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Effectiveness and drug survival of TNF-inhibitors in the treatment of psoriatic arthritis: A prospective cohort study

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ABSTRACT

Background and objectives: Tumor necrosis factor (TNF)-inhibitors are used to treat psoriatic arthritis (PsA), but only a limited number of observational studies on this subject have been published thus far. The aim of this research was to analyze the effectiveness and drug survival of TNF-inhibitors in the treatment of PsA.

Methods: PsA patients identified from the National Register for Biologic Treatment in Finland (ROB-FIN) starting their first, second, or third TNF-inhibitor treatment between 2004 and 2014 were included. Effectiveness was measured using ACR and EULAR response criteria and modeled using ordinal logistic regression. Treatment persistence was analyzed using Kaplan–Meier survival analysis and Cox proportional hazards model.

Results: The study comprised 765 patients and 990 TNF-inhibitor treatment courses. EULAR moderate treatment responses at 6 months were achieved by 68% and 37% of the users of the first and the second or the third biologic, respectively. The probabilities of discontinuing the treatment within 12 and 24 months were 20% and 28%, respectively. Adjusted treatment responses to all TNF-inhibitors were similar; however, co-therapy with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) was not associated with better effectiveness. Adalimumab [hazard ratio (HR) = 0.62; 95% confidence interval (CI): 0.44–0.88] was superior to infliximab in drug survival while etanercept (HR = 0.77, 95% CI: 0.55–1.1) and golimumab (HR = 0.75, 95% CI: 0.46–1.2) did not differ from it. Co-medication with csDMARDs did not statistically improve drug survival.

Conclusion: All available TNF-inhibitors showed similar treatment responses with or without csDMARDs. Adalimumab was associated with better drug survival when compared to infliximab.

Introduction

In psoriatic arthritis (PsA) patients with peripheral arthritis and inadequate response to at least one conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs)-intensified treatment with biological DMARDs (bDMARDs), usually TNF-inhibitors are warranted [1]. A number of randomized controlled trials on the efficacy and safety of TNF-inhibitors in the treatment of PsA have been published and their pooled results suggest that TNF-inhibitors are both an effective and relatively safe therapy for PsA [2]. Several observational studies on the effectiveness and drug survival of TNF-inhibitors in PsA, based on patient registries Denmark, Norway,

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Sweden, Finland, Spain, and UK, have been published [3–10]. In these studies, proportions of patients reaching good EULAR response at 6 months have ranged from 38 to 55 with no statistically significant association to concomitant methotrexate (MTX) therapy. Overall, 12–30% of patients have discontinued their treatment within 1 year while male sex, higher CRP levels, and concomitant therapy with MTX use have been associated with improved drug survival. A recent systematic review found that combination therapy with MTX does not improve efficacy or safety of TNF-inhibitors [11].

The aim of the present study was to describe the treatment response and long-term survival on TNF-inhibitors in PsA and to analyze whether the choice of TNF-inhibitor or concomitant csDMARD or glucocorticoid therapy affects these outcomes.

Patients and methods

Patients

The National Register for Biologic Treatment in Finland (ROB-FIN) was established in 1999 as a nationwide register to monitor long-term effectiveness and safety of biological therapies in the treatment of rheumatic diseases. Data are collected during specialized healthcare routine visits that usually occur 3 and 6 months after beginning of treatment and then semiannually or annually afterward. Data to be collected include information on patients' demographics, concurrent anti-rheumatic medication use, and disease activity including the number of swollen (0–54 and 0–28) and tender joints (0–53 and 0–928), patient-reported outcomes, and laboratory assessments (Table 1). Data collection is carried out using paper data collection forms and more recently, an electronic patient monitoring software (GoTreatIT, DiaGraphIT (Kristiansand, Norway) is the company that develops GoTreatIT software). Additional data on patients' hospital treatment and outpatient specialized healthcare visits prior to TNF-inhibitor therapy onset for reasons other than ICD10 M-class were retrieved from the National Care Register for Health Care.

Patients clinically diagnosed with PsA and starting TNF-inhibitor therapy as their first, second, or third bDMARD between 2004 and 2014 were included in this study. Individuals were excluded from effectiveness analysis if biologic therapy had been initiated before the baseline visit or treatment onset was delayed more than 6 months after the baseline visit. All patients were included in the drug survival analysis, but information on availability of the baseline visit was used as a potential confounding factor. Only patients using adalimumab, etanercept, golimumab, or infliximab were included in this study. Follow-up data on included patients were available until the end of 2015.

