Cervical Spine Involvement among Patients with Rheumatoid Arthritis Treated Actively with Treat-to-target Strategy: 10-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) in the NEO-RACo trial treated with an intensive, remission-targeted combination of conventional synthetic disease-modifying antirheumatic drugs (csDMARD) and additional infliximab (IFX) or placebo (PLA) for the first 6 months.

Methods. Ninety-nine patients with early, DMARD-naive RA were treated with a triple combination of csDMARD and prednisolone, and randomized to double-blindly receive either IFX (FIN-RACo+IFX) or PLA (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 the 10-year visit, radiographs of the cervical spine were taken of 85 patients (38 in the FIN-RACo+IFX group and 47 in the FIN-RACo+PLA group). The study was registered at ClinicalTrials.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%), both in the FIN-RACo+IFX group, and none in the FIN-RACo+PLA group. Atlantoaxial impaction was found in 1/85 patients (1.2%) in the FIN-RACo+IFX group. Subaxial subluxation was found in 1/85 patients (1.2%).

Conclusion. Early and intensive remission-targeted treatment has reduced the incidence of CSI and our results show that intensive treatment also prevents its development in the long run. (J Rheumatol First Release June 1 2020; doi:10.3899/jrheum.190139)

Key Indexing Terms:
RHEUMATOID ARTHRITIS — CERVICAL SPINE — TREATMENT
ATLANTOAXIAL SUBLUXATION — DISEASE-MODIFYING ANTIRHEUMATIC DRUG

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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)[1,2,3]. 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 1 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 patients with RA[1,8,9]. Development of CSI has been associated with inflammatory activity and severity of RA[3,7,9,10,11,12,13,14]. If CSI is suspected, cervical spine radiographs taken during flexion is the method of choice for examination, because both radiographs taken in a neutral position[15] and functional magnetic resonance imaging 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 longterm followup range widely from 16% to 88% depending on the studied population, disease characteristics, disease management, and followup time[1,2,3,4,5,9,10,11,12,17]. 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 (DMARD) reduces the prevalence of CSI[1,2,3,10,12]. However, csDMARD and bDMARD may be unable to prevent the progression of preexisting CSI[4,7].

In the NEO-RACo trial, all patients with early RA were treated initially by a combination of csDMARD, methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), and low-dose prednisolone (PSL) for 2 years, and in addition double-blindly randomized to receive either infliximab (IFX) or placebo (PLA) infusions for the first 6 months. Thereafter the treatment strategy with DMARD and glucocorticoids (GC) became unrestricted, 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[18,19,20]. At 10 years the proportion of patients in strict NEO-RACo remission were 46% in the FIN-RACo+IFX group and 38% in the FIN-RACo+PLA group. In the 28-joint count Disease Activity Score (DAS28) remission the proportions were 82% and 72%, respectively. The mean total Sharp/van der Heijde score (SvdH) in the FIN-RACo+IFX group was 9.8 and in the FIN-RACo+PLA group, 7.3[20].

To our knowledge, there are no treat-to-target trials with longterm followup assessing the development of CSI in early RA. In our study we evaluated the development of radiological changes of the cervical spine in patients with early RA participating in the NEO-RACo trial.

MATERIALS AND 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-naive with early, active RA [patients who fulfilled the American College of Rheumatology 1987 classification criteria for RA[21], had symptoms for ≤ 12 months, had ≥ 6 swollen (66 joint count) and ≥ 6 tender (68 joint count) joints] and at least 1 of the following: early morning stiffness duration ≥ 45 min, erythrocyte sedimentation rate (ESR) ≥ 30 mm/h, or C-reactive protein ≥ 20 mg/l. They were treated with an intensified FIN-RACo regimen (MTX up to 25 mg/week, SSZ up to 2 g/day, HCQ 35 mg/kg/week, and PSL 7.5 mg/day) for 2 years and in addition double-blindly randomized to receive either IFX or PLA infusions at weeks 4, 6, 10, 18, and 26. An active use of intraarticular 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, PSL was gradually tapered, followed by a slow decrease in the doses and number of DMARD. The therapies could be modified according to the judgment of the treating rheumatologist, using all available csDMARD, bDMARD and GC, aiming at all times, during the 10-year followup, at strict NEO-RACo remission. The patient was considered in strict NEO-RACo remission if 5 out of the following 6 criteria were present: morning stiffness < 15 min, no fatigue, no joint pain, no tender joints, no swollen joints, and ESR < 30 mm/h in women and < 20 mm/h in men. Patient selection and criteria as well as the treatment protocol were described in more detail earlier[18]. 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 ClinicalTrials.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 SvdH. 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+IFX group and 47 in the FIN-RACo+PLA group). The baseline data of the dropouts 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 > 3 mm during flexion. The evaluation of AAI was made from lateral-view radiographs taken during flexion. AAI was diagnosed using the Sakaguchi-Kauppi (SK) method, developed especially for screening purposes, which evaluates the

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position of the atlas in relation to the axis[22]. The SK method divides AAI into 4 grades; grade I represents normal and grades II–IV abnormal. A diagnosis of SAS was made if a vertebra had moved > 3 mm relative to the next vertebra as measured from the posterior line of the vertebral bodies.

