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Author: Wevers- de Boer, Kirsten Vera Caroline
Title: Improving disease outcomes in early phases of rheumatoid arthritis
Issue Date: 2014-03-06

CHAPTER 9

Changes in metacarpal bone mineral density in patients with undifferentiated and early rheumatoid arthritis during one year of remission steered treatment

K.V.C. Wevers-de Boer, L. Heimans, K. Visser, J. Kälvesten, J.A.P.M. Ewals, E.T.H. Molenaar, J. Groenendael, A. Peeters, I Speyer, G. Collee, T.W.J. Huizinga, C.F. Allaart

ABSTRACT

Objective

To investigate possible determinants of localized bone loss in patients with early arthritis.

Methods

Of 610 patients with early arthritis in the IMPROVED study, 442 had ≥1 measurements of metacarpal bone mineral density (BMD) by Digital X-ray Radiogrammetry (DXR-BMD) during year 1 of remission (Disease Activity Score <1.6) steered treatment. Initial treatment consisted of methotrexate and a tapered high dose of prednisone. If remission was achieved medication was tapered, if not, patients were randomized to combination therapy including low dose prednisone or adalimumab. DXR-BMD loss (≥1.5 mg/cm^2/4 months, ≥4.6 mg/cm^2/year) or gain (≥4.6 mg/cm^2/year) was compared between treatment and patient groups. Predictors for DXR-BMD loss were assessed.

Results

DXR-BMD loss occurred in 246 (56%) and 243 (55%) patients after 4 months and 1 year, DXR-BMD gain in 60 (14%) patients after 1 year. Of patients with DXR-BMD loss after 4 months, 32 (13%) regained the total loss within 1 year. Age and postmenopausal status were independent predictors of DXR-BMD loss after 1 year. Randomized patients less often showed DXR-BMD loss after 1 year than patients who achieved early remission (52 (44%) versus 170 (59%), p=0.02). Based on small numbers, patients treated with adalimumab showed the smallest loss and most often gain (14 (54%)).

Conclusions

After 1 year of remission steered treatment, metacarpal BMD loss occurs in more than half of patients with early arthritis. Our data may suggest that although initial combination therapy including a tapered high dose of prednisone may induce remission in a large proportion of patients, it may have at least a temporary negative effect on localized BMD.

INTRODUCTION

Bone loss is a clinical feature in patients with rheumatoid arthritis (RA) and occurs generalized as well as localized around inflamed joints.[1] Generalized bone loss may be caused by prolonged disease activity, immobility by functional impairment and anti-rheumatic medication such as corticosteroids.[2-5] Earlier in the disease course of RA localized bone loss occurs, possibly due to localized inflammatory processes.[1,6] In an earlier study we have shown that in RA patients who were in clinical remission for at least 1 year, an increase in localized bone mineral density (BMD) can occur. This was not found in patients who had high or even low disease activity.[7] Measuring localized bone loss in patients with early (rheumatoid) arthritis in association with treatment and treatment response may be helpful to understand possible determinants of bone loss in rheumatoid arthritis. To investigate this, we performed four-monthly metacarpal BMD measurements by Digital-X-ray Radiogrammetry (DXR, Sectra, Linköping, Sweden) during the first year in patients participating in the IMPROVED study, a remission steered clinical trial in 610 patients with undifferentiated arthritis (UA) or early RA.[8,9]

