Effectiveness and Feasibility Associated with Switching to a Second or Third TNF Inhibitor in Patients with Psoriatic Arthritis: A Cohort Study from Southern Sweden

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ABSTRACT. ***Objective.*** Because new modes of action for the treatment of psoriatic arthritis (PsA) are emerging, it is important to understand the use of switching to a second or third antitumor necrosis factor (anti-TNF) agent. This study investigated drug survival and treatment response rates of patients with PsA undergoing second- and third-line anti-TNF therapy.

Methods. Patients with PsA were monitored in a prospective, observational study. Patients who switched anti-TNF therapy once (first-time switchers, n = 217) or twice (second-time switchers, n = 57) between January 2003 and March 2012 were studied. American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) good response at 3 and 6 months, as well as drug survival, were reported and further analyzed using the Cox and logistic regression models.

Results. Median age for first-time switchers was 47 years and 42% were men. The corresponding values for second-time switchers were 48 years and 40% men. Three-month ACR20 Lund Efficacy Index (LUNDEX) response was achieved by 47% of first-time and 22% of second-time switchers; ACR50 LUNDEX rates were 21% and 14%, ACR70 LUNDEX rates were 12% and 2%, and EULAR good LUNDEX rates were 26% and 10%, respectively. Median drug survival time for patients switching anti-TNF for the first time was 64 months (95% CI 31–97) compared with 14 months (95% CI 5–23) for second-time switchers. Identified baseline predictor of ACR20 response to second-line treatment was the 28-joint Disease Activity Score values at baseline (OR 1.45, 95% CI 1.01–2.10), while higher Health Assessment Questionnaire scores predicted premature drug withdrawal (HR 1.60, 95% CI 1.03–2.48).

Conclusion. Response rates of first-time anti-TNF switchers are moderate, while the inferior response rates of second-time switchers suggest other therapeutic options should be considered in this situation. (J Rheumatol First Release December 1 2015; doi:10.3899/jrheum.150744)

Key Indexing Terms:
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Psoriatic arthritis (PsA) is a multifaceted disease associated with psoriasis in the skin and nails, chronic peripheral and/or axial arthritis, enthesopathy, and dactylitis[1]. The disease affects around 0.25% of the adult population in Sweden and often causes substantial functional impairment and decreased health-related quality of life[2,3].

The introduction of tumor necrosis factor (TNF) inhibitors has greatly improved the treatment of PsA. The soluble TNF receptor etanercept (ETN) and the monoclonal anti-TNF antibodies adalimumab (ADA), certolizumab pegol (CZP), golimumab, and infliximab (IFX) have all been shown in

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randomized, placebo-controlled trials (RCT) to induce clinical improvement in the majority of patients with PsA[4,5,6,7,8,9]. However, around 30% of patients with PsA fail to respond to their first TNF inhibitor, and yet others experience adverse events. This then leads to the question of whether TNF inhibitor-switching can be clinically beneficial because a significant number of patients need to proceed to further therapy options[4,5,6,7,8,9,10]. Moreover, work disability is also a problem in patients with PsA, especially when they fail the first anti-TNF treatment course[11]. Although anti-TNF have a central position in the treatment recommendations in PsA[12,13], therapies with new modes of action, including interleukin 12/23 inhibition as well as phosphodiesterase 4 inhibition, have been approved for PsA treatment, providing reasonable alternatives to anti-TNF therapy in clinical practice[14,15]. Moreover, abatacept has also been effective in patients with PsA[16].

Treatment response in patients undergoing a second course of anti-TNF therapy (first-time switchers) has been addressed in 2 larger registry studies[17,18]. Several smaller studies with limited power have also been conducted[19,20,21,22,23,24]. Overall, these show the efficacy and safety of the second agent to be somewhat inferior to the outcome in patients undergoing first-line anti-TNF therapy (anti-TNF-naive). Moreover, the report from the Danish Biologic Registry (DANBIO) and the Norwegian Disease Modifying Antirheumatic Drug Registry (NOR-DMARD) showed inferior drug survival rates in patients receiving their second course of anti-TNF treatment[17,18]. No RCT have addressed this clinically important issue. The observational studies reporting treatment responses have reported only per protocol outcomes without accounting for nonresponse attributable to premature treatment withdrawal[17,18]. Further, only 1 study reported treatment outcomes for third-course anti-TNF treatment[18], which makes the evidence for feasibility in the second and third courses of anti-TNF treatment rather sparse.

