Hypersensitivity to the CGRP Inhibitor Monoclonal Antibodies Galcanezumab, Erenumab, and Fremanezumab With Tolerance to Eptinezumab

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Erenumab, fremanezumab, galcanezumab, and eptinezumab are IgG monoclonal antibodies (mAbs) that act against calcitonin gene–related peptide (CGRP) and are indicated for prophylaxis of migraine. While fremanezumab, galcanezumab, and eptinezumab bind to the CGRP molecule, erenumab acts against the CGRP receptor. The drugs are administered subcutaneously and monthly, except fremanezumab, which can also be prescribed every 3 months, and eptinezumab, which is administered intravenously every 12 weeks.

Hypersensitivity to CGRP-mAbs was first described in a case of nonimmediate allergy to fremanezumab confirmed by positive results in intradermal tests (IDTs), in which tolerance to other CGRP-mAbs was not evaluated [1]. González-Cano et al [2] subsequently published a case of immediate hypersensitivity reaction to galcanezumab (confirmed by positive IDT and basophil activation test [BAT] results) with tolerance to erenumab and fremanezumab [2]. In addition, a case of symmetrical drug-related intertriginous and flexural exanthema after injection of erenumab with subsequent tolerance to fremanezumab has been reported [3]. No cases of allergy to eptinezumab have been published.

We present the case of a 52-year-old woman with chronic migraine who received a first dose of fremanezumab, which she tolerated. A few minutes after the second and third injections, she developed a maculopapular pruritic erythematous lesion at the injection site, which resolved spontaneously 4-5 days later, leaving a postinflammatory hyperpigmented lesion for 2 weeks. Fremanezumab was discontinued, and she received a single dose of erenumab, presenting a similar reaction.

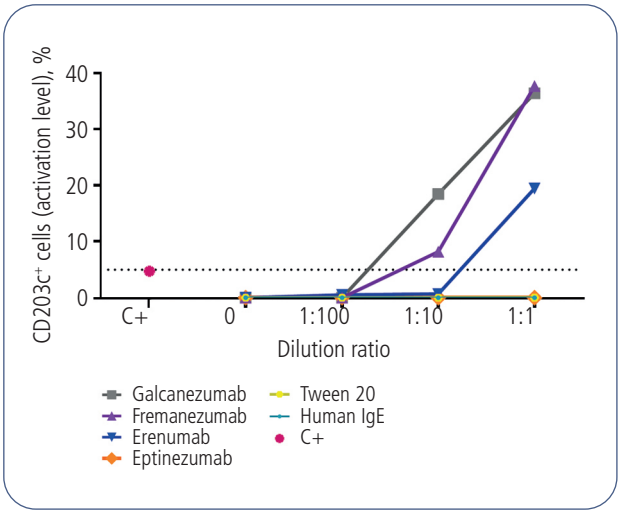

Figure. Activation of basophils.

After that, she received galcanezumab, developing a similar, somewhat more extensive lesion.

Skin prick tests with fremanezumab, erenumab, and galcanezumab yielded a negative result in the immediate and delayed readings. IDTs with fremanezumab (225 mg/mL), erenumab (70 mg/mL), and galanezumab (120 mg/mL) revealed an immediate positive result at dilutions of 1/10, 1/100, and 1/1000. An IDT with eptinezumab (100 mg/mL) was negative in the immediate and delayed readings. A BAT (BasoFlowExExbio) was performed using the biological drugs [4], the patient's blood sample, and blood from a nonatopic healthy control. The basophil population was defined as CD203cpos/SSClow by flow cytometry. The results are expressed as the percentage of CD63-positive basophils (activated basophils). Dose–response curves were constructed starting with the undiluted drug, followed by serial 1:10 dilutions in phosphate-buffered saline. A cross-linking anti-IgE antibody mixed with a stimulating peptide, N-formyl-Met-Leu-Phe, was used as a positive control. Basophils from the healthy volunteer were only activated with the positive control. Regarding the patient, addition of undiluted galcanezumab (1:1; 120 mg/mL) and a 1:10 dilution activated basophils up to 36.5% and 18.5%, respectively, in a dose–response manner (Figure). Similarly, undiluted fremanezumab (1:1; 150 mg/mL) and a 1:10 dilution activated up to 37.8% and 8.2% of basophils in each case (Figure). Finally, only undiluted erenumab caused a remarkable activation of basophils (19.5%). Interestingly, eptinezumab did not cause basophil activation, in agreement with the observations made in the skin prick test and IDT (Figure). In order to determine whether the allergic reactions were caused by any components of biological drugs, we performed a BAT with a common excipient (Tween 20, at 2 dilutions, 1:10 and 1:100) and with IgG extract (190 mg/L at 1:1, 1:10 and 1:100). We did not observe any activation. A more detailed description of the methodology is available in the supplementary material. The patient subsequently underwent a challenge with eptinezumab and now tolerates the drug.

To our knowledge, only 1 case of immediate allergy to CGRP-mAb has been published; the authors demonstrated hypersensitivity to galcanezumab with tolerance to erenumab and fremanezumab [2]. Although this case suggested probable low cross-reactivity between the subcutaneous CGRP-mAbs, the present case raises possible cross-reactivity in some patients. Differences in cross-reactivity could be due to different hypersensitivity mechanisms. Therefore, in the case of suspected hypersensitivity reactions to a CGRP-mAb, we suggest performing an allergy test for confirmation and evaluating possible alternatives.

In conclusion, we present a case of hypersensitivity to subcutaneous CGRP-mAbs (galcanezumab, erenumab, and fremanezumab) confirmed by IDT and BAT, with tolerance to eptinezumab.

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Conflicts of Interest

J.S. reports having served as a consultant to Thermo Fisher, MEDA, Novartis, Sanofi, Leti, FaesFarma, Mundipharma, and GSK. He has also received lecture fees from Novartis, GSK, Stallergenes, Leti, Sanofi, and FaesFarma and grant support for research from Thermo Fisher, Sanofi, and ALK. B.B. reports having received personal lecture fees from Roxall outside the submitted work. D.B. reports having received grant support for research from Instituto Carlos III and having served as a consultant for Astra Zeneca. M.V.M. has served as a consultant for Organon and received honoraria for lectures from GSK and Astra Zeneca. J.R.V. reports having received honoraria for lectures and presentations from Teva, Lilly, Novartis, and Lumbeck and having participated on advisory boards for Lilly and Novartis. J.M.R.M. reports receiving payments for lectures and educational events form Astra Zeneca and GSK. V.P. reports having been paid lecture fees by GSK and AstraZeneca and having received grant support for research from Astra Zeneca and Sanofi. The remaining authors declare that they have no conflicts of interest.

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