

Anti-TNF therapy of ankylosing spondylitis in clinical practice. Results from the Czech national registry ATTRA

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Abstract

Objectives

To estimate efficacy, safety and adherence to therapy of ankylosing spondylitis (AS) patients included in the Czech National Registry ATTRA, and to look for predictive factors for therapy discontinuation.

Methods

Patients were included according to the guidelines of the Czech Society for Rheumatology, which involve failure of previous therapy, BASDAI >4, and CRP >10 mg/l. Only patients with anti-TNF administered for the first time were analysed. Adherence to therapy was evaluated using Kaplan-Meier analysis and results were presented as cumulative survival. Comparison with data on patients with rheumatoid arthritis (RA) followed in the same registry was made.

Results

310 of AS patients who had reached at least 1 year as well as those who discontinued the treatment before this time point were analysed. Drug survival was longer in patients with AS than in those with RA: 84% vs. 78% and 72% vs. 49% after 1 and 3 years of treatment. Significant risk factors for treatment discontinuation were female gender (RR 2.22, $p=0.001$) and CRP (RR 1.33, $p=0.025$).

The proportion of patients with BASDAI <4 during the treatment period was higher in the etanercept group than in the infliximab group ($p<0.001$). The number of patients fully employed increased in the whole group from 48% to 63% after 1 year of treatment.

Conclusion

Follow-up of patients with AS in the national registry shows that it is an effective and safe way of treatment with longer adherence to anti-TNF therapy in comparison with RA patients.

Key words

Ankylosing spondylitis, anti-TNF therapy.

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Introduction

Ankylosing spondylitis (AS) is an inflammatory disease of axial skeleton and peripheral joints affecting 0.2–0.5% of the population (1). It is a serious condition which significantly reduces the quality of life of patients causing disability (2) comparable to situation in rheumatoid arthritis (RA).

Recommendations for the management of AS were formulated by EULAR using evidence-based medicine principles (3, 4, 19). There is an evidence of efficacy only for exercise and physical therapy (5), nonsteroidal anti-inflammatory drugs (6), intraarticular glucocorticoids (7), sulphasalazine in peripheral arthritis (8) and TNF blocking agents (9–11). Anti-TNF agents have a rapid and robust effect in AS. They alleviate pain and improve the physical function of patients. Their efficacy has been confirmed in both early and advanced stages of the disease, and even in patients who have developed “bamboo spine”. Moreover, anti-TNF agents act on all of the involved structures – *i.e.* both peripheral synovitis and enthesitis, as well as spondylitis. Potential benefit on extraarticular manifestations and associated conditions such as uveitis, inflammatory bowel disease, osteoporosis and cardiovascular mortality has also been discussed (12).

Results from a number of clinical randomised studies and their extensions have been published. Yet, data concerning the treatment of AS in routine clinical practice is relatively scarce (20) and published results from registries have focused on rheumatoid arthritis so far. The Czech national registry of patients with the three basic rheumatological diagnoses treated by biological agents was established in 2001 and currently contains over 2,000 patients. Patients with AS have been enrolled since 2003. In this paper we use this registry to describe survival rates of ankylosing spondylitis patients on individual TNF blocking agents and present the data on the efficacy and safety of this treatment in the routine rheumatological practice.

