho M[11], Jaussaud R[2], Nguyen-Thi PL[12], Bollaert PE[13], Demoly P[14], Tanno LK[14]

[1]Allergy Department, Hospital Emile Durkheim, Epinal, France
[2]Internal Medicine and Clinical Immunology Department, University Hospital, Vandoeuvre-lès-Nancy, France
[3]Emergency Department, Hospital Mercy–Metz, Ars-Laquenexy, France
[4]Occupational Diseases Department, University Hospital, Vandoeuvre-lès-Nancy, France
[5]Division of Allergy, Dermatology Department, University Hospital, Vandoeuvre-lès-Nancy, France
[6]Emergency Department, University Hospital, Vandoeuvre-lès-Nancy, France
[7]Emergency Department, Hospital Emile Durkheim, Epinal, France
[8]Pediatric Emergency Department, Hospital Emile Durkheim, Epinal, France
[9]Pediatric Emergency Department, University Hospital, Vandoeuvre-lès-Nancy, France
[10]Emergency Department, Hospital of Verdun-Saint-Mihiel, Verdun, France
[11]Biology and Immunology Laboratory, University Hospital, Vandoeuvre-lès-Nancy, France
[12]Clinical Research Platform, ESPRI-BioBase Unit, University Hospital, Vandoeuvre-lès-Nancy, France
[13]Medical Intensive Care Unit, University Hospital, Nancy, France
[14]Division of Allergy, Department of Pulmonology, University of Montpellier, France and Sorbonne University, INSERM, IPLESP, EPAR team, Paris, France

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Abstract

Background: Although anaphylaxis has been considered a priority public health issue in the world allergy community, epidemiological data on morbidity and mortality remain suboptimal. We performed the first multicenter epidemiological study in French emergency departments (EDs). The study covered 7 EDs over a period of 1 year. The objectives were to identify areas that are amenable to change and to support ongoing national and international efforts for better diagnosis, management, and prevention of anaphylaxis.
Methods: Ours was a descriptive study based on data routinely reported to French institutional administrative databases from 7 French public health institutions in the Lorraine region between January and December 2015. Data were collected based on the anaphylaxis-related codes of the International Classification of Diseases (ICD)-10, and cases were clinically validated as anaphylaxis.
Results: Of the 202 079 admissions to the EDs, 4817 had anaphylaxis-related codes; of these, 323 were clinically validated as anaphylaxis. Although 45.8% were severe, adrenaline was prescribed in only 32.4% of cases. Of the 323 cases, 57.9% were subsequently referred for an allergy work-up or evaluation (after or during hospitalization), and 17.3% were prescribed autoinjectable epinephrine.
Conclusion: Our results highlight an urgent need for improved public health initiatives with respect to recognition and treatment of anaphylaxis. We flag key problems that should be managed in the coming years through implementation of national and international actions.

Key words: Anaphylaxis. Emergency. Epidemiology. International Classification of Diseases (ICD). Management

Resumen

Antecedentes: La anafilaxia es un problema prioritario de salud pública en la comunidad mundial alergológica. Sin embargo, los datos epidemiológicos disponibles de morbilidad y mortalidad son mejorables. Presentamos el primer estudio epidemiológico multicéntrico, realizado en siete departamentos de urgencias franceses durante un año, que tuvo como objetivo identificar las cuestiones relevantes para lograr cambios en futuras estrategias, nacionales e internacionales, que deriven en un mejor diagnóstico, tratamiento y prevención de la anafilaxia.
Métodos: Se trata de un estudio descriptivo que utilizó la información proveniente de las bases de datos de siete instituciones francesas de salud pública, de la región de Lorena, desde enero hasta diciembre de 2015. Se buscaron nomenclatura y códigos relacionados con la anafilaxia, de la Clasificación Internacional de Enfermedades (CIE-10), y los pacientes fueron validados clínicamente como casos de anafilaxia.
Resultados: De los 202.079 ingresos en urgencias, 4.817 tenían códigos relacionados con la anafilaxia CIE-10, 323 de los cuales se validaron clínicamente con el diagnóstico de anafilaxia. Aunque el 45,8% presentó criterios de gravedad, la adrenalina se prescribió

solo en el 32,4% de estos casos. En total, 323 casos, el 57,9%, se remitieron posteriormente para un estudio o evaluación alergológica (después o durante la hospitalización) y el 17,3% recibió una receta de adrenalina autoinyectable.
Conclusión: Según los resultados de este estudio, existe una necesidad urgente e imperiosa de mejorar los planes de salud pública respecto al reconocimiento y tratamiento de la anafilaxia. Los problemas clave detectados en este trabajo, señalan el camino de la toma de decisiones e implementación de acciones de mejora, nacionales e internacionales, para una mejor atención de los pacientes con anafilaxia.
Palabras clave: Anafilaxia. Urgencias. Epidemiología. Clasificación Internacional de Enfermedades (CIE). Tratamiento.

Introduction

Anaphylaxis is an acute, severe, life-threatening generalized or systemic hypersensitivity reaction that requires rapid recognition and treatment [1]. It may present as very different combinations of symptoms, and apparently mild signs may unpredictably progress to fatal shock. The recognition of anaphylaxis is hampered, in part, by variability in diagnostic criteria. Consequently, administration of appropriate treatment is delayed, thus increasing the risk of death. Anaphylaxis is a recognized cause of death in all age groups.

Although this condition is considered a priority public health issue in the world allergy community, epidemiological data on morbidity and mortality remain suboptimal. The frequency of anaphylaxis in the emergency department (ED) has been reported to range from 0.04% to 0.5% of visits [2-10]. This remarkable variability is related to factors such as differences between populations and EDs, difficulty recognizing at-risk and anaphylactic patients, and the methodology applied to calculate rates.

In 2017, Tanno et al [1] reported a local incidence rate of 32 per 100 000 person-years in hospitalized patients in Montpellier, France [11] and a national mortality rate of 0.83 (0.80-0.88) [12]. However, there are currently no epidemiological studies on the morbidity of anaphylaxis in French EDs.

Ascertaining how anaphylaxis is diagnosed and treated nationally and worldwide is an important preliminary step towards the development of public health strategic action plans to identify and resolve key issues. We proposed a 1-year multicenter epidemiological study in 7 French EDs covering a population of 953 552 inhabitants in order to identify key areas for change and to support ongoing national and international efforts for better diagnosis, management, and prevention of anaphylaxis.

Methods

Data Sources and Case Definition

Ours was a descriptive study using ED data routinely reported to French institutional administrative databases. The French public hospital structure uses a system of coding alongside the length of hospital stay to determine the chargeable cost of care per patient for purposes of reimbursement. The coding system used is the World Health Organization (WHO) *International Classification of Diseases* (*ICD*), currently *ICD-10* [13]. Coding is based on review of case reports by professional coders, who take into account diagnosis, procedures, and other events reported by the care team. The data are submitted to be included in national health statistics and are used for research and planning. Since French public health institutions serve as references for patients in the regions where they located, patients are generally referred to these hospitals.

In this study, we evaluated data from 7 EDs in institutions from the University of the Lorraine urban region between January and December 2015. Data were retrieved in January 2016. Lorraine is an administrative area in the northeast of France with 32 public healthcare institutions of different complexities.

Of the 202 079 ED admissions recorded during the year 2015, we accessed all consecutive files in which the primary

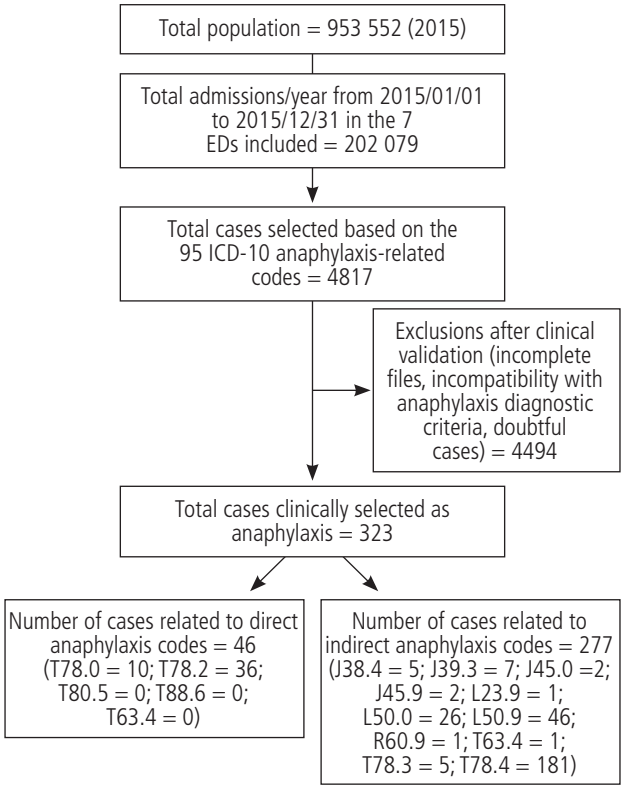

Figure. Flow chart showing patient selection and inclusion based on the *International Classification of Diseases.*

cause of admission was assigned an anaphylaxis-related *ICD-10* code (Table 1). Incidence was calculated based on the number of admissions during 2015. Of the 4817 cases coded as being anaphylaxis-related, 323 (6.7%) were clinically validated retrospectively as anaphylaxis by 2 independent allergists and based on the current accepted international diagnostic criteria and criteria for the characterization of anaphylaxis [1,14,15]. Doubtful cases were discussed openly with the coauthors (Figure). We then reviewed the corresponding *ICD-10* codes for the clinically validated cases.

Table 1. *International Classification of Diseases (ICD)-10* Anaphylaxis-Related Codes Used in the Initial Selection of Cases (n=95)

ICD-10 codes (2016) Category	Extension	Description
D69	0	Allergic purpura
H10	.1, 3, 9	Conjunctivitis
I46	.0, 9	Cardiac arrest
I95	.8	Other hypotension
J30	.1 – 4	Allergic rhinitis
J38	.4, 5	Edema of larynx and laryngeal spasm
J39	.3	Upper respiratory tract hypersensitivity reaction
J45	.0, 1, 8, 9	Asthma
J46	.X	Status asthmaticus and acute severe asthma
J67	.8, 9	Hypersensitivity pneumonitis due to other or unspecified organic dust
K52	.2	Allergic and dietetic gastroenteritis and colitis
K90	.4	Malabsorption due to intolerance or hypersensitivity
L03	.9	Cellulitis, located edema or erythema
L20	.8, 9	Atopic dermatitis
L23	.0 – 9	Allergic contact dermatitis
L24	.0 – 9	Irritant contact dermatitis
L25	.0 – 5, 8, 9	Unspecified contact dermatitis
L27	.0 – 2, 8, 9	Dermatitis or skin eruptions due to substances taken internally, drugs and medicaments
L30	.8, 9	Dermatitis and eczema
L50	.0 – 9 (excl 3, 7)	Urticaria
L53	.0, 9	Toxic or unspecified erythema
L56	.0 – 3	Drug phototoxic or photoallergic responses, photocontact dermatitis and solar urticaria
M31	.0	Hypersensitivity angiitis
M36	.4	Arthropathy in hypersensitivity reactions
O29	.3	Toxic reaction to local anesthesia during pregnancy
O74	.4	Toxic reaction to local anesthesia during labor and delivery
O89	.3	Toxic reaction to local anesthesia during puerperium
R21	.X	Rash and other nonspecific skin eruption
R60	.1, 9	Generalized or unspecified edema
T78	.0	Anaphylactic shock due to adverse food reaction
T78	.1	Other adverse food reactions
T78	.2	Anaphylactic shock, unspecified
T78	.3	Quincke edema
T78	.4	Allergic reaction, unspecified
T80	.5	Anaphylactic shock due to serum
T80	.6	Other serum reactions
T81	.1, 6	Shock or acute reaction resulting from a procedure or a substance left during a procedure
T88	.6	Anaphylactic shock due to adverse effect of correct drug properly administered
Z01	.5	Diagnostic skin and sensitization tests (allergy tests)
Z51	.6	Desensitization to allergens

Table 2. Cases of Anaphylaxis: Characteristics and Demographic Data

Demographic Data	Children (<18 y) n=106 (32.8%)	Adults (≥18 y) n=217 (67.2%)	Total (0-88 y) N=323 (100.0%)	*P* Value[a]
Gender				
Male	65 (61.3%)	119 (54.8%)	184 (57.0%)	
Female	41 (38.7%)	98 (45.2%)	139 (43.0%)	.27
Manifestations				
Cutaneous	95 (89.6%)	202 (93.1%)	297 (92.0%)	.28
Respiratory	69 (65.1%)	141 (65.0%)	210 (65.0%)	.98
Upper airway	51 (48.1%)	91 (41.9%)	142 (44.0%)	.29
Lower airway	45 (42.5%)	93 (42.9%)	138 (42.7%)	.95
Cardiovascular and/or loss of consciousness	36 (34.0%)	98 (45.2%)	134 (41.5%)	.06
Gastrointestinal	47 (44.3%)	60 (27.6%)	107 (33.1%)	.002
Biphasic reaction	8 (7.5%)	8 (3.7%)	16 (5.0%)	.13
Severity[b]				
Grade I	22 (20.8%)	47 (21.7%)	69 (21.4%)	.85
Grade II	37 (34.9%)	69 (31.8%)	106 (32.8%)	.58
Grade III	47 (44.3%)	99 (45.6%)	146 (45.2%)	.83
Grade IV	0 (0.0%)	2 (0.9%)	2 (0.6%)	.32
Cofactors				
Asthma	36 (34.0%)	25 (11.5%)	61 (18.9%)	<.001
Cardiovascular disease	3 (2.8%)	31 (14.3%)	34 (10.5%)	.002
Alcohol intake	0 (0.0%)	11 (5.1%)	11 (3.4%)	.002
Associated drugs	1 (0.9%)	65 (30.0%)	66 (20.4%)	<.001
β-blockers	0 (0.0%)	23 (10.6%)	23 (7.1%)	<.001
NSAIDs or aspirin	0 (0.0%)	29 (13.4%)	29 (9.0%)	<.001
ACEIs or ARBs	0 (0.0%)	39 (18.0%)	39 (12.1%)	<.001
PPIs	1 (0.9%)	20 (9.2%)	21 (6.5%)	.005
Etiology				
Drugs	7 (6.6%)	76 (35.0%)	83 (25.7%)	.001
ß-Lactams	2 (1.9%)	37 (17.1%)	39 (12.1%)	<.001
Other antibiotics	0 (0.0%)	8 (3.7%)	8 (2.5%)	.045
NSAIDs	2 (1.9%)	7 (3.2%)	9 (2.8%)	.49
Radiocontrast agents	0 (0.0%)	14 (6.4%)	14 (4.3%)	.008
Other or unidentified	3 (2.8%)	10 (4.6%)	13 (4.0%)	.45
Food	82 (77.4%)	55 (25.3%)	137 (42.4%)	<.001
Peanut and nuts	29 (27.3%)	9 (4.1%)	38 (11.8%)	<.001
Hen egg	6 (5.7%)	1 (0.5%)	7 (2.1%)	.003
Cow milk	9 (8.5%)	0 (0.0%)	9 (2.8%)	<.001
Fish and meat	4 (3.8%)	5 (2.3%)	9 (2.8%)	0.45
Shellfish	2 (1.9%)	17 (7.8%)	19 (5.9%)	.03
Other or unidentified	32 (30.2%)	23 (10.6%)	55 (17.0%)	<.001
Insect sting	10 (9.4%)	65 (30.0%)	75 (23.2%)	<.001
Undetermined	4 (3.8%)	21 (9.7%)	25 (7.8%)	.06
Other	3 (2.8%)	0 (0.0%)	3 (0.9%)	.01
Previous history of anaphylaxis	28 (26.4%)	37 (17.1%)	65 (20.1%)	.049
Serum tryptase measurement	8 (7.5%)	33 (15.2%)	41 (12.7%)	.05
Treatment				
Use of epinephrine	12 (11.3%)	44 (20.3%)	56 (17.3%)	.045
Administration route				
Intravenous	2 (1.9%)	20 (9.2%)	22 (6.8%)	.01
Intramuscular	5 (4.7%)	4 (1.9%)	9 (2.8%)	.14
Subcutaneous	0 (0.0%)	5 (2.3%)	5 (1.5%)	.12
Inhaled	4 (3.8%)	7 (3.2%)	11 (3.4%)	.07
Unknown	1 (0.9%)	8 (3.7%)	9 (2.8%)	.16
By severity[b]				
Grade I	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Grade II	3 (8.1%)	5 (7.2%)	8 (7.5%)	.87
Grade ≥III	9 (19.1%)	39 (38.6%)	48 (32.4%)	.02
Systemic antihistamine	89 (84.0%)	195 (89.9%)	284 (87.9%)	.13
Systemic corticosteroid	91 (85.8%)	184 (84.8%)	275 (85.1%)	.80

Continue

Table 2. Cases of Anaphylaxis: Characteristics and Demographic Data

Demographic Data	Children (<18 y) n=106 (32.8%)	Adults (≥18 y) n=217 (67.2%)	Total (0-88 y) N=323 (100.0%)	*P* Value[a]
Hospitalization	31 (29.2%)	15 (6.9%)	46 (14.2%)	< .001
Observation period at the ED				
<6 h 88 (83.0%)	149 (68.7%)	237 (73.4%)		
>6 h 18 (17.0%)	68 (31.3%)	86 (26.6%)	.006	
Referred to the allergist	78 (73.6%)	109 (50.2%)	187 (57.9%)	< .001
Prescription of autoinjectable epinephrine	26 (24.5%)	30 (13.8%)	56 (17.3%)	.02

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-2 receptor blockers; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.
[a]*P* value for test of equality of proportions.
[b]Ring & Messmer classification.

Reference Population

The geographical regions were defined using the official map of France for the year 2014. Data were collected and anonymized after approval by our institutional Advisory Committee on the Treatment of Information on Research in the Field of Health (CCTIRS) [16].

Statistical Analysis

Data were analyzed using LibreOffice and EpiData. The statistical descriptions included mean, median, and standard deviation for quantitative variables and frequencies and percentages for categorical variables. The group comparisons were made using the χ^2 test for categorical variables and the *t* test for quantitative variables. An analysis of variance (ANOVA) was performed to compare the means of multiple samples. A *P* value of <.05 was considered significant.

Results

The epidemiological and clinical characteristics of the patients and results for the management of the anaphylactic reactions are summarized in Table 2. In 2015, anaphylaxis was responsible for 0.16% of ED admissions. Extrapolating to the urban areas covered, the incidence was estimated at 34 per 100 000 person-years. Of the 323 patients with clinically confirmed anaphylaxis, 67.2% were adults aged 18 to 88.4 years, and 32.8% were children aged 2 months to 18 years. The sex ratio was 1.32 in favor of males. Adults presented mainly drug-induced and insect sting–related anaphylaxis, whereas food was the main trigger in the pediatric population (Table 2). No deaths were reported. A previous history of anaphylaxis was found in 20.1% and a biphasic reaction in 5.0% of the patients. Epinephrine was used significantly more often in adults than in children (*P*=.045). Although 45.8% (148/323) of the patients presented severe anaphylaxis (Ring & Messmer grade ≥3), epinephrine was prescribed in only 32.4% (48/148) of these cases, mostly by intravenous injection (41.7%), and more often in children than in adults (*P*=.02). Children were more frequently referred to allergists and received more prescriptions than adults (Table 2). Serum tryptase was measured in 12.7% of patients, and 60.1% were kept under observation in hospital for less than 6 hours (median, 4.7 hours).

Of the 323 cases, 57.9% were subsequently referred for an allergy work-up or evaluation (after or during hospitalization), and 17.3% were prescribed autoinjectable epinephrine (Table 2). Twenty percent of patients experienced more than 1 episode of anaphylaxis, even after the allergological diagnosis was established (37% with exposure to food allergens and 22% after drug intake).

Concomitant asthma was the only cofactor identified as being significantly (*P*<.05) associated with more severe (grade ≥3) anaphylactic episodes in children (OR, 2.37; 95%CI, 1.04-5.38). In adults, the only significantly associated cofactor was use of 1 or more of a series of drugs (β-blockers, aspirin and other nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin-2 receptor antagonists, proton pump inhibitors, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 agonists) (OR, 2.18; 95%CI, 1.20-3.94). Clinical presentations were influenced by specific factors: concomitant asthma was associated with a higher frequency of lower respiratory tract symptoms (OR, 2.26; 95%CI, 1.28-3.98), cardiovascular disorders with cardiovascular injury (OR, 2.19; 95%CI, 1.06-4.52), and food as a trigger with gastrointestinal manifestations (OR, 1.83; 95%CI, 1.15-2.92) (*P*<.05 for all).

Of the 323 confirmed cases of anaphylaxis, only 14.3% presented anaphylaxis classed as direct according to the *ICD-10* codes (Figure).

Discussion

Ours is the first study to present epidemiological data on the morbidity and management of anaphylaxis in French EDs. We highlight the need to harmonize knowledge of management of anaphylaxis. Awareness of anaphylaxis as a life-threatening medical condition has been increasing in various specialties,

and recent publications show that it is not as uncommon a condition as previously thought. However, most publications to date consider degrees of severity of anaphylaxis, and the severe forms may still well be considered rare diseases [17]. In the present study, we demonstrated that anaphylaxis was responsible for 0.16% of ED admissions, with an incidence estimated at 34 per 100 000 person-years.

Although injectable epinephrine is currently listed in the WHO list of essential drugs for the treatment of anaphylaxis, our findings were remarkable in that it was rarely prescribed, even in severe cases [18]. This finding is consistent with most recently published data in the field [2-10]. Additionally, a relevant number of patients were hospitalized or kept under observation for a shorter period than recommended [15].

In contrast to most international recommendations [14], we observed that intravenous epinephrine was administered very frequently, despite being responsible for serious complications such as acute pulmonary edema, arrhythmia, and acute coronary events. In addition, we found a reduced proportion of referral to allergists and lack of prescription of epinephrine autoinjectors. We believe that these findings may be associated with uncertainty among physicians about the diagnosis of anaphylaxis, which was defined based on anaphylaxis classed as indirect according to the *ICD-10* codes. The recent recognition of allergy as a full specialty paves the way for bilateral collaboration with other specialties and will enhance management of anaphylactic patients.

Particularly striking was the number of patients who presented a second episode of anaphylaxis, even with the allergological diagnosis. Consequently, greater awareness is necessary among patients and caregivers in order to avoid re-exposure to known triggers. Educational efforts will also help to decrease underrecognition of anaphylaxis by patients, caregivers, health professionals, health authorities, and governments. In addition, allergy academies have promoted training programs and publications in the field [1,14,15,19-22].

Serial serum (or plasma) levels of tryptase should be collected to guide the diagnosis of anaphylaxis or to exclude mast cell disorders, which can mimic anaphylaxis. However, these samples have only been collected in a limited number of severe reactions, thus indicating the need for a systematic anaphylaxis action plan. National and international guidelines have been drafted to fill these gaps [14,23-25].

Underreporting or underestimation of anaphylaxis can be explained by the difficulty in coding anaphylaxis deaths under the WHO ICD system. Limited numbers of *ICD-10* codes are considered valid for the morbidity and mortality of anaphylaxis [8], as demonstrated in patients diagnosed by direct *ICD-10* codes for anaphylaxis (46 cases) and indirect anaphylaxis *ICD-10* codes (277 cases) (Figure). For this reason, we included additional codes related to manifestations and causes that could resemble or induce anaphylaxis or even allergic reactions (Table 1). Over the last 5 years, a strategic international action plan supported by the Joint Allergy Academies and the WHO [11,17,18,26-31] was implemented to update the classifications of allergic conditions for the new edition of the ICD. These efforts resulted in the construction of the new "Allergic and hypersensitivity conditions" section in *ICD-11* [28,32], with a subsection dedicated exclusively to anaphylaxis. The availability of this new section should enable better morbidity and mortality statistics to be reported.

Recent international achievements have been accompanied by the efforts made since 2014 to recognize allergy as a full academic specialty in France. This will improve the training of health professionals in the field and support quality management of allergic patients. Anaphylaxis, as well as other allergic and hypersensitivity conditions, are systemic disorders that require a multidisciplinary approach [17]. Recognition of allergy as a full specialty will strengthen collaboration with other specialties, thus increasing scientific consistency and awareness.

