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Inhibition of periarticular bone loss is associated with clinical remission and ACR70-Response in rheumatoid arthritis

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Abstract

The aim of this study, based on a post hoc analysis of the data set used in the RAPID 1 trial, focuses on the associations between metacarpal bone mineral density, as estimated by digital X-ray radiogrammetry (DXR), and clinical remission as well as ACR70-Response in rheumatoid arthritis (RA) patients treated with certolizumab pegol (CZP). The trial evaluates a total of 345 RA patients treated with methotrexate versus CZP 200 mg versus CZP 400 mg. All patients underwent X-rays of the hand at baseline and week 52 as well as computerized calculations of bone mineral density (BMD) by DXR. Clinical remission was defined as DAS28 < 2.6. ACR70-Response was also evaluated. The radiological assessment of disease progression was estimated using the modified total Sharp Score. The mean difference for DAS28 was observed for patients treated with CZP 400 mg (median: − 3.53, minimum: − 6.77; maximum: + 0.48) and CZP 200 mg (median: − 3.13, minimum: − 6.37; maximum: − 0.52) compared to the methotrexate group (median − 2.41, minimum: − 4.76; maximum: + 0.31). The DXR-BMD showed a minor bone loss for the treatment groups undergoing therapy with CZP 200 mg (median: − 0.009 g/cm^2, minimum: − 0.059 g/cm^2; maximum: + 0.095 g/cm^2) and CZP 400 mg (median: − 0.008 g/cm^2, minimum: − 0.064 g/cm^2; maximum: + 0.080 g/cm^2). The methotrexate group presented an advanced periarticular metacarpal bone loss as measured by DXR-BMD (median: − 0.024 g/cm^2, minimum: − 0.102 g/cm^2; maximum: + 0.057 g/cm^2). In the case of clinical remission and ACR70-Response, no significant change of the DXR-BMD was observed for both CZP groups. The study highlights that patients treated with CZP show a less accentuated periarticular bone loss as estimated by DXR in comparison to patients with methotrexate plus placebo. In addition, patients with clinical remission and ACR70-Response revealed no periarticular demineralisation.

Keywords Rheumatoid arthritis · Digital X-ray radiogrammetry · Certolizumab pegol · Bone mineral density · Clinical remission · ACR70-Response

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Abbreviations

BMD	Bone mineral density (g/cm^2) estimated by digital X-ray radiogrammetry
CRP	C-reactive protein
CT	Cortical thickness (cm) estimated by digital X-ray radiogrammetry
DAS28	Disease activity score 28
DXR	Digital X-ray radiogrammetry
MCI	Metacarpal index estimated by digital X-ray radiogrammetry
MTX	Methotrexate
n.s.	Not significant
OPG	Osteoprotegerin
RA	Rheumatoid arthritis
RANKL	Receptor activators of the nuclear κB ligand

TNFα	Tumor necrosis factorα
W	Metacarpal bone width (cm) estimated by digital X-ray radiogrammetry

Introduction

Rheumatoid arthritis (RA) is the most common inflammatory disease characterized by progressive destruction of the small joints of the hand and feet [1]. The chronic inflammation in rheumatoid arthritis occurs in two forms: periarticular demineralization of the hand bones and generalized osteoporosis especially at the lumbar spine and femoral neck. The generalized osteoporosis is based on immobilization, the global inflammation by cytokines, and the chronic use of glucocorticoids detectable using the gold standard dual-energy X-ray absorptiometry (DXA) [2]. The periarticular demineralisation of the metacarpal bones is one of the earliest signs in RA and presents a closed association to inflammatory activity in RA [3, 4]. Digital X-ray radiogrammetry (DXR) is an operator-independent technique, providing automated measurements of cortical bone mineral density at the metacarpals using digitized radiographs [5]. Normative DXR data for women and men are available which present a lower bone mineral density in female compared to male with an age-dependent metacarpal bone loss [6]. The DXR technique shows a high precision (precision error 0.27%) [7] and excellent reproducibility (coefficient of variation 0.26%) [8]. In this context, DXR provides a sensitivity and specificity of 91% versus 47% (accuracy 83%) for the detection of periarticular bone loss in RA [3].