The aims of our present longitudinal observational study of patients with PsA were to report intention-to-treat (ITT) response rates using the Lund Efficacy Index (LUNDEX) correction and drug survival rates of first- and second-time anti-TNF switchers, respectively[25]. We also wanted to identify baseline predictors of response to a second anti-TNF treatment course. The primary outcome was the American College of Rheumatology (ACR) 20 response at 3 months of followup.

MATERIALS AND METHODS

Patients. Patients enrolled in the South Swedish Arthritis Treatment Group (SSATG) register, a large prospective observational study cohort involving 11 rheumatology units[10], were selected. The study period was from January 2003 through March 2012. Patients eligible for inclusion had peripheral arthritis and a diagnosis of PsA according to clinical judgment by treating physicians. The coverage of the register has been reported to be > 90% of all treatments for patients with rheumatic arthritis beginning treatment with biologics[26]. A previous validation of the treated PsA cohort showed that 92% fulfilled the CASPAR (ClASsification for Psoriatic ARthritis) criteria at study inclusion[27].

First-time switchers (n = 217) had switched therapy from 1 TNF inhibitor to another, while second-time switchers (n = 57) were undergoing treatment with a third TNF antagonist. Neither group was allowed any other prior use of biological disease-modifying antirheumatic drugs (DMARD).

The quality control character of the SSATG register comes from the documentation required by law in Sweden. No informed consent was needed for our study. The regional ethics board of the University of Lund approved linkage of laboratory and clinical data used for our study (No. 379/2011).

ETN was administered twice weekly with a 25-mg subcutaneous dosage initially; later, 50 mg once weekly was often given. IFX was infused at 3 mg/kg at 0, 2, 6, and then every 8 weeks. Depending on efficacy, the dosage of IFX could then be increased in steps of 100 mg to a maximum of 500 mg administered at 4- to 8-week intervals. The average dosage after 6 months was about 4.5 mg/kg every 8 weeks. CZP was administered 400 mg subcutaneously, initially at weeks 2 and 4, followed by 200 mg every 2 weeks. ADA was administered as a 40-mg subcutaneous dose every other week. Golimumab was administered by subcutaneous injection, 50 mg once every fourth week.

Baseline and followup assessments. At the initiation of each new anti-TNF therapy, baseline characteristics were reported by treating physicians using a standardized protocol. This included information on demographics, diagnosis and disease duration, disease activity variables allowing calculation of the 28-joint Disease Activity Score (DAS28), and details regarding past and present antirheumatic therapy[28,29]. Patients' Health Assessment Questionnaire (HAQ) scores were calculated according to the validated Swedish version[30]. Results of visual analog scales for pain and general health were also included, along with evaluators' global assessments of disease activity on a 5-grade Likert scale. At the 3-month followup, the same disease activity variables were again recorded, and improvement according to the European League Against Rheumatism (EULAR) and/or the ACR response criteria was calculated[31]. Health utilities were collected using the 5 descriptive questions of the EQ-5D; the British tariff was applied for converting EQ-5D questionnaires into utility scores. Withdrawals from anti-TNF therapy were categorized by treating physicians as attributable to adverse events, inefficacy including both primary and secondary inefficacies, or miscellaneous. The latter consisted of reasons such as pregnancies, patient decisions, poor compliance, remissions, and other unspecified causes.

Response rates at 3 months for first- and second-time switchers were computed according to the EULAR good, ACR20, ACR50, and ACR70 improvement criteria. In the SSATG register setting, patients who switched anti-TNF therapy twice may be included in both study groups. Thus, statistical analyses comparing first- and second-time switchers were not conducted. For comparison, 3-month response rates and disease activity stages of patients with PsA in the SSATG register treated with a first TNF inhibitor were also computed.

