Treatment response to a second or third TNF-inhibitor in RA: results from the South Swedish Arthritis Treatment Group Register


Objectives. To study treatment response rates of RA patients undergoing second- and third-line anti-TNF therapy and to identify baseline predictors of response to second-line treatment.

Methods. RA patients monitored in a prospective, observational study, having switched anti-TNF therapy once (first-time switchers, \( n = 337 \)) or twice (second-time switchers, \( n = 61 \))—i.e. following failures with one antibody- and one receptor-type agent—between March 1999 and December 2006, were studied. Treatment responses at 3 months were assessed by the ACR and European League Against Rheumatism (EULAR) response criteria. Predictive potentials for response to second-line treatment of demographics, baseline disease activity measures, disease and treatment characteristics were analysed using logistic regression.

Results. ACR20 response was met by 51% of first-time and 35% of second-time switchers. Corresponding ACR50 rates were 27 and 18%; EULAR overall rates (EULAR good or moderate response) 71 and 58%; EULAR good rates 25 and 9% and 28-joint disease activity score (EULAR) remission rates 16 and 6%. Identified baseline predictors of response to second-line treatment were lower age and HAQ scores, elevated DAS28 values and having ceased the former anti-TNF treatment due to adverse events rather than inefficacy. No variable was predictive for all examined response criteria.

Conclusions. Response rates of first-time anti-TNF switchers are somewhat below those of anti-TNF naïve RA patients, while the markedly inferior response rates of second-time switchers suggest other therapeutic options to be considered in this situation. Identified baseline predictors of response may be useful indicators to second-line anti-TNF therapy, but vary depending on the response criteria set studied.

Key words: RA, Anti-TNF, Switching, Predictors, Observational study.

Introduction

The introduction of TNF inhibitors has greatly improved the treatment armamentarium in RA. The soluble TNF receptor etanercept, and the two monoclonal anti-TNF antibodies infliximab and adalimumab, have all been shown in randomized, placebo-controlled trials (RCTs) to induce clinical improvement and retard radiographic progression in the majority of RA patients [1–8]. However, nearly 30% of RA patients fail to respond to their first TNF inhibitor [9], and yet others experience adverse events, raising the question of whether TNF inhibitor switching (changing from one anti-TNF drug to another) is clinically beneficial.

Treatment response in patients undergoing a second course of anti-TNF therapy (first-time switchers), has been addressed in several studies, most however with limited power [10–25]. These show the efficacy and safety of the second agent to be mostly comparable, or at least not significantly inferior, to the outcome in patients undergoing first-line anti-TNF therapy (anti-TNF naïves). Yet, recently a large report on drug survival demonstrated an increased risk of ceasing the second treatment for the same reason as the first, be it due to inefficacy or adverse events [26]. Furthermore, drug survival in first-time switchers is lower than in anti-TNF naïves, and possibly even more so in patients undergoing treatment with a third TNF inhibitor (second-time switchers) [27]. Prior inefficacy of one receptor- and one antibody-type agent, has been proposed to predict poor response to third-line anti-TNF therapy [16, 23], but data on response rates of second-time switchers remain very sparse.

Considering the high cost and potential toxicity of TNF inhibitors, it is clinically relevant to identify factors that can predict treatment response. In anti-TNF naïves, several studies have addressed this issue, showing for example, concurrent MTX use and lower HAQ scores [28] at treatment initiation, to strongly predict treatment response and drug survival [29, 30]. A study on prediction of response to a second TNF inhibitor is, however, lacking, and because of the inherent problems, this is not likely to be addressed in a formal RCT. From available information, it remains inconclusive whether response rates to a second treatment course are influenced by having discontinued the initial therapy due to inefficacy or adverse events. There are, however, results indicating escape phenomenon—i.e. diminishing efficacy after good primary response—to be more favourable than primary inefficacy, with regard to response to the second agent [21]. Furthermore, observations show no major difference in response when switching from a receptor-type TNF inhibitor to an antibody, from an antibody to receptor or indeed from antibody to antibody [11, 19, 20, 23]. The predictive potentials of other baseline characteristics remain unexplored.

The aims of the present study were to report response rates of first- and second-time anti-TNF switchers and to identify baseline predictors of response to a second anti-TNF treatment course. Second-time switchers were restricted to patients having previously failed one receptor- and one antibody-type agent. RA patients from an observational study cohort in southern Sweden were examined.

