Radiographic progression of rheumatoid arthritis in patients from the Czech National Registry receiving infliximab treatment

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Abstract

Objective

To evaluate the clinical status and radiographic progression in patients with rheumatoid arthritis (RA) being followed by the Czech National Registry of biological treatments.

Methods

Patients who failed at least two disease-modifying antirheumatic drugs and had high disease activity (DAS28 > 5.1) were treated with infliximab. Radiographic progression was measured with a modified version of the Sharp score (TSS) after 54 weeks of treatment.

Results

Ninety-nine patients with an average disease duration of 13.7 years were enrolled. The DAS28 dropped from 6.66 to 4.07 ($p < 0.001$). Before treatment the mean TSS was 90.1 and the mean estimated yearly disease progression was 8.56. After 54 weeks of infliximab, radiographic progression was 4.15 times slower than the estimated rate before treatment and 63 patients did not show any radiographic progression at all. In the remaining 36 patients, the progression rate slowed to 3.8 ± 0.9 from the estimated TSS of 10.9 ± 6.9 before the initiation of treatment ($p = 0.011$).

Conclusion

Data derived from the Czech National Registry, which reflect general clinical practice, show a significant retardation of radiographic progression in patients treated with anti-TNF and the magnitude of the improvement seen is similar to results from clinical trials.

Key words

Rheumatoid arthritis, biological treatment, radiographic progression.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized by joint synovitis resulting in functional impairment and disability as well as radiographic joint destruction. During the initial stages of RA, the disability is clearly correlated with disease activity; in the later stages, it is usually more reflective of structural destruction of the joints (1). During the course of the disease, fluctuations in disease activity are directly related to changes in radiologic progression (2). The ultimate aim of RA treatment is to maintain functionality, avoid disability and, if possible, induce remission. It is therefore critical to utilize therapeutic approaches that lead to the long-term suppression of disease activity and significantly reduce or even stop the radiographic progression of RA.

Disease-modifying antirheumatic drugs (DMARDs) reduce the inflammatory activity and can slow radiographic progression in RA (3). Recent studies suggest that biological drugs are more effective in the suppression of radiographic progression than older chemical DMARDs such as methotrexate (4-7). Medium-term studies (6–24 months) have shown that radiographic progression was virtually non-existent (8).

Even a decrease in the Sharp score after combination treatment with etanercept and methotrexate has been observed (9). Discussion is currently ongoing as to whether these findings can be interpreted as the actual healing of erosions or whether they merely reflect the inaccuracy of current evaluation techniques (10). Most of the data documenting that biological treatment slows or even stops radiographic progression have been derived from randomized clinical studies. Whether the effect of such treatment in regular clinical practice retards the development of erosive process has not been formally evaluated. The Czech National Registry of patients receiving anti-TNF treatment has allowed us to review such data and compare them with the data published in clinical studies.

Patients and methods

Patients

Patients with RA and adult patients with polyarticular juvenile idiopathic arthritis (JIA) from throughout the Czech Republic were included in the study. They were treated in 10 Centres for Biological Treatment in accordance with the protocol established by the Czech Society for Rheumatology (CSR). Information on the treatment and its results were entered in the Czech Registry of Biological Treatment with ATTRA (Anti-TNF Treatment of RA). All participating patients signed an informed consent form.

Treatment

Indication criteria for anti-TNF treatment have been proposed and published by the CSR (11). These criteria are used by the health insurance system to make decisions regarding the financing of treatment for each individual patient. RA patients receiving anti-TNF treatment were those who did not respond to at least two long-term (at least 6 months) courses of DMARDs. One of the two DMARDs had to be methotrexate administered at a dose of 20-25 mg weekly, if well tolerated. The second criterion was a DAS28 score for RA activity exceeding 5.1 (12). Therapeutic efficacy was evaluated based on a reduction in the DAS28 of at least 1.2 during the first 12 weeks of treatment. If there was no such response, the treatment was discontinued.

Currently, all three approved anti-TNF drugs are on the market in the Czech Republic. However, when this study was begun only infliximab was available, and therefore only patients treated with this drug were evaluated for radiographic progression. All patients received infliximab intravenously at a dose of 3 mg/kg at weeks 0, 2, 6 and then every 8 weeks. All patients were also treated with methotrexate.

