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ABSTRACT. Objective. The aim of this research was to describe the effectiveness and drug survival of tumor necrosis factor (TNF) inhibitors in the treatment of ankylosing spondylitis (AS) and to analyze the effect of concomitant treatment with conventional disease-modifying antirheumatic drugs.

Methods. Patients with AS identified from the National Register for Biologic Treatment in Finland starting their first TNF inhibitor treatment between July 2004 and December 2011 were included. Treatment response was measured as an improvement of 50% (or 20 mm) after 6 months of treatment onset compared to the baseline Bath AS Disease Activity Index (BASDAI) score. Treatment response and 2-year drug survival were modeled with logistic regression and time-dependent Cox proportional hazard models, respectively.

Results. The study comprised 543 patients, of whom 123 also commenced a second TNF inhibitor during the followup. Treatment was discontinued within 24 months by 25% and 28% of the users of the first and the second TNF inhibitors, respectively. BASDAI response at 6 months was achieved by 52% and 25% of the users of the first and the second TNF inhibitors, respectively. Etanercept (ETN; HR 0.42, 95% CI 0.29-0.62) and adalimumab (ADA; HR 0.48, 95% CI 0.30-0.77) were associated with better drug survival in comparison to infliximab (IFX). Also, concurrent use of sulfasalazine (SSZ; HR 0.70, 95% CI 0.49-0.99) decreased the hazard for treatment discontinuation.

Conclusion. TNF inhibitors are equipotent in the treatment of AS; however, ETN and ADA were found superior to IFX in drug survival. The use of SSZ improves treatment continuation. (First Release October 15 2015; *J Rheumatol* 2015;42:2339-46; doi:10.3899/jrheum.150389)

Key Indexing Terms:

ANKYLOSING SPONDYLITIS ANTIRHEUMATIC AGENTS TREATMENT OUTCOME
TUMOR NECROSIS FACTOR-A EPIDEMIOLOGIC METHODS SULFASALAZINE

Ankylosing spondylitis (AS) is a chronic inflammatory disease that mainly affects the axial skeleton but can also involve certain peripheral joints¹. The prevalence ranges from 0.1% to 1.4% depending on the population¹. Tumor necrosis factor (TNF) inhibitor drugs are currently recommended to patients with persistently high disease activity despite conventional treatments^{2,3}. To date, there is limited evidence

to support the concomitant use of conventional disease-modifying antirheumatic drugs (cDMARD) with TNF inhibitor treatment.

The efficacy of TNF- α inhibitors has been shown in many randomized controlled clinical trials (RCT)^{4,5,6,7,8}. However, not all patients experience the desired clinical effects, while others have to discontinue use of the drug for various reasons^{9,10,11,12}. Results of efficacy studies can differ from the drug effectiveness in real-life clinical use because of the strict inclusion criteria and short time span of the RCT¹³. This demonstrates the need for observational studies based on data from routine clinical care settings.

To date, the effectiveness and drug survival of TNF inhibitors in the treatment of AS have been documented in observational studies performed in Sweden, Finland, Denmark, Norway, Spain, and the United Kingdom^{9,10,11,12,14,15,16,17}. In these studies the proportion of patients achieving sufficient clinical response [Bath AS Disease Activity Index (BASDAI)] after 6 months has ranged from 52% to 63%, while 74% to 88% have remained on treatment after 12 months.

From the University of Helsinki, Helsinki; North Carelia Central Hospital, Joensuu; Tampere University Hospital, Tampere; Helsinki University Central Hospital, Helsinki; Turku City Hospital, Turku, Finland.

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A.V. Heinonen, BSc(pharm), University of Helsinki; K.J. Aaltonen, PhD (pharm), University of Helsinki; J.T. Joensuu, MSc(pharm), University of Helsinki; J.P. Lähteenmäki, MD, North Carelia Central Hospital; M.I. Pertovaara, MD, PhD, Tampere University Hospital; M.K. Romu, MD, Helsinki University Central Hospital; H.E. Hirvonen, MD, Helsinki University Central Hospital; A.K. Similä, MD, Turku City Hospital; M.L. Blom, PhD, Professor, University of Helsinki; DC Nordström, MD, PhD, Adj. Professor, University of Helsinki, and Helsinki University Central Hospital.

Address correspondence to A.V. Heinonen, P.O. Box 56, 00014, University of Helsinki, Helsinki, Finland. E-mail: arto.heinonen@helsinki.fi

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There exists 1 previous study describing the use of TNF inhibitors in the treatment of AS based on the Finnish population; it supports drug combinations, as is recommended by local guidelines¹⁰. The aim of our present study was to analyze the treatment response and drug survival of TNF inhibitor treatment and in addition, to analyze the effect of concomitant treatment with cDMARD.