Statistical methods. For the binary treatment outcome, ITT-corrected responses were given using the LUNDEX principle. The LUNDEX adjustment is an ITT method developed for the observational setting to account both for the withdrawals from therapy and for missing response recordings at certain points of followup[25]. Drug survival was estimated using the Kaplan-Meier analysis. Wilcoxon paired rank test was used for studying 6-month changes in the EQ-5D, HAQ, DAS28 with C-reactive protein (CRP), and CRP level. Predictor analyses of ACR20 response at 3 months (primary study outcome) were undertaken using logistic regression models. Also, stepwise deletion Cox regression modeling was done to study covariates associated with drug withdrawal. Variables included in the models (logistic regression and Cox models) — chosen based on correlation and clinical relevance — were age at therapy initiation, sex, disease duration, baseline DAS28 and HAQ scores, concurrent MTX, a termination-reason variable (adverse events/inefficacy), and the type of previous TNF inhibitor (receptor/antibody).

RESULTS

During the study period, 629 biologically naive patients with PsA in the SSATG register started treatment with a first anti-TNF treatment course. Inclusion criteria to the current study were met by 217 patients who subsequently switched therapy to a second anti-TNF agent, and by 57 patients proceeding to a second switch. Figure 1 illustrates the inclusion and flow of patients during the study period. Baseline characteristics are summarized in Table 1, while data on prior anti-TNF treatments and reasons for withdrawal are displayed in Table 2.

Response rates. Response rates of first- and second-time switchers at 3 and 6 months are presented in Table 3. Overall, the response rates in first-time switchers were markedly higher than those in second-time switchers. The primary outcome, 3 months ACR20 response, was met by 47% of first-time and 22% of second-time switchers. Notably, the LUNDEX correction had a larger effect on second-time switchers, reflecting a poor drug survival in this group of patients. Patient demographics and clinical characteristics (sex, age, disease duration, HAQ, and DAS28-CRP) at baseline for patients with recorded outcomes (n = 103) and patients missing 3 months of data (n = 96) were not statistically different for any of the studied variables ($p > 0.15$).

For first-time switchers, the mean EQ-5D gain at 6 months was 0.20 [interquartile range (IQR) 0.00–0.53, $p < 0.001$], whereas the DAS28-CRP decreased by –1.19 (IQR –2.23 to –0.57), the HAQ decreased by –0.24 (IQR –0.5 to 0.0), and the CRP level decreased by –17.6 mg/dl (–17.7 to 0.0). The corresponding values at 6 months for second-time switchers were EQ-5D gain of 0.00 (IQR –0.17 to 0.07, $p = 0.721$), decrease in DAS28-CRP of –0.99 (IQR –1.91 to –0.12, $p = 0.003$), change in HAQ of 0.04 (IQR –0.12 to 0.13, $p = 0.342$), and decrease in CRP of –9.81 mg/dl (IQR –11.0 to 0.20, $p = 0.012$).

Drug survival. Figure 2 presents estimated drug survival rates for first- and second-time switchers. Median drug survival time for patients switching anti-TNF for the first time was 64