Radiographic progression

The effect of therapy on articular damage was evaluated on the basis of radiographs that were assessed for both erosions and joint space narrowing, according to van der Heijde's modification of the Sharp scoring system (13). Scores on this scale can range from 0 to 448, with higher scores indicating more pronounced articular damage. Antero-

posterior radiographs of the hands and feet were taken at baseline and after 54 weeks. One specialist (JG) evaluated and scored all the x-ray images without knowing any clinical details of the patients.

The estimated yearly progression before the onset of the study was calculated by taking the total Sharp score before treatment and dividing it by the disease duration (number of years) for each patient (14).

Clinical response

Clinical response was assessed using the disease activity score for 28 joints (DAS28) (12). Arthritis-related functional disability was assessed using the Health Assessment Questionnaire (HAQ (15), general health status by the Medical Outcomes Study Short-Form Health Survey (SF-36) (16, 17) and general status and quality of life by EuroQol (18, 19).

Statistical analysis

Standard descriptive statistics were used to express the differences among subgroups of patients (relative frequencies for categorical variables, median and MIN/MAX values; arithmetic mean estimates supplied with 95% confidence limits). Common univariate statistical techniques were used to test the differences between compared independent subgroups of patients: the binomial test for binary outcomes, the chi-square test for ordinal categorical variables, and the two-sample t-test and one-way ANOVA technique for multiple comparisons. All parametric methods were applied with the assumption of a normal distribution and a homogeneity of variance within the compared variants. All pair-wise comparisons (*i.e.*, time-related changes in Sharp score and other parameters) were based on the paired t-test. A value $\alpha < 0.05$ was taken as the general limit that indicated statistical significance in all analyses.

Results

A total of 99 patients (68 women and 31 men) who had finished the 12-month therapeutic regimen were included in the study. The basic characteristics of the patients are shown in Table I. The initial mean DAS28 score was 6.64 (± 0.68). The initial TSS was 90.1 (± 77.55) and the yearly progression before the initiation of treatment with infliximab was estimated to 8.56 (± 8.54) Sharp units.

Table I. Basic characteristics of the patients (n = 99).

Parameter		Values	
Gender (men / women)		n = 31 / n = 68	
Age (years)	Mean (SD)	45.6	(14.52)
	Median	47.0	
	Range	20-80	
Disease duration (yrs)	Mean (SD)	13.7	(8.64)
	Median	12.1	
	Range	0.5-39.5	
DAS28 score			
Initial values	Mean (SD)	6.64	(0.68)
	Median	6.66	
	Range	5.11-8.12	
Sharp score			
Initial values	Mean (SD)	90.1	(77.55)
	Median	83.0	
	Range	0.0-312.0	
Estimated progression prior to inclusion in the study (change per 1 year)	Mean (SD)	8.56	(8.54)
	Median	6.57	
	Range	0.05-62.86	
RF positivity (n = 97)		n = 51 (52.6%)	

The effect of treatment on clinical outcome measures and quality of life

The mean DAS28 score of 6.64 (6.50; 6.77) measured at the onset of the study dropped to 4.07 (3.79; 4.35) ($p < 0.001$) in week 54 (Table II). All the components of the DAS28 decreased significantly (number of swollen joints, number of painful joints, patient's global health assessment, and erythrocyte sedimentation rate) ($p < 0.001$). The initial mean HAQ score of 1.46 (1.30; 1.62) decreased to 1.02 (0.86; 1.18) ($p < 0.001$) in week 54. Evaluation of the quality of life using the SF 36 and EuroQol questionnaires also showed significant improvement ($p < 0.001$) (Table II).

Radiographic progression

Over the course of one year, the mean

Table II. Therapy with infliximab: clinical effects.

