

Hand Bone Loss in Patients with Psoriatic Arthritis: Posthoc Analysis of IMPACT II Data Comparing Infliximab and Placebo

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ABSTRACT. Objective. In rheumatoid arthritis (RA), anti-tumor necrosis factor (anti-TNF) treatment is shown to reduce but not to arrest the rate of hand bone loss. This has not been assessed in psoriatic arthritis (PsA). Our objective was to examine changes in cortical hand bone density in patients with PsA treated with placebo or infliximab (IFX).

Methods. Patients in IMPACT II (Induction and Maintenance Psoriatic Arthritis Clinical Trial 2) were randomized to placebo or IFX. After Week 24, all received IFX. In a subset of 120 patients, cortical hand bone density was assessed at Weeks 0, 24, and 54 by digital X-ray radiogrammetry (dxr-BMD) on the same radiographs scored for joint damage.

Results. Changes from baseline to 24 weeks in dxr-BMD were -0.30% (SD 1.1%) in the placebo group and -0.08% (SD 1.4%) in the IFX group ($p = 0.63$). Between baseline and 54 weeks the changes were -0.71% (SD 2.1%) in the placebo group and 0.15% (SD 1.7%) in the IFX group ($p = 0.07$), and between 24 and 54 weeks -0.41% (SD 1.4%) and 0.23% (SD 0.8%), respectively ($p = 0.05$). No significant correlation was found between change in dxr-BMD and radiographic damage.

Conclusion. This pilot study indicates that hand bone loss in PsA patients treated with anti-TNF can be arrested. Assessment of hand bone density may thus be a potential outcome measure for bone involvement and a response variable to treatment in PsA. (First Release June 15 2013; J Rheumatol 2013;40:1344-8; doi:10.3899/jrheum.121376)

Key Indexing Terms:

HAND BONE LOSS PSORIATIC ARTHRITIS IMPACT-II INFLIXIMAB

Tumor necrosis factor- α (TNF- α) plays an important role in the inflammatory response in both psoriatic arthritis (PsA) and rheumatoid arthritis (RA)^{1,2}. Anti-TNF- α agents significantly improve clinical symptoms in both PsA and RA and reduce radiographic joint damage^{3,4,5}.

In RA, radiographic evidence of bone involvement consists of focal erosions and periarticular osteoporosis^{6,7} and treatment with anti-TNF- α agents has been shown to reduce but not to arrest inflammatory hand bone loss^{8,9}.

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Further, in RA, hand bone loss is found to be significantly correlated with radiographic changes^{7,8,10}, supporting a common mechanism for periarticular osteoporosis and erosions caused by osteoclast activation in addition to osteoblast inhibition¹¹. PsA patients, in contrast to those with RA, may show radiographic signs of both bone destruction (e.g., erosions) and bone formation (periostitis, osteophytes), suggesting that the bone involvement may include activation of both osteoblasts and osteoclasts^{11,12}. To our knowledge the effect of anti-TNF treatment on hand bone loss in PsA has not been examined. The primary objective of our study was to examine changes in cortical hand bone density in patients with PsA treated with the TNF inhibitor infliximab (IFX) in the IMPACT II trial (Induction and Maintenance Psoriatic Arthritis Clinical Trial 2).

MATERIALS AND METHODS

Data were extracted from the IMPACT II trial, a phase III, multicenter, double-blind, placebo-controlled study comparing the efficacy of IFX to placebo in patients with PsA. The study design has been described in detail⁴. Briefly, 200 PsA patients with active disease were randomized 1:1 to receive either placebo or IFX 5 mg/kg at Weeks 0, 2, and 6, and then every 8 weeks until Week 54. At Week 24 placebo patients crossed over to receive IFX. Early escape was allowed at Week 16.