Analysis

Disease Activity Score based on 28 joints (DAS28) was calculated using four variables including erythrocyte sedimentation rate (ESR) while remission was defined as DAS28 $<$ 2.6 [12]. Effectiveness was measured using both ACR and EULAR treatment response criteria [13–15]. Treatment response and remission rates at time points of 3, 6, 12, and 24 months were estimated using linear interpolation. LUNDEX-correction was applied to the results by multiplying the proportion of patients achieving response by the proportion of patients still on treatment [16]. The proportion of patients discontinuing treatment was evaluated using Kaplan–Meier survival analysis. Follow-up in survival analysis was truncated at 36 months.

Baseline differences were tested using Kruskal–Wallis and chi-squared tests for continuous and categorical variables, respectively. Univariate and multivariate ordinal logistic regression were used to identify any predictors affecting the clinical response. Non-responder imputation, in which all patients having discontinued their treatment or been lost to follow-up were considered non-

Table 1
Patient characteristics and medication at the baseline of TNF-inhibitor therapy [median (IQR)/% (*N*)]

Variable	First bDMARD	Second or third bDMARD	Total	Missing %
Age	49 (41–56)	51 (43–58)	50 (41–57)	0
Men	55% (366)	46% (149)	52% (515)	0
Patient global (VAS 0–100)	48 (23–68)	38 (14–63)	46 (19–66)	9.7
Pain (VAS 0–100)	51 (30–70)	37 (17–66)	48 (23–68)	7.0
Investigator global (VAS 0–100)	29 (12–46)	20 (9.0–32)	25 (10–42)	20
HAQ	0.75 (0.25–1.2)	0.79 (0.25–1.2)	0.75 (0.25–1.2)	17
ESR	12 (6.0–24)	11 (6.0–23)	12 (6.0–24)	12
CRP	6.0 (3.0–14)	5.0 (3.0–12)	5.0 (3.0–13)	11
Years from diagnosis	5.0 (0.96–12)	9.0 (3.9–15)	6.1 (1.7–13)	0
SJC	1.0 (0–5.0)	1.0 (0–2.0)	1.0 (0–4.0)	19
TJC	2.0 (0–7.0)	1.0 (0–4.0)	2.0 (0–6.0)	20
TJC28	1.0 (0–3.0)	0 (0–2.0)	1.0 (0–3.0)	8.7
SJC28	1.0 (0–4.0)	0 (0–2.0)	0 (0–3.0)	5.2
DAS28	3.1 (2.1–4.3)	2.6 (1.8–3.8)	2.9 (1.9–4.1)	30
Year of treatment onset	2009 (2006–2011)	2011 (2007–2013)	2009 (2007–2012)	0
Outpatient visits in the past 2 y	2.0 (0–8.0)	3.0 (1.0–11)	3.0 (0–8.0)	0
Hospital days in the past 2 y	0 (0–4.0)	0 (0–4.0)	0 (0–4.0)	0
Adalimumab	38% (254)	44% (143)	40% (397)	0
Etanercept	39% (258)	34% (108)	37% (366)	0
Infliximab	18% (120)	6.2% (20)	14% (140)	0
Golimumab	5.4% (36)	16% (51)	8.8% (87)	0
Methotrexate	53% (356)	51% (165)	53% (520)	0
Sulfasalazine	20% (130)	12% (39)	17% (169)	0
Leflunomide	11% (70)	7.1% (23)	9.4% (93)	0
Ciclosporin	6.9% (46)	4.6% (15)	6.2% (61)	0
Hydroxychloroquine	4.1% (27)	4.6% (15)	4.2% (42)	0
Any csDMARD	75% (501)	67% (217)	73% (718)	0
Oral glucocorticoids	27% (181)	34% (110)	29% (291)	0

csDMARD = conventional synthetic disease-modifying anti-rheumatic drug; CRP = C-reactive protein (mg/l); DAS28 = Disease Activity Score based on 28-joint assessment; ESR = erythrocyte sedimentation rate; HAQ = Health Assessment Questionnaire; TJC = tender joint count; SJC = swollen joint count; VAS = Visual Analog Scale.