Materials and methods

Patients with ankylosing spondylitis treated in the ATTRA Registry between

2003 and 2008 were analysed. The ATTRA registry collects data about all patients with rheumatoid arthritis and ankylosing spondylitis treated by biologics in the Czech republic. To be eligible for inclusion into the registry patients had to fulfil the following criteria of the Czech Society of Rheumatology for treatment of ankylosing spondylitis with anti-TNF drugs (13): high disease activity (BASDAI higher than 4) (14), CRP over 10 mg/l, failure to respond to nonsteroidal anti-inflammatory drugs, and to sulphasalazine and to locally administered glucocorticoids in peripheral forms with arthritis. All patients have been treated in centres of biological therapy. The selection of anti-TNF drug is left to the discretion of treating physician, with individual patient characteristics and preferences taken into account. Standard doses of TNF blocking agents were used without the possibility of dose titration: 5 mg/kg infliximab intravenously in the intervals of 0, 2 and 6 weeks and after induction every 6 weeks, 50 mg etanercept subcutaneously once a week and 40 mg adalimumab subcutaneously every other week. The monitored treatment efficacy endpoints were: BASDAI, BASFI, HAQ, Euroqol, CRP and erythrocyte sedimentation rate, global assessment of disease activity by patient and physician, radiographic progression, incapacity and inability to work. The measured values are presented as mean \pm SD. The drug survival rates and reasons for treatment discontinuation were also closely followed. This study analysed the first anti TNF drug course only. Adherence to therapy was evaluated using Kaplan-Meier analysis and results were presented as cumulative survival (95% confidence interval). Cox regression was used for the evaluation of risk factors of treatment discontinuation. Adverse events were actively monitored. Screening for latent tuberculosis infection was carried out prior to the start of treatment. All study subjects provided informed consent.

Results

In total, 310 patients who had sufficient data from at least one year of treatment or had discontinued prior to this date were analysed. The demographic data

Competing interests: none declared.

of AS patients before the start of anti-TNF treatment is provided in Table I. Table II provides demographic characteristics and endpoints of activity in relation to individual anti-TNF agents and implies that among individual groups, there were no significant differences in terms of age or disease duration and disease activity expressed by BASDAI and acute phase reactants.

Drug survival rates

Survival of the entire group of AS patients on anti-TNF agents was significantly longer than in patients with rheumatoid arthritis enrolled in the registry (84% (95% CI: 80–88%) vs. 78% (95% CI: 75–81%) after 1 year, 76% (95% CI: 71–81%) vs. 59% (95% CI: 55–62%) after 2 years, 72% (95% CI: 67–78%) vs. 49% (95% CI: 46–53%) after 3 years, $p < 0.001$) (Fig. 1). The 25th percentile of adherence to therapy was 12.4 months for rheumatoid arthritis, and 25.1 months for ankylosing spondylitis. There was no significant difference of drug survival length between agents (etanercept against infliximab, $p = 0.057$). The number of AS patients treated with adalimumab was relatively low due to later of approval for AS indication. Forty-seven of 80 patients who failed treatment were switched to a second anti-TNF agent. The analysis of the second anti TNF course is in progress.

Risk factors of treatment discontinuation

Incidence of treatment discontinuation was 49/153 (16/100 patient-years) in infliximab, 8/30 (19/100 patient-years) in adalimumab and 23/127 (8/100 patient-years) in etanercept groups.

Risk factors which may signal an increased probability of treatment discontinuation at the very start of treatment have been studied. Gender was a risk factor of treatment discontinuation, with significantly longer adherence to therapy in men than in women (RR 2.22, $p = 0.001$) (Fig. 2). An increased CRP value was another risk factor (RR 1.33, $p = 0.025$). On the other hand the risk of treatment discontinuation was not affected by the changes of BASDAI during the treatment (RR 1.14, $p = 0.487$), by disease duration (RR

Table I. Demographic characteristics of the AS and RA patient set.

Diagnosis	AS	RA
Number of patients	310	958
Mean age (years)	36.8 ± 9.7	45.9 ± 13.9
Mean disease duration (years)	8.1 ± 6.9	10.3 ± 7.5
Men / women (%)	76.8 / 23.2	23.4 / 76.6
BASDAI	6.4 ± 1.7	–
BASFI	5.4 ± 2.1	–
HAQ	1.09	1.50
CRP	31.0 ± 26.5	31.6 ± 32.7
Applied agent (counts)		
Infliximab	153	464
Etanercept	127	172
Adalimumab	30	322

Table II. Comparison of patient demographic data and individual agents in AS (n=310).

	infliximab n=153	adalimumab n=30	etanercept n=127	p-value
Age (mean ± SD)	37.3 ± 9.7	34.6 ± 8.9	36.9 ± 9.9	0.402
Disease duration (mean ± SD)	7.9 ± 6.2	9.8 ± 8.9	7.9 ± 7.1	0.740
Gender m/f (%)	82.4%	66.7%	71.7%	0.098
BASDAI	6.9 ± 1.5	6.2 ± 1.8	6.4 ± 1.7	0.078
ESR mm/hr	41.2 ± 21.8	39.0 ± 22.4	39.3 ± 24.3	0.672
CRP	30.4 ± 24.2	31.1 ± 22.2	31.6 ± 30.2	0.813