Patients and methods

Patients

Patients enrolled in the South Swedish Arthritis Treatment Group (SSATG) register, a large, prospective, observational study cohort, involving 11 rheumatology units [31], were selected. The study period comprised March 1999 through December 2006. Patients, eligible for inclusion, had a diagnosis of RA according to clinical judgement by treating physicians. In a previous validation study, 98% of these RA patients fulfilled the ACR RA classification criteria [31, 32]. First-time switchers (\( n = 477 \)) had switched therapy from one TNF inhibitor to another, while second-time switchers (\( n = 61 \)) were undergoing treatment with a third TNF antagonist, having previously failed treatments with...
one receptor- and one antibody-type agent. Neither group was allowed any other prior use of biological DMARDs. As response rates at 3 months were studied, all were required to have continued treatment for at least 12 weeks.

The quality control character of the SSATG register makes it part of the legislative documentation demanded in Sweden. Thus, no formal ethical approval was required for this study. Treatment was given as recommended by the manufacturers—for etanercept 50 mg subcutaneously every week (single injection or 25 mg twice weekly), for infliximab infusion of 3 mg/kg at 0, 2 and 6 weeks, and thereafter every eighth week and for adalimumab 40 mg subcutaneously every other week.

Baseline and follow-up assessments
At 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 28-joint disease-activity score (DAS28) [33, 34] and details regarding past and present anti-rheumatic therapy. Patients’ HAQ scores according to the validated Swedish version [35] and results of visual analogue scales for pain (VAS pain) and general health (VAS global) were also included, along with evaluators’ global assessments of disease activity on a five-grade Likert scale. At the 3 month follow-up, the same disease activity variables were again recorded, and improvement according to the European League Against Rheumatism (EULAR) and/or the ACR response criteria were calculated [36, 37]. Withdrawals from anti-TNF therapy were categorized by treating physicians as due to adverse events, inefficacies—including both primary and secondary inefficacy—or miscellaneous. The latter comprised reasons such as pregnancies, patient decisions, poor compliance, remissions and other unspecified causes.

Response rates at 3 months of first- and second-time switchers were computed according to the EULAR overall (the merging of EULAR moderate and good responders), EULAR good, ACR20, ACR50 and ACR70 improvement criteria. It was also identified whether patients had reached low disease activity (DAS28low) or remission (DAS28remission) based on DAS28, defined as values <3.2 and <2.6, respectively [33]. Patients were considered as dropouts if none of these response measures could be calculated at 3 months due to the missing data. In the SSATG register setting, patients having switched anti-TNF therapy twice, may be included in both study groups. Statistical analyses comparing first- and second-time switchers were thus not conducted. For comparison, 3 months’ response rates and disease activity stages of RA patients in the SSATG register treated with a first TNF inhibitor were also computed.

Statistics
P-values <0.05 were considered statistically significant. Differences were examined using $\chi^2$ analysis for ordinal and Mann–Whitney U-test for continuous variables. Correlations were assessed by Spearman correlation test. Predictor analyses were undertaken using logistic regression models. Outcome measures were ACR20, EULAR overall, ACR50 and EULAR good responses, each addressed in separate analyses. Variables included in the models—chosen based on correlation and clinical relevance—were age at therapy initiation (in 5-yr increments), gender, baseline DAS28 and HAQ scores, concurrent NSAID use (daily/optional or never use), concurrent corticosteroid use (yes/no), concurrent DMARD use (anti-TNF monotherapy/MTX use/use of DMARDs other than MTX), and type of previous TNF inhibitor (receptor/antibody). Disease duration was omitted because of multicolinearity with HAQ. DAS28 and HAQ were both considered essential, but due to multicolinearity, all models were analysed including only one of these parameters at a time.

Models including DAS28 showed a lower total correlation than those including HAQ. Based on this, data on other variables are presented from the former throughout. The predictive potential of having failed the previous anti-TNF therapy due to inefficacy or adverse events were assessed in separate sub-analyses ($n = 261$), introducing a termination reason variable (adverse events/inefficacy) to the otherwise unaltered regression models. Results of predictor analyses are presented as [odds ratio (OR) (95% CI)], if not stated otherwise.

Results
During the study period, 1808 biologically naïve RA patients in the SSATG register were started on a first anti-TNF treatment course, 823 receiving infliximab, 695 etanercept and 290 adalimumab. Inclusion criteria to the current study were met by 477 subjects subsequently switching therapy to a second anti-TNF agent, and by 61 patients proceeding to a second switch following failures with one antibody- and one receptor-type drug. Excluding dropouts who missed response data at 3 months ($n = 140/25$ of first-/second-time switchers), 337 first- and 36 second-time switchers were included in the study population. For both groups, no significant differences in baseline characteristics were found between dropouts and included subjects, except a less frequent use of DMARDs other than MTX among second-time switchers ($P = 0.018$ and $P = 0.029$ for first-and second-time switchers, respectively), and a higher level of anti-TNF monotherapy among first-time switcher dropouts ($P = 0.040$). Baseline characteristics are summarized in Table 1, while data on prior and current anti-TNF treatments are displayed in Table 2.

