DISEASE ACTIVITY INDICES AND C-REACTIVE PROTEIN PREDICT SWITCHING OF THE FIRST BIOLOGICAL AGENT IN ANKYLOSING SPONDYLITIS PATIENTS – A SINGLE-CENTER OBSERVATIONAL STUDY

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Abstract

Objective. The study aimed at observing drug survival and determining potential predictors of anti-TNFα switch among ankylosing spondylitis (AS) patients.

Methods. The study retrospectively recorded clinical data of patients fulfilling modified New York criteria in a single university clinic. The data were analyzed using appropriate statistical test, which were considered significant if $p < 0.05$.

Results. A total of 120 patients met the inclusion criteria. Switchers had a median BASFI score of 2.7, a median ASDASCRP of 1.59 and a 41.7% prevalence of uveitis, compared to non-switchers which had a median BASFI score of 2.0, a median ASDASCRP of 1.20 and a uveitis prevalence of 22.9% respectively ($p = 0.009$; $p = 0.025$; $p = 0.043$). After a median of 7.0 years of observation, 96 patients (80.0%) were still being treated with their first anti-TNFα agent, with a Kaplan-Meier survival time estimate of 11.5 (10.1-12.9) years. The Kaplan-Meier study of the time of treatment until switch of the first biologic agent according to ASDASCRP categories revealed 9.3 (8.8-9.8) years for inactive disease, 10.6 (8.8-12.5) years for moderately active disease and 7.1 (5.7-8.5) years for highly active disease. The switch hazard ratio for CRP was 1.019 (1.007-1.031; $p = 0.002$), for BASDAI 1.226 (1.017-1.477; $p = 0.032$), for BASFI 1.264 (1.057-1.513; $p = 0.010$) and for ASDASCRP 1.592 (1.173-2.159; $p = 0.003$).

Conclusion. Romanian AS patients on anti-TNFα agents exhibit high retention rate and drug survival of anti-TNFα agents. Switchers have significantly higher baseline disease activity indices which, along baseline acute phase reactants, can significantly predict switching of the first anti-TNFα agent. Patients with AS treated with anti-TNFα agents had a higher prevalence of uveitis than those who did not therapeutic switch.

Keywords: ankylosing spondylitis, switch, anti-TNFα agents

List of abbreviations

AS – ankylosing spondylitis
ASDAS – Ankylosing Spondylitis Disease Activity Score
BASDAI – Bath Ankylosing Spondylitis Disease Activity Index
BASFI – Bath Ankylosing Spondylitis Functional Index
BMI – body mass index
CI – confidence interval
CRP – C-reactive protein
ESR – erythrocyte sedimentation rate
HLA – human leukocyte antigen
HR – hazard ratio
IBD – inflammatory bowel disease
IL – interleukin
NSAIDs – non-steroidal anti-inflammatory drugs
TNF – tumor necrosis factor

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease which mainly involves the axial skeleton (spine, sacroiliac joints) predominantly in male carriers of the HLA-B27 gene. It produces characteristic manifestations such as clinical complaints (for example inflammatory low back pain) and anatomical lesions (for example syndesmophytes and sacroiliitis) which can cause significant disability (1). The basic medical therapeutic management plan uses rehabilitation (2), local injections with long-acting glucocorticoids, non-steroidal anti-inflammatory

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drugs (NSAIDs) (3), sulfasalazine for peripheral arthritis (4) and biologic anti-cytokine agents, such as TNFα (5) and IL-17A inhibitors (6).

