Automated joint space width quantification of hand and wrist joints: a proof of concept study

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ABSTRACT

Objective. *To compare as proof of concept the sensitivity to change of automated quantification of radiographic wrist and hand joint space width (JSW) with scoring JSW according to the Sharp/van der Heijde scoring method (SHS) in two strategy groups of a treat-to-target and tight-control early rheumatoid arthritis (RA) study.*

Methods. *Digital radiographs were assessed for JSW changes of 134 patients of the 236 patients participating in the second Computer Assisted Management in Early Rheumatoid Arthritis trial, of whom both baseline and year 2 radiographs were available (year 1 radiographs n=125). Of those 134 patients, 70 started with methotrexate and prednisone (MTX+Pred) and 64 with MTX and placebo (MTX+Plac). JSW change over 1 and 2 years of the hands and wrists was assessed, applying both the joint space narrowing (JSN) subscore of the SHS by 2 readers and the automated assessment with the JSW quantification software 'JSQ'. For both methods, progression of JSW change of the hand and wrist was analysed using linear mixed modelling (dependent variable 'JSW', factor 'strategy group', covariate 'follow-up time in years', interaction term 'strategy group*follow-up time'; radiographs of baseline, year 1 and year 2 were used). For each method the standardised mean difference (SMD) for the change in JSW from baseline to year 2 between the treatment strategies was obtained using a non-parametric method.*

Results. *Patient characteristics of the current subpopulation were similar to those of the whole study population. JSN of the hand and wrist according to SHS at 2 years was present in 16 vs. 23% in the MTX+Pred group vs. the MTX+Plac group. The mean yearly progression rates of JSW change of the hands and wrists using JSQ were -0.00mm (95% confidence interval (CI) -0.01; 0.01) for MTX+Pred vs. -0.02mm (95%CI -0.03; -0.01) for MTX+Plac, p=0.045, and using SHS JSN they were 0.19 units (95%CI 0.09; 0.30) vs. 0.30 units (95%CI 0.14; 0.45) for MTX+Pred vs. MTX+Plac, p=0.271. The SMD for the change from baseline to year 2 between the treatment strategies was 0.37 for JSQ and 0.13 for SHS JSN.*

Conclusion. *In this proof of concept study the yearly progression rate of JSW change of hand and wrist joints, according to the automated JSW quantification software package 'JSQ', was higher in the group initiating MTX+Plac than in the group initiating MTX+Pred. A similar trend was seen with the JSN assessment according to the SHS method of the hand and wrist. However, JSN of the hand and wrist according to SHS, the current gold standard to assess radiographic progression, was seen in only about 20%. Therefore, further studies are needed to conclude firmly that JSQ should be incorporated into quantitative scoring of radiographs in RA.*

Introduction

Effect of treatment of early rheumatoid arthritis (RA) has substantially improved during the past decades with the introduction of tight-control and treat-to-target strategies (1-3), and with the advent of biological disease-modifying anti-rheumatic drugs (DMARDs) (4). As a result, radiographic joint damage progression in early RA is much less prominent than in the past. Especially in short duration clinical trials, limited radiographic progression is observed (5, 6). Nevertheless, radiographic joint damage progression is still an important clinical outcome. The current gold standard for assessing it is the Sharp/van der Heijde scoring (SHS) method

