Effect of Low Dose Methotrexate on Bone Density in Women with Rheumatoid Arthritis: Results from a Multicenter Cross-Sectional Study

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ABSTRACT. ***Objective.*** To analyze the influence of low dose methotrexate (MTX) on bone using data from a large multicenter, cross-sectional study on bone mineral density (BMD) in women with rheumatoid arthritis (RA).

Methods. We selected 731 female patients with RA divided into 2 groups on the basis of MTX use: never MTX users (n = 485) and MTX users for at least 6 months (n = 246). Demographic, disease, and treatment related variables were collected for each patient. BMD was measured at lumbar spine and proximal femur by dual energy x-ray absorptiometry. Osteoporosis was defined as BMD < –2.5 T-score.

Results. The frequency of osteoporosis among never MTX users and MTX users was 29.1% and 28.3% (p = NS) for lumbar spine, and 34.8% and 37.8% (p = NS) for femoral neck, respectively. Mean T-score values at lumbar spine and femoral neck were comparable in the 2 groups, even after adjusting for age, menopausal status, body mass index (BMI), Health Assessment Questionnaire (HAQ) score, and steroid use. The generalized linear model showed that age, menopause, BMI, HAQ score, and steroid use were significant independent predictors of BMD at lumbar or at femoral level, whereas MTX use was not. Logistic procedure showed that only age, HAQ score, and BMI were significantly associated with the risk of osteoporosis.

Conclusion. We found no negative effect of low dose MTX on BMD in women with RA. (J Rheumatol 2004;31:1305–9)

Key Indexing Terms:
RHEUMATOID ARTHRITIS OSTEOPOROSIS BONE LOSS METHOTREXATE

Methotrexate (MTX) is probably the most frequently used disease modifying antirheumatic drug in rheumatoid arthritis (RA), and it is also prescribed for other rheumatic and nonrheumatic diseases, such as juvenile RA, psoriatic arthritis, polymyositis, polymyalgia rheumatica, Horton's arteritis, and inflammatory bowel disease. MTX has been reported to have negative effects on bone: the term "MTX osteopathy" was first used to refer to a clinical syndrome characterized by stress fractures of the lower extremities, diffuse bone pain, and osteoporosis in children who had been placed on longterm maintenance therapy with low dose MTX for acute lymphoblastic leukemia[1,2]. Sporadic reports of similar cases among patients taking low dose MTX for rheumatic diseases, primarily RA, have appeared more recently[3]. Further, *in vitro* studies suggest that MTX may exert toxic effects on osteoblasts[4,5]. These findings have raised concern about the longterm effects of MTX on bone. However, the majority of densitometric studies in patients with RA have detected no decreased bone mass in patients undergoing MTX treatment[6-10]; only one study[11] suggested that MTX may increase trabecular bone loss in glucocorticoid-treated patients by augmenting inhibitory effects of glucocorticoids on osteoblast function.

We analyzed the influence of MTX on bone using data from a large multicenter, cross-sectional study on bone mineral density (BMD) in RA[12].

MATERIALS AND METHODS

Subjects. Data were collected by 21 Italian rheumatology centers during a large cross-sectional survey on bone mass in 925 patients with RA[12]. The only inclusion criteria were female sex and an established diagnosis of RA according to the 1987 American College of Rheumatology (ACR) revised

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criteria. Women with a history of hysterectomy were excluded. Other exclusion criteria were diabetes, severe hepatic or renal diseases, and diseases of the thyroid gland. Women with RA who were unable to walk without assistance and those who had had total bilateral hip replacement were also excluded.

Predictor variables. At recruitment, data were collected on age, body weight, height, and age at surgical or natural menopause. Disease-related variables included disease duration, oligo versus polyarticular involvement, involvement of weight-bearing joints, presence of subchondral erosions (hands or forefeet), presence of extraarticular manifestations, number of swollen joints (where metacarpophalangeal, metatarsophalangeal, and interphalangeal were considered 3 single joints), and history of major (total hip replacement) or minor orthopedic surgery related to RA. The functional evaluation included staging of the disease according to Steinbrocker classification[13]. The measure of self-reported functional status was based on the Health Assessment Questionnaire (HAQ).