METHODS

Patients and study design

IMPROVED is a multicentre, randomized clinical trial in 479 (79%) patients with recent onset RA (according to the 2010 classification criteria for RA [10] with a symptom duration <2 years) and 122 (20%) UA patients (having at least one arthritic and one other painful joint and clinically suspected to represent early RA, regardless of symptom duration). Patients were treated according to a tight control strategy, aimed at achieving remission, defined as a Disease Activity Score (DAS) <1.6.[11] All patients started with 4 months of methotrexate (MTX) 25 mg/week and prednisone 60 mg/day, tapered to a stable dose of 7.5 mg/day in 7 weeks. Patients in remission after 4 months (early remission) started tapering medication, if possible to drug free. Patients who did not achieve early remission were randomized either to MTX 25 mg/week plus hydroxychloroquine (HCQ) 400 mg/day, sulphasalazine (SSZ) 2000 mg/day and prednisone 7.5 mg/day (arm 1) or to MTX 25 mg/week plus adalimumab 40 mg/2weeks (arm 2). Thirty-one patients who did not achieve early remission were not randomized and treated outside of protocol. Full details on the IMPROVED study protocol were previously published.[9]

Demographic and clinical variables

At baseline and every 4 months, the following clinical and laboratory variables were collected: DAS, including Ritchie Articular Index (RAI), swollen joint count, erythrocyte sedimentation rate (ESR, mm/hr) and visual analogue scale (VAS, mm) for global health,[12] and C-reactive

protein (CRP). Use of calcium and/or vitamin D supplements and bisphosphonates was assessed after one year.

Metacarpal BMD measurements

At baseline, 4 months, 8 months and 1 year, digital plain radiographs of hands and feet were made according to the protocol of the local hospitals' radiology departments. No moulds or positioning devices were used, no specific technical adaptions were applied. Metacarpal BMD was measured on X-rays of both hands using Digital X-ray Radiogrammetry (DXR-BMD) by dxr-online (Sectra, Linköping, Sweden). Three regions of interest are automatically recognized on the second, third and fourth metacarpal bone. At each region, DXR-BMD is estimated from multiple measurements of cortical thickness, bone width and porosity.[13] The mean value of both hands was used in all analyses to maximize precision and avoid bias induced by hand dominance. Previously, DXR-BMD measurements have been shown to have a very high short and long term precision in both in vitro cadaver studies (coefficients of variation (CV) of 0.22 to 1%) and in one cohort study and one clinical trial (CV of 0.25 to 0.46%).[14-17] However, because measurements in this study were done in retrospect, precision may be lower than previously published.

Absolute values of DXR-BMD were expressed in g/cm^2, changes in DXR-BMD in $mg/cm^2/4months$ or $mg/cm^2/year$. 'DXR-BMD loss' was defined as a decrease in DXR-BMD ≥ 1.5 $mg/cm^2/4months$ or ≥ 4.6 $mg/cm^2/year$ and 'BMD-DXR gain' as an increase in DXR-BMD ≥ 1.5 $mg/cm^2/4months$ or ≥ 4.6 $mg/cm^2/year$.[7]

Of the 610 patients included, 442 patients had least one DXR-BMD measurement during the first year. Of the other patients, four-monthly radiographs were available but found unsuitable for DXR-measurements by Sectra,[18] as were baseline radiographs in 148 patients (33%), 4 months-radiographs in 78 patients (18%), 8 months-radiographs in 155 patients (35%) and 1 year radiographs in 148 patients (33%) of the 442 patients included in the current analysis.

Statistical analysis

Median (IQR) DXR-BMD (change) values were shown because of skewed distributions. Because of missing DXR-BMD values multiple imputation was performed.[19] Ten datasets were created in which missing DXR-values were imputed based on a linear regression model fitting available patient and disease characteristics and DXR-values. Estimates obtained from regression analyses were automatically pooled by SPSS, other multiple estimates were averaged.

All DXR-BMD changes and percentages loss and gain were obtained from the imputed dataset. Because of the small number of patients, separate values for arm 1 and 2 were obtained from the original dataset. Non-parametric test were used for comparisons of DXR-BMD changes between various patient groups. Absolute DXR-BMD levels over time were compared between various patient groups by linear mixed models, performed on the original dataset, with time (study visit) and fulfilling of the 2010 classification criteria for RA (yes/no) or having

achieved early remission (yes/no) or being in continuous remission throughout the first study year (yes/no) as fixed effects, in an unstructured covariance structure. Regression analyses were performed on the imputed dataset with DXR-BMD loss (yes/no) as binomial dependent variable. Statistical analyses were conducted with SPSS for Windows version 20.0.