(7-9). With this method, erosions and joint space narrowing (JSN) of hands and feet are assessed separately, and combined to a total SHS score. The SHS method has a few drawbacks though. First, SHS scoring is observer dependent. It requires scoring by (ideally two) individual experts. Another drawback is the ordinal, not continuous, scale and generally a highly skewed distribution of scores within a patient cohort (10-12), which make it a suboptimal method for statistical analyses. This may specifically be an issue for JSN scoring, as frequently the distribution of these scores is even more skewed towards 0. A subset of these scores may be falsely scored as 'no JSN' and joint space width (JSW) changes may be detected when using more sensitive methods. To overcome these disadvantages several research groups have been working on the development of computerised or automated methods to detect subtle JSW changes, and have achieved some promising results. For instance, automated JSW quantification has been conducted on finger joints and semi-automated JSW quantification (manual involvement required) has been performed on foot joints and some wrist joints (13-19). (Semi-) automated JSW quantification methods have shown to be more sensitive than the SHS JSN scoring method (19), but they do have limitations. Fully automated methods cannot be performed on radiographs with poor image quality or if the image does not include complete bone structures (the small finger joints or wrist, in particular). Semi-automated methods still require operator's intervention and could be labour intensive. In addition, (semi) automated JSW quantification does not include erosion assessment. We have developed an automated in-house software package 'Joint Space Width Quantification' (JSQ) for radiographic hand JSW quantification, based on our previously proposed methods on finger and wrist joints (20) (manuscript under review). In the current proof of concept study, we primarily compared the sensitivity of the JSQ with the SHS JSN method for detecting JSW changes of hand and wrist joints. This was done in a treat-to-target and tight-control study in early RA, in which after 2 years less progression was found regarding erosion scores of hands and feet according to SHS in the MTX+Pred strategy group, compared to the MTX+Plac strategy group, but no difference between strategy groups was found for JSW (2). This study was not intended to prove superiority of the MTX+Pred strategy regarding JSW as outcome.

Materials and methods

In the Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) II trial, 236 DMARD naïve early RA patients were treated according to a tight control methotrexate-based strategy with addition of daily 10mg prednisone (MTX+Pred; n=117) or placebo (MTX+Plac; n=119), given for 2 years. Radiographs of the hands and feet were obtained at baseline, and at year 1 and year 2. JSW changes were assessed using the SHS JSN method by 2 independent observers. More details of the study have been reported previously (2). For the current substudy, digitally acquired hand radiographs and digitised hand films (hereinafter referred to as digital images) were collected from the 7 participating centres of the CAMERA-II trial and were processed by JSQ (20) (manuscript under review). First, two pre-processing steps were performed: bilateral hand radiographs were split, and non-anatomical objects - such as "L/R" labels, digital imprints, and radiograph frames - were masked out. The outcomes of these two pre-processing steps were checked by an operator and were manually corrected if necessary. Next, JSW was automatically quantified in millimetres (mm), for the proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints, and the trapezium-trapezoides-navicular (TTN), carpo-navicular-lunate (CNL) and radiocarpal joints (RC) joints. The average JSW of PIP, MCP and wrist joints (for the wrist: TTN, CNL and RC) of both left and right hands was computed for each time point. Hand and wrist JSW was computed as the average JSW of all joints and also separately per joint group.

SHS JSN of the hands and wrists are scored on a scale of 0–120 units, and SHS JSN scores of the feet on a scale of 0–48 units (0–168 units in total), where higher scores indicate more damage. In contrast, JSW values of the hands and wrists assessed by JSQ have a much lower range, of 1.1–2.3 mm in our cohort, which represents absolute JSW in mm. Higher values of JSW assessed by JSQ indicate larger absolute JSW.

Ethics

Radiographic images and clinical data were collected for the original CAMERA-II trial. This study was performed according to the declarations of Helsinki and all patients gave written informed consent.

Statistics

Baseline characteristics are shown of both the original CAMERA-II study patient group and the population of this substudy, using descriptive analyses. The primary endpoint of the original study (SHS for erosions) was compared between both strategies for the original study cohort and for the current substudy using Mann-Whitney U- tests.

All other analyses were done only for the population of this substudy.

JSW of the hand and wrist at baseline and at year 2 was graphically depicted for both SHS and JSQ. As JSQ quantifies JSW in mm and the individual joint types of the hand differ in their absolute JSW, we additionally depicted Z-scores $((\text{Observation-Mean}_{\text{baseline}})/\text{standard deviation(SD)}_{\text{baseline}})$ to make the scores of these joint types directly comparable.

The primary outcome was the yearly progression rate of JSW changes of the hand and wrist. The difference between the strategy groups was analysed using linear mixed modelling (LMM). Radiographic data of baseline, year 1 and year 2 were used. 'JSW' was modelled as dependent variable, using 'strategy group' as factor, 'follow-up time in years' as covariate, and the interaction 'strategy group*follow-up time' was included in the model. These analyses were done for both the SHS JSN and the JSQ method, and for the JSQ method, we additionally performed these analyses for each joint type separately (PIP joints, MCP joints and the wrists).

