Letters to the Editors

Comment on: Clinical efficacy of oral alendronate in ankylosing spondylitis: a randomised placebo-controlled trial

Sirs,

We have read with much interest the paper by Coates *et al*. "Clinical efficacy of oral alendronate in ankylosing spondylitis: a randomised placebo-controlled trial" (1). In this study, 180 patients with ankylosing spondylitis (AS) were randomised to receive either weekly alendronate 70 mg or placebo. The authors found no significant difference between the placebo and treatment groups in any of the recorded outcomes over the two years including clinical indices (BAS-G was the primary outcome), biomarkers, and radiographic progression. The study is well designed and we agree with the authors that oral alendronate is probably not effective in the treatment of AS. However, we disagree with their conclusion against the efficacy of all bisphosphonates in AS and we suggest an explanation for the lack of effect of oral *versus* intravenous amino-bisphosphonates.

In our experience, we showed that intravenous neridronate could be as effective as infliximab in the treatment of AS (2). Compared to Coates *et al*., our patients had higher disease activity (BASDAI 5.24±1.60 *vs*. 4.20±2.40, p=0.03) and shorter disease duration (11.83±12.08 *vs*. 19.7±10.7 years, p=0.001). Thus, the patients enrolled by Coates *et al*. had a less aggressive and long standing disease which could account for the failure to achieve the primary outcome. Moreover, a point of discussion is if the effects of amino-bisphosphonates in AS could be dose-dependent. It has been estimated that the dose of 100 mg intravenous neridronate is equivalent to 90 mg pamidronate (3), but it is probably far higher than 280 mg monthly of oral alendronate, which has a low bioavailability due to its poor absorption from the gut.

However, in our opinion there is an additional explanation concerning the discrepancy between oral and intravenous amino-bisphosphonates (neridronate, pamidronate or zoledronate) in their effects on AS patients. Amino-bisphosphonates inhibit osteoclastic bone resorption by blocking farnesyl-pyrophosphate-synthase, an enzyme in the mevalonate pathway, so accumulating isopentenyl diphosphate and dimethyl-allyl diphosphate in monocytes and resulting in the activation of adjacent γδ T cells with the release of interferon-γ and TNF and the appearance of an acute phase response (APR) (4, 5). It is well known that the occurrence of an APR is much more frequent with the intravenous amino-bisphoshonates (6). We have previously demonstrated that the risk of APR is correlated with circulating γδ T cells (7), and that the circulating γδ T cell counts decrease after the infusion of zoledronic acid, in particular in the patients who experienced an APR (8, 9). Recently, it has been suggested an important role of γδ T cells in the pathogenesis and clinical manifestations of AS. Kenna *et al*. (10) reported a three-fold higher frequency of circulating γδ T cells and five-fold higher percentage of IL-23R-expressing γδ T cells in AS patients compared with healthy controls and RA patients. Strikingly in this study, γδ T cells cells were suggested to be the dominant IL-17 producers in AS. More recently it has been reported that activated γδ T-cells are abundant in enthesis, ciliar body and aortic valve in Tcrd-H2BeGFP mice (11). We suggest that the immunomodulating effects of amino-bisphosphonates on γδ T cells, that are more frequent with intravenous *versus* oral administration, may explain their clinical effects in AS.

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Competing interests: none declared.

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