Treatment of active ankylosing spondylitis with pamidronate

SIR, Ankylosing spondylitis (AS) is a frequently appearing chronic inflammatory rheumatic disease and prototype of the spondyloarthritides (SpA) [1]. Currently, treatment of AS patients consists mainly of nonsteroidal antirheumatic drugs (NSAIDs) and physical therapy [2]. The burden of disease in AS is comparable to rheumatoid arthritis (RA). The prevalence of osteoporosis is increased in both patient groups.

Bisphosphonates are not only known to inhibit osteoclasts, improve osteoporotic bone density measurements and prevent fractures [3], they also suppress proinflammatory cytokines such as interleukin (IL-1), tumour necrosis factor (TNF)-α and IL-6, and show anti-inflammatory properties in arthritic conditions [4]. Furthermore, in three single-centre Canadian studies Maksymowych et al. [5–7] reported that pamidronate is effective in NSAID refractory AS and SpA with spinal and peripheral joint involvement. To learn more about the therapeutic potential of bisphosphonates in AS we performed an open observational study with 12 AS patients (Table 1) who fulfilled the 1984 modified New York criteria and had longstanding disease. The patients had to have active disease defined as Bath ankylosing spondylitis disease activity index (BASDAI) ≥4. The medication was provided on the basis of treating therapy resistant cases with informed consent. Pamidronate 60 mg was given intravenously at days 0, 2, 14, 28 and 56 [5]. All patients were hospitalized for 2 weeks. The total observation period was 6 months. Clinical outcome assessments included disease activity (BASDAI) [8], function (BASFI) [9], metrology (BASMI) [10], patients and physicians global assessment (VAS each), quality of
life (SF-12) [11], CRP and ESR and were measured every month. Since no definite efficacy of DMARDs and steroids has been established in AS, it was part of the protocol that such treatment was stopped 1 month prior to the start of the study. However, no patient was treated with such drugs. NSAID doses were allowed to be reduced but were counted.

The scoring of X-rays of the spine and sacroiliac joints was performed with the BASRI [12]. In five patients, at baseline dynamic MRI using gadolinium DTPA as contrast agent given intravenously at 0.1 mmol/kg body weight of sacroiliac joints and spine was performed prior to treatment to document spinal inflammation. In addition, osteodensiometry using DXA was performed at the hip and the lumbar spine in all patients, analyses method, T-scored according to WHO guidelines. Eleven out of 12 patients received all five infusions. One patient dropped out after three infusions because of a disease flare, two patients were lost follow-up due to lack of efficacy. Most patients had complete ankylosis of their sacroiliac joints (75%). In all five MRIs performed at baseline, inflammatory changes were found. As assessed by DEXA, three patients had osteoporosis and five osteopenia. None of the patients had received prior DMARDs and steroids.

A 30% BASDAI improvement was noted in 2/11 patients after 3 months and in 3/9 after 6 months of observation (Fig. 1). There was a significant change in the mean BASDAI after 3 months (mean 5.5 versus 4.6; \( P = 0.04 \)), which was not seen anymore after 6 months (mean 5.5 versus 4.7; \( P = 0.8 \)). However, patient’s global assessment improved significantly after 1 month (mean 6.9 versus 5.1; \( P = 0.02 \)) and after 2 months (mean 6.9 versus 5.4; \( P = 0.04 \)). Physicians global assessment improved after 1, 2 and 3 months (\( P = 0.03, 0.04 \) and 0.035, respectively). There was improvement of global pain after 2 weeks (mean 6.6 versus 5.0; \( P = 0.031 \)), but not later. This result might have been influenced by the intense physical therapy during the hospitalization period. The SF-12 physical score indicated significant improvement after 3 months (\( P = 0.047 \)), but was not so clear after 6 months (\( P = 0.066 \)).

Similarly, there were no significant changes at any time in BASFI, BASMI, pain, SF-12 mental score, NSAID usage, CRP and ESR.

Adverse events due to pamidronate therapy were not infrequent: mainly transient arthralgias and myalgias were reported to occur after the first intravenous infusion in 50% of patients. Two patients had a relapse of anterior uveitis, one patient had a tympanic inflammation.

Taken together, in this small open observational study with 12 active AS patients who had a mean disease duration of 20 yr, intravenous therapy with the amino-bisposonate pamidronate led to a mean improvement of disease activity after 3 months (BASDAI from 5.4 to 4.6; \( P = 0.04 \)). Patients’ and physicians’ global assessments after the first 3 months indicated significant improvement. However, when analysed in more detail, there were only two individual patients who met the primary outcome parameter of 30% improvement of BASDAI after 3 months. A 50% BASDAI improvement was found in only 1/12 patients after 3 months. On the basis of our data, we conclude that pamidronate therapy may benefit individual patients with active AS over 3 months.

Furthermore, on continuation of follow-up over a total period of 6 months, without further treatment with pamidronate, there was still some non-significant improvement of BASDAI (5.4 to 4.7; \( P = 0.8 \)). On an individual basis, three out of the remaining nine patients reported a 50% BASDAI improvement after 6 months of observation. Similarly, when using the recently proposed criteria of the ASAS group [13] an improvement of 20% was seen in 2/11 patients after 3 months, and in 4/9 patients after 6 months of observation. In the four patients who had improved clinically no significant change in CRP levels and no correlation to bone density was found.

When using ASAS 20% criteria we know from the original paper [13] and recent experience in a randomized controlled trial [14] that the placebo response is ~25%. In our observation no higher response rates were found. In a larger, dose-controlled trial [7] with younger patients, shorter disease duration and a 6-month treatment period, a significantly higher response for the 60 mg group was observed after 6 months. We conclude that randomized controlled trials with a longer treatment period are needed to confirm and establish whether pamidronate is effective to treat active AS patients.

In contrast to other open studies using a somewhat different dosage [5, 6], we did not find improvement of peripheral involvement, which was present in 4/12 patients. In our study we found no major side effects and none of them required the stopping of therapy.

Nevertheless, we believe that the concept of bisphosphonate therapy in AS is worth pursuing: (i) because the options for treating AS patients are still limited; (ii)
because we do not expect that all patients with AS can and should be treated with anti-TNF therapy, since there are subgroups who are less responsive \cite{14}; and (iii) because of the increased incidence of osteoporosis and fractures in AS. However, more data on the influence of bisphosphonates on bone density in AS are needed.

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