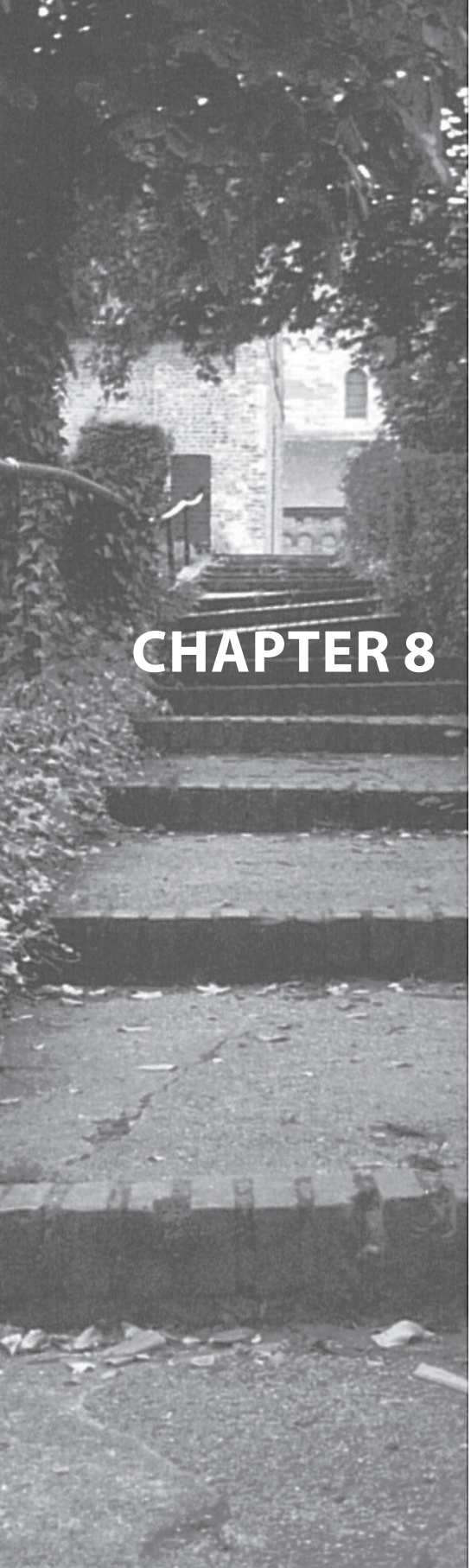

CHAPTER 8

Four-month metacarpal bone mineral density loss predicts radiological joint damage progression after one year in patients with early rheumatoid arthritis - exploratory analyses from the IMPROVED study

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ABSTRACT

Objective

To assess whether metacarpal bone mineral density (BMD) loss after 4 months predicts radiological progression after 1 year of anti-rheumatic treatment in patients with early (rheumatoid) arthritis (RA).

Methods

Metacarpal BMD was measured 4 monthly during the first year by digital X-ray radiogrammetry (DXR-BMD) in patients participating in the IMPROVED study, a clinical trial in 610 patients with recent onset RA (2010 criteria) or undifferentiated arthritis (UA), treated according to a remission (disease activity score<1.6) steered strategy. With Sharp- van der Heijde progression ≥0.5 points after 1 year (yes/no) as dependent variable, univariate and multivariate logistic regression analyses were performed.

Results

Of 428 patients with DXR-BMD results and progression scores available, 28 (7%) had radiological progression after 1 year. Independent predictors for radiological progression were presence of baseline erosions (OR (95%CI) 6.5 (1.7-25)) and early DXR-BMD loss (OR (95%CI) 1.5 (1.1-2.0)). In 366 (86%) patients without baseline erosions early DXR-BMD loss was the only independent predictor of progression (OR (95%CI) 2.0 (1.4-2.9)).