responders, was undertaken as a sensitivity analysis. This was equivalent to LUNDEX-correction at group-level. Drug persistence was analyzed using a Cox proportional hazards (PH) model with age, csDMARD, and corticosteroid use as time-dependent covariates. The proportional hazards assumption was tested for each variable and for the model in general. As the said assumption was violated for golimumab, the results were also separately analyzed for the first 6 months of follow-up and for the remaining follow-up period by including an interaction term with time in the model. A stepwise model selection based on Akaike information criteria (AIC) was used to identify the best model in each of the multivariate analysis. Effect modification between different TNF-inhibitors and csDMARD or glucocorticoid use was tested by including the appropriate interaction terms in the model. Missing data at baseline and follow-up visits were imputed by multiple imputation using predictive mean matching and 10 imputed data sets. The descriptive results are reported as medians with interquartile ranges (IQR) or percentages while the results of the regression analyses are reported either as proportional odds ratios (pOR) or hazard ratios (HR) with their respective 95% confidence intervals (95% CI). The data were analyzed using R statistical programming language version 3.2.1 (R foundation for statistical computing, Vienna, Austria).

Favorable ethical board statement was granted by the Helsinki and Uusimaa Hospital District coordinating ethical committee while the study permission was obtained from the National Institute for Health and Welfare.

Results

Patients

Of the 852 PsA patients identified from ROB-FIN, 765 patients were included in this study, of which 668, 256, and 66 initiated TNF-inhibitors as their first, second, and third bDMARD. The number of included courses of treatment was 990 (Fig. 1). Baseline characteristics of these patients are presented in Table 1. Adalimumab (40%) was the most commonly used TNF-inhibitor in this study followed by etanercept (37%), infliximab (14%), and golimumab (8.8%). More than half of the patients were male (52%) and the median age at inclusion was 50 years. Median DAS28 scores at baseline of the first or second and third bDMARD combined were 3.1 and 2.6, respectively. DAS28 scores were lower (2.4 vs. 3.3) among the patients who potentially were already receiving bDMARD treatment at the first recorded visit in comparison to those who were not. Among patients who started their treatment in 2004, the median DAS28 was 4.4 while the corresponding value in 2014 was 2.2. Statistically significant differences between users of different TNF-inhibitors were observed across all of the observed disease-activity parameters, but not in age, sex, or time from diagnosis.

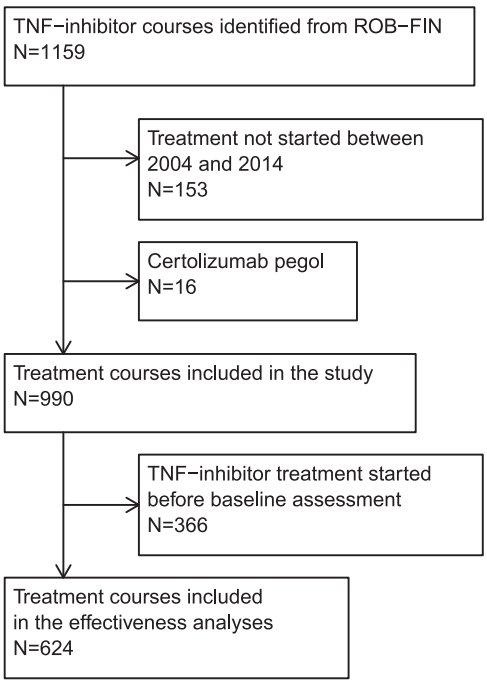

Fig. 1. Flowchart on patient selection.

Methotrexate, sulfasalazine, leflunomide, and glucocorticoids were used by 53%, 17%, 9.4%, and 29% of patients at baseline visit, respectively. The proportion of patients on biologic monotherapy at onset of their first or second and third bDMARD combined were 25% and 33%, respectively. The amount of missing data varied from 0% to 20% across the variables in the data set at baseline. Respective proportions of patients lost to follow-up within 6, 12, 24, and 36 months of treatment onset were 22%, 28%, 38%, and 44%, respectively. Median length of follow-up on TNF-inhibitor treatments was 22.2 months.

Treatment response

Overall, 366 patients were excluded from effectiveness analyses owing to the TNF-inhibitor being started before baseline assessment. After 6 months of treatment onset, 68% and 51% of the patients using TNF-inhibitors as their first bDMARD reached at least moderate EULAR and ACR20 treatment responses while 68% were in DAS28 remission (Fig. 2). After LUNDEX-correction, however, these percentages decreased to 44%, 33%, and 44%. There were no statistically significant differences in unadjusted response rates between the different TNF-inhibitors. Treatment responses to TNF-inhibitors used as the patients' second or third bDMARD were inferior compared to being used as the first bDMARD (Supplement 1). Treatment responses to TNF-inhibitors used as the patients' first bDMARD stratified by different TNF-inhibiting agents (Supplement 2) or co-therapies (Supplement 3) were similar.