MATERIALS AND METHODS

Patients. The National Register for Biologic Treatment in Finland (ROB-FIN) is a prospective cohort study established in 1999 to monitor the long-term effectiveness and safety of biological therapies in the treatment of rheumatic diseases. Data collection is based on reports submitted by rheumatologists and is to be carried out during specialized healthcare routine visits 3 and 6 months after beginning treatment and then semiannually afterward. All included patients have given their informed consent and the study has been approved by the Helsinki University Central Hospital ethics board.

The data to be collected comprises patient disease activity, concurrent medication use, and treatment-related variables including visual analog scale (VAS) of pain as well as patient's and physician's global assessments of disease activity. Swollen and tender joint count is based on 54- and 53-joint indices. Inflammation is measured by C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). BASDAI¹⁸ and Bath AS Functional Index (BASFI)¹⁹ disease activity measurements are available in ROB-FIN starting from June 2004.

Patients diagnosed with AS based on International Classification of Diseases, 10th edition disease classification and starting their first TNF inhibitor treatment between July 2004 and December 2011 were included in our study. Individuals were excluded from analysis if we found evidence of prior biologic treatment in their patient records or the treatment onset was delayed more than 3 months after the baseline visit. Patients using a second biological drug who were missing information on the first biological drug were excluded. Only patients using etanercept (ETN), adalimumab (ADA), or infliximab (IFX) were included. Followup data on the included patients were available until June 2014.

Analysis. Treatment response was defined as at least 50% or 20 mm improvement on the BASDAI score at the 6-month timepoint compared to baseline (BASDAI response)². In addition, BASFI and the AS Disease Activity Score (ASDAS) at baseline were calculated based on their respective formulae^{18,19,20}. ASDAS improvement scores were calculated at the 6-month timepoint after beginning of the treatment²¹. Missing data were imputed by multiple imputation using predictive mean matching and 20 imputed datasets²². CRP level was dichotomized with the cutoff point set at the population median. The descriptive results are reported as medians with interquartile ranges or percentages while the results of the regression analyses are reported either as OR or HR with their respective 95% CI.

BASDAI values at the timepoints of 6, 12, and 24 months were calculated using linear interpolation. Patients were required to have at least 1 subsequent visit to baseline to be included in the effectiveness analyses. As a sensitivity analysis, the patients having discontinued the treatment or been lost to followup were nonresponder imputed (NRI), i.e., considered non-responders. Drug survival was evaluated as the proportion of patients discontinuing the treatment with TNF inhibitors within 6, 12, or 24 months after treatment onset. Additionally, we performed a separate sensitivity analysis in which all patients having been lost to followup were considered discontinuers. The followup in the survival analysis was truncated at 24 months.

Univariate and multivariate logistic regression analyses were used to identify any predictors affecting the treatment response. Drug persistence was analyzed using a Cox proportional hazards model with concomitant cDMARD and oral corticosteroid therapy as time-dependent covariates. The proportional hazards assumption was tested for each variable and for the model in general²³. To comply with the proportional hazards assumption, the Cox regression models were stratified by the tertiles of the year of the

treatment onset. A stepwise model selection based on the Akaike information criterion was used to identify the best model for each multivariate analysis. Additionally, we performed all the regression analyses with all cDMARD pooled as a single covariate to summarize the effect of concomitant cDMARD therapy. Baseline differences were tested using Kruskal-Wallis and chi-squared tests for continuous and categorical variables, respectively. The data were analyzed using R statistical programming language version 3.1.1 (R Foundation for Statistical Computing).

RESULTS

Patients. Altogether, 875 individual patients being treated with TNF inhibitor were identified from ROB-FIN between July 2004 and December 2011. From these patients, 543 receiving their first TNF inhibitor and 123 patients receiving their second TNF inhibitor met our inclusion criteria and were included in this study (Figure 1). ETN, ADA, and IFX were used by 48%, 29%, and 23% of patients as their first TNF inhibitors, respectively, while the corresponding percentages for the second TNF inhibitor were 33%, 59%, and 8%, respectively. The majority of the patients starting

