**Real life experience with switching TNF-α inhibitors in ankylosing spondylitis**

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## Abstract

*Objective:* The aim of this study was to evaluate efficacy, reasons for switching and drug survival of TNF-α inhibitors (TNFi-s) used as first and second line drugs in ankylosing spondylitis (AS).

*Methods:* Data of patients suffering from AS and treated with at least one TNFi between November 2005 and November 2013 were extracted retrospectively from the database of one clinical center. Beside demographic data, the disease activity measured by BASDAI, the response rates (BASDAI50), reasons for switching and survival curves of TNFi-s were analyzed in general and in subgroups of patients treated with each of the available TNFi-s. The reasons for switching were defined as inefficacy, side effect of the given drug, patient's request, and occurence of extra-articular manifestations.

*Results:* Altogether 175 patients were on TNFi and 77 of them received at least 2 TNFi-s. The patients' age at the initiation of the first TNFi was higher among switchers compared to non-switchers (42.5±12.6 vs 38.8±11.2 years, p=0.049), otherwise gender, disease duration and initial disease activity had no influence on the risk of switching. The decrease of BASDAI was similar among non-switchers and switchers either using the first or second TNFi, but the response rates to the first and second TNFi were worse in switchers than in non-switchers. Following the failure of first TNFi, the retention on therapy was unfavourable, especially in patients on infliximab after one year of treatment. The main reason for switching from the first drug was inefficacy. The frequency of side effects that led to switching was higher in the infliximab group than in patiets treated with other agents.

*Conclusion:* Although the retention rate to a second line TNFi was somewhat worse than that to the first line TNFi, switching of TNFi-s is a good therapeutic option is AS patients who failed to respond to the first TNFi.

*Key words:* ankylosing spondylitis, anti-tumour necrosis factor-α therapy, switch

## Introduction

During the last decade, TNF-α inhibitors (TNFi-s) have revolutionized the treatment of ankylosing spondylitis (AS) patients who failed to respond to non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy. According to the meta-analysis of randomized-controlled trials (RCTs), it became evident that all available TNFi-s (adalimumab, etanercept, infliximab and golimumab) exert similar effects on signs and symptoms of the axial components of the disease (1-5).

The use of TNFi-s in patients with AS is regulated by the ASAS (Assessment in SpondyloArthritis international Society) recommendations which usually serves as a basis for national protocols. On the basis of ASAS guideline, those AS patients are eligible for TNFi therapy who has active disease as determined by BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) and do not respond to at least two NSAIDs (6). Although the ASAS/European League Against Rheumatism (EULAR) recommendation clearly states that there are no differences in efficacy among the TNFi-s on the axial and articular/entheseal disease manifestations (7), it has been documented in several clinical trials that the anti-TNF monoclonal antibodies (adalimumab, infliximab and golimumab) can be used successfully in the treatment of most common extra-articular manifestations of the disease, while etanercept has milder effect on uveitis and inflammatory bowel diseases (8;9). According to these observations the difference in gastrointestinal efficacy of each TNFi-s is suggested to be taken into account by ASAS/EULAR guidelines (7), but beyond this aspect there are no therapeutic recommendations how to choose between TNFis or how to switch between these agents.

Biological therapy provides significant improvement in disease activity, functional capacity and disease-related quality of life for most of AS patients in a long term period, even after an 8 year-long continuous treatment (10). However, some of the patients may not respond properly to the initial TNFi and their symptoms worsen over time. Another proportion of patients experience side effects related to the drug which interfere the continuation of the treatment. As the TNFi-s are structurally different and they have different mechanism of action, an unsuccessful treatment with a drug does not preclude response to another one (11).

The efficacy of switching between TNFi-s in AS and axial spondyloarthritis (SpA) has been evaluated in a limited number of large studies. In the RAPID-axSpA trial, less than 40% of patients could be successfully treated with a TNFi for a period more than 3 months before certolizumab-pegol treatment, if the reason of discontinuation was other than primary failure. The subgroup analysis of trial has not been published yet (12). In an open label trial, 26.1% of 1250 AS patients treated with adalimumab had previously received etanercept and/or infliximab. Among patients used adalimumab as second line treatment worse response rates of BASDAI50, ASAS40 and partial remission could be observed than in patients treated with this drug as first line choice (13).