In Romania, there are five anti-TNFα inhibitors approved for AS treatment (adalimumab, certolizumab, etanercept, golimumab, infliximab) and one IL-17A inhibitor (secukinumab). Romanian AS patients need to fulfill the following criteria in order to be started on biologic agents: a) diagnosis of AS according to the modified New York criteria (7); b) active disease, defined by all of the following three criteria: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI (8)) > 6 on two occasions at least 4 weeks apart; Ankylosing Spondylitis Disease Activity Score (ASDAS (9)) ≥ 2.5; erythrocyte sedimentation rate (ESR) > 28 mm/h and/or C-reactive protein (CRP) more than 3 times the upper limit of normal; c) failure of traditional therapies, defined by the following two criteria: at least two NSAIDs administered continuously for 6 weeks each, in maximum recommended or tolerated doses; in case of peripheral manifestations, at least 4 months of sulfasalazine 2-3 g/day and at least one local (joints, entheses) injection with glucocorticoids for peripheral manifestations if indicated; d) no known contraindications according to summaries of product characteristics. The biologic agent can be continued in the first year of treatment if the patient is a responder (defined by all of the following three criteria: at least 50% decrease of BASDAI; at least 50% decrease of ESR and/or CRP; a decrease of ASDAS with at least 1.1) and subsequently if the treatment target (ASDAS ≤ 1.3) is achieved. In certain clinical situations (primary non-responders, secondary non-responders or adverse events) the first biologic agent is either switched (replacing the first anti-TNFα agent with another anti-TNFα agent) or swapped (replacing an anti-TNFα agent with secukinumab or vice versa). Approximately one-third of AS patients switched biological treatment. Drug survival and response rates were lower among switchers, however, half of switchers achieved treatment response (32).

For reasons of clinical management and health economics considerations, it is important to ideally predict drug survival and to predict which patients are going to change their first biologic agent and when (10). Therefore, the present exploratory study of AS patients treated with biologic agents in a single university centre aims at observing drug survival, comparing switchers with non-switchers and determining potential predictors of treatment change.

METHODS

Patients

The study was designed to retrospectively record the clinical data of all the patients who were evaluated in the day care service of our Rheumatology Department in the random order of presentation between May 2015 and May 2017. Patients were included if they had a diagnosis of AS according to the modified New York criteria (7) and if they were receiving an anti-TNFα inhibitor (adalimumab, certolizumab, etanercept, golimumab and infliximab) prescribed by their attending rheumatologist as per drug label and national regulations. The following exclusion criteria were applied: age under 18 years; patients with psoriatic arthritis; patients receiving other/investigational biologic agents. Each patient gave written informed consent for the use of clinical data on the occasion of each day care visit and the study was approved by the local ethics committee.

Variables

The variables were retrospectively recorded from the observation sheets and the hospital's electronic clinical data system. Demographic data include age, gender, body mass index (BMI; calculated by dividing weight in kilograms by square height in meters, with a cutoff of 30 kg/m^2 for obesity), urban or rural dwelling and level of education. The disease phenotype was characterized by disease duration (the time between diagnosis and study inclusion), the presence of extra-spinal (peripheral arthritis) and extra-articular manifestations (uveitis, inflammatory bowel disease and psoriasis) and genetic predisposition (the presence of HLA-B27). AS disease activity was evaluated by dosing acute phase reactants (ESR - normal < 20 mm/h, Westergren method; CRP - normal < 5 mg/L, nephelometry; fibrinogen – normal < 490 mg/dL, enzyme-linked immunoabsorbant assay) and by calculation composite indices, such as BASDAI (8), Bath Ankylosing Spondylitis Functional Index (BASFI) (11, 12), $ASDAS_{CRP}$ (9, 13). Inflammation was defined if either acute phase reactant (ESR, fibrinogen, CRP) was above the upper limit of normal for the laboratory (20 mm/h, 490 mg/dL and 5 mg/L respectively). Disease activity according to $ASDAS_{CRP}$ was defined as follows (14): inactive ($ASDAS_{CRP}$ < 1.3), moderate (1.3 < $ASDAS_{CRP}$ < 2.1) and high ($ASDAS_{CRP}$ > 2.1).

Statistics

Data distribution normality was assessed using descriptive statistics, normality, stem-and-leaf plots and the Lillefors corrected Kolmogorov-Smirnov test. Qualitative variables were expressed as "absolute value (percentage of total)"; non-normally distributed continuous variables were reported as "median (minimum-maximum)"; normally distributed continuous variables were reported as "mean ± standard deviation". To compare two subgroups of the sample (switchers versus non-switchers), Mann-Whitney U tests were used for continuous variables (for example age) and χ^2 or Fisher tests for nominal variables (for example gender). The association of the treatment time of the first anti-TNFα agent with different other continuous variables was studied using partial bivariate correlations, controlling for BMI, gender, age, disease duration and HLA-B27. Multivariate Cox analysis identified predictors of switching using models in which the time variable was the time to switch, the status variable was the switch and the covariates were one investigated variable (peripheral arthritis, uveitis, ESR, fibrinogen, CRP, BASDAI, BASFI, $ASDAS_{CRP}$) along other generally significant covariates (BMI, gender, age, disease duration and HLA-B27). A Kaplan-Meier study of the time of treatment until switch of the first biologic agent was plotted according to $ASDAS_{CRP}$ categories. All tests were considered significant if $p < 0.05$ and were done using IBM SPSS v. 20 (IBM Inc., Armonk, New York, 2010) for Windows. The Forest plot of hazard ratios was generated using GraphPad Prism v. 7.0 for Windows (GraphPad Software, La Jolla California USA).

