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The association between Disease Activity Score and rheumatoid arthritis–associated cervical deformity: radiological evaluation of the BeSt trial

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OBJECTIVE The authors' objective was to evaluate the association of the Disease Activity Score (DAS) with cervical spine deformity in rheumatoid arthritis (RA) patients during 10-year optimal treatment of systemic disease.

METHODS The authors evaluated radiological and 10-year follow-up (FU) data of the BeSt (BehandelStrategien) trial. In 272 RA patients, atlantoaxial subluxation (AAS), presence of vertical translocation (VT), and subaxial subluxation (SAS) were evaluated. The associations of these deformities with DAS, self-assessed health (determined with the Health Assessment Questionnaire [HAQ]), and erosions of the hands and feet (Sharp–Van der Heijde score) were studied.

RESULTS After 10 years of FU, AAS (> 2 mm neutral position) was observed in 62 patients (23%), AAS (≥ 3 mm in flexion) in 24%, AAS (≥ 5 mm in flexion) in 7%, VT did not occur, and SAS was present in 60 patients (22%). In total, 135 patients (50%) were in remission (DAS < 1.6) at 10 years of 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 scores of 0.65 and 0.51, respectively, p = 0.04; 95% CI –0.29 to 0.00).

CONCLUSIONS 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 7% developed significant AAS. This indicates that even in this era of disease-modifying antirheumatic drugs and biologicals, cervical deformity is prevalent among patients with RA and should not be neglected in patient treatment plans and information.

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KEYWORDS disease activity; atlantoaxial subluxation; vertical translocation; rheumatoid arthritis; cervical spine deformity

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects 1% of the population.[1] The 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. RA 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 C1–2 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 atlantoaxial joint, which is usually accompanied by erosion of the odontoid peg, is referred to as vertical translocation (VT).[2] Apart from upper cervical deformity, subaxial subluxation (SAS) is not an uncommon phenomenon in the cervical spine of RA patients. Subsequent compression of the spinal cord and medulla oblongata can cause severe neurological deficits and even sudden death. It is generally believed that progression is inevitable once neurological deficits occur, although the rapidity of progression is highly variable.[1]

In previous years, the cervical spine was often claimed to be involved in the disease (17%–86% of RA patients),[3] but involvement of the cervical spine seems to have declined with current RA medical treatment policies. In data

ABBREVIATIONS AAS = atlantoaxial subluxation; ACPA = anticitrullinated protein antibody; BeSt = BehandelStrategien; DAS = Disease Activity Score; DAS44 = DAS measured on 44 joints; DMARD = disease-modifying antirheumatic drug; FU = follow-up; HAQ = Health Assessment Questionnaire; RA = rheumatoid arthritis; RF = rheumatoid factor; SAS = subaxial subluxation; SHS = Sharp–Van der Heijde score; VT = vertical translocation.

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TABLE 1. Inclusion and exclusion criteria

Inclusion criteria
To be eligible to participate in this study, a subject must meet all the following criteria:
Availability of lateral cervical radiographs at 5 yrs & 10 yrs of FU
Age 18 yrs or older
Diagnosed w/ RA: active disease w/ ≥6 swollen joints, ≥6 painful joints, & ≥1 of the following:
1. Westergren ESR >28 mm/hr
2. Patient's global assessment of general well-being of >20 mm measured on 100-mm horizontal VAS
Informed consent
Exclusion criteria
A potential subject who meets any of the following criteria will be excluded from participation in this study:
Previous therapy w/ DMARDs except hydroxychloroquine
Pregnant or wish to become pregnant during the study, or childbearing potential w/o adequate contraception
Concomitant treatment w/ another experimental drug
History or presence of malignancy w/in the last 5 yrs
Bone marrow hypoplasia
Elevated hepatic enzyme levels (ASAT or ALAT >3 times normal value)
Serum creatinine level >150 mmol/L or estimated creatinine clearance of <75 ml/min
Diabetes mellitus
Alcohol or drug abuse

ALAT = alanine amino transferase; ASAT = aspartate amino transferase; ESR = erythrocyte sedimentation rate; VAS = visual analog scale.