The Danish and Norwegian national registries provide data of AS patients who switched to another biologic (14;15). In the DANBIO registry data of 432 patients that switched to a second and those of 137 patients switched to a third TNFi were analyzed and compared to data of 1004 non-switchers. It was concluded that response rates and drug survival were lower

among switchers. The NOR–DMARD register evaluated the effectiveness of second TNFi-s among 77 switchers with AS and switching to a second TNFi was found to be a useful way in daily practice, although it results in lower overall effectiveness.

As available data on efficacy of primary and subsequent TNFi therapy and predictive factors of effectiveness of the second choice drug are controversial, and few systematic analyses of reasons of switching and treatment responses of each TNFi-s among switchers and non-switchers have been published, we wished to assess these issues under real-world circumstances. In the present study the reasons for switches, the effect of TNFi-s on disease activity among switchers and non-switchers, the predictive factors of effectiveness and drug survival were analysed in a relatively large number of AS patients treated in one rheumatology center.

## Patients and methods

All AS patients treated with any TNFi-s at the Department of Rheumatology, University of Debrecen, Hungary between November 1, 2005 and November 30, 2013 were included in this study. A total of 175 AS patients, as defined by modified New York criteria were included in the study. Ninety-eight patients remained on the first line TNFi, while 77 of them were treated with at least two different biologics. First and subsequent therapies were one of the following four drugs: adalimumab, etanercept, golimumab and infliximab. These biologics were used according to the standard clinical practice: adalimumab 40 mg every second week subcutaneously (sc); etanercept 50 mg weekly sc; golimumab 50 mg monthly sc; and infliximab 5 mg/kg every eight weeks intravenously (iv) after induction doses at baseline, and after 2 and 6 weeks. All biologics were administered according to the Hungarian national protocol which is similar to the ASAS recommendations (6;16). Before TNFi therapy all patients had active disease defined by elevated BASDAI (≥4 on a visual analog scale, 0-10) despite prior treatment with at least 2 different NSAIDs or at least one NSAID if it was not tolerated or without prior NSAID treatment if it was contraindicated.

The reasons for switches between TNFi-s were inadequate response to the drug as defined by elevation of BASDAI at two subsequent controls to 4 or above at 3 months after the initiation. The other reasons for stopping therapy and/or switches were side effects or patient's request (e.g. request to change from iv to sc administration or planned pregnancy) or development of a new extra-articular manifestation. The reasons for switching were classified into prespecified categories: primary and secondary inefficacy (IE), side effect of the drug (SE), appearrance of extra-articular manifestation required switching (EA) and patient's request (PR). There were 3 patients who were treated further in another rheumatology center and it was impossible to get accurate informations about their disease, so they were excluded from further data analysis.

The study design was a retrospective, one-center, observational analysis with assessments performed at baseline, and after 3, 6 and 12 months. The demographics of patients, date of

diagnosis, start and stop date of each biologic therapy, the BASDAI at baseline and during treatment, response rates (BASDAI50) and reasons for switches were collected.

We used the product limit method of Kaplan and Meier to estimate how long patient remained on a given biological drug. Drug survival was calculated as the number of months between the dates of first dose and last dose of the same drug. As adalimumab and especially golimumab were approved later for treatment AS than infliximab and etanercept the follow-up periods were shorter in the case of aforementioned drugs.

Data were analyzed using the IBM SPSS 20 statistical software. Baseline demographics and diseases characteristics were analyzed with frequency calculation and descriptive statistics (chi square test, independent sample t test and Mann-Whitney test). The estimated drug survivals were calculated by Kaplan-Meier method. We used log-rank test to compare the distributions. $P<0.05$ was considered significant.

