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First confirmed case of nonimmediate hypersensitivity to fremanezumab during chronic migraine treatment

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First published: 06 December 2021

<https://doi-org.bibliosan.clas.cineca.it/10.1111/cod.14018>

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CONTACT POINT

Fremanezumab is a humanized anti-IgG2Δa/kappa monoclonal antibody that inhibits the calcitonin gene-related peptide (CGRP), indicated for the prophylaxis of chronic migraine in adults.¹⁻³ To date, hypersensitivity reactions confirmed with skin tests have not been reported.⁴

CASE REPORT

A 52-year-old female with a 20-year history of chronic refractory migraines started a treatment with subcutaneous fremanezumab injections (AJOVY, TEVA GmbH, Ulm Germany) initiated at a dose of 225 mg every 4 weeks. Forty-eight hours after the second administration she developed a localized, itchy erythematous plaque (20 × 15 cm) at the injection site on the right lower quadrant of her abdomen (Figure 1A). She was initially treated with oral cetirizine 10 mg and topical methylprednisolone aceponate 1 mg/g, without improvement. Subsequently, microvesicles developed on the plaque and a herpes zoster infection was suspected and treated with oral acyclovir 800 mg five times daily. Topical copper sulfate 1 mg/mL and topical fusidic acid 20 mg/g was used three times per day, again without clinical improvement. In the following days the skin lesion further increased in size (20 × 22 cm) and a second smaller plaque appeared underneath (2 × 2 cm), with both lesions now showing multiple, pinhead-sized micropustules (Figure 1B), evolving into small erosions. At the Emergency Department she was eventually treated with oral desloratadine 5 mg every 24 hours and topical clobetasol propionate 0.5 mg/g, which made the skin lesions disappear in 1 week, leaving only hyperpigmentation that resolved with mild desquamation

after 4 weeks.



FIGURE 1

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(A) An erythematous plaque appeared 48 hours after the administration of a fremanezumab-containing drug on the right lower quadrant of the patient's abdomen and (B) pinhead-sized micropustules appeared on the plaque 6 days later

After obtaining informed consent, an allergy work-up was performed 4 weeks after the skin reaction. As fremanezumab itself was not available, skin test dilutions were prepared by the Pharmacy Department using the commercialized drug AJOVY 225 mg/1.5 mL (150 mg/mL), which includes polysorbate 80 and ethylenediaminetetraacetic acid (EDTA) as excipients. Patch tests, performed on the upper back and on the residual skin lesion on the abdomen with the fremanezumab-containing drug (at 1%, 5%, and 30% dilutions in pet. saline, and in dimethyl sulfoxide) using patch test chambers (Curatest) and a 2-day occlusion, showed negative results on days (D) 2, 4, and 7.

A skin prick test (SPT) to the fremanezumab-containing drug (150 mg/mL) was negative. Intradermal tests (IDTs; 0.15, 1.5, 15, and 150 mg/mL) with immediate and delayed readings (D1, D2, and D3) showed a positive result only in the delayed readings, and this for the 1.5, 15, and 150 mg/mL concentrations (Figure 2). Five healthy controls showed no immediate nor delayed reactions to these IDTs at all concentrations. An SPT to polysorbate 80 (undiluted) and IDT to polysorbate 80 at 1/100 and 1/10 dilutions also showed negative results in the delayed readings (24, 48, and 72 hours), ruling out a possible involvement of this excipient in our patient. The patient tolerated the EDTA excipient, which was found to be present in other drugs she was taking.





FIGURE 2

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Positive intradermal test results to several dilutions of a fremanezumab-containing drug (delayed readings on day 3)

DISCUSSION

Chronic migraine preventive treatments with monoclonal antibodies are a promising therapeutic target for a disease with an increasing prevalence.^{1,2,5} Although adverse events to these drugs have been reported, including self-reported suspected immunoglobulin E-mediated reactions,^{6,7} hypersensitivity reactions confirmed with skin tests have not yet been published.

Although the clinical characteristics of the skin reaction in our patient seemed to suggest an acute localized exanthematous pustulosis, a skin biopsy could not be performed. Nevertheless, the clinical presentation and skin test results are compatible with a delayed-type hypersensitivity.

Because of the lack of published data on standardized skin tests with fremanezumab-containing drugs, IDTs to several dilutions, including full-strength concentration, were performed, which confirmed that these concentrations may be useful.

In conclusion, we present a first case of a skin test-confirmed, nonimmediate (delayed-type)

hypersensitivity reaction to fremanezumab, a CGRP inhibitor monoclonal antibody.

CONFLICTS OF INTEREST

I.G-M. is a speaker and investigator and on advisory boards for Novartis, AstraZeneca, Teva, GSK, Sanofi Genzyme, Chiesi, Allergy Therapeutics, Leti, Stallergenes Greer, and Orion Pharma. The rest of the authors declare that they have no relevant conflicts of interest.

AUTHOR CONTRIBUTIONS

Beatriz Moya: Conceptualization (lead); methodology (lead); project administration (equal); resources (lead); writing – original draft (lead); writing – review and editing (equal). **Ruth Barranco:** Conceptualization (supporting); methodology (supporting); project administration (equal); supervision (supporting); writing – original draft (supporting); writing – review and editing (equal). **Ismael García-Moguel:** Conceptualization (supporting); investigation (supporting); methodology (supporting); project administration (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Mario Puerta-Peña:** Conceptualization (supporting); investigation (supporting); methodology (supporting); project administration (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Lucía Alonso:** Conceptualization (supporting); investigation (supporting); methodology (supporting); project administration (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Jesús Fernández-Crespo:** Conceptualization (supporting); methodology (supporting); project administration (supporting); writing – original draft (supporting); writing – review and editing (equal).

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