Conclusions

In early (rheumatoid) arthritis patients, metacarpal BMD loss after 4 months of treatment is an independent predictor of radiological progression after 1 year. In patients without baseline erosions, early metacarpal BMD loss is the main predictor of radiological progression.

INTRODUCTION

Early treatment of patients with rheumatoid arthritis (RA) improves disease outcomes including radiological joint damage.[1-3] Identification of patients who will have a more severe disease course may steer early treatment strategies. Since predicting disease outcome is currently not possible in a reliable way for all patients, there is a need for new predictors to improve existing prediction models.[4-7]

Periarticular osteopenia is one of the earliest radiological manifestations in RA and may already be found in the phase of undifferentiated arthritis (UA).[8,9] Metacarpal bone mineral density (BMD) loss may therefore be a potentially new predictor of disease outcome in patients with early (rheumatoid) arthritis. Previous research showed that metacarpal BMD loss is associated with disease activity [10] and metacarpal BMD loss in the first year after diagnosis is predictive for radiological damage up to five years in patients with early RA.[11-13] For clinical practice however, any predictive value of metacarpal BMD loss would be greater if it can be measured earlier in the disease course.

Therefore we investigated whether metacarpal BMD loss after 4 months of treatment, as measured by digital X-ray radiogrammetry (DXR-BMD), may be a predictor of radiological joint damage progression after 1 year in patients with undifferentiated or early RA treated according to a tight control, remission steered treatment strategy.

PATIENTS AND METHODS

Patients and study design

Data from the IMPROVED study were used, a multicenter, randomized clinical trial in 610 patients, including 479 (80%) patients with recent onset RA (according to the 2010 American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) classification criteria for RA [14] with a symptom duration <2 years), 122 patients with UA (having at least 1 joint clinically assessed as 'arthritis' and 1 other painful joint, clinically suspected of having early RA, regardless of symptom duration) and 9 patients that could not be classified because of missing data. Patients were treated according to a tight control strategy, aimed at achieving remission, defined as a disease activity score (DAS) <1.6 (DAS-remission).[15] 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 DAS-remission after 4 months started tapering medication, if possible to drug free (early DAS-remission group). Patients not in early DAS-remission were randomized either to MTX 25 mg/week plus hydroxychloroquine (HCQ) 400 mg/day, sulfasalazine (SSZ) 2000 mg/day and prednisone 7.5 mg/day (arm 1) or to MTX 25 mg/week plus adalimumab (ADA) 40 mg/2weeks (arm 2). Some patients who were not in DAS-remission after 4 months, were not randomized and treated outside of protocol

(Outside of Protocol (OP) group). Full details about the IMPROVED study protocol were previously published.[16,17]

In the current analysis we included all patients participating in the IMPROVED study whose radiological progression data after 1 year and at least 1 DXR-BMD result during the first year were available.

Demographic and clinical variables

At baseline the following variables were collected: age, gender, symptom duration, body mass index, current smoking status and alcohol use, calcium intake, postmenopausal status, previous fractures, family history on osteoporosis, anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF) status. 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) for global health, and C-reactive protein (CRP). During the first year, X-rays of hand and feet were made 4 monthly by digital radiography in all patients. Radiological progression, scored using the Sharp/van der Heijde scoring method, was assessed by two independent readers blinded for patient identity and time order of the radiographs.[18] Progression was defined as an increase in Sharp-van der Heijde Score (SHS) of ≥0.5 points. Details on inter-reader reliability were previously published.[17]

Metacarpal BMD measurements

Suitable routine digital X-rays of both hands were used to measure metacarpal BMD using Digital X-ray Radiogrammetry (DXR-BMD) measured by DXR-online (Sectra, Linköping, Sweden), a computerised method that automatically recognises three regions of interest on the second, third and fourth metacarpal bones. At each region, DXR-BMD is estimated from multiple measurements of cortical thickness, bone width and porosity.[19] The mean value of both hands was used in all analyses to avoid bias induced by hand dominance. 'DXR-BMD loss' was defined as a loss in DXR-BMD of ≥1.5 mg/cm^2/4months.[10]