To examine the effect of MTX on bone, patients were classified as never MTX users, if they had never been treated with MTX, or current MTX users. Current MTX users were further divided into 3 subgroups depending on the duration of MTX therapy: less than 6 months, 6–24 months, or more than 24 months. Only data from patients treated with MTX for more than 6 months were included into the analyses.

Steroid use was carefully evaluated. Patients were subdivided into users and nonusers; for each user, current and cumulative dose and treatment duration were recorded.

Patients were interviewed about past or current use of drugs affecting bone metabolism including estrogens, bisphosphonates, calcium, vitamin D, calcitonin, anabolic steroid, fluoride, and thiazides.

Bone mass measurements. BMD at the lumbar spine and proximal femur were measured at the time of recruitment with Hologic, Lunar, or Norland scanners. All measurements were obtained by dual x-ray absorptiometry (DXA) technique. T-scores were calculated in each center after comparison with reference values supplied by the manufacturer. Osteoporosis was defined as a T-score > –2.5 standard deviations, according to the World Health Organization definition[14].

Statistical analysis. Baseline characteristics were compared between groups (never MTX users and current MTX users) by Student t test for unpaired data for continuous variables and by chi-square test for categorical variables. Significance was reported at $p \leq 0.05$. Adjusted means were also calculated in different groups to obviate the effects of the main confounding variables using the analysis of covariance. A generalized linear model was used to analyze predictors of BMD in RA. The relative risks associated with osteoporosis were assessed by logistic models in which the presence of osteoporosis in at least one region of interest was the dependent variable. The inclusion criteria for variables in the multivariate analyses were (1) statistical significance assessed at univariate analysis, and (2) clinical relevance of the included variables on the outcome variable. All analyses were performed with SAS software.

RESULTS

Univariate analysis. The sample included 731 female patients with RA. On the basis of MTX use, 2 groups were identified: never MTX users (n = 485) and MTX users (n = 246). Among MTX users, 124 patients had been treated for 6–24 months, and 122 for more than 24 months.

Table 1 shows demographic and clinical data (mean ± SD or percentage) of the 2 groups of patients. The groups were comparable in terms of demographic data, but not in terms of disease-related characteristics. With respect to never MTX users, MTX users had significantly longer disease duration (8.6 ± 7.1 vs 7.5 ± 7.1 yrs; p = 0.04), and had higher ESR (33 ± 20 vs 30 ± 20 mm; p = 0.03), CRP (4.6 ± 11.0 vs 3.1 ± 5.6 mg/dl; p = 0.02), HAQ score (1.3 ± 0.8 vs 1.1 ± 0.8; p = 0.02), and number of swollen joints (4.0 ± 3.8 vs 3.3 ± 3.7; p = 0.02) and a higher frequency of erosive disease (80.5% vs 64.4%; p = 0.001). Further, more MTX users than never MTX users were in Steinbrocker functional class III or IV (35.5% vs 23.9%; p = 0.001) and were taking steroids (80.5% vs 55.7%; p = 0.001).

A true clinical remission according to ACR criteria[15] was diagnosed in 23/246 MTX-treated patients (9.4%) and in 79/485 non-MTX-treated patients (16%), a statistically significant difference (p = 0.01).

No difference was detected between the 2 groups with regard to oligo versus polyarticular involvement, involvement of weight-bearing joints, presence of extraarticular manifestations, and history of major or minor orthopedic surgery related to RA. Sixty women underwent surgical menopause: 43 (8.9%) in the group never treated with MTX and 17 (6.9%) in the MTX-treated group (p = NS).

