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

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CHAPTER 5

Infliximab use and cervical spine deformity in patients with Rheumatoid Arthritis

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Abstract

Objective

Over the past decades, the incidence of surgery for Rheumatoid Arthritis (RA)-associated cervical spine deformity decreased. Infliximab has been observed as a protective treatment for joint damage in hands and feet; yet, the protective association between infliximab and cervical spine has been uncertain.

Methods

Duration of infliximab use during 10 years of follow-up was evaluated in patients with new-onset RA (case control study using data from the BeSt Trial). Missing values on the exposure were imputed using last observation carried forward. Lateral X-rays at 5- and 10-year follow-up were assessed for Atlantoaxial Subluxation (AAS) and Subaxial Subluxation (SAS). Multiple logistic regression models adjusted for age, gender, baseline Disease Activity Score (DAS44), ACPA-positivity and RF-positivity were used to estimate odds ratios (ORs) and their 95% confidence intervals (CIs). Mediation analysis was performed to evaluate whether a potential association was mediated via mean DAS44.

Results

Cervical deformity (AAS and/or SAS >2 mm) was observed in 108 (40%) of 272 patients. There was 11% reduced odds for cervical spine deformity (OR: 0.89, 95% CI: 0.81-0.98; p=0.02) for every one-year increase in duration of infliximab use. Mediation analysis could not reveal an influence of DAS44 on the association between infliximab use and cervical spine outcomes.

Conclusions

There was evidence of a beneficial association between longer duration of use of infliximab and mild cervical deformity after 10 years. Thus, it is important to balance the favorable effects of infliximab use for the joints and possibly the cervical spine with the potential adverse events of this medication when used continuously.

Introduction

Rheumatoid Arthritis (RA) is a systemic inflammatory disease, which most commonly affects the large joints and smaller, peripheral joints in hands and feet. According to EULAR guidelines, treatment strategy is recommended to be based on disease activity, safety issues and other patient factors.[1] While practice differs between specialists and countries, in the Netherlands treatment strategy is mostly based on DAS28 or DAS44. The aim of treatment is to attain remission or low disease activity.[2]

DAS44 has conventionally been described to have a very strong correlation with incidence and progression of damage of joints of hands and feet.[2] Patients with high DAS44 often have more joint damage and bone erosions. Therefore, lowering DAS44 is an important goal of treatment in the Netherlands.

Treatment strategies for RA have drastically changed in the late 1990s, when biological Disease Modifying Anti-Rheumatic Drugs (bDMARDs) such as infliximab, a Tumor Necrosis Factor (TNF) inhibitor, were introduced as a treatment modality.[3] These medications have been proven to be effective in preventing RA associated peripheral joint damage.[4-6] While treatment strategy is often still based on DAS44, it was even reported that structural joint damage remained absent in patients treated with Tumor Necrosis Factor (TNF) inhibitors such as infliximab, regardless of the DAS44 values. This led to the presence of patients with only minor to no joint damage, even though DAS44 was increased repeatedly.[7-9]

Except from the peripheral joints, RA can also affect the cervical spine. The cervical vertebrae are stabilized by joints, intervertebral discs and an intricate network of ligaments. RA can cause laxity of these ligaments, which in turn can lead to subluxation of vertebral bodies and instability. This can lead to Atlantoaxial Subluxation (AAS) and Vertical Translocation (VT) in the upper cervical spine and to Subaxial Subluxation (SAS) in the subaxial spine. These deformities can lead to severe cervical myelopathy, and may give an urge for surgery to prevent severe and life-threatening symptoms.[10]

Because the decrease in interventions for RA-associated cervical spine deformity coincided with the introduction of biologicals, it is possible that biologicals such as infliximab have a protective effect on cervical spine deformity.[11] Literature provides us with mixed efficacy of infliximab to prevent deformity in the cervical spine.[11-13]

We hypothesize that an increase in duration of infliximab is associated with a lower incidence of cervical spine deformity.

Therefore, this research aimed to study the association between duration of infliximab use and the incidence of cervical spine deformity after a 10-year follow-up period.

Methods

Study design

This retrospective case control study used data from The BeSt trial; a single-blinded multicenter randomized controlled trial (RCT), designed to compare four treatment strategies in patients recently diagnosed with active RA (based on the American College of Rheumatology 1987 classification criteria), with a least 6 inflamed joints (of 62 assessed) and either a high erythrocyte sedimentation rate or a high patient rating of disease activity.[2] Patients were recruited in 18 non-university and two university hospitals in The Netherlands between 2000 and 2002. There were 508 patients enrolled in the original study. The Medical Ethics Committee of the LUMC approved the study (P08.011) and the regulatory boards of the individual hospitals approved likewise. All patients gave written informed consent.