obtained before the use of disease-modifying antirheumatic drugs (DMARDs) and biologicals, the incidence rates of cervical spine deformity have been reported, such as 61% of 113 patients who received screening for joint replacement surgery. Remarkably, of these patients with deformity, 50% had no signs or symptoms at the time of screening.[4] However, data on cervical spine involvement in the modern era are scarce and the clinical implications are unclear. We conducted a systematic review of the literature, describing the association between 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%.[5] The reported associations between DAS and cervical spine deformity varied largely. However, it is debatable whether that was due to the absence of an association or to the limited amount of data available in the literature. Differences in the definitions of AAS, SAS, and VT; the limited number of articles describing the association; and varying follow-up (FU) times limit the ability to draw conclusions.

DMARDs and biological agents are currently widely used to treat RA.[6] Several types of DMARDs and biologicals are prescribed in different stages of the disease to lower systemic disease activity. Systemic disease activity is quantified by means of the Disease Activity Score (DAS).

In a previous study, we demonstrated that initial combination therapy of multiple DMARDs and/or biological agents resulted in faster decline in disease activity in patients with early RA, as represented by lower DAS (BeSt [BehandelStrategien] 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 relationship between DAS and cervical spine deformity has not been evaluated yet.

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

Methods

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

Patients with early-onset RA were studied in the trial, in which the treatment policy was to keep systemic DAS at as low a level as possible.[7] Over 10 years, treatment response was measured every 3 months with DAS. Treatment was intensified (medication was changed or dosage was increased) at each study visit if DAS was greater than 2.4. In the 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% were in remission (DAS < 1.6 at 10 years) and 14% were in drug-free remission (DA < 1.6 for ≥ 6 months).[7]

Subjects

In total, 508 patients with RA for < 2 years according to the revised criteria of the American Rheumatism Association were included in the BeSt trial, of whom 331 completed 10 years of follow-up.[7] Patients were randomly assigned to treatment groups between 2000 and 2002. Lateral radiographs of the cervical spine, systemic DAS, and medication use of the patients were collected during a 10-year period of FU, as well as at 5 and 10 years of FU. The inclusion and exclusion criteria are stated in Table 1.

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

Study Design

This research was observational. The study had an explorative design and therefore sample size calculation was not applicable. The protocol of the BeSt trial was approved by the Leiden Medical Ethics Committee (Commissie Medische Ethiek Leiden University Medical Centre) (Netherlands Trial Register no. NTR262). Written informed consent was obtained from all patients.

Assessment of Cervical Spine Deformity

Radiological cervical deformity parameters (AAS, SAS, and VT) were evaluated on lateral radiographs obtained at 5 and 10 years of FU (Fig. 1). Evaluation was assessed by two researchers (A.B.L.V. and C.L.A.V.L.), both of whom were blinded to DAS. Agreement was reached in close cooperation.

For patients with deformity scores (AAS > 2 mm and SAS combined), if AAS, VT, or SAS was present at 5 years but radiographs were missing at the 10-year FU, then the deformity was scored to be also present at the 10-year FU. For patients with AAS scores (either ≥ 3 mm or ≥ 5 mm in the flexed position), only 10-year flexion radiographs were evaluated unless AAS ≥ 3 mm was already present at the 5-year FU.

The number of patients with atlantoaxial distance ≥ 3 mm slip in flexion, but not in the neutral position, was also evaluated.[8] The percentage of patients with slip > 2 mm was calculated.

Assessment of DAS

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

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

Additionally, the mean DAS44 during the 10-year study period was calculated, as well as the mean DAS44 between 3 and 5 years. This time period was chosen because it started at the end of the randomization period for treatment strategy (i.e., 2 years), it was sufficiently long to give an indication of severity of systemic disease during the first period of FU, and it allowed for 5-year FU until the 10-year radiographic examination.

Sustained remission at the 10-year FU, mean DAS44 over 10 years of FU, and mean DAS44 from year 3 to 5 of FU were separately compared with cervical spine deformity to assess the correlation between DAS44 and cervical spine deformity.