For the SHS JSN method we statistically compared the number of patients who were JSN-free at 2 years between the strategy groups using Fisher's exact test.

For each method the standardised mean difference (SMD) between the treatment strategies was obtained using a non-parametric method, as the SHS data was not normally distributed. First, the correlation r was assessed by dividing the z-statistic based on rank statistics by the square root of the sample size. Next this correlation was converted to the SMD using the formula $\frac{r}{\sqrt{p1p2(1-r^2)}}$ where p1 and p2 are the proportions of patients in the strategy groups (21).

An effect size ≥0.2 was considered as small, ≥0.5 as medium and ≥0.8 as large (22).

Statistical analyses were performed using IBM SPSS Statistics for Windows, v. 21.0. Armonk, NY: IBM Corp.

Results

JSQ assessment

For the current substudy digital hand and wrist images were available of 143 patients. Of 135 patients at least baseline and year 2 images were available. Of 1 patient the digital image file was damaged. This resulted in 134 patients of whom digital images of the hands and wrist were available of at least baseline and year 2 for JSQ analysis. Of these patients 125 patients also had digital hand images of year 1 available. Pre-processing of the images was performed by an operator (MVB) in 4 hours (±100 images/hour). Quantification of the JSW using the JSQ program took one minute on average per single-hand radiograph (central processing unit 2.83 GHz). The latter was done fully automatic without intervention by an operator.

Patient characteristics

Baseline characteristics of the patient group of this JSQ substudy (MTX+Pred: n=70, MTX+Plac: n=64) were similar to those of the patient group of the original study, as is shown in Table I. Also the presence of erosions as well as the median SHS erosion score at 2 years, which was the primary endpoint of the original study, were comparable between the patient group of this JSQ substudy and of the original study.

Table I. Patient characteristics of the original study compared to those of the current substudy.

Baseline variable	ORIGINAL STUDY Treatment strategy (n=236)		SUBSTUDY JSQ Treatment strategy (n=134)	
	MTX+Pred (n=117)	MTX+Plac (n=119)	MTX+Pred (n=70)	MTX+Plac (n=64)
Female sex, n (%)	70 (60)	72 (61)	41 (59)	38 (59)
Rheumatoid factor positive status, n (%)	64 (55)	73 (61)	33 (47)	41 (64)
Mean (SD) age, y	54 (14)	53 (13)	53 (14)	53 (15)
Mean (SD) morning stiffness, min	87 (53)	87 (60)	88 (51)	81 (56)
Mean (SD) VAS for general well-being, mm	58 (22)	56 (22)	59 (21)	56 (24)
Mean (SD) VAS for pain, mm	49 (26)	49 (25)	49 (25)	50 (24)
Mean (SD) tender joint pain	17 (9)	15 (9)	17 (9)	13 (8)
Mean (SD) swollen joint count	15 (9)	14 (8)	15 (8)	13 (8)
Mean (SD) HAQ score	1.0 (0.7)	1.2 (0.6)	1.1 (0.7)	1.1 (0.7)
Mean (SD) DAS28	5.8 (1.3)	5.5 (1.1)	5.8 (1.3)	5.3 (1.1)
Mean (SD) ESR, mm/h	36 (25)	34 (24)	34 (25)	32 (23)
Mean (SD) CRP level, mg/L	31 (35)	24 (27)	30 (32)	22 (22)
Erosions present, n (%)	20 (17)	14 (12)	11 (16)	6 (9)
JSN present, n (%)	25 (21)	21 (18)	11 (16)	9 (14)
Median (IQR, range) total SHS	0 (0-1, 0-53)	0 (0-0, 0-21)	0 (0-0, 0-53)	0 (0-0, 0-15)
Median (IQR, range) SHS for erosions	0 (0-0, 0-35)	0 (0-0, 0-15)	0 (0-0, 0-35)	0 (0-0, 0-15)
Median (IQR, range) SHS for JSN	0 (0-0, 0-18)	0 (0-0, 0-10)	0 (0-0, 0-18)	0 (0-0, 0-6)
Radiography at 2 years				
Erosions present, n (%)	22 (19)	34 (29)	16 (23)	21 (33)
JSN present, n (%)	26 (22)	30 (25)	16 (23)	18 (28)
Median (IQR, range) SHS for erosions*	0 (0-0, 0-50)	0 (0-2, 0-23)$	0 (0-0, 0-50)	0 (0-2, 0-23)#
Median (IQR, range) SHS for JSN	0 (0-2, 0-23)	0 (0-2, 0-51)	0 (0-0, 0-23)	0 (0-2, 0-10)
Median (IQR, range) total SHS	0 (0-3, 0-73)	0 (0-4, 0-67)	0 (0-3, 0-73)	0 (0-4, 0-29)