In the original RCT, patients were randomized to the following treatment arms: (1) sequential monotherapy (starting with methotrexate monotherapy); (2) step-up combination therapy (also starting with methotrexate monotherapy); (3) initial combination therapy with methotrexate, sulfasalazine and prednisone; and (4) initial combination therapy with methotrexate and infliximab. All 508 patients were treated according to the 'treat to target' principle, requiring protocolized treatment adjustments based on three-monthly assessments of the Disease Activity Score (DAS44, based on a 44 (for swelling)/53 (for tenderness using the Ritchie Articular Index) joint count, ESR and patient's assessment of disease activity). In case of a DAS44 > 2.4, treatment was increased according to the next step in the relevant treatment strategy arm.

Infliximab was started as step 4 in treatment arm 1. For treatment arm 2, infliximab was included in step 5. For treatment arm 3 as step 3 and for treatment arm 4, the first treatment step included infliximab. For all group dosing schedules were the same: a single dose of 3 mg/kg at week 0, 2 and 6, and subsequently every 8 weeks. An adequate

response was defined as reaching DAS<2.4. If the response was inadequate, the dose was stepwise increased to 10 mg/kg. If this gave no satisfactory response, infliximab was stopped and the next treatment step was initiated. In case of a satisfactory response to infliximab, working dose of infliximab was continued for 6 months after which it was decreased until it could be stopped. If the treatment resulted in remission (< 1.6) for at least 6 months, the strategy aimed to achieve drug-free remission.[2] If sustained remission was reached and infliximab was stopped, it could be restarted upon a flare, with the same increasing dosing schedule.

Cases of cervical spine deformity ascertainment vs. controls

No baseline cervical spine radiographs were available. Lateral X-rays of the cervical spine were collected at 5- and 10-year follow-up.

Radiological cervical deformity parameters (AAS, SAS and VT) were evaluated on lateral X-rays by two researchers (ABV and CVL), both blinded for patient characteristics.[14] Agreement was reached in close cooperation, after independent scoring. The readers did not know any of the characteristics or the timing of the study relative to study initiation, in order to optimize independent readings. If a dynamic X-ray was performed (flexion/extension), AAS was scored separately on these radiographs.

The primary outcome, cervical spine deformity of all types (mild, moderate, and severe), was defined as the presence of AAS and/or SAS > 2 mm. AAS was defined as a distance of more than 2 mm between the odontoid peg and the anterior arch of C1 in neutral position. SAS was concluded to be present in case a listhesis of more 2 mm existed in neutral position. The secondary outcome was AAS ≥ 3 mm in flexion on dynamic X-ray, which included moderate and severe cervical spine deformity. The third outcome was AAS ≥ 5 mm in flexion or neutral position, which included severe cervical spine deformity. VT was present if the tip of the odontoid peg exceeded the line of McGregor.[15] Controls were derived from the same population that gave rise to the cases. As for the controls, no cervical spine deformity was present.

If an X-ray was missing at 10-year follow-up and AAS, VT or SAS was present at 5-year follow-up, it was scored to be also present at 10-year follow-up. For the AAS ≥ 3 mm in flexion and severe AAS groups, if a flexion X-ray was missing at 10-year follow-up and AAS was not present at 5 years, the patient was not included in the sub analysis for these groups.

Reported adverse effects

During the 10-year follow-up period, side effects known to possibly occur in infliximab use, such as the development of malignancy and/or serious infection, were reported. Hence, descriptive analyses were conducted.

Assessment of use of infliximab in the trial (Exposure)

The protocol dictated the assessment of the use of medication (including infliximab) at every visit during the 10-year evaluation period. Patients were evaluated every three months. In case of missingness of infliximab data, imputation in the form of Last Observation Carried Forward (LOCF) was used. This same strategy was applied to patients that were lost to follow-up. Because of the long follow-up, some patients were followed on a yearly basis, when possible, because they were no longer willing to be seen quarterly. To investigate the association between infliximab and the prevalence of cervical spine deformity at 10 years follow-up, the duration of use during 10 years was studied.

