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## Response to: Uveitis due to Bisphosphonates: A Rare Side Effect?<sup>☆</sup>



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

To the Editor,

We read the letter published by Martín Guillén et al.<sup>1</sup> 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 Etmnan et al.<sup>2</sup> 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.<sup>3,4</sup> 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.<sup>3,5,6</sup> 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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## Similarities Between Takayasu Arteritis and Giant Cell Arteritis<sup>☆</sup>



### Similitudes entre la arteritis de Takayasu y la arteritis de células gigantes

Dear Editor,

We were very interested in the letter to the editor published in this journal in March of this year, by Drs. Martín Guillén, Álvarez de Cienfuegos and Hurtado García.<sup>1</sup>

The case they mention brought us to make certain reflections. Our patient is a 59-year-old woman at the onset of the disease, with occipital headaches accompanied by an increase in levels of acute-phase reactants. Physical examination revealed asymmetric peripheral pulses and the same was observed in temporal pulses.

Both Takayasu arteritis (TA) and giant cell arteritis (GCA) are vasculitides that predominantly affect large-sized vessels.<sup>2</sup>

There are significant differences between these 2 disorders. Takayasu arteritis is generally found in patients under 40 years of age. It mostly involves the aorta and its major branches, whereas GCA mainly affects patients over 50 years of age, and is detected in branches of the external carotid artery. Both diseases predominantly affect women, they share pathogenic mechanisms and pathological findings, and have a similar response to treatment.

The typical symptoms of GCA are headache, loss of vision, jaw claudication and symptoms of polymyalgia. However, approximately 40% of the patients have manifestations considered atypical. Within this group, clinical involvement of the aorta and its major branches is found in 10%–15% of the patients as an initial manifestation.<sup>3</sup> A study performed by Ostberg in autopsies of patients with GCA revealed the involvement of the aorta in 12 of 13 cases.<sup>4</sup> In their cohort of 168 patients with GCA, Nuenninghoff et al. found that 27% had complications affecting the large vessels. In all, 18% had aortic aneurysm/dissection and 13% had stenosis.<sup>5</sup> The majority of the cases are asymptomatic and it is underdiagnosed and, thus, its true prevalence is unknown. Patients with stenosis of the large vessels generally have fewer cranial symptoms, are found to have fewer changes in the temporal arteries on biopsies and a less marked increase in the levels of acute-phase reactants.<sup>5</sup>

The detection of the involvement of the aorta its branches increases notably when ancillary tests like ultrasound, computed tomography angiography, positron emission tomography with <sup>18</sup>F-fluorodeoxyglucose (FDG-PET) or angiography are utilized.<sup>3,6–8</sup>

The study evaluated 35 GCA patients who had not been treated with corticosteroids because of FDG-PET and found that 83% had increased FDG uptake in the large arteries. The involvement of the subclavian artery and aorta was observed in 74% and 54% of

the cases, respectively. The uptake of FDG had increased after 3 months of treatment with corticosteroids.<sup>6</sup> In another study, computed tomography angiography showed involvement of the large vessels in 67.5% of 40 patients with GCA. Those most widely affected were the aorta (65%), brachiocephalic trunk (47.5%), carotid arteries (35%) and subclavian arteries (42.5%).<sup>7</sup>

In short, their patient, at the age of 64 years, has headaches but no Doppler evidence or temporal artery biopsy, and the pre-dominating signs are arterial stenoses. She may have TA, as was suggested, or could have GCA, with stenoses involving the large vessels.

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