Parameter	Initial values[1] week 0		Final values[1] week 54		Statistical significance[2]
Therapeutic response					
DAS28 score	6.64	(6.50; 6.77)	4.07	(3.79; 4.35)	$p < 0.001$
No. of swollen joints	12.72	(11.71;13.73)	3.71	(2.84; 4.62)	$p < 0.001$
No. of painful joints	16.13	(14.85; 17.41)	4.75	(3.91; 5.59)	$p < 0.001$
Patient's global health assessment	65.66	(63.08; 68.24)	32.46	(28.48; 36.43)	$p < 0.001$
ESR	40.79	(36.04; 45.53)	26.17	(21.72; 30.62)	$p < 0.001$
Quality of life					
HAQ	1.459	(1.303; 1.615)	1.023	(0.862; 1.183)	$p < 0.001$
EuroQol	0.320	(0.242; 0.397)	0.647	(0.592; 0.702)	$p < 0.001$
SF-36	36.23	(32.78; 39.70)	56.42	(51.96; 60.88)	$p < 0.001$

[1]Estimates of the arithmetic mean and 95% confidence limits (in parentheses).
[2]Significance level of a standard pair-wise t-test.

Table III. Therapy with infliximab: radiographic progression.

Parameter	Initial values week 0		Final values week 54		Mean change[1]	Statistical significance[2]
Sharp score: total values						
Mean (95% CI)	90.08	(84.61; 95.55)	92.14	(86.56; 97.72)	2.06 (3.30)	$p < 0.001$
Median	83.0		85.0			
Erosion score						
Mean (95% CI)	46.15	(40.27; 51.04)	47.35	(41.39; 53.31)	1.20 (2.18)	$p < 0.001$
Median	37.0		40.0			
Narrowing score						
Mean (95% CI)	43.93	(38.87; 48.98)	44.79	(40.71; 48.86)	0.86 (0.72)	$p < 0.001$
Median	38.0		42.0			
Sharp score: hands						
Mean (95% CI)	60.53	(49.66; 71.39)	61.48	(50.62; 72.35)	0.96 (1.92)	$p < 0.001$
Median	55.0		58.0			
Sharp score: feet						
Mean (95% CI)	29.56	23.43; 35.68	30.66	(24.48; 36.8)	1.1 (3.7)	$p = 0.004$
Median	20.0		21.0			

[1]Mean change (Diff: week 54 – week 0) and standard deviation (s_{Diff}) – (in parentheses).
[2]Significance level of a standard pair-wise t-test (applied for the mean change in the Sharp score).

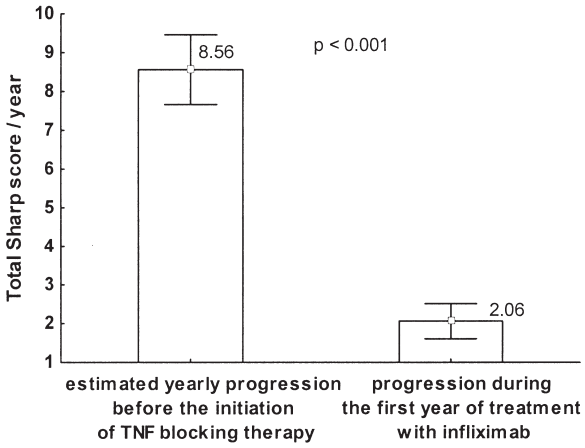

Fig. 1. Decrease in the rate of radiographic progression in patients treated with TNF blocking agent for one year (n = 99).

Table IV. Comparison of patients with and without radiographic progression based on the values prior to the initiation of infliximab therapy.

	Therapy with infliximab: radiographic progression				
Parameter	No progression (n = 63) Mean (SD)		Progression (n = 36)		Statistical significance[1]
Age (yrs)	43.7	(14.96)	48.9	(13.30)	$p = 0.456$
Initial DAS28 score	6.57	(0.73)	6.75	(0.60)	$p = 0.385$
Disease duration (yrs)	14.47	(8.38)	12.42	(9.02)	$p = 0.605$
Sharp score					
Initial values	81.97	(22.08)	104.28	(37.12)	$p = 0.034$
Progression prior to inclusion in the study (mean change per year)	7.03	(5.20)	10.90	(6.91)	$p = 0.015$
RF positivity	n = 30 (47.6%)		n = 22 (61.1%)		$p = 0.199$

