Successful Subcutaneous Desensitization to Certolizumab Pegol

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Certolizumab pegol (CZP) is a recombinant, humanized antibody Fab' fragment that targets tumor necrosis factor α (TNFα). It is conjugated to polyethylene glycol (PEG) and has an approximate molecular weight of 20 000 g/mol. CZP has been approved for chronic autoimmune and inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, and plaque psoriasis. The recommended dose is 400 mg (2 subcutaneous injections of 200 mg each on 1 day) at weeks 0, 2, and 4, followed by a maintenance dose of 200 mg every 2 weeks [1]. Adverse effects, including paradoxical psoriasiform eruptions and hypocomplementemic urticaria-vasculitis have been reported [2,3]. Hypersensitivity reactions to CZP have been described, both to the anti-TNF portion of the antibody and to the PEG component [4,5].

We present the case of a 30-year-old woman with a medical history of spondyloarthritis treated for 2 years with CZP until its suspension due to severe pain at the injection site. A year later, CZP had to be reintroduced because of ineffective treatment with golimumab. Within 60-90 minutes of the first subcutaneous injection of 400 mg of CZP, the patient developed pruritic, erythematous papules on the neck, trunk, and extremities. A 4-day treatment with oral methylprednisolone 40 mg and ebastine 10 mg was indicated, with complete resolution of the lesions and no residual hyperpigmentation or desquamation. Two weeks later, she received 400 mg of subcutaneous CZP and presented a similar reaction; therefore, treatment was interrupted, and the patient was referred to the allergy department.

After providing her written informed consent, the patient underwent a skin prick test (SPT) with certolizumab (200 mg/mL) and an intradermal test (IDT) at 2, 20, and 200 mg/mL. A positive result (5-mm wheal) was obtained 20 minutes after the 200-mg/mL IDT. Four hours later, the patient developed several slightly pruritic erythematous papules on her right forearm (where the IDT was performed). The lesions resolved within 24 hours after application of a topical corticosteroid. These concentrations were nonirritant in 4 healthy controls. Furthermore, SPTs with strawberry flavor

Table. Desensitization Protocol for Certolizumab Pegol.

Desensitization						
Step	**Time, min**	**Concentration, mg/mL**	**Volume, mL**	**Dose administered with this step, mg**	**Cumulative dose, mg**	**Comment**
1	0	2	1	2	2	X
2	30	20	0.2	4	6	X
3	60	20	0.4	8	14	X
4	90	20	0.8	16	30	X
5	120	200	0.16	32	62	X
6	150	200	0.32	64	126	X
7	180	200	0.64	128	254	X
8	210	200	0.73	146	400	X
Observation: 60 min						
Total time: 270 min						

chewable alginate antacid tablets (Gaviscon, containing PEG 20 000) were performed at 0.25, 2.5, 25, and 250 mg/mL. The results were negative, thus ruling out allergy to the excipient. Therefore, the patient was recommended to avoid TNFα inhibitors.

After 13 months of treatment with secukinumab (IgG1/κ monoclonal antibody), which proved to be ineffective, the patient was again referred to the allergy department to consider the possibility of prescribing etanercept, another TNFα inhibitor. An SPT (50 mg/mL) and IDT (0.5 mg/mL and 5 mg/mL) to etanercept yielded negative results, leading us to perform a drug challenge, which also yielded a negative result (cumulative dose of 50 mg). Unfortunately, this treatment, as well as subsequent treatment with ixekizumab (anti–IL-17A antibody), was unsuccessful. Therefore, both options were discontinued, and the patient was referred to the allergy department to undergo a desensitization procedure with certolizumab.

Cetirizine 10 mg and ranitidine 50 mg were administered 30 minutes before the procedure. CZP was administered in a 3-solution, 8-step regimen with an initial subcutaneous dose of 2 mg that was gradually increased every 30 minutes until a cumulative dose of 400 mg was reached (Table). Cetirizine 10 mg and famotidine 40 mg were prescribed daily for 3 days after the procedure. No incidents were reported. An identical procedure carried out 2 weeks later caused no adverse reactions. As the interval of 14 days did not exceed 2 half-lives of the medication, the third dose comprised the full dose of 400 mg divided between both arms, with no adverse reactions. The next dose was 200 mg, which the patient received in a single dose in a prefilled syringe with good tolerance (12 weeks) until its withdrawal due to loss of efficacy.

The positive skin test result with CZP proves that an immune mechanism could be involved in the reaction experienced by the patient. Among TNFα inhibitors, infliximab has caused the highest number of hypersensitivity reactions [6], although the literature contains few data on cross-reactivity between drugs in this group. Reactions to infliximab and subsequent tolerance to adalimumab have been reported [7,8]. However, there are no cross-reactivity studies comparing CZP and etanercept. Consequently, after confirming hypersensitivity to certolizumab, we assessed allergy to etanercept and confirmed that it was tolerated.

Desensitization procedures enable allergic patients to receive the best treatment option for their disease. Cases series of subcutaneous desensitization with biologic drugs have been described. In the case of TNFα inhibitors, desensitization protocols to adalimumab and etanercept are also available, although, to date, no desensitization protocols to golimumab or certolizumab have been published [9].

To our knowledge, we describe the first desensitization protocol to certolizumab, in a case of confirmed allergy to CZP with tolerance to another TNFα inhibitor, etanercept.

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Conflicts of Interest

R. Mielgo has received fees for her collaboration as a speaker and/or consultant on advisory boards, in research projects, and at conferences and for course attendance from Novartis, Sanofi, GSK, AstraZeneca, ALK Abello, Allergy Therapeutics, Organon, LETI, Shire, Behring, FAES, and Chiesi, all outside the current work. The remaining authors declare that they have no conflicts of interest.

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