Periarticular demineralisation as estimated by DXR strongly correlates with the established scoring methods (e.g., Larsen Score) [9] and functions as surrogate marker for radiographic progression [10]. However, the RA-specific periarticular bone loss of metacarpal bones is reliably quantified in the early and established RA by DXR [11, 12]. In this context, it should be noted that DXR can also used for the assessment of generalized osteoporosis [13].

However, only a few studies have elucidated so far the effect of anti-inflammatory therapy on hand BMD loss in RA. A published trial by Pfeil et al. [14] compared the therapeutic effects of DMARD therapy of leflunomide versus methotrexate which revealed a reduced rate of bone loss and joint destruction in patients receiving leflunomide therapy. Anti-tumor necrosis factor α (anti-TNF) treatment has proved to be more successful in the prevention of radiographic joint destruction than disease-modifying anti-rheumatic drugs (e.g., methotrexate, MTX). Further information on the effects of anti-inflammatory treatment, including anti-TNF treatment, on both periarticular and generalized osteoporosis in patients with RA is scarce. Retrospective analyses based on the data of the BeSt- and PREMIER study revealed reduced bone loss under anti-TNF treatment compared to MTX which was also demonstrated using DXR. In this context, the BeSt- and PREMIER were the first studies concerning the evaluation of DXR with respect to anti-TNF treatment in RA [2, 15].

Results from the RA prevention of structural damage 1 (RAPID 1) clinical trial have demonstrated that certolizumab pegol plus methotrexate versus placebo plus methotrexate reduced the clinical symptoms and also the disease activity with clearly limited radiological progression [16]. The effects of anti-TNF treatment by certolizumab pegol on periarticular osteoporosis have not previously been studied using a double-blind study design.

The aim of this study is to examine the effects of certolizumab pegol 200/400 mg plus methotrexate versus placebo plus methotrexate on hand bone mineral density (BMD) as measured by DXR. The study utilizes a retrospective post hoc analysis of data RAPID 1 trial sets and evaluates DXR-BMD as potential predictor of radiological progression in RA patients treated with certolizumab pegol 200/400 mg plus methotrexate versus placebo plus methotrexate. The study also considered clinical remission (DAS28 < 2.6) and the ACR70-Response.

Patient and methods

Study population

The study is based on a post hoc subanalysis of the data sets which are considered in the RAPID 1 trial; the study design consists of a 52-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study published by Keystone et al. [16]. A total of 661 RA patients with radiographs of the hands were enrolled in the study. 316 patients were excluded (inferior image quality of the X-ray for DXR analysis at baseline or week 52: $n = 244$, lack of X-ray at week 52: $n = 72$) (for details, see above); 345 patients were analyzed by the DXR technique. The RA patients were divided into three groups according to the treatment: (I) Placebo plus methotrexate ($n = 34$) (II) certolizumab pegol 200 mg plus methotrexate ($n = 155$) and (III) certolizumab pegol 400 mg plus methotrexate ($n = 156$). Every patient received a radiograph at baseline and at week 52. The baseline characteristics were comparable between the treatment groups. Detailed clinical patient characteristics are given in Table 1.

Eighty-seven patients with non-response to methotrexate were excluded due to withdrawal at week 16 from the placebo plus methotrexate group and were included entered in an open label group treated with certolizumab pegol. Only responders to placebo and methotrexate were considered in the placebo group.

Table 1 Baseline characteristics of the total study cohort ($n = 345$)

	Placebo plus methotrexate	Certolizumab pegol 200 mg plus methotrexate	Certolizumab pegol 400 mg plus methotrexate
Number	34	155	156
Women	29	120	130
Men	5	35	26
Age (in years) mean (SD)	50.6 (10.1)	50.5 (11.2)	51.6 (10.6)
Disease duration (in years) mean (SD)	6.6 (3.9)	6.4 (4.4)	5.8 (3.9)
Rheuma factor positive	79.4%	81. 3%	85.2%
C-reactive protein (in mg/l) mean (SD)	21.75 (16.38)	23.91 (26.51)	23.22 (30.61)
Erythrocyte sedimentation rate (1st hour) in mm	48.44 (22.39)	46.74 (24.08)	45.31 (21.42)
Disease activity score 28-erythrocyte sedimentation rate mean (SD)	6.90 (0.85)	6.74 (0.81)	6.81 (0.82)
Health assessment questionnaire mean (SD)	1.64 (0.74)	1.62 (0.61)	1.65 (0.58)

For the baseline characteristics, no significant difference was observed by the Mann–Whitney *U* test between the three treatment groups

SD standard deviation

Digital X-ray radiogrammetry for the quantification of periarticular bone loss

All plain radiographs were scanned (Scanner UMAX Power Look 1100, resolution 300 dots per inch) into the DXR system, producing digitized images. The DXR analysis offers a continual self-checking to maintain the quality of the digital X-ray imaging; the analysis was halted if the X-ray imaging became inferior (i.e., incorrect determination of contours and identification of bone structures).