RESULTS

Baseline and follow up clinical characteristics

Of the 442 patients selected for the current analysis, 355 (80%) patients fulfilled the 2010 criteria for RA at baseline, 82 (19%) did not (UA) and 5 patients had missing data. Compared to RA patients, UA patients had a lower disease activity (mean DAS (SD) 2.7 (0.7) versus 3.3 (0.9), p<0.001), were less often female (47/82 (57%) versus 247/355 (70%), p=0.2) and female patients less often were in a postmenopausal state (21/82 (41%) versus 134/355 (54%), p=0.03). Furthermore, 3 UA patients were anti-citrullinated protein antibodies (ACPA) positive and 3 rheumatoid factor (RF) positive, compared to respectively 246 (69%) and 244 (69%) of the RA patients (p<0.001). After 4 months, early remission was achieved in 55 UA patients (67%) and 226 RA patients (64%) (p=0.6).(table 1)

Changes in DXR-BMD

From baseline to 4 months, median (IQR) DXR-BMD loss in all patients was -2.6 (-8.1;2.2) mg/cm^2 (with a maximum of -40.3 mg/cm^2 and a minimum of 44.0 mg/cm^2), -1.5 (-7.3;3.7) mg/cm^2 in UA patients and -2.8 (-8.6;2.1) mg/cm^2 in RA patients (p=0.2). DXR-BMD loss, defined a decrease ≥1.5 mg/cm^2, was present in 246 (56%) patients, 41 (50%) UA and 205 (58%) RA patients (p=0.3). DXR-BMD gain, defined as an increase ≥1.5 mg/cm^2, was present in 129 (29%) patients, 27 (33%) UA and 102 (29%) RA patients (p=0.5).

From baseline to 1 year, median (IQR) DXR-BMD loss in all patients was -6.4 (-16.1;0.6) mg/cm^2 (with a maximum of -80.0 mg/cm^2 and a minimum of 39.8 mg/cm^2), -4.1 (-13.1;2.9) mg/cm^2 in UA patients and -6.9 (-16.6;0.1) mg/cm^2 in RA patients (p=0.08). (table 2) DXR-BMD loss after 1 year, defined as a decrease ≥4.6 mg/cm^2, was present in 243 (55%) patients, 40 (49%) UA patients and 203 (57%) RA patients (p=0.2). DXR-BMD gain after 1 year, defined as an increase ≥4.6 mg/cm^2, was present in 60 (14%) patients, 15 (18%) UA patients and 45 (13%) RA patients (p=0.3).

To investigate whether DXR-BMD loss from baseline to 4 months was regained in the following months, we evaluated changes in DXR-BMD from 4-12 months in the 246 patients with DXR-BMD loss from baseline to 4 months. In these patients, the additional median (IQR) DXR-BMD loss from 4-12 months was -3.1 (-12.0;2.5) mg/cm^2. In 123 (50%) patients the additional DXR-BMD loss was ≥3.1 mg/cm^2/8months, 56 (23%) patients had DXR-BMD gain ≥3.1 mg/cm2/8months and 67 (27%) patients had a stable DXR-BMD (loss or gain <3.1 mg/

Table 1: Demographic, clinical and laboratory characteristics at baseline and follow up of the total study population and separate for patients with undifferentiated arthritis and rheumatoid arthritis (according to the 2010 classification criteria).