[1]Significance level of the standard t-test for two independent samples and of the binominal two-sample test in the case of RF positivity.

increase in the TSS was 2.06 Sharp units, rising from 90.08 (84.6; 95.5) to 92.14 (86.6; 97.7). This score comprised both the erosion score (1.2) and the joint space narrowing score (0.86) (Table III). Progression was almost identical in the hands (1.0) and feet (1.1). The median TSS change of 2.0 was close to the mean of 2.06, which documented the symmetry in the distribution of changes. Compared to the state before biological treatment was initiated, average radiographic progression decreased from 8.56 to 2.06 (0.05; 62.86) ($p < 0.001$) (Fig. 1).

Factors predictive of radiographic progression

Among the total number of 99 patients, progression was noted in 36 patients; 63 patients showed no radiographic advancement. When both groups were compared, it was found that the initial TSS values were higher (104.3 ± 37.1 *vs* 82.0 ± 22.1; $p = 0.034$) in those patients who radiographically progressed (Table IV). Patients with any radiographic progression during the one-year treatment also had a significantly higher estimated yearly radiographic change in TSS before the initiation of biological treatment (10.9 ± 6.9 *vs.* 7.0 ± 5.2; $p = 0.015$). In the group of patients with progression, smaller radiographic changes were noted during the one-year treatment with infliximab compared to the estimated yearly progression before the treatment (yearly change in TSS: 3.84 ± 0.85 *vs.* 10.9 ± 6.9; $p = 0.011$).

There was no significant difference in rheumatoid factor status in the two groups in relation to radiographic progression (Table IV). RF positive patients had higher estimated radiographic progression before infliximab treatment (9.2 ± 6.3 in RF positive *vs.* 7.8 ± 10.8 in RF negative patients; $p = 0.029$). No difference was seen in the progression between RF positive and RF negative groups during the one-year treatment period in the whole studied population (2.3 ± 4.1 *vs.* 1.9 ± 5.0; $p = 0.2$) or when only those with radiographic progression were evaluated (5.3 ± 4.9 *vs.* 6.2 ± 7.6; $p = 0.88$). Age, disease duration and baseline ac-

tivity (DAS28) had no predictive value for radiographic progression during infliximab treatment (Table IV). No significant differences were found between the groups of patients with and without radiographic progression when comparing the changes in the activity parameters (DAS28 and its components, CRP) and the functional and quality of life assessments (Table V).

Table V. Relationship between radiographic progression and the changes in various clinical and laboratory assessments.

Parameter (difference between week 0 and week 54)	Therapy with infliximab: radiographic progression				Statistical significance[1]
	No progression (n = 63) Mean change w54 – w0 (SD)		Progression (n = 36) Mean change w54 – w0 (SD)		
DAS28 score	2.71	(1.34)	3.08	(1.86)	$p = 0.304$
No. of swollen joints	9.44	(5.64)	9.72	(5.06)	$p = 0.812$
No. of painful joints	12.11	(7.58)	12.39	(6.84.)	$p = 0.861$
CRP	16.96	(8.23)	17.46	(7.37)	$p = 0.949$
Quality of life					
HAQ	0.474	(0.507)	0.371	(0.418)	$p = 0.384$
EuroQol	0.317	(0.332)	0.341	(0.307)	$p = 0.751$
SF-36	21.94	(19.83)	18.05	(13.62)	$p = 0.343$

[1]Significance level of standard t-test for two independent samples.

Discussion

Maintaining national registries of patients receiving biological treatment is highly recommended by international organizations, consensual documents and regulatory agencies (20). The primary aim of these registries is to allow the post-marketing evaluation of rare, but serious adverse events and the documentation of long-term treatment effects. Only a few registries provide an objective evaluation of therapeutic effect (based, for example, on the DAS) or evaluate the radiographic progression of the disease. The follow-up of these variables in our registry enabled us to assess the effect of biological treatment on the radiographic progression of the disease in general clinical practice, outside the scope of a clinical study.

