Cervical spine deformity in patients with rheumatoid arthritis: from prevention to prediction

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CHAPTER 3

The association between disease activity score and rheumatoid arthritis-associated cervical deformity: radiological evaluation of the BeSt Trial.

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Abstract

Objective: To evaluate the association of Disease Activity Score (DAS) in RA patients with cervical spine deformity during 10-year optimal treatment of systemic disease.

Methods: Radiological data evaluation of 10-year FU data of the BeSt Trial. In 272 RA patients AtlantoAxial Subluxation (AAS), presence of vertical translocation (VT), and Subaxial Subluxation (SAS) were evaluated. Association with DAS values, self-assessed health (HAQ) and erosions of hands and feet (SHS) was studied.

Results: After 10 years of FU, AAS (>2 mm neutral position) was observed in 62 patients (23%), AAS (≥3mm in flexion) in 26%, AAS (≥ 5 mm in flexion) in 8%, VT was not occurring, and SAS was present in 60 patients (22%). 135 (50%) of patients were in remission (DAS<1.6) at 10 years FU. No association could be established between AAS and DAS. Patients with cervical spine deformity (AAS > 2 mm and/or SAS) at 10 years had a higher HAQ score at 10 years than patients without cervical spine deformity (HAQ of 0.65 and 0.51 respectively; p=0.04; 95% CI: -0.29 to -0.00).

Conclusion: It was observed that even though 50% of patients were in remission after 10 years and the BeSt Trial was designed to optimize treatment, 40% of patients developed at least mild RA-associated cervical spine deformity, and 8% significant AAS. This indicates that even in this era of DMARDs and biologicals, cervical deformity is prevalent among patients with RA and should not be neglected in patients' treatment plans and information.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease, which affects 1% of the population.[1] Hands and feet are most commonly involved in RA, but also the cervical spine can be affected.

The cervical vertebrae are stabilized by intervertebral discs, joints, and an intricate network of ligaments. Rheumatoid Arthritis can affect these ligaments and cause laxity, which in turn can lead to subluxation of vertebral bodies and instability. Characteristically, this leads to subluxation of the C1-C2 vertebra causing atlantoaxial subluxation (AAS), which may be accompanied by pain at the back of the head caused by compression of the major occipital nerve. A severe form of subluxation of the atlanto axial joint, which is usually accompanied by erosion of the odontoid peg is referred to as 'vertical translocation'.[2] Apart from upper cervical deformity, subaxial subluxations (SAS) are not uncommon phenomenon in the cervical spine of rheumatoid patients. Subsequent compression of the spinal cord and medulla oblongata can cause severe neurological deficits and even sudden death. It is generally believed that once neurological deficits occur, progression is inevitable, although rapidity of progression is highly variable. [1]

In previous years, the cervical spine was claimed to often be involved in the disease (17-86% of RA patients)[3], but with current RA medical treatment policies, involvement of the cervical spine seems to have declined. In data from before the use of DMARDs and biologicals, incidences of cervical spine deformity such as 61% of 113 patients who received screening for joint replacement surgery were reported. Remarkably, of these patients with deformity, 50% had no signs or symptoms at the time of screening.[4] Data on cervical spine involvement in the modern era, are however scarce and clinical implications are unclear. We conducted a systematic review of literature, describing the association of cervical deformity and systemic disease activity in RA patients: AAS was reported to be present in 7-42% of patients, SAS was present in 4-20% and VT was present in 1-43% of patients.[5] Reported associations between DAS and cervical spine deformity varied largely. It is however debatable whether that is due to absence of an association or to a limited number of data available in present literature. Differences in definitions of AAS, SAS and VT, the limited number of articles describing the association, and varying FU times limit the ability to draw conclusions.

Disease Modifying Anti-Rheumatic Drugs (DMARDs) and biological agents are currently widely used in treating Rheumatoid Arthritis.[6] Several types of DMARDs and Biologicals are prescribed in different stages of disease in order to lower systemic disease activity. Systemic disease activity is quantified by means of Disease Activity Score (DAS).

