Changes in bone mineral density during long-term treatment with adalimumab in patients with rheumatoid arthritis: a cohort study

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Abstract

Objective. To investigate the effect of long-term adalimumab treatment on BMD of the lumbar spine, total hip and hands in patients with RA.

Methods. In 184 established RA patients treated with adalimumab for at least 1 year, BMD measurements of the total hip and lumbar spine were performed using dual-energy X-ray absorptiometry. Metacarpal cortex BMD was measured using digital X-ray radiogrammetry.

Results. After 1 year of treatment, BMD of the hip and lumbar spine remained stable, while BMD of the hands decreased significantly by \(-1.41\% (\text{P}<0.0001)\). After a mean follow-up of 4.0 (s.d. 1.0) years, mean BMD change per year was \(-0.58\% and 0.07\% for the hip and lumbar spine, respectively (overall P-value of hip was \(<0.0001\) and spine was 0.67). Predictors for BMD loss of the hip were anti-CCP positivity, non-use of bisphosphonates at baseline and BMI. In European League Against Rheumatism (EULAR) non-responders at 52 weeks, BMD change of the hip and spine was \(-1.25\% and 1.08\%, respectively, for moderate responders \(-0.61\% and \(-1.87\%, respectively, and in EULAR good responders, BMD remained stable: \(-0.02\% and 0.06\%, respectively. BMD of the hands decreased in non-, moderate and good responders (\(-2.85\%, \(-1.47\% and \(-1.26\%, respectively).

Conclusion. In patients with severe, established RA, loss of BMD in the spine was arrested over 4 years of adalimumab treatment, whereas BMD of the hands and hip continued to decrease after 1 and 4 years, respectively. The changes in BMD are related to disease activity, underlining the importance of monitoring disease activity.

Key words: osteoporosis, rheumatoid arthritis, TNF inhibitor, adalimumab.

Introduction

Secondary osteoporosis is a well-known co-morbidity in RA [1, 2]. Due to the fact that the RA population predominantly consists of post-menopausal women, osteoporosis is an important co-morbidity. Generalized bone loss in osteoporosis goes beyond localized, periarticular bone loss in the affected joints. It is assumed that generalized and local bone loss share a common, inflammation-driven pathway, in which receptor activator of nuclear factor-\(\kappa\)-B (RANKL) plays an important role [3, 4]. Causes of osteoporosis in RA patients are multifactorial, including treatment with steroids, immobility and systemic inflammation [5, 6]. In addition, osteoporosis may lead to decreased quality of life due to the risk of fractures and accompanying co-morbidities.

In previous studies it has been suggested that generalized bone loss is brought to a halt when RA patients are treated for 1 year with the TNF inhibitors adalimumab or infliximab [7–10]. One of these studies demonstrated an additional benefit on BMD in infliximab-treated patients who showed good European League Against Rheumatism (EULAR) response after 1 year [10]. However, in another study, non-responders to infliximab also benefitted from a
positive effect on bone density [8]. Long-term data on the effect of TNF inhibitors on BMD and generalized bone loss are scarce. In an observational study, 52 patients were treated with infliximab for 3.5 years. BMD of the hip remained stable and BMD of the lumbar spine increased during the follow-up period [11].

In patients with early RA, cortical hand bone loss is a predictor of radiographic joint progression [12]. In later stages of RA, hand bone loss continues to progress; however, whether this bone loss also predicts (progression of) erosions remains unclear [13]. In both 1- and 3.5-year follow-up studies, hand bone loss was not arrested during treatment with infliximab in established RA patients, in contrast to bone density of the hip and spine [10, 11].

The aim of the current study was to investigate the effect of adalimumab therapy in established RA patients on hip, lumbar spine and metacarpal cortex BMD after 1 year and long-term follow-up. We wanted to investigate whether the positive/protective effect of infliximab also applied to adalimumab and whether this effect would continue during long-term follow-up.

Patients and methods

Participants in this study were consecutively selected from a prospective observational cohort of RA patients treated with adalimumab at the Jan van Breemen Research Institute Reade, Amsterdam, The Netherlands. All patients fulfilled the ACR 1987 criteria for RA and had active disease indicated by a DAS in 28 joints (DAS28) of \( \geq 3.2 \) despite earlier treatment with at least two DMARDs. The study was approved by the medical ethics committee of Reade and Slotervaart Ziekenhuis. All patients gave written informed consent, obtained according to the Declaration of Helsinki. Demographic characteristics were recorded at baseline. Disease-related data were collected at baseline and every 3 months thereafter for the first year of treatment. After 1 year, study visits were scheduled at 6-monthly intervals.

