Cervical Spine Involvement is very rare in Patients with Rheumatoid Arthritis Treated actively with Treat to Target Strategy. Ten-Year Results of the NEO-RACo Study.

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ABSTRACT

OBJECTIVE. To evaluate the development of radiological changes of the cervical spine in patients with rheumatoid arthritis (RA) treated with intensive, remission-targeted combination of conventional synthetic (cs) disease modifying antirheumatic drugs (DMARDs) and additional infliximab or placebo for the first six months.

METHODS. Ninety-nine patients with early, DMARD-naïve RA were treated with a triple combination of csDMARDs and prednisolone, and randomized to double-blindly receive either infliximab (FIN-RACo+INFL) or placebo (FIN-RACo+PLA) infusions during the first 6 months. After 2 years the treatment strategies became unrestricted, but the treatment goal was strict NEO-RACo remission. At 10-year visit radiographs of the cervical spine were taken of 85 patients (38 in the FIN-RACo+INFL group and 47 in the FIN-RACo+PLA group). The study was registered at http://www.clintrials.gov (NCT 00908089).

RESULTS. There were 4/85 patients (4.7%) with cervical spine involvement (CSI) by 10 years. Atlantoaxial subluxation was found in 2/85 patients (2.4%), 2 in the FIN-RACo+INFL group and none in the FIN-RACo+PLA group. Atlantoaxial impaction was found in 1/85 patients (1.2%) in the FIN-RACo+PLA group. Subaxial subluxation was found in 1/85 patients (1.2%)

CONCLUSIONS. Early and intensive, remission-targeted treatment has decreased the incidence of CSI and our results show that intensive treatment prevents its development also in the long-run.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that primarily affects the peripheral small joints. The cervical spine is also commonly affected (1). Clinically the most important changes in the cervical spine are anterior atlantoaxial subluxation (aAAS), atlantoaxial impaction (AAI) and subaxial subluxation (SAS) (1-3). Cervical vertebrae 1 and 2 (C1 and C2) or the atlas and axis articulation is one of the prime targets for rheumatoid pannus formation. This leads to bone destruction and laxity in the ligamentous complex leading to AAS (1,4-5). The subluxation can be anterior, posterior, lateral and rotatory, of which anterior subluxation is the most common (1). AAI results from cartilage and bone erosions of the occiput (C0)-C1 and C1-2 joints, leading to superior migration of the dens of axis. (1,3,5). SAS results from destruction of the facet joints, interspinous ligaments and intervertebral discs causing subluxation at one or multiple levels (1, 4-5). Cervical spine involvement (CSI) can, if left untreated, lead to severe and potentially life-threatening complications (6,7). The natural course of cervical spine lesions shows a progressive pattern and a combination with AAS and AAI or SAS is common in RA patients (1, 8, 9). Development of CSI has been associated with inflammatory activity and severity of RA (3, 7, 9-14). If CSI is suspected, cervical spine radiographs taken during flexion is the method of choice for examination, since both radiographs taken in a neutral position (15) and functional MRI taken in a supine position (16) fail to recognize all aAAS findings.

CSI is typically a late manifestation of RA, occurring in patients with longstanding erosive disease (5) but there have also been studies showing that CSI begins early in the course of RA (9, 17). The prevalence of CSI in RA patients with long-term follow-up range widely from 16-88 % depending on the studied population, disease characteristics, disease management and

follow-up time (1-5, 9-12, 17). The prevalence has been shown to increase over time in ineffectively treated patients. Early and effective treatment with conventional synthetic (cs) or biologic (b) disease modifying antirheumatic drugs (DMARDs) decreases the prevalence of CSI (1-3, 10, 12). However, csDMARDs and bDMARDs may be unable to prevent the progression of pre-existing CSI (4, 7).