In a previous study, we demonstrated that in patients with early RA, initial combination therapy of multiple DMARDs and/or biological agents results in faster decline in disease activity, represented by a lower DAS value (BeSt trial). [7]Targeted treatment aiming at low disease activity appeared to result in prevention of radiographic and clinical deterioration of the most commonly affected peripheral joints (hand and knee). Moreover, survival was demonstrated to normalize.[7] However, the relation between DAS and cervical spine deformity was not evaluated yet.

Patients included in the BeSt had X-rays of the cervical spine made at 5 and 10 years after inclusion. This current study evaluates prevalence and progression of cervical deformity (on cervical X rays, both in neutral and in flexion) in patients with early onset RA subjected to optimized medical treatment. Correlations between values of DAS and/or sustained remission and cervical deformity were studied in order to gain insight into the association of cervical deformity and disease activity in RA.

Methods and materials

In our department, the BeSt (Dr. C.F. Allaart) study was performed. [7] The BeSt study is a single-blinded multicenter randomized controlled trial, designed to compare four treatment strategies. In strategy 1, patients received sequential monotherapy; strategy 2 used step-up combination therapy (both starting with methotrexate monotherapy); patients in strategy 3 received initial combination therapy with methotrexate, sulfasalazine and prednisone; strategy 4 consisted of initial combination therapy with methotrexate and infliximab. Patients were recruited in 18 non-university and 2 university hospitals in The Netherlands between 2000 and 2002. After 2 years of using these treatment strategies, treatment strategy became unrestricted in order to keep systemic DAS values of all individual patients as low as possible.

In the Trial, patients were studied that were suffering from early onset RA, in which the treatment policy was to keep systemic DAS values at a level as low as possible. [7] Over 10 years, treatment response was measured every three months using DAS. Treatment was intensified (medication was changed or dosage was increased), at each study visit if DAS was greater than 2.4. In case of a continuing good response (DAS ≤2.4 for ≥6 months), dosage was tapered to a maintenance dose. If DAS remained <1.6 for ≥6 months, medication was stopped. After 10 years, 62% of patients completed the full study period. Of these patients, 53% was in remission (DAS <1.6 at 10 years) and 14% was in sustained remission (DA<1.6 for ≥6 months). [7]

Subjects

508 patients with RA according to the revised criteria of the American Rheumatism Association of less than 2 years duration, were included in the BeSt Trial, of whom 331 completed 10 years of follow-up. [7] Patients were randomized between 2000 and 2002. Lateral X-rays of the cervical spine, systemic DAS values and medication use of the patients were collected during a period of 10 years FU, at 5- and 10-years FU. Inclusion and exclusion criteria are stated in table 1. (Table 1)

Data have been saved in the BeSt database in a coded manner with written informed consent of the patients.

TABLE 1: In- and exclusion criteria

Inclusion criteria	
In order to be eligible to participate in this study, a subject must meet all of the following criteria:	
–	Availability of lateral cervical X-ray at 5 years and 10 years of follow-up
–	18 years or older
–	Diagnosed with RA; They have active disease with 6 or more swollen joints and 6 or more painful joints and at least one of the following:
	1. Westergren erythrocyte sedimentation rate (ESR) of at least 28 mm/hour.
	2. Patient's global assessment of general well-being of at least 20 mm measured on a 100 mm horizontal visual analogue scale (VAS).
–	Informed consent
A potential subject that meets any of the following criteria will be excluded from participation in this study:	
–	Previous therapy with DMARDs except for hydroxychloroquine
–	Pregnancy or wish to become pregnant during the study, or childbearing potential without adequate contraception
–	Concomitant treatment with another experimental drug
–	History or presence of malignancy within the last five years
–	Bone marrow hypoplasia

TABLE 1: *(Continued)*

Exclusion criteria
– Elevated hepatic enzyme levels (ASAT, ALAT > 3 times normal value)
– Serum creatinine level >150 umol/L or estimated creatinine clearance of <75 mL/ min
– Diabetes mellitus
– Alcohol or drug abuse

Study design

This research is observational. The study has an explorative design and therefore sample size calculation is not applicable. The protocol of the BeSt Trial was approved by the Leiden Medical Ethics Committee ("Commissie Medische Ethiek Leiden University Medical Center," decision letter P08.011). Written informed consent was obtained from all patients. (Netherlands Trial Register Number: NTR262.)