At the time of recruitment 50.3% of postmenopausal patients (267 of 531) were treated with drugs affecting bone metabolism — patients taking calcium: n = 66 (12.4%); vitamin D, 119 (22.4%); bisphosphonates, 98 (18.5%); and hormone replacement therapy, 13 (2.4%). Fifty women were being treated with drugs in different combinations. No statistically significant difference was noted between the 2 groups in this regard.

Mean unadjusted T-score values (± SD) at either lumbar spine or femoral neck were found to be comparable in the 2 groups of RA patients according to MTX use (Table 2): lumbar spine T-score was –1.60 ± 1.41 in never MTX users and –1.74 ± 1.23 in MTX users (p = NS); femoral neck T-score was –1.92 ± 1.17 and –2.06 ± 1.17, respectively (p = NS). Mean adjusted T-score values (± SE) at either measurement site were again comparable between the groups, after adjusting for age, menopausal status, BMI, HAQ score, and steroid use: lumbar spine T-score was –1.50 ± 0.08 in never MTX users and –1.59 ± 0.11 in MTX users (p = NS); femoral neck T-score was –1.89 ± 0.07 and –1.89 ± 0.09, respectively (p = NS). No significant difference was found in T-scores comparing MTX users for 6–24 months to users for > 24 months at either lumbar spine (–1.8 ± 1.3; 1.69 ± 1.1, respectively; p = 0.33) or femoral neck (–2.0 ± 1.1; –2.0 ± 1.1, respectively; p = 0.99).

The frequency of osteoporosis among never MTX users and MTX users was 29.1% and 28.2% (p = NS) for lumbar spine, and 34.8% and 37.8% (p = NS) for femoral neck, respectively (Table 2). Statistical analysis was also performed after exclusion of the patients taking bisphosphonates (n = 98) and hormone replacement therapy (n = 13). Mean T-scores and frequency of osteoporosis are shown in Table 3. Once again, no difference was noted between the 2 groups.

Multivariate analysis. We performed a multivariate analysis of data to identify the independent effect of different covari-

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Table 1. Demographic and clinical data (mean ± SD or %) of the patients with RA according to MTX use.

	Never MTX Users, n = 485	MTX Users, n = 246	p
Age, yrs	58.0 ± 12.8	56.7 ± 12.8	NS
Body mass index, kg/m^2	24.9 ± 4.1	24.6 ± 4.2	NS
Postmenopausal, %	74.7	70.9	NS
Menopause duration, yrs	14.6 ± 9.0	14.1 ± 8.6	NS
RA duration, yrs	7.5 ± 7.1	8.6 ± 7.1	0.04
Rheumatoid factor +, %	66.0	71.0	NS
ESR, mm	30 ± 20	33 ± 20	0.03
CRP, mg/dl	3.1 ± 5.6	4.6 ± 11.0	0.02
HAQ score	1.1 ± 0.8	1.3 ± 0.8	0.02
No. of swollen joints	3.3 ± 3.7	4.0 ± 3.8	0.02
Presence of erosion, %	64.4	80.5	0.001
Steinbrocker functional class, % in class III or IV	23.9	35.5	0.001
Steroid use, %	55.7	80.5	0.001
Duration of steroid use, yrs	3.4 ± 3.8	3.7 ± 4.8	NS
Mean daily steroid dose, mg	5.4 ± 4.6	5.7 ± 4.6	NS
Cumulative steroid dose, g	7.7 ± 10.0	6.7 ± 6.9	NS

Table 2. BMD (T-score, mean ± SD) and prevalence (%) of normal, osteopenic, and osteoporotic subjects in 2 groups of patients with RA according to MTX use.