Our study is the first to report epidemiological data on anaphylaxis in French EDs. It highlights regional differences in the incidence and management of the disease. Although the diagnosis of anaphylaxis is limited by the retrospective nature of the study, all cases were clinically validated manually in order to reduce the number of doubtful cases. Another known limitation is the number of participating EDs and the size of the geographic area studied, which may have affected the epidemiological findings. However, our results confirm national and international efforts for improved diagnosis and management of anaphylaxis. Broader studies are required to increase our knowledge of the epidemiology of anaphylaxis and to support advances in and the use of new classifications of allergic and hypersensitivity conditions. We intend to support the implementation process of *ICD-11* in order to ensure more accurate and comparable data on the morbidity of anaphylaxis.

In conclusion, there is an urgent need for improved public health initiatives on the recognition and treatment of anaphylaxis. The data presented here are consistent with the findings of the European Anaphylaxis Registry, which concludes that despite clear recommendations, only a small proportion of cases of anaphylaxis are treated with epinephrine [33]. We believe that the present document flags key problems, which may be managed in the coming years through implementation of national and international programs. Strategies to overcome the main barriers in anaphylaxis care should be based on bilateral partnership between allergists and emergency physicians.

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Conflicts of Interest

The authors declare that they have no conflicts of interests.

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Jeremy Corriger

Centre Hospitalier Emile Durkheim d'Epinal
Maison de santé Saint-Jean
31 rue Thiers
88000 Epinal, France
E-mail: jeremy.corriger@hotmail.fr

Luciana Kase Tanno

Division of Allergy, Department of Pulmonology
Hôpital Arnaud de Villeneuve, University Hospital of Montpellier
371, av. du Doyen Gaston Giraud
34295, Montpellier cedex 5, France
E-mail: luciana.tanno@gmail.com

ORIGINAL ARTICLE

Asthma Exacerbations in the Pediatric Emergency Department at a Tertiary Hospital: Association With Environmental Factors

Marques-Mejías MA[1], Tomás-Pérez M[1,2], Hernández I[1], López I[1], Quirce S[1,2,3]

[1]Department of Allergy, Hospital Universitario La Paz, Madrid, Spain
[2]Department of Allergy, Hospital La Paz Institute for Health Research (IDIPAZ), Madrid, Spain
[3]CIBER de Enfermedades Respiratorias CIBERES, Madrid, Spain

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Abstract

Introduction: Children with asthma experience recurrent respiratory symptoms and exacerbations due to multiple environmental factors. The aim of this study was to describe the prevalence and triggers of asthma exacerbations and their management in a cohort of pediatric patients attended in an emergency department (ED).
Methods: We performed an observational, retrospective, single-center study in the pediatric ED of Hospital Universitario La Paz, Madrid, Spain in 2015. Children with asthma exacerbations attending the ED were included after a thorough search using our institutional computer database. Pollen and atmospheric mold spore counts and pollution data were collected for that period from official websites. Multiple logistic regression was used to assess the association between daily pollution (NO_2, PM_{10}, ozone, pollen, and molds) and admissions to the ED because of asthma.
Results: During 2015, a total of 50 619 patients were attended in the ED of our hospital. Of these, 2609 (5%) were diagnosed with asthma exacerbation/bronchospasm. The patient had to be admitted to hospital in 21.7% of cases. The main triggers of asthma exacerbations were respiratory infection in 1841 cases (70.6%). A significant correlation was found between grass pollen counts and ED admissions ($P<.0001$). A positive correlation was also found between ED admissions and NO_2 0.58 (95%CI, 0.02-0.87) and PM_{10} 0.75 (95%CI, 0.31-0.93) ($P<.05$).
Conclusion: Environmental factors such as grass pollen counts and pollution (NO_2 and PM_{10}) are associated with a higher frequency of admission to the ED.

Key words: Pediatric asthma. Asthma exacerbations. Air pollutants. Asthma management.

Resumen

Introducción: Los niños con asma presentan síntomas respiratorios y exacerbaciones recurrentes debido a múltiples factores ambientales. El objetivo de este estudio es describir la prevalencia y los desencadenantes de las exacerbaciones del asma y su manejo en una cohorte de pacientes pediátricos atendidos en un servicio de urgencias (SU).
Métodos: Se trata de un estudio observacional, retrospectivo, unicéntrico, dirigido en urgencias pediátricas del Hospital Universitario La Paz (Madrid, España) en 2015. Los pacientes con diagnóstico de exacerbación de asma fueron seleccionados a partir de una búsqueda informática. La información referente a niveles de pólenes, hongos y contaminación fue recogida en portales digitales oficiales. Se realizó una regresión logística múltiple para evaluar la asociación entre la contaminación diaria (determinada por los niveles NO_2, PM_{10}, O3, recuentos de polen y hongos) y las admisiones por asma en el SU.
Resultados: En el 2015 fueron atendidos en urgencias pediátricas de nuestro hospital 50.619 niños. De estos, 2.609 (5%) tenían diagnóstico de exacerbación asmática/broncoespasmo. El 21,7% de los casos requirió ingreso. Los principales desencadenantes fueron las infecciones (70,6%). La relación entre picos de polinización de gramíneas y admisión en urgencias fue significativa ($p<10^{-4}$). Igualmente una correlación positiva fue obtenida entre ingresos en el SU y NO_2 0,58 (95% 0,02 a 0,87) y PM_{10} 0,75 (95% 0,31 a 0,93) ($p<0,05$).
Conclusión: Factores ambientales como el recuento de polen de gramíneas y partículas contaminantes (NO_2, PM_{10}) se asocian con un mayor número de episodios de broncoespasmo atendidos en urgencias.

Palabras clave: Asma pediátrica. Exacerbaciones del asma. Contaminantes ambientales. Manejo de asma.

Introduction

The prevalence of asthma among children in the European Union is currently estimated to be 9.4% [1]. The incidence of the disease continues to increase around the world [2], generating a considerable economic burden through direct and indirect costs in developed countries. A large part of the costs is related to emergency department (ED) care and hospitalization [3,4]. In Spain, asthma exacerbation episodes account for 5% of pediatric ED visits, which may reach 10%-15% at certain times of the year [5,6].

An asthma exacerbation can be defined as an increase in airway inflammation that causes airflow limitation and triggers asthma symptoms (wheezing, shortness of breath, coughing, and chest tightness). It can be considered severe if it requires systemic corticosteroids and/or ED care or hospitalization [7,8].

Children are more susceptible than adults to the negative health effects of pollutants [9,10]. In many cohorts, a positive association has been demonstrated between exposure to pollutants and mild to severe asthma exacerbations and has been directly linked to reduced lung function [7,9-11].

The air pollutants most frequently associated with severe exacerbations are daily levels of nitrogen dioxide (NO_2), fine particulate matter measuring 10 µm or less in diameter (PM_{10}) [12,13], ozone, and airborne pollen [14]. The relationship between asthma exacerbation and factors such as allergic inflammation, infection, and pollution remains unclear [15].

The aim of this study was to describe the prevalence of episodes of asthma exacerbation and their management in a cohort of pediatric patients attended in an ED in Madrid, Spain. Secondary analyses were performed to predict potential triggers. We report on management of ED admissions for asthma in the largest pediatric cohort analyzed to date. We also examine the association between asthma exacerbations and environmental factors in Spain during the last 10 years.

Material and Methods

We performed an observational, retrospective, single-center study in the pediatric ED of Hospital Universitario La Paz, Madrid, Spain from January 1 to December 31, 2015. We performed a computerized search for patients based on the key words *difficulty breathing, wheezing*, and/or *dyspnea*. Those with a diagnosis of asthma exacerbation were enrolled in the study. Data on each visit were collected from the ED computer system and hospital medical records. The variables included were sex, age, treatment received in the ED, need for hospitalization, month of the year of admission, probable cause of symptoms, and referral to the allergy or pneumology department. Information on allergy tests performed during the follow-up visits was obtained from the medical records of the pediatric allergy department.

Pollen and mold spore counts were collected for the study period from the Aerobiology Committee of the Spanish Allergy and Clinical Immunology (SEAIC) website (https://www.polenes.com/home). Environmental pollution data were retrieved from the website of the air quality section of Madrid City Council (http://www.mambiente.munimadrid.es/opencms/opencms/calaire). Air pollutants (NO_2 and PM_{10}) were monitored from Plaza Castilla station, one of the main stations in the city (2.7 km from the hospital). We calculated the mean daily, weekly, and monthly count during that period. For pollen and mold data, the mean monthly concentrations of Gramineae, Cupressaceae, and *Olea europaea* were recorded in grains per cubic meter (g/m^3); the concentration of *Alternaria alternata* was recorded in spores per cubic meter.

Statistical Analysis

The analysis was based on descriptive statistics. Continuous variables were expressed as median (IQR), and categorical variables were expressed as frequency and percentage. ANOVA or the Wilcoxon rank-sum test was used to identify differences between groups for continuous variables. The Pearson χ^2 test was used to analyze categorical variables. Multiple logistic regression was used to assess the association between daily pollution (NO_2, PM_{10}, and ozone) and admission to the ED because of asthma. The independent variables were levels of air pollutants (NO_2, PM_{10}, and ozone), pollen, and molds. Admission to the ED was considered the dependent variable. Statistical significance was set at $P<.05$. All the analyses were performed using SPSS R version 3.4.3, platform: x86_64-w64-mingw32/x64 (64-bit), running under Windows 10 ×64 (build 16299).

This study was approved in its initial version by the Ethics Committee of Hospital Universitario La Paz (code HULP: PI-2347).

Results

During 2015, a total of 50 619 patients were attended in the ED of our hospital. Of these, 2609 (5%) were diagnosed with asthma exacerbation/bronchospasm. The distribution by sex was 1534 boys (58.8%) and 1075 girls (41.2%) ($P<.0001$). The children included were between 0 and 15 years old, with a mean (SD) age of 3.59 (3.11) years.

Most cases resolved with outpatient care (78.3%), while 21.7% required admission to hospital. The mean age of admitted patients was 3.2 (2.87) years. Two or more episodes were registered in 607.8 (23.3%) patients, 23 of whom (0.9%) had experienced 6-8 episodes during that year. The number of recurrent episodes is shown by month of the year in the Table.

The most commonly used treatment was short-acting ß$_2$-agonists in 85.1% of cases, followed by systemic corticosteroids in 54.7%. Inhaled corticosteroids were used in 1.8%, and other treatments such as anticholinergics, oxygen, and antipyretics were used in 41.7% of the sample. Up to 10.8% of the patients did not receive any treatment in the ED owing to absence of symptoms during the medical assessment and/or previous medication at home or in other health centers.

The main triggers of exacerbations were infections in 1841 cases (70.6%), followed by unknown factors in 748 (28.7%). The remaining possible causes were cutaneous exposure to allergens (0.6%) and food allergy (0.1%). Although there was no systematic microbiological confirmation of suspected respiratory infections, most were believed to be secondary

Table. Number of Recurrent Asthma Exacerbation Episodes in Children That Attended the Emergency Department at Hospital Universitario La Paz During 2015

Month	No. of Recurrent Episodes	%
January	76	10.7
February	50	7.0
March	58	8.1
April	69	9.7
May	88	12.3
June	40	5.6
July	14	2.0
August	9	1.3
September	62	8.7
October	107	15.0
November	86	12.1
December	54	7.6

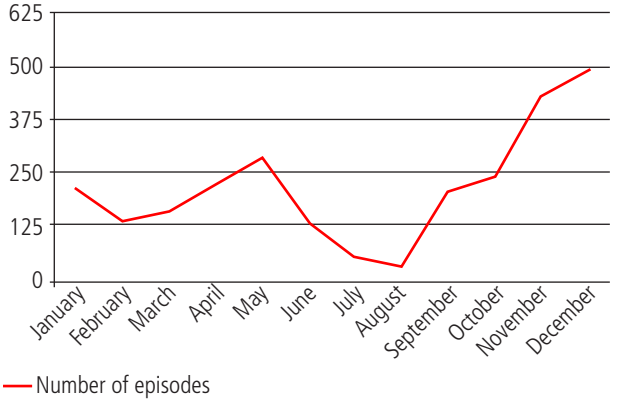

Figure 1. Number of patients with asthma exacerbations who attended the emergency department during 2015.

to viruses according to epidemiological data and clinical characteristics.

During 2015, the highest number of patients attended for asthma exacerbations was registered in December, November, May, and October in descending order (P<.0001). The highest percentage of patients being followed in allergy departments and attended in the ED was registered in May (34.1%) followed by February (29.2%) and April (28.6%). The difference between these percentages and those recorded during the rest of the year was statistically significant (P<.0001) (Figure 1).

A total of 596 out of 2609 (22.8%) patients were evaluated in allergy departments. The most prevalent sensitizer in these children was pollen (275/596 [46.1%]), followed by animal dander (136/596 [22.8%]), molds (61/596 [10.2%]), and house dust mite (39/596 [6.5%]). No sensitization was found at the time of evaluation in 14.3% of the sample.

A statistically significant (P<.0001) relationship was found between grass pollen counts and ED admissions, whereas no correlation was found between ED admissions and counts of other pollens (*Cupressus arizonica, Olea europaea*) and molds (*Alternaria alternata*) (Figure 2).

A positive correlation was found between admission to the ED and NO_2 0.58 (95%CI, 0.02-0.87) and PM_{10} 0.751 (95%CI, 0.31-0.93). Assessment of these air pollutants based on a linear regression model reinforced these findings (Figure 2). A weak negative correlation was found between ozone and ED admissions (–0.67 [95%CI, –0.9 to –0.17]) (Figure 3).

We further analyzed the effect of environmental factors by dividing our sample into 3 groups: (*1*) Children aged 0-3 years, who presented a weak but significant positive correlation

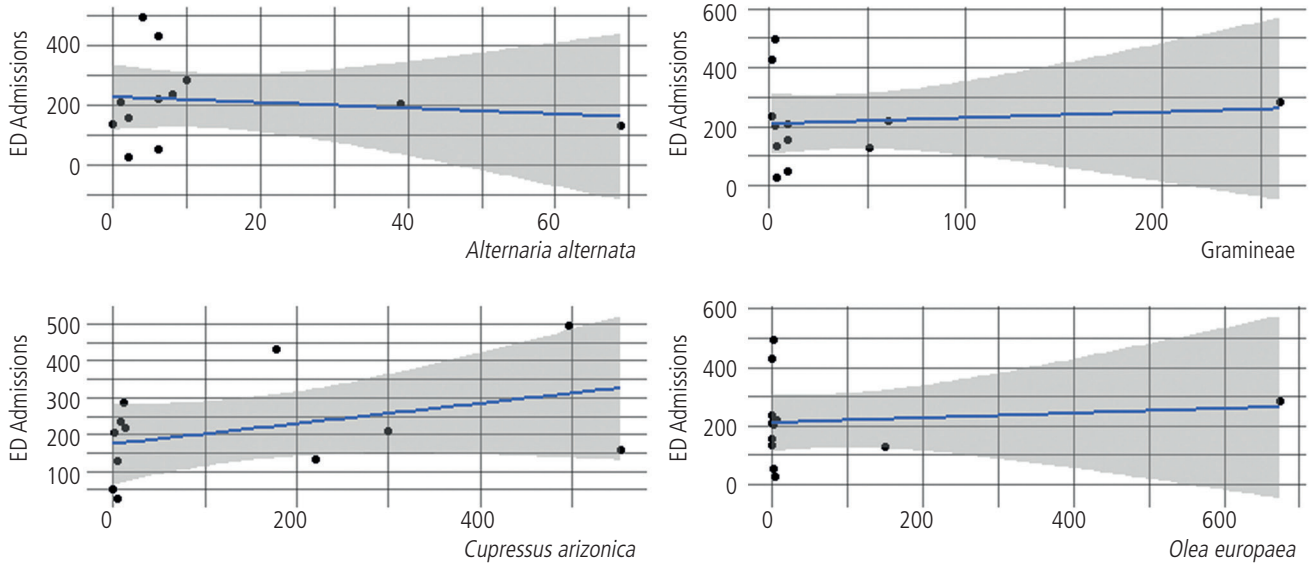

Figure 2. Correlation between pollens (Gramineae, *Cupressus arizonica, Olea europaea*), *Alternaria alternata*, and admissions to the emergency department.

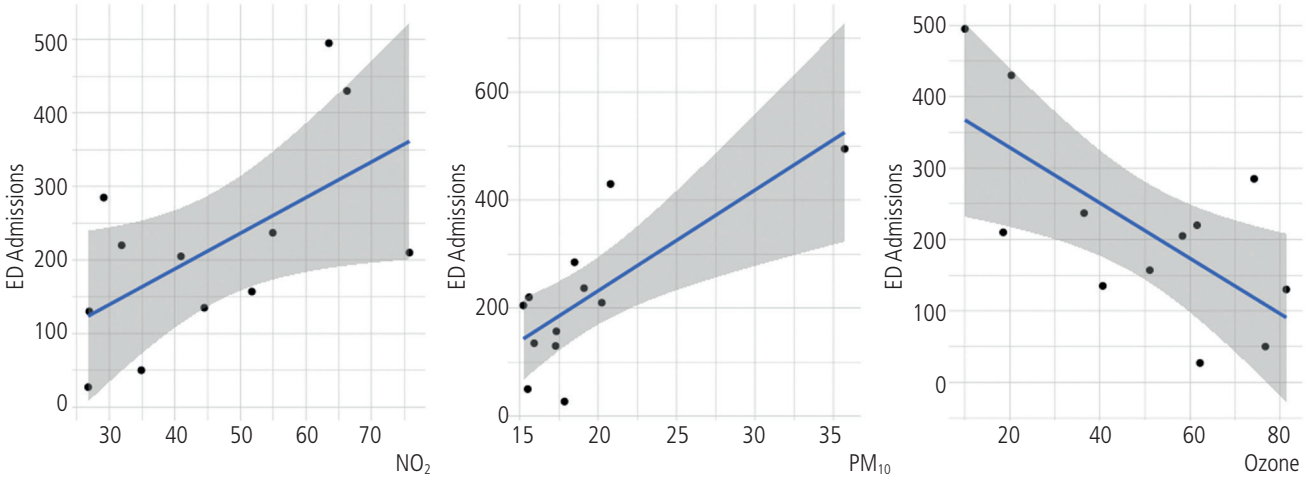

Figure 3. Correlation between air pollutants (NO_2, PM_{10}, ozone) and admission to the emergency department.

between ED admissions and PM_{10} (0.028) and grass pollen counts (0.02); (*2*) Children aged 4-7 years, who also presented a weak correlation between ED admissions and PM_{10} (0.034) grass pollen counts (0.01); (*3*) Children aged 8-14 years, who were affected by PM_{10}, NO_2, and ozone. We found a significant positive correlation between them (PM_{10} [0.060], ozone [0.027], NO_2 [0.029]). Regarding pollen counts, there was a significant though weak correlation between ED admissions and Cupressaceae and grass pollen counts (0.011).

In more than half of the patient population, there was no recorded follow-up by either the allergy or the pneumology department (57.6%). Up to 11.1% of the patients were followed up in allergy departments, 20% in pneumology departments, and 11.2% in both. Of the admitted patients, 50.7% had regular check-up visits by specialists (allergist or pneumologist). Of this percentage, 22.9% were followed up by an allergist only.

Discussion

The increase in hospital admissions for wheezing or asthma attacks is a growing health care problem in developed countries, generating considerable costs for health systems [4,16]. Since 2016, after the Melbourne thunderstorm asthma study, specialists around the world have been paying more attention to ED admissions in order to detect high-risk populations [17]. In this sense, children continue to be a vulnerable population during these types of episodes.

The treatment of asthma exacerbations is complex, since many patients continue to have asthma-related symptoms at home once they have been discharged from the ED [18]. The rising frequency of asthma exacerbations indicates that management of the disease continues to be suboptimal [18-21].

In our sample, more than 20% of the children had more than 1 asthma exacerbation in 1 year, thus reinforcing the importance of regular check-ups and adjustment of regular controller treatment in these patients. Adjustments should be based on the triggers involved in the exacerbations, the medical history, and the response to treatment in the ED.

One of the current hypotheses for the origin and persistence of wheeze in children involves the interactions between inflammatory pathways triggered by exposure to aeroallergens and respiratory pathogens that hamper the normal development of the airway tissues [22,23]. These changes can lead to phenotypic alterations that probably predispose to subsequent development of persistent wheeze [22,23]. This theory proposes that the risk for development of persistent wheeze and asthma is amplified if early sensitization is accompanied by severe lower respiratory tract infections during the first years of life [3,24].

As for infections that affect children, the prevalence of respiratory syncytial virus (RSV) in the pediatric population is estimated to be around 50% during the first year of life [25]. Sigurs [26] investigated the relationship between RSV and asthma and reported a statistically significant increase in asthma frequency in 47 children with RSV compared with a control group. Across the world, most RSV outbreaks are during early spring, fall, and winter [9]. More than 70% of asthma exacerbations attended in our hospital over 1 year are due to infections. While our findings are similar (mean age of the sample, 3 years; highest percentage of asthma exacerbations in the months of December, November, May, and October), microbiological confirmation is needed in further cohorts to clarify the origin of the infections [26].

The biological effects of pollutants and other air contaminants such as pollen and mold spores are enhanced in children because of the immaturity of the immune system and physiological characteristics such as low body weight and higher respiratory frequency [27-29]. The latter leads children to inhale greater amounts of pollutants, with subsequent inflammation of the smaller airways [28-29], which can be worsened by concurrent factors, such as infection or air pollutant peaks during pollination seasons.

The effect of air pollution on the airway varies according to the molecular weight of the particles. NO_2, PM_{10}, and ozone particles have been linked to adverse effects in the airways [17,30,31]. In our study, we found a significant correlation between NO_2 and PM_{10} and bronchospasm.

Furthermore, it has been suggested that the effect of PM_{10} depends mainly on particles measuring less than 2.5 µm, because they can remain in the atmosphere for longer periods and can access the respiratory tract easier than larger ones [31]. Ozone is responsible for an almost 10% increase in the risk of ED visits, especially in children aged 6-19 years [17]. Although we could not find strong correlations, the group most susceptible to ozone was that comprising children aged 8-15 years. This finding is consistent with previous reports [17]. For the total population, we found an inverse correlation, probably because of other factors that affect the pediatric population or because the values were obtained using different sampling devices.

The relationship we found between air pollutants and pediatric admissions to the ED in the scatterplots is similar to those obtained in other cohorts in Spain [32-33].

In industrialized countries, the prevalence of sensitization to pollen has increased in recent decades, probably owing to the interaction between pollen grains and air pollutants mainly in large cities [30,34]. Pollen concentrations have been linked to increases in the frequency of ED visits. In Madrid, data from 3 cohorts have demonstrated this association in the past 20 years [14,35,36]. Our results confirm the importance of grass pollen allergens as relevant triggers of asthma attacks during springtime, particularly as pollination peaks in May (34% of allergic patients were attended in the ED owing to exacerbations during this month). This percentage probably underestimates the number of sensitized patients attending the ED because of the low percentage of referrals to our unit (22.3% in total).

Interestingly, we did not find any correlation between ED admissions and the other pollen families analyzed (*Cupressus arizonica, Olea europaea*) or molds (*Alternaria alternata*). Further investigations must be designed to seek alternative explanations for these findings.

One of the main limitations when studying asthma in the pediatric population is the lack of objective diagnostic tools, with the result that the diagnosis is usually based on clinical data. Because this is a retrospective study, some elements of the ED visits may not have been recorded thoroughly, such as classification of the episodes by severity. Moreover, follow-up of these patients needs to be appropriate in order to clearly assess the probable causes of multiple exacerbations.

Data regarding pollutants were extracted using 2 different measurement sites—Plaza Castilla Station (NO_2, PM_{10}) and Barrio El Pilar station (ozone)—and the actual address of the patients was not registered. Both stations covered living areas considered for this analysis. However, since we do not know the distance from patients' homes and the measurement tools used, we cannot estimate individual data for exposure to pollutants. This might also explain the differences between data for our sample and previously published data.

Our study was conducted in one of the largest pediatric EDs in Madrid. Therefore, it seems reasonable to assume that a 1-year sample of care in this type of pediatric ED can be extrapolated to other tertiary hospitals. However, the same results probably cannot be generalized to smaller health care institutions, not only because of the heterogeneity of treatment protocols, but also because of the expected variability in terms of exposure to air pollutants. Individual data should also be recorded regarding exposure to irritants such as smoke.