*Primary endpoint of the original study. $Comparison of difference between MTX+Pred and MTX+Plac in original study: p=0.028 (Mann-Whitney U test). #Comparison of difference between MTX+Pred and MTX+Plac in substudy JSQ: p=0.126 (Mann-Whitney U-test).
MTX+Pred: methotrexate based tight control strategy initiating methotrexate with prednisone; MTX+Plac: methotrexate based tight control strategy initiating methotrexate with placebo; SD: standard deviation; VAS: visual analogue scale; HAQ: Health Assessment Questionnaire; DAS28: disease activity score based on 28 joints; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; IQR: interquartile range; SHS: Sharp/van der Heijde score; JSN: joint space narrowing.

Joint space narrowing of the hand and wrist using SHS between the treatment strategies

First, we graphically depicted the SHS JSN score for individual patients at baseline and at year 2 for each strategy group. In both groups SHS JSN scores were mainly 0 and the data were therefore highly skewed, as can be observed in Figure 1A. Mean (SD) SHS JSN scores of the hand for the MTX+Pred strategy group at baseline, year 1, and year 2 were 0.3 (1.1), 0.6 (1.6), and 0.7 (1.9), respectively. For the MTX+Plac strategy group these scores were 0.4 (1.3), 0.6 (1.7), and 1.0 (2.2), respectively. Median (interquartile range; IQR) SHS JSN scores of the hand were 0 (0–0) for both strategy groups at all time points. We compared the number of patients who were JSN-free (=SHS JSN score of 0) at 2 years between the two treatment strategies. This was done in analogy with the primary endpoint in the original study regarding erosions (erosion-free at 2 years) and because of the limitation of the use of parametric statistical analyses with these highly skewed data. In the MTX+Pred group 84% of the patients was JSN-free at 2 years, compared to 77% in the MTX+Plac group (p=0.28; Fig. 1B). Consequently, 16% vs 23% did demonstrate JSN according to SHS of the hand and wrist at 2 years. We did not find a statistically significant difference between the treatment strategies in the yearly progression rate of JSW changes of the hand and wrist using SHS JSN (p=0.271, linear mixed modelling, Table IIa). As the SHS JSN score has