Measurement of covariates

Age, sex, ACPA status and Rheumatoid Factor status of the patients were collected at baseline. No missing values were observed. Treatment strategy was determined after randomization between four treatment strategies.[2] During a period of 10 years, the DAS44 and Health Assessment Questionnaire (HAQ) scores were measured every 3 months, and thus 41 times in total. In case of missingness of DAS44 values, multiple imputation was used. The imputation model included terms for treatment strategy, age, sex, ACPA status, Rheumatoid Factor status, HAQ and DAS44 values. In the imputation, 20 iterations were pooled using MATLAB 2019b and combined to form the individual DAS44 data that were used to explore correlations, and also to form a mean DAS44 value.[14]

Exclusion of patients at baseline

Of the 311 patients included in the original RCT who underwent imaging of their cervical spine, thirty-nine patients were excluded because they were missing the X-ray at 10 years and had no signs of cervical deformity at 5-year follow-up. Ultimately, in this study, 272 patients had adequate radiological (radiographs at 10-year follow-up present, or cervical deformity present in the 5-year follow-up neutral radiographs) and DAS44 follow-up data, and were hence included in the case control study.[14]

Statistical Analysis

Baseline data were expressed as mean ± SD or number (%). Multiple logistic regression was performed to study the association between *increased duration of infliximab use* and each of the three different outcomes of cervical deformity. This model was adjusted for potential confounding variables such as age, gender, DAS44 at baseline, anti-CCP (ACPA) status and Rheumatoid Factor (RF) status.

The treatment protocols dictated the addition of infliximab in patients with higher DAS44 values. Because of this, more infliximab was prescribed in patients with higher DAS44 values. To be able to discern the effect of infliximab from the effect of DAS44 on cervical spine deformity, a mediation analysis was performed, using the mean DAS44 value over the 10-year follow-up as mediator. Notably, previous analyses have demonstrated that an association between DAS44 and cervical spine deformity was absent,[14] but we still deemed it useful to attempt to study the influence of DAS44 on our results. First, the association between increased duration of infliximab use and cervical spine deformity; between infliximab use and the mediator; and between the mediator and cervical deformity were assessed. Then, the effect of the mediator was determined by studying the difference in effect between the regression analysis described above and the same analysis with the mediator as an added factor, to separately determine the effect of the mediator.

Statistical analyses were performed using SPSS version 29.1[16] and MATLAB version 2019b.[17] A two-sided p-value <0.05 was deemed statistically significant.

Results

After 10 years, 62 of 272 patients (23%) had atlantoaxial subluxation (AAS) of more than 2 mm in neutral position. Of the 272 patients, 60 (22%) had subaxial subluxation (SAS). No patients had VT above the line of McGregor. In total, 108 of 272 patients (40%) had cervical spine deformity of any kind on neutral X-ray. In this latter group of patients, the mean age at baseline was 55.2 ±12.7 years, 60% were females, 69% were RF positive and 68% were ACPA positive. This was comparable to the demographic data of the patients without cervical spine deformity, except for age; at 10-year follow-up, patients with cervical spine deformity appeared older (55.2 (±12.7) years) than patients without cervical spine deformity (50.6 (±11.2) years) (**Table 1**).

TABLE 1: Baseline characteristics of rheumatoid arthritis patients with or without cervical spine deformity at 10-year follow-up.

Baseline Characteristics	Cervical spine deformity at 10-year follow-up (n=108)	No cervical spine deformity at 10-year follow-up (n=164)
Mean age (±SD)	55.2 (±12.7)	50.6 (±11.2)
Female, n (%)	65 (60%)	117 (71%)
Mean DAS44 (±SD)	4.39 (±0.89)	4.34 (±0.86)
Mean HAQ score (±SD)	1.22 (±0.66)	1.36 (±0.63)
RF-positive, n (%)	74 (69%)	112 (68%)
ACPA-positive, n (%)	73 (68%)	104 (63%)

**Abbreviations: DAS44: Disease activity score; HAQ: Health assessment questionnaire; RF: Rheumatoid factor; ACPA: Anti-citrullinated protein antibodies.*

An X-ray in flexion was available for 109 patients, of whom 26 (24%) demonstrated AAS ≥ 3 mm in flexion. Two of these patients demonstrated AAS ≥ 5 mm in flexion. Additionally, on the neutral X-rays 6 patients demonstrated an AAS ≥ 5 mm. Consequently, a total of 8 patients (3%) had AAS ≥ 5 mm in flexion and/or neutral position (severe AAS).

Infliximab use

Of the 272 patients included in the analysis, 144 patients (53%) used infliximab at least once during the 10-year follow-up. The median duration of infliximab use was 9 months (IQR 0-30 months).