Despite the limitations of this observational retrospective study, our results highlight the complex interaction between the multiple factors that can affect asthma in the pediatric population. In addition, this large-scale study stresses the need for a multidisciplinary approach in the follow-up of pediatric patients with asthma exacerbations.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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M Andreína Marques-Mejías

Department of Allergy
Hospital Universitario La Paz
Paseo de la Castellana, 261
Madrid, Spain
E-mail: mandreina.marques@gmail.com

ORIGINAL ARTICLE

Association Between Seasonal Allergic Rhinitis and Air Pollution, Meteorological Factors, and Grass Pollen Counts in Madrid (1996 and 2009)

Cabrera M[1], Garzón García B[2], Moreno-Grau S[3], Subiza J[4]

[1]Consulta de Alergia Hospital Los Madroños, Brunete, Spain
[2]Unidad de Estadística, Secretaría Adjunta de Informática, Consejo Superior de Investigaciones Científicas (CSIC), Madrid, Spain
[3]Departamento de Ingeniería Química y Ambiental, Universidad Politécnica de Cartagena, Spain
[4]Clínica Subiza, Madrid, Spain

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Abstract

Objective: The aim of this study was to assess the relationship between meteorological and pollution-related variables and the symptoms of patients with seasonal allergic rhinitis due to sensitization to grass pollen during 2 different time periods in Madrid, Spain.
Methods: Between March 23 and December 31 in 1996 and 2009, we carried out a daily count of grass pollen grains (Burkard spore trap) and recorded the rhinitis symptom scores in 2 groups of patients with a history of seasonal allergic rhinitis (n=25 in 1996 and n=23 in 2009). Descriptive statistics of the same variables during the study periods were recorded. Associations between variables were assessed using the paired-samples Wilcoxon test and categorical principal component analysis (CatPCA, SPSS24 package).
Results: The mean symptom score was low in 1996 and moderate in 2009. The 1996 and 2009 CatPCA analysis explained around 66.4% and 70.5% of the variance, respectively. The strongest relationships in 1996 were between symptoms and grass pollen counts (R=0.55) and between temperature and ozone (R=0.63). In 2009, the association between temperature and pollution-related variables was even stronger than in 1996 (ozone [R=0.53] and PM_{10} [R=0.34], with a positive sign in both cases).
Conclusions: The effect of temperature and pollution (mainly ozone, even at lower atmospheric concentrations than in established guidelines for effects on health) may have contributed to the higher seasonal allergic rhinitis symptom score recorded in 2009.

Key words: Grass pollen grains. Pollution. Temperature. Ozone. Categorical principal component analysis.

Resumen

Introducción: El objetivo de este estudio fue evaluar las relaciones de las variables meteorológicas y contaminantes en los síntomas de los pacientes con rinitis alérgica estacional con sensibilización al polen de gramíneas durante dos períodos diferentes en Madrid.
Métodos: Durante el período del 23 de marzo al 31 de diciembre de 1996 y 2009, se realizó un recuento diario de granos de polen de gramíneas (*Burkard spore trap*) y puntuación de síntomas de rinitis en dos grupos de pacientes (n = 25 en 1996 y n = 23 en 2009) con historia de rinitis alérgica estacional. Para describir cómo se relacionan las variables, se realizaron estadísticas descriptivas de las mismas variables en los períodos de estudio de 1996 y 2009, contraste no paramétrico pareado de Wilcoxon y un análisis de componentes principales (CatPCA, SPSS24).
Resultados: El valor medio de la puntuación de síntomas en 1996 fue bajo y en 2009 moderado. El análisis CatPCA de 1996 y 2009 explica aproximadamente el 66,4% y el 70,5% de la varianza, respectivamente. La relación más fuerte en 1996 fue entre los síntomas y los recuentos de polen de gramíneas (R = 0,55), la temperatura y el O_3 (R = 0,63). En 2009, la relación entre la temperatura y las variables de contaminación fue incluso mayor que en el período de 1996: O_3 (R = 0,53) y con PM10 (R = 0,34), en ambos casos con un signo positivo.
Conclusiones: El efecto de la temperatura y la contaminación (principalmente O_3, incluso a concentraciones atmosféricas más bajas que las pautas establecidas sobre sus efectos en la salud), podría contribuir a la mayor puntuación de síntomas de rinitis alérgica estacional observada en 2009.

Palabras clave: Polen de gramíneas. Contaminación. Temperatura. Ozono. Análisis por componentes principales.

Introduction

As many as 44 types of pollen coexist in Madrid, Spain, although seasonal allergic rhinitis is produced mainly by 4 specific types: Cupressaceae (January and February), Platanaceae (March and April), Poaceae, and Oleaceae (May and June) [1].

Grass pollen is the most allergenic in the area, and up to 88% of patients are polysensitized [2]. Thus, most allergy patients in the center of Spain are sensitized to 4 or 5 different types of pollen, thus implying a longer duration of symptoms throughout the year and greater difficulty when applying pharmacological or prophylactic treatment. In the Alergológica 2015 study, the prevalence of rhinitis (all causes) increased from 55.5% to 62.0% (P<.001) compared with the previous study (2005), and grass pollen grains were the principal allergen implicated, with prevalence increasing from 34.8% to 73.7%. In Madrid, this increase was from 61.9% to 87.1% [3]. The age range most affected by seasonal allergic rhinitis is 25-34 years. Consequently, the disease mainly affects young adults, although the overall range is very wide, affecting patients of practically any age [3].

Climate change is increasing the length and intensity of the pollen season, with a significant impact on the millions of patients who already have allergies [4]. Increasing temperatures lead to earlier and longer pollen and allergy seasons, with more frost-free days and earlier and longer flowering seasons [5,6]. Higher temperatures also increase ozone production, which sensitizes the respiratory tract to allergens [7]. Higher carbon dioxide levels cause greater plant growth, resulting in increased pollen production and increased pollen potency [8]. More fall-winter precipitation further contributes to increased pollen production [9].

The aim of this study was to assess the relationships between meteorological and pollution-related variables and the symptoms of patients with seasonal allergic rhinitis due to sensitization to grass pollen during 2 different time periods in Madrid.

Material and Methods

During the periods March 23 to December 31, 1996 and March 23 to December 31, 2009, we carried out the following studies:

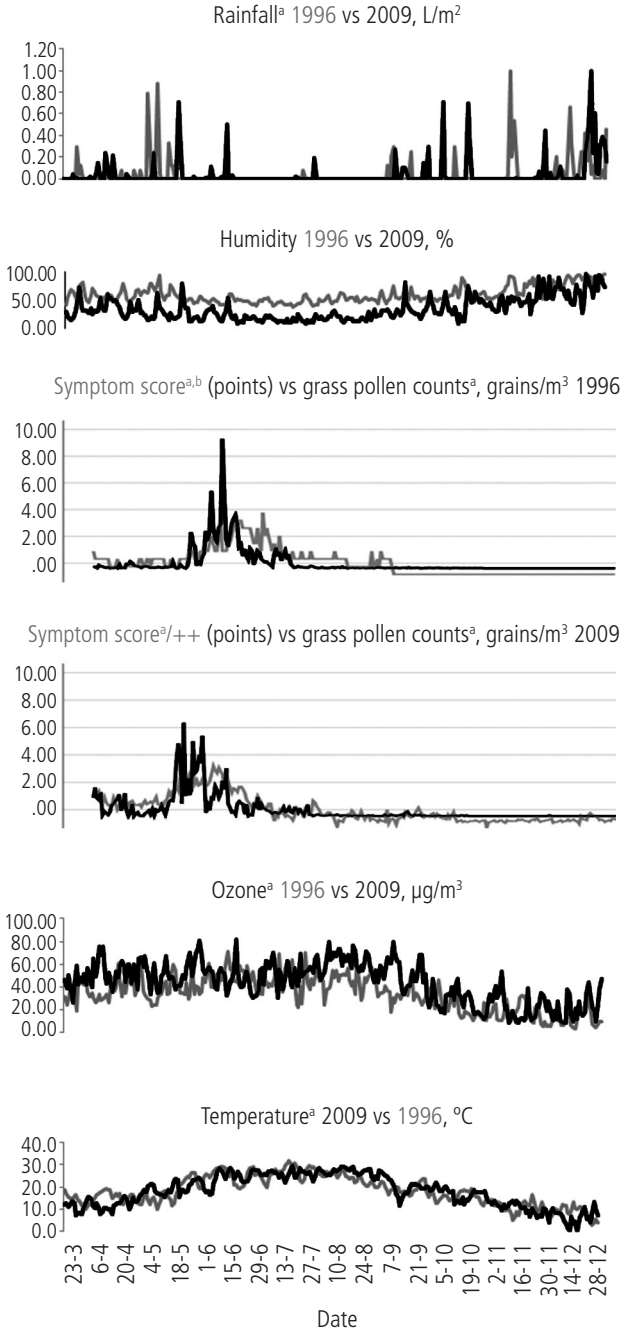
- Daily grass pollen count using a Burkard collector (Clínica Subiza, Madrid), as previously described [1]. The main pollen season ran from the first date with 10 grains/m^3 on 3 consecutive days until the date of the last 3 consecutive records at the same level.
- Daily measurement of meteorological data (temperature, rain, humidity, wind speed) using data from Barajas-Madrid station (National Meteorological Agency).
- Daily measurement of pollution (ozone, CO, SO_2, NO_2, PM10) from the Escuelas Aguirre station (Madrid City Council).

Table. Descriptive Statistics of the Main Variables Analyzed During Both Study Periods: 23 March to 31 December in 1996 and 2009

Variables[a]	No. valid	Missing	Mean (SD) Median (Minimum- Maximum)	No. valid	Missing	Mean (SD) Median (Minimum-Maximum)
Symptom score	284	81	1.45 (1.74) 1.00 (0.00-8.00)	284	81	2.33 (1.34) 1.74 (0.61-6.61)
Grass pollen counts, grains/m^3	284	81	21.8 (57.2) 2.00 (0.00-552.0)	284	81	8.28 (17.9) 1.00 (0.00-121.0)
SO_2, µg/m^3	284	81	17.7 (9.25) 15.0 (6.00-61.0)	284	81	9.87 (3.42) 9.00 (6.00-21.0)
CO, µg/m^3	284	81	13.7 (6.71) 12.0 (5.00-40.0)	284	81	0.40 (0.13) 0.37 (0.19-1.02)
NO_2, µg/m^3	284	81	64.2 (17.0) 61.5 (32.0-117.0)	282	83	52.6 (14.0) 51.0 (17.0-96.0)
PM10, µ/m^3	284	81	35.2 (8.75) 34.0 (19.0-61.0)	128	237	30.0 (10.7) 29.0 (10.0-60.0)
O_3, µg/m^3	284	81	33.7 (15.1) 34.0 (3.00-71.0)	284	81	43.6 (17.9) 45.0 (8.00-82.0)
Temperature, ºC	284	81	18.1 (6.64) 17.8 (2.50-31.7)	284	81	18.0 (7.31) 18.1 (0.00-29.8)
Humidity, %	284	81	59.0 (13.6) 55.0 (37.0-95.0)	284	81	34.1 (19.8) 29.0 (8.00-95.0)
Wind speed, m/s	284	81	16.8 (6.06) 16.0 (7.00-39.0)	284	81	14.8 (8.70) 13.0 (0.00-51.0)
Rainfall, L/m^2	284	81	0.87 (2.99) 0.00 (0.00-24.0)	284	81	8.17 (26.7) 0.00 (0.00-209.0)

[a]Significant differences (P=.000, nonparametric paired samples Wilcoxon test) were found for all variables except temperature.

– Daily count of rhinitis symptoms in 2 groups of patients (n=25 in 1996 and n=23 in 2009, after completion of daily symptom cards at home) selected on the basis of a history of seasonal allergic rhinitis during the previous 2 years. Each patient was evaluated based on a medical assessment that included a clinical history, clinical examination, and skin prick tests. The mean age of patients was 30.95 (range, 16-47) years, and all patients (100%) were sensitized to grass pollen (with wheals of 4+ [AR > AH: AR=resulting area in mm^2: allergen area – saline area]; AH [histamine area – saline area]) and to Oleaceae, Platanaceae, and Cupressaceae pollen grains (43.5%, 30.4%, and 56.5%, respectively, with smaller wheals: 2+ to 3+). Two of the patients (2009) were sensitized to *Dermatophagoides pteronyssinus* and 4 (2009) to cat dander, although the sensitization was not clinically relevant. Nasal symptoms (sneezing, itching, congestion, and rhinorrhea) were assessed in patients clinically sensitized to grass pollens in the previous 2 years. A daily electronic card was completed on a daily basis with the following scale: 0, absence of symptoms; 1, mild symptoms; 2, moderate symptoms; and ≥3, severe symptoms.
– Descriptive statistics of the same variables in 1996 and 2009 and a paired-samples Wilcoxon test (SPSS24 package) for non-normally distributed variables in order to enable any significant differences to be seen at the 2 observation points for each of the study variables.
– Categorical principal component analysis (CatPCA, SPSS24 package) [10] to describe associations between variables associated with allergy (grass pollen grains and symptoms). All of the variables were assessed in an initial analysis, and the most important or representative associations were established in the final analysis. This test allowed us to reduce associations between the variables to 2D and to represent them graphically in both the periods studied. The variance explained by this methodology expresses the ability of the analysis to summarize the relationships between the variables included.



[a]Daily measurement of all variables.
[b]Mean seasonal allergic rhinitis symptoms score recorded by 25 patients in 1996 and 23 patients in 2009.

Figure 1. Plots of the main variables studied during both time periods 23 March to 31 December in 1996 and 2009.

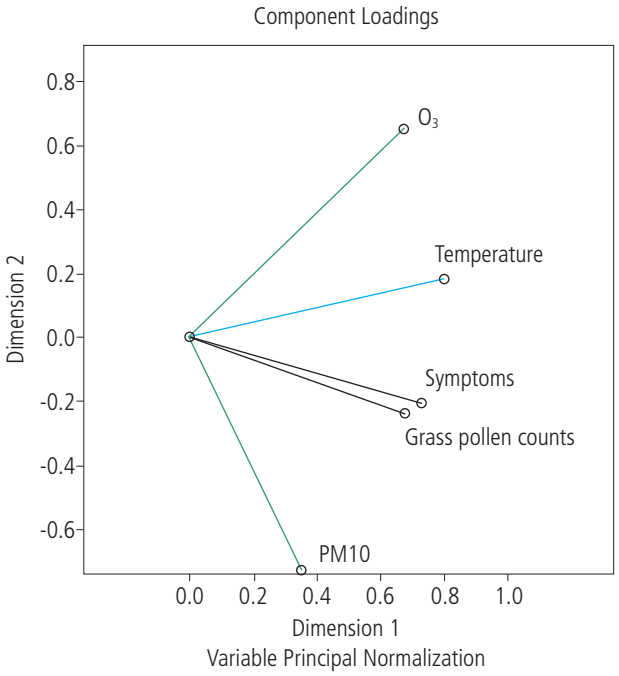
Results

Total yearly grass pollen counts in 1996 and 2009 were 6588 grains/m^3 and 2556 grains/m^3, respectively (seasonal maximum counts: June 1, with 552 grains/m^3, and May 11, with 121 grains/m^3, respectively). The main pollen seasons lasted from May 13 to July 9 and from May 2 to July 11, respectively.

The Table includes descriptive statistics for all variables for both years, highlighting significant differences (P=.000) based on the paired-samples Wilcoxon test, especially for symptoms (higher score in 2009). The exception was for temperature. This study is limited by the nonavailability of the trend in the variables studied over the years, although the temperature in Madrid has tended to increase over the last 38 years, with temperature increases of 1.4ºC during May-July from 1979 to 2016 (ie, 0.36ºC per decade) [11].

Figure 1 shows plots of the main variables studied during both time periods; the samples show that increases in grass pollen grain counts are accompanied by increases in the symptom score (mean value for 1996, low score; mean value for 2009, moderate score).

The CatPCA analysis explains around 66.4% of the variance in 1996 and 70.5% of the variance in 2009. In both cases, these percentages account for the relationships between the variables.

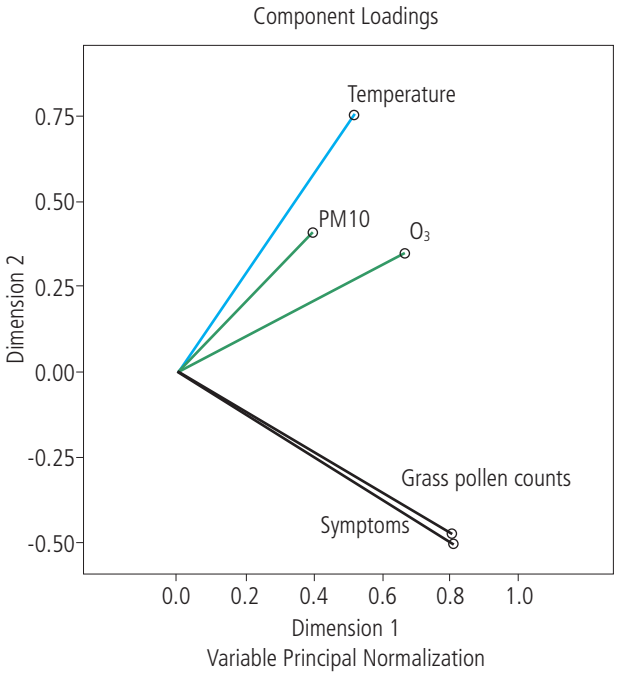


CatPCA analysis explains 66.4% of the variance

Correlations Transformed Variables

	Symptoms	Grass pollen counts	PM10	Ozone	Temperature
Symptoms	1.000		0.179		
Grass pollen counts		1.000	0.146		
PM10	0.179	0.146	1.000	-0.097	0.334
Ozone	0.278	0.222	-0.097	1.000	0.626
Temperature	0.337	0.281	0.334	0.626	1.000

Figure 2. CatPCA 1996.



CatPCA analysis explains 70.5% of the variance

Correlations Transformed Variables

	Symptoms	Grass pollen counts	PM10	Ozone	Temperature
Symptoms	1.000		0.118		
Grass pollen counts		1.000	0.186		
PM10	0.118	0.186	1.000	0.056	0.359
Ozone	0.353	0.259	0.056	1.000	0.527
Temperature	0.048	0.100	0.359	0.527	1.000

Figure 3. CatPCA 2009.

In the 1996 CatPCA analysis, symptoms were related mainly to grass pollen (R=0.55) and, to a lesser extent, to temperature (R=0.38) and ozone (R=0.28); all relationships had a positive sign (Figure 2). With PM10, the correlation coefficient was much lower (R=0.18). Temperature is related to pollen counts, symptoms, PM10, and ozone (the correlation is particularly strong for ozone, R=0.63). Given the position and proximity of the lines on the graph, the variables with the closest association are symptoms and grass pollen counts (R=0.55) and temperature and ozone (R=0.63). In both cases, the relationships are positive, meaning that high values in one parameter correspond to high values in the other, ie, higher pollen levels, higher symptoms, higher temperatures, and higher ozone levels. Temperature is also clearly related to symptoms and PM10 (R=0.34 and R=0.33); the sign for this relationship is also positive. Consequently, high temperature levels are related to high values for symptoms and PM10. Values for the association between temperature and grass pollen counts are much lower, although the sign continues to be positive (R=0.28).

Also noteworthy is the weak association between the pollution variables ozone and PM10, which, therefore, occupy distant, almost perpendicular positions on the graph. In addtion, this relationship has a negative sign (high levels of PM10 reduce ozone levels).

The 2009 CatPCA analysis (Figure 3) explains 70.5% of the variance. The relationship between symptoms and pollen becomes stronger (R=0.81) and remains positive, as does that of ozone, albeit to a lesser extent (R=0.35), with both coefficients higher than in 1996.

The difference between the analyses for 2009 and 1996 is in the association between the allergy variables and the rest of the variables (as can be clearly seen in the positions occupied by the variables on the graph). In contrast to the 1996 period, the 2009 variables (symptoms and grass pollen counts) are associated mainly with ozone (R=0.35, R=0.26). Therefore,

ozone is the closest variable in the 2009 graph and is associated with PM10, yet has almost no relationship with temperature (which is distant and almost perpendicular on the graph). The relationship between temperature and pollution variables is even higher than in the 1996 period (ozone [R=0.53] and PM10 [R=0.34], with a positive sign in both cases). The pollution variables (ozone and PM10) are still only slightly associated (R=0.06), although, here, the relationship is still positive.

Discussion

We found a higher symptom score in the 2009 period, despite lower pollen counts, than in the 1996 period. However, it is important to remember that this was a year with lower humidity, similar temperatures, and higher ozone levels (albeit lower than threshold). Consquently, these factors may have affected the longer duration and intensity of the grass pollen season that year. The specific atmospheric conditions in Madrid in spring, where marked instability leads pollen deposited on the ground to be lifted, may also have contributed.

In southern Spain, the grass pollen season is now longer as a result of rising temperatures [12]; the same is true for the Oleaceae pollen season [13]. The increase in temperature in this geographical area seems to have a positive effect on the intensity of flowering, with longer pollination periods that are often more intense. In this study, the main pollen season in 2009 was 13 days longer than in 1996. The grass pollen forecast in Madrid is always announced by March. Rainfall from October 1995 to March 1996 in Madrid was twice that of the previous period (October 1994-March 1995), thus leading to a 4-fold higher number of grains in 1996 than in 1995. Furthermore, the Spanish Society of Allergy and Clinical Immunology (SEAIC) estimated that the cumulative concentrations of grass pollen counts in 2009 exceeded 5100 grains/m^3, compared with 4000 grains/m^3 recorded in 2008. Nevertheless, the lower grass pollen counts collected in 2008 were probably due to the cleaner rain effect observed in May, which coincided with the peak grass pollen period (Figure 1), albeit in a more polluted atmosphere and with more allergenic activity, as shown by the higher seasonal allergic rhinitis score.

We suggest that this finding could be associated with the coadjuvant effect of temperature and pollution (mainly ozone), which generates more potent allergens, as well as with the direct relationship between the greater level of atopy in the 2009 group than in the 1996 group. Ozone increases allergenicity (induces larger wheals and flares in skin prick tests) [14], and exposure of *Phleum pratense* pollen to increasing ozone concentrations (from 100 ppb up to 5 ppm) results in a significant increase in naturally released pollen cytoplasmic granules, which also contain allergens [15].

Pollution is a possible cause of oxidative stress, and this stress is responsible for the higher prevalence of seasonal allergic rhinitis, which intensifies in activity as a defense from environmental pollution, thus strengthening allergenicity [16]. Pollutants such as SO_2, NO_2, and ozone can alter the allergenic proteins of pollen [16,17].

Ozone is a pollutant that usually reaches higher values in areas far from the sources of emission, that is, in semiurban and rural areas. The atmospheric conditions present in heat waves favor the formation of tropospheric ozone from precursors [18]. During the summer, the excessively high temperature in Madrid (higher than the threshold of 36.5ºC) coincides with the days on which the population must be warned about high concentrations of ozone (higher than the threshold of 180 μg/m^3) [18]. These thresholds were not exceeded in 2009, although mean annual values tended to increase [19]. In Madrid in 2017, the number of times the ozone threshold was exceeded (>25 times) was recorded in the 2011-2017 report [20]. As ozone is a secondary pollutant, the measures adopted were aimed at reducing the emission of precursors, mainly NOx and volatile organic compounds [18]. In a recent report from Ecologistas en Acción (2018), 2 of the stations measured high ozone values in winter that were similar to those recorded in spring in the same places (San Agustín de Guadalix and Puerto de la Morcuera), namely, 70 and 80 μg/m^3 [21].

With regard to photochemical pollutants or the synergistic effect of ultraviolet radiation on pollutants, study of the effects of UV-B rays and ozone shows that the pollen tube was shortened considerably, more than by the stress itself, despite low levels of ozone [22].

Differences have been found in the allergenicity of pollens from groups of trees of the same species and grass pollen, which, although relatively close in terms of taxonomy, are found in areas with different pollution levels (city/countryside) and temperatures (valley/mountain) [23]. In Spain in 2002, Armentia et al [23] reported that the grass pollen in rural areas of the province of Valladolid was less damaged than the same species in urban areas, where grass pollen is subject to a polluted environment, repeated mowing that lets very few spikes flourish, and pesticides applied by local authorities [23]. In 2007, Feo-Brito et al [24] reported that the air pollution levels in Puertollano (high pollution levels) were associated with a greater risk of asthma symptoms in pollen-allergic asthmatic patients than in a similar group from Ciudad Real (lower pollution levels) [24]. The largest contribution was by ozone, especially in Puertollano [24]. In 2007 and 2010, Mur Gimeno et al [25] and Feo-Brito et al [26] reported that pollen-allergic asthmatics in Puertollano presented poorer clinical progress and became decompensated earlier than those from Ciudad Real, and that this could be due to air pollution. Consequently, urbanization and high levels of vehicle emissions induce more symptoms of bronchial obstruction (in particular bronchial asthma) in people living in urban areas than in those living in rural areas.