## Results

*General characteristics*

Of the 175 AS patients who treated with any of the TNFi-s, 77 switched to a second and 11 out of 77 to a third TNFi. Infliximab was the most commonly administered TNFi as first choice treatment. Out of 68 patients treated with this drug, 39 patients (57%) required switch to a seccond TNFi. These ratios were 10 out of 40 (25%) with adalimumab, 25 out of 58 (43%) with etanercept and 3 out of 9 (33%) with golimumab, respectively. As third choice treatment, golimumab was used most often (6 patients) followed by adalimumab and etanercept (3 and 2 patients, respectively) (figure 1.).

The baseline characteristics for patients treated with and without switching of TNFi-s are summarized in table 1. Significant differences were found between the two groups with regards to age of patients at the initiation of the first TNFi. Patients who switched TNFi during the course of their disease were older compared to non-switchers (42.5±12.6 v. 38.8±11.2; p=0.049).

*Effectiveness of treatment*

The effect of treatment assessed by BASDAI was followed during the first 12 months. The improvement of BASDAI to the first choice drug was similarly significant among switchers and non-switchers (at start of treatment: 7.06±1.30 and 7.11±1.18; p=0.468, at month 3: 2.38±1.21 and 3.15±1.98; p=0.058 among non-switchers and switchers, respectively). Although a worsening of BASDAI could be seen among switchers used golimumab between 6th and 12th months, but it can be explained by increase of this value of a single patient. As the number of patients on golimumab was rather small compared to other treatment groups, this result is difficult to interpret. The data of patients came through 2 switches were not

analyzed because of low number of patients belonging to each treatment groups. Analyzing BASDAI values after switching all of the second TNFi-s led to similar improvements between 0 and 3 months as it could be observed by using first TNFi (5.44±2.40 and 2.16±1.58, respectively), although the initial BASDAI values before switching were lower than in TNFi naïve patients, as a significant proportion of them switched due to side effect to the first drug and it was associated with low BASDAI value before starting the second TNFi. However, after this period a significant worsening of BASDAI could be detected in 8 patients treated with infliximab and this unfavourable change continued between the 6th and 12th months (figure 2.).

The response rates to the first TNFi measured by BASDAI50 were generally inferior in 77 switchers than in 98 non-switchers (at 3rd, 6th and 12th months 72.3%, 74.6%, 70.8% in non-switchers and 56.0%, 51.0% and 54.3% in switchers, repectively). The treatment with the second TNFi after 3, 6 and 12 months achieved similar BASDAI50 responses (51.6%, 50.9% and 46.9%, respectively) than those of among switchers to the first TNFi.

*Reasons for switching*

The reason for switching to a second TNFi was IE in most cases (42 patients out of 77). Switching was necessary due to any type of AEs in 23 patients. These AEs most often included infusion reactions in patients treated with infliximab and localised/generalised reactions to sc injections. The patient's request was the cause of switching in 5 cases resulted in 4 switches in the infliximab and one in the adalimumab group. During TNFi therapy, 6 extra-articular manifestations (3 uveitis flares, 2 inflammatory bowel diseases and one psoriasis) developed that required switching. Most of these patients were treated with etanercept and after occurrence of these manifestations they were switched to any of the anti-TNF monoclonal antibodies which can be used more effectively in these comorbidities. While the most common reasons for switching were IE in the adalimumab, etanercept and golimumab groups, the ratio of IE and SE necessitated stop of first choice drug were almost equal among infliximab treated patients (table 2).

*Drug survival*

In our study, the overall survival times of first line TNFi-s was better than it could be observed with second line drugs (62.88 months (CI 95%: 56.67-69.09) and 39.29 months (CI 95%: 31.29-47.03), p=0.05, respectively). Comparing the various TNFi-s used as first line drugs, the longest retention times were observed with adalimumab (66.6 months (CI 95%: 56.84-76.50)) and etanercept (66.8 months (CI 95%: 56.20-77.56)). The mean drug survival times for infliximab and golimumab were 52.5 (CI 95%: 42.82-62.26) and 33.4 (CI 95%: 23.14-43.66), respectively, however we should note that golimumab received European approval for treatment AS much later than the other TNFi-s. When these drugs were administered as second line treatment, the drug retention times were 41.2 (CI 95%: 30.53-52.00) months with adalimumab, 31.3 (CI 95%: 10.42-52.29) months with etanercept, 36.6 (CI 95% 29.20-44.11) months with golimumab and 9.3 (CI 95%: 3.36-15.24) months with infliximab.

