Rheumatoid Atlantoaxial Subluxation Can Be Prevented by Intensive Use of Traditional Disease Modifying Antirheumatic Drugs

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ABSTRACT. ***Objective.*** To evaluate the 5-year incidence of cervical spine disorders in patients with early rheumatoid arthritis (RA) treated by 2 different disease modifying antirheumatic drug (DMARD) strategies.

Methods. In a national, multicenter, prospective FIN-RACo-trial, a cohort of 199 patients with early, clinically active RA was randomly assigned to treatment with a combination of 3 DMARD and prednisolone (Combi group) or with a single DMARD (Single group) with or without prednisolone, aiming to induce remission. After 2 years, the DMARD therapy was unrestricted. Lateral view cervical spine radiographs during full flexion and extension were taken at the 5-year followup visits. The presence of anterior atlantoaxial subluxation (aAAS), atlantoaxial impaction (AAI), and subaxial subluxation (SAS) was assessed in the 149 patients with radiographs available (80 Single and 69 Combi).

Results. At the 5-year visits, aAAS, AAI, and SAS were found in 13 (9%), 6 (4%), and 9 (6%) patients, respectively. The corresponding Single/Combi group ratios were 11/2, 5/1, and 5/4. Of the baseline data, only poor physical function [Health Assessment Questionnaire (HAQ); p = 0.024] and Single treatment strategy (p = 0.019) were significantly associated with aAAS. Worse HAQ scores and Disease Activity Score 28 values were found in patients who developed aAAS during the 5-year followup.

Conclusion. RA patients with sustained clinical disease activity and poor HAQ are at increased risk of developing aAAS. The development of aAAS during the first 5 years of RA was rare among the patients treated with a combination of DMARD for at least 2 years from the diagnosis. Intensive treatment with traditional DMARD prevents or retards the development of aAAS in patients with recent-onset RA. (First Release Dec 15 2008; J Rheumatol 2009;36:273–8; doi:10.3899/ jrheum.080429)

Key Indexing Terms:
RHEUMATOID ARTHRITIS CERVICAL SPINE ATLANTOAXIAL SUBLUXATION
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Structural changes in the cervical spine are rather common and potentially dangerous abnormalities in patients with rheumatoid arthritis (RA)[1-11]. Clinically, the most important changes are anterior atlantoaxial subluxation (aAAS), atlantoaxial impaction (AAI), and subaxial subluxation (SAS)[1-11]. Injury in the stabilizing ligaments of the upper cervical spine leads to aAAS. AAI develops much later due to cartilage and bone erosions of the atlantoaxial facet joints, but degenerative changes may also contribute to its development[12,13]. Chronic inflammation may lead to development of SAS, but it may also be present because of degeneration of the intervertebral discs[2].

The prevalence of aAAS after 2 years of RA has been reported to be about 10%[9-11]. The prevalence has been declining due to earlier and more intensive use of disease modifying antirheumatic drugs (DMARD), as shown by the FIN-RACo group and by van Eijk, *et al*[14,15]. Cross-sectional studies of longterm RA have reported high frequencies of cervical spine disorders (e.g., aAAS in as many as 70% of patients), but there is a lack of prospective longterm followup studies[1-4,6]. We extend the 2-year followup report to 5 years, with information regarding other clinical data.

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MATERIALS AND METHODS

Patients. From April 1993 to May 1995, a total of 199 DMARD-naive patients with recent-onset RA (duration of symptoms < 2 yrs, median 6 mo) were admitted to this multicenter, parallel-group, randomized study comparing the efficacy and tolerability of a therapy with a combination of methotrexate, sulfasalazine, hydroxychloroquine, and prednisolone (Combi group) with the efficacy and tolerability of therapy with a single DMARD (initially sulfasalazine; the Single group) with or without prednisolone. The study design and patient selection criteria have been described[16,17]. After 2 years, the choice of DMARD and prednisolone treatments was unrestricted, but the aim of the treatment was still to maintain or achieve remission. Thus the Single patients with insufficient response could also be treated with combinations of DMARD. On the other hand, the drug treatment of patients in remission was allowed to be tapered. If their RA reactivated, the latest medication with which remission was maintained was reinstituted. A total of 160 patients (78 in the Combi group, 82 in the Single group) completed the 5-year extension study[17].

Assessment. Patients were assessed clinically by their own rheumatologists at baseline and at the 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60 month visits. The 2- and 5-year outcome of the patients has been reported[16,17]. Clinical activity of RA was determined by the 28-joint Disease Activity Score (DAS28)[18]. The Health Assessment Questionnaire (HAQ) was used to evaluate physical function[19].