Patients were selected if they had at least 1 year of follow-up and if a dual-energy X-ray absorptiometry (DEXA) scan was performed at baseline and after 1 year and/or long-term follow-up. Radiographs of the hands where taken every other year. BMD of the lumbar spine (L1–L4) and total left hip was measured using DEXA (GE Lunar, Madison, WI, USA). BMD of the second, third and fourth metacarpal cortex was measured using digital X-ray radiographymetry (DXR) (Sectra, Linköping, Sweden). To avoid bias regarding dominant and non-dominant hand, the mean of both hands was used. Due to transition from analogue to digital recording of radiographs during the study period, paired radiographs in the same modality were not available for all patients, and if available, in most patients for only 1 year of follow-up.

BMD was referred to as normal range if the \( t \)-score (s.d. for a reference population) was \( > -1 \), as osteopenia if \( t < -1 \) to \( > -2.5 \) and as osteoporosis if the \( t \)-score of the hip or spine was \( < -2.5 \). This is in accordance with the criteria for BMD of the World Health Organization (WHO).

Statistical analysis

To compare baseline and follow-up measurements of BMD, paired sample \( t \)-test was used and differences in BMD between groups were analysed using an independent \( t \)-test or Mann–Whitney U-test as appropriate. Differences between EULAR response groups were analysed using linear regression. The threshold for significance was set at \( P = 0.05 \). Data are shown as mean (s.d.), median (range) or percentage. The distribution of variables was tested for normality.

Linear regression analysis was used to investigate the effects of variables on relative change in BMD. Relative changes of the hip, spine and hands were dependent variables. Independent baseline variables with \( P < 0.1 \) were subsequently included in backward stepwise multiple linear regression analysis. Only variables with \( P < 0.05 \) were considered predictors of BMD change. Time average DAS28 was calculated using the area under the curve (AUC) calculated as defined by Altman. The software used for statistical analysis was SPSS for Windows, version 17.0 (SPSS, Chicago, IL, USA).

Results

Baseline characteristics of 184 patients included in this study are displayed in Table 1. Due to difficulty with positioning of the hands because of extensive joint damage or metacarpal-phalangeal protheses in some patients \( n = 12, 6.5\% \) with long-standing RA, and transition from analogue to digital recording of radiographs \( n = 69, 37.3\% \).
37.5%) during the follow-up period, paired plain or paired digital radiographs of the hands were available for 103 patients with a mean interval duration of 13 months (s.d. 3.9). After a mean of 24.5 (s.d. 3.4) months paired hand radiographs were available for 31 patients. Mean BMD at baseline for both hands was 0.532 (s.d. 0.096) g/cm².

In two patients, a DEXA scan of the hip was not performed because of bilateral total hip replacement. The mean (s.d.) BMD of the hip at baseline for 182 patients was 0.874 (0.16) g/m² with a mean t-score of −0.8, which is in the range of normal BMD.

BMD of the lumbar spine at baseline was not representative in two patients due to sclerosis of the spine; these measurements were excluded from the analyses. Mean (s.d.) BMD of the lumbar spine at baseline for 182 patients was 1.088 (0.19) g/cm² with a mean t-score of −0.6, in the range of normal BMD. At the start of adalimumab treatment, 45.7% (84/184) of the patients had a normal BMD, 40.2% (74/184) had osteopenia and 14.1% (26/184) had osteoporosis according to the WHO criteria. Eighteen of these 26 patients used bisphosphonates at baseline.

After 1 year of follow-up, the decrease in BMD was statistically significant, at −1.41% (P < 0.0001) after 1 year of adalimumab treatment (Table 2).

After 4 years of follow-up, the decrease in BMD of the hip was statistically significant: −2.45% (P < 0.0001). BMD of the lumbar spine remained stable (0.28%, P = 0.666) (Table 2). Mean BMD change per year was −0.58% and 0.07% for the hip and lumbar spine, respectively, during a mean follow-up period of 4 years. For patients with paired radiographs available (n = 31) after a mean of 24.5 months, loss of BMD of the metacarpal cortex continued: −2.24% (P = 0.006) (Table 2).