Based on Figure 3. there is an impression that retention to first line therapy was superior among patients treated with adalimumab and etanercept compared with infliximab users. Among patients used infliximab as first line drug a sharp decrease could be observed in drug survival between 13th and 17th months of treatment (at month 13: 84.5%, at month 17: 71.0%). Due to the above mentioned reason, the retention curve of golimumab is shorter than those of other drugs. Although the number of treated patients in each groups are rather low after switching, the best drug adherence could be experienced in golimumab, the worst one in the influximab-treated patients.

**Discussion**

According to our one-center observational study, almost half of the AS patients treated with TNFi switch their firstly used drug to another one, while only a small proportion of them would switch to a third TNFi during a follow-up period of up to 8 years. Switches could be detected more frequently among older patients. Although the efficacy of first and second TNFi-s seemed to be similar, as no differences could be measured between each TNFi-s by decrease of BASDAI values, the retention rate of infliximab was worse than those of other TNFi-s. The most common reasons for switching were the loss of effect among adalimumab, etanercept and golimumab treated patients, while in infliximab treated patients the ratio of inefficacy and side effect led to switching were almost equal.

The effectiveness and safety of biological drugs in AS have been proved by RCTs. Cost-effectiveness models with input from RCTs, however, represent results obtained under rigorous experimental conditions. The precision and applicability of these data to other settings may be argued. In the real world of prescription and use, drugs are applied in a broader population, use of concomittant medicines may vary, the same as patients' compliance and their expectations for health (17). Moreover, biological drug sequences that do indeed occur in everyday practice (e.g., switch to a third or fourth drug, return back to a previous one) have never been studied in RCTs. These discrepancies may alter both effectiveness and safety, as well as drug survival rates. Thus alongside the growing body of actual practice data with biologicals there is an increasing need to use registry data in cost-effectiveness analyses that reinforces their value. Moreover, the demand for health technology assessments (HTA) based on local data is getting higher and higher (18-22).

National registries and observational studies have proven that the frequencies of switches between biologics are higher among patients with rheumatoid arthritis and psoriatic arthritis than in AS, even though patients with peripheral arthritis are usually treated with disease modifying antirheumatic drugs (DMARD), which, at least theoretically, should postpone the loss of effect. The ratio of AS patients switched to a second TNFi out of TNF naive patients were 15% and 30 % in Norwegian and Danish nationwide registries in a 8-9 years of follow-up. Similar switching frequencies (13-15%) have been published in observational studies included around 100 AS patients (23;24). In contrast, in our retrospective study much higher frequency of switching could be detected. It can be explained by the strict Hungarian regulation of monitoring of effectiveness during the course of treatment. According to this

regulation the TNFi is considered to be effective if the BASDAI value decrease at least 50% or 2 units between 0 and 3rd months of treatment and BASDAI do not exceed the value observed at months 3 at 2 following visits. Thus, a relatively large proportion of patients underwent switching despite only moderate worsening of symptoms.

We found that disease activity, measured by BASDAI decreased significantly both in group of non-switchers and switchers under the treatment of first line TNFi-s, but among switchers this improvement was somehow less. On one hand, the primary lack of efficacy and early switching due to loss of efficacy (ie. before the end of 1 year follow-up) may cause this difference, but on the other hand, the milder effect of first line drug before switching can also influence this result. As in our study only 5 out of 77 switchers were primary non-responders to TNF-i, we can suppose that the decrease of BASDAI may be in connection with the risk of subsequent switching.

In our cohort, the age of the switchers was significantly higher than those of non-switchers at start of first TNFi. No differences could be demonstrated in initial BASDAI values and disease duration. Switchers were more frequently women than men, but this difference was not statistically significant. This finding seems to be logical as the TNFi-s are able to decrease inflammation which is typical in earlier stage of the disease and presumably in younger age, but this difference was not reflected by the disease duration. In national registries the higher median values of initial BASDAI were congruent, but the higher percentage of women, shorter disease and symptom duration, higher diasease activity and functional indices were found among switchers compared to non-switchers (14;15).