Flowchart on patient selection

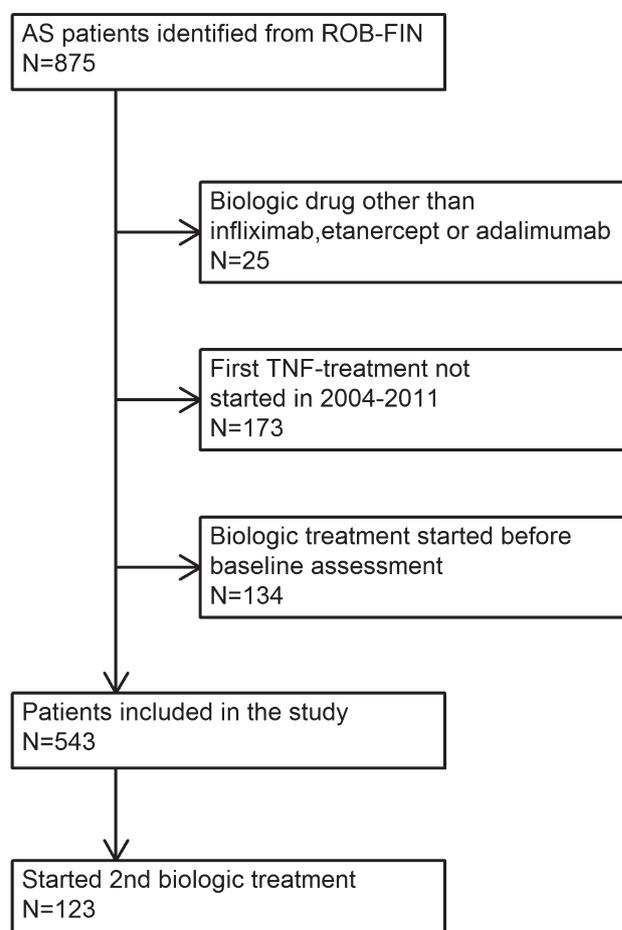


Figure 1. Patient selection. AS: ankylosing spondylitis; ROB-FIN: National Register for Biologic Treatment in Finland; TNF: tumor necrosis factor.

their first TNF inhibitor treatment were men (62%). The median time from diagnosis was 7.7 years. Median BASDAI and ASDAS scores were 5.8 and 3.3, respectively. Additional baseline information is presented in Table 1.

The most common cDMARD used at the baseline of the first TNF inhibitor were methotrexate (MTX; 49%) and sulfasalazine (SSZ; 45%). Any cDMARD was used by 78% and 67% of patients starting their first and second TNF inhibitor treatments, respectively. The use of cDMARD was similar among the different TNF inhibitor users. Statistically significant differences in baseline measures were observed between the users of different TNF inhibitors in ESR value ($p = 0.008$) and the year of treatment onset ($p < 0.001$). The total amount of missing data was 14%. After 6 months of treatment, 26% of the users of the first biologic treatment were lost to followup, while the corresponding percentages for 12 and 24 months were 32% and 37%, respectively.

Treatment response. Overall, 52% and 25% of the patients achieved BASDAI response after 6 months with their first and second anti-TNF treatments, respectively. BASDAI response at 6 months after the initiation of the first TNF inhibitor was reached by 57% of ETN users as compared to 47% and 49%

of ADA and IFX users, respectively. The proportions of patients achieving BASDAI response and remaining on treatment at different timepoints are shown in Table 2. Clinically important ASDAS improvement after 6 months was achieved by 54% of the ETN users as compared to 48% and 51% of ADA and IFX users, respectively. Clinically important and major ASDAS improvements after 6 months were reached by 52% and 25% of all the patients, respectively.

Adjusted logistic regression analyses showed no statistically significant differences between the TNF inhibitors in treatment effectiveness. The use of cDMARD was not associated with increased odds for reaching BASDAI response (Figure 2A). However, higher baseline BASDAI score (OR 1.4, 95% CI 1.2–1.7) and the year of treatment onset were statistically significant predictors for reaching BASDAI response. Younger age was associated with better treatment response in a non-statistically significant manner (OR 0.97, 95% CI 0.95–1.0). The variables included in the

Table 1. Baseline characteristics of patients starting their first or second TNF inhibitor.