Digital X-ray radiogrammetry (Pronosco X-Posure System™, Version 2.0; Sectra; Sweden) was applied to determine the bone mineral density (BMD in g/cm^2), cortical thickness (CT in cm), metacarpal bone width (W in cm), and metacarpal index (MCI; a dimensionless parameter based on the mean cortical thickness normalized with the mean outer bone diameter of the metacarpals) [17]. The computer algorithms automatically defined regions of interest around the narrowest bone parts of the metacarpals II, III, and IV, and, subsequently, determined the outer and inner cortical edges of the cortical metacarpal bone parts. The DXR technique automatically estimated BMD in g/cm^2, MCI (a dimensionless parameter), CT in cm, and W in cm (see detailed technical informations in the reference published by Pfeil et al. [10]).

Scoring of hand radiographs

The radiographs were scored by the modified total Sharp Score as recommended by Keystone et al. [16].

Statistical analysis

The primary objective of the statistical analysis was to quantify the changes in bone mineral density in patients with rheumatoid arthritis under therapy with certolizumab pegol 200/400 mg plus methotrexate versus placebo plus methotrexate.

1. The Kolmogorow–Smirnow test was used to compare baseline characteristics between the three treatment groups.
2. The absolute differences of each patient were calculated for the following parameters between baseline and week 52: DXR parameters, modified total Sharp score, DAS28, and C-reactive protein (CRP). The changes were provided as median difference and also mean difference.

   The secondary objective was to evaluate the associations of DXR-BMD on clinical remission (DAS28 ≤ 2.6) and ACR70-Response in patients treated with certolizumab pegol 200/400 mg plus methotrexate.
3. The study cohort was divided according to the fact whether the patient experienced clinical remission (clinical remission DAS28: ≤ 2.6, no clinical remission DAS28: > 2.6). The mean difference between baseline and week 52 for the DXR parameters and the modified Sharp Score were compared by Wilcoxon signed-rank tests.
4. To evaluate the associations of DXR parameters with the modified Sharp Score as well as the ACR70-Response, the cohort was separated into the following groups:

ACR70-Response versus ACR70 Non-Response The mean difference between baseline and week 52 for the DXR parameters and the modified Sharp Score were compared by Wilcoxon signed-rank tests.

A significance level of p value < 0.05 was considered as statistically significant; statistical analysis was performed using SPSS® version 22.0 (IBM SPSS Statistics, Chicago, Illinois, USA), for Windows.

Results

Disease activity

The placebo plus methotrexate group revealed a median difference with −2.41 (minimum: −4.76; maximum: +0.31) of the Disease Activity Score (DAS28-ESR) between baseline and week 52. For the C-reactive protein (CRP), a decrease of −3.0 mg/l (minimum: −37.0 mg/l; maximum: 32.0 mg/l) was observed for the median difference over 52 weeks.

The certolizumab pegol 200 mg plus methotrexate group presented a significant median difference of the DAS28-ESR with −3.13 (minimum: −6.37; maximum: −0.52) and for CRP with 7.0 mg/l (minimum: −87.0 mg/l; maximum: +44.0 mg/l) from baseline to week 52. Similar results were demonstrated for the certolizumab pegol 400 mg plus methotrexate group with a significant median difference of DAS28-ESR (median: −3.53, minimum: −6.77; maximum: 0.48) and CRP (median: −7.0 mg/ml, minimum: −73.0 mg/l; maximum: 44.0 mg/l).

Periarticular demineralisation estimated by digital X-ray radiogrammetry (see Table 2)

For the placebo plus methotrexate group, the BMD was reduced with a median difference of −0.024 g/cm^2 (minimum: −0.102 g/cm^2; maximum: +0.057 g/cm^2) between baseline and week 52. The median difference from baseline to week 52 was observed for MCI with −0.014 (minimum: −0.058; maximum: +0.016), CT with −0.010 cm (minimum −0.033 cm; maximum: +0.020 cm) and W with −0.013 cm (minimum: −0.124 cm; maximum: +0.068 cm).