After exclusion of patients with bisphosphonate use at baseline (n = 41, 22%), BMD decreased in the remaining patients. The BMD of the hip changed by −0.90% (P = 0.008) and −3.02% (P < 0.001) after 1 and 4 years, respectively. For the lumbar spine this was −0.68% (P = 0.033) and −1.23% (P = 0.076), respectively. Mean BMD of the hands changed by −1.43% (P < 0.001) in 13 months and −2.26% (P = 0.015) in 24 months.

In a multiple linear regression model, predictors for change in BMD of the hip at long-term follow-up were anti-CCP status (positive/negative) (P = 0.029), bisphosphonate use at baseline (P = 0.029) and BMI (P = 0.029).

Predictors for change in BMD of the lumbar spine after 4 years were disease duration (P = 0.008) and bisphosphonate use at baseline (P < 0.0001). Predictors of bone loss in the metacarpal cortex over 13 months were baseline DAS28 (P = 0.008), number of previously used DMARDs (P < 0.0001) and menopausal status (P = 0.038).

**Disease activity and BMD**

After 1 year of treatment, DAS28 decreased to 2.9 (s.d. 1.4, P < 0.0001) and remained stable thereafter, indicating low disease activity. AUC DAS28 was 606 over 4 years of adalimumab treatment, corresponding to an average DAS28 of 2.9 (s.d. 0.95). According to the EULAR response criteria, at 52 weeks, 13.5% of the patients in this study were non-responders, 21.8% of patients had

**Table 2** Change in BMD

<table>
<thead>
<tr>
<th></th>
<th>BMD hip, g/cm²</th>
<th>BMD lumbar spine, g/cm²</th>
<th>BMD hand, g/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>One-year follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>170</td>
<td>169</td>
<td>103</td>
</tr>
<tr>
<td>Baseline, mean (s.d.)</td>
<td>0.877 (0.163)</td>
<td>1.091 (0.186)</td>
<td>0.532 (0.096)</td>
</tr>
<tr>
<td>1-year follow-up, mean (s.d.)</td>
<td>0.872 (0.158)</td>
<td>1.088 (0.182)</td>
<td>0.525 (0.095)</td>
</tr>
<tr>
<td>ΔBMD, mean (s.d.)</td>
<td>−0.005 (0.044)</td>
<td>−0.003 (0.042)</td>
<td>−0.007 (0.014)</td>
</tr>
<tr>
<td>Percentage change</td>
<td>−0.57</td>
<td>−0.27</td>
<td>−1.41</td>
</tr>
<tr>
<td>P-value</td>
<td>0.145</td>
<td>0.373</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Long-term follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>89</td>
<td>89</td>
<td>31</td>
</tr>
<tr>
<td>Baseline, mean (s.d.)</td>
<td>0.886 (0.150)</td>
<td>1.076 (0.179)</td>
<td>0.536 (0.082)</td>
</tr>
<tr>
<td>Long-term follow-up∥, mean (s.d.)</td>
<td>0.864 (0.145)</td>
<td>1.079 (0.172)</td>
<td>0.524 (0.084)</td>
</tr>
<tr>
<td>ΔBMD, mean (s.d.)</td>
<td>−0.022 (0.046)</td>
<td>0.003 (0.066)</td>
<td>−0.012 (0.023)</td>
</tr>
<tr>
<td>Percentage change</td>
<td>−2.45</td>
<td>0.28</td>
<td>−2.24</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td>0.666</td>
<td>0.006</td>
</tr>
</tbody>
</table>

∥Four-year period for hip and spine BMD and 2-year period for hand BMD.
a moderate response and 64.7% were good responders. DAS28 (s.d.) at 52 weeks of treatment was 4.9 (1.4), 4.0 (1.0) and 2.1 (0.7) for non-, moderate and good responders, respectively. For patients achieving EULAR good, moderate and non-response at 52 weeks, time average DAS28 was 2.7 (AUC 140), 4.0 (AUC 207) and 4.1 (AUC 211), respectively (\( P < 0.001 \) for good vs moderate and for good vs non-response).