Response rates
Response rates and disease activity stages of first- and second-time switchers at 3 months are presented in Table 3. Also included are response rates and disease-activity stages of first-time switchers grouped according to withdrawal reason of the previous anti-TNF therapy (adverse events or inefficacy). ACR20 and ACR50 response criteria were met by 51 and 27% of first-time switchers, respectively. For EULAR overall and EULAR good, corresponding rates were 71 and 25%, respectively. Outcome rates of second-time switchers were clearly inferior to those of first-time switchers. This was most apparent regarding the more stringent response measures ACR70 (7 and 3% of first- and second-time switchers, respectively) and EULAR good (25 and 9%) and the likewise stringent disease activity stages DAS28low (30 and 9%) and DAS28remission (16 and 6%). The trend, however, was seen throughout.

ACR50, EULAR overall and EULAR good good response rates of first-time switchers having failed the former anti-TNF treatment due to adverse events were significantly better than those of patients having switched due to inefficacy. Likewise, significantly more patients in the former group had a low disease activity (DAS28low) at 3 months.

For comparison, 3 months response rates of all RA patients in the SSATG register treated with a first TNF inhibitor were: ACR20: 61%; ACR50: 37%; ACR70: 13%; EULAR overall: 76% and EULAR good: 34%. Thirty-eight percent of first-time users had a low disease activity (DAS28low) and 23% were in remission (DAS28remission) at 3 months.

Predictors of treatment response
Results of regression analyses are presented in Table 4. No variable was predictive of response according to all criteria sets used. Lower baseline HAQ scores were shown to predict ACR50.
Treatment response to 2nd and 3rd TNF inhibitor in RA

Table 1. Baseline characteristics of subjects included in analyses

<table>
<thead>
<tr>
<th></th>
<th>First-time switchers</th>
<th>Missing data (n)</th>
<th>Second-time switchers</th>
<th>Missing data (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs), mean (s.d.)</td>
<td>56 (13)</td>
<td></td>
<td>58 (12)</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>276 (82)</td>
<td></td>
<td>28 (78)</td>
<td></td>
</tr>
<tr>
<td>Disease duration (yrs), mean (s.d.)</td>
<td>14 (10)</td>
<td></td>
<td>15 (10)</td>
<td></td>
</tr>
<tr>
<td>DAS28-score, mean (s.d.)</td>
<td>5.5 (1.3)</td>
<td>21</td>
<td>5.8 (1.2)</td>
<td>2</td>
</tr>
<tr>
<td>28 SJC, mean (s.d.)</td>
<td>8.4 (5.9)</td>
<td></td>
<td>10 (6.3)</td>
<td></td>
</tr>
<tr>
<td>28 TJC, mean (s.d.)</td>
<td>9.3 (6.8)</td>
<td></td>
<td>11 (7.8)</td>
<td></td>
</tr>
<tr>
<td>BAS global (mm), mean (s.d.)</td>
<td>62 (22)</td>
<td>17</td>
<td>65 (21)</td>
<td>2</td>
</tr>
<tr>
<td>BAS pain (mm), mean (s.d.)</td>
<td>61 (22)</td>
<td>17</td>
<td>65 (20)</td>
<td>2</td>
</tr>
<tr>
<td>Doctor global assessment (mm), mean (s.d.)</td>
<td>2.3 (0.8)</td>
<td>12</td>
<td>2.6 (0.7)</td>
<td>2</td>
</tr>
<tr>
<td>ESR (mm/h), mean (s.d.)</td>
<td>36 (25)</td>
<td></td>
<td>41 (29)</td>
<td></td>
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<tr>
<td>CRP (mg/l), mean (s.d.)</td>
<td>28 (35)</td>
<td>16</td>
<td>37 (34)</td>
<td>2</td>
</tr>
<tr>
<td>HAQ score, mean (s.d.)</td>
<td>1.4 (0.6)</td>
<td></td>
<td>1.5 (0.6)</td>
<td>3</td>
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<tr>
<td>Previous number of DMARDs, mean (s.d.)*</td>
<td>4.7 (1.9)</td>
<td>2</td>
<td>6.0 (1.6)</td>
<td>2</td>
</tr>
<tr>
<td>Concurrent NSAID use:</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Never users, n (%)</td>
<td>87 (27)</td>
<td></td>
<td>9 (27)</td>
<td></td>
</tr>
<tr>
<td>Optional users, n (%)</td>
<td>38 (12)</td>
<td></td>
<td>2 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Everyday users, n (%)</td>
<td>199 (61)</td>
<td></td>
<td>23 (68)</td>
<td></td>
</tr>
<tr>
<td>Concurrent corticosteroid use, n (%)</td>
<td>218 (68)</td>
<td>14</td>
<td>25 (74)</td>
<td>2</td>
</tr>
<tr>
<td>Weekly corticosteroid dose (mg), mean (s.d.)</td>
<td>50 (26)</td>
<td></td>
<td>43 (26)</td>
<td></td>
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<tr>
<td>Anti-TNF monotherapy, n (%)</td>
<td>106 (32)</td>
<td></td>
<td>13 (36)</td>
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<tr>
<td>Concurrent MTX use, n (%)</td>
<td>76 (25)</td>
<td></td>
<td>14 (39)</td>
<td></td>
</tr>
<tr>
<td>Weekly MTX dose (mg), mean (s.d.)</td>
<td>14 (6.0)</td>
<td></td>
<td>16 (6.2)</td>
<td></td>
</tr>
<tr>
<td>Concurrent DMARDs, other than MTX, n (%)</td>
<td>55 (16)</td>
<td></td>
<td>9 (25)</td>
<td></td>
</tr>
<tr>
<td>Reason for terminating previous anti-TNF:</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Adverse events, n (%)</td>
<td>138 (46)</td>
<td></td>
<td></td>
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<tr>
<td>Inefficacy, n (%)</td>
<td>137 (46)</td>
<td></td>
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<tr>
<td>Miscellaneous, n (%)</td>
<td>23 (7.7)</td>
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</table>