In addition to TNF-inhibiting agent and the use of concomitant csDMARDs and glucocorticoids, the covariates used in the adjusted model were age, sequential count of bDMARD therapies physician's and patients' global assessments of disease activity, HAQ, and DAS28 (Supplement 4). Adjusted ordinal logistic regression analyses revealed no statistically significant differences between the TNF-inhibitors in achieving ACR20, 50, or 70 response at 6 months with or without adjusting for confounding or patient attrition (Fig. 3). Patients treated with MTX (pOR = 1.2, 95% CI: 0.70–1.9) or other csDMARDs (pOR = 1.1, 95% CI: 0.63–2.1) had similar proportional odds of achieving treatment response, as the ones on biologic monotherapy. The use of glucocorticoids was not statistically significantly associated with improved treatment response. None of the interactions tested were statistically significant and were therefore excluded from the final models.

Drug survival

Within 3, 6, and 12 months of treatment onset, 45 (4.5%), 93 (9.4%), and 170 (17%) of the patients had discontinued their treatment, respectively. Based on Kaplan–Meier survival analysis, the probabilities of discontinuing TNF-inhibitor therapy within 3, 6, 12, 24, and 36 months were 4.9%, 10%, 20%, 28%, and 34%, respectively (Table 2). These discontinuation probabilities were quite similar between users of the first, second, or third bDMARD.

The final Cox PH model comprised TNF-inhibiting agent, use of concomitant csDMARDs, and glucocorticoids, as well as the year of treatment onset, sex, availability of a valid baseline visit, patient global assessment of disease activity, and tender joint count (0–28)