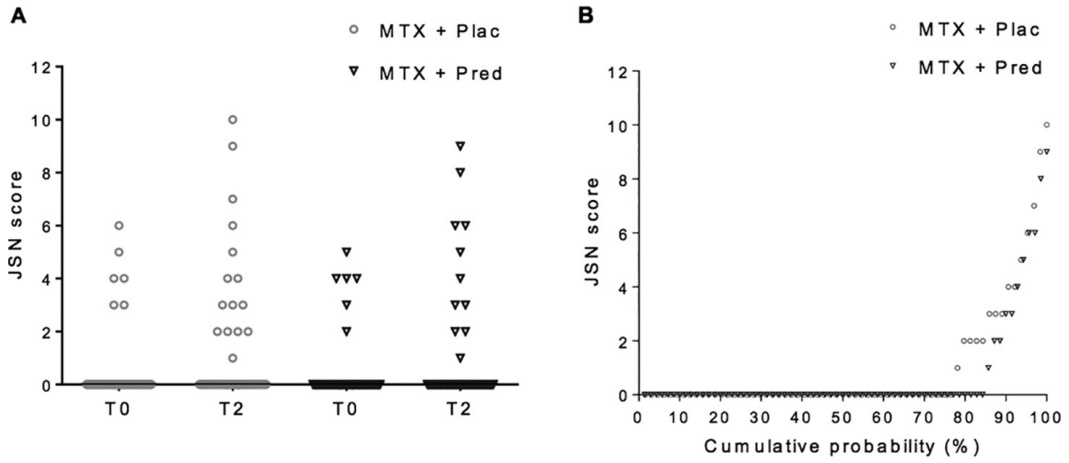

Fig. 1. Sharp/van der Heijde joint space narrowing of the hand at baseline and after 2 years in the CAMERA-II trial.
A. Sharp/van der Heijde (SHS) joint space narrowing (JSN) score distribution at baseline (T0) and year 2 (T2).
B. Cumulative probability (%) of SHS JSN scores of the hand at year 2.

been developed for assessment of both hand and foot, we performed an additional analysis for this combined SHS JSN score. Similarly, we did not find a statistically significant difference between the treatment strategies of the yearly JSN progression rate of hand and foot (p=0.311; Table IIA).

Joint space narrowing of the hand and wrist using JSQ between the treatment strategies

Next, we compared the change in JSW from baseline up to year 2 between the two treatment strategies using JSQ. The JSW data as quantified by JSQ was normally distributed both at baseline and at year 2 (see Fig. 2). The JSW of the hand and wrist assessed using JSQ decreased statistically significantly more per year in the MTX+Plac strategy group than in the MTX+Pred strategy group (p=0.045; Table IIB). Of note, radiographic progression scores were larger for the SHS JSN method (units) than for the JSQ method (millimeters).

For the individual joint types there was no statistically significant difference between the treatment strategy groups. However, the wrist provides most information to the difference between the treatment strategy groups seen in the sum score of all joints.

The SMD for the change from baseline to year 2 between the treatment strategies was 0.37 for JSQ and 0.13 for SHS JSN (d >0.2 and <0.5 indicates small effect size).

We performed sensitivity analyses excluding outliers based on absolute JSW at a time point, both for the full hand and for individual joint types (up to 3%, data not shown). These observations did not change our conclusions.

Table IIA. Mean (95% CI) JSN progression rate per year using SHS.

	MTX+Pred	MTX+Plac	p-value
SHS Hand (units)	0.19 (0.09; 0.30)	0.30 (0.14; 0.45)	0.271
SHS Hand + Foot (units)	0.30 (0.16; 0.44)	0.42 (0.23; 0.61)	0.311

SHS Hand: sum of all hand joints (range in our cohort: 0-7). SHS Hand + Foot: sum of all hand and foot joints (range in our cohort: 0-7).

Table IIB. Mean (95% CI) JSN progression rate of the hand per year using the automated joint space width quantification software 'JSQ'.

	MTX+Pred	MTX+Plac	p-value
JSQ Hand (mm's)	-0.00 (-0.01; 0.01)	-0.02 (-0.03; -0.01)	0.045
JSQ PIP (mm's)	-0.00 (-0.01; 0.01)	-0.01 (-0.01; -0.00)	0.339
JSQ MCP (mm's)	-0.00 (-0.02; 0.01)	-0.02 (-0.03; -0.00)	0.138
JSQ Wrist (mm's)	0.00 (-0.02; 0.03)	-0.03 (-0.05; -0.00)	0.072

JSQ Hand: average of PIP, MCP and wrist joints. mm: millimeter (range in our cohort: -0.19 - 0.30).

Discussion

As far as we know, this is the first report on automated JSW change assessment in a clinical trial in RA including both hand and wrist joints. In this proof of concept study, we quantified JSW of the hand and wrist using the automated JSW quantification software package 'JSQ' and showed that the progression rate of JSW change was lower in the strategy group additionally receiving 10mg prednisone daily than in the strategy group additionally receiving placebo. A similar trend was observed when using the SHS method for JSN progression of the hand and wrist. However, it should be recognised that only a limited fraction of patients demonstrated JSN in this cohort. Thus, although the JSQ method may seem more sensitive to detect progression of JSW change of the hand and wrist than the SHS JSN method of the hand and wrist, no firm conclusions can be drawn and additional studies are needed to confirm our findings.