When missing data, valid percent is used; doses given as mean (s.d.) of users only.  

Table 2. Anti-TNF treatments and switching order

<table>
<thead>
<tr>
<th></th>
<th>First-time switchers (n=337)</th>
<th>Second-time switchers (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First anti-TNF therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept, n (%)</td>
<td>66 (20)</td>
<td>11 (33)</td>
</tr>
<tr>
<td>Infliximab, n (%)</td>
<td>245 (73)</td>
<td>21 (64)</td>
</tr>
<tr>
<td>Adalimumab, n (%)</td>
<td>26 (7.7)</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Missing information, n (total percentage)</td>
<td></td>
<td>3 (8.3)</td>
</tr>
<tr>
<td>Second anti-TNF therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept, n (%)</td>
<td>195 (58)</td>
<td>22 (67)</td>
</tr>
<tr>
<td>Infliximab, n (%)</td>
<td>28 (8.3)</td>
<td>10 (30)</td>
</tr>
<tr>
<td>Adalimumab, n (%)</td>
<td>114 (34)</td>
<td>3 (13.0)</td>
</tr>
<tr>
<td>Missing information, n (total percentage)</td>
<td></td>
<td>3 (8.3)</td>
</tr>
<tr>
<td>Third anti-TNF therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab, n (%)</td>
<td>2 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Adalimumab, n (%)</td>
<td>–</td>
<td>34 (94)</td>
</tr>
<tr>
<td>Switching order of anti-TNF agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept–Infliximab, n (%)</td>
<td>26 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Etanercept–adalimumab, n (%)</td>
<td>40 (12)</td>
<td></td>
</tr>
<tr>
<td>Infliximab–etanercept, n (%)</td>
<td>171 (51)</td>
<td></td>
</tr>
<tr>
<td>Infliximab–adalimumab, n (%)</td>
<td>74 (22)</td>
<td></td>
</tr>
<tr>
<td>Adalimumab–etanercept, n (%)</td>
<td>24 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Adalimumab–infliximab, n (%)</td>
<td>2 (0.6)</td>
<td></td>
</tr>
<tr>
<td>ETA-INF–adalimumab, n (%)</td>
<td>–</td>
<td>10 (30)</td>
</tr>
<tr>
<td>ETA–ETN–infliximab, n (%)</td>
<td>–</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>ETA–ADA–infliximab, n (%)</td>
<td>–</td>
<td>21 (64)</td>
</tr>
<tr>
<td>INF–ETA–adalimumab, n (%)</td>
<td>–</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>ADA–ETA–infliximab, n (%)</td>
<td>–</td>
<td>3 (8.3)</td>
</tr>
</tbody>
</table>

Valid percent used except when specified. ETA: etanercept; INF: infliximab; ADA: adalimumab.