Radiological examinations. Radiographs of the hands and feet were taken at baseline and at 24 and 60 months and scored by the Larsen method[20].

Lateral-view cervical spine radiographs (during flexion and extension) were taken at the 24 and 60 month visits using a 150 cm tube-to-plane distance. A diagnosis of aAAS was made if the distance between the anterior aspect of the dens and the posterior aspect of the anterior arch of the atlas was > 3 mm during flexion. Posterior AAS (pAAS) was diagnosed if the posterior aspect of the anterior arch of the atlas was situated posteriorly in relation to the anterior aspect of the dens in the lateral-view radiographs during extension[21]. Lateral-view radiographs taken during flexion were used for evaluation of AAI. AAI was diagnosed using the Sakaguchi-Kauppi (S-K) method developed for screening purposes in particular, and which evaluates the position of the atlas in relation to the axis[22]. It divides the condition into 4 grades (Grade I represents normal and Grades II–IV abnormal). SAS was diagnosed if a vertebra had moved more than 3 mm in relation to the next vertebra when measured from the posterior line of the vertebral bodies.

Radiographs of 149 patients (80 Single and 69 Combi) were available for evaluation. Cervical spine radiographs were evaluated separately by 2 authors (MN and KL) blinded to knowledge of the therapy and the patients. Those found or suspected pathological by any reader were reevaluated and judged by a third author (MK), without any patient information.

Statistical analysis. Results were expressed as mean or median, standard deviation (SD) or interquartile range (IQR), and 95% confidence intervals (95% CI). Statistical significance between groups was evaluated by t test, permutation base tests (Monte Carlo p value), or the chi-square test. Multivariate logistic regression analyses were used to identify the appropriate predictors of cervical spine disorders. We calculated "areas under the curve" (AUC) with the trapezoidal method in terms of longitudinal DAS28 and HAQ. AUC was divided by the total time of study and the results are depicted in time-weighted mean scores. We also performed logistic regression analysis to predict aAAS after 5 years; the independent variables were gender, age, rheumatoid factor (RF), HAQ, DAS28, and Larsen score at baseline.

The study was performed according to the principles of the Declaration of Helsinki. The protocol was approved by the national health authorities and the ethics committees in all 18 participating hospitals. All patients gave written informed consent.

RESULTS

The prevalences of the typical cervical spine disorders after 5 years of RA were aAAS 13 cases/149 patients (9%), AAI 6 cases/149 patients (4%), and SAS 9 cases/149 patients (6%). Combinations of 2 disorders were seen in 3 patients: aAAS + AAI in 2 and AAI + SAS in one. No case of aAAS + SAS was found, and there was no patient with pAAS.

The baseline data for cases, categorized as "with aAAS" and "without aAAS," are shown in Table 1. Only the self-reported physical function (HAQ) and the DMARD treatment strategy during the first 2 years differed between these groups in a statistically significant manner at baseline.

Occurrence of aAAS was more common in the Single group (14%) than in the Combi group (3%), while the occurrences of AAI and SAS were comparable in both treatment arms (Table 2). The patients with SAS in the 5-year followup were significantly older than those without [mean age 56 (SD 5) yrs and 47 (SD 10) yrs, respectively; p = 0.001], a difference not seen with the atlantoaxial disorders.

The AUC of the DAS28 indexes over the 5-year followup period were compared between the patients with and those without aAAS, AAI, and SAS (Figure 1). Patients with any of the 3 cervical spine disorders had significantly higher DAS28 AUC than patients without them. The DAS28 was higher particularly during the first 2 years of therapy in those patients who developed aAAS or AAI during the 5-year followup period, compared to patients without those cervical disorders.

Patients who developed aAAS during the 5-year followup period had a tendency to self-report physical function (HAQ) less favorably than other patients. This difference was statistically significant at baseline and the tendency remained throughout the followup period (Table 1, Figure 2). No statistically significant differences were seen between the patients with and those without SAS. The number of cases with AAI was too low for relevant statistical assessments. The Larsen score at 5-year followup was not significantly associated with aAAS (p = 0.48) or SAS (p = 0.95).

In the logistic regression analysis to predict aAAS after 5 years, the HAQ regimen was the only statistically significant variable in predicting aAAS (Table 3). The independent variables in the analyses described patients and disease at baseline, and the treatment strategy was not included in it.