In the NEO-RACo trial, all patients with early RA were treated initially by a combination of csDMARDs, methotrexate (MTX), sulphasalazine (SASP), hydroxychloroquine (HCQ) and low dose prednisolone (PRD) for 2 years, and in addition double blindly randomized to receive either infliximab (INFL) or placebo (PLA) infusions for the first 6 months. Thereafter the treatment with DMARDs and glucocorticoids (GCs) became free aiming at all times at remission. This treatment strategy resulted in excellent clinical and radiographic (hands and feet) outcomes at 2, 5, and even at 10 years (18-20). At 10 years the proportion of patients in strict NEO-RACo remission were 46% in the FIN-RACo+INFL group and 38% in the FIN-RACo+PLA group. In DAS28 remission the proportions were 82% and 72% respectively. The mean total Sharp van der Heijde score in the FIN-RACo+INFL group was 9.8 and in the FIN-RACo+PLA group 7.3 (18).

To our knowledge, there are no treat-to-target trials with long term follow-up assessing the development of CSI in early RA. In this study we evaluate the development of radiological changes of the cervical spine in patients with early RA participating in the NEO-RACo trial.

METHODS

Study design and patients

In this investigator initiated, multicenter study, 99 patients were recruited between March 2003 to April 2005. These patients were DMARD and GC naïve with early, active RA (patients which fulfilled the ACR 1987 classification criteria for RA (24), had symptoms for ≤ 12 months, had ≥ 6 swollen (66 joint count) and ≥ 6 tender (68 joint count) joints and at least one of the following: early morning stiffness duration ≥ 45 min, erythrocyte sedimentation rate (ESR) ≥ 30 mm/h or C-reactive protein (CRP) ≥ 20 mg/l) and were treated with an intensified FIN-RACo regimen (MTX up to 25mg/week, SASP up to 2g/day, HCQ 35mg/kg/week and PRD 7.5mg/day) for two years and in addition double blindly randomized to receive either INFL or PLA infusions at weeks 4, 6, 10, 18 and 26. An active use of intra-articular GC injections to all inflamed joints was part of the protocol. If the patient was in strict NEO-RACo remission at the 2-year visit PRD was gradually tapered off followed by slow decrease in the doses and number of DMARDs. The therapies could be modified according to the judgement of the treating rheumatologist, using all available synthetic and biological DMARDs and GCs, aiming at all time, during the 10-year follow-up, at strict NEO-RACo remission, in which the patient was considered to be if 5 out of the following 6 criteria was present: morning stiffness <15min, no fatigue, no joint pain, no tender joints, no swollen joints, ESR <30mm/h in women and <20mm/h in men. Patient selection and criteria as well as the treatment protocol have been described in more detail earlier (19). The study protocol was approved by the national health authorities and by the ethics committee of the Hospital District of Helsinki and Uusimaa (approval number 676/E5/02). The study was conducted according to the Declaration of Helsinki. All patients gave informed written consent. The study was registered at http://www.clintrials.gov (NCT 00908089).

Radiological examination

Radiographs of the hands and feet were taken at baseline and at 2, 5, 7 and 10 years, and scored according to the modified Sharp/van der Heijde method (SHS). Lateral-view cervical spine radiographs during flexion and extension were taken at baseline and at 10 years. Of the 99 patients 86 remained in the study at 10 years and radiographs of the cervical spine were taken of 85 patients (38 in the FIN-RACo+INFL group and 47 in the FIN-RACo+PLA group). The baseline data of the drop-outs did not differ from the baseline data of those who continued in the trial (data not shown). The radiographs were read by an experienced radiologist (LL), aware of the chronology of the radiographs but blinded for the treatment arm and clinical data. AAS was diagnosed if the distance between the anterior aspect of the dens of the axis and the posterior aspect of the anterior arch of the atlas was >3mm during flexion. The evaluation of AAI was made from lateral-view radiographs taken during flexion. AAI was diagnosed using the Sakaguchi-Kauppi (S-K) method, developed especially for screening purposes, which evaluates the position of the atlas in relation to the axis (22). The S-K method divides AAI in to 4 grades in which Grade I represents normal and Grades II-IV abnormal. A diagnosis of SAS was made if a vertebra had moved >3mm relative to the next vertebra as measured from the posterior line of the vertebral bodies.