Hand bone density decreased over 1 year of treatment in all three response groups and was statistically significant for good and moderate responders; in non-responders (\( n = 7 \)) it was a trend (Table 3). However, hip and lumbar spine BMD remained stable over 1 year in good responders, while in moderate responders bone density of the hip remained stable (\( -0.61\%\, P = 0.390 \)) and BMD decreased in the spine (\( -1.87\%\, P < 0.001 \)). For EULAR non-responders this was different: BMD of the hip showed a trend to decrease over time (\( -1.25\%\, P = 0.087 \)), whereas BMD of the lumbar spine remained stable (\( 1.08\%\, P = 0.222 \)) (Table 3 and Fig. 1). After exclusion of patients on bisphosphonates, in good responders, BMD of the hip and spine remained stable, whereas in moderate responders BMD of the hip as well as the spine decreased. In non-responders, BMD of the hip decreased and BMD of the lumbar spine remained stable.

### Table 3 Change in BMD at 52 weeks per EULAR response group

<table>
<thead>
<tr>
<th>EULAR response at 52 weeks</th>
<th>Good responders (( n = 110 ))</th>
<th>Moderate responders (( n = 37 ))</th>
<th>Non-responders (( n = 23 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hip</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \Delta ) BMD hip, mean (s.d.), g/cm(^2)</td>
<td>(-0.002 (0.032))</td>
<td>(-0.010 (0.071))</td>
<td>(-0.012 (0.031))</td>
</tr>
<tr>
<td>Percentage change(^a)</td>
<td>0.02</td>
<td>-0.61</td>
<td>-1.25</td>
</tr>
<tr>
<td>( P )-value</td>
<td>0.579</td>
<td>0.390</td>
<td>0.087</td>
</tr>
<tr>
<td><strong>Spine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \Delta ) BMD spine, mean (s.d.), g/cm(^2)</td>
<td>0.001 (0.039)</td>
<td>-0.021 (0.047)</td>
<td>0.011 (0.042)</td>
</tr>
<tr>
<td>Percentage change(^b)</td>
<td>0.06</td>
<td>-1.87</td>
<td>1.08</td>
</tr>
<tr>
<td>( P )-value</td>
<td>0.873</td>
<td>&lt;0.001</td>
<td>0.222</td>
</tr>
<tr>
<td><strong>Hands</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \Delta ) BMD hands, mean (s.d.), g/cm(^2)</td>
<td>-0.007 (0.014)</td>
<td>-0.007 (0.013)</td>
<td>-0.013 (0.019)</td>
</tr>
<tr>
<td>Percentage change(^a)</td>
<td>-1.26</td>
<td>-1.47</td>
<td>-2.85</td>
</tr>
<tr>
<td>( P )-value</td>
<td>&lt;0.001</td>
<td>0.020</td>
<td>0.110</td>
</tr>
</tbody>
</table>

\(^a\)No statistical difference between good, moderate and non-responders. \(^b\)Good–moderate, \( P = 0.005 \); moderate–non, \( P = 0.004 \); good–non, \( P = 0.314 \).

**Fig. 1** Percentage change in BMD for EULAR response criteria.
Discussion

In the current study, we demonstrated that in a large cohort of established, severe RA patients treated with adalimumab, generalized bone loss at the spine and hip was arrested during the first year, however, bone loss in the hands continued. Furthermore, the effect on bone density during the first year of treatment was strongly influenced by disease activity. During long-term treatment, bone loss in the hip and hands was observed. Our findings on changes in BMD in the first year of treatment are in line with earlier findings in previous studies in established RA patients treated with TNF inhibitors [7], showing an arrested generalized bone loss without bringing hand bone loss to a halt [10].

From previous studies, before the introduction of biologic therapeutics, it is assumed that generalized bone loss takes place mainly in the early course of disease, however, in established disease bone loss continues unrestrained [14–16]. Therefore, it is interesting that not only with infliximab, but also with adalimumab long-term generalized bone loss could be halted. The positive effect of adalimumab during 1 year of treatment was already demonstrated [7]. However, we showed in addition that bone loss in RA is not fully under control, since we observed high bone loss in the hands during 1 year of treatment. Furthermore, we observed high bone loss at the hips during 4 years of treatment. In addition, after exclusion of patients treated with bisphosphonates, BMD of the hip and spine decreased during 1 year of adalimumab treatment.

