

Effects of High Dose Methylprednisolone Pulse Therapy on Bone Mass and Biochemical Markers of Bone Metabolism in Patients with Active Rheumatoid Arthritis: A 12-Month Randomized Prospective Controlled Study

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ABSTRACT. Objective. To study the effects of one year of high dose 6-methylprednisolone pulse therapy (MPPT) on bone mass, serum bone alkaline phosphatase (sBAP), and urinary deoxypyridinoline (uDpyr) in patients with active rheumatoid arthritis (RA), and to compare results with those of patients with active RA treated with oral methylprednisolone (OMP).

Methods. Thirty-one women with active RA were given 1000 mg of MP IV for 3 alternate days, with a mean interval of administration of 76 days (± 8.3 SD) for one year (MPPT group). Bone mineral density (BMD) (total body, lumbar spine, and femur neck), plasma levels of sBAP, and urinary concentrations of uDpyr were assessed at the beginning of the treatment and every 3 months until the end of the study. Moreover, erythrocyte sedimentation rate (ESR), Thompson joint score, and early morning stiffness were assessed at study entry and every month. The control group, 31 women with active RA treated with oral MP, was followed in the same way (OMP group).

Results. In the MPPT group there was no significant reduction of BMD at any site compared to significant reductions in lumbar BMD at 6 and 12 months and total body BMD and femur neck BMD at 12 months in the OMP group. Also in the OMP group, a significant reduction in the mean sBAP was observed. The mean uDpyr levels were not significantly reduced in either group.

Conclusion. Our results show that MPPT, compared to continuous therapy with oral corticosteroids, preserves bone mass without modifying the biochemical markers of bone metabolism. (J Rheumatol 2004;31:1083–7)

Key Indexing Terms:

GLUCOCORTICOID PULSE THERAPY
RHEUMATOID ARTHRITIS
BONE MINERAL DENSITY

CORTICOSTEROID-INDUCED OSTEOPOROSIS
DUAL ENERGY X-RAY ABSORPTIOMETRY
BONE TURNOVER

Corticosteroids (CS) are used frequently in the management of patients with rheumatoid arthritis (RA). CS may be used with different routes of administration [oral, intramuscular, and intravenous (IV)], with different doses and for different periods of time.

Longterm usage of low dose CS is associated with an increased risk of osteoporosis (OP) and related fractures¹⁻⁴.

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Submitted May 16, 2003; revision accepted December 30, 2003.

A significant adverse effect on bone mineral density (BMD) was reported in patients taking > 4 mg prednisone/day⁵⁻⁸. Continuous steroid use promotes bone loss through decreased production and increased resorption of bone⁹⁻¹².

IV administration of high doses of CS pulse therapy (CPT) is used in RA as a bridge therapy and as an alternative to low doses of oral CS when starting disease modifying antirheumatic drugs (DMARD) to suppress inflammation¹³⁻¹⁴. Significant benefits in terms of functional outcome have been reported with short term use¹⁵⁻²⁰. One report on the prolonged use of CPT for children with rheumatic diseases has been published²¹.

Short term studies have shown that CPT may have fewer and more transitory effects on bone formation and on bone resorption than continuous oral CS treatment²²⁻²⁷.

Only one study has reported the preservative effects of infusion of CPT on 3 consecutive days on BMD in patients with multiple sclerosis²⁸.

Our study evaluates BMD and bone turnover after prolonged use of CPT with 6-methylprednisolone (MP) in patients with active RA.

MATERIALS AND METHODS

Study design. In this open label study, 62 women with active RA treated with methotrexate (MTX) and low dose CS were randomized to 2 one-year treatments: the first group was treated with MTX, sulfasalazine (SSZ) and CPT with MP (MPPT); the second group was treated with MTX, SSZ, and oral MP (OMP). After randomization, the investigators, the outcome assessors, and the patients were aware of the treatment allocation.

All patients were diagnosed according to the American College of Rheumatology criteria²⁹; active disease was defined as the presence of an erythrocyte sedimentation rate (ESR) > 30 mm/h and at least one of the following criteria: Thompson joint score > 10, early morning stiffness > 1 h. An assessment of ESR, Thompson joint score, early morning stiffness, and clinical evaluation was conducted at study entry and each month in both treatment groups.