RESULTS

General characteristics

A total of 120 patients met the inclusion criteria (Table 1). The sample was predominantly male, with a mean age of 44.5 years. Regarding the disease, it had a mean duration of 12.1 years, half of the cases had peripheral manifestations and almost all of the patients were HLA-B27 carriers. Almost all the patients took prescribed NSAIDs and 49.2% of the patients took sulfasalazine knowing that 47.5% of the patients had peripheral manifestations which warranted this treatment.

All of the patients received anti-TNFα agents (Fig. 1), out of which 24 patients (20.0%) switched to the second anti-TNFα agent, 7 patients (5.8%) received their third anti-TNFα agent and 4 patients (3.3%) made a forth switch.

Switchers versus non-switchers

By dividing the study sample in two subgroups, patients who switched their first anti-TNFα agent and patients who did not switch it by the end of the observation period, two significant differences emerged (Table 2): compared to non-switchers,

TABLE 1. *General characteristics of the sample (n = 120)*

1. *demographics*		2. *disease phenotype*	
age (years)	44.5 ± 11.6	disease duration (years)	12.1 ± 8.4
male gender	103 (85.8%)	peripheral arthritis	57 (47.5%)
BMI (kg/m^2)	25.2 ± 2.7	coxitis	8 (6.7%)
obesity	5 (4.2%)	uveitis	32 (26.7%)
urban dwelling	88 (73.3%)	IBD	4 (3.3%)
higher education	9 (7.5%)	psoriasis	0 (0.0%)
3. *disease activity*		HLA-B27	115 (95.8%)
ESR (mm/h)	23 ± 14	4. *treatment*	
CRP (mg/L)	4.28 (0.4-142)	NSAIDs	118 (98.3%)
fibrinogen (mg/dL)	387 (45-789)	sulfasalazine	59 (49.2%)
BASDAI	1.0 (0-9.0)	anti-TNFα agents	120 (100%)
BASFI	2.0 (0-9)		
$ASDAS_{CRP}$	1.30 (0.64-5.54)		

- variables are reported as: "mean ± standard deviation" (continuous normal distribution); "median (minimum-maximum)" (continuous non-normal distribution); "absolute value (fraction of total)" (nominal variables).
- $ASDAS_{CRP}$ = Ankylosing Spondylitis Disease Activity Score using CRP; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BMI = body mass index; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; HLA = human leukocyte antigen; IBD = inflammatory bowel disease; NSAIDs = non-steroidal anti-inflammatory drugs.

