Delayed Injection Site Reaction to Fremanezumab for Chronic Migraine Treatment

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ABSTRACT

Introduction: Fremanezumab is a humanized monoclonal antibody administered through a subcutaneous injection. It is used for treatment of migraines, and occasional injection site reactions have developed after usage.

Case Presentation: This case report describes a nonimmediate injection site reaction on the right thigh of a 25-year-old female patient after starting treatment with fremanezumab. The injection site reaction presented as 2 warm, red annular plaques 8 days following a second injection of fremanezumab and about 5 weeks following the first injection. She was prescribed a 1-month course of prednisone that relieved her symptoms of redness, itching, and pain.

Discussion: Similar nonimmediate injection site reactions have been reported before, but this particular injection site reaction was significantly more delayed.

Conclusions: Our case illustrates that injection site reactions to fremanezumab can be delayed after the second dose and may require systemic therapy to alleviate symptoms.

INTRODUCTION

Fremanezumab is a subcutaneously injected monoclonal antibody used to treat migraines. Injection site reactions (ISR) have been described occasionally.[1-5] We report an ISR with 2 annular plaques adjacent to an injection site 8 days after the second dose of treatment.

CASE PRESENTATION

A 25-year-old woman presented to dermatology clinic with a warm, annular plaque on her right thigh with pruritus and sharp pain. She had severe, refractory migraines that failed to respond to several treatments, including galcanezumab-gnlm. She did not have any ISRs with other humanized monoclonal antibody treatment against calcitonin gene-related peptide (CGRP). Approximately 5 weeks prior to presentation, she received the first injection of fremanezumab in her right upper arm and did not report rash or complication. However, 8 days following the second injection in her right thigh, 2 round red plaques that quickly expanded appeared around the second injection site. They did not improve with clobetasol, diphenhydramine, cetirizine, acetaminophen, or cold packs. She denied mucosal lesions and otherwise felt well. There was no past or family history of rashes. She had no known allergies to the listed active and inactive ingredients in fremanezumab.

On examination, she had a bright, erythematous, warm, and slightly indurated annular plaque without secondary change (Figure 1). There was a similar but faint plaque inferior to this. A punch biopsy for routine histology was taken of the larger annular plaque (Figure 2). It showed a superficial and deep infiltrate with lymphocytes, eosinophils, and some neutrophils. Bacterial and fungal cultures were negative. The findings were consistent with an ISR.

She discontinued fremanezumab due to the ISR and was switched to incobotulinumtoxinA injections. A 1-month prednisone taper was prescribed, starting at 40 mg daily. Within a few days, the itching, pain, and redness improved.

DISCUSSION

Fremanezumab is a humanized monoclonal antibody that directly inhibits CGRP, which is part of a migraine signaling pathway.

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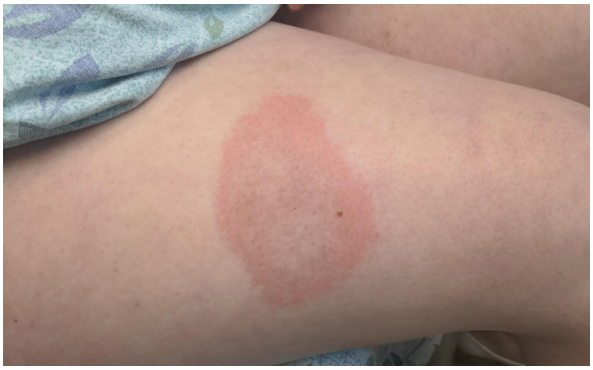
Figure 1. Delayed Injection Site Reaction to Fremanezumab



Clinical photograph of the patient's right thigh shows the bright, erythematous, and slightly indurated annular plaque and the second plaque inferior to it.

The most common adverse reaction is ISR manifesting as localized induration, pain, hemorrhage, or erythema.[6] However, few detailed reports and images exist. The Table provides a summary of publications reporting skin eruptions associated with the use of fremanezumab for treatment of chronic migraines.

