Cytokine Release Reaction After Subcutaneous Daratumumab: Possible Relationship With Hymenoptera Allergy

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To the Editor:

Daratumumab, the first human IgG1κ monoclonal antibody to target apoptosis-inducing CD38 cells, has been approved for use in the treatment of relapsed/refractory multiple myeloma. Daratumumab has demonstrated a significant improvement in progression-free survival and overall survival in this disease. It produces infusion-related reactions in 26.8% of patients, mostly with the first infusion [1].

To date, only 2 cases of reactions to intravenous daratumumab have been published [2,3]. Recently, and in this same journal, Carrón-Herrero et al [2] reported a case of severe infusion-related reaction with negative skin test and basophil activation test results; desensitization was based on a 4-bag, 16-step protocol. Villareal-Gonzalez et al [3] reported a case of severe anaphylaxis with negative skin test results; desensitization was based on a 3-bag, 12-step protocol. In both cases, first-line treatment was successfully continued.

A subcutaneous formulation of daratumumab has been marketed to provide an efficacy and safety profile similar to that of intravenous daratumumab, albeit with a shorter infusion time and lower rate of infusion-related reactions. Subcutaneous daratumumab (Darzalex 1800 mg 15 mL) is reformulated with recombinant human hyaluronidase PH20 (rHuPH20), an enzyme that facilitates subcutaneous drug delivery by promoting the degradation of the glycosaminoglycan hyaluronan in subcutaneous cellular tissue. Analysis of the immunogenicity profile of rHuPH20 in clinical studies did not confirm rHuPH20-neutralizing antibody activity or adverse effects associated with positive rHuPH20 antibody titers. Other monoclonal antibodies coformulated with rHuPH20 are trastuzumab (Herceptin SC) and rituximab (MabThera SC) [4].

We report the case of a reaction to subcutaneous daratumumab in a 76-year-old man with IgGκ multiple myeloma. The patient was a beekeeper by profession and had no history of reaction after bee sting. As premedication, he received oral montelukast 10 mg, dexchlorpheniramine 5 mg IV, paracetamol 1 g IV, and dexamethasone 20 mg IV. Immediately after the first administration of subcutaneous daratumumab (1200 mg, 10 mL), he developed facial erythema, generalized sensation of warmth, pharyngeal itching, blurred vision, dizziness, pallor, profuse sweating, and nausea with vomiting. Drug administration was discontinued. Oxygen saturation was 94%, blood pressure 80/50 mmHg, and heart rate 126 bpm. Dexchlorpheniramine 1 mg IV, hydrocortisone 200 mg IV, and adrenaline 0.5 mg IM were administered, with progressive recovery within 30 minutes. After 1 hour of observation at the oncology infusion center, the patient reported chills, and his temperature was 37.6°C. He was treated with metamizole 2 g IV and methylprednisolone 60 mg IV. One hour later, a serum sample was drawn, and the patient was sent home without symptoms. The complete blood count was normal. Total IgE was 6.74 kU/L. Postreaction tryptase was 6.8 µg/L (baseline, 6.5 µg/L); postreaction IL-6 was 3210 pg/mL (baseline, 14.3 pg/mL). The patient was finally diagnosed with cytokine release reaction caused by subcutaneous daratumumab.

Hematology confirmed the need to continue treatment with daratumumab weekly for 8 cycles and thereafter every 2 weeks. Although the patient received subcutaneous treatment, based on risk stratification, a 1-bag, 12-step desensitization protocol was run with intravenous daratumumab. The patient underwent a total of 7 desensitization cycles with no breakthrough reactions. The results of skin prick testing (20 mg/mL) and intradermal testing (0.2 mg/mL and 2 mg/mL) performed after completion of the seventh desensitization were negative. To facilitate continuity of treatment and patient comfort, the intravenous rapid drug desensitization protocol was switched to a more cautious subcutaneous drug provocation test [5].

Given that the patient was a beekeeper, specific IgE to hyaluronidase (Api m 2) from honeybee venom was determined prior to the subcutaneous drug provocation test, which was negative. A drug provocation test with subcutaneous daratumumab (1, 2, 4, and 8 mL at 30-minute intervals) was tolerated without incident.

Insect stings are the leading cause of severe local reactions and severe anaphylaxis in adults. Up to 41.6% of the general

adult population have venom-specific IgE antibody (sIgE) levels above 0.35 kU_A/L. Most of the population with positive sIgE levels are usually asymptomatic, and their sensitization is not clinically relevant. The hyaluronidase group includes Api m 2 from honeybee, Ves v 2 from yellow jacket, and Pol d 2 from *Polistes dominula* [6].

In addition to its use as a monoclonal antibody, hyaluronidase is widely used in ophthalmic surgery. It is administered to depolymerize hyaluronic acid in connective tissue, better diffuse locally injected anesthetic, and improve the efficacy of nerve blocks. The incidence of allergic reaction to hyaluronidase is approximately 1/2000, and most cases are documented in the ophthalmological literature [7].

The main risk factor associated with the development of hypersensitivity to hyaluronidase reactions could be previous injections of hyaluronidase or bee/wasp venom–induced sensitization to hyaluronidase [8].

The use of hyaluronidase in patients with known bee allergy has not been studied and remains controversial in clinical practice [9]. It is important for the patient with unstudied Hymenoptera sting allergy to be evaluated by the allergist before receiving a subcutaneous drug formulated with hyaluronidase [10].

Therefore, patients with severe reactions to subcutaneous drugs reformulated with hyaluronidase should always be asked about previous reactions to hymenoptera stings or risky activities that increase the possibility of sensitization to venoms. In these patients, sensitization to hyaluronidase should be investigated by venom skin test or determination of sIgE against Api m 2, Ves v 2, and Pol d 2.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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