In the eastern United States and Europe, the highest regional ozone levels are recorded when a slow-moving, high-pressure system develops in summer. This is when the days are longest, when solar radiation is most direct (the solar zenith angle is lower), and air temperatures are high. As the slow-moving air in the shallow boundary layer passes over major metropolitan areas, precursor concentrations rise; as the air slowly flows around the high-pressure system, photochemical production of ozone occurs at peak rates [27]. We suggest that high temperatures in Madrid, even with low levels of ozone concentrations (which was higher 13 years later), could be a factor that has contributed to the increase in symptoms even at lower grass pollen counts in 2009 than in 1996.

Ozone levels are mostly higher in rural areas than in cities. Ozone is degraded by NO, which is also involved in its formation. This degradation occurs more often in cities than in rural areas, because there is more NOx in cities. For this reason, ozone concentrations are higher in rural areas than in cities [27].

According to the review of evidence on health aspects of air pollution in the REVIHAAP Project (Technical Report) (2013) [28], the European threshold of 180 μg/m^3 for informing the population may thus not be viewed as an effective threshold value under which absolutely no one will experience any effect at all. However, the World Health Organization (WHO) postulated that the effects of concentrations lower than 200 μg/m^3 will be limited in severity and will only prevail in less than 5% of the total population [29]. Warning the whole population at lower concentration levels is therefore not advised. As such, the threshold values can be considered a sliding scale, and—albeit somewhat artificially—it is possible to talk about a mild response at (hourly mean) concentrations of 180-240 μg/m^3, a moderate response at 240-360 μg/m^3, and a severe response above 360 μg/m^3 [28,29]. The review concludes that a considerable amount of new scientific information on the adverse health effects of particulate matter, ozone, and NO_2 observed at levels commonly present in Europe in recent years [28]. This new evidence supports the scientific conclusions of the WHO air quality guidelines, last updated in 2005, and indicates that, in some cases, the effects occur at air pollution concentrations lower than those serving to establish these guidelines [29].

Pollution particles also contain diesel exhaust particles. At present, 70% of all particles and 90% of those <5 μm (respirable particles) are produced from its combustion, which induces important biological changes, such as a more marked T_H2 response [30,31].

The rising frequency of obstructive respiratory diseases during recent years, in particular allergic asthma, can be partially explained by changes in the environment, with the increasing presence in the atmosphere of chemical triggers (particulate matter and gaseous components such as NO_2 and ozone) and biologic triggers (aeroallergens). Consequently, measures need to be taken to mitigate the future impact of climate change and global warming [32]. Over the last 50 years, the earth's temperature has risen markedly, likely because of growing concentrations of anthropogenic greenhouse gas [32]. For this reason, it is important to emphasize to patients that climate change is increasing exposure to allergens and suggest what they can do to minimize their exposures and thus reduce allergy and asthma symptoms, such as checking pollen levels frequently. In Spain, patients can sign up for free alerts from the Spanish Society of Allergy and Clinical Immunology Aerobiology Network. For patients with asthma, it is important to check ozone levels.

Conclusions

The effect of temperature and pollution (mainly ozone, even at lower atmospheric concentrations than those established in guidelines about its effects on health) could contribute to the higher seasonal allergic rhinitis symptom score observed in 2009.

We highlight the need to continue research into the impact of these changes and into strategies and policies to reduce greenhouse gas emissions and air pollution.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentation

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Martha Cabrera Sierra

Servicio de Alergia
Hospital los Madroños
Carretera M-501, Km 17,9
28690 Brunete, Madrid
E-mail: marthacs65@gmail.com

Usefulness of the Basophil Activation Test in the Diagnosis of Hypersensitivity to Amiodarone

Vílchez Sánchez F[1], Lluch Bernal M[1], González Muñoz M[2], Marques Mejías MA[1], Quirce S[1,3], Cabañas Moreno R[1]
[1]*Department of Allergy, Hospital La Paz Institute for Health Research (IdiPaz), Madrid, Spain*
[2]*Department of Immunology, Hospital La Paz, Madrid, Spain*
[3]*CIBER de Enfermedades Respiratorias, CIBERES, Madrid, Spain*

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Palabras clave: Alergia a amiodarona. Hipersensibilidad inmediata. Test de activación de basófilos.

Amiodarone is a class III antiarrhythmic agent that inhibits outward potassium channels. It also has class I sodium channel–blocking effects, class II antiadrenergic effects, and class IV calcium channel–blocking effects and is widely prescribed owing to its efficacy in the management of ventricular and supraventricular arrhythmia [1].

Although prolonged use of amiodarone may cause numerous adverse effects (affecting the thyroid gland, liver, lungs, eyes, and skin), hypersensitivity reactions to amiodarone are rare. Moreover, few case reports include a thorough allergy work-up (anaphylaxis confirmed with determination of mast cell tryptase levels and skin testing [2], angioedema confirmed with positive oral challenge results [3,4], and amiodarone-induced hypersensitivity pneumonitis confirmed with positive results in skin testing and basophil degranulation tests [5]).

We report the first 2 cases of immediate amiodarone hypersensitivity reaction with a positive basophil activation test (BAT) result. An anaphylactic reaction was recorded in 1 of the cases.

A 48-year-old man was referred to our allergy department after experiencing an anaphylactic reaction in the operating room. An intravenous injection of amiodarone (50 mg) to treat atrial fibrillation was followed immediately by a decrease in blood pressure (60/40 mmHg), oxygen desaturation (<90%), and rash all over his body. The patient had also received treatment with etomidate, fentanyl, and rocuronium to induce anesthesia for cholecystectomy.

He was treated with methylprednisolone 100 mg, hydrocortisone 100 mg, and infusion of noradrenaline at 30 mL/h. The symptoms of anaphylaxis resolved gradually. Tryptase levels were as follows: 4.79 µg/L when the anaphylaxis occurred, 4.6 µg/L 2 hours later, and 1.47 µg/L on the following day.

The medical history revealed dilated cardiomyopathy, hypothyroidism, and permanent atrial fibrillation. Nevertheless, the patient had no history of allergy. Negative results were recorded in the skin prick test with an anaphylaxis panel (including latex, panallergens, and the most allergenic food) and prick and intradermal tests with etomidate, fentanyl, and rocuronium.

In an attempt to clarify the underlying mechanism and the culprit agent, BAT was performed with etomidate (1-100 µg/mL), fentanyl (1-100 µg/mL), rocuronium (5-500 µg/mL), and amiodarone before skin tests for safety reasons owing to the severity of the initial reaction.

The BAT methodology is detailed elsewhere [6-8]. Briefly, 100 µL of heparinized blood was incubated with 20 µL of intravenous amiodarone (0.2, 0.1, and 0.01 µg/mL) for 15 minutes at 37ºC. Negative and positive controls were included by incubating the blood without the drug and with 20 µL (10 mg/mL) of anti-IgE (BD Bioscience), respectively. Basophil activation was determined by CD63 upregulation using flow cytometry (FACSCanto II, BD Bioscience) for the identification and quantification of alterations in specific activation markers on the basophil surface membrane (using CD63/CD123/Anti-HLA-DR, BD Bioscience). At least 400 basophils were acquired. The results are expressed as the percentage of CD63-positive basophils and the stimulation index (SI, that is, the ratio of the percentage of activated basophils after stimulation to the percentage of activated basophils in negative controls). The result is considered positive when the percentage of basophils activated after stimulation with the drugs was 5% or more and the SI >3 [7].

BAT was positive with intravenous amiodarone (37% activation) (Figure), with an SI of 5.11 at an amiodarone concentration of 0.1 mg/mL (SI of 1 in the control) and 13.6

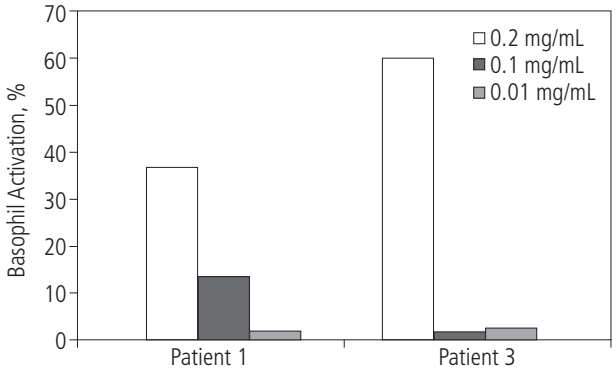

Figure. Basophil activation with intravenous amiodarone. Bars represent the percentage of CD63-positive basophils after incubation with amiodarone (0.2, 0.1, and 0.01 mg/mL).

at 0.2 mg/mL (0.8 in the control), and negative with etomidate, fentanyl, and rocuronium. The patient was diagnosed with anaphylaxis to amiodarone.

An 84-year-old woman with hypertension and hyperlipidemia and no history of allergy was examined in the emergency room for palpitations. She had paroxysmal atrial fibrillation and was treated with intravenous amiodarone. Fifteen minutes after the amiodarone infusion she developed severe genital itching and redness with rash. The symptoms resolved with antihistamines and corticosteroids.

The patient was referred to our allergy department. An appropriate clinical history was taken, and a complete physical examination was performed. The total serum IgE level was 113 kU/L. BAT with amiodarone based on the protocol described above was performed for safety reasons. The result was positive with intravenous amiodarone (60% activation) (Figure), with an SI of 30 and an amiodarone concentration of 0.2 mg/mL (SI of 1.3 in the control); therefore, the patient was diagnosed with immediate allergic rash induced by amiodarone.

We present the first 2 cases of immediate hypersensitivity to amiodarone with a positive BAT result.

Hypersensitivity reactions to drugs account for 15% of all adverse drug reactions [10] and represent a major health problem with significant morbidity and mortality. In the diagnosis of drug hypersensitivity, in vitro measurement of specific IgE is available for a limited number of drugs (it is often impossible to bind the molecules or their metabolites into a solid phase), which generally display low sensitivity and for which BAT is a very suitable complementary approach. Although rare, systemic reactions with skin tests have been described.

BAT seems to be a promising complementary in vitro technique in the allergological work-up of anaphylactic reactions to drugs.

The sensitivity of BAT in the diagnosis of drug allergy is about 50%, and the specificity can reach 93% [7], although these data depend on the drug in question [10].

BAT is recommended for diagnosing hypersensitivity reactions to penicillins and neuromuscular blocking agents and can complement other in vitro tests. In addition, BAT can be recommended for diagnosing IgE-mediated allergy to pyrazolones, fluoroquinolones, and radiocontrast media. In life-threatening reactions or in high-risk patients, BAT, when available, should be performed before in vivo approaches, including skin testing, according to the position paper of the ENDA/EAACI Drug Allergy Interest Group on in vitro testing for drug hypersensitivity reactions [10]. Despite the fact that we report only 2 cases, our results indicate that BAT is a useful diagnostic technique in hypersensitivity reactions to amiodarone.

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Conflicts of Interest

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Francisca Vílchez Sánchez
Servicio de Alergología
Hospital Universitario La Paz
Paseo de la Castellana, 261
28046 Madrid, Spain
E-mail: franvilsan@gmail.com

Induction of Oral Tolerance in a Case of Severe Allergy to Coconut

Hernández-Santana GL[1], Rodríguez-Plata E[1], González-Colino CE[1], Martínez-Tadeo JA[1], Bartolomé B[2], García-Robaina JC[1], Pérez-Rodríguez E[2]

[1]*Allergy Department, Hospital Universitario La Candelaria, Santa Cruz de Tenerife, Spain*

[2]*Spain Research and Development Department, Roxall, Bilbao, Spain*

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Palabras clave: Inducción a la tolerancia oral. Alergia. Coco.

Food allergy has increased in frequency in the last 2-3 decades. Some studies report a prevalence of up to 10% [1] depending on the study population (age range, dietary habits, allergen exposure, geographic location) and on the evaluation method used. In addition, more globalized dietary habits mean that it is increasingly frequent to find patients sensitized to allergens that are not part of traditional Western cuisine, such as coconut.

Several cases of coconut allergy have been reported. Most were systemic reactions and anaphylaxis [2-7]. We present the case of a patient who underwent oral desensitization to treat coconut allergy.

A 47-year-old Thai woman living in Tenerife (Canary Islands, Spain) was assessed at our unit for suspected coconut allergy. She had a previous history of severe allergic rhinoconjunctivitis and sensitization to house dust mite that were treated with specific immunotherapy, to which she responded well. The patient reported her first coconut allergy episode 4 years earlier. She presented with dysphonia, dyspnea, and palmoplantar pruritus immediately after eating grated coconut and subsequently reduced her intake of coconut, albeit not entirely. She occasionally experienced oropharyngeal pruritus after eating small amounts of coconut-containing foods, until she experienced a second episode of anaphylaxis with coconut milk curry and was referred to our unit.

Skin tests were positive for commercial coconut extract (8 mm), Aroy-D coconut milk (8 mm), Dunn coconut milk (7 mm), and dehydrated coconut (8 mm) with a 4-mm histamine-induced wheal.

Coconut-specific IgE measured using the ImmunoCAP System (Thermo Fisher) was 17.7 kUA/L.

Oral challenge with coconut milk Aroy-D was not performed owing to positive results in the rub test, namely, palmoplantar and oral pruritus and dysphonia that required treatment with adrenaline.

SDS-PAGE immunoblotting with coconut pulp extract and coconut milk extract was performed according to Laemli [8]. IgE-binding proteins of approximately 70 kDa, 66 kDa, 43/40 kDa, 26.5 kDa, 22 kDa, and 17 kDa were detected in coconut pulp extract, and bands of 45 kDa, 40 kDa, 37 kDa, 26 kDa, 24 kDa, and 20.5 kDa were revealed in coconut milk extract.

Table. Protocol, Adverse Reactions, and Treatment

First Phase	Dilution[a]	Dose, mL	Amount of Protein, g	Reaction	Treatment
Day 1	1/100	1	0.00016	No	
	1/100	2	0.00032	No	
	1/100	4	0.00064	No	
	1/100	8	0.00128	No	
	1/10	1.6	0.00256	No	
Day 2	1/10	1.6	0.00256	Pharyngeal pruritus	None
	1/10	3.2	0.00512	No	
	1/10	6	0.0096	No	
	1/1	1.2	0.0192	No	
	1/1	2.5	0.04	Pharyngeal pruritus	None
Day 3	1/1	2.5	0.04	No	
	1/1	7.5	0.12	Pharyngeal pruritus	Desloratadine 5 mg
Day 4	1/1	7.5	0.12	No	
Day 5	1/1	10	0.16	No	
Day 6	1/1	15	0.24	No	
Second Phase[b]		Dose, mL	Amount of Protein, g	Reaction	Treatment
Day 7		2	0.136	No	
Day 8		4	0.272	No	
Day 9		6	0.4	No	

[a]Dilution of coconut milk (Aroy-D) (60% coconut in water).
[b]Grated coconut (Hacendado).

The patient was diagnosed with coconut allergy and prescribed a strict avoidance diet and autoinjectable adrenaline. Nevertheless, she presented with a new episode of anaphylaxis after inadvertent contact with coconut and required adrenaline and emergency care.

As she went to Thailand every year and spent some months there, avoiding coconut was very difficult for her. In Thailand, coconut is a ubiquitous allergen that is found in sauces, soups, desserts, and bakery. Therefore, we proposed desensitization.

The protocol and adverse reactions and management are summarized in the Table. For the first phase, we used commercial coconut milk Aroy-D (60% coconut in water) administered with dose increases every 24 hours. The second phase was performed with increasing doses of grated coconut (Hacendado) at 48-hour intervals, with maintenance of the dose reached safely at home, until a dose of 6 g was reached. No reactions appeared during this phase. A maintenance dose of 6 g of grated coconut (0.4 g of protein) was prescribed 3-4 times per week. We did not increase the dose in order to avoid excess fat intake.

Today, 2 years after finishing the tolerance induction procedure, the patient maintains a regular intake of 6 g of grated coconut 3-4 times per week and follows an open diet, thus enabling the intake of any food with coconut as an ingredient, but not coconut itself. She has not presented new reactions. In a recent assessment, specific IgE levels to coconut had decreased to 1.98 kU_A/L.

Coconut is a tropical fruit obtained from the palm tree *Cocos mucifera*, which belongs to the Arecaceae family and is also known as tree nut. Coconut and products obtained from it are widely used in the food industry, as well as in body care products and medicines. Asian countries are leading consumers and exporters.

Coconut is an oval fruit that measures about 20-30 cm and weighs around 2.5 kg. It consists of a thick outer shell (exosperm), a thick intermediate layer (mesocarp), and a hard inner layer (endocarp) to which the pulp (endosperm) is attached. The endosperm is the edible part of this white and aromatic fruit. The internal space houses the coconut water.

The endosperm contains a high percentage of globulins and a smaller percentage of albumins. The 2 globulins described as food allergens to date are 7S (Coc n 2) and 11S (Coc n 4), also known as cocosin [8].

Owing to sensitization to these proteins, cases of cross-reactivity have been reported between coconut, walnuts, hazelnuts, and lentils [2,4,5]. Monosensitization to coconut has also been reported [3].

In the present case, allergenic proteins were not identified, although taking into account the molecular weights of the detected bands, some could correspond to subunits of 7S globulin (156-kDa, 24-kDa, 22-kDa, and 16-kDa). Protein sequencing may have helped to identify the culprit allergens.

At present, avoidance is the recommended treatment for coconut allergy. Such a measure could considerably impact quality of life in some cultures owing to widespread consumption, with the consequent risk of accidental contact. Oral tolerance has been successfully induced to treat food allergy, mainly to milk, egg, and peanut. For other foods, there are only single case reports. To our knowledge, this is the first report of desensitization to coconut. As sensitization profiles vary from patient to patient, we do not know whether patients sensitized to proteins such as cocosin would respond in the same way. Data on desensitization to milk and egg suggest that high titers of specific IgE against casein and ovomucoid correlate with a poorer outcome of desensitization [9]. A similar phenomenon may occur with coconut and other foods. Nevertheless, we think that desensitization should always be taken into consideration when a patient presents severe allergy to a food that is widely present in his or her environment.

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Conflicts of Interest

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Guacimara Lucía Hernández-Santana
Allergy Department
Hospital Universitario La Candelaria
Carretera del Rosario s/n
38010 Santa Cruz de Tenerife (Canary Islands) Spain
E-mail: guacim1@hotmail.com

Allergy and Anaphylactic Reaction to Loquat (*Eriobotrya japonica*) Are Induced by a Bet v 1 Homolog

Takaoka Y[1], Kondo Y[2], Matsunaga K[3], Aoki Y[3,4,5], Hasegawa E[3,5], Tokuda R[6], Fujisawa T[7], Morikawa A[8], Doi S[9]
[1]*Department of Pediatrics, Osaka Habikino Medical Center, Habikino, Japan*
[2]*Department of Pediatrics, Fujita Health University, Bantane Hospital, Nagoya, Japan*
[3]*Department of Integrative Medical Science for Allergic Disease, Fujita Health University School of Medicine, Nagoya, Japan*
[4]*Department of Respiratory Medicine, Fujita Health University School of Medicine, Nagoya, Japan*
[5]*General Research and Development Institute, Hoyu Co., Ltd., Nagoya, Japan*
[6]*Tokuda Family Clinic, Ise, Japan*
[7]*National Hospital Organization Mie Hospital, Tsu, Japan*
[8]*Kita Kanto Allergy Institute Kibounoie Hospital, Midori, Japan*
[9]*Faculty of Education, Shitennoji University, Habikino, Japan*

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Palabras clave: Alérgeno. Anafilaxia. *Eriobotrya japonica*. Mal d 1. Bet v 1 homólogo.

Fruit allergens from plants belonging to the *Rosaceae* (rose) family cross-react with pollen from plants of the Betulaceae (birch) family [1]. The causative allergens include Bet v 1 [2]. Typically, the primary symptoms of allergic reactions to Bet v 1 homologs are oral, although there are reports of generalized symptoms in the case of soybean allergies [3]. Loquat (*Eriobotrya japonica*), which is grown in Asia and several other locations, is also a member of the *Rosaceae* family.

Loquat allergy is diagnosed based on the clinical history and skin prick test results [4]. However, the primary allergen responsible for loquat allergy remains unidentified. In this study, we collected the serum of individuals with loquat allergy—including those who had experienced anaphylactic responses—to identify the causative allergen. This approach may lead to better prognostic and therapeutic options for the treatment of loquat allergy.

Fifteen patients with positive results in prick-prick testing with fresh loquat (wheal diameter of 3 mm or more) using a bifurcated needle (Tokyo M.I CO. Inc) were selected for this study (Supplementary Table 1). There were 13 complaints of oral symptoms induced by loquat and 2 of systemic symptoms. The titers of white birch pollen (Bet v 1) and Mal d 1–specific IgE antibodies were positive in all the patients for whom residual serum was available. Serum samples from 2 healthy volunteers without food allergy and umbilical cord blood from infants born at Fujita Medical University were used as controls.

The study was approved by the Research Ethics Committee of Fujita Medical University (Approval Number 10-216), and written informed consent was obtained from the patients and parents of patients aged under 19 years of age.

We electrophoresed the loquat extract proteins as described by Laemmli [5] using 4%-12% Bis-Tris gels (Thermo Fisher Scientific). Following SDS-PAGE, loquat-extracted proteins were transferred to an Immobilon-P polyvinylidene fluoride membrane (pore size, 0.45-μm; Millipore) and reacted with 20-fold diluted serum. Alkaline phosphatase–labeled polyclonal goat antihuman IgE (ε) antibody (Kirkegaard & Perry Laboratories) and 5-bromo-4-chloro-3-indolyl phosphate/nitroblue tetrazolium phosphatase substrates (1-Component System; Kirkegaard & Perry Laboratories) were used to detect IgE antibodies bound to the antigen. Target protein analysis with a mass spectrometer (TripleTOF; AB Sciex) was performed following the method reported by Yagami et al [6]. Protein analysis was performed using ProteinPilot software version 5.0 (AB Sciex), and proteins were identified using sequence data from UniProt.

Several protein bands that reacted with patient IgE were detected by immunoblotting; these bands ranged in size from 15 kDa to 50 kDa (Figure). The bands that reacted with more than half of the samples had a molecular weight of 15 kDa (93% positive) or 17 kDa (100% positive). In the immunoblot, the 15-kDa band was thinner than the 17-kDa band.

The 15- and 17-kDa bands were identified by mass spectrometry as Mal d 1.02 (accession number Q9S7M5). Protein coverage for each band was 100% (159 aa/159 aa for 17 kDa) and 95.6% (152 aa/159 aa for 15 kDa). The N-termini of the 15-kDa bands showed complete homology with Mal d 1. However, the degree of homology of the corresponding C-termini of the 15-kDa bands indicated C-terminal deletions after the 153rd amino acid sequence. We believe that the 15-kDa proteins may be identical to the 17-kDa proteins, albeit with C-terminal deletions. The binding capacity of 15-kDa proteins may be lower than that of 17-kDa proteins because the presence of epitopes has been reported at the C-terminus of Mal d 1 [7].

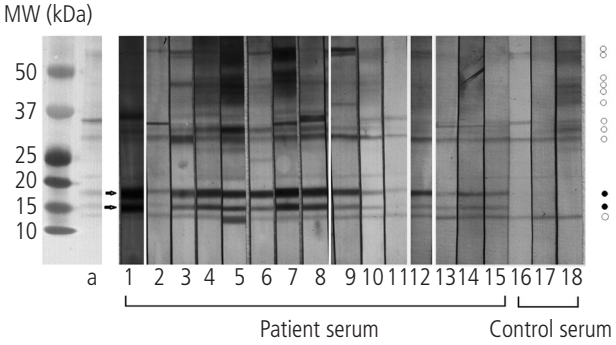

Figure. Immunoblot assay of sera from patients with confirmed loquat allergy and controls. More than half of the patients presented specific IgE–binding bands with relative molecular weights (MW) of 15 and 17 kDa (indicated by arrows and ●). The white circle indicates a specific IgE–binding band. Lane a, loquat proteins stained with amido black.

