

Does Anti-TNF Therapy Cause A Less Significant Fall In Bone Mineral Density In Patients With Rheumatoid Arthritis?

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Citation

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Abstract

Fifty eight patients with rheumatoid arthritis (RA) were assessed retrospectively to investigate whether anti-tumour necrotic factor (anti-TNF) therapy reduces bone mineral density (BMD) less significantly as assessed by dual-energy X ray absorptiometry (DXA) scan compared to those treated with conventional disease modifying drugs (DMARDs). Patients were divided into two groups: group A and B. Group A received anti-TNF therapy and group B received DMARDs. Patients who received bisphosphonate and other osteoporosis treatments such as hormonal replacement therapy were excluded. Changes in spine BMD and T-score between the baseline and the repeat DXA scan were assessed. Mean percentage change per year in spine BMD and T-score in each group were calculated. In group A, there was no significant reduction in spine BMD and T-score between baseline and repeat scan ($P=0.353$ and $P=0.344$ respectively). In group B, there was almost a significant reduction in spine BMD ($P=0.058$) and a significant reduction in spine T-score ($P=0.013$) between two scans. Although reduction of spine BMD and T score between baseline and repeat scan were more significant in group B, in terms of mean percentage change of spine BMD and T-score per year, there were no statistically significant differences ($P=0.593$ and $P=0.185$ respectively) between these groups.

INTRODUCTION

Do rheumatoid arthritis patients treated with anti - TNF therapy have a less significant fall in bone mineral density compared to those treated with conventional DMARDs?

Rheumatoid arthritis is a chronic inflammatory polyarthritis with multi - system involvement. Although the exact cause of the disease remains unknown, there is now a better understanding of the genetic, environmental and immunological factors that play a part. These factors potentially initiate immune mechanisms resulting in an inflammatory process that causes articular and extra - articular manifestations of rheumatoid arthritis. Juxta - articular osteoporosis and generalized osteoporosis are well recognised complications of rheumatoid arthritis [1, 2]. Since the late 1980's and early 1990's the understanding of the role of cytokines in the pathogenesis of rheumatoid arthritis has increased greatly [3, 4]. Pro-inflammatory cytokines are thought to have a major role in the development of bone diseases in rheumatoid arthritis. There have also been a few animal experiments [5, 6, 7] which have shown that tumour necrosis factor has increased

osteoclast activity and reduced osteoblast activity which leads to increased bone resorption. It has always been an interest to determine whether anti - TNF therapy reduces BMD less significantly in patients treated with anti-TNF therapy compared to those treated with conventional DMARDs therapy.

The aim of this retrospective study is to determine the effect of anti - TNF therapy on BMD in patients with rheumatoid arthritis as assessed by dual-energy X-rays absorptiometry (DXA) scan. The study will also investigate whether anti - TNF therapy results in a less significant reduction in bone mineral density compared to those treated with conventional DMARDs.

MATERIALS AND METHODS

INCLUSION CRITERIA

Patients with rheumatoid arthritis who received DMARDs therapy for at least one year before the first DXA scan.

Patients with rheumatoid arthritis who have had a follow up DXA scan at least 1 year after starting anti - TNF therapy and DMARDs therapy.

All patients with rheumatoid arthritis who meet the inclusion criteria and have had a repeat scan between September 2008 and September 2010.

EXCLUSION CRITERIA

Rheumatoid arthritis patients who were con-currently receiving a bisphosphonate therapy or who had received bisphosphonate therapy in the past.

Rheumatoid arthritis patients who were con-currently receiving a hormonal replacement therapy or who had received hormonal therapy in the past.

Rheumatoid arthritis patients who have other co-morbidities which significantly affect bone metabolism; for example: hypogonadism, liver disease, renal failure, Paget's disease, primary hyperparathyroidism, malabsorption.

Rheumatoid arthritis patients with significant degenerative spine disease.

