

Ulcerative injection-site reaction associated with dupilumab therapy



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INTRODUCTION

Dupilumab (dupilumab; Regeneron Pharmaceuticals, Inc.) is a fully human monoclonal antibody that inhibits interleukin 4 (IL-4) and IL-13 signaling by specifically binding to the IL-4R- α subunit shared by the IL-4 and IL-13 receptor complexes.¹ Dupilumab is approved by the US Food and Drug Administration (FDA) in patients 6 years or older with moderate-to-severe atopic dermatitis (AD). Additionally, it is approved for moderate-to-severe asthma and chronic rhinosinusitis.^{2,3}

Despite the promising outlook of dupilumab as a therapy for AD, there are a few adverse effects, including injection-site reactions (ISRs), conjunctivitis, nasopharyngitis, and bacterial and herpetic skin infections, that have been reported.⁴ Multiple dupilumab clinical trials have listed nonspecific reports of mild or moderate ISRs.^{2,5} We present what is to our knowledge the first reported case of repeated ulcerative ISRs induced by dupilumab at 2 different injection sites during treatment of AD.

CASE PRESENTATION

A 17-year-old Latina female presented to our clinic with severe AD affecting the face, neck, trunk, and upper extremities. She had previously been treated with short courses of cyclosporine and managed her condition for many years with topical corticosteroids; subsequently, she developed cutaneous atrophy. She was initiated on FDA-approved dupilumab with a 600-mg loading dose, followed by a 300-mg biweekly maintenance dose. She reported clearance of her AD after an initial dose to her abdomen at the office without any complications. She did not report complications after her at-home administration of the second dose to her abdomen. Upon at-home administration of the third injection, the patient

Abbreviations used:

AD: atopic dermatitis
FDA: Food and Drug Administration
ISRs: injection-site reactions

developed erythema, pain, and swelling, which progressed to an ulcer at her abdominal injection site over the following few days. Nine days later, the patient arrived at the office for an examination, where she noted decreased redness and swelling, but her pain persisted. To rule out hematoma from an improper injection technique, the patient received her fourth dose on the upper portion of the arm at the office by a trained nurse, 5 days following her recent office visit. The patient reported that she developed what she described as a “hematoma” at the site of the injection later that day. Over the next 5 days, the lesion progressively became tender and erythematous and began oozing purulent fluid, leading her to the emergency department.

She was admitted to the inpatient service for concerns of infection at the injection site. On examination, an indurated eschar with moderate perilesional erythema at the injection site was noted. A computed tomography scan showed soft tissue edema in the upper portion of the arm, read as “possibly consistent with cellulitis, but no abscess or hematoma formation.” However, viral and bacterial culture results were negative, and the patient remained afebrile without leukocytosis. Given the clinical and radiologic evidence, the most likely culprit was a repeat ulcerative reaction with perilesional soft tissue swelling. Biopsy was not pursued as the ulcer was clinically improved at posthospital appointment (Fig 1).

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Fig 1. Ulcer at site of fourth injection on the upper portion of the arm.

Dupilumab therapy was discontinued and cyclosporine therapy was restarted. The patient was given samples of hydrocolloid dressings at the clinic to dress the injection site. After the samples were used, the patient was instructed to apply petrolatum and bandages until the ulcers healed. The ulcerations at both the abdomen and upper portion of the right arm resolved within 1 and 2 months, respectively, and have not recurred since.

DISCUSSION

Dupilumab is a monoclonal antibody that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4R- α subunit shared by the IL-4 and IL-13 receptor complexes. The antibody formulation is composed of the active ingredient dupilumab and inactive ingredients L-arginine hydrochloride, L-histidine, polysorbate 80, sodium acetate, sucrose, and water.

Across multiple clinical trials, dupilumab-treated patients had higher incidences of mild or moderate ISRs.² However, there are limited data on the specific types of ISRs. When comparing dosing schedules, ISRs are seen in 7.2% of placebo groups, 12.3% of groups given dupilumab 300 mg every 2 weeks, and 16.7% of groups given dupilumab 300 mg every week.⁵ The FDA has not released information about specific ISRs induced by dupilumab. To the best of our knowledge, we are the first to report ulcerative ISRs associated with dupilumab therapy. Rare reports of similar ulcerating reactions to vaccines have been attributed to the adjuvants such as aluminum salts.⁶ Other potential causes suggested are improper injection technique and superinfection.⁷ Superficial bacterial culture and

viral polymerase chain reaction results were negative, suggesting that infection was less likely in our case.

The course of ISRs varies with each biologic. ISRs can appear during the first week after each injection within the first 2 months of treatment and can manifest as redness, itching, bruising, pain, swelling, and/or irritation. ISRs typically decrease gradually in frequency and severity and last for 3-5 days. Immediate or delayed hypersensitivity reactions have been reported with other biologics prescribed for psoriasis.⁸

Injectable monoclonal antibody formulations are formulated with excipients to increase solubility, reduce viscosity, and enhance stability. Polysorbate 80 is a common excipient in this and other monoclonal antibody formulations. Polysorbates can activate complement, cause acute hypersensitivity and systemic immunostimulation reactions, and form oxidative degradation products that function as haptens with proteins. Reactive degradation of products forms adducts, creating potential neoantigens that may be associated with the ISRs.⁹ Other monoclonal antibodies with polysorbate excipients, including adalimumab, certolixumab pegol, etanercept, ixekizumab, secukinumab, and ustekinumab, have been associated with ISRs.¹⁰

Given the lag time of our patient's 2 ISRs, we hypothesize that the initial injections sensitized her to the excipients and subsequent injections induced an intradermal type IV mediated reaction. ISRs must be monitored closely, and further studies must be conducted to evaluate the relationship between monoclonal antibody excipients and ISRs. We have informed the company and producer of this antibody formulation about this new side effect. We present this case in hopes of raising awareness and clinical knowledge of this adverse effect.

Dupilumab has been shown to be effective for moderate-to-severe AD and asthma. Adverse effects include conjunctivitis, headache, nasopharyngitis, and ISRs. ISRs and severe reactions like the one experienced by our patient may be associated with excipients such as polysorbate 80. We hope to raise awareness about this serious adverse effect of dupilumab and encourage other clinicians to share their experiences with specific ISRs.

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