The median difference of BMD in the certolizumab pegol 200 mg plus methotrexate group was −0.009 g/cm^2 (minimum: −0.059 g/cm^2; maximum: +0.095 g/cm^2) between baseline and week 52. Regarding MCI, CT, and W, a median difference with −0.004 (minimum: −0.045; maximum: +0.017), −0.003 cm (minimum: −0.024 cm; maximum: 0.046 cm) and −0.007 cm (minimum: −0.082 cm; maximum: 0.167 cm) was revealed.

Regarding the certolizumab pegol 400 mg plus methotrexate group, a median difference of the BMD of −0.008 g/cm^2 (minimum: −0.064 g/cm^2; maximum: +0.080 g/cm^2) between baseline and week 52 was presented. In addition, a median difference was observed for the MCI with −0.006 (minimum: −0.053; maximum: +0.077), for the CT with −0.004 cm (minimum: −0.024 cm; maximum: +0.034 cm)

Table 2 Mean and median changes according to all therapy groups using digital X-ray radiogrammetry between baseline and week 52

	Placebo plus methotrexate Median difference (minimum; maximum) Mean difference ± standard deviation $n = 34$	Certolizumab pegol 200 mg plus methotrexate Median difference (minimum; maximum) Mean difference ± standard deviation $n = 155$	Certolizumab pegol 400 mg plus methotrexate Median difference (minimum; maximum) Mean difference ± standard deviation $n = 156$
BMD in g/cm^2	−0.024 (−0.102; 0.057) −0.029 ± 0.033	−0.009 (−0.059; 0.059) −0.008 ± 0.026	−0.008 (−0.064; 0.080) −0.006 ± 0.027
MCI	−0.014 (−0.058; 0.016) −0.016 ± 0.015	−0.004 (−0.045; 0.017) −0.007 ± 0.012	−0.006 (−0.053; 0.077) −0.007 ± 0.014
CT in cm	−0.010 (−0.033; 0.020) −0.011 ± 0.011	−0.003 (−0.024; 0.046) −0.003 ± 0.010	−0.004 (−0.024; 0.034) −0.003 ± 0.009
W in cm	−0.013 (−0.124; 0.068) −0.023 ± 0.051	−0.007 (−0.082; 0.167) −0.002 ± 0.039	−0.002 (−0.073; 0.131) −0.003 ± 0.037
Total Sharp Score in units	0.00 (−5.00; 10.50) 1.45 ± 3.41	0.00 (−9.75; 61.69) 0.42 ± 5.68	0.00 (−20.00; 61.50) 0.16 ± 5.91
Erosion Score in units	0.00 (−5.00; 9.50) 0.83 ± 2.79	0.00 (−9.75; 27.65) 0.16 ± 3.02	0.00 (−11.67; 34.50) 0.01 ± 3.37
Joint Space Narrowing Score in units	0.00 (0.00; 7.69) 0.62 ± 1.37	0.00 (−9.00; 36.16) 0.28 ± 3.42	0.00 (−13.50; 28.00) 0.05 ± 3.21

and W with − 0.002 cm (minimum: − 0.073 cm; maximum: + 0.131 cm).

At baseline, there was no significant difference of the DXR parameters between all three treatment groups.

Radiographic progression (see Table 2)

289 patients present erosions at the beginning of the study. The modified total Sharp Score enclosing the joint space narrowing segment and the erosion segment showed no significant change regarding the median between baseline and week 52 for all three treatment groups.

In the placebo plus methotrexate group, a mean difference was observed for the modified total Sharp Score (1.45 ± 3.41 Units), for the Joint Space Narrowing Score (0.62 ± 1.37 Units) and of the Erosion Score (0.83 ± 2.79 Units) after the treatment for 52 weeks.

