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The Impact of Low-Dose Disease-modifying Antirheumatics Drugs (DMARDs) on Bone Mineral Density of Premenopausal Women in Early Rheumatoid Arthritis

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ABSTRACT

Introduction. Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by symmetrical polyarthritis and multisystemic involvement. Objective. The aim of this study was to assess the impact of low dose of methotrexate on bone mineral density (BMD) in patients with early rheumatoid arthritis (RA). Materials and methods. This paper follows a retrospective study, which involves 60 female patients with early onset RA diagnosed according to the American Rheumatism Association Criteria (ACR/EULAR 2010). The patients were divided into two groups: group I was composed of thirty patients treated with dose of 7.5 mg/weekly methotrexate (MTX), while group II included thirty patients treated with dose of 2 g/daily sulfasalazine (SSZ). The Disease Activity was measured by a combination of Erythrocyte Sedimentation Rate (ESR) and Disease Activity Score (DAS-28). Bone mineral density of the lumbar spine (L2-4), and femoral neck, was measured by dual energy X-ray absorptiometry (DEXA) (Stratos 800). Laboratory findings included: serum calcium, phosphorus and alkaline phosphatase. Results. In this study, we found no negative effect on BMD in RA patients treated with low dose MTX in comparison to patients treated with SSZ. There was not observed significant difference in BMD of the lumbar spine, femur neck or trochanter, of MTX and SSZ patients in the pretreatment phase, nor after 12 months of treatment. No significant change in the biochemical parameters of the both groups. Conclusion. Based on the results of our study, low dose of methotrexate has no negative effect on BMD in premenopausal RA patients. We believe that these results might provide new insights and that further longitudinal studies with larger groups of premenopausal RA patients are required.

Key words: Rheumatoid arthritis, bone mineral density, methotrexate.

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by symmetrical polyarthritis and multisystemic involvement. In a great number of patients, the disease causes joint destruction, disability, and complications, one of which is generalized osteoporosis (1). Osteoporosis is a metabolic disease characterized by low bone mass and deterioration of bone tissue, that leads to increased bone fragility and risk of fractures (2). Patients with RA are at increased risk for osteoporosis for many reasons. Factors which show to play important role in osteoporosis in patients with RA are long disease duration, persistently active disease, disease-modifying anti-rheumatic drugs (DMARDs) and steroid treatment (3). Methotrexate is one of the most widely used DMARD in the treatment of RA. While the safety profile of methotrexate in low doses is generally good, several studies have shown that it may have negative effects on bone. Studies also show that bone loss in RA may occur as a direct result of the disease (4).

2. OBJECTIVE

The aim of the study was to investigate the impact of low-dose methotrexate on bone mineral density (BMD) in premenopausal patients with early RA.

3. PATIENTS AND METHODS

Sixty female patients with recent-onset RA according to the American Rheumatism Association Criteria were enrolled in this retrospective, 12-month study. Age: 32-47 years, in Rheumatology Clinic of University Clinical Centre of Kosovo between 2014 and 2015. Inclusion criteria included: premenopausal stage disease duration <12 months, no previous DMARD or corticosteroid. Exclusion criteria included: hypersensitivity-drugs, hepatic, renal, hematologic, pulmonary, cardio-vascular disease, active peptic ulcer, medication that affect bone turnover. Thirty patients in group I were treated with 7.5 mg/week of MTX po, and 30 patients in group II with 500 mg of SSZ po, dosage of 2g/day (initial dose 500 mg/day first week, rising to 1.0 g at second week, to 1.5 g at third week and maintain dose of 2 g/day at fourth week). In addition to DMARD therapy, we allowed all patients to take 2 g/day of paracetamol, if necessary. Disease activity was assessed by using the EULAR modified disease activity score calculator (DAS-28). Bone mineral density of the lumbar spine (L2-4) and femoral neck, was measured by Dual Energy X-ray Absorptiometry (DEXA) (Stratos 800). Laboratory findings that were done at baseline and in the end of the study included: serum calcium, phosphorus and alkaline phosphatase. Statistical analysis was followed through SPSS. Data were expressed as means \pm standard deviation (SD). Testing of categorical data was done with Fisher's exact test of continual data where the distribution was normal with T-test and when the distribution was not normal with Mann-Whitney's test and Wilcoxon matched pairs test. The probability level was expressed by p-value of <0.05.