Statistical analysis. Data are presented as means with SD or as counts with percentages. Statistical comparisons between the groups were made using the t test, chi-square test, or Fisher's exact 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) 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 2 patient groups. At baseline, radiographs of the cervical spine were also taken with normal findings in all the patients.

At 10 years, 4 (4.7%) of the 85 patients with cervical spine radiographs (38 in the FIN-RACo+IFX group and 47 in the FIN-RACo+PLA group) had slight CSI. AAS was found in 2/85 patients (2.4%), both in the FIN-RACo+IFX group. Both AAS cases were slight (3.1 mm and 3.9 mm). One (1.2%) in the FIN-RACo+IFX group had a slight (SK grade II) AAI, and 1 case with slight SAS (1.2%; 3.5 mm) 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 4 patients with CSI were seropositive and entered rapidly into sustained remission during the whole followup time. No difference was found in the annual cumulative area under the curve 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 versus 45 ± 8 years, respectively (p = 0.67).

DISCUSSION

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

CSI in longterm followup 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 patients with RA having developed CSI in 6.5 years despite active treatment with csDMARD from the diagnosis, and Neva, *et al*[24] found a percentage of 42 after 20 years in patients treated with csDMARD. Since then, the prevalence has been declining concurrent with earlier and more intensive use of DMARD. In the FIN-RACo study, only 10% of the patients treated initially with a combination of 3 DMARD developed CSI after 5 years versus 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

Table 1. Demographic data, clinical characteristics, and radiographic findings at baseline in patients randomized to receive initial infliximab (FIN-RACo+IFX) or initial placebo infusions (FIN-RACo+PLA) for 6 months in addition to a combination of 3 DMARD and low-dose prednisolone.

Characteristics at Baseline	Initial Randomization Group	
	FIN-RACo+IFX, n = 38	FIN-RACo+PLA, n = 47
Demographic data		
Female, n (%)	28 (74)	29 (62)
Age, yrs, mean (SD)	48 (9)	47 (11)
Duration of symptoms (mos), median (IQR)	4 (2–6)	4 (2–6)
RF present, n (%)	30 (79)	34 (72)
Measures of disease activity, mean (SD)		
No. swollen joints (0–66)	15 (5)	16 (8)
No. tender joints (0–68)	19 (9)	21 (11)
ESR, mm/h	32 (22)	33 (22)
PtGA (0–100 VAS, mm)	51 (25)	48 (27)
Pain (0–100 VAS, mm)	54 (28)	53 (27)
PGA (0–100, VAS, mm)	49 (22)	55 (20)
DAS28	5.53 (0.94)	5.60 (1.39)
Physical function (HAQ)	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, n (%)	18 (47)	14 (30)

* Radiologic score by modified Sharp/van der Heijde method. DAS28: 28-joint count Disease Activity Score; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; IQR: interquartile range; PGA: physician's global assessment; PLA: placebo; PtGA: patient's global assessment; RF: rheumatoid factor; VAS: visual analog scale.

Table 2. Main characteristics of the 4 patients who developed cervical spine involvement at the 10-year followup.

Characteristics	Patients			
	A FIN-RACo+PLA	B FIN-RACo+IFX	C FIN-RACo+IFX	D FIN-RACo+IFX
Baseline				
Age, yrs	34	45	47	52
Sex	Female	Male	Female	Female
RF	Positive	Positive	Positive	Positive
CRP, mg/l	5	44	9	56
HAQ	0	0.75	1.00	1.62
SvdH	0	10	0	0
At 10-year followup				
CRP, mg/l	< 3	4	5	39
HAQ	0.37	0	0.25	0.12
SvdH	22	12	3	3
DMARD	Single csDMARD	Single csDMARD + bDMARD	Single csDMARD	Single csDMARD
Use of PSL	No	No	No	No
Cervical spine radiographs	SAS	AAS	AAI	AAS

PLA: placebo; IFX: infliximab; RF: rheumatoid factor; CRP: C-reactive protein; HAQ: Health Assessment Questionnaire ; SvdH: Sharp/van der Heijde score; DMARD: disease-modifying antirheumatic drugs; csDMARD: conventional synthetic DMARD; bDMARD: biological DMARD; PSL: prednisolone; SAS: subaxial subluxation; AAS: atlantoaxial subluxation; AAI: atlantoaxial impaction.

FIN-RACo study. Compared with the FIN-RACo study, the patients in the NEO-RACo trial started treatment earlier, the remission target was stricter and thus treatment was more intensive including also the availability of bDMARD.

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 the Health Assessment Questionnaire, long duration of RA, low body mass index, DMARD failure, and longterm GC treatment[3,4,7,9,10,11,12,13,14]. In the NEO-RACo trial, all patients were treated actively to target throughout the 10-year followup. Most patients, regardless of treatment group, achieved very low disease activity and preserved their 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 4 patients with CSI were in remission during the followup; only one of the patients had significant progression of the SvdH in radiographs of the hands and feet. Owing 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 followup. It is also a limitation that spinal radiographs have been read with a known time order and by only 1 reader. The random reading and the use of 2 readers might have increased the accuracy of the results. The strengths of our study are that the patients were treated actively from the diagnosis and the majority was followed up prospectively up to 10 years.

CSI is very rare in patients with early RA treated with intensive treat-to-target strategy and active modification of treatment during followup. 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 a long history of active RA.

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