Assessment of cervical spine deformity

Radiological cervical deformity parameters (AAS, SAS and VT) are evaluated on lateral X-rays that were performed at 5 years and 10 years of follow-up. (figure 1) Evaluation is assessed by two researchers (ABV and CVL), both blinded for DAS values. Agreement was reached in close cooperation.

For deformity scores (AAS > 2mm and SAS combined): if an X ray was missing at 10 years FU and AAS, VT or SAS was present at 5 years, it was scored to be also present at 10 years FU. For the AAS scores (either more than or equal to 3 mm or more than or equal to 5 mm in flexed position), only the 10-year flexion X rays were evaluated, unless AAS of more than or equal to 3 mm was already present at 5 years FU.

It was evaluated in how many patients the atlantoaxial distance exceeded or was equal to a 3 mm slip in flexion, but not in neutral position.[8] The percentage of patients in which there was a slip of 2mm of more was calculated.

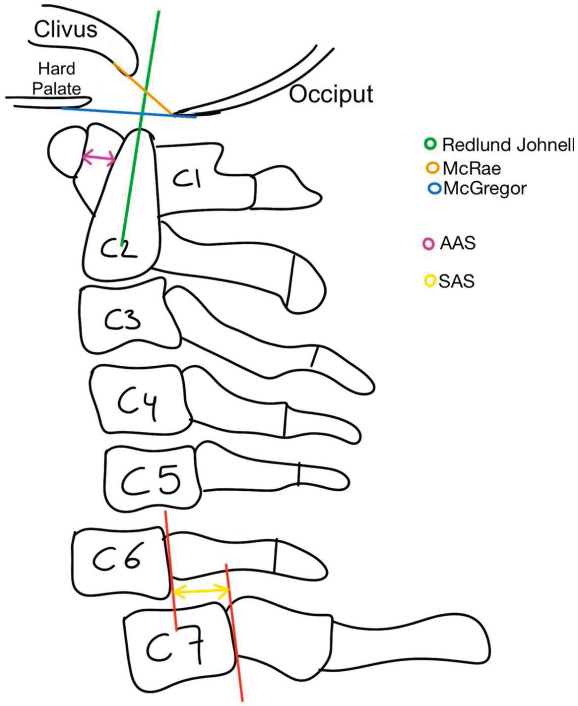

FIGURE 1: Cervical deformity
THIS FIGURE shows the definition of cervical spine deformity used in this study.

AtlantoAxial Subluxation (AAS): The AtlantoAxial interval is measured as the distance between the anterior border of the odontoid peg (C2) and the posterior border of the anterior arch of the C1 vertebra in neutral and in flexion position. (Figure 1). If this interval in neutral position was larger than 2 mm, AAS was scored to be present. If this interval in flexed position was 3 mm or larger, this was scored as AAS in flexion, and if this interval was equal to or exceeded the 5 mm distance in flexion this was scored as 'significant AAS'.
Vertical translocation (VT): Vertical translocation is determined by measuring the distance with which the line of Redlund Johnell (which is a vertical line in the dens) crossed the line of McGregor (line between the anterior aspect of the occiput and the point of the clivus) and/or the line of McCrae (line placed between the anterior aspect of the occiput and posterior hard palate). Crossing the line in either method was scored as VT being present (Figure 1).
Subaxial Subluxation (SAS): There is evidence of subaxial subluxation if the posterior sides of the bodies of two consecutive vertebra have shifted more than 2 millimeters. The subaxial subluxation will be evaluated on all cervical levels (C23, C34, C45, C56 and C67).