Statistical analysis

Almost half of the available X-rays were found unsuitable for DXR-measurements. This resulted in missing DXR-BMD values in 141/428 patients (33%) at baseline, 73/428 (17%) after 4 months, 148/428 (35%) after 8 months and 140/428 (33%) after 1 year. To avoid possible bias induced by missing data and to increase power, multiple imputation was performed. 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.[20] Estimates obtained from regression analyses were automatically pooled by SPSS, other multiple estimates were averaged.

Median (IQR) DXR-BMD changes are shown because of a skewed distribution. Mann Whitney U test was used for comparisons of DXR-BMD changes between patients with and without radiological progression. To identify independent predictors of radiological progression, we performed univariate followed by multivariate regression analyses. From previous literature, the following potential predictors for (rapid) radiological progression were identified and entered in a univariate logistic regression model with radiologic progression (yes/no) as dependent variable: presence of ACPA and/or RF, baseline swollen joint count, baseline ESR and CRP levels, baseline total SHS, baseline erosion score and treatment.[4,6,7] In addition, we selected age, gender, fulfilling the 2010 ACR/EULAR criteria for RA and achieving DAS-remission after 4 months. Next to baseline erosion score we also entered presence of erosions, defined as ≥1 erosions, as covariate. Because only 28 (7%) patients had radiological progression, multivariate regression in the total study population was powered for about three variables.[21,22] Therefore, in addition to DXR-BMD loss from baseline to 4 months, we selected the 2 univariate significant predictors (using a significance level of 0.10) with the highest effect size for multiple regression. As radiological progression was present in <10% of the patients and therefore can be classified as 'rare', we argued that Odds Ratios (OR) obtained from all logistic regression analyses can be interpreted as relative risks (RR).[23]

All statistical analyses were conducted with SPSS for Windows version 20.0.

RESULTS

Clinical characteristics

We included 428 patients in the current analyses. Baseline characteristics of these patients did not differ significantly from those participating in the IMPROVED study where no SHS or DXR data were available (data not shown). Twenty-eight (7%) patients had radiological progression after 1 year and 400 (93%) had no radiological progression. For those with radiological progression, the median (IQR) progression score was 0.5 (0.5-1.4). One patient had rapid radiological progression (progression score ≥5 points) [24] after 1 year (18 points).

Compared to patients without progression, patients with progression were older, more often postmenopausal and ACPA positive, and more often fulfilled the 2010 criteria for RA. Furthermore, they had more often ≥1 erosions at baseline and a higher median total baseline SHS and, only at 8 months, a slightly higher DAS. (table 1)

DXR-BMD change

Table 2 shows absolute DXR-BMD values and DXR-BMD changes during the first year. Compared to patients without radiological progression after 1 year, patients with radiological progression had lower absolute DXR-BMD values at baseline and after 4, 8 and 12 months follow up. From baseline to 4 months, median DXR-BMD changes were significantly larger

Table 1: Clinical characteristics at baseline and during one year follow up of the total study group and separate for patients with and without radiological progression.