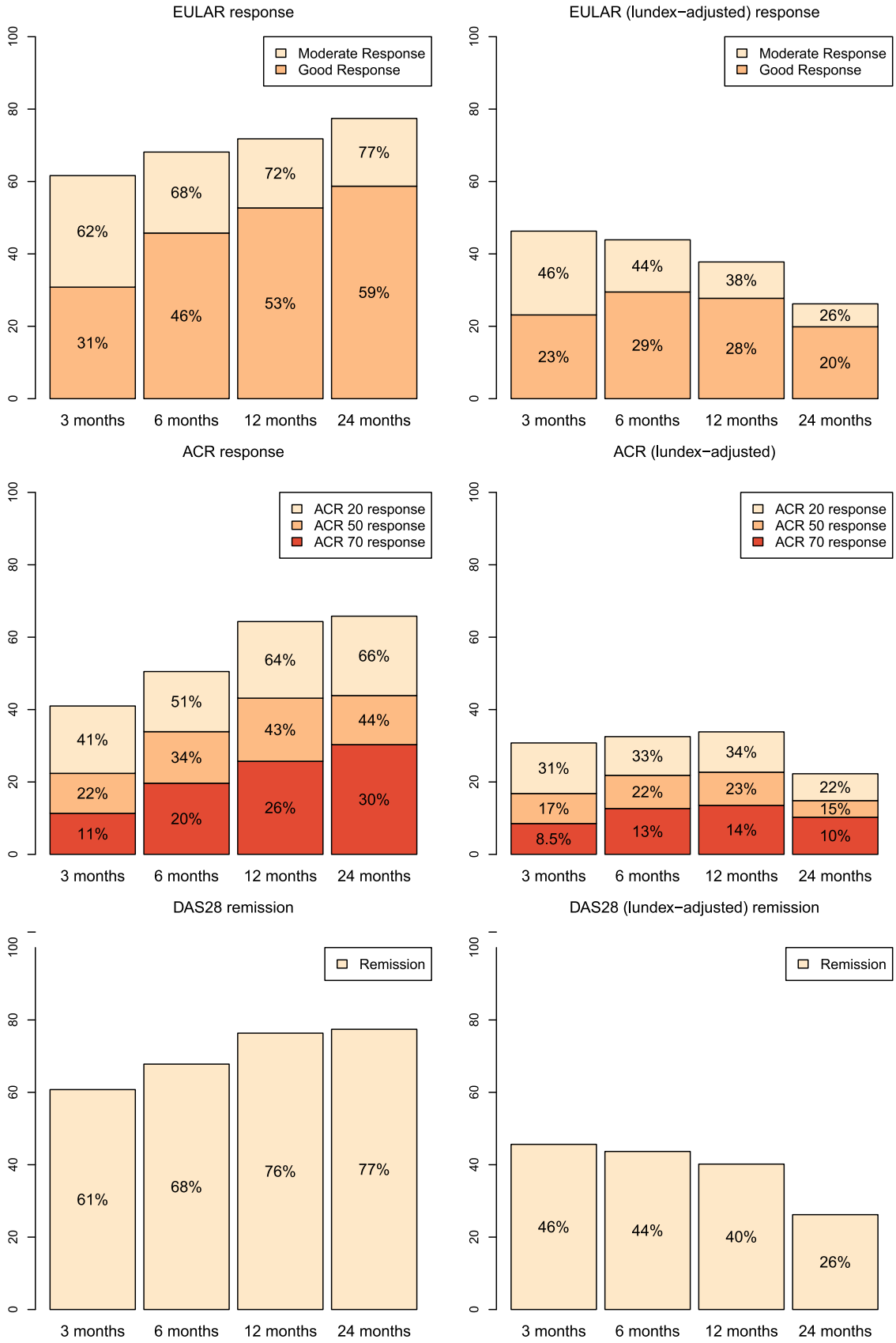

Fig. 2. Treatment responses and remission rates of TNF-inhibitors used as the patients' first bDMARD therapy at 3, 6, 12, and 24 months within treatment onset.

as covariates (Supplement 4). Adalimumab (HR = 0.62, 95% CI: 0.44–0.87) was superior to infliximab in drug survival while etanercept (HR = 0.77, 95% CI: 0.55–1.1) and golimumab (HR = 0.75, 95% CI: 0.46–1.2) did not differ from it (Fig. 4). The hazards did not remain constant for the duration of the follow-up. Within the first 6 months of follow-up, HRs for adalimumab, etanercept,