	Never MTX Users, n = 485	MTX Users, n = 246	p
Lumbar spine	–1.60 ± 1.41	–1.74 ± 1.23	NS
Femoral neck	–1.92 ± 1.17	–2.06 ± 1.17	NS
Lumbar spine, %			
Normal	29.5	26.4	
Osteopenic	41.4	45.4	
Osteoporotic	29.1	28.2	NS
Femoral neck, %			
Normal	18.2	16.3	
Osteopenic	47.0	44.9	
Osteoporotic	34.8	37.8	NS

Table 3. BMD (T-score, mean ± SD) and prevalence (%) of normal, osteopenic, and osteoporotic subjects in 2 groups of patients with RA according to MTX use, after exclusion of the patients using bisphosphonates or hormone replacement therapy.

	Never MTX Users, n = 420	MTX Users, n = 200	p
Lumbar spine	–1.51 ± 1.41	–1.64 ± 1.24	NS
Femoral neck	–1.83 ± 1.17	–1.91 ± 1.17	NS
Lumbar spine, %			
Normal	33.5	27.4	
Osteopenic	42.0	49.4	
Osteoporotic	24.5	23.2	NS
Femoral neck, %			
Normal	21.3	17.0	
Osteopenic	49.4	50.3	
Osteoporotic	29.3	32.7	NS

ates that could influence osteoporosis in RA. The generalized linear model was applied at lumbar and femoral sites to identify independent predictors of BMD in our population. Due to missing values, 566 observations were evaluated for lumbar spine and 519 for femoral neck. In this model, age, menopause, BMI, HAQ score, and the use of steroids were significant independent predictors of BMD at lumbar spine or at the femoral level, whereas MTX use was not, even after exclusion of patients using bisphosphonates or hormone replacement therapy (Table 4).

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Table 4. Generalized linear model of lumbar and femoral BMD in women with RA.

Variable	Lumbar Spine		Femoral Neck	
	ß Coefficient	p	ß Coefficient	p
Age	–0.02	0.0001	–0.02	0.0001
Menopause	0.47	0.006	0.31	0.04
BMI	0.08	0.0001	0.09	0.0001
HAQ	–0.23	0.005	–0.11	NS
Disease duration	–0.0001	NS	0.0006	NS
Steinbrocker stage	–0.005	NS	0.07	NS
Use of steroids	0.23	0.05	0.19	0.05
Methotrexate use*	0.09	NS	0.02	NS

* After exclusion of patients using bisphosphonates or hormone replacement therapy, ß coefficient was 0.10 (p = NS) for lumbar spine BMD and –0.019 (p = NS) for femoral neck BMD.

The logistic model was also applied with the presence of osteoporosis in at least one site of measurement (i.e., lumbar spine or femoral neck) as the dependent variable. In this model (630 observations), age (OR 1.06, 95% CI 1.04–1.07), HAQ score (OR 1.50, 95% CI 1.20–1.88), and BMI (OR 0.88, 95% CI 0.84–0.93) were significantly associated with the risk of osteoporosis.

DISCUSSION

In accord with results of cross-sectional[6,7,9] and longitudinal studies[8,10], this cross-sectional study suggests that low dose MTX does not exert negative effects on trabecular and cortical bone of female patients with RA. Katz, *et al*[6] measured BMD, using dual photon absorptiometry, in 10 female patients with RA who had received a mean cumulative MTX dose of 625 mg, and in 19 matched controls: no significant differences in BMD values were detected between the groups in observations from the lumbar spine, femoral neck, intertrochanter, and Ward's triangle.

Buckley, *et al*[11] reported on BMD changes (measured by DXA) in both male and female RA patients treated with MTX (n = 68) (mean cumulative dose 1375 mg) or with another disease modifying drug (n = 27) after a followup of 3 years. The change in BMD, adjusted for age, sex, HAQ results, and prednisone use, was similar in MTX and non-MTX-treated patients, with a difference of –2.0% (p = 0.359) in the lumbar spine and +0.85% (p = 0.58) in the femoral neck. However, patients treated with prednisone ≥ 5 mg/day plus MTX showed an 8.08% greater loss of BMD in the lumbar spine than patients treated with a similar dose of prednisone without MTX (p = 0.004), which suggests that MTX may increase trabecular bone loss in glucocorticoid-treated patients.