Assessment of DAS

DAS is based on the combination of the number of swollen joints, the number of tender joints (severity determined using the Ritchie articular index[9], erythrocyte sedimentation rate, and patient's assessment of global health on a visual analogue scale (range 0 to 100 mm). DAS44 is based on a swollen joint count in 44 joints with a range of 0.23-9.87. [10]

During a period of 10 years, DAS44 was measured every 3 months, and thus 41 times in total. The DAS44 endpoint was assessed using the DAS44 value at 10 years, where a value of <1.6 was considered remission. Sustained remission was reached when DAS44 < 1.6 for ≥6 months. Remission is an important endpoint in this study, as it indicates the possibility to stop treatment.

Additionally, the mean DAS44 during the 10 years study period was calculated, as well as the mean DAS44 between three and five years. This time-period was chosen, as it starts at the end of the randomization period for treatment strategy (ends after 2 years), it is sufficiently long to give an indication of the severity of systemic disease during the first period of follow-up, and it allows for 5-year FU until the 10-year X-ray.

Sustained remission at 10 years FU, mean DAS44 during 10 years and mean DAS44 during year three until five were separately compared with cervical spine deformity to assess the correlation between DAS44 and cervical spine deformity.

Health Assessment Questionnaire (HAQ)

Results of the HAQ give an indication on patients' self-reported disability and is scored from 0 (best) to 3 (worst). [11] Mean HAQ at baseline and at 10 years was assessed. Also, mean HAQ during year 1 until 10 was calculated and compared to cervical spine deformity.

Sharp- Van der Heijde Score (SHS)

SHS was used to assess severity of hand and feet erosions and is scored between 0 (best) and 448 (worst). SHS at baseline was calculated. Also, average change between 5 and 10 years of follow-up was calculated. [12]

Statistical Analysis

For each of the radiological parameters an incidence in the total group of patients was calculated at 5- and 10-years FU. The number of patients with cervical spine deformity (AAS or SAS) was calculated in which AAS was defined as a distance exceeding 2 mm. For the calculations on AAS the flexion X rays were evaluated and the number of patients with AAS in flexion and 'significant AAS' were calculated.

The DAS44 value was categorized, as there is a known interpretation of the DAS44 scale for patients with and without remission. The cut-off point for remission was a

DAS44 lower than 1.6 for six consecutive months. This dichotomic categorization will be used in the analysis to correlate systemic disease activity to cervical spine deformity. After multiple imputation of the DAS44, DAS44 values of patients at baseline, 5 and 10 years were correlated exploratively to the radiological parameters of cervical deformity. The imputation model included terms for treatment strategy, age, gender, ACPA positive or negative, Rheumatoid Factor positive or negative, HAQ and DAS44 values. 20 data sets were imputed using MATLAB 2019b, then the iterations were combined to form the DAS44 data that was used to explore correlations.

Baseline data were expressed as mean ±SD or number (%) and analyzed by descriptive statistics using independent T test or Wilcoxon Rank-sum test for continuous data and Chi square test or Fisher's Exact test for categorical data.

Correlations were tested using independent T test for continuous data and Chi square test for categorical data.

Binomial logistic regression was performed in order to study the correlation between cervical deformity, AAS in flexion, significant AAS and remission at 10 years, sustained remission at 10 years, mean DAS44 overall, mean DAS44 between 3 and 5 years, Delta SHS between 5 and 10 years and HAQ at 10 years. Age, sex, RF-status, ACPA-status and treatment strategy were also considered in the logistic regression. Binomial logistic regression on AAS ≥5mm at 10 years was not performed, as the number of cases was too low. Therefore, correlations were tested using independent T test for continuous data and Chi square test for categorical data.

