Erythema Multiforme After Intake of Risedronate: A Cross-Reactivity Study

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J Investig Allergol Clin Immunol 2021; Vol. 31(5): 457-458
doi: 10.18176/jiaci.0668

Key words: Erythema multiforme. Risedronate. Cross-reactivity. Alendronate.

Palabras clave: Eritema multiforme. Risedronato. Reactividad cruzada. Alendronato.

Bisphosphonates, or diphosphonates, are a group of drugs used for the prevention and treatment of diseases involving bone resorption, such as osteoporosis, Paget disease, and cancer with bone metastases. Etidronate, risedronate, and alendronate are the most commonly used members of this family. Several clinical reports have been published on hypersensitivity to risedronate and alendronate, although these do not include complete cross-reactivity studies.

A 53-year-old woman came to our allergy department with pruritus, generalized hives, and several blisters 3 days after taking risedronate (35 mg) to reduce bone resorption secondary to Paget disease. The clinical diagnosis was vasculitis-like syndrome (Figure). The patient did not have fever. No other symptoms or reasons to explain the reaction were observed (eg, cough, dyspnea, or excess sputum). Bisphosphonates had not been prescribed previously. The reaction was self-limiting and resolved without treatment in 3-4 days. A dermatologist performed a biopsy to rule out other diagnoses (differential diagnosis of vasculitis-like syndrome) and reported keratinocyte necrosis, mononuclear cell infiltration, and edema, which are compatible with erythema multiforme.

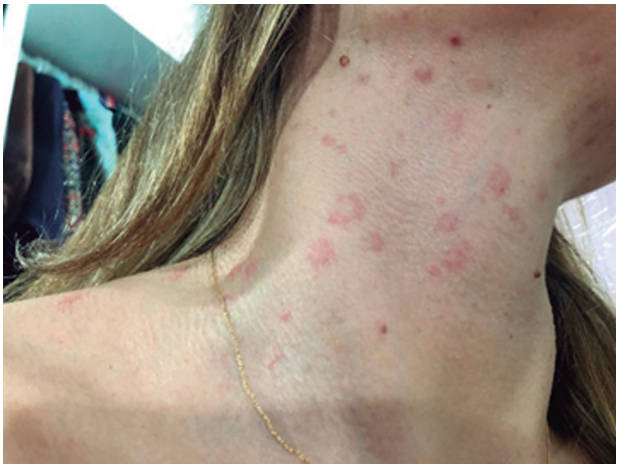

Figure. Photograph of the reaction.

Serology testing to rule out other causes yielded negative results for HIV, autoimmune disorders, and hepatitis B and C. The only positive result was for hepatitis B antibodies (vaccinated 5 years previously). No other serology tests (eg, *Chlamydia*, mycoplasma) were performed.

The patient came to our allergy department for further tests. After signature of the informed consent document, we performed a patch test with risedronate diluted in petrolatum (10 mg/mL) [1]. Tests yielded a positive result on days 2 and 4, according to the guidelines of the European Society of Contact Dermatitis [2]. Testing was also performed with alendronate and etidronate diluted in petrolatum at 10% [3] (7 and 20 mg/mL) and in saline solution at 1% and 0.1% (0.7 and 2 mg/mL and 0.07 and 0.2 mg/mL, respectively), with a negative result on days 2 and 4. Testing to rule out a possible irritant effect also yielded negative results in 5 healthy controls.

In order to confirm these in vivo results, and before the drug provocation test, we performed a T lymphocyte transformation test, which yielded a strongly positive result (stimulation index [SI] = 4) against risedronate and a negative result for the other 2 drugs tested (SI = 1.25 to alendronate and SI = 1.5 to etidronate). Different concentrations (0.1 mg, 0.5 mg, and 1 mg) of each drug were added during stimulation with phytohemagglutinin (PHA) in 5 healthy donors: the only concentration used was 1 mg, which did not inhibit PHA-induced proliferation by more than 15%. A positive result in the T lymphocyte transformation test was defined as an SI >3 [4].

Once we had confirmed a diagnosis of erythema multiforme after intake of risedronate, we performed a simple-blind placebo-controlled drug provocation test with alendronate 70 mg (placebo-35 mg-35 mg) in order to recommend this drug as an alternative for treatment of Paget disease. According to the criteria of the European Academy of Allergy and Clinical Immunology [5], the result was negative after 2 hours as an in-patient in our allergy ward and after 48 hours at home. The same protocol was performed with etidronate (placebo-100 mg-100 mg) to offer an alternative and to rule out cross-reactivity between the most commonly used bisphosphonates.

Bisphosphonates are used for the treatment of osteoporosis and osteopenia, with good clinical results and very few allergic reactions. Cutaneous adverse drug reactions, such as erythema multiforme–like or Stevens-Johnson syndrome have been reported after intake of risedronate [6], and esophagitis has been reported after intake of alendronate [7]. Occupational rhinitis [8] has been reported after inhalation of alendronate.

Despite the large number of cases reported, only 1 included a cross-reactivity study (the authors performed a patch test with the culprit drug and with 2 alternative drugs and recommended 1 alternative drug on the basis of the patch test result without a drug provocation test) [6]. In some cases, the positive result was based on a clinical report and in others on a positive in vitro test. In a review article [9], the authors explain their experience with these drugs (albeit in very few patients) and the alternatives they used, all of which were well tolerated (other members of the same family).

In terms of molecular structure, bisphosphonates have the same core and different side chains (Supplementary

Figure) [10]. They all share the P-C-P structure, which is similar to the P-O-P structure of native pyrophosphate. Bisphosphonates differ from each other only at the 2 "R" groups. Alendronate, neridronate, ibandronate, pamidronate, risedronate, and zoledronic acid have a nitrogen group and are known as nitrogen-containing bisphosphonates, in contrast with etidronate and tiludronate, which do not have a nitrogen group. In the case we report, there was no cross-reactivity between family members (the patient tolerated etidronate and alendronate), and hypersensitivity reactions were based on the side chain structure, which was recognized by T-cell receptors.

We report the case of a patient with a positive in vivo result (patch test) and in vitro result (T lymphocyte transformation test) to risedronate, a negative in vivo and in vitro result to etidronate and alendronate, and a negative drug provocation test result. This is the first clinical report to focus on possible cross-reactivity with other family members demonstrated with in vivo, in vitro, and drug provocation testing, all of which were negative.

To conclude, diagnosis must be confirmed with in vivo and/or in vitro tests. Alternative treatments should be sought in order to improve patients' quality of life.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Manuscript received June 13, 2020; accepted for publication January 12, 2021.

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