		Radiologic progression		
	Total population	**Yes**	**No**	**p-value**
Baseline	n=428	n=28	n=400	
Age, years, mean±SD	52 ± 13	58 ± 11	52 ± 13	0.01
Female, no (%)	294 (69)	22 (79)	272 (68)	0.2
BMI, kg/m^2, mean±SD	26 ± 4	25 ± 4	26 ± 4	0.6
Current smoking, no (%)	127 (30)	11 (39)	116 (29)	0.3
Current alcohol use, no (%)	250 (58)	17 (61)	233 (58)	0.9
Postmenopausal status, no (%), n=294	156 (53)	17 (89)	139 (58)	0.01
Previous fractures, no (%)	142 (33)	8 (29)	134 (34)	0.7
Familial osteoporosis, no (%)	72 (17)	6 (21)	66 (17)	0.5
Calcium intake, mg/day, median (IQR)	800 (600-1050)	875 (725-1069)	778 (600-1030)	0.2
25(OH) Vitamine D, nmol/l, median (IQR)	55 (38-75)	46 (25-75)	55 (39-75)	0.3
DAS (mean±SD)	3.2 ± 0.9	3.3 ± 0.9	3.2 ± 0.9	0.8
RA(2010), no (%)	344 (80)	26 (93)	318 (80)	0.04
Symptom duration, weeks, median (IQR)	18 (9-33)	20 (9-47)	18 (9-32)	0.5
ACPA positive, no (%)	247 (58)	23 (82)	224 (56)	0.008
RF positive, no (%)	241 (56)	18 (64)	223 (56)	0.2
ACPA and RF positive, no (%)	205 (48)	19 (68)	186 (47)	0.04
SHS total score	0 (0-0)	0.5 (0-4.5)	0 (0-0)	<0.001
Presence of erosions, no (%)	62 (14)	11 (39)	51 (13)	<0.001
4 months follow up				
DAS (mean±SD)	1.5 ± 0.9	1.5 ± 0.8	1.5 ± 0.9	0.9
Remission, no (%)	275 (64)	17 (61)	258 (65)	0.7
Early remission Group, no (%)	281 (66)	17 (61)	264 (66)	0.6
Arm 1 MTX+SSZ+HCQ+pred, no (%)	60 (14)	4 (14)	56 (14)	0.97
Arm 2 MTX+adalimumab, no (%)	57 (13)	5 (18)	52 (13)	0.5
Outside of Protocol Group, no (%)	30 (7)	2 (7)	28 (7)	0.98
8 months follow up				
DAS (mean±SD)	1.5 ± 0.8	1.8 ± 1.0	1.5 ± 0.8	0.05
Remission, no (%)	246 (57)	12 (43)	234 (61)	0.1
1 year follow up				
Use of Bisphosphonate, no (%)	129 (30)	9 (32)	120 (30)	0.8
Use of Calcium and/ or Vitamine D, no (%)	204 (48)	16 (57)	180 (45)	0.2
DAS (mean±SD)	1.6 ± 0.9	1.6 ± 0.9	1.6 ± 0.9	0.7
Remission, no (%)	235 (55)	16 (57)	219 (55)	0.8
SHS progression	0 (0-0)	0.5 (0.5-1.4)	0 (0-0)	<0.001

ACPA, Anti-Citrullinated Protein Antibodies; arm 1, patients not in early remission who were randomized to arm 1; arm 2, patients not in early remission who were randomized to arm2; BMI, Body Mass Index (kg/m2); DAS, Disease Activity Score; Early remission group, patients who were in remission after 4 months and started tapering medication; HCQ, hydroxychloroquine; IQR, interquartile range; MTX, methotrexate; no, number; Outside of Protocol group, patients not in early remission but not randomized and treated outside the protocol; Presence of erosions, defined as ≥1 erosions; pred, prednisone; RA(2010), rheumatoid arthritis according to the ACR/EULAR 2010 classification criteria for RA; RF, Rheumatoid Factor; remission, defined as DAS<1.6; SD, standard deviation; SHS, Sharp- van der Heijde Score; SSZ, sulfasalazine.

Table 2: Metacarpal bone mineral density measured by digital X-ray radiogrammetry during the first study year of the total study population and separate for patients with and without radiological progression.