Results

331 of 508 patients completed 10 years of follow-up. 20 patients were excluded as they were missing both X-ray images at 5 and 10 years of follow-up and 39 patients were excluded because they were missing the X-ray at 10 years and had no signs of cervical deformity at 5 years FU. Eventually 272 patients had data of both cervical radiographs and DAS44 values. (Figure 2) In the group of patients with cervical spine deformity, mean age at baseline was 55.2 years (±12.7), 65 (60%) of the 108 patients was female, 74 (69%) of patients were RF positive and 73 (68%) patients were ACPA positive. 117 (71%) of 164 patients without cervical spine deformity after 10 years was female, mean

age at baseline was 50.6 (±11.2) years, 112 (68%) patients were RF positive and 104 (63%) patients were ACPA positive. (Table 2)

Of 132 patients X rays in flexion were available. However, of only 102 patients a reliable conclusion on AAS in flexion could be drawn, since of 30 patients only a 5-year FU flexion X-ray was available, not demonstrating AAS, while the 10-year X-ray was missing.

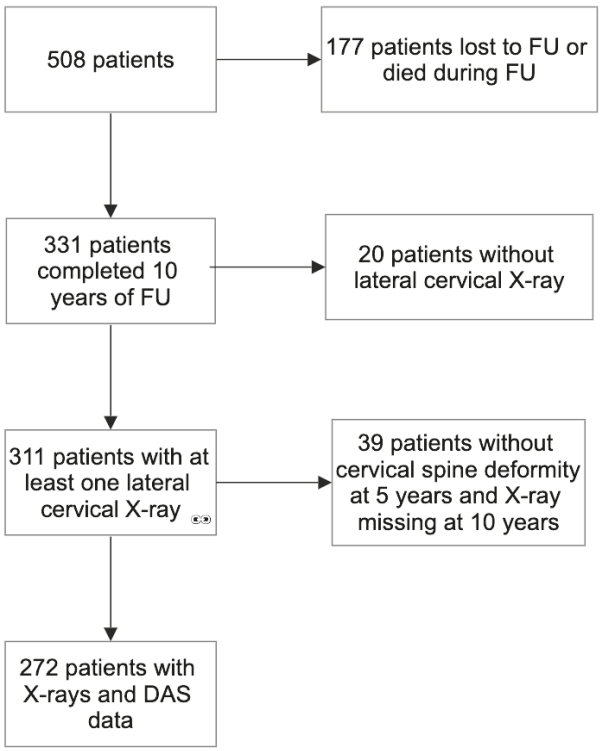

FIGURE 2: Flowchart of patient inclusion
THIS FIGURE shows the path of patient inclusion in this study.

TABLE 2 Baseline characteristics

Variable	Cervical spine deformity at 10 years FU (n=108)	No cervical spine deformity at 10 years FU (n=164)	p-value (95% Confidence Interval)
Univariate			
Mean age at baseline (SD)	55.2 (±12.7)	50.6 (±11.2)	0.002 (-7.6; -1.7)
Female, n (%)	65 (60%)	117 (71%)	0.06
Mean DAS between 3 and 5 years of FU (SD)	1.91 (±0.56)	1.82 (±0.53)	0.186 (-0.22; 0.04)
Mean DAS at baseline (SD)	4.39 (±0.89)	4.33 (±0.86)	0.63 (-0.26; 0.16)
Mean HAQ score at baseline (SD)	1.22 (±0.66)	1.36 (±0.63)	0.08 (-0.02; 0.05)
Mean SHS at baseline (SD)	4.44 (±7.05)	4.26 (±7.23)	0.84 (-1.92; 1.57)
RF-positive, n (%)	74 (69%)	112 (68%)	0.97
ACPA-positive, n (%)	73 (68%)	104 (63%)	0.48

Disease activity

At baseline, mean DAS44 was 4.39 (±0.89) in the group of patients with cervical spine deformity and 4.33 (±0.86) in the group of patients without cervical spine deformity (p = 0.63). After 10 years of follow-up, 135 (50%) of patients were in remission (DAS<1.6). 84 (31%) patients reached sustained remission at 10 years FU (DAS<1.6 for 6 months).