Characteristics	First TNF Inhibitor, n = 543	Second TNF Inhibitor, n = 123
Age, yrs, median (IQR)	42 (33–51)	43 (35–49)
Men, n (%)	335 (62)	66 (54)
Time from diagnosis, yrs, median (IQR)	7.7 (2.8–15)	7.9 (3.7–15)
Year of treatment onset, median (IQR)	2007 (2006–2009)	2009 (2007–2011)
Drug treatment, n (%)		
Infliximab	127 (23)	10 (8)
Etanercept	261 (48)	41 (33)
Adalimumab	155 (29)	72 (59)
Methotrexate	266 (49)	55 (45)
Sulfasalazine	244 (45)	41 (33)
Leflunomide	27 (5)	2 (2)
Hydroxychloroquine	26 (5)	1 (1)
Oral corticosteroids	158 (29)	23 (19)
CRP, mg/ml, median (IQR)	10 (5.0–21)	5.0 (3.0–10)
Patient's global assessment, VAS mm, median (IQR)	52 (31–70)	44 (18–61)
VAS pain, mm, median (IQR)	60 (34–72)	48 (19–65)
Physician's global evaluation, VAS mm, median (IQR)	38 (22–56)	18 (6–38)
Peripheral arthritis, n (%)	293 (54)	50 (41)
BASDAI, median (IQR)	5.8 (4.1–7.3)	5.2 (2.8–6.8)
BASFI, median (IQR)	4.0 (2.5–5.4)	3.6 (1.9–5.1)
ASDAS, median (IQR)	3.3 (2.6–3.9)	2.8 (1.8–3.5)

TNF: tumor necrosis factor; IQR: interquartile range; VAS: visual analog scale; CRP: C-reactive protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ASDAS: Ankylosing Spondylitis Disease Activity Score.

Table 2. The numbers and proportion of patients achieving BASDAI response and discontinuing the treatment within 6, 12, and 24 months of treatment onset.

	First TNF Inhibitor	Second TNF Inhibitor
BASDAI response* at 6 months, n (%), NRI (%)		
All anti-TNF	184 (52, 34)	13 (25, 11)
IFX	36 (49, 28)	—
ETN	104 (57, 40)	—
ADA	44 (47, 28)	—
BASDAI response* at 12 months, n (%), NRI (%)		
All anti-TNF	164 (58, 30)	11 (24, 8.9)
IFX	30 (56, 24)	—
ETN	94 (59, 36)	—
ADA	40 (57, 26)	—
BASDAI response* at 24 months (%), NRI (%)		
All anti-TNF	124 (60, 23)	8 (25, 6.5)
IFX	24 (59, 19)	—
ETN	75 (64, 29)	—
ADA	25 (52, 16)	—
Discontinued, 6 months, n (%)		
All anti-TNF	50 (9.2)	20 (16)
IFX	22 (17)	—
ETN	21 (8.1)	—
ADA	7 (4.5)	—
Discontinued, 12 months, n (%)		
All anti-TNF	86 (16)	26 (21)
IFX	32 (25)	—
ETN	37 (14)	—
ADA	17 (11)	—
Discontinued, 24 months, n (%)		
All anti-TNF	135 (25)	34 (28)
IFX	50 (39)	—
ETN	55 (21)	—
ADA	30 (19)	—

*BASDAI response = BASDAI 50% or 20 mm improvement compared to baseline. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; NRI: nonresponder imputation (patients having discontinued the treatment or been lost to followup are considered nonresponders); TNF: tumor necrosis factor; IFX: infliximab; ETN: etanercept; ADA: adalimumab.

