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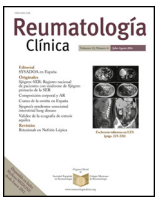

Letters to the Editor

Familial Mediterranean Fever Treated With Anakinra: A Case Report☆

Fiebre mediterránea familiar en tratamiento con anakinra: a propósito de un caso

To the Editor,

The treatment of familial Mediterranean fever (FMF) has several objectives: achieving relief from the symptoms, preventing and managing acute attacks, and avoiding the development of secondary amyloidosis. Classically, the drug of choice is colchicine. Now, however, we also have interleukin 1β (IL-1β) inhibitors.

We report the case of a 37-year-old man, with no familial history or known allergies, who underwent appendectomy and had Ménière's disease in right ear. He began in 1996, at the age of 17 years, with fevers that peaked at up to 40 °C, abdominal pain in right iliac fossa and occasional vomiting. These episodes lasted 2 or 3 days. He also customarily complained of pleuritic pain, but pleural effusion was never detected.

Since 2005, he also mentioned pain with swelling in his hands. This responded partially to treatment with ibuprofen, as did the occasional arthralgia in knees and ankles. He underwent genetic testing for FMF, which detected an alteration on exon 10: 2082G>A mutation in a homozygote, leading to a change to Met694Ile. He began therapy with colchicine at a dose of 2 mg every 24 h, and the number of attacks decreased.

In 2013, the number of episodes increased, requiring maximum doses of colchicine, with no clear improvement. Physical examination revealed a rigid, board-like abdomen, with no other noteworthy finding. A blood test only showed a mean corpuscular volume of 110 fL, fibrinogen 366 g/L and γ-glutamyl transpeptidase 79 IU/L. Systematic urinalysis, serological tests, a chest radiograph and abdominal ultrasound provided no evidence of disease.

In December 2014, the patient began with subcutaneous anakinra at a dose of 100 mg daily, and has continued to take colchicine. Since that time, he has remained asymptomatic.

Resistance to colchicine is defined as 2 or more attacks each month while receiving the maximum dose. This occurs in 5%–10% of patients with FMF, although in some cases, it may be due to poor treatment adherence.[1,2] True cases of colchicine resistance are usually found in patients who are homozygous for the M694V.[3]

The mechanism of action of agents that inhibit IL-1β in the etiology and pathogenesis of this disease is well known. The protein, pyrin, is a fundamental part of the so-called inflammasome, the intracellular organelle necessary for the expression of IL-1β[2,4] which, ultimately, causes the patients' symptoms. The IL-1β inhibitors most widely used are anakinra, rilonacept and canakinumab.

The biologic agent chosen for our patient was anakinra prescribed for compassionate use, as it has achieved good responses in other inflammatory diseases, such as rheumatoid arthritis and juvenile idiopathic arthritis.[5,6]

Our patient continued to receive colchicine associated with the biologic therapy. There is no consensus on that point in this respect: logically, it would be justifiable to discontinue it, but some authors recommend maintaining it as an adjuvant therapy.[7] In this context, the satisfactory response to the treatment was a sufficiently good reason to decide not to change the initial therapeutic proposal.

The uses of anakinra approved in Spain include the treatment of symptoms and signs of rheumatoid arthritis, in combination with methotrexate, in those patients who have not responded well.[8] The secondary effects of this drug, such as pruritus and erythema, are infrequent and appear during the first 4 weeks. There have been no reports of deaths due to severe opportunistic infection.[9] Since 2006, 22 studies have been published involving 64 patients from 10 different countries. In all, 76.5% of those treated with this drug achieve a complete response. It has been ineffective in only 3 patients, and the remainder had a partial response.[10]

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Response to: Uveitis due to Bisphosphonates: A Rare Side Effect?☆

Respuesta a: Uveítis por bifosfonatos: ¿un raro efecto secundario?

To the Editor,

We read the letter published by Martín Guillén et al.[1] very attentively. They presented a case of uveitis associated with treatment with bisphosphonates, and we would like to comment on our experience with this adverse effect, which we help might contribute to the proper identification of these cases.

We performed a retrospective observational study in which we included the cases of uveitis that developed *de novo* during treatment with bisphosphonates. The study was performed in the emergency department of Hospital Universitario Ramón y Cajal in Madrid, between January 2003 and December 2012. The variables analyzed included age, sex, indication for antiresorptive therapy, comorbidities, type of bisphosphonate, time between starting treatment and the onset of uveitis, clinical manifestation, associated ocular inflammatory signs and symptoms and outcome.

There were 18 cases of uveitis associated with bisphosphonates, all in women, with a mean age at the time of diagnosis of 64.9 ± 11.3 years (range: 38–82); 61% had taken alendronate and 39% had received risedronate. The indication for treatment was primary osteoporosis in 10 cases and secondary in 6. In 5 cases (27%), there was a history of autoimmune disease, but without episodes of ocular inflammation prior to taking the bisphosphonate; the diagnoses were inflammatory bowel disease with or without associated spondyloarthritis (n = 3), adult-onset Still's disease (n = 1) and primary biliary cirrhosis (n = 1). The time between starting treatment and the development of uveitis was 30.4 ± 18 months (range: 8–63). All the patients had unilateral (89%) or bilateral (11%) acute anterior uveitis, and the most widespread clinical presentation was the association of pain and ocular inflammation (56%). In 2 (11%), there were other concomitant ocular inflammatory disorders (superficial punctate keratitis [SPK] and follicular conjunctivitis, respectively), and 10 patients (56%) developed complications (cataracts 22%, synechiae 16%, vitreous detachment 16% and macular edema 5%). Retrospectively, we learned that, prior to uveitis, 3 patients had had other episodes of ocular inflammation during bisphosphonate therapy, corresponding to scleritis, episcleritis and SPK/blepharitis, respectively. All of the aforementioned patients received treatment with topical corticosteroids and cycloplegic agents. Bisphosphonate therapy was discontinued because of the ocular event in only 1 case (6%) and for another cause in 2 (11%), and was maintained in the rest (83%). During the follow-up period, after the first episode of uveitis (74 ± 20.4 months), remission was achieved in 72% of the cases and recurrent disease in 28%; however, 44% developed other ocular inflammatory events, including conjunctivitis, SPK and blepharitis.

In our series, most of the cases of uveitis associated with bisphosphonates occurred in women over the age of 60 years, with no previous history of autoimmunity or any other predisposing ocular disease. This profile coincides with that reported in the study of the cohort of Canadian veterans by Etminan et al.[2] All of the patients had received oral aminobisphosphonates, generally for a long period of time, until the adverse effect developed. In the published cases, there is an ample range from the initiation of the drug until the onset of uveitis, which goes from less than 24 h to several months, and is shorter with intravenous administration and longer with oral medication.[3,4] In our series, there was also a high frequency of other associated ocular inflammatory signs and symptoms. Bisphosphonates have been related to a wide variety of ocular disorders, mostly inflammatory, including conjunctivitis, scleritis, episcleritis, keratitis, orbital inflammatory disease and retrobulbar neuritis.[3,5,6] Bisphosphonate therapy was discontinued in only 1 of our patients because of uveitis, whereas, it was maintained in the majority, and this may have contributed to the rates of recurrence and the development of other ocular inflammatory disorders and sequelae.

Although the development of uveitis during bisphosphonate therapy is an uncommon adverse event, it is important that clinicians who prescribe these agents recognize this association, and that patients be informed about its signs and symptoms for its early diagnosis and treatment.

Conflicts of Interest

The authors declare they have no conflicts of interest concerning the publication of this article.

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