We were able to detect a difference in JSW change using the JSQ program, even while radiographic progression over the total range was limited. This small difference is not clinically relevant. However, our finding, although preliminary, is a first indication that the JSQ method might be a sensitive method for JSW change assessment of the hand in early RA clinical trials in which limited radiographic progression is expected.

If we compare the JSW change progression rates in the current study with yearly progression rates of between -0.03

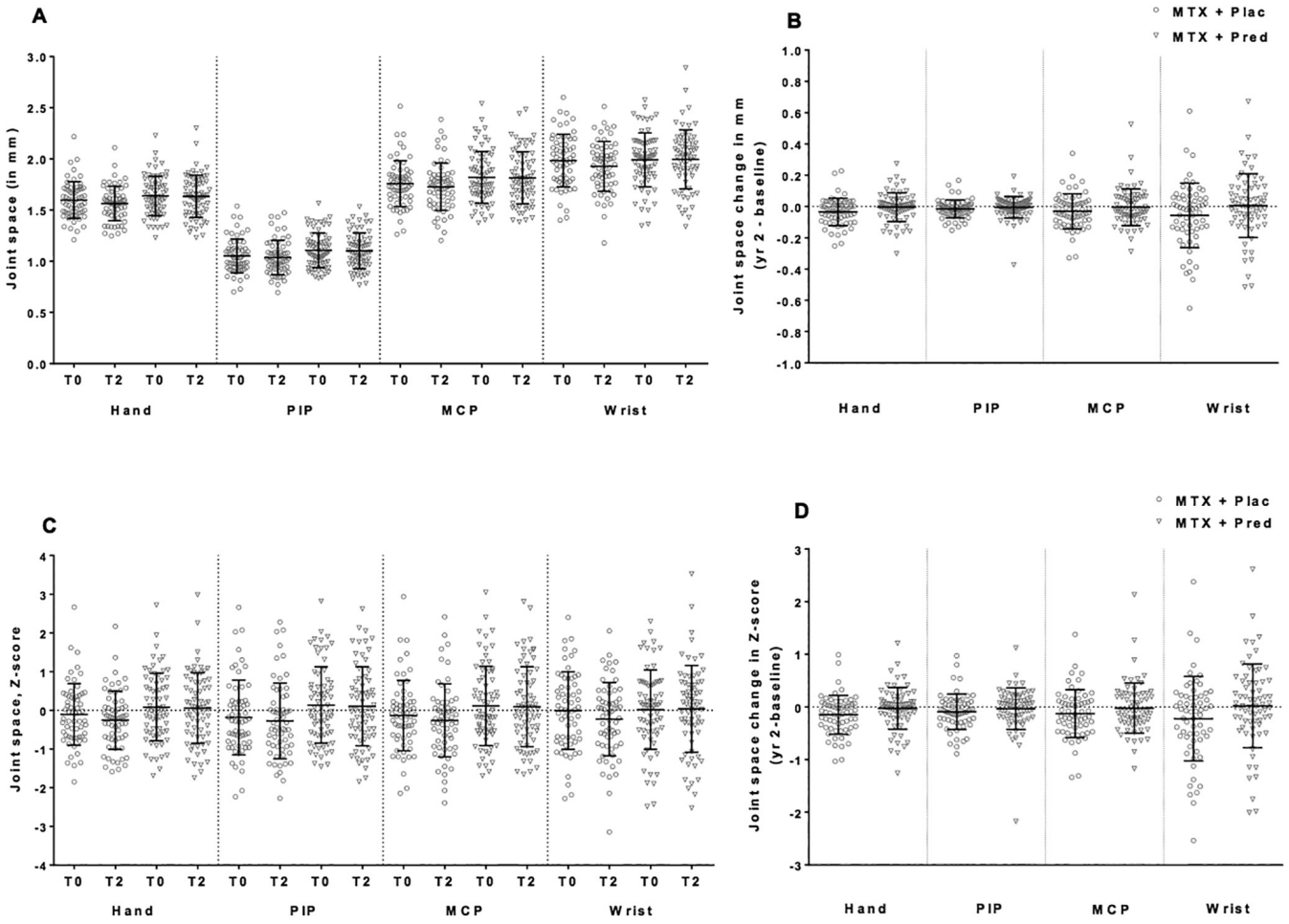

Fig. 2. Joint space width (change) quantified by JSQ of the hand and wrist, and of individual joint types.
A. JSW at baseline (T0) and year 2 (T2). B. JSW change from baseline to year 2. C. JSW Z-score at baseline (T0) and year 2 (T2). D. JSW Z-score change from baseline to year 2. Hand: average of proximal interphalangeal (PIP), metacarpophalangeal (MCP) and wrist joints (wrist: average of trapezium-trapezoides-navicular, carpo-navicular-lunate and radiocarpal joints). Z-scores are shown to make the scores of different joint types directly comparable.

up to -0.10 shown previously by other groups using (semi-) automated assessment methods (13, 15, 23), the progression rates we observed were relatively low. This is in line with the lower SHS JSN progression rate observed in our study compared to these studies.

As can be appreciated from our study, the wrist joints were the main contributors to the observed JSW changes of the hand joints. It could thus be argued that for JSQ assessment PIP, and perhaps even MCP, joints can be left out of the assessment, although including these joint types may lead to higher sensitivity of the method.

Potentially, automated scoring of JSW changes using JSQ is time-efficient compared to SHS JSN scoring. For the JSQ method some time is invested by an operator for pre-processing of the images after which JSW quantification is done fully automated without intervention by an operator. The latter could, for example, even be performed overnight. SHS JSN requires ideally two experts individually scoring the radiographs, which costs time. However, the additional time burden of scoring JSN when already scoring erosions according to the SHS method may be limited. As we did not collect data on the time that was invested to perform SHS JSN scoring of the hand specifically we cannot draw any conclusions on this issue. In future studies, this time expenditure issue should be further investigated.