The MPPT regimen comprised 3 doses of 1000 mg MP given through an IV infusion on alternate days. The MPPT was repeated at the monthly check if the disease was active. If the disease was not active the MPPT was reconsidered for the following month. OMP was administered at a dose of 16 mg/day for at least 1 month.

If the disease was not active, an attempt was made to reduce the dosage of OMP by 4 mg every month but the minimum dosage of MP was never less than 4 mg/day.

BMD was evaluated at study entry and every 3 months by means of fan-beam radiograph densitometry using a Lunar-Expert, version 1.72. The following regions were evaluated: lumbar spine (L2–L4), femur neck, and total-body. The results were expressed as g/cm². The time frame of 3 months was chosen because prospective studies of longterm steroid use have shown that most of the associated bone loss occurs in the first 3 to 6 months of treatment³⁰. The short term precision of this densitometry, expressed as the coefficient of variation, is 1.0 for lumbar spine, 1.3 for femur neck, and 0.7 for total body.

Laboratory investigation. Seric bone alkaline phosphatase (sBAP) was determined every 3 months as an index of bone formation rate using an enzyme-linked immunosorbent assay (ELISA, Alkphase-B, Metra Biosystems, Mountain View, CA, USA). According to the manufacturer, the normal range for post-menopausal women was 14.2–42.7 U/l. The precision of this assay, expressed as the coefficient of variation, is 3.9 (within-run) and 5.0 (between-run).

Urinary deoxypyridinoline (uDpyr) was determined every 3 months as an index of bone resorption rate using an ELISA (Pyrilinks-D, Metra Biosystems). According to the manufacturer, the normal range for post-menopausal women was 3.0–7.4 nmol/mmol. The precision of this assay, expressed as the coefficient of variation, is 4.3 (within-run) and 4.6 (between-run).

At baseline and during the followup, blood tests for biochemical markers were performed before the dose of MP was administered.

Statistical analysis. Student's unpaired t test (for normal distribution), the Wilcoxon rank test (for non-Gaussian distributions), and the Kruskal-Wallis test (for nonparametric analysis of variance, ANOVA) were performed to compare quantitative variables. All statistical tests were 2-sided. A value of $p < 0.05$ was considered statistically significant.

RESULTS

The clinical and demographic characteristics of the 2 groups are shown in Table 1. There are no significant differences between the 2 groups.

Figures 1, 2, and 3 show mean BMD values at basal, and

at 3, 6, 9, and 12 months in the total, lumbar, and femoral regions respectively.

Total body mean BMD values were significantly reduced at 12 months in the OMP group (baseline: 1.057 g/cm² vs 12 months: 0.975 g/cm², $p < 0.05$). In the MPPT group BMD was not significantly reduced (baseline: 1.050 g/cm² vs 12 months: 0.975 g/cm², p not significant). The mean values of BMD of the 2 groups at 12 months appeared to be significantly different ($p < 0.05$) (Figure 1).

Lumbar mean BMD values were significantly reduced at 6, 9, and 12 months in the OMP group (baseline: 0.997 g/cm² vs 6 months: 0.931 g/cm², $p < 0.05$; vs 9 months: 0.917 g/cm², $p < 0.05$; vs 12 months: 0.904 g/cm², $p < 0.01$). In the MPPT group BMD was not significantly reduced. Also the mean values of BMD of the 2 groups at 9 and 12 months appeared significantly different ($p < 0.05$) (Figure 2).

Mean BMD values at the femur neck were significantly reduced at 12 months in the OMP group (baseline: 0.871 g/cm² vs 12 months: 0.784 g/cm², $p < 0.05$). In the MPPT group BMD was not significantly reduced (baseline: 0.872 g/cm² vs 12 months: 0.826 g/cm², p not significant). The mean values of BMD of the 2 groups were not significantly different (Figure 3).

Figures 4 and 5 show mean values of sBAP and uDpyr respectively at baseline, 3, 6, 9, and 12 months in the 2 groups.

Mean values of sBAP were significantly reduced at 12 months in the OMP group (baseline: 25 UI/l vs 12 months:

Table 1. Demographic and clinical characteristics of the groups studied. Results are expressed as mean (standard deviation). There were no significant differences between the 2 groups.