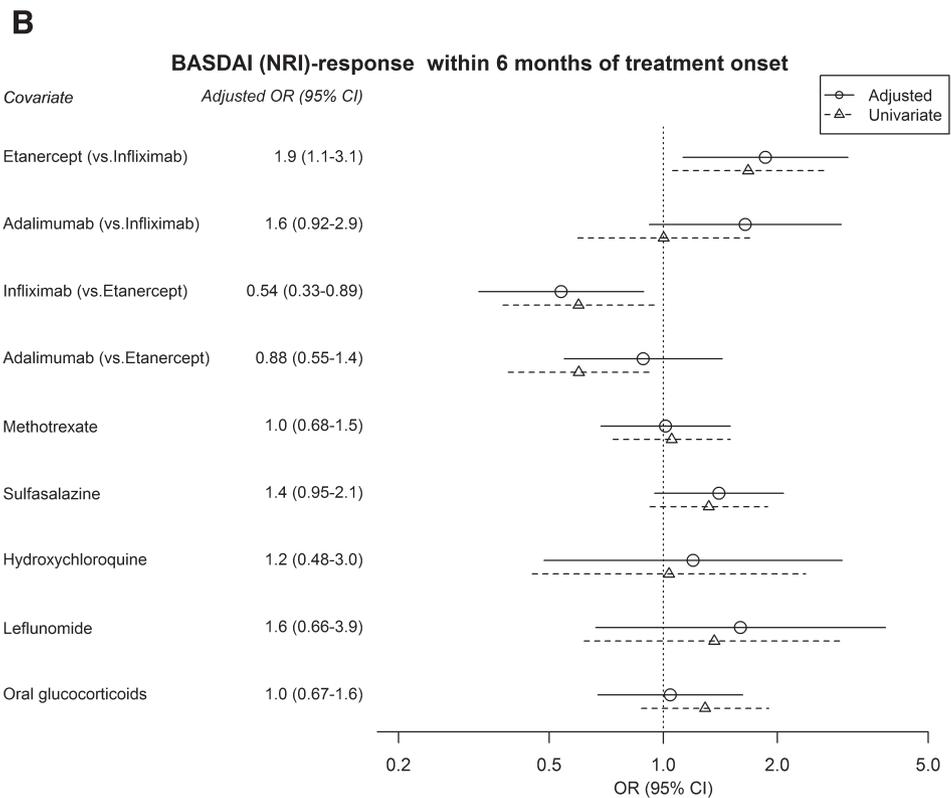
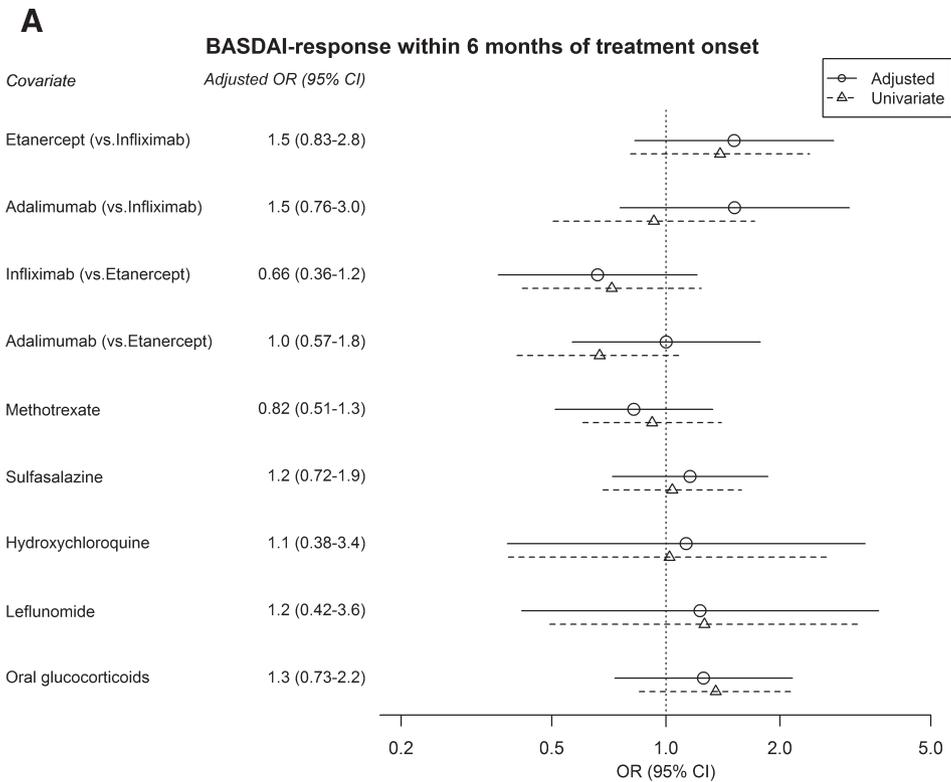


Figure 2. Univariate and multivariate logistic regression analysis for BASDAI response (BASDAI 50%/20 mm) at 6-month timepoint (A) with only patients remaining on treatment included, and (B) with all patients included in the study after NRI. NRI: nonresponder imputation; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

model for BASDAI response at 6 months were age in years, use of oral corticosteroids, year of treatment onset, ESR, BASFI, and BASDAI.

The model based on NRI BASDAI response at 6 months (Figure 2B) identified the same predictors for reaching BASDAI response as the non-adjusted model. In addition, use of ETN (OR 1.9, 95% CI 1.1–3.1) when compared to IFX and younger age (OR 0.97, 95% CI 0.95–0.99) were statistically significant predictors for reaching BASDAI response. The variables included in the NRI model were the TNF inhibiting agent taken, use of SSZ, year of treatment onset, ESR, BASFI, and BASDAI. Concomitant cDMARD therapy as a pooled covariate was not significant in the non-NRI model (OR 0.67, 95% CI 0.37–1.2) or in the NRI model (OR 0.99, 95% CI 0.62–1.6).