Health Assessment Questionnaire

The results of the Health Assessment Questionnaire (HAQ) indicate the patient's self-reported disability and is scored from 0 (best) to 3 (worst).[11] The mean HAQ scores at baseline and 10 years were assessed. Also, the mean HAQ score from year 1 to 10 was calculated and compared with cervical spine deformity.

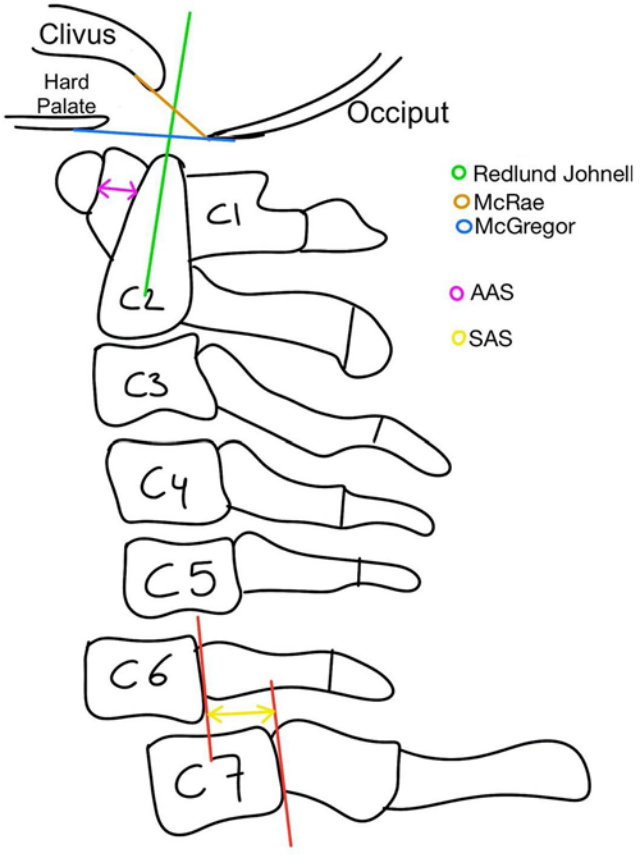

FIG. 1. Cervical deformity. This figure shows the definition of cervical spine deformity used in this study. AAS: the atlantoaxial interval is measured as the distance between the anterior border of the odontoid peg (C2) and the posterior border of the anterior arch of the C1 vertebra in neutral and flexion positions. If this interval in the neutral position was > 2 mm, AAS was scored as present. If this interval in the flexed position was ≥ 3 mm, this was scored as AAS in flexion. If this interval was ≥ 5 mm distance in flexion, this was scored as significant AAS. VT: 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 McRae (*line* placed between the anterior aspect of the occiput and posterior hard palate). Crossing the line with either method was scored as VT being present. SAS: evidence of SAS if the posterior sides of the bodies of 2 consecutive vertebra had shifted > 2 mm. SAS was evaluated on all cervical levels (C2–3, C3–4, C4–5, C5–6, and C6–7). Figure is available in color online only.

Sharp–Van der Heijde Score

The Sharp–Van der Heijde score (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, the average change between 5 and 10 years of FU was calculated.[12]