Variable	MPPT	OMP
n	31	31
Age, yrs	57.4 (6.1)	57 (6.1)
YSM	7.3 (4.8)	7.1 (4.1)
Height, cm	157.2 (4.1)	158 (4.4)
Weight, kg	54.3 (5.3)	54.1 (5.6)
BMI, kg/m ²	22.3 (2.6)	22.1 (3.0)
Disease duration, mo	38.4 (9.3)	36.7 (8.9)
MTX, mg/wk	12.5 (2.3)	12.8 (2.2)
Oral corticosteroids, mg/day	4.5 (1.2)	4.6 (1.4)
ESR, mm/h	68 (15.9)	65 (16.3)
Early morning stiffness	1.5 (0.2)	1.4 (0.3)
Thompson joint score	120 (30)	128 (34)
sBAP, UI/l	29 (6.8)	25 (6.6)
uDpyr, nmol/mmol	3.8 (1.3)	3.6 (1.1)
BMD (T-score)		
Total body	1.057 (0.103)	1.049 (0.090)
Spine, L2–L4	0.999 (0.122)	0.997 (0.134)
Femur neck	0.872 (0.133)	0.871 (0.134)

MPPT: 6-methylprednisolone pulse therapy group; OMP: oral methylprednisolone group; YSM: years since menopause; BMI: body mass index; MTX: methotrexate; ESR: erythrocyte sedimentation rate; sBAP: seric bone alkaline phosphatase; uDpyr: urinary deoxypyridinoline; BMD: bone mineral density.

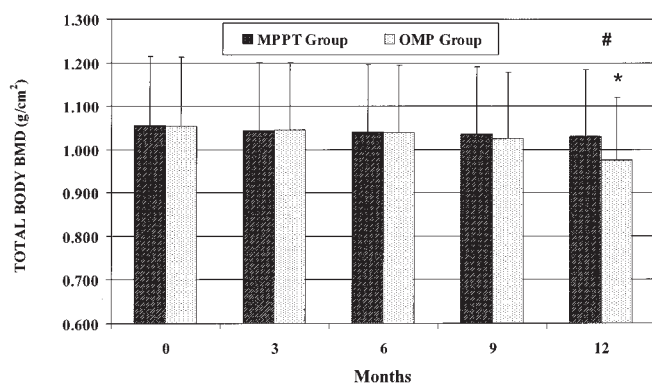


Figure 1. Mean total body BMD values at baseline, 3, 6, 9, and 12 months in the 2 treatment groups. MPPT: methylprednisolone pulse therapy; OMP: oral methylprednisolone. Comparison within the same group: * $p < 0.05$ (ANOVA). Comparison between different groups at the same time: # $p < 0.05$ (unpaired Student's t test).

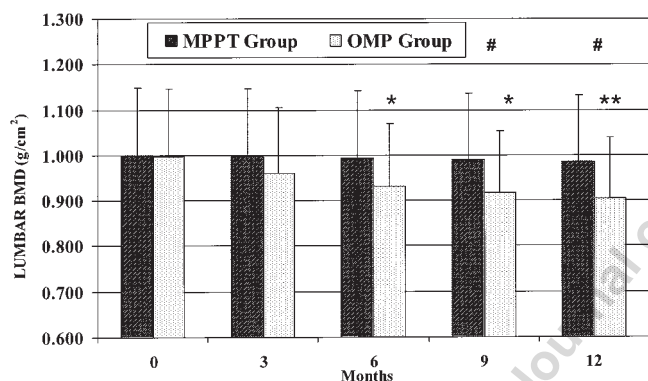


Figure 2. Mean lumbar BMD values at baseline, 3, 6, 9, and 12 months in the 2 treatment groups. Comparison within the same group: * $p < 0.05$, ** $p < 0.01$ (ANOVA). Comparison between different groups at the same time: # $p < 0.05$ (unpaired Student's t test).

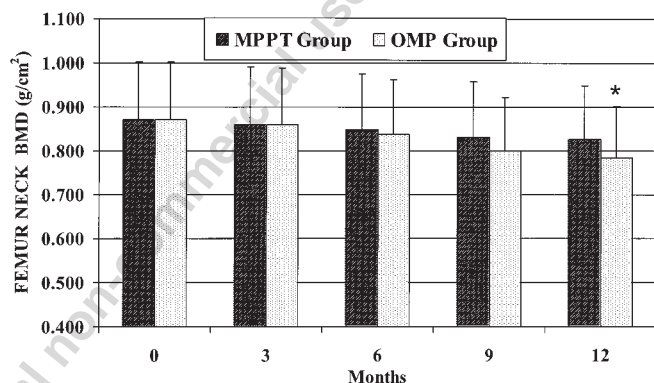


Figure 3. Mean femur BMD values at baseline, 3, 6, 9, and 12 months in the 2 treatment groups. Comparison within the same group: * $p < 0.05$ (ANOVA).