Statistical analysis

Data are presented as means with standard deviations (SD) or as counts with percentages. Statistical comparisons between the groups were made using the t-test, chi-square test, or Fisher test. A bootstrap method was used when the theoretical distribution of the test statistics was unknown or in the case of a violation of the assumptions (e.g. non-normality). The Stata 14.1, StataCorp LP (College Station, TX, USA) statistical package was used for the analysis.

RESULTS

Table 1 shows the demographic data, clinical characteristics and radiographic (feet and hands) findings at baseline of the two patient groups. At baseline radiographs of the cervical spine were also taken with normal findings in all the patients.

At 10 years, four (4.7%) of the 85 patients with cervical spine radiographs (38 in the FIN-RACo+INFL group and 47 in the FIN-RACo+PLA group) had slight CSI. AAS was found in 2/85 patients (2.4%), both of the two in the FIN-RACo+ INFL group. Both AAS cases were slight (3.1 mm and 3.9 mm). One individual (1.2%) in the FIN-RACo +INFL group had a slight (S-K grade II) AAI, and one case with slight SAS (1.2%; 3,5mm) was found in the FIN-RACo + PLA group. Table 2 shows the characteristics of the 4 patients with CSI at baseline, and at 10 years. All the 4 patients with CSI were seropositive and entered rapidly in sustained remission during the whole follow-up time. No difference was found in the annual cumulative AUC of DAS28 from baseline to 10 years between the patients with CSI (2.03; SD 0.59) and those without (2.00; SD 0.71) (p=0.59). Neither was there any difference in the baseline ages of the patients: 47 ± 10 years vs. 45 ± 8 years, respectively (p=0.67).

DISCUSSION

To our knowledge, there are no present-day treat-to-target trials with long-term follow-up on the CSI in early RA. We show here that CSI is very rare in actively treated RA patients even in long-term follow up. This suggests that modern effective treatment does prevent the development of clinically significant CSI.

Cervical spine involvement in long-term follow-up has been rather common in historical RA cohorts. In old studies, the prevalence of AAS has been 10% already after 2 years of RA (23).

Paimela et al (9) reported 30% of RA patients having developed CSI in 6.5 years despite active treatment with csDMARDs from the diagnosis, and Neva et al (24) found a percentage of 42 after 20 years in patients treated with csDMARDs. Since that, the prevalence has been declining concurrent with earlier and more intensive use of DMARDs. In the FIN-RACo study, only 10% of the patients treated initially with a combination of three DMARDs developed CSI after 5 years vs. 26% of the patients treated initially with a single DMARD, even though treatment strategies were unrestricted after 2 years (3). In this NEO-RACo study the result was even better than in the FIN-RACo study. Compared with the FIN-RACo study the patients in the NEO-RACo trial started treatment earlier, remission target was stricter and thus treatment was more intensive including also the availability of bDMARDs.

Development of CSI has been associated with positive rheumatoid factor, peripheral joint erosions, previous joint surgery, markers of high disease activity, poor functional capacity by Health Assessment Questionnaire (HAQ), long duration of RA, low body mass index, DMARD failure, and long term GC treatment (3-4, 7, 9-14). In the NEO-RACo trial, all patients were treated actively to target throughout the 10-year follow-up. Most patients, regardless of treatment group, achieved very low disease activity and perceived functional ability at 2, 5 and even at 10 years and had minimal to no radiographic joint damage progression. Thus, in the present study, only 4.7% of the patients with incident, very active RA had slight CSI after 10 years, and the findings have presumably no clinical significance. All four patients with CSI were in remission during the follow-up, only one of the patients had significant progression of the Sharp van der Heijde score in radiographs of the hands and feet. Due to a low number of CSI findings no associations or predictive factors for CSI could be calculated.

The limitation of our study is the small study population size and the lack of a control group who were treated less actively during follow-up. It is also a limitation that spinal X-rays have been read with a known time-order and by only one reader. The random reading and the use of two readers might have increased the accuracy of the results. The strengths of this study are that the patients were treated actively from the diagnosis and the majority was followed-up prospectively up to 10 years.