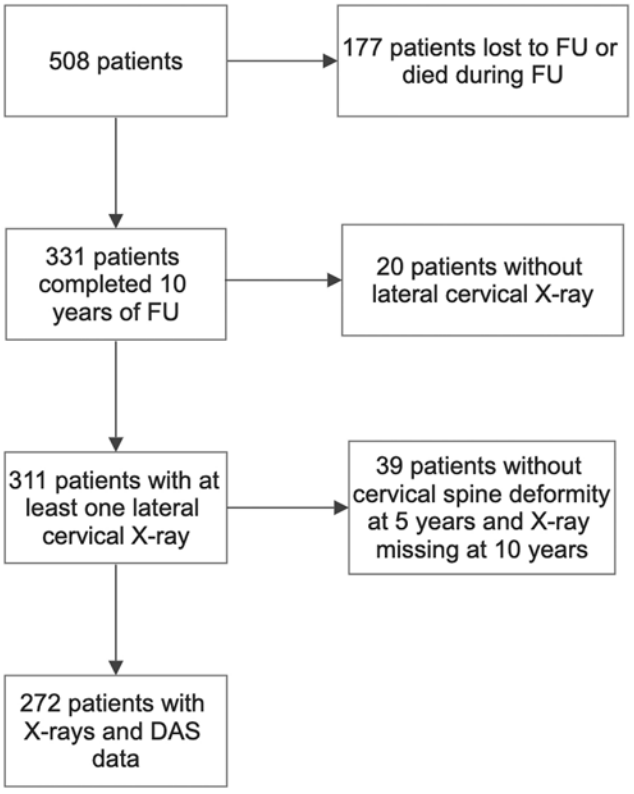

FIG. 2. Flowchart of patient inclusion. This figure shows the path of patient inclusion in this study.

Statistical Analysis

For each radiological parameter, the incidence rate for the total group of patients was calculated at the 5- and 10-year FU evaluations. The number of patients with cervical spine deformity (AAS or SAS) was calculated, in which AAS was defined as a distance exceeding 2 mm. AAS was evaluated on flexion radiography, and the numbers of patients with AAS and significant AAS in flexion were calculated.

The DAS44 was categorized because there is a known interpretation of the DAS44 scale for patients with and without remission. The cutoff point for remission was DAS44 < 1.6 for ≥ 6 consecutive months. This dichotomic categorization was used in the analysis to correlate systemic disease activity with cervical spine deformity. After multiple imputations of DAS44, DAS44 of the patients at baseline and 5 and 10 years were correlated exploratively to the radiological parameters of cervical deformity. The imputation model included terms for treatment strategy, age, sex, anticitrullinated protein antibody (ACPA) (positive or negative), rheumatoid factor (RF) (positive or negative), HAQ score, and DAS44. In the imputation, the mean of 20 iterations was pooled using MATLAB 2019b (MathWorks, Inc.) and combined to form the DAS44 data used to explore correlations. Baseline data were expressed as mean ± SD or number (%) and analyzed with descriptive statistics, including the independent t-test for continuous data and the chi-square test or Fisher's exact test for categorical data. Correlations were tested using the independent t-test for continuous data and the chi-square test for categorical data.

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

Results

In total, 331 of 508 patients completed 10 years of FU. Twenty patients were excluded because they were missing both radiographic images at 5 and 10 years of FU, and 39 patients were excluded because they were missing radiographs at 10 years and had no signs of cervical deformity at 5 years of FU. In total, 272 patients had both cervical radiographs and DAS44 (Fig. 2). In the group of patients with cervical spine deformity, the mean ± SD age at baseline was 55.2 ± 12.7 years, 65 (60%) of 108 patients were female, 74 (69%) patients were RF positive, and 73 (68%) patients were ACPA positive. After 10 years of FU, 117 (71%) of 164 patients without cervical spine deformity were female, the mean ± SD age at baseline was 50.6 ± 11.2 years, 112 (68%) patients were RF positive, and 104 (63%) patients were ACPA positive (Table 2).

Radiographs in flexion were available for 132 patients. However, a reliable conclusion regarding AAS ≥ 3 mm flexion could be drawn for only 109 patients and regarding ≥ 5 mm in flexion for 107 patients because some patients had only 5-year FU flexion radiographs, which did not demonstrate AAS, and the 10-year radiographs were missing.

Disease Activity

At baseline, the mean ± SD 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 FU, 135 (50%) patients were in remission (DAS < 1.6) and 84 (31%) were in sustained remission (DAS < 1.6 for 6 months).

The mean DAS calculated from year 3 to 5 (measuring points 9–20 of 41) was 1.76. The 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 SAS, and 62 patients had AAS of > 2 mm in the neutral position. No patients had VT.