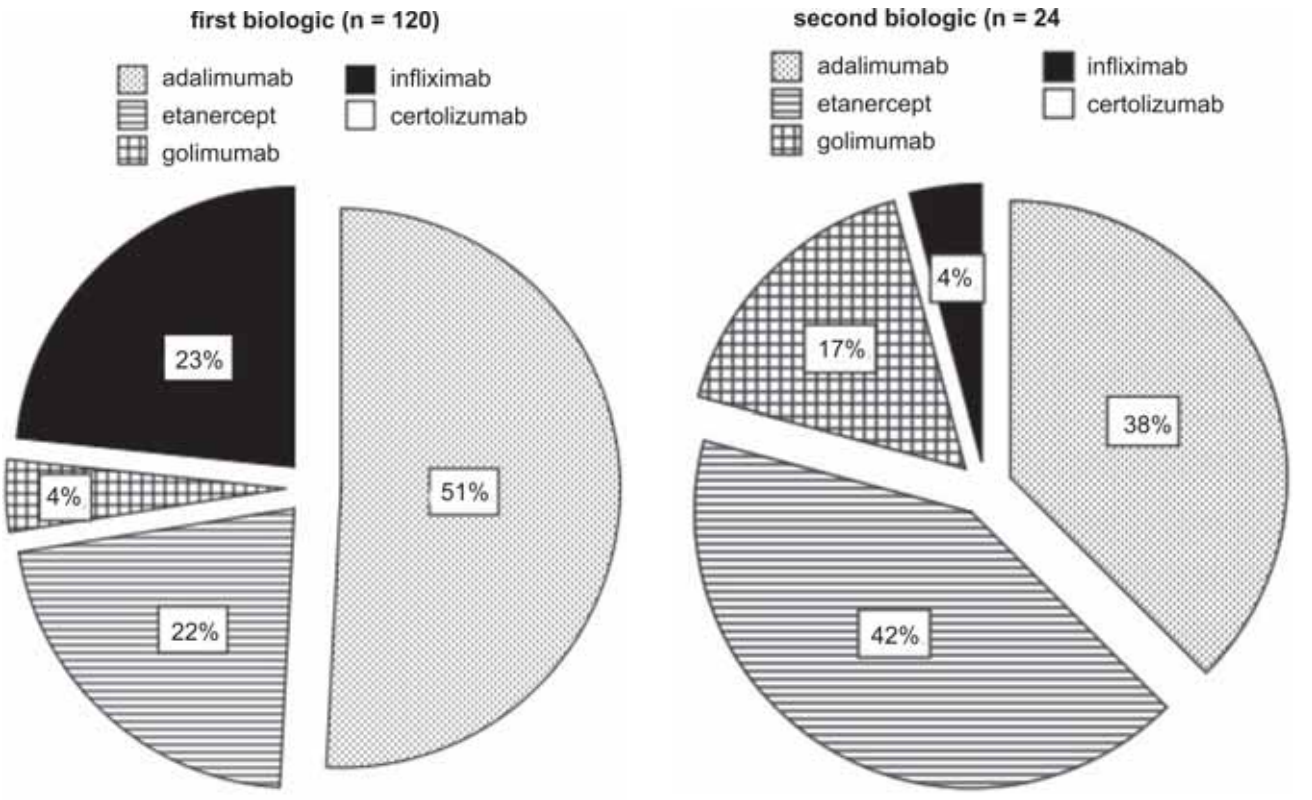


*FIGURE **1.** The specific anti-tumor necrosis factor α agents used to treat patients as first line (left) and after switch (right).*

switchers had significantly higher median disease activity indices (BASFI, $ASDAS_{CRP}$) and a significantly higher prevalence of uveitis.

Treatment survival

The median treatment duration (the duration of time from initiation to discontinuation of therapy) of

***TABLE 2.** Comparison of baseline variables between switchers and non-switchers of the first biologic agent (n = 120).*

	non-switchers (n = 96)	*switchers (n = 24)*	*p*
age (years)	44 (18)	42 (13)	0.346#
disease duration (years)	9 (11)	11 (7)	0.207#
BMI (kg/m^2)	25.2 (4.1)	23.9 (4.5)	0.192#
ESR (mm/h)	14 (18)	15 (29)	0.238#
fibrinogen (mg/dL)	354 (132)	394 (180)	0.698#
CRP (mg/L)	3.4 (7.3)	6.4 (11.9)	0.177#
BASDAI	1.0 (1.2)	1.2 (1.7)	0.086#
BASFI	2.0 (2.0)	2.7 (1.3)	*0.009*#
$ASDAS_{CRP}$	1.20 (0.75)	1.59 (0.64)	*0.025*#
male gender (%)	84.4%	91.7%	0.519&
urban dwelling (%)	85.4%	66.7%	0.409*
obesity (%)	4.2%	4.2%	0.739*
peripheral arthritis (%)	47.9%	45.8%	0.855*
uveitis (%)	22.9%	41.7%	*0.043**
inflammation (%)	47.9%	66.7%	0.100*
HLA-B27 present (%)	94.8%	100%	0.582&
NSAIDs (%)	97.9%	100%	0.639&
sulfasalazine (%)	47.9%	54.2%	0.584*