The total number of patients was 58 (n=58). (9) Male and (49) female patients were included. These patients were under the care of the rheumatology team at St George's Hospital, London and they were from multi-ethnic origins. Patients were divided into two groups: group A and B. Group A received anti - TNF therapy either adalimumab or etanercept or infliximab and group B received either single DMARD such as methotrexate, sulfasalazine, leflunomide, hydroxychloroquine or a combination of DMARDs. The age range was between (28) and (81) years. Mean age $\pm$ SD (years) for group A was 56.57 ± 11.15 and group B was 63.46 ± 11.33 .

Data for this study was collected from computerized medical records and clinic letters. The demographic and clinical characteristics of the individuals were analysed (Table 1). Types of DMARDs and anti-TNF therapy, concomitant significant co-morbidities and other risk factors for osteoporosis were also studied. The results of bone mineral density (g/cm²) with T - score and Z - score of spine and hip were analysed in this study.

Student's t test was used for normally distributed data and Mann - Whitney signed rank test was used for not normally distributed data to determine the statistical differences in the study. All data is presented as mean $\pm$ S.D and p values were calculated. P value <0.05 was considered as a significant for all data analysis and interpretation.

RESULTS

Group A (anti-TNF) patients were younger than group B patients (DMARDs) (mean age (yr) $\pm$ SD 56.57 ± 11.15 (A) vs 63.46 ± 11.33 (B), $P=0.023$). There is no statistically a difference in mean post menopausal age between group A and B (mean post menopausal age (yr) $\pm$ SD 47.98 ± 2.49 (A) vs. 48.14 ± 1.37 (B), $P=0.942$). Group A patients had higher disease activity (mean ESR $\pm$ SD 37 ± 6.8 (A) vs 16 ± 3.2 (B), $P=0.007$) and they needed more steroid dose than group B (mean daily steroid dose $\pm$ SD 7.5 ± 3.1 (A) vs 6.1 ± 2.8 (B), $P=0.013$). Group A also received repeat DXA scan earlier than group B (mean time interval between scan (months) $\pm$ SD 46.5 ± 17.00 (A) vs 77.76 ± 38.97 (B), $P=0.001$). Group A have used more concomitant calcium and vitamin D treatment than group B (78% vs. 73%). There was no significant difference of mean duration of disease (yrs) between both groups (mean $\pm$ SD 11.32 ± 5.56 (A) vs. 10.36 ± 5.56 (B), $P=0.287$). (Table 1)

Table 2 has shown changes in spine BMD and T-score between baseline scan and repeat scan in the same group over the period of time. In group A patients with anti - TNF therapy, there was no significant reduction in spine BMD between baseline scan and repeat scan (mean $\pm$ SD 0.98 ± 0.15 vs. 0.97 ± 0.16 , $P=0.353$). There was also no significant change in spine T-score (mean $\pm$ SD -0.70 ± 1.50 vs. -0.81 ± 1.60 , $P=0.344$). In group B patients, there was almost a significant reduction in spine BMD between baseline scan and repeat scan (mean $\pm$ SD 1.03 ± 0.20 vs. 1.00 ± 0.17 , $P=0.058$). There was a significant reduction in spine T - score (mean $\pm$ SD -0.05 ± 1.83 vs. -0.47 ± 1.53 , $P=0.013$). (Table 2)

Although reduction of bone mineral density and spine-T score between baseline and repeat scan were more significant in group B, in terms of mean percentage change of spine bone mineral density and spine T-score per year, there were no statistically significant differences between these two groups (mean $\pm$ SD -0.20 ± 1.46 (A) vs. -0.40 ± 1.37 (B), $P=0.593$ and mean $\pm$ SD -4.20 ± 17.59 (A) vs. -13.41 ± 32.44 (B), $P=0.185$ respectively). (Table 3)

Limitations of this retrospective study are as follows:

Small sample sizes of both groups
(Group A n = 28, Group B n = 30)