This pilot study evaluated a subset of patients from the IMPACT II study, selecting patients with the largest positive and negative changes in radiographic scoring at 24 weeks, 60 from each treatment arm. This approach was thought to be the most sensitive way to investigate for

changes in digital X-ray radiogrammetry (dxr-BMD) findings between the groups. Two patients were excluded because they had arthritis mutilans. Radiographs were scored using a modification of the Sharp/van der Heijde scoring method that included, in addition to the joints scored in RA, the second through fifth distal interphalangeal (DIP) joints of each hand, to address the joint involvement considered characteristic for PsA, using a scale of 0 to 528 (0–360 for the hands, 0–168 for the feet).

The same hand radiographs used for radiographic joint scoring obtained at Weeks 0, 24, and 54 were used to measure cortical bone mineral density (BMD) at the second, third, and fourth metacarpal bones by dxr-BMD (Sectra)¹³. The dxr-BMD method is highly sensitive for bone assessment, with excellent precision^{13,14,15}. Because of unknown resolution of some radiographs, a number of them could not be analyzed for dxr. Because the equation for dxr-BMD is based on volume per area, it requires a known resolution, because a distance in a digitized radiograph cannot be measured when the resolution is unknown. All images with unknown resolution were analyzed by assuming 254 dots per inch (dpi; the scanning resolution for the radiographs before scoring). Several radiographs were, however, clearly a resolution other than 254 dpi, most likely because these radiographs had been printed in non-true size before scanning. To exclude the radiographs with a resolution other than 254 dpi we used a deviation from baseline width greater than 1% to indicate an incorrect value. This was based on analyses from studies with a controlled resolution⁸. Among 120 patients, 76 patients could be analyzed for dxr-BMD change (72 patients at 24 weeks and 52 patients at 54 weeks).

Statistical analysis. Analysis was performed using SPSS v. 19, applying descriptive statistics and group comparison (chi-square tests, T test). Spearman correlation analyses were performed with change in dxr-BMD and baseline variables selected from clinical evaluations: C-reactive protein (CRP), Health Assessment Questionnaire (HAQ), Psoriasis Area and Severity Index score (PASI), use of corticosteroids, and use of IFX. Loss in dxr-BMD is expressed as a negative value. Cumulative probability plots were used to show the dxr-BMD change in each patient for both groups.

The protocol for IMPACT II was approved by the institutional review boards at each of the participating sites¹⁶.

RESULTS

Among the subset of patients selected from the trial for our

study, baseline characteristics for patients with dxr-BMD data available and those without dxr-BMD data were not significantly different except for sex (Table 1).

Changes in dxr-BMD. The mean changes in dxr-BMD for all patients were -0.31% (SD 1.2%) at 24 weeks (n = 74) and -0.36% (SD 1.9%) at 54 weeks (n = 52). Regarding the patients with values at both timepoints (n = 49), the dxr-BMD changes were -0.20% and -0.33% , respectively.

Stratified for treatment, mean dxr-BMD changes were -0.30% (SD 1.1%) and 0.08% (SD 1.4%) at 24 weeks in the placebo group and in the IFX group, respectively (p = 0.63). Between baseline and 54 weeks the changes were -0.71% (SD 2.1%) and 0.15% (SD 1.7%) (p = 0.07), and between 24 and 54 weeks of followup dxr-BMD changes were -0.41% (1.4%) and 0.23% (0.8%), respectively (p = 0.05).

A cumulative probability plot for dxr-BMD changes stratified for treatment group at 54 weeks is shown in Figure 1, revealing that a large proportion of patients with PsA gained bone density, particularly patients treated with IFX.

Correlation between dxr-BMD and radiographic changes. No significant correlation was seen between change in dxr-BMD and change in PsA-modified van der Heijde-Sharp score⁴ at 24 weeks (r = 0.08, p = 0.53) and at 54 weeks (r = -0.17 , p = 0.24).

For erosions the correlation was 0.06 at 24 weeks (p = 0.63) and -0.22 at 54 weeks (p = 0.12). For joint space narrowing the correlation was -0.04 at 24 weeks (p = 0.77) and -0.02 (p = 0.87) at 54 weeks.

