Vertebral bone mineral density changes in female rheumatoid arthritis patients treated with low-dose methotrexate

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Abstract

Objective
To assess vertebral bone mineral density (BMD) changes in rheumatoid arthritis (RA) patients taking low-dose methotrexate (MTX).

Methods
We evaluated in a 2-year, longitudinal study female RA patients, who had recently started a disease-modifying antirheumatic drug (DMARD), divided into two groups: group A, receiving MTX, and group B, receiving other DMARDs. Lumbar spine BMD was assessed at baseline and every year; RA activity was assessed every 3 months.

Results
Sixty-two patients were enrolled in the study; 40 completed the follow-up period: 22 of group A, and 18 of group B. The results after 2 years showed that both groups lost bone significantly vs baseline (p < 0.001) in a comparable fashion: group A (mean ± SD) -3.9 ± 4.9 % vs group B -3.0 ± 3.7 % (p = NS). The patients who showed active disease lost significantly (p < 0.05) more bone (-5.5 ± 3.8%) than those with less active disease (-1.1 ± 3.6%), independently of their DMARD.

Conclusion
Low-dose MTX in RA does not seem to exert relevant effects on trabecular bone.

Key words
Rheumatoid arthritis, methotrexate, osteoporosis.
Bone mineral density and methotrexate in RA / M. Mazzantini et al.

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Introduction
Generalized osteoporosis has been recognized as a common complication of rheumatoid arthritis (RA) (1). The aetiology-pathogenesis of this bone loss is multifactorial, but parameters such as reduced mobility (2), glucocorticoid (GC) treatment (3-5), and a systemic effect of some cytokines (6) have been implicated. Recently, it has been suggested that methotrexate (MTX), which is widely used in RA, may exert negative effects on bone mass. Tibial and metatarsal atraumatic fractures have been reported in patients on chronic low-dose MTX therapy (7-10); furthermore, it is known that high-dose MTX causes osteoporosis and fractures in children with leukemia (11-14). It has been shown that in RA patients MTX can be detected in the synovial membrane and in both cortical and trabecular bone at concentrations 10.5, 13.0, and 11.5-fold higher, respectively, than the simultaneous plasma concentrations (15). Moreover, MTX causes bone loss in rats by suppressing osteoblast activity and stimulating osteoclast recruitment, resulting in increased bone resorption (16) even at very low concentrations (17). Finally, MTX strongly inhibits osteoblast proliferation (18).

The clinical relevance of such findings in terms of bone loss in RA remains to be established. In cross-sectional studies (19, 20) involving a small number of RA patients no significant difference was observed in cortical and trabecular bone mineral density (BMD) between patients taking MTX and controls. In a 3-year study (21) assessing the effects of calcium and vitamin D supplementation on BMD of patients with RA it has been shown that MTX use in non-steroid treated patients was not associated with significant changes in femoral neck or lumbar spine BMD; on the contrary, MTX plus GC seemed to induce more bone loss than GC alone, suggesting an additional effect of MTX on osteoblasts. We conducted a longitudinal, two-year study in RA patients primarily aimed at assessing BMD changes during treatment with MTX and other disease modifying anti-rheumatic drugs (DMARDs).

Patients and methods
Female RA (22) patients attending the out-patient rheumatologic service of our clinic from October 1994 to June 1996, were enrolled in this longitudinal, 2-year study if they had started any DMARDs in the preceding 3 months. The patients gave their written consent to participate in the study, which was approved by the local Ethics Committee.

Exclusion criteria during recruitment were: the presence of abnormalities on spinal radiographs such as severe osteoporosis, scoliosis, spinal fusion, fracture deformation or body habitus that would preclude precise densitometric measurements; any disease known to affect bone turnover; current GC therapy comprising > 6.0 mg/day of 6-methylprednisolone (6-MP) or an equivalent drug, or one of these drugs started at any dosage within one year prior to study entry; the use, within the past six months, of anabolic steroids, calcitonin, supplemental vitamin D or hydroxy-vitamin D derivatives; the use, within the past year, of any bisphosphonate, fluoride, and estrogen; the presence of a functional impairment > class II according to Steinbrocker (23); the consumption of more than 5 cigarettes or 30 g of alcohol per day.

Exclusion criteria during the study were either the institution or withdrawal of GC; a daily dose of GC > 6.0 mg/day of 6-MP; treatment with any drug that could interfere with bone turnover; or the discontinuation of DMARDs therapy for more than 3 months during the follow-up. The lumbar (L2-L4) BMD was measured at baseline and every 12 months by dual-energy x-ray absorptiometry (DEXA, Lunar DFX, Lunar Radiation Corp., Madison, Wisconsin, USA). The precision of this method in our laboratory was found to be 0.8% in vitro and 1.4% in vivo in 100 normal subjects (age range 25-70 years) scanned four times consecutively; the long term in vitro precision was found to be 1.5%.