DISCUSSION

Rheumatoid cervical spine disorders are rather common in historical reports, even in early RA, and their prevalence increases over time[1-13]. They are potentially dangerous, and may lead to severe and even fatal complications[1,2,4,23,24]. Consequently, it would be important to be able to retard or prevent the development of these disorders. The means to identify the patients at high risk of developing cervical spine disorders early in the course of RA would facilitate allocating the diagnostic and treatment efforts.

In cross-sectional studies, the development of aAAS has

Table 1. Baseline demographic, clinical, and radiographic characteristics of patients (N = 149) whose cervical spine radiographs at 5-year followup were available, divided into groups "with aAAS" and "without aAAS."

Characteristic	Radiographic Cervical Spine Findings at 5 Years		p
	No aAAS, N = 136	aAAS present, N = 13	
Demographic			
No. females, n (%)	88 (65)	11 (85)	0.22
Age, yrs, mean (SD)	48 (10)	47 (8)	0.79
Duration of disease, mo, median (IQR)	6 (4, 10)	8 (3, 10)	0.91
Rheumatoid factor present, n (%)	99 (73)	9 (69)	0.75
Treatment strategy during the first 2 years, n (%)			0.019
Single therapy	69 (51)	11 (85)	
Combination therapy	67 (49)	2 (15)	
Measures of disease activity			
Erythrocyte sedimentation rate, mm/h, median (IQR)	33 (20, 54)	33 (27, 52)	0.73
No. swollen joints, median (IQR)	13 (9, 16)	12 (9, 17)	0.98
No. tender joints, median (IQR)	17 (13, 23)	18 (12, 25)	0.62
Patient global assessment (VAS), median (IQR)	47 (29, 61)	45 (31, 64)	0.63
Physician global assessment (VAS), median (IQR)	40 (31, 56)	49 (42, 69)	0.094
Pain (VAS), median (IQR)	47 (25, 63)	50 (36, 61)	0.27
DAS28, mean (SD)	5.53 (1.03)	5.65 (0.96)	0.72
Physical function (HAQ), mean (SD)	0.82 (0.56)	1.26 (0.69)	0.024
Radiographic			
No. of radiographs available	131	13	
Larsen score, median (IQR)	2 (0, 6)	2 (0, 7)	0.85
Erosions in hand or foot radiographs, n (%)	67 (51)	7 (54)	0.86

VAS: visual analog scale; HAQ: Health Assessment Questionnaire.

Table 2. The 5-year occurrence of 3 cervical spine disorders according to the DMARD treatment strategy (Single or Combi) during the first 2 years of RA.

Cervical Spine Disorders	Single (N = 80), n (%)	Combi (N = 69), n (%)	p†
Anterior atlantoaxial subluxation	11 (13.8)	2 (2.9)	0.032
Atlantoaxial impaction	5 (6.2)	1 (1.4)	0.47
Subaxial subluxation	5 (6.2)	4 (5.8)	0.49

† Adjusted for sex, age, rheumatoid factor, and DAS28 score at baseline.

Table 3. Multiple logistic regression analysis for the odds to anterior atlantoaxial subluxation after 5 years.

Variables at Baseline	OR (95% CI)	p
Sex female	2.94 (0.56 to 15.4)	0.20
Age	0.99 (0.93 to 1.05)	0.69
Rheumatoid factor present	0.85 (0.22 to 3.25)	0.81
Physical function (HAQ)	5.81 (1.64 to 20.52)	0.006
DAS28	0.65 (0.32 to 1.31)	0.23
Larsen score	1.05 (0.96 to 1.14)	0.29

been associated with erosive changes of the peripheral and shoulder joints, RF seropositivity, and the presence of rheumatoid nodules[3,7,9,10,25-27]. These aspects reflect active and destructive inflammation and are in accord with our findings of continuous disease activity (DAS28) associated with the presence of aAAS. The use of systemic glucocorticoid therapy has also been reported as a risk factor of aAAS, although the finding most probably is confounded by the indication of the medication. Our previous 2-year followup results from the FIN-RACo trial showed that in early RA, an active combination DMARD strategy including prednisolone retarded the development of aAAS significantly[14]. The present 5-year followup data confirmed the importance of both early and continuous disease control in preventing the development of aAAS.