A lower mean difference was revealed in the modified total Sharp Score of the certolizumab pegol 200 mg plus methotrexate group (0.42 ± 5.68 Units) and the certolizumab pegol 400 mg plus methotrexate group (0.16 ± 5.91 Units). Similar results were obtained for the Erosion Score (certolizumab pegol 200 mg plus methotrexate: 0.16 ± 3.02 Units; certolizumab pegol 400 mg plus methotrexate: − 0.01 ± 3.37 Units) and the Joint Space Narrowing Score (certolizumab pegol 200 mg plus methotrexate: 0.28 ± 3.42 Units; certolizumab pegol 400 mg plus methotrexate: 0.05 ± 3.21 Units).

At baseline, there was no significant difference of the modified total Sharp Score between all treatment groups.

Cortical bone mass and radiographic progression in patients with clinical remission in week 52 (see Table 3)

Patients with clinical remission (DAS28 ≤ 2.6) presented a non-significant periarticular bone loss between baseline and week 52 as measured by DXR-BMD [certolizumab pegol 200 mg plus methotrexate: mean difference − 0.0014 g/cm^2, median difference − 0.006 (− 0.051; 0.092), p = n.s.; certolizumab pegol 400 mg plus methotrexate: mean difference − 0.0015 g/cm^2, median difference − 0.003 (− 0.037; 0.069), p = n.s.] compared to the patients without clinical remission. The patients without clinical remission (DAS28 > 2.6) showed a significant ($p < 0.01$) periarticular bone loss with a mean difference − 0.0092 g/cm^2 [median difference: − 0.009 (− 0.059; 0.095)] for patients treated with certolizumab pegol 200 mg plus methotrexate and − 0.0071 g/cm^2 [mean difference: − 0.010 (− 0.064; 0.080)] for those in the certolizumab pegol 400 mg plus methotrexate group over 52 weeks. For the modified total Sharp Score, no significant change was observed in the patients, depending on clinical remission (DAS ≤ 2.6) over 52 weeks.

Table 3 Changes between baseline and week 52 according to all therapy groups in patients depending on clinical remission

	DXR-BMD in g/cm^2 Median difference (minimum; maximum) Mean difference Relative difference between baseline and week 52 (significance)	Total Sharp Score Median difference (minimum; maximum) Relative difference between baseline and week 52 (significance)
No clinical remission DAS28 ≥ 2.6		
Certolizumab pegol 200 mg plus methotrexate	− 0.009 (− 0.059; 0.095) − 0.0092 − 1.7% ($p < 0.01$)	0 (− 9.75; 61.69) + 1.3 + 3.5% (p = n.s.)
Certolizumab pegol 400 mg plus methotrexate	− 0.010 (− 0.064; 0.080) − 0.0071 − 1.3% ($p < 0.01$)	0 (− 20.0; 61.50) + 0.2 + 0.6% (p = n.s.)
With clinical remission DAS28 ≤ 2.6		
Certolizumab pegol 200 mg plus methotrexate	− 0.006 (− 0.051; 0.092) − 0.0014 − 0.2% (p = n.s.)	0 (− 5.41; 3.50) + 0.5 + 1.9% (p = n.s.)
Certolizumab pegol 400 mg plus methotrexate	− 0.003 (− 0.037; 0.069) − 0.0015 − 0.2% (p = n.s.)	0 (− 12.00; 6.00) − 0.6 − 2.1% (p = n.s.)

Cortical bone mass and radiographic progression in patients with ACR70 response in week 52 (see Table 4)

Patients with ACR70-Response revealed lower periarticular bone loss compared to the ACR70 Non-responder between baseline and week 52. The ACR70 responders treated with certolizumab pegol 200 mg plus methotrexate demonstrated a non-significant (p = n. s.) periarticular bone loss with a mean difference − 0.0069 g/cm^2 [median difference: − 0.010 (− 0.059; 0.092)] versus 0.0056 g/cm^2 [median difference: − 0.009 (− 0.064; 0.069)] for the patients under the therapy with certolizumab pegol 400 mg plus methotrexate over 52 weeks. ACR70 Non-responders showed increased periarticular bone loss over 52 weeks of a mean difference with − 0.0111 g/cm^2 [median difference: − 0.011 (− 0.051; 0.065); $p < 0.01$] for the certolizumab pegol 200 mg plus methotrexate group and of − 0.0098 g/cm^2 [median difference: − 0.010 (− 0.045; 0.070); $p < 0.01$] for the certolizumab pegol 400 mg plus methotrexate group.

The modified total Sharp Score has not shown significant changes over 52 weeks in both treatment groups with certolizumab pegol application depending on the ACR70-Response.