At baseline and once every 3 months, RA disease activity was assessed based on the number of swollen joints (range 0-44), Ritchie’s articular index (24) (RI), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). At each visit the individual disease was conventionally defined as being active if at least 3 of the following 4 criteria were present: number of swollen joints > 8; RI > 10;
ESR > 30 mm/1st hr; and CRP > 2.5 mg/dl. After the 24-month follow-up the patients were classified into two groups based on their RA activity, using the criterion of evidence of active disease during the majority of the scheduled visits, i.e. in at least 5 out of 9 visits. The patient evaluations were always performed at the same hour (between 8.30 and 9.30 am), and by the same physician throughout the study period.

Student’s t-test and chi-squared tests were used where appropriate to compare the data from the two groups. For repeated measures, changes within and between groups were analyzed by ANOVA. Linear regression analysis was used to estimate the effect of the cumulative dose of MTX on percentage changes in BMD. Data are expressed as the mean ± standard deviation (SD).

Results

One hundred and fifteen patients were screened and 62 were enrolled: 32 were under treatment with MTX (group A), 30 with other DMARDs (group B: antimalarials 11, injectable gold compounds 8, cyclosporine 5, sulfasalazine 4, D-penicillamine 2). Twenty-two patients (10 from group A, 12 from group B) dropped out during the follow-up period and were excluded from the analysis. The reasons for dropping-out were withdrawal of DMARDs due to side effects or lack of efficacy (6 from group A, 7 from group B), withdrawal of GC (2 from group A, 2 from group B), voluntary withdrawal from the study (1 from group B), treatment with drugs affecting bone turnover (1 from group A, 1 from group B), or loss to follow-up (1 from group A, 1 from group B).

Table I shows the characteristics and baseline data on the patients (22 in group A, 18 in group B) who completed the follow-up period and were excluded from the analysis.

The average dose of GC (6-MP) that the patients received over the two years was 5.1 mg in group A and 5.2 mg in group B (p = NS), with a daily dose range for both groups of 4-6 mg; the cumulative dose of MTX was 1209 ± 161 mg, with a weekly dose range of 7.5-15.0 mg, given parenterally.

Figure 1 shows the percentage variations in the lumbar BMD versus basal values. At the end of the study period, both groups lost bone significantly versus baseline (p < 0.001), but no difference was detected between those taking MTX and those taking other DMARDs. The decrease in lumbar BMD at 24 months versus baseline was -3.9 ± 4.9% in group A and -3.0 ± 3.7% in group B. No correlation was found between individual cumulative dose of MTX and changes in BMD (at 24 months: r = -0.14, p = 0.55).

According to the conventional criteria for assessment of disease activity, 20 patients (11 treated with MTX, 9 with other DMARDs) were affected by more active disease, and 20 (11 treated with MTX, 9 with other DMARDs) by less active disease (Table II). Figure 2 shows the percentage variations in the lumbar BMD versus basal values. At the end of the study, the patients who showed more

<table>
<thead>
<tr>
<th>MTX (n = 22)</th>
<th>Other DMARDs (n = 18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59 ± 9</td>
<td>57 ± 12</td>
</tr>
<tr>
<td>BMI</td>
<td>23.2 ± 1.8</td>
<td>23.8 ± 1.8</td>
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<tr>
<td>N° in menopause</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Years of menopause</td>
<td>13 ± 7</td>
<td>11 ± 8</td>
</tr>
<tr>
<td>Disease duration</td>
<td>9 ± 9</td>
<td>9 ± 10</td>
</tr>
<tr>
<td>N° taking GC</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Years of GC</td>
<td>3.3 ± 1.6</td>
<td>3.0 ± 2.2</td>
</tr>
<tr>
<td>RF+</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Ritchie index</td>
<td>11 ± 4</td>
<td>11 ± 4</td>
</tr>
<tr>
<td>N° swollen joints</td>
<td>10 ± 5</td>
<td>12 ± 4</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>44 ± 19</td>
<td>41 ± 20</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>2.7 ± 2.1</td>
<td>2.6 ± 2.3</td>
</tr>
<tr>
<td>N° with active disease</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Lumbar BMD (g/cm²)</td>
<td>0.98 ± 0.13</td>
<td>1.05 ± 0.16</td>
</tr>
<tr>
<td>T-score</td>
<td>-1.7 ± 1.1</td>
<td>-1.5 ± 1.5</td>
</tr>
</tbody>
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Fig. 1. Changes in lumbar BMD, expressed as % of the basal value, after 12 and 24 months, in the two treatment groups. * p < 0.001 vs basal value.
active disease lost significantly more bone compared to baseline (-5.5 ± 3.8%, p < 0.001), whereas those with a less active disease showed an insignificant decrease in their BMD (-1.1 ± 3.6%). The difference between the two groups was significant (p < 0.05).