Interestingly, only 8 patients presented symptoms of apple allergy. Immunological analysis of Mal d 1 and Bet v 1 showed that diversity of allergenicity was determined mainly by the difference in allergen expression levels [8]. Bet v 1 homologs of loquat and Mal d 1 were also considered to have different expression levels. Further investigation of the differences between the properties of the Bet v 1 homolog of loquat and Mal d 1 is needed.

The limitations of this study included its small sample size, especially with respect to patients who experienced anaphylaxis. It is necessary to investigate more cases of anaphylaxis to loquat in order to determine the exact protein identities of possible allergens.

Our results indicated that the main allergen causing loquat allergy was a Bet v 1 homolog with a sequence similar to that of Mal d 1, but with a different immunoblot pattern. These findings may contribute to the development of improved prognostic and therapeutic tools for loquat allergy and loquat-related anaphylaxis.

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Conflicts of Interest

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Yasuto Kondo
Department of Pediatrics, Fujita Health University
Bantane Hospital
3-6-10 Otobasi, Nakagawa, Nagoya, Aichi, 454-8509
Japan
E-mail: ykondo@fujita-hu.ac.jp

Mepolizumab for the Treatment of Eosinophilic Granulomatosis With Polyangiitis: Our Experience

Díaz-Campos RM[1,*], Prudencio-Ribera VC[1,*], García-Moguel I[2], Fernández-Rodríguez C[2], Corral-Blanco M[1], Jarrin-Estupiñan ME[1], Melero-Moreno C[3]

[1]*Severe Asthma Unit. Pneumology Service, Hospital Universitario 12 de Octubre, Madrid, Spain*

[2]*Severe Asthma Unit. Allergology Service, Hospital Universitario 12 de Octubre, Madrid, Spain*

[3]*Institute for Health Research (i+12), Hospital Universitario 12 de Octubre, Madrid, Spain*

[*]*These authors contributed equally to this manuscript.*

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Eosinophilic granulomatosis with polyangiitis (EGPA) is considered a hybrid condition comprising a hypereosinophilic disorder and systemic antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis. It is characterized by the presence of asthma, eosinophilia, multiorgan involvement, and, sometimes, serum ANCA [1]. Its incidence has been reported to be 0.5 to 6.8 new cases per million habitants in the asthmatic population [2].

Systemic corticosteroids are the first-line treatment for EGPA. As their short- and long-term consequences are well-known, therapy is generally with corticosteroid-sparing immunomodulators, such as methotrexate or azathioprine [3].

Advances in knowledge of the pathophysiology of EGPA have led to a range of new treatments, such as omalizumab, which enables corticosteroids to be spared. However, reducing the dose of corticosteroids can increase the risk of severe EGPA flares [4]. Mepolizumab is an anti–interleukin-5 (IL-5) monoclonal antibody that reduces the absolute eosinophil count with clinical improvement in patients with other eosinophilic disorders, such as severe eosinophilic asthma [5].

Since the serum IL-5 level is increased in EGPA, targeted therapy against this cytokine has proven to be an effective alternative.

Mepolizumab has been used successfully in patients with relapsing or refractory EGPA at an intravenous dose of 750 mg once every 4 to 6 weeks [6,7]. In a multicenter phase 3 study, Wechsler et al [8] administered mepolizumab subcutaneously at 300 mg every 4 weeks and compared it with placebo in 126 patients [8]. Since mepolizumab led to more accrued weeks of remission than placebo, corticosteroid use could thus be reduced. Furthermore, the time to first relapse was longer with mepolizumab, and the exacerbation rate was significantly lower during the treatment period than during the nontreatment period. However, manifestations of EGPA recurred on discontinuation [6-8]. A systematic review of the results of these 3 studies was published in 2019 [9].

A recent post hoc analysis investigated the clinical benefit of mepolizumab in patients with relapsing or refractory EGPA and found that compared with the previous trial [8], significantly more patients experienced remission or a ≥50% reduction in corticosteroid dose or were relapse-free with mepolizumab, mainly in specific subgroups (blood eosinophil count <150/μL and weight >85 kg) [10].

We report 2 patients with corticosteroid-refractory EGPA treated successfully with 300 mg of subcutaneous mepolizumab every 4 weeks, according to the 2017 United States Food and Drug Administration recommendation for adult EGPA treatment.

A 43-year-old nonsmoking woman with a history of allergic asthma, positive prick test results for dog epithelium and house dust mite (*Dermatophagoides pteronyssinus, Dermatophagoides farinae, Lepidoglyphus destructor, Blomia tropicalis*), rhinosinusitis, and chronic suppurative otitis media presented multiple mononeuritis, erythematous skin lesions compatible with biopsy-proven vasculitis, and bilateral, patchy, ground glass opacities with an upper lung distribution in a chest computed tomography (CT) scan. Blood tests revealed a positive ANCA titer, eosinophilia (37%), increased IgE level (234 IU/mL), and a normal C-reactive protein level (CRP, 0.76 mg/dL). The patient was initially treated with prednisone 0.5 mg/kg/d, followed by 6 cyclophosphamide pulses (750 mg each) and azathioprine in order to spare treatment with corticosteroids. The lowest dose reached was 10 mg/d of prednisone, because symptoms recurred when the dose was reduced. Omalizumab was subsequently administered for 1 year, although it was discontinued because of lack of efficacy (frequent asthma exacerbations and episodes of suppurative otitis media). Subcutaneous mepolizumab was tried at 300 mg every 4 weeks. Before starting mepolizumab (while the patient was receiving 10 mg/d of prednisone), the laboratory values were as follows: eosinophil blood count, 13%; serum IgE level, 234 IU/mL; and CRP, 2.07 mg/dL. The Birmingham Vasculitis Activity Score (BVAS) was >3, and FEV_1 was 103% of predicted. Six months later, the asthma and otic symptoms had improved significantly, the Asthma Control Test (ACT) score had increased 3 points (22 to 25), blood eosinophilia and CRP had decreased (1.1% and 0.26 mg/dL, respectively),

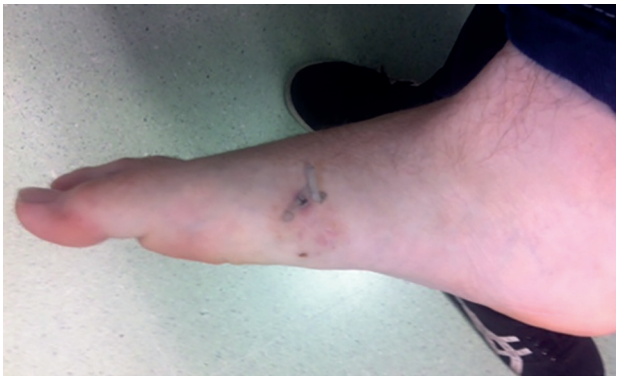

Figure. Erythematous skin lesions in a patient with eosinophilic granulomatosis with polyangiitis.

the BVAS was 0, and FEV_1 was 92% of predicted. There were no exacerbations, and we were able to reduce prednisone to 2.5 mg/d.

The other patient was a 27-year-old nonsmoking man with a long history of recurrent nasal polyposis and eosinophilic asthma treated with high-dose inhaled corticosteroids and long-acting $ß_2$-agonists, antileukotrienes, and oral corticosteroids. His symptoms were uncontrolled, and he had considerable peak flow variability (>15%). He presented with erythematous skin lesions (Figure) compatible with biopsy-proven eosinophilic extravascular granuloma and bilateral, patchy, ground glass opacities, with an upper lung distribution on the chest CT scan (Supplementary Material). The blood tests revealed eosinophilia (40%), increased CRP and IgE levels (2.28 mg/dL and 2970 IU/mL, respectively), and negative ANCA titers. FEV_1 was 115% of predicted. The patient was initially treated with prednisone 60 mg/d (0.75 mg/kg/d), with 10 mg/d the lowest dose reached because of recurrent symptoms when it was reduced. Subcutaneous mepolizumab was started at 300 mg every 4 weeks. Before starting mepolizumab, the laboratory values were as follows: blood eosinophil count, 35%; serum IgE, 996 IU/mL; and CRP, 0.26 mg/dL. The BVAS was >3, and FEV_1 was 108% of predicted. Six months later, the patient was asymptomatic without exacerbations. In addition, blood eosinophilia and IgE levels decreased (1.2% and 209 IU/mL, respectively), BVAS was 0, and FEV_1 was 89% of predicted. Therefore, the dose of corticosteroid was reduced.

No allergic reactions or adverse events or relapses were associated with mepolizumab in either case.

In summary, our results are consistent with those of previous studies [6-8]. Mepolizumab may be considered a therapeutic option in patients with refractory corticosteroid EGPA in order to reduce the dose of corticosteroids and their adverse effects and thus improve quality of life.

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Conflicts of Interest

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The remaining authors declare that they have no conflicts of interest.

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Vania Cecilia Prudencio Ribera
E-mail: prudenciovania@yahoo.com

Safe and Successful Protocol for Desensitization to Abiraterone

Núñez-Acevedo B[1], Rubio-Pérez M[1], Padial-Vilchez A[1], de la Morena-Gallego JM[2], Barro-Ordovás JP[3], Reche-Frutos M[1], Valbuena-Garrido T[1]

[1]*Allergy Department, Hospital Universitario Infanta Sofía, San Sebastián de los Reyes, Madrid, Spain*

[2]*Urology Department, Hospital Universitario Infanta Sofía, San Sebastián de los Reyes, Madrid, Spain*

[3]*Pharmacy Department, Hospital Universitario Infanta Sofía, San Sebastián de los Reyes, Madrid, Spain*

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Palabras clave: Abiraterona. Desensibilización. Alergia a medicamentos.

Abiraterone acetate is used for the treatment of castration-resistant metastatic prostate cancer. It acts as a selective inhibitor of the enzyme 17 α-hydroxylase/C17,20-lyase (CYP17). Expression of this enzyme is necessary for the synthesis of androgens in the testicles, adrenal glands, and prostate tumor tissue; therefore, inhibition leads to reduced production of androgens. Given that inhibition of CYP17 also leads to increased production of mineralocorticoids by the adrenal glands, abiraterone should be taken with prednisone. While abiraterone is generally well tolerated, the summary of product characteristics and various studies list hypertension, hypokalemia, and hepatotoxicity as common adverse effects [1,2]. We present the case of a 63-year-old man with a personal history of hypothyroidism and sleep apnea hypopnea syndrome treated with continuous positive airway pressure who was diagnosed with prostate cancer (Gleason 4+5) and bone metastasis (T10 and left iliac spine). The patient had an initial clinical response to treatment with enzalutamide. As he remained asymptomatic, his urologist decided to maintain hormone treatment instead of taxane-based therapy, starting with abiraterone 1000 mg every 24 hours, together with prednisone 5 mg every 12 hours. After 4 days of treatment, the patient developed a fairly symmetrically distributed micropapular rash on the trunk (mainly the abdomen), both groins, and the root of the upper limbs. He also complained of axillary pruritus, although no lesions were visible at this level. There was no fever or mucous membrane involvement. He was evaluated in the urology department, where treatment was suspended. The rash resolved 4 days later, with minimum fine desquamation and no residual lesions.

We carried out an allergological work-up starting with skin prick tests at 200 mg/mL, although the result was negative. We decided not to perform patch tests, because standardized options with abiraterone are lacking. Even though the rash was indicative of a drug reaction, the fact that it was not severe led us to assess oral tolerance after adding ebastine 20 mg as premedication in an attempt to reintroduce the drug with tolerance. A provocation test was programmed for 2 days to achieve a total dose of 1000 mg of abiraterone. The protocol on the first day comprised 50 mg, 150 mg, and 300 mg, with a 1-hour interval between doses and 2 hours of observation after the last dose (cumulative dose, 500 mg). Ten hours after the challenge was completed, the patient developed a pruriginous micropapular rash on the thorax, affecting the groins and the axillas (Supplementary Material, Photo). Once the Urology Department confirmed that abiraterone was the first-choice agent for this patient, we developed a desensitization protocol (Table) in collaboration with the Pharmacy Department. Doses were prepared by weighing the corresponding amount of powder (10 mg, 30 mg, and 125 mg) and filling empty gelatine capsules. Dextrin maltose was used as the excipient. The desensitization protocol was stepped up every 3 days at the hospital, starting with the 10-mg dose; the patient maintained the maximum tolerated dose at home (Table). We decided to premedicate the patient with ebastine 20 mg/24 h and prednisone 15 mg/12 h. Once the total dose was reached, ebastine was stopped, and prednisone was stepped down, continuing with 10 mg/12 h during the following 2 days and maintaining 5 mg/12 h, as per the summary of product characteristics of abiraterone. The patient did not experience any problems or adverse events during the protocol, which was fully tolerated. Allergic reactions to anticancer drugs are a growing problem in allergology clinics, and desensitization protocols are useful when the drug involved is a first-choice option [3]. Rapid desensitization in IgE-mediated reactions has well-defined pathophysiological mechanisms, and while the procedure is risky, it has proven to be safe and efficacious [4]. In the case of late reactions (ie, more than 1 hour after administration), which are similar to those in the present case and are also frequently managed with rapid desensitization [5], there is no consensus on the ideal protocol,

Table. Desensitization Protocol

Day 1	
Doses administered at hospital with 30-minute intervals	10 mg 20 mg 40 mg 60 mg 125 mg
Day 2 and Day 3	
Dose at home	125 mg
Day 4	
Dose at hospital	250 mg
Day 5 and Day 6	
Doses at home	250 mg
Day 7	
Dose at hospital	500 mg
Day 8 and 9	
Doses at home	500 mg
Day 10	
Dose at hospital	1000 mg

with those published ranging from hours to several weeks [6,7]. While it is desirable to reach the therapeutic dose as soon as possible, rapid protocols are commonly associated with a greater risk of adverse reactions [8]. Verdu et al [9] reported a case of desensitization to abiraterone without previous oral challenge in a patient who experienced 2 reactions to the drug. The authors designed a rapid 1-day protocol. The patient experienced mild skin rash on the thorax; therefore, the protocol was extended to 4 days and completed with premedication comprising antihistamines and corticosteroids. In the case we report, we selected an intermediate protocol in order to reach the therapeutic dose as quickly as possible and with the minimum risk of reactions. After 10 days of desensitization, the patient was able to tolerate the complete dose without reactions or adverse events, and excellent tolerance was maintained after 2 months of treatment, with normal eosinophil counts and liver enzyme values. We present the case of a patient with allergy to abiraterone confirmed using controlled oral challenge. The patient managed to tolerate the full dose of the drug after a slow desensitization procedure with no reactions. It is remarkable that owing to the desensitization protocol, abiraterone could be used to avoid the toxicity induced by docetaxel—the alternative chemotherapy agent in this patient—while maintaining first-line therapy. We highlight the need for oral challenge in patients who experience nonsevere drug reactions in order to confirm hypersensitivity and consider our protocol to be a safe and effective option for achieving tolerance.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Beatriz Núñez-Acevedo
E-mail: bnunezacevedo@yahoo.es

Stability of Asthma Control Implies No Changes in microRNAs Expression

Rial MJ[1,3]*, Rodrigo-Muñoz JM[2,3]*, Sastre B[2,3], Sastre J[1,3], del Pozo V[2,3]

[1]*Department of Allergy, Hospital Universitario Fundación Jimenez Diaz, Instituto de Investigación Sanitaria Fundacion Jimenez Diaz (IIS-FJD, UAM), Madrid, Spain*

[2]*Department of Immunology, Instituto de Investigación Sanitaria Hospital Universitario Fundacion Jimenez Diaz. (IIS-FJD, UAM), Madrid, Spain*

[3]*CIBER de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Spain*

**These authors contributed equally to the manuscript.*

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Palabras clave: Asma. miRNA. Biomarcadores. Eosinófilos. Exosomas.

Asthma is a chronic disease that affects 4.3% of the population worldwide [1]. Pulmonary function tests and bronchial provocation tests are still the gold standard in diagnosing and assessing the severity of respiratory diseases; however, they are not able to differentiate between the clinical phenotypes responsible for specific manifestations. An ideal biomarker must be measurable with minimal invasiveness, be specific and sensitive, and be able to be detected quickly and accurately. In this context, microRNAs (miRNAs) present in body fluids have been reported to meet several of these criteria and are used as diagnostic markers in many areas [2-4]. Eosinophils, which play a key role in the pathogenesis of asthma, have the ability to secrete exosomes. These structures contain miRNAs, which are single-stranded RNA sequences (around 19-22 nucleotides) that do not code for proteins with crucial functions in the development and maintenance of the pathogenic mechanisms of asthma, but may instead be implicated in the pathophysiology of asthma by regulating the translation of proteins related to asthma processes [5]. miRNAs can be encapsulated in exosomes or bound to proteins in biofluids; in both cases, they are highly resistant to degradation by RNases [6,7].

Released exosomes and the miRNAs inside them have been found in serum. However, neither the precise role of miRNAs in asthma nor their stability in the same patient over time has been fully defined [3-5].

In order to establish whether expression of miRNA in clinically stable asthma patients remains steady over time, we selected 20 asthmatic patients from a national cohort (MEGA project) [8]. These patients were recruited randomly in the Allergy Department of Fundación Jiménez Díaz University Hospital, Madrid, Spain. Clinical and epidemiological characteristics are shown in the Supplementary Material. Patients received all necessary information and gave their written informed consent to participate. The study was conducted following the principles of the Declaration of Helsinki and approved by Fundación Jiménez Díaz Ethics Committee. All selected patients had a confirmed diagnosis of asthma with >12% improvement in FEV_1 15 minutes after inhaling salbutamol (400 µg) or methacholine airway hyperresponsiveness (PC_{20} methacholine <16 mg/mL) [9]. They also had moderate persistent asthma and were being treated with a combination of inhaled corticosteroids/long-acting ß-agonists at medium doses (400 µg of budesonide and 12 µg of formoterol fumarate dihydrate daily or equivalent). No change was made in the treatment received for asthma during the study period, ie, from baseline to the follow-up visits. Serum was obtained by centrifugation and stored at –80ºC before analysis for no more than 2 years.

Serum miRNAs were extracted using the miRCURY RNA Isolation Kit-Biofluids (Qiagen) and retrotranscribed to cDNA using the Universal cDNA Synthesis kit II (Qiagen) following the manufacturer's instructions. Synthetic spike-ins were added during the RNA extraction (Sp2, Sp4, and Sp5) and reverse transcription (Sp6) processes to ensure appropriate extraction and cDNA synthesis. miRNA expression was evaluated using quantitative polymerase chain reaction as previously described [10] at baseline and 6-12 months later at follow-up visits.

The miRNAs analyzed were miR-320-a, miR-144-5p, miR-1246, miR-21-5p, and miR-185-5p. These miRNAs were selected because we previously found that their profile in eosinophils can be used as a serum biomarker of asthma [10]. MiR-191-5p was measured as the endogenous control, and Sp2, Sp4, Sp5, and Sp6 were measured to ensure correct extraction and reverse transcription.

The statistical analysis was carried out using the GraphPad Instat program. The *t* test was performed for normally distributed samples (those meeting a Gaussian distribution) and the Mann-Whitney test for non-normally distributed samples. Paired tests were performed to compare baseline data with follow-up data.

Asthma was stable over time in terms of the mean (SD) Asthma Control Test score (21.1 [3.7] vs 20.8 [3.1]) and lung function (FEV_1%, 97.7 [12.9] vs 97.5 [13.9]). In addition to the stable clinical parameters, no statistically significant differences were found between the results obtained in asthmatics at baseline and follow-up visits for any of the

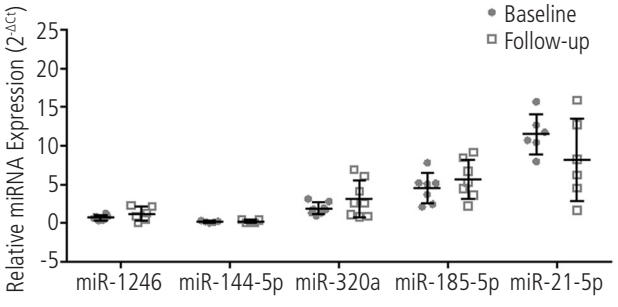

Figure. Expression of miRNAs by qPCR at baseline and at follow-up visits. Relative expression ($2^{-\Delta Ct}$) is shown as mean (SD).

miRNAs analyzed. The baseline expression values ($2^{-\Delta Ct}$) compared with the follow-up values were as follows: miR-1246, 0.72 (0.33) vs 1.21 (0.89) (*P*=.34); miR-144-5p, 0.18 (0.11) vs 0.22 (0.22) (*P*=.70); miR-320a, 1.89 (0.75) vs 3.14 (2.30) (*P*=.22); miR-185-5p, 4.50 (1.95) vs 5.70 (2.53) (*P*=.34); and miR-21-5p, 11.53 (2.59) vs 8.22 (5.32) (*P*=.19) (Figure).

The lack of significant differences between baseline and follow-up visits in asthmatic patients (whose therapy remained unchanged) could mean that the miRNAs remain stable over time in the same patient, with no change in therapy or clinical parameters. Our hypothesis is that changes in the expression of miRNAs in the same asthmatic patient over time could be due to spontaneous modifications in health status or new therapeutic interventions.

As expression of these miRNAs does not change in clinically stable asthma patients, we can deduce that their expression may prove useful for diagnosis when the circumstances of asthma are unchanged.

To our knowledge, this is the first study to show the stability of miRNAs over time in asthmatic patients in whom no changes were made to treatment and no clinical changes were observed. Stable miRNA expression implies that these biomarkers may be used for diagnosis of asthma at different time points during the disease course.

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Conflicts of Interest

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Manuel Jorge Rial
Victoria del Pozo
Instituto de Investigación Sanitaria
Hospital Universitario Fundacion Jimenez Diaz
Avenida Reyes Católicos, 2
28040 Madrid, Spain
E-mail: manuel.rial@quironsalud.es vpozo@fjd.es

Selective Allergy to Conger Fish due to Parvalbumin

Argiz L[1], Vega F[1], Castillo M[2], Pineda F[2], Blanco C[1,3]
[1]*Department of Allergy, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IP), Madrid, Spain*
[2]*Application Laboratory, Diater Laboratories, Madrid, Spain*
[3]*RETIC ARADYAL RD16/0006/0015, Instituto de Salud Carlos III, Madrid, Spain*

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Palabras clave: Congrio. Parvalbúmina. Alergia selectiva. Alergia a pescado. Alergia alimentaria.

Fish is one of the most frequent causes of food allergy, affecting up to 0.3% of the world's population [1]. Most fish-allergic patients show marked clinically relevant cross-reactivity, while a minority of patients experience selective allergy to specific fish species, with good tolerance to other fish families [2].

We report the case of a 32-year-old woman with mild rhinoconjunctivitis due to pollens and animal dander. In 2017, she developed generalized urticaria, cough, oral pruritus, dysphagia, and abdominal pain immediately after ingestion of a small piece of fideuá, a typical Spanish dish made with noodles, prawns, squid, and fish, which in this case was conger, although hake or snuff are more frequently used. Conger belongs to the subclass Actinopterygii, order Anguilliformes, which also includes eel and moray. Broth made from the head, thorns, and skin of fish is used as water for cooking fideuá. The patient's condition improved hours after symptomatic treatment in the emergency department. She subsequently tolerated pasta and several other types of fish (eg, hake, monkfish, cod, sardine, tuna, salmon, and swordfish).

The allergy work-up included the following (see Supplementary Material):

- Skin prick-tests with commercial extracts and prick-by-prick tests with foods, which yielded positive prick-by-prick results to both raw conger body (12×11 mm) and cooked conger body (10×9 mm).
- Serum specific IgE (kU_A/L) using ImmunoCAP, which yielded positive results to eel (0.81), hake (0.74), rooster (0.5), carp parvalbumin (rCyp c 1) (0.7), and cod parvalbumin (rGad c 1) (0.65) and negative results to cod, salmon, sole, sardine, and anchovy.

Good tolerance to prawns and squid was also confirmed. The patient was diagnosed with anaphylaxis due to conger allergy, and a conger-free diet was recommended.

SDS-PAGE was performed under reducing and nonreducing conditions (Supplementary Material). No relevant differences between both conditions were revealed, suggesting that the proteins involved were mainly monomeric proteins.