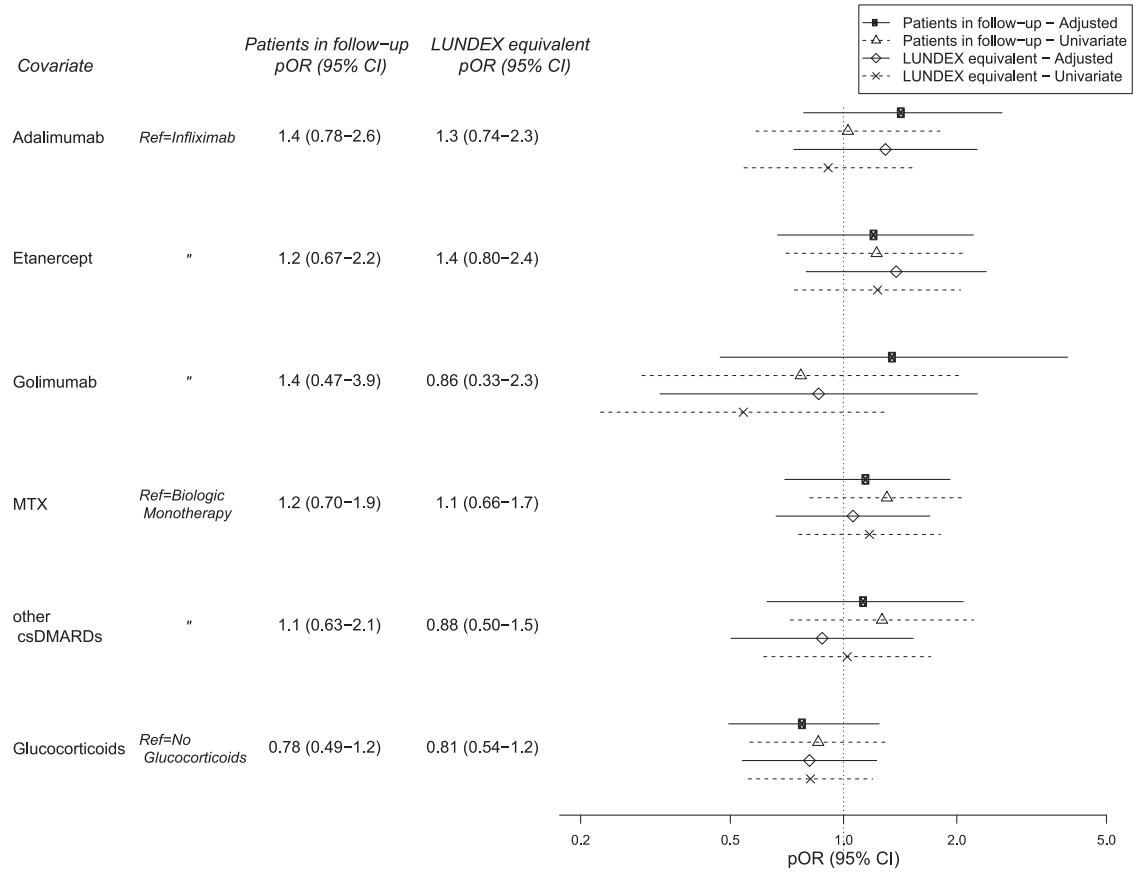

Fig. 3. The results of ordinal logistic regression analyses on reaching ACR treatment response at 6 months on TNF-inhibitors used as the patients first, second, or third bDMARD either excluding or including patients having discontinued the treatment or lost to follow-up. Additional model results are presented in Supplement 4.

and golimumab were 1.09 (95% CI: 0.32–3.71), 1.78 (95% CI: 0.53–5.97), and 2.17 (95% CI: 0.39–12.20), respectively, while the corresponding figures were 0.50 (95% CI: 0.34–0.74), 0.54 (95% CI: 0.36–0.81), and 0.41 (95% CI: 0.21–0.81) for the remaining period, respectively. Neither MTX (HR = 0.82, 95% CI: 0.61–1.1) nor other csDMARDs (HR = 0.86, 95% CI: 0.59–1.2) differed from biologic monotherapy in drug survival, but the use of glucocorticoids was associated with poorer treatment persistence (HR = 1.7, 95% CI 1.3–2.2). The interactions between TNF-inhibitors and the use of csDMARDs or glucocorticoids were not statistically significant, and hence, excluded from the final model.

Discussion

This present study updates previous findings on TNF-inhibitor treatment among PsA patients based on the ROB-FIN register with extended follow-up and additional analyses on treatment response

Table 2
Discontinuation proportions of TNF-inhibitors

	3 Months	6 Months	12 Months	24 Months	36 Months
TNF-inhibitors used as the first bDMARD %, (95% CI)					
Adalimumab	1.9 (0.11–3.7)	7.8 (4.2–11)	16 (11–20)	24 (17–29)	29 (22–35)
Etanercept	5.2 (2.3–8.0)	9.5 (5.6–13)	15 (10–20)	24 (18–29)	30 (23–36)
Golimumab	9.4 (0–19)	13 (0.24–24)	26 (8.8–40)	26 (8.8–40)	26 (8.8–40)
Infliximab	5.2 (0.93–9.2)	9.2 (3.6–15)	27 (18–35)	43 (32–52)	48 (37–57)
Total	4.1 (2.5–5.7)	9.0 (6.6–11)	18 (15–21)	27 (24–31)	33 (29–37)
TNF-inhibitors used as the second or third bDMARD %, (95% CI)					
Adalimumab	2.4 (0–5.1)	8.3 (3.2–13)	17 (10–24)	25 (16–33)	31 (21–39)
Etanercept	11 (4.5–17)	17 (9.5–25)	28 (18–36)	35 (24–44)	39 (28–49)
Golimumab	12 (1.5–21)	24 (9.9–36)	35 (18–48)	38 (20–51)	45 (26–60)
Infliximab	0 (0–0)	0 (0–0)	21 (0–40)	37 (4.8–58)	37 (4.8–58)
Total	6.5 (3.6–9.3)	13 (9.3–17)	24 (19–29)	31 (25–36)	36 (30–42)
TNF-inhibitors uses as the first, second, or third bDMARD, (95% CI)					
Adalimumab	2.1 (0.58–3.6)	8.0 (5.1–11)	16 (12–20)	24 (19–29)	30 (24–35)
Etanercept	6.8 (4.0–9.4)	12 (8.3–15)	19 (15–23)	27 (22–32)	33 (27–38)
Golimumab	11 (3.4–17)	19 (9.6–28)	31 (19–41)	33 (21–43)	37 (24–48)
Infliximab	4.5 (0.80–8.0)	8.0 (3.1–13)	26 (18–33)	42 (32–51)	46 (36–55)
Total	4.9 (3.5–6.3)	10 (8.3–12)	20 (17–23)	28 (25–32)	34 (30–37)

