EFFICACY DIFFERENCES BETWEEN CLASSICAL AND BIOLOGICAL TREATMENT IN ANKYLOSING SPONDYLITIS

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Abstract

Objectives. The study aims at comparing classical and biological treatment of ankylosing spondylitis (AS) in terms of efficacy and to determine which treatment type is a significant predictor of low disease activity in a real-life clinical situation.
Methods. The study was cross-sectionally designed to include all the patients randomly admitted between January and July 2015 to the "Sfanta Maria" Clinical Hospital Department of Rheumatology and discharged with a diagnosis of AS according to their attending physicians. The retrospectively collected variables (demographics, disease phenotype and activity, treatment, laboratory measures) were analyzed using appropriate statistical tests (Mann Whitney, $\chi 2$, linear and logistic regression).
Results. The study sample included 105 cases of established AS with a mean age of 43.2 years: 64 patients (60.9%) were on tumor necrosis factor inhibitors (TNFi: adalimumab, etanercept or infliximab), 55 (52.4%) took non-steroidal anti-inflammatory drugs (NSAIDs) and 30 (28.6%) had sulfasalazine. TNFi were associated with lower disease activity compared to NSAIDs and sulfasalazine and they were significant predictors for low BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), either as mono-therapy or combined with NSAIDs and/or sulfasalazine.
Conclusion. TNFi are more efficacious than NSAIDs and sulfasalazine for the treatment of AS. A combination of TNFi with NSAIDs (and sulfasalazine for peripheral arthritis) would be the ideal therapeutic association.

Keywords: ankylosing spondylitis, TNF inhibitors, NSAIDs, sulfasalazine

INTRODUCTION

The pharmacological treatment of ankylosing spondylitis (AS) relies on three systemic principles (1,2): non-steroidal anti-inflammatory drugs (NSAIDs) (3), tumor necrosis factor inhibitors (TNFi: adalimumab (4), certolizumab (5), etanercept (6), golimumab (7), infliximab (8)) and the disease-modifying anti-rheumatic drug sulfasalazine (9). Newer therapeutic targets, such as interleukin 17 (10), and newer molecules, such as bifosphonates (11), are currently under clinical investigation for the treatment of AS (12). About three quarters of AS patients treated with first line NSAIDs report substantial improvement in symptoms (13), but the use of NSAIDs, especially in maximum doses for long periods of time, is associated with significant cardiovascular, gastrointestinal and renal side effects (14). Recent evidence suggests that a strategy to reduce the risk of side effects is to administer NSAIDs on demand rather than continuously (15). TNFi are currently second line efficacious agents for the treatment of AS, but their use is associated with a higher cost (16, 17) and risk of infection (18, 19). Sulfasalazine is only effective on peripheral manifestations of AS, namely peripheral arthritis (1), with no proven efficacy for axial involvement. There are limited data regarding head-to-head comparisons between these three therapeutic principles in AS (20,21), which would presumably provide useful information for both clinical management strategies and health economics strategies. Within this context, the study aims at comparing classical and biological treatment of AS in terms of efficacy and at determining which treatment type is a significant predictor of low disease activity in a real-life clinical situation, information which would help justify future prospective studies.

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METHODS

Patients

The study was cross-sectionally designed to include all the patients randomly admitted to the hospital between January and July 2015 to the "Sfanta Maria" Clinical Hospital Department of Rheumatology and discharged with a diagnosis of AS according to their attending physicians. On admission, all patients gave a written informed consent regarding the scientific use of clinical data. The protocol was approved by the local ethics committee.

Variables

The clinical observation sheets served as retrospective sources of information regarding the age, gender and residence of each patient. Smoking status, as declared by the patient, and disease duration, as certified by the physician, were collected from the clinical interview recorded in writing in each observation sheet. As part of the clinical interview, patients were asked to fill BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), BASFI (Bath Ankylosing Spondylitis Functional Index) and ASDAS (Ankylosing Spondylitis Disease Activity Score) questionnaires, which were recorded in the observation sheets. The clinical examination recorded by the observation sheets allowed collection of information regarding peripheral manifestations (arthritis, enthesitis, tenosynovitis) and extra-articular manifestations: (uveitis, inflammatory bowel disease – IBD, psoriasis and aortic insufficiency). Medical documents contained by the observation sheets (such as test results and prescriptions) allowed the recording of HLA B27 status and treatment received at that time: NSAIDs, sulfasalazine, TNFi (adalimumab, etanercept, infliximab). The local laboratory determined for each case the erythrocyte sedimentation rate (ESR), using an automated Westergren method, and C-reactive protein (CRP), using a commercially available immunonephelometric method.