The DMARD treatment strategy was restricted by the study protocol for 2 years, after which doctors were free to decide how to treat their patients. Thus, the effects of DMARD on further development of cervical disorders remain obscure. On the other hand, our previous reports have shown that intensive DMARD treatment during the first 2 years of the disease translates into better outcomes for patients even after 5 years[17,28]. This effect was also seen in the prevalence of atlantoaxial disorders; aAAS and AAI were more common in the patients treated with the Single

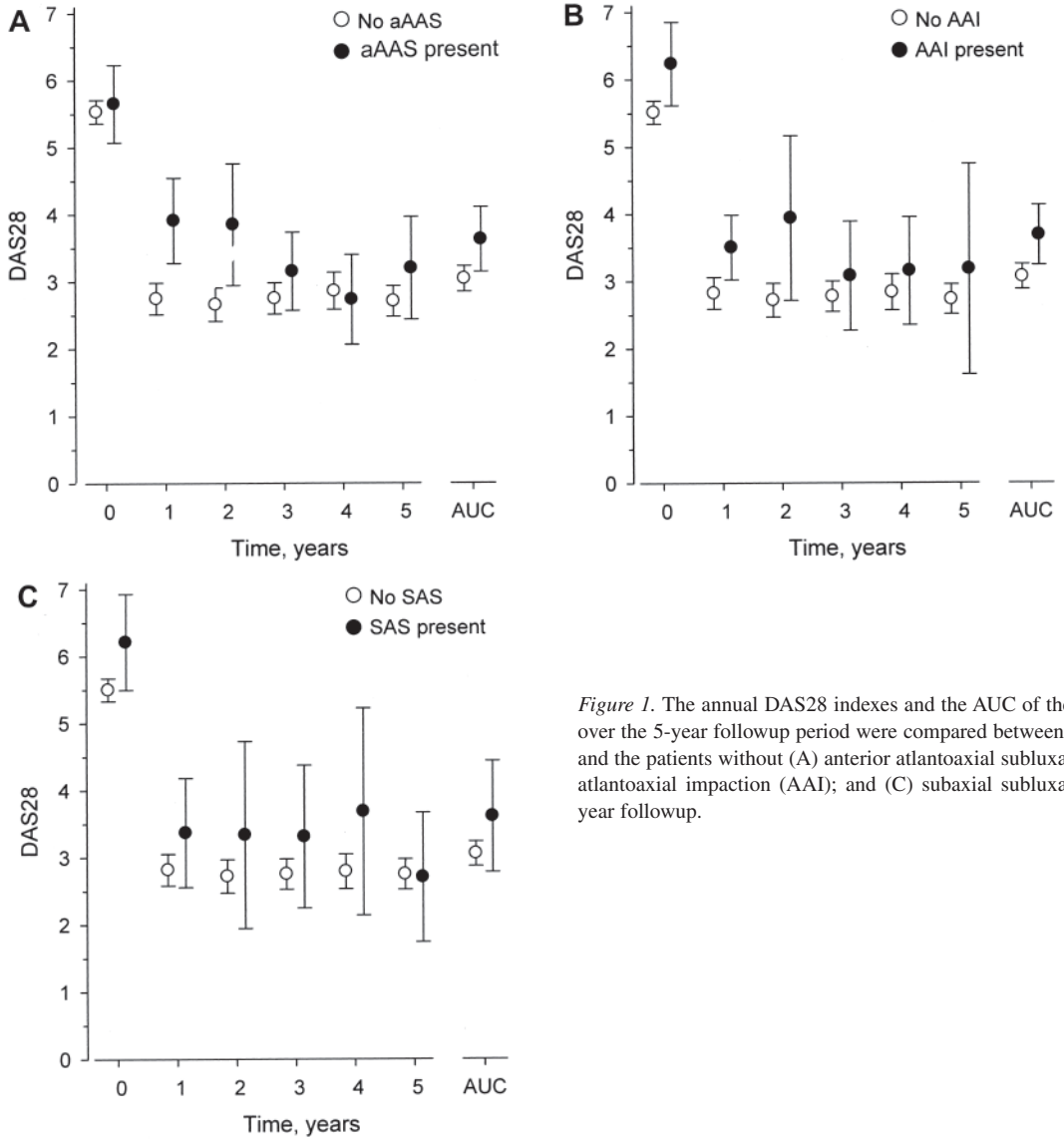

Figure 1. The annual DAS28 indexes and the AUC of the DAS28 indexes over the 5-year followup period were compared between the patients with and the patients without (A) anterior atlantoaxial subluxation (aAAS); (B) atlantoaxial impaction (AAI); and (C) subaxial subluxation (SAS) at 5-year followup.

strategy than in those who received the Combi strategy DMARD therapy, while the figures for SAS were about equal (Table 2). This finding may indicate that the development of SAS is a more multifactorial process than that of aAAS and AAI. The degenerative process probably plays a central role in the development of SAS, since the patients with SAS were older than those without the disorder, and the same patients in this cohort did not develop both aAAS and SAS during the first 5 years of RA.