Correlation between change in dxr-BMD and baseline clinical markers. As shown in Table 2 the dosage of corticosteroids correlated negatively to change in dxr-BMD at 24 weeks. Patients with high HAQ score tended to have greater

Table 1. Baseline characteristics for patients with digital X-ray radiogrammetry (dxr-BMD) data available and those without dxr-BMD data.

Characteristics	Patients in Study, n = 76	Patients with No dxr-BMD Data, n = 44	p
Demographic			
Age, yrs, mean (SD)	46.3 (11.0)	46.3 (11.6)	1.00
Female, n (%)	35 (46.1)	12 (27.2)	0.04*
Clinical			
Duration of PsA, yrs, mean (SD)	6.4 (6.3)	6.9 (6.9)	0.94
Infliximab treatment, n (%)	39 (51.3)	21 (47.7)	0.70
Methotrexate at baseline, n (%)	37 (49.7)	22 (50.0)	0.88
Corticosteroids at baseline, n (%)	8 (10.5)	7 (15.9)	0.39
Tender joint count (0–66; median)	23.5 (13.3)	23.4 (14.0)	0.97
Swollen joint count (0–66)	14.1 (7.2)	13.4 (9.1)	0.65
C-reactive protein, mg/l (median)	23.1 (33.0)	20.9 (35.4)	0.62
HAQ-DI (0–3; median)	1.1 (0.6)	1.2 (0.6)	0.60
PASI (0–72; median)	67.1 (83.2)	78.6 (98.9)	0.52
Modified TSS (0–528)			
Mean (SD)	32.0 (55.2)	33.2 (55.9)	
Median (25th–75th percentile)	8.0 (2.0–44.3)	10.5 (1.8–39.8)	0.78

* p < 0.05. PsA: psoriatic arthritis; PASI: Psoriasis Area and Severity Index score; HAQ-DI: Health Assessment Questionnaire Damage Index; TSS: Total Sharp Score.

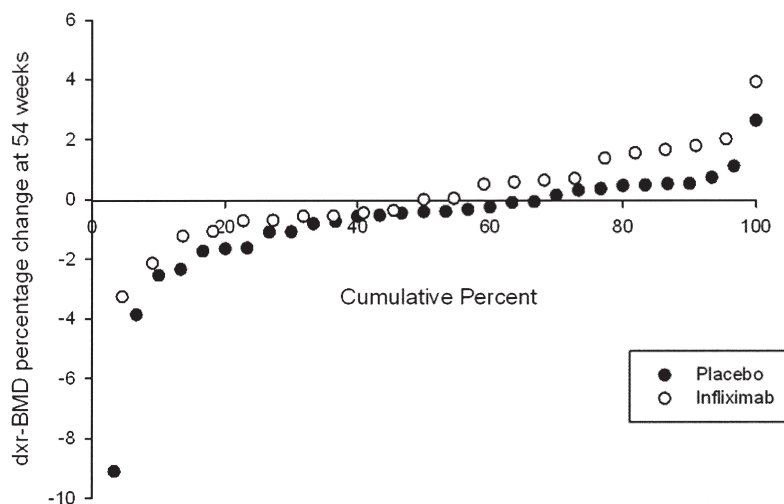


Figure 1. Cumulative probability plot with dxr-BMD changes stratified for treatment at 54 weeks. All patients received infliximab from Week 24. dxr-BMD: digital X-ray radiogrammetry.

Table 2. Association between baseline clinical markers and percentage changes in digital X-ray radiogrammetry (dxr-BMD) at 24 and 54 weeks, expressed as correlation coefficient calculated by Spearman analysis.