At 10-year follow-up, 51 out of 108 (47%) cases of cervical spine deformity (AAS and/or SAS > 2 mm) used infliximab at any time during follow-up, which was lower than 93 out of the 164 (57%) controls without cervical spine deformity. Moreover, the median duration of infliximab use among the cases of cervical deformity at 10 years of follow-up was 0 months (IQR 0-19.5), which was shorter than median of the controls patients without cervical spine deformity: 9 months (IQR 0-43.5).

Association between infliximab duration and cervical spine deformity

To visualize the association between duration of infliximab use and the presence and severity of atlantoaxial subluxation, a scatter plot was produced (**Figure 1**). It is demonstrated that there is a trend of decreasing duration of infliximab use in the more severe AAS categories.

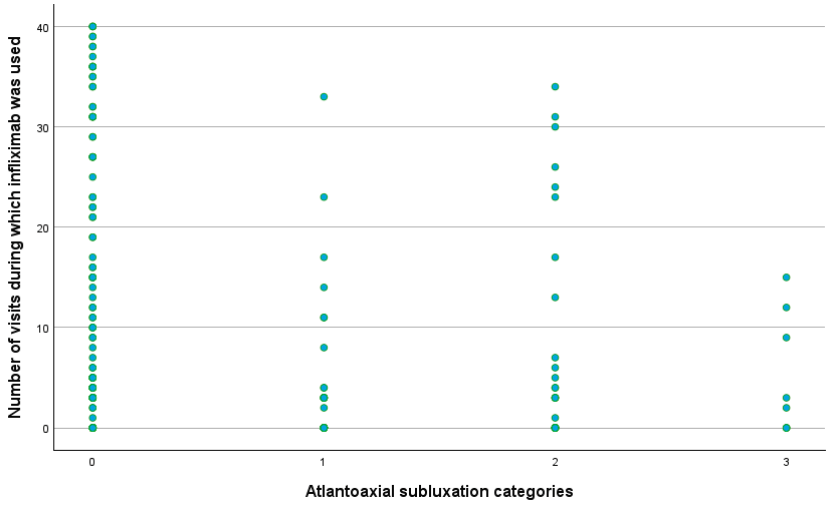

FIGURE 1 – Duration of infliximab use per category of atlantoaxial subluxation

This figure shows the duration of infliximab (expressed as number of visits, where a visit took place once every three months) of the patients in the different atlantoaxial subluxation categories.

After adjustment for the potential confounders including age, gender, DAS44 at baseline, ACPA-status and RF-status, a one-year increase in duration of infliximab was associated with a statistically significant 11% reduced odds of cervical spine deformity of all types, after 10 years (OR: 0.89; 95% CI: 0.81-0.98; p=0.02). For patients with AAS ≥ 3 mm in flexion, the OR was 0.95 (95% CI: 0.81-1.14; p=0.64) and for patients with severe cervical spine deformity (AAS ≥ 5 mm in flexion or neutral), the OR was 0.91 (95% CI: 0.66-1.25; p=0.56). Adding average DAS44 during 10-year follow-up did not materially change the odds ratio in each of the three different models. (**Table 2**)

TABLE 2: Multiple logistic regression for duration of infliximab use in relation to different outcomes of cervical spine deformity at 10 years follow-up.

Variables in the model	Outcomes of cervical spine deformity	Sample size	Multivariable Odds Ratio (95% confidence interval)	P-value
Duration of infliximab use (years)†	Mild, moderate, or severe AAS >2 mm and/or SAS >2mm	272	0.89 (0.81, 0.98)	0.02
Duration of infliximab use (years) + average DAS44 score‡			0.87 (0.78, 0.96)	0.01
Duration of infliximab use (years)†	Moderate or severe AAS ≥ 3 mm in flexion	109	0.95 (0.81, 1.13)	0.58
Duration of infliximab use (years) + average DAS44 score‡			0.95 (0.80, 1.13)	0.57
Duration of infliximab use (years)†	Severe AAS ≥ 5 mm in flexion or neutral	107	0.87 (0.61, 1.22)	0.41
Duration of infliximab use (years) + average DAS44 score‡			0.87 (0.61, 1.22)	0.41

†All three models for the three different outcomes of mild, moderate, or severe cervical spine deformity were adjusted for age at baseline, sex (male or female), anti-CCP positivity, Rheumatoid Factor positivity, and baseline DAS score.
‡Adjusted for the previous multivariable model plus mean DAS during the 10-year follow-up.
**Abbreviations: DAS44: Disease Activity Score; AAS: Atlantoaxial Subluxation; SAS: subaxial subluxation.*

Reported adverse effects

Of the 272 patients included in this study, 13 patients developed a malignancy and 34 patients experienced a severe infection during follow-up. Of the 13 patients with a malignancy, 8 patients were treated with infliximab. Only 4 of these patients (31%) used infliximab for longer than one year, being comparable to the group without malignancy in which 85 patients (33%) used infliximab for longer than one year.

