Erythema Multiforme after Risedronate Intake: Cross-Reactivity Study

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

A 53 year-old woman came to our Allergy Department referring pruritus, generalized hives and several blisters three days after risedronate intake (35 mg) to reduce bone resorption secondary to Paget´s disease, the clinical diagnosis corresponded to a vasculitis-like syndrome (see figure1). No fever. No other symptoms or reasons to explain the reaction were observed, such as cough, dyspnoea or excess sputum. Bisphosphonates had not been prescribed previously. The reaction was self-limited and resolved without treatment in three-four days. A dermatologist performed a biopsy to rule out other diagnoses (differential diagnosis of vasculitis-like syndrome) andreported a keratinocyte necrosis and mononuclear cell infiltration and oedema, compatible with erythema multiforme.

To discard other aetiologies, a serology was performed with negative results for HIV, autoimmune disorders, B and C hepatitis. Our patient only had a positive result for B hepatitis antibodies (vaccination 5 years before). No other serologies (Chlamydia, mycoplasma, etc) were performed.

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She came to our allergy department for further tests. After signing the informed consent, we performed a patch test with risedronate diluted in Vaseline in a concentration of 10 mg/ml[1]. Tests were read with a positive result on day (D)2 and D4 according to ESCD guidelines[2], and with alendronate and etidronate diluted in Vaseline in a concentration of 10%[3] (7 and 20 mg/ml) and in a saline solution in a concentration of 1% and 0.1% (0.7 and 2 mg/ml and 0.07 and 0.2 mg/ml respectively) with a negative result on D2 and D4. Five healthy controls were tested to rule out a possible irritating effect, with negative results too.

In order to confirm these in vivo results, and before the Drug Provocation Test, a T lymphocyte transformation test was performed, showing us a strongly positive result (Stimulation Index (SI) = 4) in a drug lymphocyte stimulation test against risedronate and a negative result for the other two 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 to phytohaemagglutinin (PHA)-stimulations of five healthy donors: only 1 mg concentration, which did not inhibit the PHA-induced proliferation by more than 15% was used. The T lymphocyte transformation test positivity criteria were defined as SI >3[4].

With the diagnosis of erythema multiforme after risedronate intake 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 to treat her Paget´s disease. It was negative (according to EAACI recommendations[5]) after 2 hours as an in-patient in our Allergy Ward and after 48 hours in her home. The same protocol was performed with etidronate (placebo-100 mg-100 mg) in order to offer an alternative and to confirm no cross-reactivity between the most commonly used biphosphonates.

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Bisphosphonates are used for the treatment of osteoporosis/osteopenic patients with good clinical results, with very few allergic reactions described. In the literature, there are reports of several cutaneous adverse drug reactions, such as an erythema multiform-like or Stevens-Johnson syndrome[6]after risedronate intake, or esophagitis[7]after alendronate intake. Occupational rhinitis[8]has also been reported after alendronate inhalation.

Although several clinical reports have been published, as explained above, there is only one [6]which included a cross reactivity study (they performed a patch test with the culprit drug and with two alternatives and recommended one alternative drug on the basis of the patch test result without a DPT). In some published clinical reports the positive result was based on a clinical report and in others on a positive in vitro test. A review has also been published[9]in which the authors explain their experience with these drugs (but on very few patients), and the alternatives they used, all of which were well-tolerated (they used other members of the family with good tolerance).

Focusing on the molecular structure, biphosphonates all have the same core and different side chains (as shown in supplementary Figure)[10].All bisphosphonates 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 two "R" groups. Alendronate, neridronate, ibandronate, pamidronate, risedronate, and zoledronic acid have a nitrogen group and are called nitrogen-containing bisphosphonates, in contrast with etidronate and tiludronate, which do not. In our case, there was no cross-reactivity between family members (she tolerated etidronate and alendronate), and hypersensitivity reactions were based on the side chain structure, being recognized by T cell receptors.

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In this clinical report, we present a patient with a positive in vivo (patch test) and in vitro test (T lymphocyte transformation test) to risedronate, with a negative in vivo and in vitro study to etidronate and alendronate, and a negative Drug Provocation Test to them too. This is the first clinical report that focuses on a possible cross-reactivity with other family members demonstrated with an in vivo, an in vitro and a drug provocation test, all of which were negative.

To conclude, it is essential to confirm the diagnosis with in vivo and/or in vitro tests, and to look for alternatives to treat the disease for which this treatment is indicated, in order to improve the patient´s quality of life.

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Conflicts of interests

None.

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Figure 1. Photo of the reaction

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