	Time point		SHS progression		
	(months)	Total n=428	Yes: n=28	No: n=400	p-value
DXR-BMD g/cm^2, median (IQR)	0	0.593 (0.527-0.640)	0.558 (0.501-0.601)	0.597 (0.529-0.642)	0.03
	4	0.590 (0.526-0.637)	0.546 (0.486-0.587)	0.593 (0.529-0.640)	0.008
	8	0.590 (0.525-0.639)	0.544 (0.482-0.589)	0.593 (0.528-0.642)	0.009
	12	0.585 (0.522-0.636)	0.541 (0.472-0.586)	0.588 (0.524-0.638)	0.008
Change in DXR-BMD mg/cm^2, median (IQR)	0 - 4	-2.4 (-7.6 ; 2.2)	-9.6 (-15.2 ; -2.7)	-2.0 (-7.2 ; 2.5)	0.007
	4 - 8	-1.1 (-6.0 ; 3.2)	-2.2 (-8.1 ; 3.9)	-1.1 (-5.8 ; 3.1)	0.5
	8 -12	-3.1 (-9.0 ; 1.3)	-4.5 (-14.0 ; 0.05)	-3.1 (-8.7 ; 1.5)	0.3
	0 - 12	-5.7 (-15.4 ; 0.6)	-15.8 (-27.4 ; -2.3)	-5.4 (-14.2 ; 0.9)	0.007
Change in DXR-BMD, % from baseline	0 - 4	-0.4 (-1.3 ; 0.4)	-1.7 (-2.9 ; -0.5)	-0.3 (-1.2 ; 0.4)	0.007
	4 - 8	-0.2 (-1.1 ; 0.5)	-0.4 (-1.5 ; 0.7)	-0.2 (-1.0 ; 0.5)	0.5
	8 -12	-0.5 (-1.5 ; 0.2)	-0.8 (-2.7 ; 0.008)	-0.5 (-1.5 ; 0.2)	0.2
	0 - 12	-1.0 (-2.7 ; 0.1)	-2.8 (-4.9 ; -0.4)	-0.9 (-2.4 ; 0.2)	0.006

DXR-BMD, metacarpal bone mineral density measured by digital X-ray radiogrammetry; IQR, inter quartile range; SHS progression, defined as progression after 1 year ≥0.5 points.

in patients with radiological progression (median (IQR) -9.6 (-15.2;-2.7) mg/cm^2) than in patients without (-2.0 (-7.2;2.5) mg/cm^2, p=0.007). Twenty-four (86%) patients with radiological progression had DXR-BMD loss within the first 4 months, compared to 212 (53%) patients without radiological progression (p=0.01). One patient with rapid radiological progression (18 points after 1 year) had a change in DXR-BMD within the first 4 months of -27.4 mg/cm^2.

Treatment steps

Seventeen (61%) patients with radiological progression after 1 year had been in early DAS-remission after 4 months and subsequently had started tapering prednisone to zero, 9 (32%) had not achieved early remission and were randomized, and 2 were treated outside of protocol. Of the 17 in early DAS-remission, 5 patients relapsed after tapering prednisone and restarted it, whereas 12 remained in remission and started tapering MTX to zero. Six patients relapsed after tapering MTX and restarted it and 6 did not relapse and were in drug free remission after 1 year. The median (IQR) early DXR-BMD change of all 17 patients was -10.9 (-14.5;-2.5) mg/cm^2 (corresponding to -2.7 (-3.6;-0.6 mg/cm^2/month)), compared to -1.8 (-7.3;2.4) mg/cm^2 (corresponding to -0.5 (-1.8;0.6 mg/cm^2/month)) in 258 patients who achieved early DAS-remission and had no radiological progression after 1 year (p=0.02). DXR-BMD loss after 4 months was present in 14/17 (82%) patients in early DAS-remission who had radiological progression after 1 year, compared to 134 (52%) patients in early DAS-remission without radiological progression after 1 year (p=0.053).

Table 3a: Univariate logistic regression analysis with radiological progression (yes/no) as dependent variable in the total study population.