Mean DAS was calculated during year 3 till 5 (measuring point 9-20 of 41) and was 1.76. Mean DAS over the 10-year period (year 0-10) was 1.86.

Radiological parameters

After 10 years, 108 patients had cervical spine deformity: 60 patients had subaxial subluxation (SAS) and 62 patients had Atlantoaxial subluxation (AAS) of more than 2 mm in neutral position. No patients had VT.

Correlating cervical spine deformity and DAS44

The groups of patients with and without cervical spine deformity did not differ significantly in terms of mean DAS44 from year three till five (mean DAS 3-5 years 1.79 and 1.73 respectively; p=0.45; 95% CI: -0.20 to 0.09) or mean DAS during 10 years (1.91 and 1.82 respectively; p=0.19; 95% CI: -0.22 to 0.04). (Table 3)

No significant correlation could be demonstrated between remission (p = 0.88) or sustained remission (p=0.09) at 10 years of FU and the presence of cervical spine deformity (either AAS or SAS). (Table 3)

Hand and feet erosions

At baseline, mean SHS of patients with cervical spine deformity was 4.44 (±7.05) being comparable to mean SHS of patients without cervical deformity after 10 years FU (4.26 ±7.23). Delta SHS, which indicated the increase of SHS, between year 5 and 10 did not differ between patients with (5.3) and without cervical spine damage at 10 years of FU (4.0; p=0.40; 95%CI: -4.49 to 1.79). (Table 3)

HAQ

At baseline, patients with cervical deformity at 10 years had an average HAQ of 1.22 (±0.66). Patients without cervical spine deformity had a mean HAQ of 1.36 (±0.63) at baseline. Patients with cervical spine deformity at 10 years had a higher HAQ score (worse result) at 10 years (0.65 on a scale from 0-3) than patients without cervical spine deformity (0.51; p=0.04; 95% CI: -0.29 to -0.00). (Table 3)

Mean HAQ score (year 1 – 10) did not differ between patients with and without cervical deformity (0.60 and 0.55 respectively; p=0.35; 95%CI: -0.15 to 0.05). (Table 3)

A binomial logistic regression was performed to ascertain the effect of average HAQ at 10 years on the prevalence of cervical spine deformity at 10 years (table 4). It was observed that there was no significant difference in HAQ at 10 years between patients with and without cervical deformity at 10 years FU (p=0.115; 95% CI: 0.892 to 2.884).

TABLE 3: comparing cervical spine deformity and no cervical spine deformity at 10 years FU.

	Cervical spine deformity at 10 years FU (n=108)	**No cervical spine deformity at 10 years FU (n=164)**	**p-value**	**Total (n=272)**
Univariate				
Remission at 10 years FU (%)	53 (49%)	82 (50%)	0.88	135 (50%)
Sustained remission at 10 years FU (%)	27 (25%)	57 (35%)	0.09	84 (31%)
Mean DAS overall (year 0-10)	1.91 (±0.56)	1.82 (±0.53)	0.19	1.86 (±0.55)
Mean DAS between 3 and 5 years of FU (SD)	1.79 (±0.62)	1.73 (±0.57)	0.45	1.76 (±0.59)
Delta SHS between year 5 and 10 (SD)	5.33 (±13.67)	4.0 (±9.48)	0.40	4.45 (±11.09)
HAQ at 10 years of FU (SD)	0.65	0.50	0.04	0.56 (±0.54)
Mean HAQ year 1 to 10 (SD)	0.60	0.55	0.35	0.57 (±0.42)

TABLE 4: Binomial logistic regression (for cervical deformity at 10 years FU: SAS > 2mm and/or neutral AAS > 2mm)