Statistics

Data distribution normality was assessed using descriptive statistics, normality plots, stem-and-leaf plots and the Lillefors corrected Kolmogorov-Smirnov tests. Qualitative data were expressed as "absolute value (percentage of group)" and were studied using cross-tabs with χ^2 or Fisher tests. Excepting age, the other scale variables exhibited a non-normal distribution and were reported as "median (interquartile range)" and their correlations and differences were assessed using nonparametric tests: Mann-Whitney U and Kruskal-Wallis for differences of scale variables in groups with two (e.g. gender) or more categories (e.g. type of treatment). Post-hoc analyses were performed in order to determine which categories of multi-level nominal variables had produced significant Mann-Whitney and χ^2 tests: one-way ANOVA with post-hoc analysis (Tukey and Bonferroni multiple comparisons) and respectively the study of adjusted standardized residuals. To assess the independent predictive capacity of treatment variables for disease activity outcomes, standard multiple linear and binary logistic regression models were created. All statistical tests were carried out us-

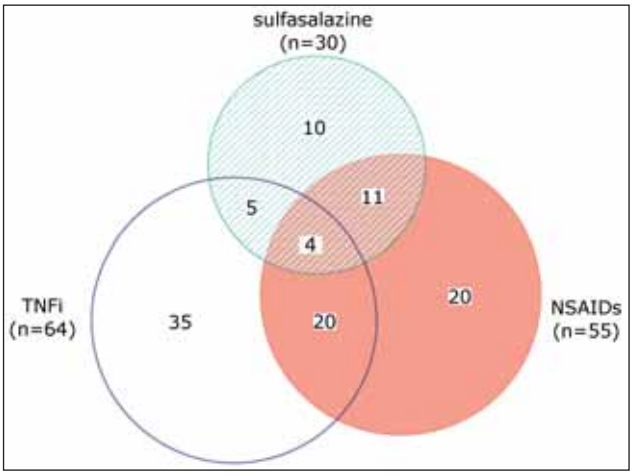

***FIGURE** 1. A diagram of observed treatment types (n = 105). TNFi refer to infliximab, adalimumab and etanercept. A total of 4 (3.8%) patients had triple therapy (NSAIDs, sulfasalazine and one biologic agent), while 20 (19.1%) were receiving NSAIDs and one biologic agent, 11 (10.5%) were receiving NSAIDs and sulfasalazine and 5 (4.8%) were receiving sulfasalazine and one biologic agent. Ten (9.5%) patients were taking only sulfasalazine, 20 (19.1%) were taking only NSAIDs and 35 (33.3%) were taking only a biologic agent.*

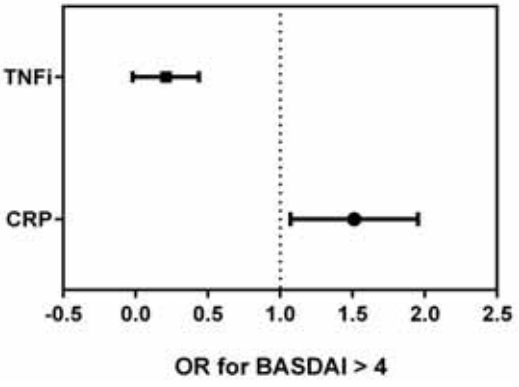

***FIGURE 2.** The odds ratios (OR) for being classified as BASDAI > 4. The only significant predictors in the binary logistic regression model were C-reactive protein (CRP), which proved to be a risk factor, and the presence of TNFi, which proved to be a protective factor.*

ing IBM SPSS v.20 (IBM Inc., Armonk, N.Y., 2010) for Windows and were considered significant if $p < 0.05$. Fig. 1 was computed using eularAPE (22) and Fig. 2 was generated using GraphPad Prism 6.0 (GraphPad Software, La Jolla California, SUA).

RESULTS

General characteristics

The study sample included 105 cases of established AS with a mean age of 43.2 years (Table 1). Compared to female patients, males had significantly higher median CRP values (7.9 mg/L compared to 2.6 mg/L; $p = 0.021$) and significantly lower ERS values (10 mm/h compared to 13 mm/h; $p = 0.048$). Compared to patients without concomitant psoriasis, patients with psoriasis had a significantly higher median ASDAS (2.6 compared to 1.3; $p = 0.045$) and a significantly higher frequency of cases categorized as ASDAS $\geq$ 2.1 (17.6% compared to 0%; $p = 0.021$). Cigarette smokers displayed a significantly higher median ASDAS compared to non-smokers (2.9 compared to 1.3; $p = 0.037$).