Baseline	dxr-BMD Change 0–24 wks, r (n = 72)	p	dxr-BMD Change 0–54 wks, r (n = 52)	p	dxr-BMD Change 24–54 wks, r (n = 50)	p
Age	–0.24	0.04*	–0.21	0.14	–0.17	0.23
CRP	–0.06	0.64	–0.17	0.23	–0.18	0.20
PASI	0.06	0.60	0.11	0.46	0.08	0.58
HAQ	–0.20	0.09	–0.24	0.09	–0.23	0.10
Corticosteroid	–0.27	0.02*	–0.21	0.15	0.12	0.94
Infliximab treatment	–0.03	0.23	0.04	0.35	0.26	0.07
Early escape	–0.23	0.05	–0.23	0.10	0.07	0.65
Change in CRP	0.09	0.45	0.14	0.34	0.20	0.16
Change in PASI	0.09	0.50	–0.14	0.31	0.16	0.28
Change in HAQ	0.18	0.12	–0.15	0.28	0.01	0.24

* $p < 0.05$. PASI: Psoriasis Area and Severity Index; HAQ: Health Assessment Questionnaire; CRP: C-reactive protein.

dxr-BMD loss at both 24 and 52 weeks ($r = -0.20$ and -0.24 , $p = 0.09$, for both).

No correlation was found between baseline values of CRP, PASI, or use of methotrexate (MTX) and dxr-BMD loss.

Correlations between changes in dxr-BMD and changes in CRP, HAQ, and PASI were not significant, as shown in Table 2.

DISCUSSION

The main finding in our pilot study was that patients who received IFX were more protected from bone loss than patients who received placebo. This indicates that IFX may arrest inflammatory hand bone loss in PsA. This bone loss in PsA seems less than that reported in results from studies

exploring hand bone loss in patients with RA, where bone loss has been shown to be reduced but not arrested^{8,9}. In a subanalysis from the PREMIER study, patients with RA receiving adalimumab and MTX lost less hand bone compared to patients with RA who received MTX alone; however, they still lost 2.2% at 54 weeks⁸. In the BeSt study, patients with RA treated with IFX lost 0.9% at 1 year⁹. This continuous hand bone loss despite TNF inhibition was also seen for IFX-treated RA patients assessed by dual energy X-ray absorptiometry (DEXA). In a small double-blind randomized study comparing IFX and MTX, patients receiving IFX still had DEXA hand bone loss of 2.1% during 1 year, whereas DEXA hip bone loss was arrested¹⁷. The literature supports the hypothesis that both osteoclasts and osteoblasts are part of the pathophysiological mechan-

isms of bone in PsA, whereas in RA the involvement is dominated by the increased activity of osteoclasts and suppression of osteoblasts¹¹. Significant differences in the effect of anti-TNF treatment on bone damage assessed by radiographs have also been shown comparing ankylosing spondylitis (AS) and RA. Whereas bone damage expressed as erosions (osteoclast activity) in RA is significantly reduced in patients treated with anti-TNF, bone damage on spine radiographs (expressed as new bone formation, i.e., osteoblast activity) is not reduced compared to placebo^{11,18}. Interestingly, differences in bone involvement between RA and AS have also been hypothesized using DEXA. Bone loss has been shown to be arrested at the lumbar spine and hip in anti-TNF-treated patients with RA¹⁹; whereas in AS, patients treated with anti-TNF were shown to have significantly increased bone density at spine and hip^{20,21}.