Age mis - match between the groups (year)
(Group A 56.57 ± 11.15 , Group B 63.46 ± 11.33 , $p = 0.023$)

Discrepancy between duration of scans (months)
(Group A 46.5 ± 17.00 , Group B 77.76 ± 38.97 , $p = 0.001$)

Difference in amount of daily steroid consumption (mg)
(Group A 7.5 ± 3.1 , Group B 6.1 ± 2.8 , $p=0.001$)

Difference in disease activity status (ESR)
(Group A 37 ± 6.8 , Group B 16 ± 3.2 , $p=0.001$)

DISCUSSIONS

To the best of our knowledge following a literature search, this study is the first attempt to identify the effect of anti-TNF therapy compared to DMARDs on bone mineral density in rheumatoid arthritis patients.

There have been a few studies which have supported that anti - TNF therapy may provide a positive effect on bone metabolism in patients with rheumatoid arthritis [8, 9]. In 2005, there was a prospective open - label pilot study by Lange and Teichmann et al [8]. Twenty-six rheumatoid arthritis patients who received infliximab were studied. Patients who received bisphosphonate or hormonal therapy were not included in the study. The BMD in both the spine and hip was measured with DXA scan at baseline and repeated 12 months after. The authors have revealed that there was a significant increase in BMD in both spine ($p = <0.001$) and hip ($p= <0.001$). In conclusion, this study has supported the fact that anti-TNF therapy may result in an increase in bone mineral density in patients with rheumatoid arthritis.

In a retrospective cohort analysis by Pazianas et al (2006) [10], the effect of infliximab (with and without bisphosphonate) on spinal bone mineral density has been studied in patients with Crohn's disease ($n=61$). Subgroup analyses were also performed in patients taking corticosteroids. The results revealed that patients with concurrent infliximab and bisphosphonate treatment have shown a greater increase in bone mineral density compared to those on bisphosphonate alone ($+6.7\%/year$ vs. $+4.46\%/year$, $P=0.045$). However, infliximab alone did not have any effects on bone mineral density. Although the results showed an improvement in BMD for patients taking infliximab compared to bisphosphonate alone this was not proven to be statistically significant. Authors also discussed that the positive effect of infliximab alone may not be visible because of the small sample size of the study and they have emphasized that larger sample size will be needed to confirm the effect of infliximab on bone mineral density in these

patients.

The reason for a reduction or increase in bone mineral density in rheumatoid arthritis patients is multi-factorial. When analysing and interpreting the results as many confounding factors as possible have been taken into account, these factors are highlighted and discussed in the following paragraphs.

AGE FACTOR AND POSTMENOPAUSAL STATUS IN PATIENTS WITH RHEUMATOID ARTHRITIS

Age is an important confounding factor when assessing bone mineral density. The impact of the aging process on bone mineral density depends on the individual's physical activities. Long - term high level weight bearing physical activities are also shown to have increased bone mineral density [11]. In men aged between 69 to 97 years old, age reduces both the cortical and trabecular volumetric BMD [12].

Post menopausal status is a well known important factor in assessing bone mineral density. Recently, a pooled analysis of the data from four phase III double-blinded randomized placebo-controlled studies has shown that in postmenopausal women with osteoporosis, irrespective of treatment, both vertebral and non-vertebral fracture risks were greater in older postmenopausal women patients ($P<.001$). On average, for every one year increase in age, patient's risk for osteoporosis - related fracture increased by 3.6% (95% confidence interval = 2.3-5.0%) [13].

In this study, mean age (yrs) $\pm$ SD for group A and B is 56.57 ± 11.15 vs. 63.46 ± 11.33 respectively and p value is <0.05 . Group A patients are significantly younger than group B patients. However, in terms of mean postmenopausal age, there is no statistically a difference between group A and B (mean post menopausal age (yr) $\pm$ SD 47.98 ± 2.49 (A) vs. 48.14 ± 1.37 (B), $p>0.05$). Patients who have used or have been using hormonal replacement therapy were already excluded in this study.