	Univariate Logistic regression		
	Crude OR	95%CI	R^2
RA according to 2010 criteria	6.5	0.9-48.8	0.04
Presence of baseline erosions	4.4	2.0-10.0	0.07
ACPA/RF			
Both negative	ref		0.04
One positive	2.6	0.6-11.3	
Both positive	3.9	1.1-13.2	
Early DXR-BMD loss, mg/cm^2/month	1.4	1.1-1.8	0.13
Female gender	1.7	0.7-4.4	0.01
Erosion score at baseline	1.1	0.99-1.1	0.01
Baseline total SHS	1.1	0.996-1.0	0.02
Age, years	1.0	1.0-1.1	0.04
Baseline ESR	1.0	0.999-1.0	0.02
Baseline CRP	1.0	0.997-1.0	0.01
Baseline TJC	0.97	0.9-1.1	0.003
Treatment Group			
Early remission group	ref		0.003
Arm 1 MTX+SSZ+HCQ+pred	1.1	0.4-3.4	
Arm 2 MTX+adalimumab	1.5	0.5-4.2	
Outside of Protocol group	1.1	0.2-5.1	
Early DAS-remission	0.8	0.4-1.9	0.001

ACPA, anti-citrullinated protein antibodies; arm 1, patients not in early remission who were randomized to methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ) and low dose prednisone; arm 2, patients not in early remission who were randomized to MTX plus adalimumab; CI, confidence interval; CRP, C-reactive protein; DXR-BMD, metacarpal bone mineral density measured by digital X-ray radiogrammetry; Early DXR-BMD loss, change in DXR-BMD between baseline and 4 months; Early remission group, patients who were in remission after 4 months and started tapering medication; Early DAS-remission, remission (DAS<1.6) after 4 months; Erosion score, Sharp-van der Heijde erosion score; ESR, erythrocyte sedimentation rate in mm/hr; OR, odds ratio; Outside of protocol group, patients not in early remission but not randomized and treated outside the protocol; Presence of baseline erosions, defined as ≥1 erosions at baseline; RA, rheumatoid arthritis according to the 2010 ACR/EULAR classification criteria; RF, rheumatoid factor; ref, reference category; SHS, Sharp-van der Heijde Score; TJC, tender joint count.

Table 3b: Multivariate logistic regression with radiologic progression (yes/no) as dependent variable in the total study population.

Multivariate logistic regression	**Adjusted OR**	**95%CI**
Presence of baseline erosions	3.9	1.6-9.5
Early DXR-BMD loss, mg/cm^2/month	1.4	1.1-1.7
RA according to 2010 criteria	4.9	0.6-37

CI, confidence interval; DXR-BMD, metacarpal bone mineral density measured by digital X-ray radiogrammetry; Early DXR-BMD loss, change in DXR-BMD between baseline and 4 months; OR, odds ratio; Presence of baseline erosions, defined as ≥1 erosions, RA, rheumatoid arthritis according to the 2010 ACR/EULAR classification criteria.

Predictors of radiological progression

Univariate predictive variables for radiologic progression after 1 year were: fulfilling the 2010 criteria for RA (p=0.07), presence of baseline erosions (yes/no) (p<0.001), presence of both ACPA and RF (p=0.03), early DXR-BMD loss after 4 months (p=0.008), baseline total SHS score (p=0.07), age (p=0.01), baseline ESR (p=0.06) and baseline tender joint count (p=0.05). Female gender, presence of either ACPA or RF, symptom duration, baseline erosion score, CRP level and treatment group were not predictive. Achieving DAS-remission after 4 months was also not predictive for radiological progression after 1 year.(table 3a)

Together with early DXR-BMD loss, presence of baseline erosions and fulfilling the 2010 criteria for RA were selected for inclusion in the multivariate regression analysis. Both presence of baseline erosions and early DXR-BMD loss were predictive for radiological progression after one year independent of each other and independent of fulfilling the 2010 criteria for RA.(table 3b).