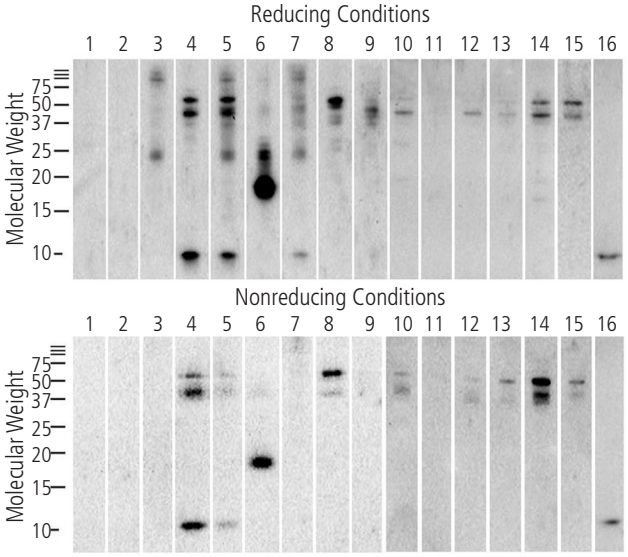

Figure. IgE-immunodetection performed with the patient's serum and the following extracts: Lane 1, Eel; 2, Eel skin; 3, Conger head; 4, Conger body; 5, Conger bone; 6, Conger eye; 7, Conger skin; 8, Salmon; 9, *Anisakis*; 10, Tuna; 11, Cod; 12, Carp; 13, Sole; 14, Hake; 15, Sardine; 16, Cooked conger.

Immunoblotting with the patient's serum and the above-mentioned extracts (Figure) showed that IgE recognized multiple bands, including the following:

1. A 40-50–kDa band, which was detected in raw conger and in all other tested raw fish extracts, but not in cooked conger.
2. A 12-kDa band, which was detected only in raw and cooked conger, but was absent in all other fish tested.
3. A 18-kDa band, which was detected only in the conger eye extract.

The eye of the conger is the part of the head used for making the broth of fideuá. This band was not further studied, because fish eyes are not eaten in Spain and the patient had not experienced problems with broth from other types of fish.

Immunoblotting-inhibition was performed with carp and conger extracts under reducing and nonreducing conditions, and the patient's serum was preincubated with conger extract. As a result, IgE no longer recognized the proteins in the extracts, thus indicating that primary sensitization was probably due to conger. Disappearance of the 40-50–kDa bands suggests that these proteins were similar in both extracts.

Peptide mass fingerprinting was performed with conger extract using spectrometry to characterize the 12-kDa band, since this was thought to have induced the patient's reaction. The band was both conger-specific and thermoresistant. The 4 most relevant peptides were selected after a process of enzymatic digestion, and a specific search for the MASCOT peptide sequence combining MS (proteins) and MSMS (peptides) was performed in NCBI Chordata. The only match found was for an 11–amino acid peptide with the ß-parvalbumin of the fish *Scleropages formosus* in 1 of the 4 peptides (Supplementary Figure). This 11–amino acid peptide has a homology of >80% with many other fish parvalbumins.

Thus, the 12-kDa conger allergen we identified proved to be a ß-parvalbumin.

In terms of gastronomy, conger is one of the 30 main commercial fish species in Europe. Only 3 cases of mild conger allergy have previously been reported, and in all 3 the patients had multiple fish allergies. In addition, the proteins involved were not identified [3,4]. *S formosus* is also known as Malay tongue. It belongs to the order Osteoglossiformes, which is very distant from the order Anguilliformes. To our knowledge, it has never been reported to cause allergic reactions.

ß-Parvalbumins are the main fish allergens and are recognized by 95% of fish-allergic patients [5]. Although ß-parvalbumins are considered to be highly cross-reactive, especially between closely related fish species, isolated clinical allergy to a single fish species has been described for swordfish, tuna/marlin, salmon, sole, tilapia, and pangasius/tilapia [6]. We think this ß-parvalbumin probably behaves as a selective allergen of the Congridae family, because it was not recognized in the other fish extracts tested, including eel extract, and the patient tolerated all other fish species (both cooked and raw). We think that our commonly identified LFLQNFASGAR sequence does not include relevant IgE-binding epitopes and that clinically relevant conger parvalbumin epitopes must be located in different parts of the protein and show no homology with other parvalbumins, thus explaining the lack of cross-reactivity between conger allergens and other allergenic parvalbumins in fish.

Parvalbumins are classified into 2 different families, namely, α and ß parvalbumins. α-Parvalbumins are present in birds, amphibians, cartilaginous fish, mammals, and crocodiles. To date, the only reports of allergy caused by α-parvalbumin involved one patient with allergy to frog leg and another with allergy to crocodile and cartilaginous fish [7,11]. In contrast, ß-parvalbumins are present in bony fish, especially white fish, and are highly allergenic. They have a single 113–amino acid chain, with 2 specific calcium-binding sites. ß-parvalbumins are thermostable proteins with a molecular weight of around 12-14 kDa. In addition, they are resistant to denaturation and enzymatic digestion, which can cause severe reactions [6]. Fish allergenicity depends on the amount of white muscle and processing (canned, cooked, raw) [8].

The 40-50–kDa protein recognized by the patient in the present report is probably enolase or aldolase [9], the second most frequent fish allergens (albeit with doubtful clinical relevance), which are recognized by around 50% of patients. These antigens cannot be responsible for symptoms with cooked conger, since they are thermolabile proteins. Furthermore, they have no clinical relevance in the present case, given that the patient did not have symptoms with other raw fish species. Less frequent fish allergens that have been described include collagen, tropomyosin, aldehyde dehydrogenase, and protamine. In some cases, they seem to be species-specific.

In summary, we report the first case of anaphylaxis due to conger allergy. We also describe the first allergen in conger (ie, a ß-parvalbumin), and a new selective parvalbumin in fish. Interestingly, conger can also behave as a hidden allergen, since it is used to add a fish flavor to typical dishes.

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Conflicts of Interest

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Laura Argiz Álvarez
C/ Diego de León, 62
Hospital Universitario La Princesa
Servicio de Alergia
28006 Madrid, Spain
E-mail: largizalvarez@gmail.com

What Physical Education Teachers Know About Asthma: Impact of a Training Course

Couto M[1], Marques J[2], Silva D[3], Paiva M[4], Jacinto T[5,6], Câmara R[7]
[1]*Immunoallergology – José de Mello Saúde, Portugal*
[2]*Imunoalergologia – Centro Hospitalar de Lisboa Central, Lisboa, Portugal*
[3]*Serviço de Imunoalergologia – Centro Hospitalar São João, Porto, Portugal*
[4]*Serviço de Imunoalergologia Dona Estefânia, Lisboa, Portugal*
[5]*Porto Health School, Polytechnic Institute of Porto, Porto, Portugal*
[6]*CINTESIS, Faculty of Medicine of University of Porto, Porto, Portugal*
[7]*Unidade de Imunoalergologia, Hospital Dr. Nélio Mendonça, SESARAM EPE, Funchal, Portugal*

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Key words: Asthma. Education. Exercise. School. Teachers.

Palabras clave: Asma. Educación. Ejercicio. Escuela. Profesores.

Given the current prevalence of asthma in developed countries, there are likely to be at least 2 or 3 asthmatic children in most classes. However, few teachers have received training on how to manage the disease [1,2]. A previous study in Portugal showed teacher knowledge of asthma to be deficient [3]. Asthma is particularly challenging for physical education (PE) teachers, because they must motivate asthmatic students and instruct them on how to participate in physical activities, which may prove to be a powerful trigger of asthma [4]. Therefore, it is essential that PE teachers have appropriate knowledge of exercise-induced asthma. Training can improve teachers' knowledge of the disease, thus leaving them more prepared to manage asthmatic students [5]. We aimed to assess PE teachers' knowledge of asthma and to evaluate the effects of a training course.

During 2015, the Interest Group of Allergy, Asthma and Sports of the Portuguese Society of Allergy and Clinical Immunology provided PE teachers with 5 modules of a course entitled "Allergic Diseases in Sports". The course, the program, and the speakers were approved by the National Scientific and Pedagogic Committee of Education, and accreditation was granted. Each module comprised theoretical and practical areas and took 16 hours over 2 consecutive days. The program also included lessons on rhinitis, anaphylaxis, and urticaria. The 5 modules were repeated in 5 different regions of Portugal (Ponta Delgada, Coimbra, Lisboa, Madeira, and Porto). All modules had exactly the same contents, and the presentations previously prepared by the speakers remained unchanged throughout the program. The course was free of charge.

We developed a 20-item self-administered questionnaire based on prior existing asthma knowledge questionnaires (Supplementary Material) [2,3]. Each question had a score of 1 (maximum total score, 20). The questionnaire included 4 different categories of questions: 6 questions related to general knowledge of the disease, 3 questions related to common beliefs, 4 questions related to asthma triggers, and 7 questions related to treatment and prevention of asthma. Additionally, there were 3 questions regarding personal and/or family history of asthma and previous contact with asthmatic children. Before starting the lessons, the attendees were asked to complete the questionnaire, which was anonymous and coded. The participants were asked to memorize the code, and, at the end of the course, the same questionnaire was filled in and coded to pair for statistical analysis.

Categorical variables are expressed as absolute values (%) and continuous variables as mean (SD). The McNemar test was used to assess changes between baseline and after the intervention. The analyses were performed with IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp).

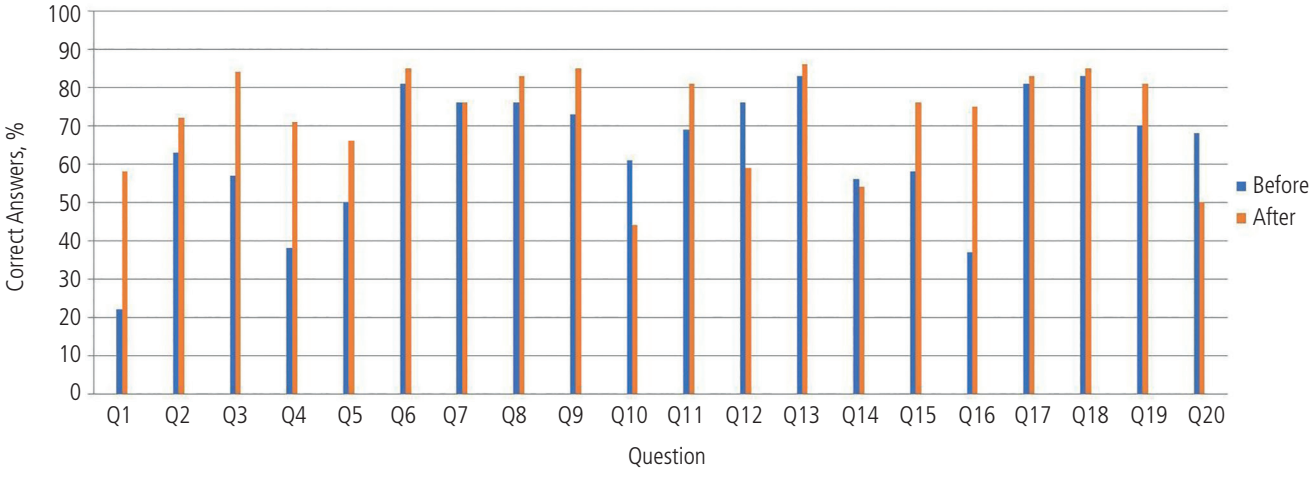

Figure. Percentage of correct answers before and after the course.

A total of 86 PE teachers from the 5 regions returned the completed matching questionnaires (mean [SD] age 47.9 [8.1] years; 58 females [67%]) (Supplementary Material). The score improved after the course for most questions (Figure), except questions 7 (general knowledge), 10, 12, 20 (beliefs), and 14 (treatment). At baseline, 74% of answers were positive (mean score, 15.57 [1.86]), increasing after training to 85% (17.23 [1.67]). This increase was statistically significant for questions regarding general knowledge about asthma ($P<.001$), triggers ($P<.001$), and treatment ($P<.001$), but not for questions targeting beliefs. Eighty-four PE teachers (98%) had ≥1 asthmatic student in their class. An analysis of the possible effect of personal contact with asthma (n=12; 14%) or family contact with asthma (n=20; 23%) revealed no significant differences.

The teachers in this sample showed a reasonable degree of knowledge about asthma. Our findings are better than those reported by other authors [3], who found knowledge of asthma among general teachers to be deficient (mean score, 17.7 out of 30). However, in that study only 60% of the teachers had or had had an asthmatic student [3], compared with 98% in our sample. Therefore, we would expect even better results.

Also important is the fact that we included only PE teachers, whose understanding of exercise-induced asthma was not ideal. A low proportion were aware that exercise may induce wheezing or that it could be prevented by pretreatment. About 70% of PE teachers knew that exercising in cold weather can exacerbate asthma, although only about 50% knew that exercise was a common trigger. It is important that PE teachers are able to recognize when an asthmatic child is becoming symptomatic and to be aware of the stimuli that might trigger an exacerbation. Still, asthmatic children should be encouraged to fully participate in school sports and activities while taking appropriate medication. Therefore, PE teachers must have proper knowledge in order to feel confident in this role. Bearing in mind how relevant it is to recognize asthma attacks and to treat them promptly with a bronchodilator inhaler, it is important to promote training courses with a practical part during which teachers are trained in inhaler technique. Given the close relationship between asthma and allergy, courses should include other allergy-related conditions (eg, rhinitis, anaphylaxis, and urticaria), as was the case in our program. Specific training on anaphylaxis has been shown to be effective [6].

Our study is subject to limitations. Although based on existing questionnaires, the current one has not been validated. Given the anonymization process, we were unable to assess whether demographic characteristics were associated with better baseline knowledge or more marked improvement. Furthermore, we were unable to assess differences between age groups or sexes. Although we have offered courses in the most representative areas of Portugal, our results cannot be generalized, and selection bias is probable, since those who signed up were particularly interested in this issue [7]. In any case, these data clearly demonstrate some lack of knowledge of asthma among PE teachers, and even about the association between asthma and sports. We showed that a training course enables a significant improvement.

Asthma management is difficult, and treatment involves both a personalized and a global approach [8]. The magnitude of the asthma burden and its social and economic impact justifies the implementation of asthma training programs in schools. By improving knowledge of asthma, clarifying erroneous beliefs, and promoting the organization of basic medical care for asthma exacerbation in schools, we can contribute to the full integration of asthmatics and to reduce the social and economic costs of asthma. Our data reinforce the importance of sharing knowledge between different professional groups as a means of improving the care of patients with asthma.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Mariana Couto
Immunoallergology, José de Mello Saúde
Portugal
E-mail: marianafercouto@gmail.com

Treating "Asthma" With A Scalpel: Achalasia Mimicking Asthma

Nittner-Marszalska M, Kopeć A, Jędrzejewska J, Pawłowicz R
Department of Internal Medicine and Allergology, Wroclaw Medical University, Wroclaw, Poland

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Palabras clave: Asma. Bronquiolisis difusa por aspiración. Acalasia.

When asthma remains partially controlled or even uncontrolled despite qualified treatment, experts stress the need to verify the diagnosis and rule out conditions that can mimic asthma [1,2]. According to some reports, misdiagnosis of nonasthmatic conditions treated as uncontrolled asthma is as frequent as 12%-30%; hence, a certain degree of skepticism is recommended [3].

An 18-year-old woman was referred to our Allergy Department with a diagnosis of severe asthma. Her asthma was partially controlled and sometimes uncontrolled, with signs of bronchial obstruction that persisted despite intensive treatment (GINA guidelines, step 5: daily doses of fluticasone propionate 1000 µg and salmeterol 100 µg, with prednisone 20-40 mg/d for 5-7 d every second or third month). Since the onset of her disease (age 13 years), the main symptoms were cough, breathlessness, and wheezing that occurred predominantly at night, causing frequent nocturnal awakening. She also reported rhinorrhea during sleep. The patient's mother described the nocturnal symptoms as "noisy breathing". During the last 2 years, the patient had pneumonia twice, and several episodes of "bronchitis" treated with antibiotics. The patient denied having experienced paroxysmal dyspnea, exercise-triggered dyspnea, or dyspnea induced by other factors (specific or nonspecific). Similarly, she did not report any other symptoms, particularly gastric symptoms. She was sensitized to house dust mite, but had no family history of atopy or asthma and had never smoked cigarettes.

Physical examination and laboratory test results during hospitalization revealed no abnormalities. Spirometry confirmed a moderate obstructive picture (FEV_1, 1.92 L [59.7%]; FVC, 3.61 L [98.2%]; FEV_1/FVC, 53.2%). Postbronchodilator spirometry revealed lack of response to inhaled bronchodilators. Body plethysmography showed elevated airway resistance, both inspiratory and expiratory (respectively 305% and 300% of predicted) and increased residual volume (254%). Blood gasometry and FeNO (7 ppb) were normal. Neither sputum eosinophilia nor nasal discharge were recorded. The blood eosinophil count was normal. Chest radiograph findings were unremarkable. The chest CT scan revealed a massively dilated esophagus filled with food residue and, consequently, tracheal compression (Figure). It also revealed parenchymal lung changes in the form of distal diffuse

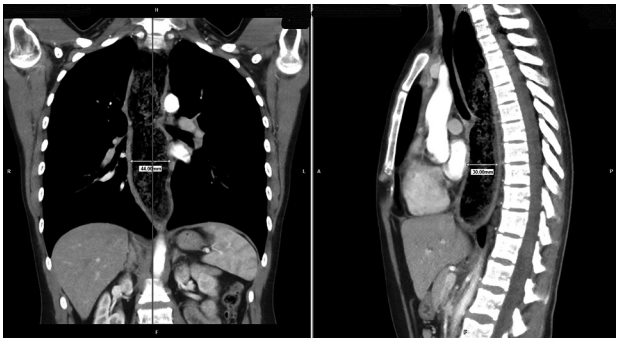

Figure. Computed tomography scan showing massive dilatation of the esophagus and tracheal compression.

consolidation, areas of ground-glass opacity, micronodules, and tree-in-bud opacities. Esophagogastroscopy showed a dilated esophagus. Esophageal high-resolution manometry revealed a hypertensive lower esophageal sphincter that did not relax on swallowing; similarly, there was no peristaltic wave in the esophagus. The patient was diagnosed with achalasia.

When the test results had been collected and the medical history was being completed, the patient reported that for at least 3 years, she had experienced nocturnal vomiting containing undigested food; her nasal discharge had also contained food particles. The symptoms were associated with persistent cough.

Once the diagnosis of achalasia was confirmed, the patient was referred for surgery (peroral endoscopic myotomy). A check-up 2 months after surgery revealed that cough, dyspnea, rhinorrhea, and nocturnal vomiting had considerably abated. All asthmatic medications were discontinued. Spirometry results returned to normal values (FEV_1, 3.89 L [121%]; FVC, 4.3 L [117%]; FEV_1/FVC, 90%). The result of the methacholine challenge test performed at that time was negative.

The present case concerns a patient with respiratory symptoms resulting from achalasia that were misdiagnosed as severe asthma. In fact, the symptoms reported were caused by recurrent aspiration of small amounts of gastric content that occurred largely at night over a period of a few years. The chest CT scans performed on admission to the Allergy Department were characteristic of bronchiolitis and reflected chronic bronchiolocentric inflammation caused by recurrent aspiration. The clinical picture and imaging scans pointed to a diagnosis of diffuse aspiration bronchiolitis (DAB) complicated by incidents of aspiration pneumonia. The term diffuse aspiration bronchiolitis was first used by Matsuse et al [4] as a name for a chronic inflammation of the bronchioles produced by frequent aspiration of foreign particles. Although DAB is usually diagnosed in the elderly, it has been reported in younger patients, with clinical manifestations similar to those found in the elderly [5-8]. In younger patients, the major risk factors responsible for DAB are dysphagia due to achalasia and gastroesophageal reflux disease with concomitant recurrent aspiration.

In the case we report, the diagnostic delay may have been caused by various factors. First, apart from a 5-year history of vomiting that was erroneously interpreted as a consequence rather than the cause of coughing, there were no accompanying symptoms characteristic of achalasia. Second, auscultatory phenomena were interpreted as asthmatic wheezing, while they might in fact have resulted from pressure on the trachea and/or bronchiolitis, which can also be responsible for variations in airflow obstruction in spirometry. Third, achalasia is a rare disorder, diagnosed mostly in elderly adults (generally during the sixth decade of life, with an estimated prevalence and incidence, respectively, of 10.82 cases per 100 000 and 1.63 cases per 100 000 [9]). Fourth, the primary symptoms of achalasia are mostly gastrointestinal, whereas respiratory symptoms are less frequent. In up to 40% of cases of achalasia, pulmonary disorders such as cough, wheezing, and recurrent aspiration can occur, although DAB is very rare [10]. Bronchiolitis associated with chronic aspiration can considerably hamper diagnosis. DAB should be considered in patients with respiratory symptoms such as chronic cough, wheezing, obstruction, persistent radiologic abnormalities in high-resolution CT, and a high risk of aspiration. Given the scope of the respiratory changes we report, the possible consequences of a further delay in surgical treatment of achalasia could be serious. Our findings confirm the prevailing stance of asthma experts who claim that if asthma symptoms persist despite intensive pharmacological treatment, it is advisable to revisit the patient's clinical history, bearing in mind the possibility of a diagnosis that mimics asthma.

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Conflicts of Interest

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Kopeć Agnieszka
Department of Internal Medicine and Allergology
Wroclaw Medical University
M. Curie-Skłodowskiej 66
50-367 Wroclaw, Poland
E-mail: astyrc@wp.pl

A Novel *TTC37* Mutation Causing Clinical Symptoms of Trichohepatoenteric Syndrome Such as Pyoderma Gangrenosum and Immunodeficiency Without Severe Diarrhea

Karaca Edeer N[1], Aykut A[2], Pariltay E[2], Aksu G[1], Cogulu O[1,2], Kutukculer N[1]
[1]*Ege University Faculty of Medicine, Department of Pediatrics, Izmir, Turkey*
[2]*Ege University Faculty of Medicine, Department of Medical Genetics, Izmir, Turkey*

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Palabras clave: Síndrome tricohepatoentérico. Inmunodeficiencia. Pioderma gangrenoso.

Targeted next-generation sequencing (TNGS) is used to identify specific cohorts of mutations by sequencing a panel of diseases. Reverse phenotyping can play a crucial role in diagnosis.

TTC37 deficiency is included in the "predominantly antibody deficiency" group of the IUIS-2017 phenotypic classification of primary immunodeficiency disorders [1,2]. We report the case of a patient with recurrent infections and pyoderma gangrenosum–like lesions. Reverse phenotyping was used to confirm diagnosis of trichohepatoenteric syndrome (THES) without severe diarrhea due to a novel homozygous mutation in the *TTC37* gene.

The patient was a 22-month-old boy and the third child of consanguineous-parents. He was born at term (3400 g, percentile 25-50), and his developmental milestones were normal. He was admitted for recurrent skin abscesses and oral lesions. Physical examination revealed oral aphthous lesions and ulcerous lesions on his hands. His weight was 11 kg (percentile 3-10) and his height was 82 cm (percentile 3-10). Laboratory investigations showed leukocytosis, thrombocytosis, and high IgG/IgM and low IgA levels (Supplementary Material), with adequate antibody responses to childhood vaccines. Normal results were recorded for lymphocyte subgroups, CD11a-CD18 expression on neutrophils, quantitative oxidative-burst activity, and IgE levels, thus excluding severe combined immunodeficiency, chronic granulomatous disease, leukocyte adhesion defects, and hyper-IgE syndromes. Clinical and laboratory findings improved with antibiotic therapy. The patient was discharged with a diagnosis of selective IgA deficiency.

The patient also had coarse hair and sterile erythematous-violaceous pyoderma gangrenosum–like plaques on his neck and developed a 1/6 systolic murmur at the apex 3 months later (Figure). Skin biopsy showed hyperkeratosis, acanthosis, and inflammatory infiltration. The result of a purified protein

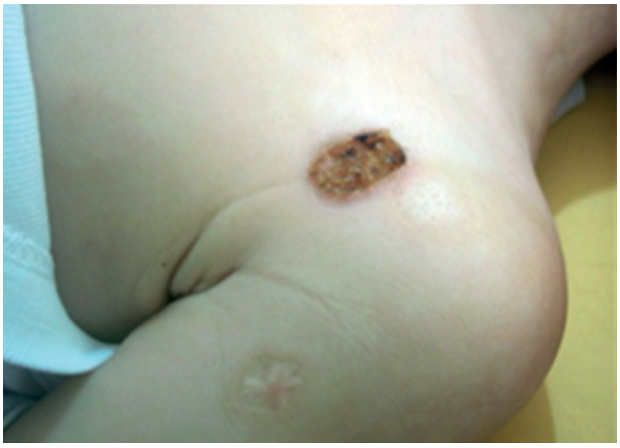

Figure. Pyoderma gangrenosum–like skin lesions.

derivative skin test was negative. There were no mutations in the *MEFV, PSTPIP2*, or *IL1RN* genes. Autoantibody titers (antinuclear antibody, antineutrophil cytoplasmic antibody, rheumatoid factor) were negative. Echocardiography showed minimal tricuspid valve regurgitation. Dermatitis herpetiformis was ruled out by normal small bowel histopathology and negative antigliadin and antiendomysial antibody titers. The patient was treated with intravenous antibiotics and discharged with trimethoprim/sulfamethoxazole prophylaxis.