	Total population n=442	UA n=82	RA n=355*	p-value
Baseline				
Age, years, mean±SD	52 ± 14	52 ± 15	52 ± 13	0.8
Female, no (%)	303 (69)	47 (57)	247 (70)	0.2
BMI, kg/m², mean±SD	26 ± 4	26 ± 4	26 ± 5	0.98
Current smoking, no (%)	132 (30)	18 (22)	112 (32)	0.1
Current alcohol use, no (%)	259 (59)	47 (57)	209 (59)	0.8
Postmenopausal status, no (%), n=268 women**	159 (59)	21 (41)	134 (54)	0.03
Calcium intake, mg/day, median (IQR)	800 (600-1050)	825 (725-1075)	800 (600-1050)	0.2
25(OH) Vitamine D, nmol/l, median (IQR)	55 (37-75)	52 (39-74)	56 (37-76)	0.7
DAS (mean±SD)	3.2 ± 0.9	2.7 ± 0.7	3.3 ± 0.9	<0.001
Symptom duration, weeks, median (IQR)	18 (9-33)	17 (8-28)	18 (9-34)	0.2
ACPA positive, no (%)	253 (57)	3 (4)	246 (70)	<0.001
RF positive, no (%)	251 (57)	3 (4)	244 (71)	<0.001
SHS total score, median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	0.9
Presence of erosions, no (%)	62 (14)	7 (9)	54 (15)	0.1
Follow up				
Remission after 4 months, no (%)	284 (64)	55 (67)	226 (64)	0.6
Remission after 1 year, no (%)	240 (54)	48 (59)	189 (53)	0.3
Calcium and/or vitamin D suppletion during year 1, no (%)	210 (48)	36 (44)	172 (48)	0.5
Bisphosphonate use year 1, no (%)	135 (31)	28 (34)	106 (30)	0.5
Treatment groups				
Early remission group, no (%)	289 (65)	57 (70)	229 (65)	
Arm 1: MTX+SSZ+HCQ+prednisone, no (%)	60 (14)	13 (16)	47 (13)	
Arm 2: MTX+adalimumab, no (%)	57 (13)	7 (9)	48 (14)	
Outside of protocol group, no (%)	31 (7)	4 (5)	27 (8)	

*Five patients could not be classified according to the 2010 classification criteria for RA because of missing data. **35 women had missing data on postmenopausal status.
ACPA, anti-citrullinated protein antibodies; BMI, body mass index; DAS, disease activity score; IQR, inter quartile range; no, number; RA, rheumatoid arthritis (2010 ACR/EULAR classification criteria); RF, rheumatoid factor; SD, standard deviation; SHS, Sharp-van der Heijde Score; UA, undifferentiated arthritis.

cm²/8months). Only 32 (13%) patients regained all the DXR-BMD loss (or more) that occurred from baseline to 4 months.

Table 3 shows results of the univariate regression analyses with DXR-BMD loss after 4 months and 1 year as dependent outcomes. Of tested baseline variables, age and postmeno-pausal status were predictors for DXR-BMD loss after 4 months (respectively OR (95%CI) 1.03 (1.01-1.05), p=0.002 and 2.9 (1.6-5.2), p=0.001), although not independently of each other. DAS at 4 months was not associated with DXR-BMD loss after 4 months (0.96 (0.7-1.3), nor

Table 2: Metacarpal bone mineral density measured by digital X-ray radiogrammetry during the first year for all patients and separate for patients with undifferentiated and rheumatoid arthritis.