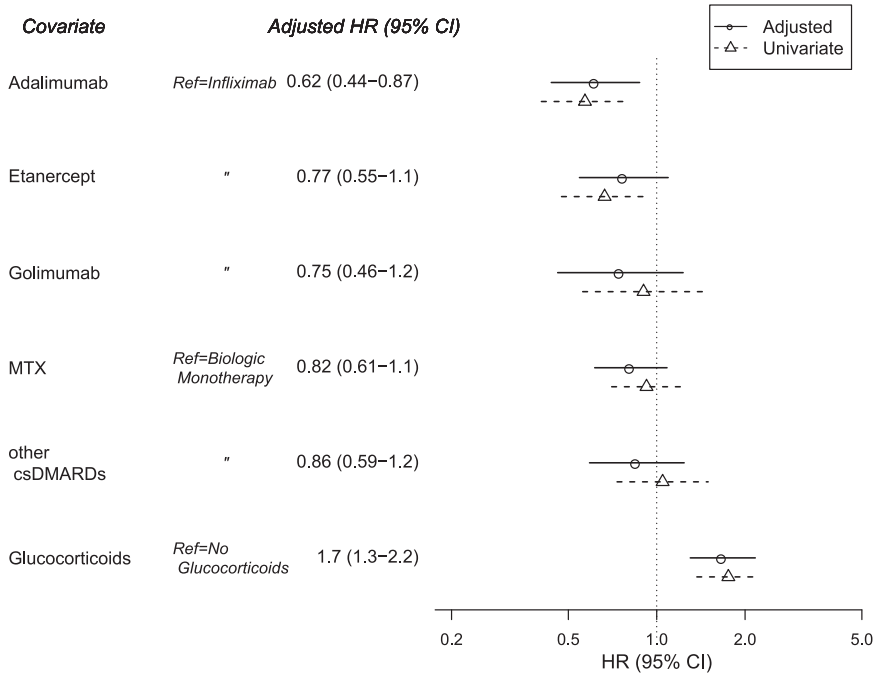

Fig. 4. The results of a Cox proportional hazards model on the discontinuation of TNF-inhibitor therapy within 36 months of treatment onset. Additional model results are presented in Supplement 4.

and persistence [6]. Although some previous literature on the subject exists, our study is the first to include golimumab. Our findings are based on real-world evidence and are therefore invaluable to supplement the results of randomized controlled trials, whose stringent inclusion criteria and often brief follow-up time limit their generalizability.

Patients and methods

Inclusion and exclusion criteria were driven by both the availability of data and our efforts to ensure the validity of the study. DAS28 scores were included in the ROB-FIN starting from 2004, prohibiting the use of older data. The decision to exclude patients with prior biologic treatment from effectiveness analyses was due to our assumption that exposure to biologics would confound baseline disease activity, which is crucial for valid calculation of treatment responses. For drug survival analyses, we included all patients but used an indicator of validity of the baseline measurement as a potential confounding variable, although it was excluded from the final model owing to insufficient explanatory value. Only infliximab, etanercept, adalimumab, and golimumab were included in this study because the number of patients using certolizumab pegol was very low owing to the lack of marketing authorization. Golimumab did not enter clinical use until 2010, and hence, the median year of treatment onset among patients using it was later as compared to patients on other included TNF-inhibitors. Requirement for a valid follow-up visit was necessary for effectiveness analyses as otherwise any change in disease activity would have been impossible to detect. In sensitivity analyses, however, patients who discontinued their treatment or were lost to follow-up were included as non-responders regardless of whether or not they had any successive visits to baseline.

This Finnish cohort differs in some areas from observational studies previously reported. A DAS28 score as high as 6.4 was observed in a study based on a British population while Danish and Swedish studies reported median DAS28 scores of 4.8 and 4.9, respectively [3,4,8]. In our population, median DAS28 was 2.9, indicating less severe or better managed disease as compared to these previous studies. In fact, our data showed a significant reduction in disease activity over time among patients starting their biologic treatment. Also, some of the included patients may have already been receiving treatment at their first recorded visit. Penetration of MTX use was nevertheless similar between our study and previous ones. Owing to differences in healthcare practices and guidelines between countries, caution is required when generalizing these findings outside Finland.