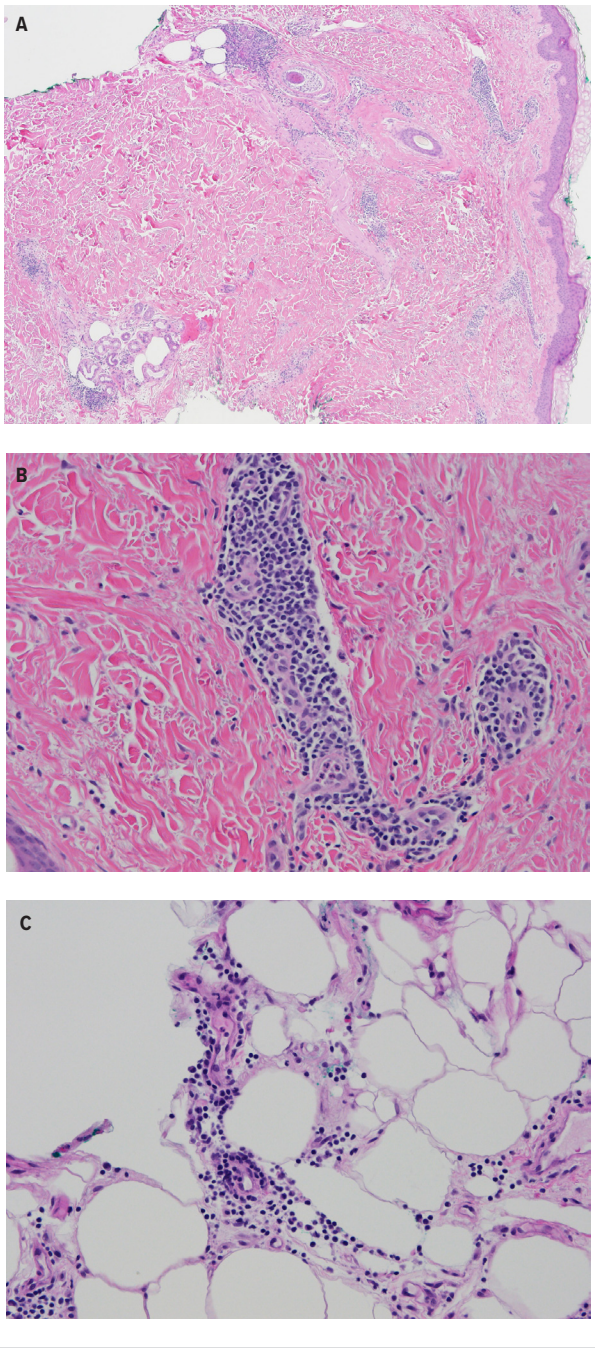
Thomaidou and Ramot classified biologic ISRs or their excipient into 3 types: type α, type β, and recall reactions.[7] Type α reactions are irritative and immediate due to an increase in proinflammatory cytokines from the injected substance. Type β reactions are immunogenic and can be either immediate or delayed responses due to antibody or T-cell induction, respectively. Recall reactions develop at sites where medication was administered previously. The ISR demonstrated in our case would most likely be a type β delayed reaction, which falls under the Type IV hypersensitivity reaction category based on the onset.

Moya et al[1] reported a case of delayed-type ISR to fremanezumab in a 52-year-old woman, which occurred within 48 hours after the second dose. The exanthem was described initially as an erythematous pruritic plaque on the right lower abdomen. Several herpetiform microvesicles then developed. A second plaque with micropustules formed inferiorly. The rash eventually responded to desloratadine and topical clobetasol propionate within a week.

Our case had some overlap but also differences from Moya et al.[1] The ISRs in both cases did not develop until after the second fremanezumab injection, but the onset in our case was even more delayed. Both ISRs had two separate plaques, but ours did not develop vesicles or pustules. It is plausible their case might have been acute localized exanthematous pustulosis or perhaps contact dermatitis, but a biopsy was not obtained.