Another difference between hand bone loss in RA and in PsA is that change in dxr-BMD in RA was found to be significantly correlated to radiographic changes, with correlation coefficients between 0.25 and 0.55^{7,8,10}. We found no correlations between changes in dxr-BMD and radiographic damage. The difference between hand bone loss in RA and that in PsA could theoretically be explained by differential activation of osteoblasts and osteoclasts. In RA there is massive activation of osteoclasts due to activation of RANKL by cytokines (e.g., TNF- α) and inflammatory cells causing bone destruction⁶. In addition, osteoblasts are downregulated because of suppression of the Wnt signaling pathways and bone morphogenetic protein pathways, enhancing the consequences of osteoclast activation^{21,22}. PsA, in contrast to RA, shows radiographic signs of both bone destruction and bone formation (periostitis and osteophytes). Our knowledge about effects of anti-TNF therapy on structural damage in PsA is confined to the erosive component of the disease, because the scoring system for radiographic damage in PsA is the same as that used in RA to evaluate joint space narrowing and erosions, except that it includes more joints⁴. Therefore it remains unclear whether the anti-TNF therapy affects bony overgrowth¹¹. Our study may indicate that cellular mechanisms in PsA include both osteoclast and osteoblast activation, and further, that osteoblasts are not suppressed in active PsA.

From the CORRONA registry it has been reported that PsA patients with erosions in the hands had significantly lower spine BMD than those without erosions²³. Further, BMD levels in spine and hip were found to be similar for RA and PsA patients²⁴, suggesting that osteoclast activation in PsA is also an important mechanism for bone involvement. However, none of these studies examined hand bone loss; in RA studies this was shown to be greater in the hands than in the hip and spine⁹.

Our study has limitations, mainly that several radiographs could not be analyzed for dxr-BMD because of technical issues; this was also observed in other studies⁸.

Moreover, all patients received IFX from Week 24 onward. As this was a pilot study we selected patients with the largest radiographic joint changes in the IMPACT II study. Further, we did not have information about antiosteoporotic medication that may have influenced the results. Due to subjects' relatively low mean age (46.1 years) and the high percentage of male participants (54%), we believe that osteoporosis treatment was not frequently used in the study population.

Our findings indicate that hand bone loss in patients with PsA treated with anti-TNF therapy may be arrested. Hand bone density measures may thus have potential as outcome measures for bone involvement and as a response variable to treatment in PsA. Larger studies are needed to examine how PsA affects bone, particularly of the hand.

REFERENCES

1. Partsch G, Steiner G, Leeb BF, Dunky A, Broll H, Smolen JS. Highly increased levels of tumor necrosis factor-alpha and other proinflammatory cytokines in psoriatic arthritis synovial fluid. *J Rheumatol* 1997;24:518-23.
2. Ritchlin C, Haas-Smith SA, Hicks D, Cappuccio J, Osterland CK, Looney RJ. Patterns of cytokine production in psoriatic synovium. *J Rheumatol* 1998;25:1544-52.
3. Mease PJ. Adalimumab: an anti-TNF agent for the treatment of psoriatic arthritis. *Expert Opin Biol Ther* 2005;5:1491-504.
4. van der Heijde DM, Kavanaugh A, Gladman DD, Antoni C, Krueger GG, Guzzo C, et al. Infliximab inhibits progression of radiographic damage in patients with active psoriatic arthritis through one year of treatment: results from the Induction and Maintenance Psoriatic Arthritis Clinical Trial 2. *Arthritis Rheum* 2007;56:2698-707.
5. St. Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 2004;50:3432-43.
6. Redlich K, Hayer S, Maier A, Dunstan CR, Tohidast-Akrad M, Lang S, et al. Tumor necrosis factor alpha-mediated joint destruction is inhibited by targeting osteoclasts with osteoprotegerin. *Arthritis Rheum* 2002;46:785-92.
7. Hoff M, Haugeberg G, Odegard S, Syversen S, Landewe R, van der Heijde DM, et al. Cortical hand bone loss after 1 year in early rheumatoid arthritis predicts radiographic hand joint damage at 5-year and 10-year follow-up. *Ann Rheum Dis* 2009;68:324-9.
8. Hoff M, Kvien TK, Kalvesten J, Elden A, Haugeberg G. Adalimumab therapy reduces hand bone loss in early rheumatoid arthritis: Explorative analyses from the PREMIER study. *Ann Rheum Dis* 2009;68:1171-6.
9. Guler-Yuksel M, Allaart CF, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, van Groenendaal JH, Mallee C, et al. Changes in hand and generalised bone mineral density in patients with recent-onset rheumatoid arthritis. *Ann Rheum Dis* 2009;68:330-6.
10. Forslund K, Boonen A, Albertsson K, Hafstrom I, Svensson B. Hand bone loss measured by digital X-ray radiogrammetry is a predictor of joint damage in early rheumatoid arthritis. *Scand J Rheumatol* 2009;38:431-8.
11. Schett G, Coates LC, Ash ZR, Finzel S, Conaghan PG. Structural damage in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: Traditional views, novel insights gained from TNF blockade, and concepts for the future. *Arthritis Res Ther* 2011;13 Suppl 1:S4.