Correlation Between Cervical Spine Deformity and DAS44

The patients with and without cervical spine deformity did not differ significantly in terms of mean DAS44 from years 3 to 5 (mean DAS 3–5 years 1.79 vs 1.73, respective-

TABLE 2. Baseline characteristics

Variable	Cervical Spine Deformity at 10-yr FU (n = 108)	No Cervical Spine Deformity at 10-yr FU (n = 164)	p Value (95% CI)
Mean age at baseline, yrs	55.2 ± 12.7	50.6 ± 11.2	0.002 (–7.6 to –1.7)
Female	65 (60)	117 (71)	0.06
Mean DAS btwn 3 & 5 yrs of FU	1.91 ± 0.56	1.82 ± 0.53	0.186 (–0.22 to 0.04)
Mean DAS at baseline	4.39 ± 0.89	4.33 ± 0.86	0.63 (–0.26 to 0.16)
Mean HAQ score at baseline	1.22 ± 0.66	1.36 ± 0.63	0.08 (–0.02 to 0.05)
Mean SHS at baseline	4.44 ± 7.05	4.26 ± 7.23	0.84 (–1.92 to 1.57)
RF positive	74 (69)	112 (68)	0.97
ACPA positive	73 (68)	104 (63)	0.48

Values are shown as number (%) or mean ± SD unless indicated otherwise.

ly, p = 0.45; 95% CI –0.20 to 0.09) or mean DAS over 10 years (1.91 and 1.82, respectively, p = 0.19; 95% CI –0.22 to 0.04) (Table 3).

No significant correlation was 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, the mean ± SD SHS of the patients with cervical spine deformity was 4.44 ± 7.05, which was comparable to the mean SHS of the patients without cervical deformity at 10 years of FU (4.26 ± 7.23). Delta SHS, which indicated the increase of SHS between years 5 and 10, did not differ between patients with cervical spine damage (mean 5.3) and those without cervical spine damage (mean 4.0) at 10 years of FU (4.0) (p = 0.40; 95% CI –4.49 to 1.79) (Table 3).

Health Assessment Questionnaire. At baseline, patients with cervical deformity at 10 years had a mean ± SD HAQ score of 1.22 ± 0.66. Patients without cervical spine deformity had a mean HAQ score of 1.36 ± 0.63 at baseline. Patients with cervical spine deformity at 10 years had a higher HAQ score (i.e., worse result) at 10 years (0.65 on a scale from 0 to 3) than patients without cervical spine deformity (0.51) (p = 0.04; 95% CI –0.29 to –0.00) (Table 3). The mean HAQ scores (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).

Binomial logistic regression was performed to ascertain the effect of average HAQ score at 10 years on the prevalence of cervical spine deformity at 10 years (Table 4). There was no significant difference in HAQ scores at 10 years between patients with and without cervical deformity at 10 years of FU (p = 0.115; 95% CI 0.892–2.884).

Correlation Between AAS and DAS44

Radiographs in flexion were evaluated to determine the correlation between AAS and DAS. In 24 of 132 patients for whom radiographs in flexion were available (either at 5 or 10 years of FU), AAS in flexion was ≥ 3 mm but < 3 mm in the neutral position. In 26 of 109 patients (24%) who had FU of 10 years, AAS was ≥ 3 mm. In 8 of 107 patients (7%), AAS was ≥ 5 mm. In 12 patients, the slip in AAS was > 2 mm from the neutral to the flexed position of the neck (10%).

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

The groups of patients with and without AAS in flexion did not differ significantly in terms of mean DAS44

TABLE 3. Comparison of patients with cervical spine deformity and those with no cervical spine deformity at 10-year FU

Variable	Cervical Spine Deformity at 10-yr FU (n = 108)	No Cervical Spine Deformity at 10-yr FU (n = 164)	p Value	Total (n = 272)
Univariate				
Remission at 10-yr FU	53 (49)	82 (50)	0.88	135 (50)
Sustained remission at 10-yr FU	27 (25)	57 (35)	0.09	84 (31)
Overall mean DAS btwn 0 & 10 yrs of FU	1.91 ± 0.56	1.82 ± 0.53	0.19	1.86 ± 0.55
Mean DAS btwn 3 & 5 yrs of FU	1.79 ± 0.62	1.73 ± 0.57	0.45	1.76 ± 0.59
Delta SHS btwn 5 and 10 yrs of FU	5.33 ± 13.67	4.0 ± 9.48	0.40	4.45 ± 11.09
HAQ at 10-yr FU	0.65	0.51	0.04	0.56 ± 0.54
Mean HAQ over 1 & 10 yrs of FU	0.60	0.55	0.35	0.57 ± 0.42

Values are shown as number (%) or mean ± SD unless indicated otherwise.