	Time point (months)	Total n=442	UA patients n=82	RA patients n=355	p-value
Absolute DXR-BMD g/cm^2, median (IQR)	0	0.592 (0.528-0.640)	0.599 (0.538-0.647)	0.590 (0.527-0.638)	0.6
	4	0.590 (0.528-0.637)	0.602 (0.535-0.653)	0.589 (0.527-0.634)	0.4
	8	0.590 (0.585-0.639)	0.598 (0.537-0.645)	0.589 (0.525-0.636)	0.5
	12	0.585 (0.523-0.637)	0.589 (0.525-0.649)	0.585 (0.522-0.635)	0.4
Change in DXR-BMD mg/cm^2, median (IQR)	0 - 4	-2.6 (-8.1 ; 2.2)	-1.5 (-7.3 ; 3.7)	-2.8 (-8.6 ; 2.1)	0.2
	4 - 8	-1.4 (-6.5 ; 3.3)	-1.5 (-6.5 ; 3.0)	-1.4 (-6.6 ; 3.4)	0.6
	8 -12	-2.9 (-8.9 ; 1.8)	-1.4 (-7.8 ; 3.1)	-3.5 (-9.1 ; 1.6)	0.2
	0 - 12	-6.4 (-16.1 ; 0.6)	-4.1 (-13.1 ; 2.9)	-6.9 (-16.6 ; 0.1)	0.08
DXR-BMD loss ≥4.6 mg/cm^2 after 1 year, no (%)		243 (55)	40 (49)	203 (57)	0.2
DXR-BMD gain ≥4.6 mg/cm^2 after 1 year, no (%)		60 (14)	15 (18)	45 (13)	0.3

DXR-BMD, bone mineral density measured by digital X-ray radiogrammetry; IQR, interquartile range; no, number; RA, rheumatoid arthritis according to the 2010 ACR/EULAR classification criteria; UA, undifferentiated arthritis.

Table 3: Univariate regression analyses with metacarpal bone mineral density loss after 4 months and 1 year (yes/no) measured by digital X-ray radiogrammetry as dependent variable.

	4 months DXR-BMD loss		1 year DXR-BMD loss	
Univariate regression analyses	Crude OR	95% CI	Crude OR	95% CI
Age	1.03	1.01-1.05	1.07	1.04-1.09
Female gender	0.9	0.6-1.4	1.09	0.7-1.8
Postmenopausal status	2.9	1.6-5.2	7.2	3.5-14.8
Baseline DAS	1.03	0.8-1.3	1.03	0.8-1.4
Baseline DXR-BMD (g/cm^2)	0.7	0.02-24.2	0.02	0.001-0.4
Presence of ACPA	1.5	0.9-2.6	1.3	0.9-2.0
Presence of RF	1.0	0.6-1.8	1.02	0.6-1.7
Fulfilling 2010 criteria for RA	1.3	0.7-2.4	1.4	0.8-2.3
Symptom duration	1.003	0.99-1.01	0.996	0.985-1.006
Baseline TJC	0.97	0.93-1.02	0.97	0.92-1.01
Baseline SJC	1.02	0.98-1.1	1.009	0.96-1.06
Baseline ESR	1.01	0.995-1.02	1.01	1.001-1.02
Baseline CRP	1.0	0.99-1.02	1.01	1.001-1.02
Baseline SHS	1.1	0.98-1.2	1.2	1.006-1.3
Baseline erosions (yes/no)	0.7	0.4-1.3	0.8	0.4-1.5

ACPA, anti-citrullinated protein antibodies; CRP, C-reactive protein; DAS, disease activity score; DXR-BMD, bone mineral density measured by digital X-ray radiogrammetry, ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; RF, rheumatoid factor; SHS, Sharp-van der Heijde Score; SJC, swollen joint count; TJC, tender joint count.

was achieving remission after 4 months (0.96 (0.6-1.5)). Univariate predictors for DXR-BMD loss after 1 year were age (1.07 (1.04-1.09), p<0.001), postmenopausal status (7.2 (3.5-14.8, p<0.001), baseline DXR-BMD (0.02 (0.001-0.4), p=0.012), both baseline ESR (1.01 (1.001-1.02), p=0.03) and CRP (1.01 (1.001-1.02), p=0.03) and baseline Sharp-van der Heijde Score (SHS) (1.2 (1.006-1.3), p=0.04). Of these, again only age and postmenopausal status were independent predictors of DXR-BMD loss after 1 year (respectively 1.04 (1.003-1.07), p=0.03 and 3.3 (1.4-7.9), p=0.008). Regression analyses performed on the original dataset showed similar trends (data not shown).