NSAIDs, sulfasalazine and TNFi differences

Almost two thirds of the patients were treated with TNFi (Figure 1), while the others received classical treatment (NSAIDs and/or sulfasalazine). Dichotomously dividing the study sample into subgroups according to treatment type irrespective of other concomitant SA medication produced significant differences (Table 2): compared to patients not taking the respective drug (NSAIDs/sulfasalazine/TNFi), patients on NSAIDs and patients on sulfasalazine had a higher disease activity, while patients on TNFi had a lower disease activity. Monotherapy subgroups were further created by eliminating from the analysis 5 patients on sulfasalazine and TNFi, 20 patients on NSAIDs and TNFi, 11 patients on NSAIDs and sulfasalazine and 4 patients on triple therapy. The differences between the resulting mono-therapy subgroups remained the same (Table 3): patients on TNFi mono-therapy had a significantly lower disease activity (BASDAI) and a significantly lower functional limitation (BASFI) compared to patients on NSAIDs mono-therapy or on sulfasalazine mono-therapy. Additionally, patients treated exclusively with TNFi were significantly younger than patients treated exclusively with NSAIDs or sulfasalazine. In order to exclude an independent effect on diseases activity measures (in the sense that, compared to younger patients, older patients may report pain unrelated with AS, for ex-

TABLE 1. *General characteristics of the study sample (n = 105)*

demographics		*disease type*	
age (years)	43.2 ± 11.4	disease duration (years)	10 (9.8)
males (n)	78 (74.3%)	peripheral disease (n)	50 (47.6%)
urban habitat (n)	72 (68.6%)	extra-articular disease (n)	43 (40.9%)
smoking (n)	18 (17.1%)	uveitis (n)	21 (20.0%)
disease activity		IBD (n)	15 (14.3%)
ESR (mm/h)	13 (21)	psoriasis (n)	6 (5.7%)
ESR > 20 mm/h (n)	33 (31.4%)	aortic insufficiency (n)	8 (7.6%)
CRP (mg/L)	5.9 (16.4)	HLA B27 present (n)	85 (80.9%)
CRP > 5 mg/L (n)	51 (48.6%)	*treatment type*	
BASDAI	3.0 (4.1)	NSAIDs (n)	55 (52.4%)
BASDAI > 4	35 (33.3%)	sulfasalazine (n)	30 (28.6%)
BASFI	3.2 (3.0)	infliximab (n)	16 (15.2%)
BASFI > 4 (n)	21 (20.0%)	adalimumab (n)	31 (29.5%)
ASDAS	1.3 (1.9)	etanercept (n)	17 (16.2%)
ASDAS ≥ 2.1 (n)	17 (37.8%)	TNFi (n)	64 (60.9%)

***Notes*:**
– Normally distributed scale variables are reported as "mean ± standard deviation"; non-normally distributed scale data are reported as "median (interquartile range)"; nominal data are reported as "absolute value (percent of sample size – 105)".
– According to the local laboratory, the upper limits of normal are: 20 mm/h for ESR and 5 mg/L for CRP.
– Terms used: peripheral disease refers to arthritis, enthesitis and tenosynovitis; extra-articular disease refers to uveitis, IBD, psoriasis and aortic insufficiency; TNFi refers to the administration of infliximab, adalimumab or etanercept.
***Abbreviations*:**
ASDAS – Ankylosing Spondylitis Disease Activity Score; BASDAI – Bath Ankylosing Spondylitis Disease Activity Index; BASFI – Bath Ankylosing Spondylitis Functional Index; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; HLA – human leukocyte antigen; IBD – inflammatory bowel disease; n – number of; NSAIDs – non-steroidal anti-inflammatory drugs; TNFi – tumor necrosis factor inhibitors.