11 UI/l, $p < 0.01$). In the MPPT group, the sBAP was not significantly reduced. The mean values of sBAP at 12 months in the 2 groups were significantly different ($p < 0.01$) (Figure 4).

Mean values of uDpyr were not significantly reduced in the OMP group or in the MPPT group (Figure 5).

Attrition occurred in 21 cases during the 12 months of followup because of loss of contact ($n = 5$: 3 in the OMP group and 2 in the MPPT group), increase in blood pressure ($n = 8$: 3 in the OMP group and 5 in the MPPT group), hyperglycemia ($n = 5$: 2 in the OMP group and 3 in the MPPT group), and headache and facial flushing ($n = 3$, all in the MPPT group).

The weight and the body mass index (BMI) of the patients increased at the end of the study, both in the MPPT group and in the OMP group, with no significant difference between the 2 groups: weight 55.5 kg (± 6.1) and BMI 22.6 (± 3.1) in the MPPT group and weight 55.9 kg (± 5.8) and BMI 22.5 (± 3.2) in the OMP group.

The average interval between administrations of MPPT was 76 days (± 8.3), equal to 18.9 g of MP (± 4.2) for each patient in one year. In the OMP group the average yearly dose was 3.06 g of MP (± 1.3) with an average daily dose of 8.4 mg/day of MP (± 1.9) for each patient.

Of the 102 MPPT infusions in the 18 patients controlled for one year, 51 were done with an interval of 2 months, 49 with 3 months, and 2 with a 4-month interval.

DISCUSSION

One of the most important side effects of longterm use of CS is osteoporosis, characterized by decreased bone formation and unchanged or increased bone resorption²²⁻²⁷.

This uncoupling of bone formation and bone resorption may lead to bone loss, and eventually to fractures²⁴.

One way to reduce the effects of CS on bone can be to

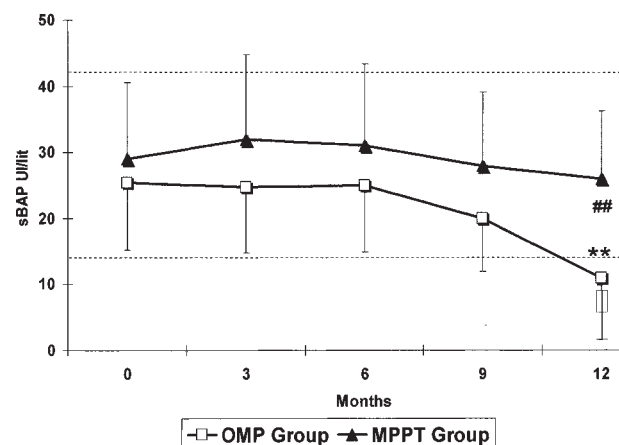


Figure 4. Mean seric bone alkaline phosphatase (sBAP) values at baseline, 3, 6, 9, and 12 months in the 2 treatment groups. Comparison within the same group: ** $p < 0.01$ (ANOVA). Comparison between different groups at the same time: ## $p < 0.01$ (unpaired Student's t test).: normal range.

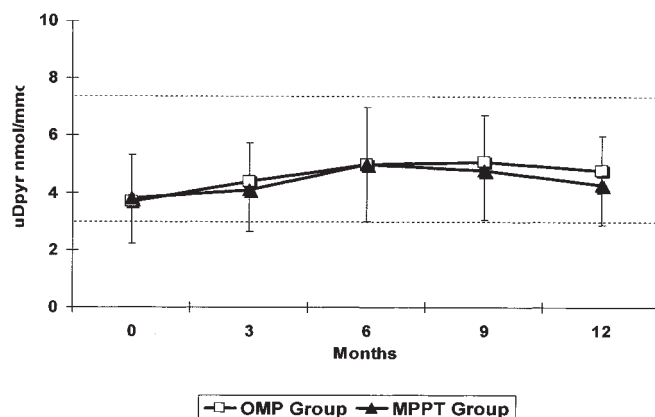


Figure 5. Mean urinary deoxypyridinoline (uDpyr) values at baseline, 3, 6, 9, and 12 months in the 2 treatment groups.: normal range.

modify the administration. Treatment on alternate days does not appear useful in this regard³¹.