Early remission versus randomization

To evaluate how early remission and subsequent tapering of prednisone affects DXR-BMD, we compared the results of the 289 (65%) patients who achieved early remission (of whom 277 tapered and stopped prednisone) with the 117 (26%) patients who did not achieve early remission and were randomized to either MTX, SSZ, HCQ and low dose prednisone (arm 1, 60 patients) or MTX plus adalimumab (arm 2, 57 patients).

At baseline, patients who achieved early remission had a lower baseline disease activity than randomized patients and after 1 year they more often achieved remission than randomized patients. Also, fewer patients in early remission were female. On the other hand, more patients in early remission were ACPA and RF positive and they less often used bisphosphonates than randomized patients.(table 4) Overall during the first year, absolute DXR-BMD levels were higher in patients who had achieved early remission than in patients who were randomized, although the difference was not significant (mean difference 10.3 (-6.4;26.9), p=0.2, randomized patients set as reference).

After 1 year, patients in early remission had a larger median (IQR) DXR-BMD loss than randomized patients (-7.2 (-16.3;-0.1) versus -3.4 (-13.3;2.4), p=0.051).(table 5) DXR-BMD loss ≥4.6 mg/cm^2 after 1 year occurred in 170 (59%) patients who had been in early remission and in 52 (44%) patients who were randomized (p=0.02). DXR-BMD gain ≥4.6 mg/cm^2 after 1 year was present in 36 (12%) patients who achieved early remission and 22 (19%) patients who were randomized (p=0.2). In the original data set, DXR-BMD gain ≥4.6 mg/cm^2/year was present in 7/33 (21%) patients in arm 1 and 14/26 (54%) in arm 2 (p=0.015).

The smallest DXR-BMD loss during the first year was seen between 4-8 months, both in patients who achieved early remission and in randomized patients (median (IQR) -2.0 (-7.1;3.0) and -0.3 (-5.0;4.3) mg/cm^2 respectively, p=0.07). (table 5) In the original data set, the median (IQR) DXR-BMD change from 4-8 months in arm 1 (MTX+SSZ+HCQ+low dose prednisone) was -0.8 (-4.6;1.3) mg/cm^2 and in arm 2 (MTX+adalimumab) 2.0 (-3.1;3.6) mg/cm^2 (p=0.16).

Continuous remission versus no continuous remission

Over year 1, 132 (30%) patients were in continuous remission, 285 (64%) were not (in 25 patients remission data were missing on ≥1 time points). Patients in continuous remission

Table 4: Demographic and clinical characteristics and treatment steps at 8 months of patients in remission after 4 months versus randomized patients.

	Early remission n=289	Randomized n=117	p-value
Baseline			
Age, years, mean±SD	52±14	51±14	0.3
Female, no (%)	181 (63)	92 (79)	0.002
Postmenopausal status, no (%), n=241 women**	92 (58)	47 (57)	0.9
DAS, mean±SD	3.1±0.9	3.5±0.9	<0.001
Symptom duration, weeks, median (IQR)	18 (9-32)	19 (8-34)	0.97
ACPA positive, no (%)	179 (62)	57 (49)	0.008
RF positive, no (%)	173 (60)	58 (50)	0.08
SHS total score, median (IQR)	0 (0-0.25)	0 (0-0)	0.6
Presence of erosions, no (%)	44 (15)	18 (15)	0.96
Baseline DXR-BMD g/cm^2, median (IQR)	0.603 (0.532-0.650)	0.582 (0.540-0.627)	0.2
Treatment steps at 8 months follow up			
Restarting prednisone (7.5 mg/day)	62 (21)	-	
Tapering MTX	158 (55)	-	
Tapering SSZ, HCQ and prednisone (arm 1, n=60)	-	20 (33)	
Switching to adalimumab (arm 1, n=60)	-	25 (42)	
Tapering adalimumab (arm 2, n=57)	-	16 (28)	
Increasing adalimumab dose (arm 2, n=57)	-	24 (42)	
No or other steps	69 (24)	32 (27)	
1 year follow up			
Remission, no (%)	194 (67)	36 (31)	<0.001