12. Gladman DD. Psoriatic arthritis. *Dermatol Ther* 2009;22:40-55.
13. Rosholm A, Hyldstrup L, Backsgaard L, Grunkin M, Thodberg HH. Estimation of bone mineral density by digital X-ray radiogrammetry: theoretical background and clinical testing. *Osteoporos Int* 2001;12:961-9.
14. Dhainaut A, Hoff M, Kalvesten J, Lydersen S, Forslind K, Haugeberg G. Long-term in-vitro precision of direct digital X-ray radiogrammetry. *Skeletal Radiol* 2011;40:1575-9.
15. Hoff M, Dhainaut A, Kvien TK, Forslind K, Kalvesten J, Haugeberg G. Short-time in vitro and in vivo precision of direct digital x-ray radiogrammetry. *J Clin Densitom* 2009;12:17-21.
16. Antoni CE, Kavanaugh A, Kirkham B, Tutuncu Z, Burmester GR, Schneider U, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: Results from the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). *Arthritis Rheum* 2005;52:1227-36.
17. Haugeberg G, Conaghan PG, Quinn M, Emery P. Bone loss in patients with active early rheumatoid arthritis: infliximab and methotrexate compared with methotrexate treatment alone. Explorative analysis from a 12-month randomised, double blind, placebo-controlled study. *Ann Rheum Dis* 2009;68:1898-901.
18. Schett G. Structural bone changes in spondyloarthritis: mechanisms, clinical impact and therapeutic considerations. *Am J Med Sci* 2011;341:269-71.
19. Vis M, Havaardsholm EA, Haugeberg G, Uhlig T, Voskuyl AE, van de Stadt RJ, et al. Evaluation of bone mineral density, bone metabolism, osteoprotegerin and receptor activator of the NF-kappa-B ligand serum levels during treatment with infliximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2006;65:1495-9.
20. Marzo-Ortega H, McGonagle D, Jarrett S, Haugeberg G, Hensor E, O'Connor P, et al. Infliximab in combination with methotrexate in active ankylosing spondylitis: a clinical and imaging study. *Ann Rheum Dis* 2005;64:1568-75.
21. Grandaunet B, Syversen SW, Hoff M, Sundan A, Haugeberg G, van der Heijde DM, et al. Association between high plasma levels of hepatocyte growth factor and progression of radiographic damage in the joints of patients with rheumatoid arthritis. *Arthritis Rheum* 2011;63:662-9.
22. Schett G, Zwerina J, David JP. The role of Wnt proteins in arthritis. *Nat Clin Pract Rheumatol* 2008;4:473-80.
23. Anandarajah AP, El-Taha M, Peng C, Reed G, Greenberg JD, Ritchlin CT. Association between focal erosions and generalised bone loss in psoriatic arthritis. *Ann Rheum Dis* 2011;70:1345-7.
24. Reddy SM, Anandarajah AP, Fisher MC, Mease PJ, Greenberg JD, Kremer JM, et al. Comparative analysis of disease activity measures, use of biologic agents, body mass index, radiographic features, and bone density in psoriatic arthritis and rheumatoid arthritis patients followed in a large U.S. disease registry. *J Rheumatol* 2010;37:2566-72.