IV CS pulses have often proved efficient in the treatment of immunologic diseases like RA, giant cell arthritis, and multiple sclerosis^{6,13,16,21,28,32,33}.

In patients with RA, CPT is used during the delay between the introduction of DMARD and the onset of their therapeutic effects, or in patients with particularly active disease not responding to conventional longterm treatments¹⁴.

Many studies of patients with active RA have reported good effects of CPT in short term evaluation of disease activity, psychosocial well-being and physical functioning^{16,18}.

Alterations of bone metabolism during high dose CPT have been reported²³⁻²⁶. However these changes were small and reversible in a few days. Kollerup, *et al*²⁶ reported transient reduction of urinary pyridinoline after CPT. Lems, *et al*²³⁻²⁴ reported a transient decrease in osteocalcin, carboxyterminal propeptide of type I procollagen, and carboxyterminal cross-linked telopeptide of type I collagen after CPT. Van der Veen, *et al*²⁵ reported a transient increase in 1,25-dihydroxyvitamin D concentration and in urinary calcium excretion.

Because of these short term negative effects on bone formation, it is presumed that the global longterm effect of CPT on bone may be relatively mild²⁴.

Only one longterm study of 6 months reports data on the effects of CPT on BMD in patients with multiple sclerosis²⁸. This study found that repeated CPT did not reduce femoral BMD (only in patients not confined to bed) and resulted in an increase in lumbar BMD.

Our study evaluated BMD and bone turnover after a prolonged use of CPT in patients with active RA.

Our results confirm the hypothesis that CPT does not bring about a reduction of BMD in patients with active RA. In fact, in all the sites examined, BMD was not significantly

reduced compared to baseline values. However, BMD was significantly reduced in all areas examined in patients treated with OMP. It is noteworthy that the cumulative dose of MP in the 2 groups was decidedly higher in the group treated with CPT.

Regarding bone metabolism markers, our results show that sBAP (a bone formation marker) was significantly reduced after 12 months in the OMP group only. These data confirm the results of a previous short term study²⁴ and other studies that evaluated other bone formation markers^{23,25} that showed a return of these markers to normality 24 hours after CPT.

Our study did not show any significant change from baseline in the urinary concentration of uDpyr in the 2 groups. This is in agreement with previous studies that showed a progressive and relatively rapid return to normality of bone resorption markers such as uDpyr^{24,26} and other analogous markers²⁵.

As far as the side effects of CPT are concerned, both treatments were associated with few serious events. Although no osteonecrosis was observed in our case study, this risk does exist with both treatments.

The drop-out rate was not significantly different in the 2 groups. Similarly, incidences of hyperglycemia and cardiovascular disorders (including combined hypertension and flushing) were not significantly different between the 2 groups.

The effects of the 2 therapeutic regimens differed with respect to bone mass but not with respect to disease activity indices. In fact, the average values of the ESR, Thompson joint score, and early morning stiffness were significantly reduced compared to their values at baseline, 6 months ($p < 0.01$), and 12 months ($p < 0.01$) in the 2 groups, without any significant differences between the groups. In particular, the average ESR values in the MPPT group and in the OMP group were reduced, respectively, from initial values of 68 mm/h (± 15.9) and 65 mm/h (± 14.3) to average values of 28 mm/h (± 8) and 26 mm/h (± 7) at 6 months and to average values of 26 mm/h (± 6) and 25 mm/h (± 7) at 12 months.

Evaluating disease activity was not the primary aim of our study in the followup year and this reduction in disease activity could be at least partially responsible for the prevention of bone resorption in both the treated groups.

The results of our study are in agreement with those demonstrated by Buttgerit, *et al* who hypothesized that beneficial clinical results of high-dose CS in active RA may not be interpreted exclusively as a higher quantitative expression of the therapeutic effect, but may also reflect the additional contribution of qualitatively different, nongenomic actions of CS³⁴. The nongenomic effect is particularly evident with MP compared to prednisone and to betamethasone³⁵.

In conclusion, our study showed that 6-MPPT, compared to continuous therapy with oral CS, preserves bone mass without modifying bone turnover with no less effectiveness on disease activity.

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