The 5-year incidence figures of upper cervical spine disorders are very low compared to figures from historical cross-sectional studies. The historical incidence[9-11] of aAAS after 2 years of RA is only slightly lower than that seen here in Single-therapy patients (10% vs 14%, respectively), while the 5-year incidence of aAAS in the Combi cases was lower than that seen in Single patients after 2 years (3% vs 6%). Our figures match the report by van Eijk, *et al*[15] well and confirm that the development of cervical spine disorders in the first years of RA is rare among patients treated early and intensively by DMARD. The progress in the means to control inflammation may make these rheumatoid cervical spine disorders even more uncommon in the future, but they should still be borne in mind when dealing with patients chronic with erosive changes in other joints, and in refractory cases.

The patients with poor self-reported function (HAQ; n = 19) at baseline and continuously high disease activity (DAS28; n = 18) during the 5-year followup were at risk of developing aAAS and AAI. A poor HAQ score at baseline should naturally be taken into account when choosing a DMARD therapy for a patient with early RA. Development of rheumatoid cervical spine disorders is rare during the first 5 years of RA when the disease is managed effectively, aiming to suppress the disease activity using current medical

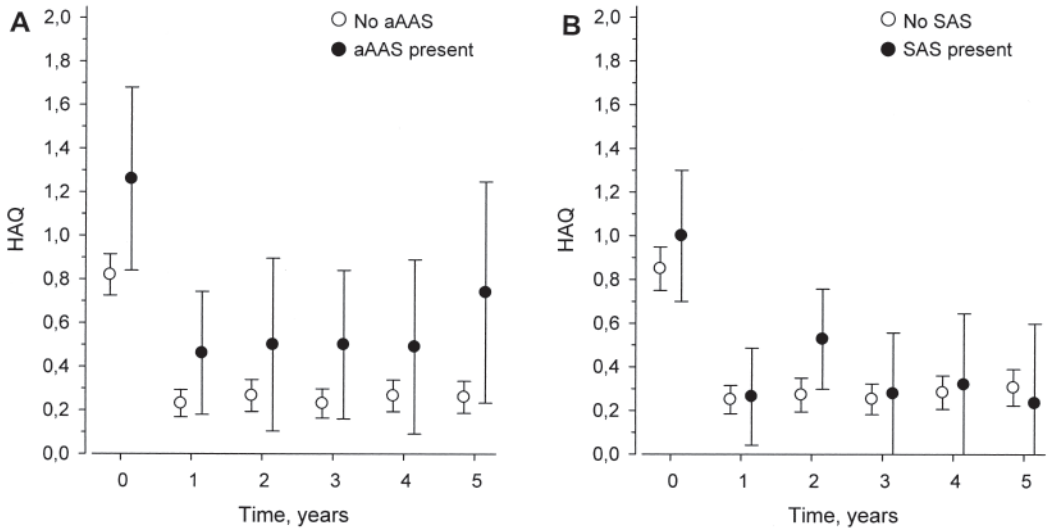

Figure 2. The annual HAQ values over the 5-year followup period among patients (A) with and without aAAS; and (B) with and without SAS at 5-year followup.

strategies. This finding reflects especially well the pure effect of systemic medications, since intraarticular glucocorticoid injections are not given in the atlantoaxial joints.

The cervical spine disorders may remain asymptomatic and the ranges of cervical spine movements may stay within reference limits in plain aAAS[29]. Thus this abnormality may be impossible to diagnose clinically. Radiological examinations are not needed routinely for every patient during the first 5 years of RA. However, these disorders may still develop in rather early RA, calling for radiographic examinations among selected patients with refractory inflammation even during the first 5 years of RA.

We conclude that the development of aAAS is very rare during the first 5 years of RA among patients treated intensively with combinations of traditional DMARD. Active and early DMARD treatment prevents or retards the development of aAAS in RA. The patients with refractory inflammation (continuously high DAS28) and with poor function (HAQ) are still at risk of developing aAAS, and radiographic screening is indicated among these cases during the first 5 years of RA.

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