BASDAI: BATH Ankylosing Spondylitis Diseases Activity Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

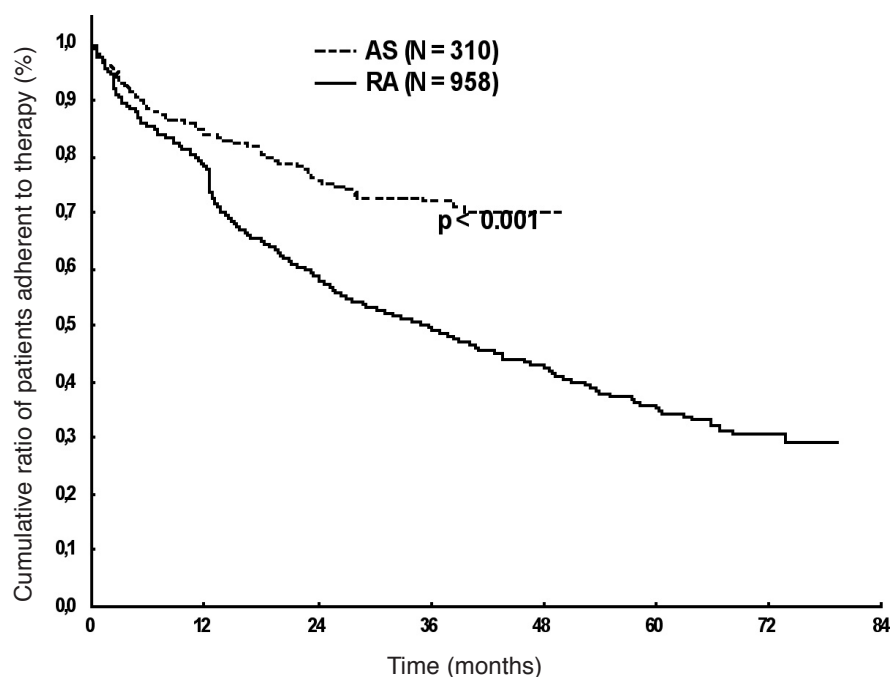
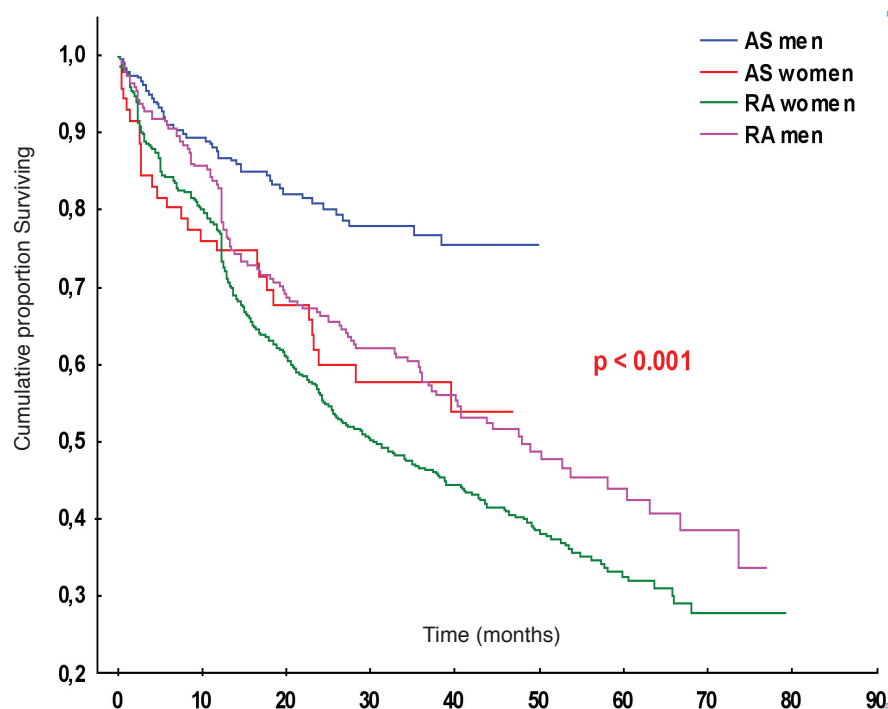


Fig. 1.