The first question was whether the introduction of biological treatment in our group of patients would slow the radiographic progression. The patients in this study were suffering from severe RA, with an average disease duration of almost 14 years; they had failed on average 2–5 therapeutic courses with DMARDs, had very high disease activity, and the radiological damage accumulated at the start of the study was 90 TSS units. Their estimated yearly radiographic progression was 8.6 TSS units, which corresponds to or exceeds the described progression in longitudinal as well as therapeutic studies (5, 6, 21, 22).

The results in our cohort confirmed the remarkable effect of infliximab on radiographic progression. After one year of treatment, 63 out of 99 patients did not show any progression of the disease, in contrast to the rapid yearly progression of 7 units shown by them as a group before the introduction of infliximab. Further evidence of this comes from 36 patients who continued to show radiographic progression during treatment, but whose yearly progression decreased from almost 11 Sharp units to less than 4 units. In the entire group progression was reduced 4-fold, from 8.6 units before the treatment to 2.1 units after the treatment with the anti-TNF agent. This absolute rate of progression (2.1) was slightly higher than in the ATTRACT trial, which showed a yearly radiographic change in the group of patients treated with the same scheme of only 1.3 ± 6.0 units (5). The higher radiographic progression in our patients could be due to difference in the groups studied. Our group contained patients who were the first to be treated with this anti-TNF agent in the country and this may have led to a selection bias as the patients enrolled were most likely those with most severe and resistant disease. The level of estimated yearly progression in our patients (8.6) was also somewhat higher than in the ATTRACT study (7.7), which would support this hypothesis.

It may be argued that the rate of the previous estimated yearly progression is not comparable to the actual observed progression during treatment. Estimated progression is limited by errors in the dates of disease onset and is less valid in patients with a short disease duration (14). However, if the patient groups are of sufficient size, the mean change scores will approximate linearity over time and any variability in progression will become more uniformly distributed (14). Recently, it was demonstrated in a review of 3 of 4 randomized control trials that mean changes in composite scores in the placebo groups approximated or exceeded the estimated yearly progression rates (14). It seems that in patients with a long disease duration this approach can be used to compare the rate of progression during the treatment, particularly when the effect of the drug allows clear distinctions.

Another question that was addressed was the difference at baseline between patients who either did or did not show radiological progression during further treatment. No significant differences were noted between these two groups with regard to the disease activity measured by DAS28 and CRP, age or disease duration. The rate of radiographic changes and the number of lesions accumulated before infliximab treatment were higher in those patients who later showed radiological progression. Rheumatoid factor positive patients progressed more rapidly before the treatment and this effect was lost during infliximab therapy. In a recent report, anti-CCP antibodies above 100 u/ml were more frequent in non-responders to anti-TNF treatment than in responders (23). In our patients, we could not confirm this negative predictive effect of rheumatoid factor on the clinical response or on radiographic progression during infliximab treatment. Our study was started before anti-CCP detection

had become a routine procedure and in most cases pre-study sera were not available for additional measurements to allow a comparison of anti-CCP antibodies.

In the majority of studies, the strongest predictors of radiographic progression were found to be sustained high levels of acute phase reactants and RF positivity (24). Our study showed that a single evaluation of disease activity by DAS28 and CRP had no predictive value. The selection of patients who have long-standing serious disease with a one-time determination of disease activity could have affected this result. The uncoupling of inflammatory disease activity and radiological progression has been observed in recent clinical trials, such as the ASPIRE study (5, 25, 26). Here the clinical and laboratory indicators had no predictive value in the group of patients treated with infliximab + MTX. On the other hand, the higher Sharp scores and the estimated faster progression at baseline in those of our patients who later progressed are in good agreement with the published data (24, 27). Similarly, in the ASPIRE study it was established that the initial Sharp score and faster progression in individual patients had a significant predictive value (26).

In conclusion, we have shown that in the setting of normal clinical practice the administration of TNF blocking therapy for 12 months led to a 4-fold slowing in radiographic progression. More than 60% of patients did not show any progression at all. Changes in clinical outcomes did not correlate with radiographic progression. The total Sharp score evaluated at baseline and the estimated rate of radiographic changes before the initiation of the study were predictive factors of further progression.

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