Discussion

The aim of this study was to identify the effects of treatment regime with certolizumab pegol 200/400 mg plus methotrexate versus placebo plus methotrexate on hand bone mineral density as measured by DXR and to evaluate DXR-BMD as potential predictor of radiological progression in RA patients treated with certolizumab pegol 200/400 mg plus methotrexate versus placebo plus methotrexate depending on clinical remission (DAS28 ≤ 2.6) and ACR70-Response.

Change in cortical bone mineral density in patients undergoing therapy with certolizumab pegol plus methotrexate

A potential advantage of DXR is the detection of therapy-induced alterations of the hand BMD [18]. The study presented progressive periarticular demineralisation for the methotrexate and placebo group (DXR-BMD median difference: − 0.024 g/cm^2) comparable with the results published by Pfeil et al. [14]. Both certolizumab pegol groups showed reduced periarticular demineralisation; certolizumab pegol 200 mg plus methotrexate (DXR-BMD median difference: − 0.009 g/cm^2 over 52 weeks); certolizumab pegol 400 mg plus methotrexate (DXR-BMD median difference: − 0.008 g/cm^2 over 52 weeks). The post hoc analysis of the PREMIER study showed that anti-tumor necrosis factor-α therapy with adalimumab in combination with methotrexate (DXR-BMD median percentage changes: − 1.63% per year) provided a better bone protection with the limited BMD loss than either adalimumab (DXR-BMD median percentage changes: − 1.97% per year) or methotrexate monotherapy (DXR-BMD median percentage changes: − 1.86% per year) [15]. Krieckaert et al. [19] reported, in their cohort study, a hand bone loss per year of − 1.41% estimated by DXR for patients treated with adalimumab. Thus, DXR is able

Table 4 Changes between baseline and week 52 according to all therapy groups in patients depending on response to ACR70

	DXR-BMD in g/cm^2 Median difference (minimum; maximum) Mean difference Relative difference between baseline and week 52 (significance)	Total Sharp Score Median difference (minimum; maximum) Mean difference Relative difference between baseline and week 52 (significance)
ACR70 Non-response		
Certolizumab pegol 200 mg plus methotrexate	− 0.011 (− 0.051; 0.065) − 0.0111 − 2.1% ($p < 0.01$)	0 (− 8.50; 61.69) + 1.1 + 2.9% (p = n.s.)
Certolizumab pegol 400 mg plus methotrexate	− 0.010 (− 0.045; 0.070) − 0.0098 − 1.9% ($p < 0.01$)	0 (− 20.0; 12.5) − 0.1 − 0.3% (p = n.s.)
ACR70 Response		
Certolizumab pegol 200 mg plus methotrexate	− 0.010 (− 0.059; 0.092) − 0.0069 − 1.3% (p = n.s.)	0 (− 5.5; 9.50) + 0.9 + 3.3% (p = n.s.)
Certolizumab pegol 400 mg plus methotrexate	− 0.009 (− 0.064; 0.069) − 0.0056 − 0.9% (p = n.s.)	0 (− 12.0; 61.5) + 0.7 + 2.1% (p = n.s.)

to detect the smallest differences in the efficacy of various therapeutic regimens based on the quantification of periarticular bone mass [14]. Furthermore, anti-TNFα therapeutic strategies reduce the progression of radiographically visible joint damage in RA patients [20, 21].

In this context, TNFα-inhibition reduced bone loss with the inhibition of inflammation in RA [22]. Güler-Yüksel et al. [2] point out, based on a DXR analysis of the BeSt-study, that the suppression of inflammation with an effective treatment strategy is essential for the prediction of hand bone loss as measured by DXR and erosive joint destruction. An earlier randomized-controlled trial by Haugeberg et al. [23] evaluated the therapeutic effects of prednisolone on periarticular BMD compared to placebo and highlighted that the anti-inflammatory effect of prednisolone was associated with a reduced bone loss as measured by DXR. In addition, the RA-related periarticular bone loss is influenced by receptor activators of the nuclear κB ligand (RANKL) and osteoprotegerin (OPG) which are mediators for bone resorption and the Wnt-pathway, a key pathway in bone formation [24]. TNFα promote the RANKL production of osteoblasts and activated T cells, resulting in osteoclast recruitment with prolonged activation and survival [25–27]. Inflammatory cytokines (in particular TNFα) trigger the synthesis of Dickkopf 1 which inhibits bone formation and the differentiation of mesenchymal precursors to osteoblasts. In addition, TNFα induces the expression of sclerostin in osteocytes which leads to a further inhibition of bone formation [24]. Therefore, immune-modulated therapy can protect RA-related bone loss and joint destruction.