TABLE 4. Binomial logistic regression analysis of cervical deformity at 10-year FU (SAS > 2 mm and/or neutral AAS > 2 mm)

Variable	B	SE	Wald	df	p Value	OR
Remission at 10-yr FU	−0.532	0.435	1.494	1	0.222	0.587
Sustained remission at 10-yr FU	0.437	0.385	1.290	1	0.256	1.548
Mean DAS btwn 3 & 5 yrs of FU	−0.148	0.308	0.231	1	0.631	0.862
Delta SHS btwn 5 & 10 yrs of FU	0.009	0.013	0.531	1	0.466	1.009
HAQ at 10-yr FU	0.472	0.299	2.489	1	0.115	1.604

from year 3 through 5 (mean DAS 3–5 years 1.76 vs 1.86, respectively, p = 0.46; 95% CI −0.16 to 0.35) or mean DAS over 10 years (1.91 and 1.90, respectively, p = 0.94; 95% CI −0.25 to 0.23).

Eight patients had an atlantoaxial interval of ≥ 5 mm in the flexed position. No significant correlation was 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 3 through 5 (mean DAS 3–5 years 1.89 vs 1.84, respectively, p = 0.82; 95% CI −0.47 to 0.37) or mean DAS over 10 years (2.14 vs 1.89, respectively, p = 0.20; 95% CI −0.64 to 0.14).

Discussion

In the BeSt trial, patients were followed for 10 years in order to evaluate management of early RA while striving for low DAS via the use of the 4 different treatment methods. This study evaluated the effect of adequate treatment of systemic RA disease, as demonstrated by decreasing DAS, on the occurrence of cervical spine deformity. 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, 24% developed AAS, and 7% demonstrated significant atlantoaxial distance in flexion. Slip of > 2 mm in the atlantoaxial distance was observed in 10% of patients. This is in big contrast with the observed trend in contemporary orthopedic and neurosurgical practice, in which a decrease in the incidence rate of RA-related cervical deformities has been observed.

It is remarkable that patients with well-managed DAS still developed RA-associated cervical deformity during the 10 years of FU. The study setup did not aim to report cervical pain or disability, and thus it is impossible to correlate the radiological outcome data to the clinical data in order to specifically evaluate those issues. Only a general functional capacity outcome scale was evaluated (i.e., the HAQ score). This score measures self-reported disability during daily activities. And indeed, it was reported that the patients with cervical deformity had worse general functional capacity. However, regarding the difference in HAQ scores at 10 years (Table 3), clinical relevance seems absent. Also, this difference was not observed when considered in the logistic regression model. It is, however, feasible that this could be attributed to higher SHS score, indicating more deformity of the hand and foot joints. Specific patient-reported outcome measures should be included in future research, with the aim of evaluating neck pain and disability.

The definitions we applied to evaluate AAS, SAS, and VT are commonly used, but several variances are possible. Because there is much discussion regarding the most appropriate definition of AAS, several methods were applied to evaluate AAS. The distance between the atlas and axis of 5 mm in flexion is the most convincing parameter that a pathological relation exists. We consider the most striking result that 7% of this group of patients received careful disease monitoring and optimal treatment from their physicians and still developed significant AAS. Moreover, it is remarkable that there was no trend of any kind that indicated that disease activity was poorly controlled in this group of patients. However, the definition of VT 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 had encountered any patient with suspicion of VT; however, this was not the case.[2]

There were several limitations to this study. First, it would have been optimal if we had radiographs in the