ACPA, anti-citrullinated protein antibodies; arm 1, randomized to treatment with MTX+SSZ+HCQ+prednisone; arm 2: randomized to treatment with MTX+adalimumab; DAS, disease activity score; DXR-BMD, bone mineral density measured by digital X-ray radiogrammetry; HCQ, hydroxychloroquine; IQR, inter quartile range; mg, milligram; MTX, methotrexate; no, number; RF, rheumatoid factor; SHS, Sharp-van der Heijde Score; SSZ, sulfasalazine; SD, standard deviation.

had a lower baseline disease activity (DAS 2.9 (0.8) versus 3.4 (0.9), p<0.001) and included fewer females (74 (56%) versus 212 (74%), p<0.001), compared to patients not in continuous remission. On the other hand, patients in continuous remission used less often calcium and vitamin D supplements (53 (40%) versus 150 (53%), p=0.007) and bisphosphonates (29 (22%) versus 104 (36%), p=0.003) during the first year. Median baseline DXR-BMD levels of patients in continuous remission were 0.603 (0.546-0.659) mg/cm2 and of patients not in continuous remission 0.589 (0.521-0.637) mg/cm2 (p=0.09). Over the first year, absolute DXR-BMD levels were higher in patients in continuous remission than in patients not in continuous remission, although not significantly (mean difference 12.0 (28.3;4.4) mg/cm2, patients not in continuous remission set as reference, (p=0.15)).

Table 5: Changes in metacarpal bone mineral density measured by digital X-ray radiogrammetry during the first year, separate for patients who achieved early remission and patients who were randomized.

	Time point (months)	Early remission N=289	Randomized N=117	p-value
Change in DXR-BMD mg/cm², median (IQR)	0 - 4	-2.7 (-8.4;2.2)	-2.2 (-7.2;2.7)	0.4
	4 - 8	-2.0 (-7.1;3.0)	-0.3 (-5.0;4.3)	0.07
	8 - 12	-3.2 (-8.6;1.8)	-2.2 (-8.7;2.7)	0.4
	0 - 12	-7.2 (-16.3;-0.1)	-3.4 (-13.3;2.4)	0.051
DXR-BMD loss ≥4.6 mg/cm2 after 1 year, no (%)		170 (59)	52 (44)	0.02
DXR-BMD gain ≥4.6 mg/cm2 after 1 year, no (%)		36 (12)	22 (19)	0.2

DXR-BMD, bone mineral density measured by digital X-ray radiogrammetry; Early remission, remission after 4 months of treatment with MTX and a tapered high dose of prednisone; IQR, inter quartile range; no, number; randomized, patients who did not achieve early remission and were randomized to either MTX, sulphasalazine, hydroxychloroquine and low dose prednisone or MTX plus adalimumab.

Median (IQR) DXR-BMD loss and percentages patients with DXR-BMD loss ≥4.6 mg/cm²/ year after 1 year were comparable between patients in continuous remission and patients who were not (-6.3 (-14.8;0.1) compared to -6.4 (-16.6;0.6) mg/cm², p=0.5 and 72 (55%) versus 157 (55%), p=0.5). DXR-BMD gain was present in 16 (12%) patients who were in continuous remission and in 40 (14%) patients who were not in continuous remission.

DISCUSSION

We investigated metacarpal BMD loss in patients with early (rheumatoid) arthritis, treated initially with MTX and a tapered high dose of prednisone, with subsequent treatment adjustments aiming at remission. This is the first clinical trial in which metacarpal BMD was monitored this intensively and this early in the disease course of RA, while disease activity was effectively suppressed in the majority of patients by the current treatment strategy. However, we are aware that results were obtained from frequent measurements and imputed data and that observed differences generally were small. Future studies are needed to demonstrate the relevance of our results.