The inhibition of periarticular demineralisation is associated with clinical remission and ACR70-Response

Hand bone loss in RA patients has been shown to be associated with high inflammatory activity and high disease activity [28]. The DXR technique reflected a significant decline of cortical bone mass (up to − 16.1%) in patients with a DAS28 > 5.1 compared to RA patients with a DAS28 < 3.2 [29]. A longitudinal study over 5 years by Hoff et al. [30] showed that elevated disease activity, as measured by DAS28 (> 5.1), is an independent predictor of cortical hand bone loss using DXR.

This study demonstrated an increased reduction of CRP and DAS28 in patients with clinical remission and ACR70-Response for both certolizumab pegol 200/400 plus MTX groups. For clinical remission and ACR70-Response, a non-significant change of the DXR-BMD was observed, whereas patients without clinical remission and ACR70-Response showed a significant reduction of periarticular bone loss over 52 weeks. Furthermore, the reduction of DXR-BMD was significantly lower in the ACR70-Non-response group for certolizumab pegol plus MTX compared to the placebo plus MTX. Focusing on the modified total Sharp Score, no significant change was revealed for the patients depending on clinical remission as well as on ACR70-Response. A recently published study demonstrated differences between both groups treated with two Disease-Modifying Anti-Rheumatic Drugs using DXR and its bone analysis, but no differences could be documented by detailed scoring of the Sharp Score [31].

Further perspectives

Furthermore, effective therapeutic strategies based on biological treatment need the visualization of structural integrity rather than the inhibition of radiographic progression [32]. DXR has a clear potential to evaluate structural integrity based on a more detailed analysis of the radiographs than the established scoring methods [33]. However, DXR-BMD can be recommended as an outcome measure and may be a valid surrogate marker for structural integrity; periarticular demineralization is still present even if radiographically visible joint damage on X-rays does not show alterations [15]. In addition, metacarpal bone loss as measured by DXR over the initial 3 months of the early RA predicts radiographic joint damage [12]. Measurement of structural integrity in RA is now available using DXR [33], and the detection of minor differences in structural changes when assessing therapeutic strategies is now possible [31].

The limitation of the study is the small number of patients in the placebo plus MTX group which is explained by the fact that the withdrawn patients at week 16 enter the open label group with certolizumab pegol.

In conclusion, the development of digital imaging techniques has promoted the precise quantification of hand BMD calculated by DXR. The clinical use of DXR allows the quantification of therapeutically induced differences in hand BMD in RA patients treated with certolizumab pegol compared to methotrexate. Clinical remission and ACR70-Response are associated with the inhibition of periarticular demineralisation as detected by DXR. The modified Sharp Score was not able to detect differences between patients depending on clinical remission or ACR70-Response. DXR should now be considered as a tool, sensitive enough to assess minor differences archiving in therapies for patients with RA and also allowing a more optimal individualized treatment.

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Author contributions AP designed the study, analyzed the radiographs, performed the statistical analysis, wrote the manuscript, and revised the manuscript. AN performed the BX-measurements and participated on the statistical analysis as well as on the study design. DR analyzed the radiographs, interpreted the radiograph data, and helped to draft the manuscript. CJ performed the statistical analysis and interpreted the data. LR performed the data collection and participated on the statistical analysis. PO edited the manuscript. AM printed the radiographs and evaluated the radiographs. GW interpreted the data and edited the manuscript. JB participated on the study design, read the hand X-ray, and wrote the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval was obtained at each site as described previously [15]. The study protocol including the prespecified analysis of X-rays was registered in clinical trials.gov (trial identifier: NCT00152386). In addition, all examinations were performed in accordance with the rules and regulations of the local Human Research and Ethics Committee of the Friedrich-Schiller-University Jena. The study is a retrospective post hoc analysis of data sets which are considered in the RAPID 1 trial [15]. Based on the regulations of the ethics committee of the Friedrich-Schiller-University Jena, a registration and a separate consent from any patient were not necessary.

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