Previously it has been shown for biological therapeutics, as well as for traditional DMARDs, that adequate suppression of disease activity leads to stabilization of bone loss [8, 10, 17, 18]. This is in line with the current study where we found that EULAR good responders at 52 weeks did not have significant decreases in BMD of the hip and spine.

For prednisone, data are contradictory: glucocorticoids are known to decrease BMD [5]. On the other hand, there are data suggesting that during treatment with short-term low-dose prednisone bone turnover is balanced in RA patients, at least partly related to the immunomodulating effect of prednisone, which counteracts the negative effect of prednisone on bone [7, 19, 20]. Nevertheless, no benefits of prednisone use on BMD were found in this study.

In the current study, time average DAS28 was 2.9, indicating low disease activity. This means that not all inflammation is blocked in all patients and one could expect that the effects of inflammation on bone continue to progress to a greater or lesser extent, especially localized bone loss. Bone loss in the hands may therefore suggest that the negative effects of RA are not fully blocked in all patients. These results underline the importance of strict management of RA patients, for the long-term impact of inflammation not only on local bone and the formation/progression of erosions, but also on generalized bone loss, osteoporosis and the additional risk of fractures. The decrease in hand bone loss continued throughout the study follow-up period. In previous literature it has been shown that changes in hand BMD in early RA patients are predictive for erosions, even up to 20 years, as has recently been demonstrated [21, 22]. In our cohort, patients had established disease and 75% already had erosions at baseline. Whether a decrease in hand bone loss is as predictive for erosions in patients with established disease as in patients with early disease is questionable, and data regarding this subject are lacking.

In 214 early RA patients treated with MTX and adalimumab and 188 treated with MTX monotherapy, hand bone loss was assessed [23]. In both groups there was loss of hand bone density during the 2-year study period. For patients with low disease activity or remission there was no difference between the groups (−2.4% vs −2.2%, respectively). However, for patients with active disease, bone loss was significantly greater in the MTX monotherapy group (−3.3% vs −2.2%).

With respect to local bone loss, it has to be investigated whether this will lead to (progression of) erosions in patients with established RA. When regular anti-inflammatory therapy is not tightly controlled, and is therefore unable to arrest inflammation as well as local bone loss, it has to be investigated if combining strong anti-resorptive, e.g. with potent bisphosphonates and/or denosumab, and anti-inflammatory therapy will be effective [24, 25].

Due to the observational nature of this study, results apply to patients continuously on medication. For patients dropping out of the study prematurely (within 1 year), no follow-up DEXA was available and therefore these patients do not contribute to the data. Data in this study probably provide favourable results because patients who discontinued adalimumab within 1 year were most likely to have higher disease activity during treatment and after discontinuation. Biomarkers for bone turnover or adipocytokines were not measured in this study, therefore the effect of adalimumab treatment on these biomarkers could not be investigated.

Several studies reported an increase in BMI during 2 years of anti-TNF therapy (infliximab in early RA, and infliximab and etanercept in long-standing SpA) [26, 27]. This increase in BMI might have an effect on generalized bone loss, due to the release of adipocytokines, although the role of adipocytokines in bone turnover remains debatable [28]. In addition, an increase in BMI might also have a bone-sparing effect due to estrogens and other sex hormones. In conclusion, strict management of disease activity benefits not only RA itself but also its co-morbidity, in this case generalized and local osteoporosis.

Rheumatology key messages

- In adalimumab-treated RA patients, generalized bone loss is arrested over 1 year.
- In adalimumab-treated RA patients bone loss in the hands continues during long-term follow-up.
- Strict management of RA influences the long-term impact of inflammation on bone.
Acknowledgements

The study sponsors had no involvement in the study design, in the collection, analysis and interpretation of data, in the writing of the report or in the decision to submit the article for publication.

Funding: The clinical part of this study was partially supported by Abbott Laboratories. In addition, this investigation was also facilitated by the Research and Education Division of the Jan van Breemen Research Institute Reade.

Disclosure statement: M.T.N. has been an ad hoc consultant and received speaking fees from Abbott, Pfizer, UCB, MSD and Roche. W.F.L. is a member of a speakers’ bureau for Merck, Eli Lilly, Amgen, Procter & Gamble and Servier. All other authors have declared no conflicts of interest.

References