TABLE 5. Binomial logistic regression of AAS of ≥ 3 mm at 10-year FU

Variable	B	SE	Wald	df	p Value	OR
Remission at 10-yr FU	1.574	0.875	3.240	1	0.072	4.827
Sustained remission at 10-yr FU	−1.399	0.819	2.918	1	0.088	0.247
Mean DAS btwn 3 & 5 yrs of FU	−0.022	0.512	0.002	1	0.966	0.979
Delta SHS btwn 5 & 10 yrs of FU	0.016	0.018	0.867	1	0.352	1.016
HAQ at 10-yr FU	0.086	0.445	0.038	1	0.846	1.090

TABLE 6. Comparison between patients with and without ≥ 5 mm of AAS in flexion or neutral at 10 years of FU

Variable	AAS ≥5 mm at 10-yr FU (n = 8)	No AAS ≥5 mm at 10-yr FU (n = 99)	p Value
Univariate			
Remission at 10-yr FU	3 (38)	50 (51)	0.48
Sustained remission at 10-yr FU	1 (13)	28 (28)	0.33
Overall mean DAS btwn 0 & 10 yrs	2.14 ± 0.43	1.89 ± 0.54	0.20
Mean DAS btwn 3 & 5 yrs of FU	1.89 ± 0.52	1.84 ± 0.58	0.82
Delta SHS btwn 5 & 10 yrs of FU	6.33 ± 5.30	4.2 ± 10.87	0.74
HAQ at 10-yr FU	0.88 ± 0.84	0.56 ± 0.55	0.23
Mean HAQ over 1 to 10 yrs of FU	1.02 ± 0.63	0.54 ± 0.40	0.067

Values are shown as number (%) or mean ± SD unless indicated otherwise.

flexion, extension, and neutral positions for all patients at the 5- and 10-year FU evaluations. Furthermore, we would want these radiographs at baseline, too, but they were unavailable. However, we do think that the data that we could extract from the available radiographs are noteworthy because these deformities usually take years to develop and are therefore not expected at baseline in a population of early-onset RA patients with disease duration < 2 years.[13]

Another limitation of the study was that, in some cases, the radiographs were challenging to interpret and quantify. The radiographs were made in the workflow of a study that aimed to evaluate clinical parameters, and the evaluations were not done instantly. In daily practice, a radiograph of the cervical spine of an RA patient is obtained and evaluated carefully; if interpretation is difficult, then another radiograph is obtained. That would have yielded more qualitative radiographs in some cases. Furthermore, 2-mm listhesis of the subaxial cervical spine may be caused by general degeneration and does not necessarily originate from RA; however, we could not make this determination with the current data.

Finally, evaluation of clinical parameters with the aim of evaluating the condition of the neck and neurological symptoms would have been very informative. RA 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 need to include parameters for evaluation of neck disability and neurological symptoms. However, the current results give rise to the suggestion that future research in this direction would be worthwhile.

Conclusions

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 consideration of patients' treatment plans and information, the condition of the cervical spine still needs our concern.

Key Points

- Patients with well-managed DAS still developed RA-associated cervical deformity over 10 years of FU.
- Patients with cervical deformity had worse general functional capacity based on HAQ scores.
- In consideration of patients' treatment plans, the condition of the cervical spine still needs our concern.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Lebouille-Veldman, Allaart, Vleggeert-Lankamp. Analysis and interpretation of data: all authors. Drafting the article: Lebouille-Veldman, Allaart. Critically revising the article: Lebouille-Veldman, Allaart, Vleggeert-Lankamp. Reviewed submitted version of manuscript: Lebouille-Veldman, Vleggeert-Lankamp. Approved the final version of the manuscript on behalf of all authors: Lebouille-Veldman. Statistical analysis: Lebouille-Veldman, Spenkelink. Study supervision: Allaart, Vleggeert-Lankamp.

Supplemental Information

Previous Presentations

Portions of the preliminary results of this work were presented as an oral presentation at the Cervical Spine Research Society, Paris, France, May 28, 2021.

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