Treatment response

Good or moderate EULAR response after 6 months of treatment onset was reached in 68% of the patients, which is less than 75% and 91% reported in previous studies [4,8]. However, the results of observational studies may not be fully comparable owing to the differences in data collection routines, healthcare settings, and national treatment guidelines between countries [17]. TNF-inhibitors were found to be equipotent in effectiveness with and without adjusting for potential confounding. Similarly, neither MTX-based nor non-MTX-based csDMARD combinations were associated with improved treatment response. Similar results have been observed in previous studies [8,10].

Drug survival

In previous studies, 12–30% of patients have discontinued their treatment within 1 year and 19–43% within 2 years of follow-up [3,6,7,9]. Our respective results of 20% and 28% serve as a confirmation to these previous findings. Our results suggested that the hazard for discontinuing TNF-inhibitor therapy did not differ between TNF-inhibitors during the first 6 months, but from that point onward, infliximab was significantly inferior in terms of drug survival in comparison to adalimumab, etanercept, or golimumab. Infliximab has been linked to inferior drug survival previously [3], yet prior studies have not reported results separately for different time periods. Based on a meta-analysis of randomized controlled trials, short-term safety and effectiveness

of TNF-inhibitors are mostly equivalent in PsA, offering no explanation to our findings [18]. The difference in drug survival and also the non-proportional hazards might arise from the fact that infliximab is administered intravenously and thus is covered by the hospital budget instead of reimbursed by the National Insurance Institution, which is the case with other TNF-inhibitors. Although the majority of expenses are ultimately covered by society in both the cases, hospitals may have sought to discontinue infusion treatments in favor of self-administered ones to save money. This trend was however absent in a related study among patients with ankylosing spondylitis [19]. In any case, the HRs considering TNF-inhibitors reported in Figure 3 should be interpreted as averages over time as hazards do not remain proportional to each other for the entire duration of the follow-up period. Concomitant use of MTX or other csDMARDs was not statistically significantly associated with improved drug survival in our data whereas some prior studies have found MTX improving treatment persistence [3,4,10]. Our finding on glucocorticoids being associated with poorer drug survival could be a sign of residual confounding as the need to use glucocorticoids often arises from poorer response to TNF-inhibitors, which actually might be the main reason for treatment discontinuation.

Limitations of the study

There were some limitations in this study. Within 36 months of treatment onset, 45% of patients had been lost to follow-up. In the effectiveness analyses, we explored the effect of patient attrition using LUNDEX-correction and equivalent adjustment to ordinal logistic regression. However, survival analyses assume non-informative censoring, or in other words, that the patients lost to follow-up do not differ from the ones remaining on treatment or discontinuing it in a manner that would introduce bias to results. Data were collected as a part of a tightly scheduled routine care, and as a result, some data are missing. We assumed that data were missing at random and imputed the missing values using multiple imputations. Although ROB-FIN fails to cover 100% of bDMARD therapies in Finland, we do not have any reason to suspect systematic error to the results as a consequence. Regretfully, we were unable to analyze the reasons for TNF-inhibitor discontinuation as this information was too infrequently reported. In the absence of more accurate comorbidity data, we used hospital treatments and outpatient visits to specialized healthcare as summary measures for them. The downside of this approach was that comorbidities treated in community health centers such as high blood pressure could not be accounted for. Outpatient visits due to rheumatic diseases were ignored as bDMARDs are currently only prescribed for PsA patients treated within specialized healthcare. The joint count used in our data fell short of the full 66/68 joint counts traditionally used in calculation of ACR responses. As the ACR responses measure a proportional reduction in the number of swollen and tender joints rather than an absolute one, calculation of ACR response was possible with the joint counts available to us. However, we cannot ascertain if the responses would be exactly similar in case of a full 66/68 joint count could have been used instead.

Conclusion

In this study, we found that 68% and 51% of PsA patients treated with TNF-inhibitors as their first bDMARD reached at least moderate EULAR and ACR20 response after 6 months of treatment onset, respectively. We found signs of concomitant csDMARD therapy improving treatment response and drug survival, but these findings were not statistically significant. Different TNF-inhibitors were mostly equipotent in effectiveness, but treatment persistence on infliximab was inferior as compared to other TNF-inhibitors, especially after 6 months of treatment onset.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.semarthrit.2016.09.005.

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