4. RESULTS

The average age in the Group I was 43.7 ± 3.1 , while in Group II average age was 43.6 ± 3.9 . The duration of the disease in the Group I was 7.1± 1.5 months while in the group II was 7.1 ± 1.8 months. The Disease Activity, measured by a combination of ESR and Disease Activity Score (DAS-28) was higher in both groups at the beginning of the study in group I was 5.0 ± 1.2 and group II was 5.1 ± 1.0 (p=0.994) compared to the values at the end of the study in group I was 3.9 ± 0.7 and group II was 4.2 \pm 0.9 (p=0.486), not statistically significant. Rheumatoid factor (RF) in Group I was positive in 23 (83.5%) and in Group II, in 24 (85.7%) of patients (Table 1). In this study, we found no negative effect on BMD in RA patients treated with low dose MTX in comparison to patients treated with SSZ. At 12 months, there were no significant differences in BMD of the lumbar spine and femoral neck. At the baseline Bone Mineral Density (BMD-g/cm²), at the lumbar spine in group I was 0.95 ± 0.14 and in group

	Group I	Group II	P Value *
Average Age (years)	43.7 ± 3.1	43.6 ± 3.9	0.744
Disease duration (months)	7.1 ± 1.5	7.1 ± 1.8	0.958
RF positivity	23 (88.5%)	24 (85.7)	0.999
The DAS28 score at the beginning	5.0 ± 1.2	5.1 ± 1.0	0.994
The DAS28 score at the end	3.9 ± 0.7	4.2 ± 0.9	0.486

*The probability level was expressed by p-value of <0.05.

Table 1. Demographic and clinical characteristics of examined patients

	Group	Baseline	12 months	P Value *	
L2–4 BMD (g/ cm2)	Ι	0.95 ± 0.14	0.95 ± 0.12	0.95	
	II	0.97 ± 0.12	0.93 ± 0.19	0.073	
Femur neck BMD (g/cm2)	I	0.88 ± 0.10	0.86 ± 0.09	0.708	
	II	0.87 ± 0.11	0.86 ± 0.11	0.222	
*The probability level was expressed by p-value of <0.05.					

Table 2. Bone Mineral Density (BMD) changes at the lumbar spine and femoral neck region

II 0.97 \pm 0.12 compared at the results after 12 months treatment where in group I, BMD was 0.95 \pm 0.12 and in group II was 0.93 \pm 0.19, higher at the baseline but not statistically significant (p=0.954 vs p=0.073). Also, BMD in femoral neck region at baseline in group I was 0.88 \pm 0.10 and in group II was 0.87 \pm 0.11 compared after 12 months treatment in group I was 0.88 \pm 0.09 and group II was 0.86 \pm 0.11, higher at the baseline but not statistically significant (p=0.708 vs p= 0.222) (Table 2).

5. DISCUSSION

We have the results from a retrospective study of 60 early RA patients in whom the impact of low dose MTX in BMD was studied. Although the optimal approach to the treatment of RA remains controversial, methotrexate is considered the standard DMARD, and an increasing number of patients are being treated with it. Since RA patients have many other risk factors for osteoporosis and receive methotrexate for long periods, it is important to assess its effect on bone. In previous studies, most patients were postmenopausal and had long disease duration and some disability, factors known to impair bone mass (5). In a recent study, Cranney evaluated the effect of low-dose methotrexate on cortical and trabecular bone in patients with RA and suggested that it had no negative effect on bone density at either site (6). Similarly, Mazzantini et al. evaluated female RA patients who had recently started methotrexate in a 2-year, longitudinal study and reported that low-dose methotrexate did not seem to exert relevant effects on bone (7). Furthermore, Minaur et al, showed in their results of 116 examined patients with RA, that in patients treated with MTX where reduced BMD occurred, it was more likely related with disease activity and adjacent joint damage rather than a toxic effect of MTX (8). In another placebo-controlled study, RA patients treated for three years with DMARDs and prednisolone resulted in greater bone loss in lumbar spine site compared with treatment without prednisolone, whereas, low dose MTX alone without

corticosteroids did not change BMD values of lumbar spine or femoral neck (9). Many other factors of bone loss such as persistent of disease activity, aging, functional impairment, vitamin D deficiency have to be considered as contributing factors of decrease BMD (10, 11). The results of the study by Book et al. in which DMARD treated patients were compared with the non-treated patients showed that BMD changes at both lumbar spine and femoral neck were not significantly different, where the BMD values did not vary from baseline (12). Our results were consistent with studies suggesting that methotrexate has no negative effect on bone mass.

6. CONCLUSION

If methotrexate has negative effect on bone, it would be more likely to be observed in premenopause, since women usually experience marked bone loss after menopause. We believe that these results might provide new insights and that further longitudinal studies with larger groups of premenopausal RA patients are required and, our results, as those of previous studies, suggest that low dose of methotrexate use does not lead to bone loss in patients with RA. Strength of the study is that in our study we only evaluated patients who has never been on oral corticosteroids for RA, to avoid the effects in BMD that are associated with corticosteroids.

- Author's contribution: all authors were included in all phases of preparing this article, including final proof reading.
- Conflicts of interest: The study has been completed within resources of University Clinical Center of Kosova and no additional funds have been used. There are no conflicts of interest to declare.
- Abbreviations: RA Rheumatoid Arthritis, DMARDs Disease Modifying Antirheumatic Drugs, BMD - Bone mineral Density, MTX - Methotrexate, SSZ-Sulfasalazine, DAS-28- Disease Activity Score - 28, ESR-Erythrosedimentation Rate, RF-Rheumatoid Factor, DEXA - Dual Energy X-ray Absorptiometry, ST-Standard Deviation.

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