Our data suggest that the annual decrease in metacarpal BMD in patients with early arthritis may be somewhat lower than previously found in patients with early RA (varying from 9 to 22 mg/cm²/year).[15,20-22] However, still more than half of the early arthritis patients had metacarpal BMD loss after 4 months of treatment with MTX and a tapered high dose of prednisone. In subsequent months, only 13% of the patients regained this DXR-BMD loss. Patients who had achieved early remission and tapered medication, showed more metacarpal BMD loss than patients who were randomized to extended combination therapy either including low dose prednisone or adalimumab. Although based on small numbers, we observed that

patients treated with adalimumab showed the smallest loss in metacarpal BMD and most often showed gain after 1 year (54%, compared to 21% in patients randomized to combination therapy including prednisone and 12% of early remission patients).

Our finding that metacarpal BMD loss after 4 months may be present in more than half of the patients with early arthritis, may be due to initial disease activity, the use of prednisone or both. The effect of the initial treatment cannot be elucidated since in the first 4 months all patients receive the same medication. However, results from the regression analyses may suggest that metacarpal BMD loss after 4 months was not dependent of baseline or 4 months disease activity, but only on age and postmenopausal status. This may indicate that the use of a tapered high dose of prednisone initially causes metacarpal BMD loss, a loss that was regained during the subsequent months in only a minority of the patients. Longer follow up data are needed to see whether more patients may regain the loss in the second year or later.

The finding that patients not achieving remission after 4 months who were randomized, may have less metacarpal BMD loss after 1 year and more gain than patients who did achieve early remission, may be explained by the intensive combination treatment that randomized patients received, either including low dose prednisone or adalimumab. Previously, treatment with anti-TNF-alpha or low dose prednisone has been shown to reduce hand BMD loss in patients with early RA.[15,23,24] However, the possibly larger metacarpal BMD loss in the early remission group might also be explained by the finding that randomized patients more often used bisphosphonates.

Despite small patients numbers, our results may suggest that patients treated with combination therapy including adalimumab had even less hand BMD loss and more gain than patients treated with a combination of DMARDs with low dose prednisone. Previously, TNF blockers have been shown to reduce joint damage progression,[25] and generalized as well as hand bone mineral density loss.[23,26-28] It has been suggested that this reduction may occur independently of the clinical response to TNF blockers.[28,29]

We found no differences in metacarpal BMD loss or gain between patients who were in continuous remission during the first year and patients who were not. In an earlier study in patients with recent onset RA, who had achieved sustained remission for at least one year, metacarpal BMD gain was found in 32% of patients.[7] These patients however achieved sustained remission for at least 1 year and later in the course of treatment after prolonged low disease activity, which may enable metacarpal BMD gain.

We found no differences in metacarpal BMD loss between UA and RA patients, although UA patients had a lower baseline disease activity at inclusion. This might be related to the similar symptom duration at study entrance and the fact that with the current treatment strategy disease activity was equally well suppressed during the first year in both groups.

A limitation of this study is the large amount of missing data. Radiographs were taken before we planned to measure DXR-BMD, and not for this purpose. To deal with this problem, we used multiple imputation, which is considered as a highly valid method to impute missing

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data.[19] Results from the original dataset, although based on small numbers, showed similar trends.

In conclusion, during 1 year of remission steered therapy in patients with undifferentiated or early RA, metacarpal BMD loss seemed not to be influenced by disease activity, classification as RA or antibody status, but depends largely on age and postmenopausal status. Initial loss during treatment with a combination of methotrexate and a tapered high dose of prednisone may be substantial, and despite high remission rates and overall low disease activity, metacarpal BMD loss may only partially be recovered in the subsequent 8 months. These results may suggest that although initial combination therapy including a tapered high dose of prednisone may induce low disease activity and (sustained) remission in a large proportion of early arthritis patients, it may have at least a temporary negative effect on localized BMD.

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