TABLE 2. *Significant differences and associations of subgroups*

NSAIDs	*no (n = 47)*	*yes (n = 55)*	*p*	*test*
BASDAI	2 (2.9)	3.4 (4.4)	0.009	MW
sulfasalazine	*no (n = 74)*	*yes (n = 30)*		
BASDAI	2.7 (3.0)	4.1 (3.5)	0.009	MW
ASDAS	1.3 (1.0)	2.4 (2.9)	0.046	MW
TNFi	*no (n = 41)*	*yes (n = 64)*		
BASDAI	5.0 (4.1)	2.0 (2.2)	<0.001	MW
BASDAI > 4 (n)	51.2% (21)	7.7% (5)	<0.001	χ^2
BASFI	4.2 (3.7)	2.9 (2.8)	0.021	MW
BASFI > 4 (n)	68.3% (28)	12.5% (8)	0.016	χ^2
disease duration	*> 2 y (n = 92)*	*≤ 2 y (n = 13)*		
sulfasalazine (n)	21.7% (20)	61.5% (8)	0.004	χ^2
BASDAI	2.9 (3.9)	4.9 (3.7)	0.045	MW
BASDAI > 4 (n)	27.2% (25)	61.5% (8)	0.021	χ^2
biologics (n)	63.1% (58)	23.1% (3)	0.003	χ^2

***Notes*:**
– continuous values are reported as "median (interquartile range)"; nominal values are reported as "percent of subgroup (number of cases)"
***Abbreviations*:**
ASDAS – Ankylosing Spondylitis Disease Activity Score; BASDAI – Bath Ankylosing Spondylitis Disease Activity Index; BASFI – Bath Ankylosing Spondylitis Functional Index; MW – Mann Whitney test; NSAIDs – non-steroidal anti-inflammatory drugs; TNFi – tumor necrosis factor inhibitors; y – years.

ample caused by osteoarthritis), age was therefore included in the regression models as a covariate.

BASDAI prediction

A standard multiple linear regression was computed in order to predict the BASDAI score using target variables (NSAIDs, sulfasalazine and TNFi) and other independent but potentially significant covariates (sex, age, disease duration, CRP). The model was significant ($F = 5.68$, $df = 7$, $p < 0.001$, $R^2 = 0.311$), but the only significant predictor in the model ($B = -2.21$, $se = 0.53$, 95% CI: -3.27 to -1.15, $\beta = -0.45$, $t = -4.15$, $p < 0.001$) was the presence of TNFi (coded as "1" for "yes" and "0" for "no"), which proved to be a protective factor.

A binary logistic regression was performed in order to quantify the effect of target variables (NSAIDs, sulfasalazine and TNFi) and other independent but potentially significant covariates (sex, age, disease duration, CRP) on the likelihood that patients had a high disease activity defined by BASDAI > 4 (coded as "1" for "yes" and "0" for "no"). The model was significant ($\chi^2 = 27.78$, $df = 7$, $p = 0.004$), it accurately predicted 78.6% of cases (compared to 67.9% observed) and it explained one third of the variance of BASDAI > 4 classification. Two variables were

TABLE 3. *Significant differences and associations of mono-therapy subgroups*

	NSAIDs monotherapy (n = 20)	*Sulfasalazine monotherapy (n = 10)*	*TNFi monotherapy (n = 35)*	*p*	*test*
Age (years)	56 (22)*	47 (29)	38 (10)*	0.040	KW
BASDAI	5.0 (2.8)*	5.3 (2.0)#	2 (2.8)*,#	<0.001	KW
BASDAI > 4 (n)	65.0% (13)*	80.0% (8)#	14.3% (5)*,#	<0.001	χ^2
BASFI	4.2 (2.2)	4.4 (2.5)*	2.1 (2.8)*	0.019	KW
BASFI > 4 (n)	25.0% (5)	60.0% (6)*	11.4% (4)*	0.005	χ^2
ASDAS	2.0 (1.5)	3.0 (2.2)*	1.2 (0.9)*	0.043	KW

***Notes*:**
– continuous values are reported as "median (interquartile range)"; nominal values are reported as "percent of subgroup (number of cases)"
– subgroups which differ significantly and explain the overall significant test, as determined by post hoc analysis, are marked with "*" or "#"
***Abbreviations*:**
ASDAS – Ankylosing Spondylitis Disease Activity Score; BASDAI – Bath Ankylosing Spondylitis Disease Activity Index; BASFI– Bath Ankylosing Spondylitis Functional Index; KW – Kruskal Wallis test; NSAIDs – non-steroidal anti-inflammatory drugs TNFi – tumor necrosis factor inhibitors.

significant predictors (Fig. 2): patients with high CRP were more likely to have BASDAI > 4, while patients on TNFi were less likely to have BASDAI > 4.