Of the 34 patients who developed a severe infection, 20 patients (59%) used infliximab during follow-up. Of these patients, 12 patients (35%) were treated with infliximab for longer than one year. In the group of patients without serious infection 32% of patients used infliximab for longer than one year.

Discussion

This study was one of the first to study cervical deformity in early onset RA patients during a long period of follow-up, where there was strict monitoring of infliximab use. After adjustment for the potential confounders including age, gender, DAS44 at baseline, ACPA-status and RF-status, there was strong evidence of a protective association between increased duration of infliximab and cervical spine deformity of all

types, after 10 years. This could be a potential explanation for the decrease in surgical interventions for cervical deformity over the past decades as described in literature.[18]

Kaito et al. report that the use of infliximab can halt the incidence of de novo cervical spine lesions , while the use of infliximab does not halt progression once cervical spine deformity has developed in RA patients.[11,12] Kanayama et al. described that progression can be less severe in patients who used infliximab.[13] These studies further underscore the protective effect of infliximab for the cervical spine in RA. While it was not possible to study progression in the current study, the results are in agreement with the study of Kanayama et al. and Kaito et al. on the efficacy of infliximab.[13]

Takahashi et al., however, was not able to show the effect of biologics on the lowered prevalence of cervical spine deformity compared to previous reports before the approval of biologicals.[19] Takahashi et al. studied the difference in biological use between patients who developed AAS, SAS or VT and those who did not develop deformity. A subset of their data containing 84 patients was used for this analysis, of whom only 22 patients used biologics. It could be possible that the difference between this study and the current study is a lack of power.

Infliximab was not freely prescribed in this population of patients, but dictated by predefined treatment strategies. This led to a strict regimen in which patients that demonstrated higher DAS44 were more likely to receive infliximab. It is remarkable that a lower OR for cervical spine deformity was observed in the group of long-term infliximab users, who were the patients with higher inflammation values and more RA activity. So, our results might be an underestimation of the true effect of infliximab on cervical spine deformity; if infliximab would not have been terminated upon decrease in systemic inflammation parameters, cervical spine deformity may have been even less.

The clinical consequences of prescribing infliximab chronically to prevent cervical spine deformity, however, are debatable as the use of this medication can lead to toxicity and adverse effects when used for prolonged periods of time.[20] The adverse effects scored in the current patient cohort did not reveal deleterious effects in those that used infliximab for a longer duration, but the total number of included patients is too limited to draw firm conclusions. Therefore, the optimal regimen to use infliximab to prevent cervical deformity, cannot be determined yet.

Out study had some limitations. First, it would have been optimal if we had X-rays in flexion, extension and neutral position of all patients at baseline, 5- and 10-year follow-up. Secondly, X-rays were occasionally challenging to interpret and quantify. The X-rays were made in the workflow of a study aiming at clinical parameters and the evaluations were not done instantly. In daily practice, if an Xray of the cervical spine in RA patients was performed, it was evaluated carefully and, if difficult to interpret, taken again. That would have yielded more qualitative X-rays in some cases, and a better follow-up over the years. Furthermore, the exclusions of patients who missed their 10-year follow-up X-ray after their 5-year X-ray demonstrated no deformity, is possibly inducing some selection bias. This could lead to underestimation of the true presence of deformity. Fortunately, the incidence of the latter occurrence was low. Also, because of the long follow-up period, there were some missing data in this study. However, we used imputation in the form of last observation carried forward until the end of the study period for these missing datapoints. While we think this method best fits our data and the type of data imputed, this may introduce some bias.

Despite these limitations, our study had several strengths. This study had a long follow-up duration of 10 years, where patients with early-onset RA were followed and assessed at quarterly intervals. In addition, we performed multiple imputation for missing DAS44 values, we adjusted for multiple possible confounding variables and performed a mediation analysis for DAS44 during 10-year follow-up.

Conclusions

In conclusion, there was evidence of a protective association between longer duration of use infliximab use and mild cervical deformity after 10 years. Hence, it becomes important to balance the possible favorable effects of infliximab use for the cervical spine with the potential side effects of the long term-use of this medication. It is important to note that the use of biological DMARDs such as infliximab, is deeply embedded in the ACR and the EULAR.[1,21]

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