In an additional multivariate model including early DXR-BMD loss, presence of baseline erosions and presence of both ACPA and RF, presence of both ACPA and RF was not an independent predictor of radiological progression, whereas DXR-BMD loss and presence of baseline erosions both were (data not shown).

After leaving out the one patient with rapid radiological progression, the results above did not significantly change (data not shown).

Patients without baseline erosions

In 366 (86%) patients no baseline erosions were present. Of these 366 patients, 17 patients (5%) showed radiological progression after 1 year (61% of all 28 patients with radiological progression) and 349 (95%) did not. Median DXR-BMD change from baseline to 4 months was -11.8 (-16.7;-4.7) mg/cm^2 in patients with progression and -2.0 (-7.0;2.4) mg/cm^2 in patients without progression (corresponding to -2.9 (-4.2;-1.2) and -0.5 (-1.7;0.6) mg/cm^2/months, respectively). Univariate significant predictors for progression after 1 year in patients without baseline erosions were age (p=0.004), baseline total SHS (in these patients reflecting baseline joint space narrowing) (p=0.009), baseline ESR level (p=0.096) and early DXR-BMD loss (p=0.02).(table 4a)

Early DXR-BMD loss and total baseline SHS were selected for inclusion in the multivariate regression analysis. Early DXR-BMD loss was predictive for radiological progression after 1 year independent of baseline total SHS in patients without baseline erosions.(table 4b)

Table 4a: Univariate logistic regression analysis with radiological progression (yes/no) as dependent variable in patients without baseline erosions.

	Univariate Logistic regression		
	Crude OR	95%CI	R^2
RA according to 2010 criteria	4.1	0.5-31.3	0.02
ACPA/RF			
Both negative	ref		0.03
One positive	3.0	0.5-17	
Both positive	3.2	0.7-15	
Early DXR-BMD loss, mg/cm^2/month	1.4	1.1-1.9	0.13
Female gender	2.1	0.6-7.5	0.01
Baseline total SHS	1.3	1.1-1.6	0.06
Age, years	1.1	1.0-1.1	0.08
Baseline ESR, mm/hr	1.0	0.997-1.0	0.02
Baseline CRP	1.0	0.99-1.0	0.002
Baseline TJC	0.97	0.9-1.1	0.004
Treatment Group			
Early remission group	ref		0.01
Arm 1 MTX+SSZ+HCQ+pred	1.6	0.4-5.9	
Arm 2 MTX+adalimumab	1.7	0.5-6.6	
Outside of Protocol group	1.8	0.4-8.8	
Early DAS-remission	0.6	0.2-1.7	0.007

ACPA, anti-citrullinated protein antibodies; arm 1, patients not in early remission who were randomized to methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ) and low dose prednisone; arm 2, patients not in early remission who were randomized to MTX plus adalimumab; CI, confidence interval; CRP, C-reactive protein; DXR-BMD, metacarpal bone mineral density measured by digital X-ray radiogrammetry; Early DXR-BMD loss, change in DXR-BMD between baseline and 4 months; Early remission group, patients who were in remission after 4 months and started tapering medication; Early DAS-remission, remission (DAS<1.6) after 4 months; ESR, erythrocyte sedimentation rate in mm/hr; OR, odds ratio; Outside of protocol group, patients not in early remission but not randomized and treated outside the protocol; RA, rheumatoid arthritis according to the 2010 ACR/EULAR classification criteria; RF, rheumatoid factor; ref, reference category; SHS, Sharp-van der Heijde Score; TJC, tender joint count.

Table 4b: Multivariate logistic regression with radiologic progression (yes/no) as dependent variable in patients without baseline erosions

Multivariate logistic regression	Adjusted OR	95%CI
Early DXR-BMD loss, mg/cm^2/month	1.4	1.1-1.8
Baseline total SHS	1.3	1.0-1.6

CI, confidence interval; DXR-BMD, metacarpal bone mineral density measured by digital X-ray radiogrammetry; Early DXR-BMD loss, change in DXR-BMD between baseline and 4 months; OR, odds ratio; SHS, Sharp-van der Heijde Score.