$p < 0.001$
 AS men x AS women $p = 0.001$
 RA men x RA women $p = 0.004$
 AS men x RA men $p < 0.001$
 AS women x RA women $p = 0.279$

Fig. 2.

Table III. Reasons for discontinuation of treatment.

	Infliximab (n=49/153)	Adalimumab (n=8/30)	Etanercept (n=23/127)
Incidence of discontinuation of treatment	16/100 py	19/100 py	8/100 py
Adverse events	13 (26.5%)	3 (37.5%)	7 (30.4%)
Lack of efficacy	10 (20.4%)	1 (12.5%)	7 (30.4%)
Loss of effect	3 (6.1%)	0	0
Remission	4 (8.2%)	0	2 (8.7%)
Patient's request or other reasons	10 (20.4%)	3 (37.5%)	4 (17.4%)
Death	3 (6.1%)	0	0
Unknown	6 (12.3%)	1 (12.5%)	3 (13.1%)

Py: person-years.

Table IV. Efficacy of anti-TNF therapy in treatment of AS (all anti-TNF agents) (n=310) (LOCF).

	Baseline (n=310)	3 months (n=286)	6 months (n=271)	9 months (n=263)	12 months (n=256)	24 months (n=148)	36 months (n=78)
BASDAI	6.4 ± 1.7	3.6 ± 2.6	3.1 ± 2.5	3.2 ± 2.6	3.1 ± 2.6	2.9 ± 2.5	3.0 ± 2.5
CRP	31.0 ± 26.5	5.2 ± 10.2	5.7 ± 10.6	6.5 ± 14.5	6.7 ± 14.0	7.5 ± 15.6	7.5 ± 16.2
ESR	40.2 ± 22.9	9.7 ± 11.0	10.7 ± 11.5	11.6 ± 12.8	11.8 ± 13.5	11.9 ± 13.1	12.1 ± 14.0
BASDAI < 4 (%)	7.6	60.1	65.9	63.8	67.0	70.0	69.3

BASDAI: BATH Ankylosing Spondylitis Diseases Activity Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

1.01, $p = 0.712$) and by presence of hip involvement (RR 0.67, $p = 0.181$).

Reasons for treatment discontinuation

Adverse events were the most frequent reason for treatment discontinuation, accounting for 30.4% of cases of treatment discontinuation in patients treated with etanercept, 37.5% in those with adalimumab and 26.5% with infliximab. Lack of efficacy caused 30.4% treatment discontinuations in etanercept, 20.4% in infliximab and 12.5% in adalimumab groups (Table III). Statistical comparison was not performed due to different length of follow up of agents used and different number of patients treated in particular years.

Efficacy of treatment

The BASDAI score is the most frequently used measurement of AS activity (14). Upon the start of treatment, the mean BASDAI value was 6.4 ± 1.7 . After 3 months, a drop to mean values of 3.6 ± 2.6 was observed, after 12 months of treatment the mean BASDAI value was 3.1 ± 2.6 . This effect persisted similarly both in month 24 and 36 (Table IV).

CRP values and erythrocyte sedimentation rate (ESR) are the most important laboratory measures of disease activity. Initial mean CRP values were 31.0 ± 26.5 mg/l and a significant drop was apparent as early as after 3 months of treatment (5.2 ± 10.2 mg/l). This effect then persisted for up to 3 years of follow-up. A similar change is apparent also in the levels of ESR (Table IV).

The proportion of patients with BASDAI < 4 was higher in etanercept than in infliximab group. This difference was significant from month 3 (n=286, $p = 0.004$) to month 36 (n=78, $p < 0.001$) (Fig. 3).

Ability to work

The proportion of patients who were fully employed increased from 48% at baseline to 63% after one year of therapy with anti-TNF agents.