IgA levels increased and IgG levels decreased over time (IgG, 598 mg/dL) (Supplementary Material, Table 1). Findings for lymphocyte proliferation were normal, as were those for class-switched memory B cells. The patient's coarse facial appearance (large ears, broad flat nose, and prominent forehead) and diffuse xerosis became increasingly evident (Supplementary Material, Figure 1). At age 4 years, he began to receive intravenous immunoglobulin therapy to control recurrent skin and oral lesions following upper respiratory tract infections. He benefited from regular intravenous immunoglobulin, although he had severe episodes of oral mucositis requiring hospitalization twice per year. He also had peg teeth; his primary teeth had emerged quickly, with rapid development of caries and short root anomaly (Supplementary Material, Figure 1).

At age 6 years, a homozygous mutation in the *TTC37* gene (c.2210T>C,p.Val737Ala) was detected by TNGS with a comprehensive Ion AmpliSeq PID Panel designed for sequencing 264 PID genes (Supplementary Material, Figure 2). *TTC37* mutations cause THES, which is characterized by early-onset diarrhea. After the genetic diagnosis, the patient was reevaluated for THES; liver values were normal, and trichorrhexis nodosa was detected in the hair shafts (Figure). He had mild intermittent diarrhea lasting 2-3 days following infections. Colonoscopy findings were normal. The parents were heterozygous for the same mutation.

THES is caused by loss-of-function mutations in the tetratricopeptide repeat domain–containing protein 37 gene (*TTC37*) and superkiller viralicidic activity 2 gene (*SKIV2L*) [3,4]. The condition is characterized by intractable diarrhea, facial dysmorphism, hair abnormality, intrauterine growth retardation, immunodeficiency, skin abnormalities, liver disease, and platelet abnormalities (Supplementary Material, Table 2) [3-6].

The present case clearly shows that THES can cause immunodeficiency and pyoderma gangrenosum–like skin lesions without significant diarrhea. This patient had typical facial features of THES, wooly and coarse hair, trichorrhexis nodosa, and hypogammaglobulinemia. He did not have chronic/intractable diarrhea or liver disease. His height and weight percentiles were 50%, with normal intelligence at 7 years of age (Supplementary Material, Figure 3). He also had peg teeth and short root anomaly. Peg teeth were reported in a patient with an *SKIV2L* mutation, although they had not previously been reported in patients with a *TTC37* mutation [6]. Pyoderma gangrenosum is usually associated with systemic diseases such as inflammatory bowel disease, rheumatologic disorder, immunodeficiency, or autoinflammation [7,8]. The presentation we report on here involved recurrent oral aphthous lesions and pyoderma gangrenosum–like skin eruptions. Deficiency of IL-1R-antagonist (DIRA) and IL-36R (DITRA) and PAPA (pyogenic arthritis, pyoderma gangrenosum, acne) are autoinflammatory disorders with cutaneous pustular lesions [7,8]. No mutations were found in the *MEFV, PSTPIP2*, or *IL1RN* genes. Half of all children with THES have cutaneous abnormalities such as cafe-au-lait spots, xerosis, and rubbery skin. To our knowledge, there are no previously described cases of THES presenting with pyoderma gangrenosum.

Approximately 90% of THES cases have immunodeficiency, which takes the form of hypogammaglobulinemia, defective specific antibody production, reduced memory B cell counts, and abnormal T lymphocyte proliferation [6,9,10]. In the present case, the patient had selective IgA deficiency at admission, although he had decreasing IgG levels. IgA levels returned to normal over time.

The spectrum of THES is widened by pyoderma-like scarring skin lesions and dental abnormalities, in addition to classic findings such as immunodeficiency and trichorrhexis nodosa. To date, mutations have been described in more than 300 different genes causing primary immunodeficiency disorders. Diagnosis can be costly and time-consuming because of the genetic and phenotypic heterogeneity of these disorders. TNGS enables rapid genetic testing across a large number of diseases in clinical practice and facilitates the diagnosis of atypical PID presentations. The power of reverse phenotyping needs to be emphasized in cases involving uncertain features or when findings become obvious with age.

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Conflicts of Interest

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Neslihan Edeer Karaca
Ege University Faculty of Medicine, Children's Hospital
Second Floor, Bornova, 35100 Izmir, Turkey
E-mail: neslihanedeer@gmail.com

Selection of Biologics for Severe Type-2 Asthma

Yilmaz I
Erciyes University School of Medicine, Department of Chest Diseases, Division of Immunology and Allergy, Kayseri, Turkey

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Palabras clave: Asma grave. Atopia. Eosinófilo. Pólipo nasal. Biológicos.

To the Editor:

We read with great interest the report of Sanchez-Jereno et al [1], who reported the first case of severe uncontrolled allergic eosinophilic asthma with the failure of 2 biological therapies (anti-IgE and anti-IL13 monoclonal antibodies [mAbs]) and marked improvement with anti-IL5 mAb. We would like to thank Sanchez-Jereno et al for their contribution to the literature with a case report that suitably addresses the selection of biologics in severe asthma. We would also like to share our clinical experience and opinions on this case report.

The authors state that although several biologics have been approved for uncontrolled severe asthma, no specific biomarkers have been developed to predict a good response to these biologics. However, in the GINA severe asthma guideline published at the end of 2018, suggestions were made on which biologics should be given for the type-2 high asthma phenotype, and it was emphasized that factors determining the response to treatment should be taken into consideration [2]. Therapy should start with anti-IL5/anti-IL5R mAbs in patients with uncontrolled severe asthma and a blood eosinophils ≥300/μL. The factors that may predict a good response to anti-IL5/anti-IL5R biologics are as follows: (*a*) higher blood eosinophil counts (strongly predictive), (*b*) more frequent severe exacerbations during the previous year (strongly predictive), (*c*) adult-onset asthma, and (*d*) nasal polyposis (treated with maintenance oral corticosteroids [OCS]). Anti-IgE should be started in patients with uncontrolled severe asthma who are sensitized to inhaled allergen(s) in skin prick testing or specific IgE. The factors that may predict a good response to anti-IgE mAb are as follows: (*a*) blood eosinophils ≥260/μL, (*b*) FeNO ≥20 ppb, (*c*) allergen-driven symptoms, and (*d*) childhood-onset asthma. The issue to be discussed here is the approach to be adopted if the characteristics that determine the choice of treatment coincide in some patient groups, as in the case reported by the authors. The patient, who had a type-2 high asthma phenotype, was treated with anti-IL5 mAbs because he had late-onset asthma, nasal polyps, and high eosinophilia. The patient was also given anti-IgE therapy because of atopy and blood eosinophils ≥260/μL. However, what is important here is whether the patient's atopy status is really appropriate, given the clinical history (childhood allergic asthma, comorbidities such as atopic dermatitis/allergic rhinitis, and respiratory symptoms with exposure to aeroallergens). We think that starting anti-IgE therapy based only on atopy (determination of positivity with skin prick testing and/or determination of specific IgE to common aeroallergens) may not be the ideal approach and that the clinical history should be taken into consideration. In this case, the first-choice biological agent should be an anti-IL5/anti-IL5R mAb owing to the presence of strong predictive markers suggesting a good response to mAbs, such as higher blood eosinophil counts and a higher number of severe exacerbations in the previous year, as well as other predictors such as nasal polyps, late onset, and dependence on OCS [2,3].

Unfortunately, strong evidence for the comparative efficacy and effectiveness of biologics in severe asthma is lacking, since there are no head-to-head studies comparing anti-IgE and anti-IL5/anti-IL5R therapy. Data from recent reports on the selection of biologics for severe asthma screened using biomarkers, as well as the GINA recommendations [4-7], indicate that if the main clinical target is to reduce the maintenance dose of OCS, omalizumab should not be the first-choice biologic in patients with OCS-dependent severe eosinophilic asthma [4], because there are no clear data to support reducing OCS in patients treated with omalizumab. However, decreasing the total use of OCS has been shown to facilitate complete weaning from chronic OCS (14%-50%) in patients treated with anti-IL5/anti-IL5R mAbs [4,8]. In fact, some patients with eosinophilic asthma require sustained use of OCS to maintain disease control. In any case, long-term use of OCS is associated with significant adverse effects. Bel et al [9] showed that mepolizumab led to a 50% reduction in OCS dosage in patients with eosinophilic asthma taking chronic OCS. The effects of reduced exacerbations and improved asthma control were maintained despite the reduction.

In eosinophilic asthma with chronic nasal polyposis, the most appropriate biologic would be an anti-IL5/anti-IL5R mAb, since the main mechanisms are dysregulation of leukotriene synthesis and chronic epithelial damage and activation by agents such as superantigens and environmental pollutants, which release epithelial cell-derived cytokines such as TSLP, IL-25, and IL-33. These cytokines stimulate type-2 innate lymphoid cell activation, which leads to overproduction of IL-5[10-12]. In our clinic, we also prefer anti IL5/anti-IL5R as the first-choice mAb in severe eosinophilic asthma (atopic or nonatopic) with nasal polyposis [13].

In conclusion, current or future biologics for severe type-2 high asthma should be chosen wisely following logical recommendations, which can currently be made based on the mechanisms of action of the drugs and the underlying pathophysiology of various asthma phenotypes. Unfortunately,

trials comparing efficacy and combination trials with anti-IgE and anti-IL5/anti-IL5R are lacking and should be performed in the near future.

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Insu Yilmaz

Erciyes University School of Medicine
Department of Chest Diseases
Division of Immunology and Allergy
Kayseri, Turkey
E-mail: insu2004@yahoo.com

Basophil Activation Test in Amiodarone Hypersensitivity and Non–IgE-Mediated Allergy

Vella A[1], Bjørklund G[2], Chirumbolo S[2,3]
[1]*AOUI –University Hospital, Section of Immunology, Verona, Italy*
[2]*Council for Nutritional and Environmental Medicine (CONEM), Mo i Rana, Norway*
[3]*Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy*

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Palabras clave: Test de activación de basófilos. CD63. CD203c. Amiodarona.

To the Editor:

The recent article by Sánchez et al [1] investigated the fundamental role played by the application of a basophil phenotyping protocol including the CD123 and HLA-DR markers for electronically capturing cells in flow cytometry. The authors described 2 cases of immediate hypersensitivity to amiodarone that were successfully diagnosed using a $CD123^{pos}$/$HLA\text{-}DR^{neg}$ gating protocol, with CD63 as the activation marker. Interestingly, the authors reported an increase in the CD63 percentage in peripheral blood samples treated with amiodarone 0.2 mg/mL, although the activation did not appear to follow a dose-response relationship. In the case of a purported anaphylactic reaction, CD63 upregulation increased by 37% (stimulation index, 5.11 [≥3]), while in the 84-year-old patient with no apparent allergy background but who was treated with antihistamine and corticosteroid therapy for itching and a red rash 15 minutes after taking amiodarone, CD63 upregulation reached 60% with a stimulation index of 30 [1]. The merit of this paper is that it shows the ability of the basophil activation test (BAT) to detect an allergic episode very early and to prevent the adverse effects associated with a skin prick test. We expected to observe a more pronounced CD63 response in the case of anaphylaxis in the 48-year-old patient, who also responded to the lowest doses of amiodarone (0.1 mg/mL), with a CD63 percentage of 14%-15%, while the second patient did not. Notwithstanding, the findings led to us raise some questions.

Basophils express A1 adenosine receptors, which are targeted by amiodarone [2,3]. The rapid up-regulation of the tetraspanin LAMP3, ie, CD63, is associated with a type of degranulation known as anaphylactic degranulation, which is also the mode used by a non–IgE-mediated basophil response (as occurs for fMLP) some seconds after piecemeal degranulation [4]. Therefore, in the patient with the higher stimulation index for CD63, we may describe the event as a "threshold" effect of the amiodarone-mediated action on basophil A1 purinergic receptors, while for the anaphylactic patient we cannot exclude a real hypersensitivity mechanism. In these circumstances, as the phenotyping protocol is based on a panel of markers that excludes CD203c, the authors should select CD203c to determine whether their finding can be explained by a non–IgE-mediated mechanism [5]. It is well known that adenosine receptors in basophils downregulate cellular activation expressed via histamine release and the degranulation event, and it can be suggested that amiodarone, which dampens the sensitivity of A1 adenosine receptors, rapidly increases the anaphylactic degranulation mechanism of CD63 upregulation, resulting in the considerable CD63 percentage observed by the authors [1-3]. This speculation of ours seems to find some support in the evidence that the 84-year-old woman did not have a history of allergy to amiodarone. In the case of the 48-year-old man, however, who was clearly allergic to amiodarone, there was a dose-dependent increase in the CD63 percentage [1], with no threshold effects caused by mechanisms of receptor binding and recycling at some distance from the FcεRI/IgEs signaling pathway.

In conclusion, we would like to propose that the use of a BAT with a $CD45^{dim}$/$CD123^{high}$/$HLA\text{-}DR^{neg}$/$CD63^{pos}$ protocol makes it possible to introduce 2 activation markers, ie, CD63 and CD203c, which may enable us to discriminate between an IgE-mediated response and a non–IgE-mediated response. In this paper, BAT emerges as a worthy tool for diagnosis of hypersensitivity and non–IgE-dependent immune responses to drugs. It should certainly be considered an essential tool in allergy diagnosis.

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Conflicts of Interest

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Salvatore Chirumbolo

Department of Neuosciences, Biomedicine and Movement Sciences
University of Verona
Strada Le Grazie 9
37134 Verona (Italy)
E-mail: salvatore.chirumbolo@univr.it

Acute Generalized Pustular Bacterid: An Uncommon Dermatosis That Commonly Presents With Acral Pustules

Zhou HW, Tan C
Department of Dermatology, Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, China

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Palabras clave: Alergia. Dermatología. Pústulas.

To the Editor:

We read with great interest the very well-presented article entitled "Acute Localized Exanthematous Pustulosis Due to Bemiparin" by Gómez Torrijos et al [1]. The authors reported the case of a patient with pustular eruptions on the palms, which were finally diagnosed as a localized subtype of acute generalized exanthematous pustulosis (AGEP). We recently saw a similar case with acral pustular eruptions, in which the diagnosis of acute generalized pustular bacterid (AGPB) was established based on the triad of acral distribution of the pustules, sudden onset of the disease, and concomitant remote localized bacterial infections.

A 42-year-old man had a 2-day history of pustular eruption on both hands that had developed suddenly. Several days earlier, he had had a sore throat with fever of 38.5°C. He denied having taken drugs and had no history of drug allergy, including to cefuroxime. Similarly, he had no history of psoriasis. Physical examination showed many isolated, discrete pustules on both hands (Figure). The results of routine testing of blood (6.2×10^9/L), urine, and stool and a basic biochemistry panel (ALT, 34 µ/L; AST, 26 µ/L) were normal. Laboratory results revealed C-reactive protein of 53 mg/dL and an erythrocyte sedimentation rate of 35 mm/h. Bacterial culture from a throat swab demonstrated multiple group A ß-hemolytic streptococci. Repeated cultures of pus for bacteria and fungus were negative. Skin biopsy of a pustule showed subcorneal spongiform accumulation of neutrophils, slight dermal edema, and perivascular infiltration (Supplementary Figure). No evidence of leukocytoclastic vasculitis was found. The patient was diagnosed with AGPB. Intravenous cefuroxime was administered at a single dose of 1.5 g twice daily for 7 days. The pustules cleared, with gradual resolution of the sore throat. No pustules were observed during the 1-year follow-up.

Skin manifestations of infections in other organs and tissues are diverse and are often the first observed signs of a disease. AGPB was first described by Andrews et al [2] in 1935. It has also been called pustular bacterid or pustulosis acuta generalisata [3], which is characterized by the presence of acral pustulosis, mostly with a focal infection [4].

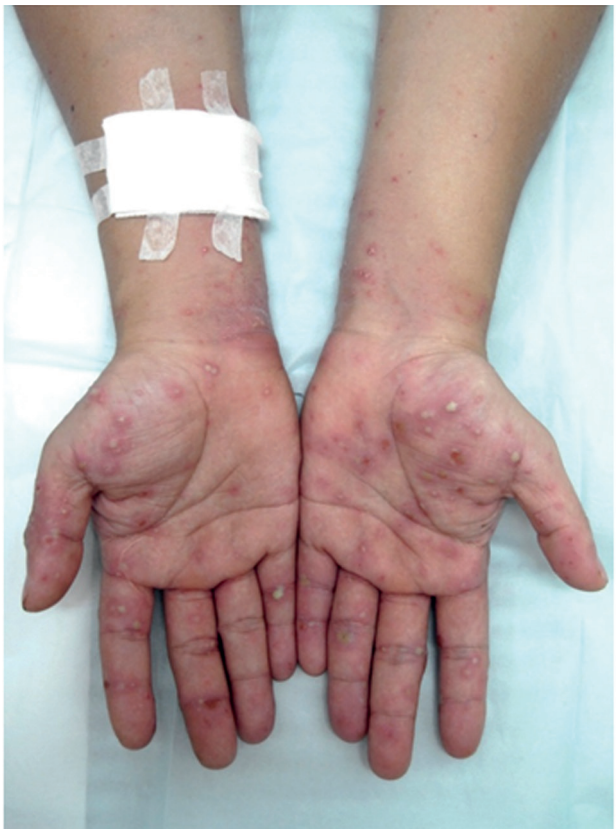

Figure. Multiple isolated discrete pustules surrounded by a narrow rim of erythema. The pustules vary in size from 2 to 6 mm in diameter and are distributed on both hands and, to a lesser extent, the forearms.

AGPB manifests as sterile, isolated, small pustules with an erythematous halo. The rash is neither edematous nor scaly, and the diameter of the pustules has a range of several millimeters. AGPB mainly affects the palms and the soles, and, to a lesser extent, other parts of the limbs [4]. Occasionally, AGPB is generalized. There is usually intermittent fever, and a few cases present rare complications (eg, glomerulonephritis, arthralgia, and ankylosing spondylitis) as the disease progresses. AGPB sometimes co-occurs with Tietze syndrome and sternocostoclavicular hyperostosis. Most pustules resolve within 12 days after onset. Skin specimens in AGPB show subcorneal spongiform accumulation of neutrophils and perivascular infiltration. Leukocytoclastic vasculitis and neutrophilic panniculitis can sometimes be observed [4].

The features that point us to the correct diagnosis of AGPB include absence of psoriasis or other skin conditions, focal

infection (eg, tonsils, gums, sinuses, vagina), and clearance of the pustules by eradication of the infection [2,4]. The triad of sudden onset of the disease, acral distribution of the pustules, and concomitant sore throat with high fever in the case we report was consistent with AGPB. The differential diagnosis for AGPB is exhaustive and includes pustular psoriasis, AGEP, palmoplantar pustulosis (PPP), and dermatophytid reaction (Supplementary Material). Unlike patients with AGPB, most patients with pustular psoriasis have a relapsing course with Munro microabscesses and psoriasiform acanthosis, which are diagnostic. The patient with AGEP usually has a history of drug intake, and the pustules are tiny and mostly affect the inguinal folds or other intertriginous areas [5]. All these features are sufficient to confirm AGPB. PPP is a recalcitrant recurrent afebrile pustular dermatosis. In contrast to AGPB, the typical PPP pustule is confined to the palms and the soles. Although similar pustules present in dermatophytid reaction, they take the form of generalized eczematous eruptions caused by remote localized infection by tinea or staphylococcal colonization, which can be excluded in the case we report.

Many factors contribute to the formation of pustules in AGPB. Onset is usually shortly after a focal infection such as pharyngitis or tonsillitis by group A β-hemolytic streptococci or other bacteria [4,6]. It is speculated that superantigens and toxins from the bacteria upregulate the expression of tumor necrosis factor α and interferon γ, leading to activation of the complement C3 and C5a cascade. Complement C5a has been proven to be an attractant for neutrophil accumulation in the epidermis and results in pustular eruptions.

There is a proven causative relationship between AGPB and focal bacterial infections, and AGPB usually follows a focal bacterial infection. Clinicians should consider this diagnosis in individuals with sudden onset of acral pustular eruptions. Recognizing and eradicating focal infections are the most important steps in the management of AGPB and can reduce misuse and overuse of antibiotics. Pustules in AGPB usually resolve spontaneously in 7-14 days without relapse; therefore, most authors agree that aggressive treatment is unnecessary [4]. Antibiotics are still one of the mainstays of treatment and improve outcomes in those who have previously been infected or who could develop complications of glomerulonephritis and reactive arthritis [4]. The fact that AGPB with tonsillitis is aggravated after tonsillectomy indicates that eradication of the infection alone is not a radical cure for some patients. Corticosteroids showed no beneficial effect on the patient, although methotrexate and group A streptococcal vaccination have proven effective in some patients.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Cheng Tan

Department of Dermatology, Affiliated hospital of Nanjing University of Chinese Medicine
155 Hanzhong Road, Nanjing, China, 210029
E-mail: tancheng@yeah.net