- statistical tests: # – Mann Whitney U test; & – Fisher's exact test; * – χ^2 test;
- inflammation is defined as either acute phase reactant (ESR, fibrinogen, CRP) above the upper limit of normal for the laboratory (20 mm/h, 490 mg/dL and 5 mg/l respectively);
- BMI was calculated by dividing weight in kilograms with square height in meters, and obesity was defined as a BMI ≥ 30 kg/m^2;
- $ASDAS_{CRP}$ = Ankylosing Spondylitis Disease Activity Score using CRP; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BMI = body mass index; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; HLA = human leukocyte antigen; NSAIDs = Nonsteroidal anti-inflammatory drugs.

the first biologic was 6.0 (1.0-15.0) years. At the end of the observation period (after a median of 7.0 years of observation) 96 patients (80.0%) were still being treated with their first anti-TNFα agent, with a Kaplan-Meir survival time estimate of 11.5 (10.1-12.9) years (standard error 0.75). Several disease activity indices significantly and negatively correlated with the treatment time of the first biologic, namely CRP ($r = –0.219$; $p = 0.016$), BASDAI ($r = –0.394$, $p < 0.001$), BASFI ($r = –0.381$, $p < 0.001$) and $ASDAS_{CRP}$ ($r = –0.380$, $p < 0.001$). Compared to patients with rural dwelling, patients with urban dwelling had significantly higher median drug persistence on the first anti-TNFα agent, namely 6.0 (1.0-15.0) years versus 4.5 (2.0-12.0) years ($p = 0.044$).

Survival on the first anti-TNFα agent differed according to baseline $ASDAS_{CRP}$ category (Figure 2): patients with inactive disease had the longest survival on treatment with the first biologic, while patients with highly active disease had the shortest survival on treatment with the first biologic.

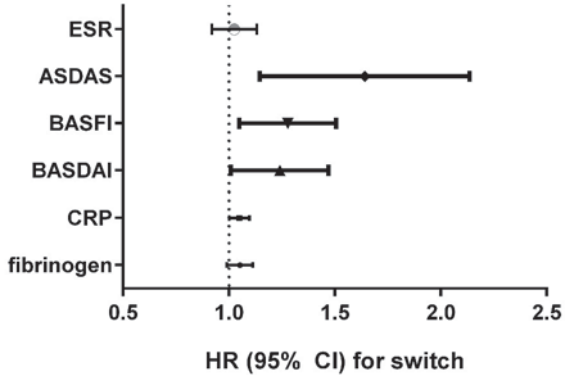


FIGURE 2. *Kaplan-Meier study of the time of treatment until switch of the first biologic agent according to $ASDAS_{CRP}$ categories: 9.3 (8.8-9.8; se = 0.25) years for inactive disease, 10.6 (8.8-12.5; se = 0.94) years for moderately active disease and 7.1 (5.7-8.5; se = 0.74) years for highly active disease (Mantel-Cox $\chi^2(2) = 10.3$, $p = 0.006$; Breslow $\chi^2(2) = 13.2$, $p = 0.001$; Tarone-Ware $\chi^2(2) = 12.1$, $p = 0.002$). ASDAS categories are defined as inactive ($ASDAS_{CRP} < 1.3$), moderate ($1.3 < ASDAS_{CRP} < 2.1$) and high ($ASDAS_{CRP} > 2.1$). $ASDAS_{CRP}$ = Ankylosing Spondylitis Disease Activity Score using CRP; CRP = C-reactive protein; se – standard error.*

Predictors of switching

The multivariate Cox regression analysis revealed that baseline acute phase reactants markers (CRP, fibrinogen) and baseline disease activity indices (BASDAI, BASFI, $ASDAS_{CRP}$) were able to predict switching of the first anti-TNFα agent in the study sample (Table 3), while extra-spinal (peripheral arthritis) and extra-articular (uveitis) manifestations were not significant predictors of switching.