Drug survival. The proportion of patients discontinuing biologic treatment within 6, 12, and 24 months of onset of the first TNF inhibitor were 8%, 16%, and 25%, respectively. The 24-month discontinuation rate of the second TNF inhibitor was 28%. The main results of univariate and multivariate Cox proportional hazards analysis of the drug survival are presented in Figures 3A and 3B.

Multivariate analysis suggested that the use of ETN (HR 0.42, 95% CI 0.29–0.62) and ADA (HR 0.48, 95% CI 0.30–0.77) showed an improved drug survival when compared to IFX. Other factors increasing drug survival were concurrent use of SSZ (HR 0.70, 95% CI 0.49–0.99), male sex (HR 0.57, 95% CI 0.41–0.81), longer time from diagnosis (HR 0.96, 95% CI 0.94–0.99), and lower baseline BASFI score (HR 1.1, 95% CI 1.0–1.3). The variables included in the model for drug survival at 24 months were the TNF inhibiting agent taken, use of SSZ, time from diagnosis, BASFI, and sex.

Additional sensitivity analyses based on all patients lost to followup being considered as discontinuers suggested that the use of MTX (HR 0.80, 95% CI 0.64–0.99) increased drug survival. ETN retained superiority over IFX in drug survival, but ADA lost statistical significance (HR 0.75, 95% CI 0.56–1.0). The variables included in this model were the TNF inhibiting agent taken, use of SSZ and MTX, age, time from diagnosis, sex, and VAS global and pain. Concomitant cDMARD therapy as a pooled covariate did not have significant effect for drug survival in the main analysis (HR 1.0, 95% CI 0.65–1.6) or sensitivity analysis (HR 0.85, 95% CI 0.66–1.1).

DISCUSSION

This observational study of 543 patients treated in Finnish specialized outpatient healthcare centers offers additional evidence to what has already been reported about the effectiveness of treatment with TNF inhibitors in AS¹⁰. BASDAI response after 6 months was achieved by 52% and 25% of the patients with their first and second anti-TNF treatments, respectively. We aimed not only to describe the treatment response of ETN, ADA, and IFX, but to identify the effec-

tiveness of concomitant cDMARD and patient characteristics at baseline.

The inclusion and exclusion criteria were driven by both the availability of the data and our efforts to ensure the validity of the study. BASDAI scores were included in the ROB-FIN database starting from July 2004, prohibiting the use of older data. We excluded patients with prior biologic treatment because of our assumption that exposure to biologics would confound the baseline disease activity. Only IFX, ETN, and ADA were included because the number of patients using certolizumab pegol and golimumab was very low. Requirement for a valid followup visit was necessary for effectiveness analyses because otherwise any change in disease activity would have been impossible to detect.

The data are collected as part of tightly scheduled routine care, and as a result, some of the data were missing. We assumed that the data were missing at random and imputed the missing values using multiple imputation. HLA-B27 is included in ROB-FIN, but its status was missing too frequently to warrant the imputation. The coverage of ROB-FIN has been estimated at 60% of all Finns using biologic treatments for rheumatic diseases, which should not introduce significant selection bias²⁴.

BASDAI response after 6 months of treatment onset was reached by 52% of the patients, which is similar to the 52% to 63% reported in previous studies^{11,14}. NRI reduced the fraction of BASDAI responders to as low as 34%, which probably can be explained by the high percentage of patients lost to followup. At group level, the results produced by the NRI are identical to the LUNDEX adjustment, in which the fraction of responders are multiplied by the fraction of patients remaining in the study²⁵.

The use of MTX (49%) and other cDMARD at baseline was higher when compared to 18%, 41%, and 34% of MTX users in the observational studies of AS in Norway, Denmark, and Sweden, respectively^{9,11,15}. However, the results of observational studies may not be fully comparable owing to the differences in healthcare settings and national guidelines between countries. Good treatment experience with cDMARD in other spondyloarthritic diagnoses might have affected the treatment decisions with continuing cDMARD use in AS. Our cohort featured a similar percentage (54%) of patients with peripheral arthritis when compared to previous study results ranging from 50% to 52%^{9,26}.

Younger age and higher baseline BASDAI have been previously linked to achieving BASDAI response^{11,14,27}; we also observed that link in our study. We found the year of treatment onset to be a significant factor, which might be explained by giving TNF inhibitors primarily to patients with more severe disease and higher BASDAI score, making them more likely to reach relative improvement in treatment response. The year of treatment onset might also reflect temporal changes in treatment guidelines and unmeasured patient characteristics.