DISCUSSION

In patients with early rheumatoid or undifferentiated arthritis, metacarpal BMD loss measured by DXR after four months of treatment with MTX and a tapered high dose of prednisone is predictive for future joint damage after 1 year of remission steered treatment. In patients without baseline erosions (86%), metacarpal BMD loss was the main predictor of future joint damage.

These data suggest that DXR measurements over a period of 4 months from baseline can help to decide which patients with early arthritis should start anti-rheumatic treatment to prevent joint damage or damage progression, one of the main goals in the treatment of RA.[25] Early treatment and suppression of disease activity has been shown to be associated with better suppression of radiological damage progression.[1-3] To facilitate this, in 2010 new classification criteria for RA were formulated.[14] In the IMPROVED trial we included not only patients with RA (according to the 2010 classification criteria) but also patients with UA, who were judged to represent RA in an early phase of the disease by the treating rheumatologist. Starting treatment so early in disease course carries the risk of overtreatment of patients who are misdiagnosed as RA, but a treatment delay means risking irreversible joint damage progression.

To individualize treatment, predictive factors for damage progression have been identified and prediction models built.[4,6,7] But in particular in patients without baseline damage, predicting which patients will develop joint damage may be difficult. We predicted metacarpal BMD loss since this was linked with both disease activity and joint damage progression in patients with early and established RA, and metacarpal BMD loss after 1 year has been shown to have predictive value additional to known predictors.[11,12] Our paper is the first to report metacarpal BMD changes already after 4 months, and we found that changes do occur.

Ideally, an outcome predictor can be identified already at baseline. In this early arthritis population, presence of baseline erosions was the only independent baseline predictor of radiological progression after 1 year besides metacarpal BMD loss after 4 months. Another obvious outcome after 4 months, remission yes or no, was not predictive of radiological progression after 1 year. Some patients who had radiological joint damage after 1 year even were in remission throughout the whole year and tapered all medication according to the study protocol. Our results indicate that after 4 months, a strong predictor of progression may help to decide if adjustments of the chosen treatment strategy should be made in patients with early arthritis.

One limitation of this study is the fact that, due to the inclusion of patients with early and relatively mild disease, progressively treated with the aim of achieving remission, only a few patients had radiological damage progression. Our results however reached statistical significance, although we acknowledge that the damage scores are hardly of clinical relevance this early in the disease phase. But as RA treatment more and more aims at achieving total

disease and damage control in an early phase of the disease, we think that our findings may be relevant for daily practice.

Another limitation was that we found many of the 'routinely' acquired radiographs to be unsuitable for DXR. To handle missing metacarpal BMD data, we performed multiple imputation [20] to account for potential bias caused by data 'missing at random', meaning that missingness depends on other observed patient characteristics rather than on the fact whether metacarpal BMD measurements were possible or not.

A third possible limitation may be that, as DXR-measurements in this study were done in retrospect on X-rays taken in 12 different hospitals using imaging protocols not adjusted to DXR, precision of the method may be lower than previously published. DXR-BMD has 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%).[26-29] However, supported by the consistency of our results, precision in this study may still be considered as high.

If metacarpal BMD is to be applied in clinical practice using the DXR online method, neither low precision nor missing values may be problematic, as X-rays will then be taken according to a predefined protocol (Sectra, Sweden). Precision may reach values described above, and in case of mal positioning, direct feedback will be given, which makes it more suitable for use in clinical practice.

In conclusion, we showed that loss of metacarpal bone mineral density measured by DXR after the first 4 months of treatment is an independent predictor of future bone damage in patients with early (rheumatoid) arthritis. This suggests that 4 monthly metacarpal BMD measurements can help to guide treatment decisions in individual patients or may be added to improve the predictive value of existing prediction models for disease outcome in RA.

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