Our study has several limitations. First, we performed this study in a subgroup of the original CAMERA-II study group because of limited availability of series of radiographs. However, we have shown that patient and disease characteristics, including radiography, of this subgroup were similar to those of the whole study population. We therefore have no indication that our results would have been different if the total patient group would have been investigated. Second, we did not include the feet and have investigated JSN progression of the hand and wrist only. JSW quantification of the foot joints has not yet been developed for JSQ. Interestingly, the JSQ method of the hand and wrist appeared more sensitive than the SHS JSN method of both hand and wrist, and foot. Because of the similar bone structure of toes and fingers, probably a similar assessment method can be applied to the joints of the feet. This should be investigated. Third, we have only performed JSW change assessment in one study; results should be replicated in other studies. Moreover, our observation has been

done in an early RA study population. It may be challenging to perform JSQ assessment in advanced disease. Our observations therefore cannot be generalised to trials of more advanced RA populations. Fourth, we ultimately aim for automated or computerised quantification of joint erosions as well, for the same reasoning as for JSW change: automated and computerised assessments could be more sensitive to detect change and could be highly time-efficient. Finally, JSN was seen in only 20% of patients at all, and was minimal in many of these patients, so robust conclusions are not possible.

Nonetheless, only small differences in radiographic progression between treatment groups are to be expected in future clinical trials because of advances in treatments. More sensitive methods than the traditional available methods for the detection of all aspects of radiographic progression are therefore needed. To date, so far no computerised method for accurate detection of joint erosions based on x-rays has been developed (24, 25). This is primarily because of the three dimensional nature of erosions and the two dimensional image of x-rays, which renders it difficult to detect the presence and quantify the volume of joint erosions accurately and reliably.

In conclusion, in this proof of concept study we found a difference between the treatment strategy groups in the yearly progression rate of JSW change of hand and wrist using the JSQ method, and a similar trend for the SHS JSN method of the hand and wrist. Only a small fraction of patients demonstrated JSN of the hand and wrist according to SHS, the current gold standard to assess radiographic progression, and no firm conclusion can be drawn. However, the current data suggests desirability of further exploration of the combined assessment of erosions by the SHS method with the measurement of JSW by the JSQ method to attempt to improve quantitative radiographic scoring toward better patient outcomes.

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