Discussion

Nowadays, the drug survival duration is considered to be an important measure of performance of biological agents. This is sometimes referred to as

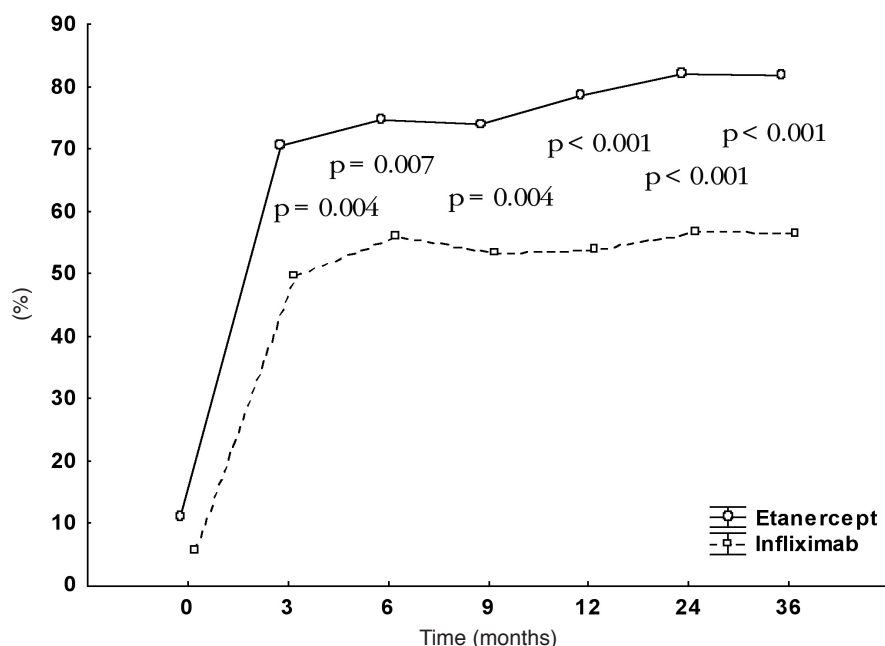


Fig. 3. Percentage of patients with BASDAI <4.

'adherence to therapy'. It is a composite measure comprising both clinical efficacy factors and tolerance to an agent as well as factors associated with the administration of a given agent. Registries of patients treated with biological therapy represent the most important source of information on drug survival of patients (15, 16).

The first finding of the current study is a known fact, namely that adherence to therapy is better in AS than in RA, this has also been confirmed by randomised studies as well as cohort monitoring in registries and in clinical practice. The reason for this phenomenon is not well understood; the possible causes are: more frequent concomitant medication in RA patients, higher proportion of men than women (men showing better adherence to therapy) or lower age of patient sets in AS compared to RA. Availability of fewer alternative treatments for AS may also be the cause. Our results are in line with Finnish authors' experience, who have observed treatment discontinuation in the first two years of treatment with the first anti-TNF agent in only 7% of cases due to lack of efficacy, and in 6% of cases due to adverse events (15).

The female gender and CRP values were risk factors for treatment discontinuation in our ATTRA registry. No

association has been found between treatment discontinuation and disease duration, BASDAI values, and presence of hip involvement. This fact needs to be highlighted, as some studies have shown better results in patients with shorter disease duration (17).

There was a trend with borderline significance of longer drug survival for etanercept than for infliximab which was previously reported in RA patients (18). Our cohort study has confirmed that anti-TNF therapy in AS has high efficacy with rapid and lasting effect (9, 16). The proportion of non-responders in AS is significantly lower than in RA and it has already been verified that patients without clinical response can be, in most cases, successfully managed by switching to another agent (18).

Ankylosing spondylitis is often linked with an inability to work and significant loss of work days, followed by partial or total disability. In previous study, we have found that up to 60% of patients with AS have some kind of disability (2). Analysis from ATTRA registry has shown that the proportion of working patients was 48% at baseline, and increased to 63% after one year of treatment. This fact may lead to a significant decrease of indirect costs associated with treatment of this chronic condition.

It may be concluded that results from the Czech national registry of AS patients treated with anti-TNF agents confirm a very good efficacy with low occurrence of adverse events and good adherence to therapy.

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