Discussion
Many rheumatologists select MTX as a therapy for RA given its predictable benefit and long-term tolerability. More than 50% of patients taking MTX continue the drug beyond 3 years, longer than any other DMARD (25), and an increasing number of patients are being so treated. For these reasons, the long-term side effects of MTX must be carefully studied and monitored.

The present study was aimed at assessing the effect of low-dose MTX on trabecular BMD in RA, since a potential negative effect on bone has been suggested (15-18). A cross-sectional densitometric study (19) in a small group of RA patients reported that MTX (cumulative dose 625 mg) does not exert osteopenic effects at vertebral or femoral sites, and this has been recently confirmed retrospectively in patients who had taken MTX for an average of 5.6 years (20). Buckley et al. (21) have published data from a prospective, 3-year trial assessing the effects of calcium and vitamin D supplementation on BMD in patients with RA: 68 patients received MTX (mean cumulative dose 1375 mg), and 27 other DMARDs. At the end of 3 years of follow-up, there were no significant differences in the change in BMD of the femoral neck and lumbar spine between MTX and non-MTX treated patients. However, patients treated with prednisone ≥ 5 mg/day plus MTX had greater loss of lumbar BMD than those treated with a similar dose of GC without MTX, which suggests that MTX may add to the negative effects of GC on bone turnover. The study of Buckley et al. has some limitations: estrogen replacement therapy was used concurrently in about 25% of the patients, calcium and vitamin D supplementation in about 50%, and there was a lack of information about the timing of the use of GC and MTX itself. Nonetheless, the results provide some evidence against a relevant effect of MTX on lumbar BMD and seem to exclude any effect at the femoral site.

Our prospective, two-year study did not show a significant difference in lumbar BMD decreases between patients taking MTX (-3.9 ± 4.9%) and patients taking other DMARDs (-3.0 ± 3.7%), suggesting that MTX in RA patients possibly exerts only slight effect on trabecular bone. Either reduced production or reduced activity of interleukin 1 (IL-1) have been shown in monocytes treated with MTX (26), and spontaneous monocyte-derived IL-1β production may be reduced in vivo after MTX treatment (27). As IL-1 is a potent stimulator of bone resorption, it is possible that reductions in IL-1 concentrations after MTX treatment may counteract some of the effects of MTX on bone turnover. This
could explain the lack of MTX-induced negative effects on bone mass in RA, whose activity is closely related to the production of IL-1 (6, 28). Thus, the effect of MTX on bone metabolism in inflammatory disorders may not be similar to that under normal condition, as demonstrated by Segawa et al. (29) in adjuvant-induced arthritic rats.

The results of this study must be interpreted cautiously. In fact, MTX could exert bone toxicity after more than 2 years. Furthermore, we only evaluated a small number of subjects. We did not study cortical BMD in our patients; however, MTX has been found in cortical and trabecular bone at very similar concentrations (15), and this finding, together with the evidence of an inhibitory effect of MTX on osteoblasts and an increase in osteoclast activity (16), should account for trabecular as well as cortical bone loss. On the other hand, stress fractures of tibial and metatarsal bones have been described in RA patients never treated with MTX (30, 31) and an increased risk for such fractures in those treated with MTX has not been documented in controlled studies.

Preston et al. (32) studied the effect of MTX on UMR 106 rat osteoblast-like osteosarcoma cells, and found that the addition of folic acid prevented MTX toxicity at 1-10 µM concentrations. Thus, folic acid administration in vivo might prevent MTX toxicity on bone cells in RA patients. All the patients of the present study received folic acid after MTX administration. It is to be highlighted that the DEXA procedure is considered to be the most precise one for detecting BMD variations over time, and that we excluded patients with spinal abnormalities which would preclude the accuracy of the method. Furthermore, attention was taken to minimize the role of factors known to induce bone loss in RA, such as GC treatment. Therefore, we excluded patients who had started GC at any dosage within one year prior the start of the study, since it is known that GC can induce rapid trabecular bone loss. We also excluded from further follow-up and final evaluation those patients who had stopped GC during the observation period, since it seems that a partial recovery of bone loss may occur (5).

In conclusion, low-dose MTX in RA seems to be safe with regard to trabecular bone after 2 years. Studies in larger groups of patients are needed to confirm these results.

References