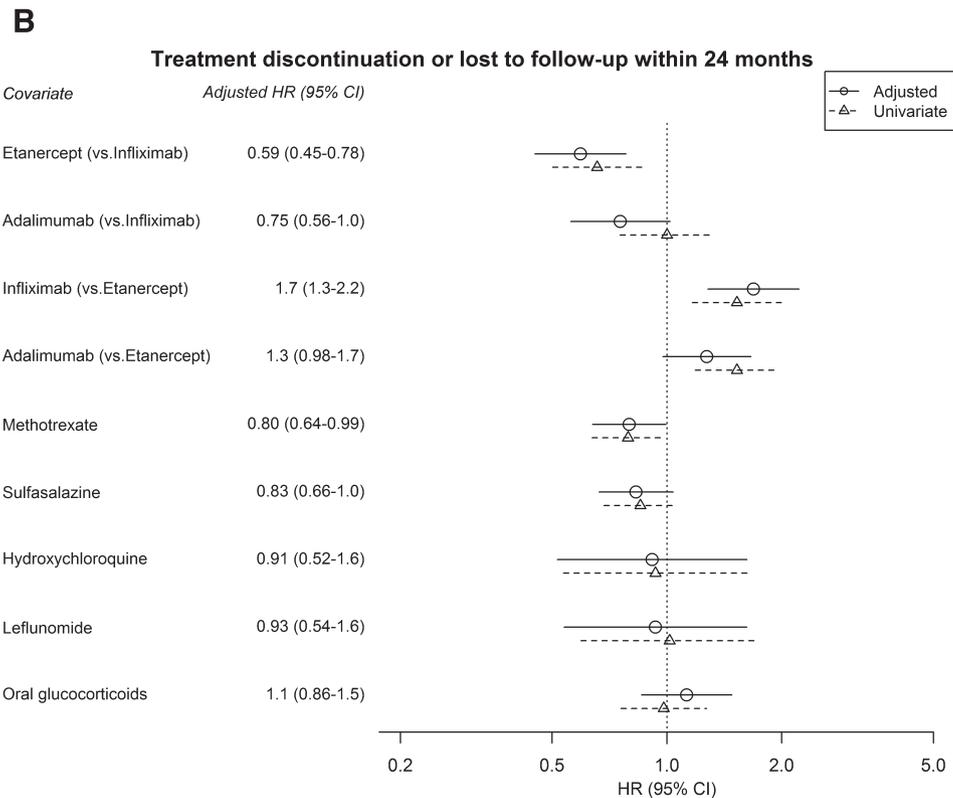
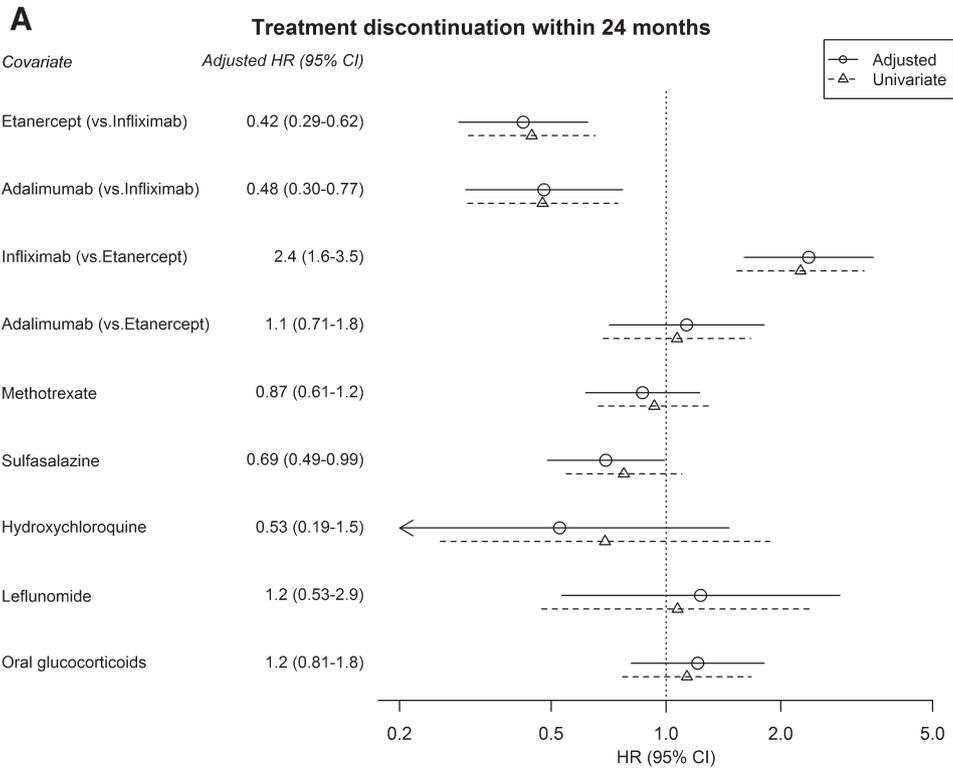