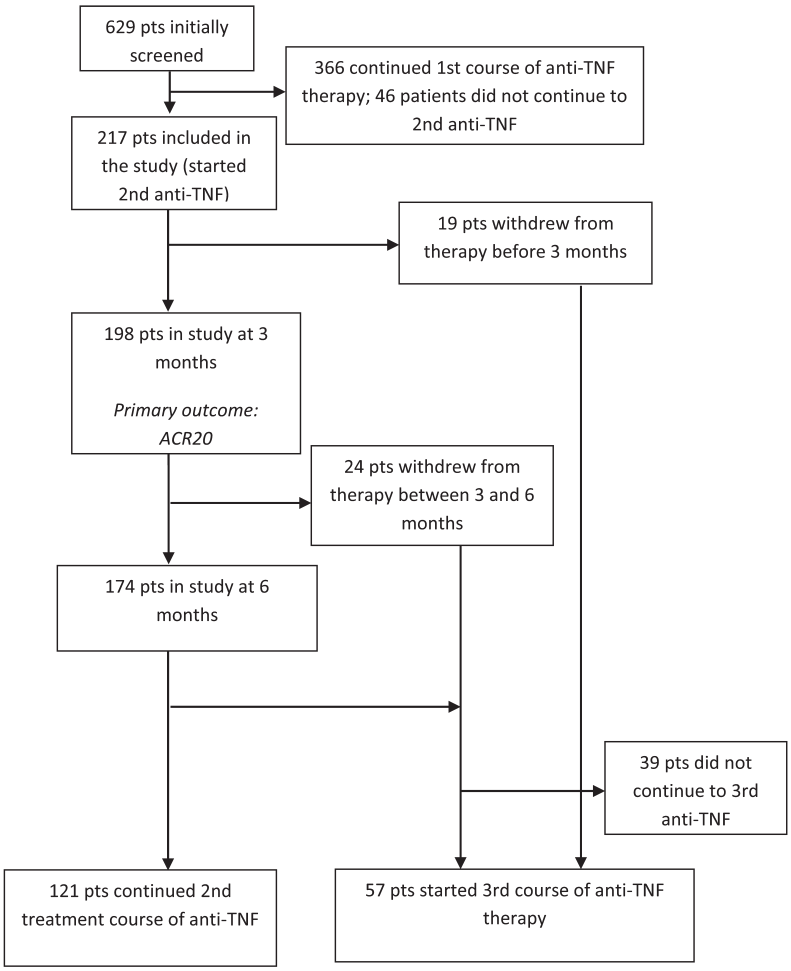

Figure 1. The flow of patients with PsA included and followed in our study. PsA: psoriatic arthritis; pts: patients; ACR20: American College of Rheumatology 20% improvement criteria; TNF: tumor necrosis factor.

Table 1. Baseline characteristics of subjects included in the study. When data are missing, percent of valid is used. Values are median (interquartile range) unless otherwise specified.

Characteristics	First-time Switchers, n = 217	Second-time Switchers, n = 57
Age, yrs	47 (38–56)	48 (39–56)
Males, % (n)	42 (91)	40 (23)
Disease duration, yrs	7.3 (3.9–13.8)#	9.3 (5.5–15.3)
CRP, mg/dl	6 (1–16)##	7 (1–18)*
HAQ	1.0 (0.63–1.5)###	1.0 (0.72–1.63)**
VAS pain, 100 mm	70 (51–81)###	67 (48–80)**
VAS global, 100 mm	70 (54–80)###	69 (51–71)**
DAS28-CRP	4.2 (3.2–5.0)###	4.6 (3.8–5.2)***
Previous DMARD, n	3 (2–3)####	4 (3–5)
Concomitant MTX, % (n)	53 (116)	40 (23)
Adalimumab, % (n)	36 (79)	49 (28)
Certolizumab, % (n)	1 (2)	0
Etanercept, % (n)	55 (119)	25 (14)
Golimumab, % (n)	2 (5)	12 (7)
Infliximab, % (n)	6 (12)	14 (8)

n = 214. ## n = 194. ### n = 192. #### n = 215. * n = 49. ** n = 50. *** n = 45. CRP: C-reactive protein; HAQ: Health Assessment Questionnaire; VAS: visual analog scale; DAS28: 28-joint Disease Activity Score; DMARD: disease-modifying antirheumatic drug; MTX: methotrexate.

Table 2. Treatment history of the first course of antitumor necrosis factor treatment in switchers.

Treatment History	% (n)
Stop for adverse event*	31 (57)
Stop for failure*	57 (104)
Stop for other reason*	11 (20)
Adalimumab	23 (49)
Certolizumab	1 (2)
Etanercept	31 (67)
Golimumab	0 (0)
Infliximab	46 (99)

* Thirty-six patients missed the recording of withdrawal reason.

months (95% CI 31–97) compared with 14 months (95%CI 5–23) for patients receiving their third course of anti-TNF treatment. Five-year estimated drug survival for first-time switchers was 51%, and 23% for second-time switchers.

Predictors of treatment response and drug survival in first-time switchers. Cox regression modeling identified higher HAQ as a significant predictor of drug withdrawal (HR 1.60, 95% CI 1.03–2.48, p = 0.036). Other corresponding values for variables remaining in the regression model after backward deletion were male sex (0.74, 0.46–1.19, p = 0.215), age per year (1.01, 0.99–1.03, p = 0.132), CRP level per unit (0.99, 0.98–1.00, p = 0.091), DAS28-CRP (0.84, 0.67–1.04, p = 0.113), and previous withdrawal because of adverse events (1.36, 0.85–2.18, p = 0.207).

Logistic regression showed that baseline DAS28-CRP predicted ACR20 response at 3 months of followup (OR 1.45, 95% CI 1.01–2.10). Other variables remaining in model after deletion were previous withdrawal because of adverse event (2.15, 0.82–5.64, p = 0.121), age per year (0.97, 0.93–1.0, p = 0.072), and HAQ (0.48, 0.22–1.04, p = 0.063).

