Evolution of bone mineral density after 5 years of TNF-alpha inhibitors in axial spondyloarthritis

Sirs,

It is well established that ankylosing spondylitis (AS) is responsible for a reduction in bone mineral density (BMD) at the spine, total hip and femoral neck, with an increased risk of fracture (1). Regarding BMD measurement, BMD at the femoral neck is more effective than BMD at the lumbar spine for evaluating patients with AS. The short-term effects of TNF-alpha inhibitors (TNFi) on BMD in spondyloarthritis (SpA) are well documented. In a systematic review of the literature with meta-analysis, Haroon *et al*. showed that TNFi increased BMD at the lumbar spine and total hip at one and two years, with no effect on the femoral neck at one year (2). Only two studies have assessed the effect of TNFi over the longer term (3, 4). We studied the change in BMD at the spine, hip and femoral neck in patients with axial SpA treated with TNFi for five years. Patients with axial SpA meeting Assessment of SpondyloArthritis international Society (ASAS) criteria were part of the prospective RCVRIC cohort (no. ID-RCB 2014-A01847 -40). Patients treated for the first time with TNFi and who had continued TNFi for five years were analysed. Patients who received biphosphonates during follow-up were excluded. BMD was measured by DXA (Hologic) at inclusion (M0) and after one year (M12) and five years (M60) of follow-up, and assessed in g/cm^2.

Statistical analysis was performed using Stata software (v. 15 StataCorp, College Station, Texas, USA). All tests were two-sided, with an alpha level set at 5. Quantitative data are presented as mean ± standard deviation or median (25^{th}; 75^{th} percentiles). Longitudinal analyses were carried out by linear mixed models considering the time as a fixed effect, and the patient as a random effect.

Forty-six axial SpA patients (56.5% male, mean age 42.6±10.8 years) were followed up. Twenty-four had radiographic SpA, 22 had non-radiographic SpA (16 with positive MRI, 6 by the B27+ arm) and 38 (82.6%) were B27+. The median duration of SpA was 5.9 years [0.8; 16.4]. SpA was active, with mean Bath Ankylosing Spondylitis Disease Activity Index Score (BASDAI) and Ankylosing Spondylitis Disease Activity Score C-reactive protein (ASDAS-CRP) of 5.3±1.5 and 3.08±0.65, respectively. Eighteen patients (39.1%) were smokers and mean BMI was 27.1±5.8 kg/m^2. Eighteen patients received the same TNFi for five years (12 golimumab, 2 certolizumab, 2 etanercept, 1 adalimumab and 1 infliximab) and 28 several TNFi. BMD at the spine increased significantly between M0 and M60 (1.04±0.16 to 1.08±0.18 g/cm^2, p<0.001) as well as at the total hip (0.98±0.14 to 0.99±0.14 g/cm^2, p=0.04), and decreased at the femoral neck (0.84±0.13 to 0.82±0.13 g/cm^2, p<0.001). Disease activity decreased over the five years of follow-up (ASDAS-CRP M0: 3.08±0.65, M12: 1.91±0.82, M60: 1.79±0.75, p<0.001 *vs*. M0) as well as the median level of CRP (M0: 4.2 mg/L [2.9; 15.0], M12: 2.9 mg/L [2.9; 5.0], M60: 3.0 mg/L [2.9; 5.2], p<0.001 *vs*. M0). BMI increased significantly between M0 and M60, from 27.1±5.8 to 28.5±6.0 kg/m^2 (p<0.001). Among the factors studied (age, sex, smoking, CRP, BASDAI response, ASDAS-CRP response), only the decrease in CRP was associated with an increase in lumbar BMD (Spearman's correlation coefficient: -0.39, p=0.008).

As in our study, Maas *et al*. showed a greater improvement in BMD at the lumbar spine and total hip after four years of treatment in 105 patients treated with TNFi than in patients who did not sustain vertebral fractures during follow-up (4). The same was true in the study of 135 consecutive patients with AS treated for four years with TNFi (3). Lumbar BMD increased by 7.2% at the lumbar spine and 2.2% at the total hip. Despite the improvement in BMD and the reduction in disease activity, new vertebral fractures occurred (19.6% at four years *vs*. 11.1% at baseline), with more severe fractures (Genant score >2 of 25.9% at four years *vs*. 21.4% at baseline). Similarly, the mean radiological progression evaluated by the Modified stoke ankylosing spondylitis spinal score (mSASSS) increased significantly from a median of 4.0 (1.5;16.0) at baseline to 6.5 (2.1;22.9) after four years of TNFi treatment.

In our study, we also reported an increase in trabecular bone mineral density, but there was no change in cortical bone mineral density at five years, which could be explained by a lesser effect of TNFi on cortical bone. Long-term monitoring of BMD in patients with SpA treated with TNFi drugs seems to us to be a matter for regular measurement.

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