DISCUSSION

The retrospective comparison and analysis of the three treatment principles of AS in a real-life single-center clinical setting allowed the observation that TNFi were associated with lower disease activity compared to NSAIDs and sulfasalazine and were significant predictors of low BASDAI, either as mono-therapy or in combination with NSAIDs and/or sulfasalazine, i.e. this data suggest that TNFi are more effective than NSAIDs and sulfasalazine in the treatment of AS. This observation regarding the TNFi – sulfasalazine comparison is in accordance with the few literature data from studies which investigated etanercept compared to sulfasalazine for the treatment of AS (20,21,23). However, according to our knowledge, a direct designed comparison of efficacy in AS between NSAIDs and TNFi has not been studied so far. Generally, the studies which compared TNFi to placebos allowed patients to take NSAIDs as symptomatic medication with some restriction during the observation period [for a comprehensive review see Maxwell *et al.* (19)]. However, NSAIDs are the first line of treatment in AS (1) since they control symptoms (24) and delay radiographic progression (25), they are relatively cheaper and their therapeutic response is a useful classification criterion for spondyloarthritis (26). Therefore a comparison between NSAIDs and TNFi is recommended. Even though our data are cross-sectional and retrospective and may be biased by the nature of patient-health system interaction (on one hand AS patients who are admitted to hospital are generally worse and on the other hand the Romanian health system requires AS patients on TNFi to come to hospital every one to three months to get their prescription irrespective of disease activity), the results can offer a glimpse into this unstudied chapter. A question remains to be answered: how efficacious is TNFi mono-therapy compared to NSAIDs mono-therapy for inducing and maintaining remission and LDA in AS? A prospective clinical trial to address this issue in early AS would answer this question, since Baraliakos *et al.* (27) found that early disease (duration ≤ 2 years), young age (≤ 40 years) and the presence of HLA-B27 are significant predictors for etanercept response at 12 weeks (an observation which we were able to confirm only in the case of early disease – Table 2).

The mechanism of the observed higher efficacy of TNFi over NSAIDs may be the greater cellular effects of TNF on immune cells (activation, adhesion, biosynthesis) compared to prostaglandin E2 (vasodilation, algesia, fever). This higher efficacy may have implications reaching from clinical practice to economic health policies. In Romania, an AS patient must simultaneously fulfill the following criteria in order to receive a TNFi (28): AS classification according to the modified New York criteria (29); active and severe disease (BASDAI > 6; ASDAS ≥ 2.5; ESR > 28 mm/h; CRP ≥ 3 times the upper limit of normal); failure of traditional therapy (at least two NDAIDs administered continuously for 6 weeks each at the maximum recommended/tolerated doses; sulfasalazine administered at least 4 months for peripheral arthritis in regular doses of 2-3 g/day); absence of known contraindications of TNFi. Statistically, there is a greater chance of noncompliance to treatment: in a series studied by de Klerk *et al.* (30), only 22% of the AS patients took their NSAID once daily every day. Therefore, after 6 weeks of NSAID treatment, an apparent highly active disease which would be a good candidate for receiving a TNFi is actually due to noncompliance rather than non-responsiveness. In case of good compliance to maximum dose NSAID treatment, it seems more likely that a patient will respond at least partially and remain in a state of moderate to high disease activity (ASDAS 1.3-2.5) without the possibility to receive the more effective drug (TNFi). These assumptions are best quantified in a prospective study with an affordability and opportunity cost analysis, but at this point it seems ethical and scientifically justified to offer first line TNF inhibitors to AS patients (or at least their biosimilars) in combination with NSAIDs in a step-down management plan.

There are several study limitations which can influence the significance and relevance of the results, the most important being the lack of data regarding treatment duration for each drug. In spite of the randomly chosen time frame and the random request/requirement of medical attention by the included AS patients, there may still be sampling bias due to the fact that hospital admission for AS is not based solely on severity: patients on NSAIDs and/or sulfasalazine may be admitted for disease severity, while patients on TNFi doing well may be admitted in order to receive their chronic medication prescription. The

large number of statistical tests increases the risk of an alpha error; consequently the p threshold for statistical significance of 0.05 may be overestimated. There were no available data regarding safety and other forms of extra-articular involvement (osteoporosis, kidney or lung disease).

CONCLUSION

TNFi are more efficacious than NSAIDs and sulfasalazine for the treatment of AS in a single center real-life clinical setting. Therefore a combination of biologics with NSAIDs (and sulfasalazine for peripheral arthritis) would be the ideal therapeutic pharmacological association in terms of radiographic progression and symptom control.

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