Similar adverse injection site reactions have been reported with other anti-CGRP monoclonal antibodies. The majority of ISRs for galcanezumab-gnlm occurred on the day of the injection, with only 3 participants having it after 2 weeks.[8] The majority spontaneously resolved and did not lead to treatment discontinuation.

Figure 2. Delayed Injection Site Reaction to Fremanezumab



Punch biopsy with a superficial and deep perivascular and interstitial mixed infiltrate with lymphocytes, eosinophils, and rare neutrophils.
2A: 40x, 2B: 200x superficial; 2C: 200x deep.

Tepper et al reported injection site pain without rash in 4% of patients treated with erenumab (humanized monoclonal antibody targeting the CGRP receptor).[9]

CONCLUSIONS

Our case and review of the literature serve as a reminder that ISRs to fremanezumab can be significantly delayed after a second dose,

Table. Injection Site Reactions (ISR) Associated With Fremanezumab for Treatment of Chronic Migraines

Publication	Demographics	Fremanezumab Regimen	Rash Morphology	Time to Rash Onset	Patient Outcome
Moya et al[1] case report	52-year-old woman	225 mg every 4 weeks	Local, itchy erythematous plaque, 20 x 15 cm at injection site. Microvesicles then developed on plaque followed by pinhead-sized micropustules	48 hours after 2nd dose; delayed ISR	Skin lesion healed in 1 week with oral desloratadine 5 mg every 24 hours and topical clobetasol propionate 0.5 mg/g
Alex et al, retrospective study[2]	n = 16, age range 41.8 ± 16.2 years; female: n = 15 (93.8%)	Baseline 225 mg, followed by monthly doses of 120 mg for 6 months	Not presented	n = 1 (6.3%); acute ISR (within 1 hour)	Symptoms resolved
Sakai et al, clinical trial[3]	n = 25, age range 45.8 ± 7.0 years; female: n = 19 (76.0%)	Quarterly (675 mg at baseline and every 3 months)	Erythema Pruritus	n = 5 (20.0%); acute ISR (within 1 hour) n = 1 (4.0%); information not provided	Symptoms resolved; 1 patient discontinued treatment
	n = 25, age range 46.8 ± 7.9 years; female: n = 23 (92.0%)	Monthly (675 mg at baseline and 225 mg every month for a year)	Erythema Pruritus	n = 7 (28.0%); acute ISR (within 1 hour) n = 2 (8.0%); information not provided	Symptoms resolved; 1 patient discontinued treatment
Goadsby et al, clinical trial[4]	n = 551, age range 43.7 ± 12.0 years; female: n = 484 (88%)	Quarterly (single dose of 675 mg at baseline and placebo at weeks 4 and 8)	Erythema	n = 138 (25%); acute ISR (within 1 hour)	Symptoms resolved
	n = 559, age range 42.6 ± 11.8 years; female: n = 494 (88%)	Monthly (675 mg at baseline and 225 mg at weeks 4 and 8)	Erythema	n = 171 (31%); acute ISR (within 1 hour)	Symptoms resolved
Silberstein et al, clinical trial[5]	n = 376, age range 42.0 ± 12.4 years; female: n = 331 (88%)	Quarterly (single dose of 675 mg at baseline and placebo at weeks 4 and 8)	Erythema	n = 80 (21%); acute ISR (within 1 hour)	Symptoms resolved
	n = 379, age range 40.6 ± 12.0 years; female: n = 330 (87%)	Monthly (675 mg at baseline and 225 mg at weeks 4 and 8)	Erythema	n=75 (20%); acute ISR (within 1 hour)	Symptoms resolved

necessitating a careful history. The reaction might not occur at all injection sites or might be multiple and adjacent to the injection. Finally, systemic therapy might be required.

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