Although the national registries and observational studies included relatively large number of patients undergoing TNFi switching, no data are available about outcome of treatment with each TNFi-s, which is in connection with survival rate of these drugs. It is obvious, that our study is underpowered due to the limited number of switches and the non-randomised study design, but noticeable results were obtained with respect to reasons for stopping of each biological agent. In general, inefficacy was the most common cause of switching of primary treatment, which usually occured at least 3 months after the start of treatment, so it was secondary loss of effect. However, in the infliximab group, the ratio of side effects that led to switching was higher than in the other three groups. Most of these side effects were mild or moderate infusion reactions, which were sometimes overweighed and resulted in earlier switches than it would have been necessary. But these side effects, and of course the secondary loss of efficacy, can be explained by the unique chemical structure of this drug (25). The chimeric monoclonal antobody induces production of anti-drug antibodies more intensively than the humanised ones (adalimumab and golimumab) and the receptor fusion protein etanercept. It was published recently, that in patients with spondyloarthropathies anti-drug antibodies could be detected in 25.9% of patients, most frequently in infliximab treated ones (81.8%) compared to those ones treated with adalimumab (18.2%) and etanercept (0%) (26). As these anti-drug antibodies are responsible for treatment failures at least in some of the cases, it may support the validity of our results. Moreover, in our study a sharp decrease were observed in retention on infliximab between 13th and 17th months of treatment. These results agree with the above mentioned study which could detect the appearance of anti-drug

antibodies mainly at the end of first year of the treatment (12.89±5.92 months). In a meta-analysis that evaluated the presence and effects of anti-drug antibodies in patients with different inflammatory diseases, such as rheumatoid arthritis, spondyloarthropathies and inflammatory bowel diseases, the drug response was reduced if anti-drug antibodies could be detected in the sera of patients. Among different diseases the effect of anti-drug antibody positivity on TNFi responses was more pronounced in AS and spondyloarthropathies than in other diseases (27). As concomittant treatment with methotrexate or other immunosuppressive drugs reduces the production of these antibodies, and as in axial form of spondyloarthropathies these type of drugs are usually not administered, it may highlight the necessity of determination of anti-drug antibodies in cases of loss of efficacy in AS, which may give further support for the decision of switching.

Among switchers, the effect of firstly and secondly used TNFi-s on disease activity measured by BASDAI and the response rates measured by BASDAI50 were similar during the one-year follow-up period in our retrospective analysis. Although the rate of patients achieving BASDAI50 was somewhat higher than the values published recently by other investigators (14;15), our findings are comparable with those results. However, the drug survival times of TNFi-s used second-line were worse than in first line treatment. These data suggest that switching to another TNFi may be a useful option and in general, the response is not worse, however the risk of switching is higher over time.

Limitations of this study include the retrospective, one-center design, lack of unequivocal definitions for switching, and short follow-up to detect the patients' responses to the treatment. However, we investigated a reasonably large population of patients treated in real-life setting, which allowed us to analyze efficacy, side-effects and survivals of each TNFi-s among patients with AS. In conclusion, our data indicate that switching between TNFi-s is a good therapeutic option if the patient failed to respond or intolerant to the formerly used agent, but the humanized monoclonal antibodies or receptor fusion protein should be preferred.

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Legends to the figures

Figure 1. Patterns of treatment courses of ankylosing spondylitis patients. Numbers show the number of patients treated with each TNF blockeres as first choice drugs and after switching.

Table 1. Baseline characteristics of patients remained on initiating TNFi treatment and switched to another one.

Figure 2. Mean BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) values among patients remained on firstly used TNF blockers (A) till the end of observation, and among those ones who switched to a second drug before (B) and after (C) switching.

Table 2. Reasons of switching of fist choice TNFi among ptients treated with adalimumab, etanercept, golimumab and infliximab.

Figure 3. Kaplan-Meier drug survival curves of adalimumab, etanercept, golimumab and infliximab used as first choice treatment (A) and after switching (B).

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