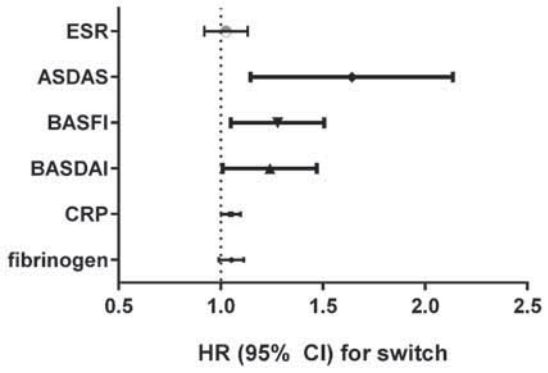
DISCUSSION

The study objective included the observation of drug survival, the comparison of switchers with non-switchers and the identification of potential predictors of treatment change. In this sense, we observed an 80% retention rate of the first biologic, with 11.5 years of drug survival time estimate. Generally, observational studies report a varying retention rate of 50-80% in observational periods from 2 to 7 years both in independent studies (10, 15-21) and in national registry-based studies (22-24), values which are similar to our observation. It is notable that our retention rate is among the highest reported in the literature, an observation which needs further research in terms of determining factors which can be extrapolated to other treatment indications and groups. Some studies report that sulfasalazine treatment can increase drug survival on anti-TNFα agents (17, 25), a hypothesis which was not reproduced in our sample. However, our observed estimate of drugs survival is twice that of other reported studies, which revolve around 5 years (10, 24). This finding is relevant if reproduced in other Romanian cohorts and should be compared as a future research direction with the data from the Romanian Registry of Rheumatic Diseases (RRRD), which holds information about all the AS patients treated with biologics in our country.

In our sample, switchers had significantly higher median disease activity indices, an observation which is consistent with some studies (for example (23)), but in contradiction with others (26), which report no effect of disease activity indices on switching outcomes. Since higher values of baseline disease activity indices are the expression of a more aggressive disease phenotype and represent poor prognosis factors (27), it is reasonable to expect higher baseline disease activity indices in patients who switched their first anti-TNFα agent because of primary or secondary non-responsiveness. This hypothesis was further elaborated in our regression analysis which showed that baseline acute phase reactants and disease activity indices can significantly predict switches. Furthermore, higher disease activity class at baseline according to $ASDAS_{CRP}$ was associated with shorter time on the first anti-TNFα agent. The mechanism behind this association of active disease with inconsistent and temporary treatment response warrants further research. Is seems evident that the current approved treatment princi-

TABLE 3. *Predictors of switching the first biologic agent*

model	*HR (95% CI)*	*p*
arthritis	0.883 (0.387-2.015)	0.768
uveitis	1.948 (0.841-4.509)	0.120
ESR	1.012 (0.997-1.028)	0.110
fibrinogen	1.011 (1.003-1.021)	*0.047*
CRP	1.019 (1.007-1.031)	*0.002*
BASDAI	1.226 (1.017-1.477)	*0.032*
BASFI	1.264 (1.057-1.513)	*0.010*
$ASDAS_{CRP}$	1.592 (1.173-2.159)	*0.003*



- each model of multivariate Cox regression analysis also included as covariates BMI, gender, age, disease duration and HLA-B27;
- $ASDAS_{CRP}$ = Ankylosing Spondylitis Disease Activity Score using CRP; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BMI = body mass index; CI = confidence interval; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; HLA = human leukocyte antigen; HR = hazard ratio.

ples are not capable to efficiently manage disease phenotypes with poor prognosis factors, which means that new treatment strategies and new biological targets are needed to fill this gap (28).

Acute phase reactants and CRP especially were proved to be highly significant in the management of AS. Observational studies have shown that baseline CRP is a predictor of treatment benefit at a biomarker level (29), of radiographic progression (30), of the retention rate (31) and drug survival of anti-TNFα agents (24), and that CRP is a risk factor for drug discontinuation (18). In our sample, CRP was negatively correlated with drug survival and it was a significant predictor of switchers. These observations are particularly relevant in the national context in which patients can receive their first biologic agent if they have a CRP more than three times the upper limit of normal and if they score above 6 on the BASADI scale. Since according to our data and according to the cited literature reports these patients are the most likely to switch their first anti-TNFα agent, it seems ethical to lower the mentioned cut-offs with a proper health-economics analysis. In addition, AS patients with such laboratory and clinical markers should be monitored and treated more intensively in order to decrease as much as possible the associated treatment and prognosis risks.

The observations we made are limited by of number of study design characteristic, namely the lack of date regarding the reason for switching, the retrospective design which limited the control of the recorded variables and the relatively small sample size.

CONCLUSIONS

Romanian AS patients on anti-TNFα agents exhibit a high retention rate and drug survival of anti-TNFα agents. Switchers have significantly higher baseline disease activity indices which, along baseline acute phase reactants, can significantly predict switching of the first anti-TNFα agent. These observations warrant further studies using the national registry of biologic agents used in AS.

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