Variable	B	SE	Wald	df	P	Odds Ratio	95% Confidence Interval for OR	
							Lower	Upper
Remission at 10 years FU	-0.532	0.435	1.494	1	0.222	0.587	0.250	1.378
Sustained remission at 10 years FU	0.437	0.385	1.290	1	0.256	1.548	0.728	3.293
Mean DAS between 3 and 5 years of FU	-0.148	0.308	0.231	1	0.631	0.862	0.471	1.578
Delta SHS between year 5 and 10	0.009	0.013	0.531	1	0.466	1.009	0.984	1.035
HAQ at 10 years of FU	0.472	0.299	2.489	1	0.115	1.604	0.892	2.884

Correlating AAS and DAS44

For the correlations of AAS and DAS, the X rays in flexion were evaluated. In 24 of 132 patients for which an X ray in flexion was available (either at 5 or at 10 years FU), AAS in flexion was 3 mm or more, while it was less than 3 mm in neutral position. In 26 of 102 patients that had a FU of 10 years, AAS was 3 mm or more (26%). In 8 of 102 patients AAS was 5 mm or more (8%). In 12 patients the slip in AAS exceeded 2 mm from neutral to flexed position of the neck (10%).

26 patients had an atlantoaxial interval of 3 mm or more in flexed position. No significant correlation could be demonstrated between remission (p = 0.072) or sustained remission (p= 0.088) at 10 years of FU and the presence of AAS in flexion. (Table 5)

The groups of patients with and without AAS in flexion did not differ significantly in terms of mean DAS44 from year three till five (mean DAS 3-5 years 1.76 and 1.86 respectively; p=0.46; 95% CI: -0.16 to 0.35) or mean DAS during 10 years (1.91 and 1.90 respectively; p= 0.94; 95% CI: -0.25 to 0.23).

8 patients had an atlantoaxial interval of 5 mm or more in flexed position. No significant correlation could be demonstrated between remission (p = 0.48) or sustained remission (p= 0.33) at 10 years of FU and the presence of significant AAS. (Table 6)

The groups of patients with and without significant AAS did not differ significantly in terms of mean DAS44 from year three till five (mean DAS 3-5 years 1.89 and 1.84 respectively; p=0.82; 95% CI: -0.47 to 0.37) or mean DAS during 10 years (2.14 and 1.89 respectively; p=0.20; 95% CI: -0.64 to 0.14).

TABLE 5: Binomial logistic regression (for AAS at 10 years FU more than or equal to 3mm)

Variable	**B**	**SE**	Wald	df	P	Odds Ratio	95% Confidence Interval for OR	
							Lower	Upper
Remission at 10 years FU	1.574	0.875	3.240	1	0.072	4.827	0.869	26.799
Sustained remission at 10 years FU	-1.399	0.819	2.918	1	0.088	0.247	0.050	1.229
Mean DAS between 3 and 5 years of FU	-0.022	0.512	0.002	1	0.966	0.979	0.359	2.670
Delta SHS between year 5 and 10	0.016	0.018	0.867	1	0.352	1.016	0.982	1.052
HAQ at 10 years of FU	0.086	0.445	0.038	1	0.846	1.090	0.456	2.607

TABLE 6: comparing AAS in flexion or neutral of more than/equal to 5mm at 10 years FU.

	AAS ≥5mm 10 years FU (n=8)	**No AAS ≥5mm 10 years FU (n=99)**	**p-value**
Univariate			
Remission at 10 years FU (%)	3 (38%)	50 (51%)	0.48
Sustained remission at 10 years FU (%)	1 (13%)	28 (28%)	0.33
Mean DAS overall (year 0-10) (SD)	2.14 (±0.43)	1.89 (±0.54)	0.20
Mean DAS between 3 and 5 years of FU (SD)	1.89 (±0.52)	1.84 (±0.58)	0.82
Delta SHS between year 5 and 10 (SD)	6.33 (±5.30)	4.2 (±10.87)	0.74
HAQ at 10 years of FU (SD)	0.88 (±0.84)	0.56 (±0.55)	0.23
Mean HAQ year 1 to 10 (SD)	1.02 (±0.63)	0.54 (±0.40)	0.067

Age was compared between patients with and without significant AAS: mean age in group without significant AAS (mean age 53 years) and with significant AAS (mean age 51 years): p=0.55 with 95% CI: -3.249 to 6.120.