Sensitivity analysis. The drug survival rates for ADA, ETN, and IFX in first-time switchers were similar (p = 0.823). Kaplan-Meier plots are presented in Supplementary Figure 1 (available from the authors on request). Likewise, the 3- and 6-month response rates were in the same range with nonsignificant differences, as presented in Supplementary Table 1 (available from the authors on request).

DISCUSSION

The response rates of first-time anti-TNF switchers presented in our study are somewhat lower than those previously reported regarding patients naive to anti-TNF[4,5,6,7,8,9,10] and compatible with what has been reported in the NOR-DMARD[17]. In contrast, our current study shows the response to a third anti-TNF treatment course to be markedly

Table 3. Clinical responses (LUNDEX corrected and per protocol) at 3 and 6 months of followup for the second and third courses of anti-TNF treatment in PsA. Values are % responders (95% CI).

Responses	3 Mos		6 Mos	
	First Switch, n = 103	Second Switch, n = 29	First Switch, n = 70	Second Switch, n = 18
Response LUNDEX corrected				
ACR20 LUNDEX	47 (37–57)	22 (7–37)	41 (29–53)	21 (2–40)
ACR50 LUNDEX	21 (13–29)	14 (1–27)	24 (14–34)	4 (0–13)
ACR70 LUNDEX	12 (6–18)	2 (0–7)	10 (3–17)	0 (NA)
EULAR good LUNDEX	26 (18–34)	10 (0–21)	29 (18–40)	12 (0–27)
Response as observed				
ACR20 per protocol	49 (39–59)	28 (12–44)	44 (32–56)	33 (11–55)
ACR50 per protocol	22 (14–30)	17 (3–31)	26 (16–36)	6 (0–17)
ACR70 per protocol	12 (6–18)	3 (0–9)	11 (4–18)	0 (NA)
EULAR good per protocol	27 (18–35)	13 (1–25)	31 (20–42)	19 (1–37)

LUNDEX: Lund Efficacy Index; anti-TNF: antitumor necrosis factor; PsA: psoriatic arthritis; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; NA: not applicable.

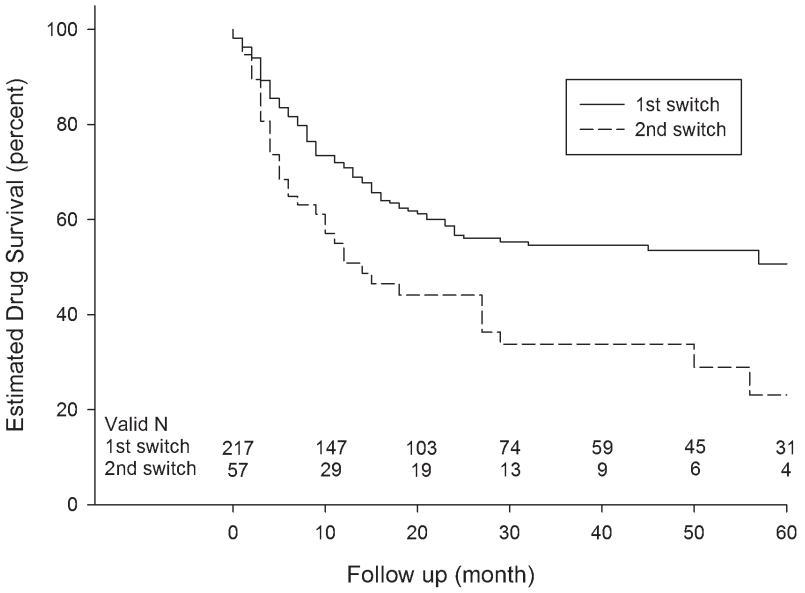

Figure 2. Drug survival of second and third course of antitumor necrosis factor treatment in patients with psoriatic arthritis.

lower than to a first or second treatment, suggesting that switching to biological DMARD with other mode of actions should be more beneficial when 2 trials of anti-TNF agents have been tried unsuccessfully. Likewise, drug survival rates were superior for patients receiving the second course of anti-TNF compared with the third course. The 6-month decreases in HAQ, DAS28-CRP, and CRP levels were all numerically higher for first-time switchers compared with second-time switchers. Moreover, only first-time switchers showed significant utility gain, i.e., EQ-5D changes, at 6 months, indicating differences in cost utility for first-time switchers compared with second-time switchers.