TIME INTERVAL (MONTHS) BETWEEN THE SCANS

Time interval (months) between two scans for both group A and B were mean $\pm$ SD 46.50 ± 17.00 and 77.76 ± 38.97 (p value < 0.05) respectively. Patients receiving anti-TNF therapy have had a repeat bone scan sooner than patients receiving DMARDs. In terms of severity of disease, patients

who have needed anti - TNF therapy have a more severe disease than patients receiving DMARDs and have needed a higher steroid dose before they received anti- TNF therapy. Severity of the disease and the need for the higher steroid dose could be the main factors that have made medical professionals to decide to repeat the bone scan earlier.

USE OF STEROID DRUG AND DISEASE ACTIVITY OF RHEUMATOID ARTHRITIS

Use of steroids in the treatment of rheumatoid arthritis and their impact on osteoporotic bone disease have been highly analysed in the literature. It is known that low dose oral corticosteroid (6.6 mg - 8.5 mg/day) does not increase the risk of generalised osteoporosis in patients with rheumatoid arthritis [14, 15]. In postmenopausal women with rheumatoid arthritis, steroid induced osteoporosis is more evident at the hip than the spine. In these patients, reduction in the BMD is mainly due to cumulative steroid dose and disability due to active disease condition [16]. On the other hand, the independent effect of corticosteroids is also questionable because the use of corticosteroids indicates the severity of the disease.

Severity of rheumatoid arthritis is itself an independent risk factor for osteoporosis. Laan et al [17] has found that the higher the ESR is within the six months before bone mineral assessment, the lower the bone mineral density in the hip in patients with rheumatoid arthritis.

In this study, mean daily steroid dose (mg) $\pm$ SD for group A (anti-TNF) was 7.5 ± 3.1 and for group B (DMARDs) is 6.1 ± 2.8 ($P = 0.013$). Mean ESR $\pm$ SD for both groups were 37 ± 6.8 (A) and 16 ± 3.2 (B) respectively ($P = 0.007$). In terms of mean steroid dose and ESR, there were statistical differences between two groups and it has indicated that group A patients have a higher disease activity and they may have lower bone density before they received anti - TNF treatment compared to group B patients.

USE OF BISPHOSPHONATES THERAPY IN PATIENTS WITH RHEUMATOID ARTHRITIS

Oral bisphosphonates have been widely used as a treatment of osteoporosis in patients with inflammatory arthropathies. These are pyrophosphate analogs and their main action is on osteoclasts [18]. They are regarded as strong inhibitors of osteoclasts and antagonise the bone resorption of osteoclasts. Bisphosphonates are found to have improved BMD in patients who have had steroid induced osteopaenia and osteoporosis, including postmenopausal osteoporosis [19,

20]. It is also found to be effective in the prevention of bone fractures in these patients. Therefore, in this study, patients who have used or have been using bisphosphonates are excluded so that the effects of anti - TNF therapy on bone mineral density can be assessed isolated from the known benefits of bisphosphonate therapy.

CONCLUSIONS

This study has concluded that although anti - TNF therapy could suppress the osteoclastic activities and prevent further development of osteoporosis bone disease in patients with rheumatoid arthritis, reasons for a reduction in bone mineral density in these patients are multi - factorial. In rheumatoid arthritis patients with low bone density, all other possible causes need to be looked at and treated if indicated. The effect of anti -TNF therapy on bone mineral density might be beneficial if accompanied by bisphosphonate therapy; however, anti -TNF alone may not deter falling in bone mineral density in rheumatoid arthritis patients. On the other hand, the beneficial effect of anti -TNF may not be obvious because of the low sample sizes of both groups. Age - matched groups and equal time interval between two scans are preferable. Further studies with larger power will be able to confirm the effect of anti-TNF on bone disease in patients with rheumatoid arthritis.

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