Discussion

In the BeSt Trial, patients were followed for 10 years in order to evaluate management of early rheumatoid arthritis while striving at a low DAS using 4 different treatment methods. This study evaluated the effect of adequate treatment of systemic RA disease, demonstrated by lowering DAS values, on the occurrence of cervical spine deformity. It was observed that even though 50% of patients were in remission after 10 years, with 30% of patients even reaching sustained remission, 40% of patients developed RA-associated cervical spine deformity, 26% developed AAS and 8% even demonstrated a significant atlantoaxial distance in flexion. In 10% of patients a slip of more than 2 mm in the atlantoaxial distance was observed. This is in big contrast with the observed trend in contemporary orthopedic and neurosurgical practice, in which a decrease in incidence of rheumatoid arthritis related cervical deformities is observed.

It is remarkable that patients with well-managed DAS still developed RA-associated cervical deformity during the 10 years of follow-up. The study set up was not aimed at reporting cervical pain or disability, it is thus not possible to correlate the radiological outcome data to clinical data specifically evaluating those issues. Only a general functional capacity outcome scale was evaluated, the HAQ score. This score measures self-reported disability during daily activities. And indeed, it was reported that the patients with cervical deformity had a worse general functional capacity. Regarding the difference in HAQ at 10 years (table 3), the clinical relevance seems absent, though. Also, this difference is not observed when considered in a logistic regression model. It is however feasible that this can be attributed to a higher SHS score, indicating more deformity of the hand and foot joints. In future research, specific patient reported outcome measures should be included aiming at neck pain and disability.

The definitions we applied to evaluated AAS, SAS and VT are commonly used, but several variances are possible. Since there is much discussion on the most appropriate definition for AAS, several methods were applied to evaluate AAS. The distance between atlas and axis of 5 mm in flexion is the most convincing parameter that a pathological relation exists. We consider it the most striking result that in this group of patients, in which their treating physicians monitored the disease activity carefully and treated it optimally, still 8% of patients developed a significant AAS. Moreover, it is remarkable that there was no trend of any kind that in this group of patients the disease activity was poorly controlled. The definition of VT we used could have been optimized. Kauppi et al introduced a more precise method to quantify VT, which would have been applied by us if we would have encountered any patient with the suspicion of VT. This was however not the case. [2]

There are several limitations to this study. First, it would have been optimal if we would have had X rays in flexion, extension and neutral position of all patients at 5- and 10-years FU. We furthermore would have wanted these X rays at baseline. They were however not available. We do think however, that the data we could extract from the available radiographs are noteworthy as these deformities usually take years to develop and are therefore not expected at baseline in a population of early-onset RA patients with a disease duration of less than two years[13]

Another limitation of the study is that the X rays are in some cases challenging to interpret and quantify. The X rays were made in the work flow of a study aiming at

clinical parameters and the evaluations were not done instantly. In daily practice, if an X ray of the cervical spine in RA patients is performed, it is evaluated carefully and, if difficult to interpret, made again. That would have yielded more qualitative X rays in some cases. Furthermore, the 2 mm listhesis of the subaxial cervical spine could have been caused by general degeneration, and does not necessarily originate from RA. However, with the current data we cannot discern this.

Finally, clinical parameters aiming at evaluation of the condition of the neck and neurological symptoms would have been very informative. Rheumatoid arthritis affects the joints to such an extent, that clinical symptoms may easily conceal neurological symptoms, which may in turn be triggered by cervical spine problems. Future studies will include parameters evaluating neck disability and neurological symptoms. However, the current results give rise to the suggestion that it is worthy to perform future research in this direction.

Conclusion

In conclusion, this study indicates that even in this era of DMARDs and biologicals, cervical deformity is prevalent among patients with RA and should be closely monitored. In considering patients' treatment plans and information, the condition of the cervical spine still needs our concern.

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