Figure 3. A. Time-dependent Cox regression analysis of patients having discontinued their treatment within 24 months of treatment onset. B. Analysis in which patients lost to followup are classified as discontinuers.

Our results suggest similar first-year (75%) and second-year (72%) survival rates with the first TNF inhibitor treatments, as reported in prior studies. The 1-year survival rate with the first TNF inhibitor has varied from 88% to 74% in previous publications^{9,10,11,12,15,17,28}. The concomitant use of SSZ was associated with improved drug survival as was MTX in sensitivity analyses in which all patients lost to followup were considered discontinuers. However, our results should be taken critically because we did not have information about prior medication use or other unknown factors that might have affected the analysis. Patients using concomitant cDMARD might differ from a mono-TNF inhibitor group with clinical characteristic differences we could not account for in our analyses.

Based on 2 systematic reviews, no concrete evidence exists to support the efficacy of MTX or SSZ in the treatment of axial AS^{29,30}. Nevertheless, use of SSZ may have some efficacy in patients with peripheral spondyloarthritis, based on current recommendations^{3,31}. In a recent observational study, concurrent therapy with either MTX or other cDMARD was associated with better drug survival³², supporting our results. The beneficial effect of cDMARD was more distinct than in our study, which is likely explained by a larger number of patients and longer followup time. However, 59% of patients did not receive any cDMARD, which differs from 22% when compared to our study.

The results of a metaanalysis suggest that concomitant MTX use is reversely correlated with the formation of antidrug antibodies against TNF inhibitors³³, and that increased immunogenicity might lead to treatment discontinuation^{34,35}. The mechanism of cDMARD affecting the formation of the antidrug antibodies is still largely unknown but this might prove to be an important clinical aspect to consider when treating AS patients with anti-TNF treatment. It has been speculated that cDMARD suppress early T and B cell expansion, leading to less immunogenicity. Alternatively, the effect of MTX or other cDMARD with TNF inhibitor might synergistically reduce inflammation. Unfortunately, antidrug antibodies were not available at the time of this report.

Other factors connected to increased survival were male sex, lower baseline BASFI score, longer time from diagnosis, and the use of ETN or ADA when compared to IFX. These results are similar to those reported in previous observational studies. Men have been shown to continue treatment longer than women in many studies^{9,11,14,16,17,27}, perhaps because men are often found to have a more severe disease with elevated CRP. Elevated CRP levels have been associated with better therapy responses and increased drug survival in other studies^{11,14,27,36}, but we did not find this to be a significant predictor in our patient cohort. Considering the difference in survival rates between TNF inhibitors, it is possible that some of the difference might be explained by hospital budgetary reasons favoring the use of self-administered drugs over intravenously administered ones.

There were some limitations to our study. Patients being lost to followup may cause bias in the results. Therefore, our study used alternative outcomes for effectiveness and drug survival such as sensitivity analyses, which accounted for the patients being lost to followup. In reality, only some of the patients lost to followup failed to achieve treatment response or discontinued treatment, while others have continued the treatment with no further reports submitted to ROB-FIN, for undisclosed reasons. Therefore, it is plausible that the true effectiveness and drug survival fall somewhere between our main results and the results of the sensitivity analyses. Any findings that retain their statistical significance in both the main analysis and the sensitivity analysis could therefore be considered less likely to be affected by bias due to patients being lost to followup. ROB-FIN does not include data on comorbidities or smoking status of the patients; that absence could confound or influence the treatment outcomes and survival results. The number of users of the second TNF inhibitor was relatively small in our study, prohibiting multivariate regression analyses.

We found that 34-52% of patients with AS treated first with TNF inhibitors reached BASDAI response after 6 months of treatment onset, while 25% discontinued the treatment within 2 years. Concomitant cDMARD do not improve the treatment effectiveness, but the use of SSZ and possibly MTX is associated with decreased treatment discontinuation. Different TNF inhibitors are equipotent in treatment effectiveness, but ETN and ADA are discontinued less often than IFX.

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