1. NOMBRE DEL MEDICAMENTO. Bilaxten 20 mg comprimidos. **2. COMPOSICIÓN CUALITATIVA Y CUANTITATIVA.** Cada comprimido contiene 20 mg de bilastina. Para consultar la lista completa de excipientes ver sección 6.1. **3. FORMA FARMACÉUTICA.** Comprimido. Comprimidos blancos ovales biconvexos y ranurados (longitud 10 mm, anchura 5 mm). La ranura sirve únicamente para fraccionar y facilitar la deglución pero no para dividir en dosis iguales. **4. DATOS CLÍNICOS. 4.1 Indicaciones terapéuticas.** Tratamiento sintomático de la rinoconjuntivitis alérgica (estacional y perenne) y de la urticaria. Bilaxten 20 mg comprimidos está indicado en adultos y adolescentes (edad igual o superior a 12 años). **4.2 Posología y forma de administración.** Posología. Adultos y adolescentes (edad igual o superior a 12 años). 20 mg de bilastina (1 comprimido) una vez al día para el alivio de los síntomas de la rinoconjuntivitis alérgica (RAE y RAP) y de la urticaria. El comprimido debe administrarse una hora antes o dos horas después de la ingesta de alimentos o de zumos de frutas (ver sección 4.5). Poblaciones especiales. Pacientes de edad avanzada. No se requiere ajuste de dosis en pacientes de edad avanzada (ver secciones 5.1 y 5.2). Insuficiencia renal. No se requiere ajustar la dosis en pacientes con insuficiencia renal (ver sección 5.2). Insuficiencia hepática. No hay experiencia clínica en pacientes con insuficiencia hepática. Teniendo en cuenta que bilastina no es metabolizada y que el aclaramiento renal es su principal vía de eliminación, no se espera que la insuficiencia hepática aumente la exposición sistémica por encima del margen de seguridad. Por ello, no se requiere ajustar la dosis en pacientes con insuficiencia hepática (ver sección 5.2). Población pediátrica. El uso de bilastina en niños de entre 0 y 2 años de edad para las indicaciones de rinoconjuntivitis alérgica y urticaria no es relevante. No se ha establecido todavía la seguridad y eficacia de bilastina en niños menores de 12 años de edad. Duración del tratamiento: Para rinitis alérgica el tratamiento debe limitarse al periodo de exposición a los alérgenos. Para rinitis alérgica estacional el tratamiento puede interrumpirse cuando se hayan resuelto los síntomas y reiniciarse en caso de que estos reaparezcan. En rinitis alérgica perenne se puede proponer al paciente el tratamiento continuado durante los periodos de exposición a los alérgenos. Para urticaria la duración del tratamiento depende del tipo, duración y evolución de los síntomas. Forma de administración. Vía oral. El comprimido puede tragarse con agua. Se recomienda administrar la dosis diaria en una única toma. **4.3 Contraindicaciones.** Hipersensibilidad al principio activo o a alguno de los excipientes incluidos en la sección 6.1. **4.4 Advertencias y precauciones especiales de empleo.** Población pediátrica. La eficacia y seguridad de bilastina en niños menores de 12 años de edad no han sido establecidas. En pacientes con insuficiencia renal moderada o severa la administración concomitante de bilastina con inhibidores de la P-glicoproteína, tales como p.ej., ketoconazol, eritromicina, ciclosporina, ritonavir o diltiazem, puede aumentar los niveles plasmáticos de bilastina y por tanto aumentar el riesgo de reacciones adversas de bilastina. Por ello, la administración concomitante de bilastina e inhibidores de la P-glicoproteína debe evitarse en pacientes con insuficiencia renal moderada o severa. **4.5 Interacción con otros medicamentos y otras formas de interacción.** Interacción con alimentos: Los alimentos reducen significativamente la biodisponibilidad oral de bilastina en un 30%. Interacción con zumo de pomelo: La administración concomitante de bilastina 20 mg y zumo de pomelo disminuyó la biodisponibilidad de bilastina en un 30%. Este efecto puede ocurrir también con otros zumos de frutas. El grado de reducción en la biodisponibilidad puede variar entre fabricantes y frutos. El mecanismo responsable de esta interacción es la inhibición del OATP1A2, un transportador de captación, del cual bilastina es sustrato (ver sección 5.2). Los medicamentos que sean sustratos o inhibidores del OATP1A2, tales como ritonavir o rifampicina, podrían igualmente reducir las concentraciones plasmáticas de bilastina. Interacción con ketoconazol o eritromicina: La administración concomitante de bilastina y ketoconazol o eritromicina aumentó el AUC de bilastina en 2 veces y la C_{max} en 2-3 veces. Estos cambios se pueden explicar debido a la interacción con transportadores intestinales de excreción, ya que bilastina es sustrato de la P-gp y no es metabolizada (ver sección 5.2). Estos cambios no parecen afectar al perfil de seguridad de bilastina y ketoconazol o eritromicina, respectivamente. Otros medicamentos que sean sustratos o inhibidores de la P-gp, tal como ciclosporina, podrían igualmente aumentar las concentraciones plasmáticas de bilastina. Interacción con diltiazem: la administración concomitante de bilastina 20 mg y diltiazem 60 mg aumentó la C_{max} de bilastina en un 50%. Este efecto se puede explicar por la interacción con transportadores intestinales de excreción (ver sección 5.2) y no parece afectar al perfil de seguridad de bilastina. Interacción con alcohol: El rendimiento psicomotor tras la administración concomitante de alcohol y 20 mg de bilastina fue similar al observado tras la administración de alcohol y placebo. Interacción con lorazepam: La administración concomitante de bilastina 20 mg y lorazepam 3 mg durante 8 días no potenció los efectos depresores del SNC causados por lorazepam. Población pediátrica. Los ensayos de interacciones se han realizado sólo en adultos. Se espera que el grado de interacción con otros medicamentos y otras formas de interacción sea similar en la población pediátrica de 12 a 17 años de edad. 4.6 Fertilidad, embarazo y lactancia. Embarazo. No hay datos o éstos son limitados relativos al uso de bilastina en mujeres embarazadas. Los estudios en animales no sugieren efectos perjudiciales directos ni indirectos en términos de toxicidad para la reproducción, el parto o el desarrollo postnatal (ver sección 5.3). Como medida de precaución, es preferible evitar el uso de Bilaxten 20 mg comprimidos durante el embarazo. Lactancia. No se ha estudiado en humanos la excreción de bilastina en la leche. Los datos farmacocinéticos disponibles en animales muestran que bilastina se excreta en la leche (ver sección 5.3). Se debe decidir si es necesario interrumpir o abstenerse del tratamiento con Bilaxten 20 mg comprimidos tras considerar el beneficio de la lactancia para el niño y el beneficio del tratamiento para la madre. Fertilidad. No hay datos clínicos o éstos son limitados. En un estudio en ratas no se detectó ningún efecto negativo sobre la fertilidad (ver sección 5.3). 4.7 Efectos sobre la capacidad para conducir y utilizar máquinas. Un estudio realizado para evaluar los efectos de bilastina sobre la capacidad de conducción demostró que el tratamiento con 20 mg no afectó al rendimiento durante la conducción. No obstante, se debe informar a los pacientes de que muy raramente algunas personas experimentan somnolencia, lo que puede afectar a su capacidad para conducir o utilizar máquinas. 4.8 Reacciones adversas. Resumen del perfil de seguridad. La incidencia de acontecimientos adversos en pacientes afectados de rinoconjuntivitis alérgica o urticaria crónica idiopática tratados con bilastina 20 mg en los estudios clínicos fue comparable a la incidencia en pacientes que recibieron placebo (12,7% frente a 12,8%). Los ensayos clínicos de fase II y III realizados durante el desarrollo clínico incluyeron 2.525 pacientes tratados con diferentes dosis de bilastina, de los cuales, 1.697 recibieron 20 mg de bilastina. Adicionalmente, en estos ensayos 1.362 pacientes recibieron placebo. Las reacciones adversas notificadas más frecuentemente por los pacientes tratados con bilastina 20 mg para la indicación de rinoconjuntivitis alérgica o urticaria crónica idiopática fueron cefalea, somnolencia, mareo y fatiga. Estos acontecimientos adversos ocurrieron con una frecuencia similar en los pacientes que recibieron placebo. Resumen tabulado de reacciones adversas.La siguiente tabla muestra las reacciones adversas al menos posiblemente relacionadas con bilastina y notificadas en más del 0,1% de los pacientes tratados con bilastina 20 mg durante el desarrollo clínico (N = 1.697). Las frecuencias se han clasificado de la siguiente forma: Muy frecuentes (≥1/10). Frecuentes (≥1/100 a <1/10). Poco frecuentes (≥1/1.000 a <1/100). Raras (≥1/10.000 a <1/1.000). Muy raras (<1/10.000). Frecuencia no conocida (no puede estimarse a partir de los datos disponibles). Las reacciones raras, muy raras y de frecuencia no conocida no se han incluido en la tabla. Frecuencia no conocida (no puede estimarse a partir de los datos disponibles): se han observado palpitaciones, taquicardia y reacciones de hipersensibilidad (como anafilaxia, angioedema, disnea, erupción cutánea, edema localizado/hinchazón local y eritema) durante el período de post-comercialización. Descripción de las reacciones adversas relevantes. Las reacciones adversas más notificadas fueron dos frecuentes (somnolencia y cefalea) y dos poco frecuentes (mareo y fatiga). Las frecuencias en bilastina frente a placebo fueron 3,06 % vs. 2,86% para somnolencia; 4.01% vs. 3,38% para cefalea; 0,83% vs. 0,59% para mareo y 0,83% vs. 1,32% para fatiga. En casi todas las reacciones adversas mencionadas en la tabla anterior, se observó una incidencia similar en pacientes tratados con 20 mg de bilastina y en pacientes tratados con placebo. La información recogida durante la post-comercialización ha confirmado el perfil de seguridad observado durante el desarrollo clínico. Población pediátrica. Durante el desarrollo clínico, la frecuencia, el tipo e intensidad de las reacciones adversas en adolescentes (de 12 a 17 años) fueron las mismas que las observadas en adultos. La información recogida en esta población (adolescentes) durante la post-comercialización ha confirmado los resultados de los ensayos clínicos. Notificación de sospechas de reacciones adversas. Es importante notificar sospechas de reacciones adversas al medicamento tras su autorización. Ello permite una supervisión continuada de la relación beneficio/riesgo del medicamento. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas a través del Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano: **www.notificaRAM.es**. 4.9 Sobredosis. La información relacionada con sobredosis aguda de bilastina se recoge de la experiencia de los ensayos clínicos realizados durante el desarrollo y durante la post-comercialización. En los ensayos clínicos, tras la administración de bilastina a dosis de 10 a 11 veces la dosis terapéutica (220 mg como dosis única o 200 mg/día durante 7 días) a voluntarios sanos, la frecuencia de acontecimientos adversos tras el tratamiento fue dos veces superior a la observada tras la administración de placebo. Las reacciones adversas más frecuentemente notificadas fueron mareo, cefalea y náusea. No se notificaron acontecimientos adversos graves ni prolongaciones significativas del intervalo QTc. La información recogida durante la post-comercialización coincide con la información obtenida en los ensayos clínicos. La evaluación crítica del efecto de dosis múltiples de bilastina (100 mg durante 4 días) sobre la repolarización ventricular en un estudio cruzado de "thorough QT/QTc" realizado con 30 voluntarios sanos no mostró ninguna prolongación significativa del intervalo QTc. En caso de producirse una sobredosis se recomienda tratamiento sintomático y de soporte. No se conoce ningún antídoto específico para bilastina. **5. PROPIEDADES FARMACOLÓGICAS. 5.1 Propiedades farmacodinámicas.** Grupo farmacoterapéutico: Antihistamínicos de uso sistémico, otros antihistamínicos de uso sistémico. Código ATC: RO6AX29. Bilastina es un antagonista de la histamina no sedante y de acción prolongada, con afinidad antagonista selectiva por los receptores H1 periféricos y sin afinidad por los receptores muscarínicos. Tras la administración de una dosis única bilastina inhibió durante 24 horas las reacciones cutáneas de habón y eritema inducidas por histamina. En ensayos clínicos realizados en pacientes adultos y adolescentes con rinoconjuntivitis alérgica (estacional y perenne), bilastina administrada en una única dosis diaria de 20 mg durante 14-28 días fue eficaz para aliviar los síntomas, tales como estornudos, rinorrea, picor nasal, congestión nasal, picor ocular, lagrimeo y enrojecimiento ocular. Bilastina controló los síntomas de forma eficaz durante 24 horas. En dos ensayos clínicos realizados en pacientes con urticaria crónica idiopática, bilastina administrada en una única dosis diaria de 20 mg durante 28 días fue eficaz para aliviar la intensidad del prurito y el número y tamaño de los habones, así como el malestar de los pacientes derivado de la urticaria. Los pacientes obtuvieron una mejoría en la calidad del sueño y en la calidad de vida. En los ensayos clínicos realizados con bilastina no se observó ninguna prolongación del intervalo QTc ni ningún otro efecto cardiovascular clínicamente relevantes, incluso a dosis hasta 200 mg diarios (10 veces la dosis terapéutica) durante 7 días en 9 sujetos o incluso cuando se administraron de forma concomitante inhibidores de P-gp, tales como ketoconazol (24 sujetos) y eritromicina (24 sujetos). Además se ha llevado a cabo un estudio "thorough QT" en 30 voluntarios. En los ensayos clínicos controlados realizados con la dosis recomendada, 20 mg una vez al día, el perfil de seguridad de bilastina sobre el SNC fue similar al placebo y la incidencia de somnolencia no fue estadísticamente diferente a placebo. Bilastina a dosis hasta 40 mg q.d. no afectó al rendimiento psicomotor en los ensayos clínicos y no afectó a la capacidad de conducción en un estudio estándar de conducción. La eficacia y seguridad de bilastina en los pacientes de edad avanzada (≥ 65 años) incluidos en los estudios de fase II y III no mostraron diferencias con respecto a pacientes más jóvenes. Un estudio post autorización con 146 pacientes de edad avanzada no mostró diferencias en el perfil de seguridad con respecto a la población adulta. Población pediátrica. En el desarrollo clínico se incluyeron adolescentes (de 12 a 17 años). Durante los ensayos clínicos 128 adolescentes recibieron bilastina (81 en ensayos doble ciego de rinoconjuntivitis alérgica). Otros 116 adolescentes fueron asignados al azar a comparadores activos o placebo. No se observaron diferencias en eficacia ni en seguridad entre adultos y adolescentes. La Agencia Europea de Medicamentos ha concedido un aplazamiento para presentar los resultados de los ensayos realizados con Bilaxten en un grupo de la población pediátrica en el tratamiento de la rinoconjuntivitis alérgica y en el tratamiento de la urticaria (ver sección 4.2 para consultar la información sobre el uso en población pediátrica). **5.2 Propiedades farmacocinéticas.** Absorción. Bilastina se absorbe rápidamente tras la administración oral con un tiempo hasta alcanzar la concentración plasmática máxima de aproximadamente 1,3 horas. No se ha observado acumulación. La biodisponibilidad oral media de bilastina es del 61%. Distribución. Estudios in vitro e in vivo han demostrado que bilastina es un substrato de la P-gp (ver sección 4.5 Interacción con ketoconazol, eritromicina y diltiazem) y del OATP (ver sección 4.5 Interacción con zumo de pomelo). Bilastina no parece ser un substrato del transportador BCRP ni de los transportadores renales OCT2, OAT1 y OAT3. En base a los estudios in vitro, no cabe esperar que bilastina inhiba los siguientes transportadores a nivel de la circulación sistémica: P-gp, MRP2, BCRP, BSEP, OATP1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT1, OCT2, y NTCP, ya que sólo se detectó una ligera inhibición para P-gp, OATP2B1 y OCT1, estimándose una $CI_{50} \geq 300$ µM, muy superior a la concentración plasmática máxima C_{max} y por ello, estas interacciones carecen de relevancia clínica. Sin embargo, en base a estos resultados no se puede descartar que bilastina sea inhibidor de transportadores presentes en la mucosa intestinal, como por ejemplo P-gp. A las dosis terapéuticas la unión de bilastina a las proteínas plasmáticas es de 84-90%. Metabolismo o Biotransformación. En estudios in vitro bilastina no indujo ni inhibió la actividad de los isoenzimas del CYP450. Eliminación. En un estudio de balance de masas realizado en voluntarios sanos, tras la administración de una dosis única de 20 mg de ^{14}C-bilastina, casi el 95% de la dosis administrada fue recuperada en orina (28,3%) y heces (66,5%) como bilastina inalterada, confirmando que bilastina no es significativamente metabolizada en humanos. La vida media de eliminación calculada en voluntarios sanos fue de 14,5 h. Linealidad/ No linealidad. Bilastina presenta una farmacocinética lineal en el rango de dosis estudiado (5 a 220 mg), con una baja variabilidad interindividual. Insuficiencia renal. En un estudio realizado en sujetos con insuficiencia renal la $AUC_{0-\infty}$ media (DE) aumentó de 737,4 (±260,8) ngxhr/ml en sujetos sin insuficiencia (IFG: > 80 ml/min/1,73 m^2) a: 967,4 (±140,2) ngxhr/ml en sujetos con insuficiencia leve (IFG: 50-80 ml/min/1,73 m^2), 1384,2 (±263,23) ngxhr/ml en sujetos con insuficiencia moderada (IFG: 30 - <50 ml/min/1,73 m^2), y 1708,5 (±699,0) ngxhr/ml en sujetos con insuficiencia severa (IFG: < 30 ml/min/1,73 m^2). La semivida de eliminación (media ± DE) de bilastina fue de 9,3 h (± 2,8) en sujetos sin insuficiencia, 15,1 h (± 7,7) en sujetos con insuficiencia leve, 10,5 h (± 2,3) en sujetos con insuficiencia moderada y 18,4 h (± 11.4) en sujetos con insuficiencia severa. La excreción urinaria de bilastina fue completa tras 48 -72 h en todos los sujetos. No cabe esperar que estos cambios farmacocinéticos tengan una influencia clínicamente relevante sobre la seguridad de bilastina, ya que los niveles plasmáticos de bilastina en pacientes con insuficiencia renal continúan estando dentro del rango de seguridad de bilastina. Insuficiencia hepática. No hay datos farmacocinéticos en sujetos con insuficiencia hepática. Bilastina no es metabolizada en humanos. Puesto que los resultados del estudio en insuficiencia renal indican que la vía renal es la principal responsable de la eliminación cabe esperar que la excreción biliar sólo esté implicada de forma marginal en la eliminación de bilastina. No se espera que los cambios en la función hepática tengan una influencia clínicamente relevante en la farmacocinética de bilastina. Pacientes de edad avanzada. En sujetos mayores de 65 años sólo se dispone de datos farmacocinéticos limitados. No se han observado diferencias estadísticamente significativas en la farmacocinética de bilastina en pacientes de edad avanzada (mayores de 65 años) comparados con la población adulta de edad comprendida entre 18 y 35 años. Población pediátrica. No se dispone de datos farmacocinéticos en adolescentes (de 12 a 17 años) aunque se considera apropiada la extrapolación a partir de los datos disponibles en adultos. 5.3 Datos preclínicos sobre seguridad. Los datos de los estudios no clínicos no muestran riesgos especiales para los seres humanos según los estudios convencionales de farmacología de seguridad, toxicidad a dosis repetidas, genotoxicidad y potencial carcinogénico. En los estudios de toxicidad para la reproducción únicamente se observaron efectos de bilastina sobre el feto (pérdidas pre- y post-implantación en ratas y osificación incompleta de huesos craneales, esternón y miembros en conejos) a dosis tóxicas para la madre. Los niveles de exposición determinados por las NOAEL son superiores (> 30 veces) a los niveles de exposición alcanzados en humanos a la dosis terapéutica recomendada. En un estudio sobre lactancia se detectó bilastina, en la leche de ratas en periodo de lactancia, tras la administración de una dosis única oral (20 mg/kg). Las concentraciones de bilastina en la leche fueron de alrededor de la mitad de las del plasma materno. Se desconoce la relevancia de estos resultados para los humanos. En un estudio de fertilidad en ratas, la administración oral de bilastina a dosis hasta 1000 mg/kg/día no indujo ningún efecto sobre los órganos reproductivos de los machos ni de las hembras. Los índices de apareamiento, fertilidad y gravidez no se vieron afectados. Tal y como se observó en un estudio de distribución en ratas con determinación de las concentraciones de fármaco por autorradiografía, bilastina no se acumula a nivel del SNC. **6. DATOS FARMACÉUTICOS. 6.1 Lista de excipientes.** Celulosa microcristalina. Carboximetilalmidón sódico tipo A (derivado de patata). Sílice coloidal anhidra. Estearato magnésico. **6.2 Incompatibilidades.** No procede. **6.3 Periodo de validez.** 5 años. **6.4 Precauciones especiales de conservación.** Este medicamento no requiere condiciones especiales de conservación. **6.5 Naturaleza y contenido del envase.** El medicamento está envasado en un blíster, que consta de dos partes: 1. Laminado, compuesto por poliamida orientada (cara exterior del laminado), aluminio y PVC (cara interior del laminado). 2. Película de aluminio. Después del moldeado y llenado con comprimidos, la película de aluminio es termosellada al laminado con una laca de sellado por calor (copolímero de PVC-PVAC y resinas de butilmetacrilato). Cada blíster contiene 10 comprimidos. Los blísters están envasados en estuches de cartón. Tamaños de envase: 10, 20, 30, 40 o 50 comprimidos. Puede que solamente estén comercializados algunos tamaños de envases. **6.6 Precauciones especiales de eliminación y otras manipulaciones.** La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él, se realizará de acuerdo con la normativa local. **7. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN. FAES FARMA, S.A.** Máximo Aguirre, 14. 48940 – Leioa. **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN.** 73.027. **9. FECHA DE LA PRIMERA AUTORIZACIÓN/ RENOVACIÓN DE LA AUTORIZACIÓN.** Fecha de la primera autorización: 23 de noviembre de 2010. Fecha de la última renovación: 07 de octubre de 2015. **10. FECHA DE LA REVISIÓN DEL TEXTO.** Enero 2017. **11. PRESENTACIÓN Y P.V.P. I.V.A.:** Bilaxten 20 mg, 20 comprimidos, P.V.P. I.V.A. 12,80 €. **12. CONDICIONES DE PRESCRIPCIÓN Y DISPENSACIÓN:** Con receta médica. Reembolsable por el Sistema Nacional de Salud. Para más información consulte la ficha técnica completa en www.aemps.gob.es.

Clasificación por órganos del sistema		Bilastina 20 mg N=1697	Bilastina cualquier dosis N=2525
Frecuencia	**Reacción adversa**		
Infecciones e infestaciones			
Poco frecuentes	*Herpes labial*	2 (0,12%)	2 (0,08%)
Trastornos del metabolismo y de la nutrición			
Poco frecuentes	*Aumento de apetito*	10 (0,59%)	11 (0,44%)
Trastornos psiquiátricos			
Poco frecuentes	*Ansiedad*	6 (0,35%)	8 (0,32%)
	Insomnio	2 (0,12%)	4 (0,16%)
Trastornos del sistema nervioso			
Frecuentes	*Somnolencia*	52 (3,06%)	82 (3,25%)
	Cefalea	68 (4,01%)	90 (3,56%)
Poco frecuentes	*Mareo*	14 (0,83%)	23 (0,91%)
Trastornos del oído y del laberinto			
Poco frecuentes	*Tinnitus*	2 (0,12%)	2 (0,08%)
	Vértigo	3 (0,18%)	3 (0,12%)
Trastornos cardiacos			
Poco frecuentes	*Bloqueo de rama derecha*	4 (0,24%)	5 (0,20%)
	Arritmia sinusal	5 (0,30%)	5 (0,20%)
	Electrocardiograma QT prolongado	9 (0,53%)	10 (0,40%)
	Otras anomalías del ECG	7 (0,41%)	11 (0,44%)
Trastornos respiratorios, torácicos y mediastínicos			
Poco frecuentes	*Disnea*	2 (0,12%)	2 (0,08%)
	Molestias nasales	2 (0,12%)	2 (0,08%)
	Sequedad nasal	3 (0,18%)	6 (0,24%)
Trastornos gastrointestinales			
Poco frecuentes	*Dolor abdominal superior*	11 (0,65%)	14 (0,55%)
	Dolor abdominal	5 (0,30%)	5 (0,20%)
	Náusea	7 (0,41%)	10 (0,40%)
	Molestias gástricas	3 (0,18%)	4 (0,16%)
	Diarrea	4 (0,24%)	6 (0,24%)
	Sequedad bucal	2 (0,12%)	6 (0,24%)
	Dispepsia	2 (0,12%)	4 (0,16%)
	Gastritis	4 (0,24%)	4 (0,16%)
Trastornos de la piel y del tejido subcutáneo			
Poco frecuentes	*Prurito*	2 (0,12%)	4 (0,16%)
Trastornos generales y alteraciones en el lugar de administración			
Poco frecuentes	*Fatiga*	14 (0,83%)	19 (0,75%)
	Sed	3 (0,18%)	4 (0,16%)
	Mejoría de una condición preexistente	2 (0,12%)	2 (0,08%)
	Pirexia	2 (0,12%)	3 (0,12%)
	Astenia	3 (0,18%)	4 (0,16%)
Exploraciones complementarias			
Poco frecuentes	*Aumento de Gamma-glutamiltransferasa*	7 (0,41%)	8 (0,32%)
	Aumento de Alanin aminotransferasa	5 (0,30%)	5 (0,20%)
	Aumento de Aspartato aminotransferasa	3 (0,18%)	3 (0,12%)
	Aumento de creatinina plasmática	2 (0,12%)	2 (0,08%)
	Aumento de triglicéridos plasmáticos	2 (0,12%)	2 (0,08%)
	Aumento de peso	8 (0,47%)	12 (0,48%)

BIBLIOGRAFÍA: 1. Datos internos de la compañía 2. Bilaxten 20 mg, comprimidos. Bilastina 20 mg. Titular Faes Farma S.A, Ficha Técnica autorizada. Revisión del texto enero 2017.

Journal of
Investigational Allergology
and Clinical Immunology

PREMIO PROFESOR ALBERTO OEHLING

La SEAIC, en agradecimiento a la labor desarrollada por el Profesor Alberto Oehling, uno de los pioneros de la Alergología en España y fundador de la revista *Journal of Investigational Allergology and Clinical Immunology*, ha decidido convocar bianualmente los premios "Profesor Alberto Oehling".

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1. Este premio tiene por objetivo incentivar la publicación de artículos originales de calidad en el *Journal of Investigational Allergology and Clinical Immunology*, órgano oficial de la SEAIC.
2. Se concederá un primer premio de 5.000 euros y un accésit de 2.000 euros.
3. Optarán a los premios todos los artículos originales publicados en el JIACI en el periodo de tiempo comprendido desde el 1 de octubre del presente año hasta el 30 de septiembre del año siguiente, en los que al menos un firmante sea Socio Numerario de la Sociedad Española de Alergología e Inmunología Clínica, salvo deseo expreso de los autores de no optar al mismo.
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