We conclude that CSI is very rare in patients with early RA treated with intensive treat-to-target strategy and active modification of treatment during follow-up. Based on this, routine radiological screening is not needed even after 10 years of disease duration in analogous patient cohorts. However, in real life there are many patients whom rheumatologists are not personally following up from initial diagnosis to 10 years. Understanding what the disease activity burden over time in such patients has been may be challenging. CSI should still be kept in mind in patients with persistently high disease activity or in disabled patients those with deformities, or those with long-lasting history of active RA.

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Table 1. Demographic data, clinical characteristics and radiographic findings at baseline in patients randomized to receive initial infliximab (FIN-RACo+INFL) or initial placebo infusions (FIN-RACo+PLA) for 6 months in addition to a combination of three DMARDs and low-dose prednisolone.

Characteristic	The initial randomisation group	
	FIN-RACo+INFL N=38	FIN-RACo+PLA N=47
Demographic data at baseline		
Female, no. (%)	28 (74)	29 (62)
Age (years), mean (SD)	48 (9)	47 (11)
Duration of symptoms (months), median (IQR)	4 (2 , 6)	4 (2 , 6)
Rheumatoid factor present, n (%)	30 (79)	34 (72)
Measures of disease activity at baseline		
Number of swollen joints (0-66), mean (SD)	15 (5)	16 (8)
Number of tender joints (0-66), mean (SD)	19 (9)	21 (11)
Erythrocyte sedimentation rate (mm/h), mean (SD)	32 (22)	33 (22)
Patient's global assessment (0-100, VAS, mm), mean (SD)	51 (25)	48 (27)
Pain (0-100, VAS, mm), mean (SD)	54 (28)	53 (27)
Physician's global assessment (0-100, VAS, mm), mean (SD)	49 (22)	55 (20)
DAS28, mean (SD)	5.53 (0.94)	5.60 (1.39)
Physical function (HAQ), mean (SD)	1.08 (0.59)	0.91 (0.71)
Radiography at baseline		
Erosion score, mean (SD)*	2.9 (7.6)	1.3 (2.9)
Narrowing score, mean (SD)*	0.6 (1.7)	0.3 (0.6)
Total score, mean (SD)*	3.4 (8.9)	1.6 (3.2)
Erosions in hand or foot radiographs (%)	18 (47)	14 (30)

*Radiologic score by modified Sharp-van der Heijde method.

DAS28, 28-joint disease activity score; HAQ, Health Assessment Questionnaire; INFL, infliximab; n, number of patients; PLA, placebo; VAS, visual analogue scale.

Table 2. Main characteristics of the four patients who developed a cervical spine involvement at 10-year

	Patients			
	A	**B**	**C**	**D**
Baseline				
Randomisation group	FIN-RACo+PLA	FIN-RACO+INFL	FIN-RACO+INFL	FIN-RACO+INFL
Age, years	34	45	47	52
Gender	Female	Male	Female	Female
Rheumatoid factor	Positive	Positive	Positive	Positive
CRP mg/l	5	44	9	56
HAQ	0	0.75	1.00	1.62
SHS	0	10	0	0
At 10-year				
CRP, mg/l	<3	4	5	39
HAQ	0.37	0	0.25	0.12
SHS	22	12	3	3
DMARDs	Single csDMARD	Single csDMARD + bDMARD	Single csDMARD	Single csDMARD
Use of PRD	No	No	No	No
Cervical spine radiographs	SAS	AAS	AAI	AAS

PLA, placebo; INFL, infliximab; CRP, C-reactive protein; HAQ, Health Assessment Questionnaire ; SHS, Sharp/van der Heijde score; DMARDs, disease modifying antirheumatic drugs; cs, conventional synthetic; b, biological; PRD, prednisolone; SAS, subaxial subluxation; AAS, atlantoaxial subluxation; AAI, atlantoaxial impaction