With regard to the suggested additive effect of MTX and glucocorticoids on vertebral BMD, in 12 patients with polymyalgia rheumatica treated with prednisone (mean cumulative dose after 1 year 1.84 g) and MTX 10 mg weekly, vertebral BMD, assessed by DXA, did not change after 1 year compared to basal values: 0.75 vs 0.76 g/cm^2 (p = NS); in contrast, significant bone loss occurred in 12 patients treated with prednisone alone (mean cumulative dose 3.2 g): 0.78 vs 0.82 g/cm^2 (p = 0.002)[16]. Carbone, *et al*[7] compared lumbar spine and femoral neck BMD, assessed by DXA, in 2 groups of postmenopausal patients with RA, one group treated with MTX (n = 10; treatment duration > 3 yrs) and one that was not (n = 10). No significant difference was detected, but the results were not corrected for age, which was significantly higher in those not receiving MTX.

Mazzantini, *et al*[8] have reported the results of a 2-year longitudinal study to evaluate lumbar BMD changes assessed by DXA in female RA patients who had recently started disease modifying antirheumatic drug (DMARD) therapy. Exclusion criteria included any disease or use of drug that could affect bone turnover. Glucocorticoids were allowed if started more than 12 months prior to the study entry, at a dose not exceeding 7.5 mg prednisone or equivalent. Patients taking glucocorticoids at baseline had to continue their treatment during the entire study period at a dose range of 5.0–7.5 mg of prednisone, and those starting or stopping glucocorticoids were excluded from densitometric analysis, as significant changes in BMD could have occurred. After 2 years, 22 patients treated with MTX (mean cumulative dose 1209 mg) and 18 patients treated with other DMARD had lost a comparable amount of bone, the difference being –0.9% (p = NS). No correlation was found between the cumulative dose of MTX and the changes in BMD after 2 years (r = –0.14, p = NS). Cranney, *et al*[9] compared lumbar spine and femoral BMD, assessed by DXA, in male and female RA patients treated with MTX (n = 30) (mean cumulative dose 2810 mg) or with another DMARD (n = 30), and found no significant difference between the 2 groups. Minaur, *et al*[10] prospectively assessed BMD changes after 1 year in non-steroid-treated RA patients of both sexes treated with MTX (n = 64) or other DMARD (n = 52). Univariate analysis of covariance revealed that MTX at baseline was associated with reduced BMD at the femoral neck. However, femoral neck BMD was also associated significantly with disease severity.

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Multivariate analysis showed that reduced BMD associated with MTX was due to confounding factors such as disease activity. In our study, MTX users showed a more active disease at the time they were enrolled, as expressed by higher ESR, CRP, HAQ score, and number of swollen joints. Neverthless, BMD results showed no statistically significant difference with respect to patients who had never used MTX. In this regard, we note that the more active disease in the MTX group would have resulted in a negative bias, that is, making it more likely to see an apparent effect of MTX if MTX had a negative effect on bone.

Our study has some limitations, since it was not conducted in a longitudinal fashion. Further, at the time of patients' recruitment the duration of current or past DMARD therapy was assessed only semiquantitatively (i.e., < 6 months, 6–24 months, > 24 months), and mean and cumulative doses of each DMARD were not recorded. Thus we have no information about the exact duration of MTX treatment and the mean weekly and cumulative doses of MTX in our patients. It is reasonable that most of our patients were taking MTX at a dose range of 7.5–15 mg/week. Therefore, our results should not be extrapolated to patients treated with higher doses of MTX (15–30 mg/week) that are increasingly being used in RA.

Another limitation is the lack of information about folinic acid supplementation, which has been shown to prevent MTX-induced toxicity in osteoblast-like cells; it may also act to prevent osteoporosis in patients taking MTX[17].

We found no negative effect of low dose MTX on BMD in women with RA at either cortical or trabecular sites.

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APPENDIX

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