Comparing the current results with previously reported outcomes to anti-TNF therapy switching is complicated by the diverse spectrum of study settings and outcome measures used. However, the prior study from NOR-DMARD showed consistent and similar 3-month response rates for ACR20, 50, and 70, as well as EULAR good compared with our current study[17]. On the other hand, the DANBIO study reported lower 3-month ACR and EULAR good response rates to a second course of anti-TNF treatment[18], while the reported outcomes for the third course of anti-TNF treatment were consistent with the findings of our current study. Also, the drug survival rates for first-time switchers are in the range of drug retention rates reported from a published Canadian study, as well as an Italian cohort, of patients with PsA[32,33]. However, the rate of second-time switchers from our current study was markedly lower.

Notably, to our knowledge, this is the first study reporting ITT response rates according to the LUNDEX method in a population of patients with PsA cycling anti-TNF (Table 3). The results illustrate that adjusting for drug withdrawal during observational studies is important, especially when studying late responses in populations with poor drug survival, i.e., 6-month response in second-time switchers[25].

The abilities of baseline HAQ and DAS28 scores to predict drug survival and ACR20 response, respectively, in first-time anti-TNF switchers should be borne in mind when initiating the second course of anti-TNF treatment. The DANBIO study also identified HAQ and DAS28 as important predictors; however, no consistent pattern across different regression models and outcome measures was identified in that study either[18].

Regarding DAS28, this is partly explained by the variable's relation to response criteria. Higher disease activity at therapy-switching implies a better chance to fulfill the less-stringent ACR20. As a marker of physical disability, HAQ scores also reflect the degree of irreversible joint damage. Thus, the finding that variations in baseline HAQ scores affect chances to continue anti-TNF therapy is not surprising. Similar results have been seen in rheumatoid arthritis (RA) cohorts of patients naive to anti-TNF[34,35].

Our current study failed to identify an association between drug response or drug survival and reason for TNF withdrawal or mechanism of TNF blockade (antibody vs receptor-ligand interaction). This has been found important in previous studies of TNF cycling in RA[36]. The reasons for this are complex because they may rest either with extended effects of the first treatment course or with differing response rates to the second treatment unrelated to the prior experience, or both. The uneven and in some places limited distribution of the withdrawal reason and agents in the

first- and second-line treatment arms (Table 1 and Table 2) render interpretations even more complicated.

Further, interobserver variance in classification of withdrawal reason among scoring physicians cannot be disregarded. The absence of predefined washout periods in the current observational study can weaken the power of our results, because disease activity measures of patients switching because of adverse events may be influenced by the remaining drug activity from the previous remedy (the "carry over" effect).

In switchers, concurrent MTX use did not yield better response compared with monotherapy according to the regression modeling. The reasons for this are probably related to switchers representing a more selected population, many of whom have already demonstrated a poor response to the combination of anti-TNF therapy and MTX.

Strengths and limitations. The open, nonrandomized characteristic of the observational study cohort used for the current analyses inherently entails limitations regarding assignment of treatments, the possibility of selection bias, and absence of washout periods. On the other hand, patient inclusion was not limited by any predefined level of disease activity, rigid treatment guidelines, or economic aspects. Decisions to start or stop therapies with a certain agent rested solely with treating physicians. Moreover, the centralized, prospective collection and entry of data optimized uniformity of interpretation of forms and results. Treatments with CZP, golimumab, IFX, ETN, and ADA were pooled to investigate response and drug survival. While all are potent blockers of TNF bioactivity, the agents were not equally distributed in any of the first-, second-, or third-line treatment groups (Table 1 and Table 2). These differences, however, were mostly driven by varying drug availability and approvals on the Swedish market during the study period, thus reducing possible selection bias.

Benefits of first-time switching of anti-TNF therapy are feasible and supported by available evidence. But our results suggest that other therapeutic options be considered after 2 courses of anti-TNF treatment have failed. When switching to a second TNF inhibitor, a better response is predicted by elevated baseline DAS28 values, and lower HAQ values are associated with prolonged drug survival.

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