[OR 0.63 (95% CI 0.40, 1.00)] and—more strongly—EULAR good [0.33 (0.19, 0.56)] responses at 3 months, but not the less stringent outcome measures. Higher baseline DAS28 values were predictive of ACR20 [1.44 (1.19, 1.75)] and EULAR overall [1.43 (1.16, 1.78)] responses, while not reaching significance for ACR50 [1.21 (0.98, 1.50)]. In contrast, regarding EULAR good, the predictive value of a higher DAS28, showed an opposite tendency [OR 0.85 (0.69, 1.05)]. Lower age was identified to predict ACR50 response [0.86 (0.78, 0.95)], and a similar trend was seen for the other outcome measures too. Likewise consistent, there was a trend for patients to respond better, having previously failed treatment with an antibody-type agent, rather than a receptor-type agent. This, however, remained non-significant throughout. Interestingly, concurrent MTX use was not shown to be clearly superior to anti-TNF monotherapy in any of the models, even if the trivalent DMARD use variable as a whole did in fact reach significance regarding EULAR overall (P = 0.036). Predictive values of age, HAQ and DAS28 scores are summarized in Fig. 1.

Also included in Fig. 1 are predictive data from sub-analyses regarding the termination reason variable. Sub-analyses (n = 261), revealed patients to be less likely to achieve a EULAR overall [0.49 (0.27, 0.90), P = 0.021] and/or EULAR good response [0.55 (0.30, 1.01), P = 0.054], having ceased the former treatment due to inefficacy, rather than adverse events. This was repeated for ACR criteria, though non-significant [ACR20: 0.72 (0.42, 1.22), P = 0.133].

Discussion

The response rates of first-time anti-TNF switchers presented in this study are similar, or at least not markedly inferior, to those previously reported regarding anti-TNF naïves [1–8]. In contrast, the current study shows response to a third anti-TNF treatment course, following failures with one antibody- and one receptor-type agent, to be markedly lower than that of a first or second treatment. Identified baseline predictors of response to second-line anti-TNF therapy were lower age and HAQ scores, higher DAS28 values and having ceased the former treatment due to adverse events rather than inefficacy. No variable, however, was significantly associated with all response measures examined, thus putting some limits as to the generalizability of our results and conclusions.

The response rates of first-time switchers found in the current study are given subsequently, but generally in the vicinity of those reported by RCTs of anti-TNF therapy in anti-TNF naïves [1–8]. The same relation is also seen within the SSATG register setting, comparing response rates of first-time switchers to those of all
patients treated with a first TNF-inhibitor. This is in accordance
with earlier findings from smaller materials [15, 18, 20, 22, 25].
Thus, the available evidence suggests that the 3 months’ response
rates to anti-TNF therapy are only slightly compromised by a
history of failing one prior TNF inhibitor. Response to a third
TNF antagonist, after failures with one receptor- and one
antibody-type agent, were, on the other hand, markedly reduced
due to the limited number of second-time switchers studied. Yet,
the results may suggest that switching to another class of
DMARDs could be more beneficial, when both types of anti-
TNF agents have been tried unsuccessfully. Responses after
having tried two anti-TNF remedies with the same mode of action
might give different results, but we had too few cases of infliximab
and adalimumab-treated patients given etanercept as a third
biologic treatment to allow meaningful analyses.

Related to this, a recent observational study showed rituximab
to be more effective than an alternative TNF inhibitor in reducing
DAS28 scores in RA patients, having previously failed one or two
anti-TNF therapies [38]. Interestingly, previous failures with >1
anti-TNF agent (vs previous failure with one anti-TNF agent)
were shown to significantly predict a less beneficial DAS28
response to the following treatment. The better outcome seen with
rituximab thus strengthens the case for trying other therapeutic
options following failures with two anti-TNF agents. The
relatively worse response to anti-TNF switching in that study
may be partly explained by the high percentage of second-time
switchers included (mean number of previous anti-TNF in the
anti-TNF switching group: 1.53). However, face-to-face compar-
isons with our findings are not possible given differences in
assessment measures and follow-up times.

Comparing the current results with previously reported response rates to anti-TNF therapy switching is complicated by
the diverse spectrum of outcome measures used. However, prior
studies of first-time switching report EULAR overall rates mostly
similar to ours, though displaying variations in both directions
regarding EULAR good [14, 19, 21, 22]. Previously reported
ACR20 rates are consistently higher than those of the present
study, while more agreement is seen regarding ACR50 and
ACR70 [15, 18, 20, 22, 25]. Most differences are probably
explained by varying inclusion criteria and limited power of earlier
studies.

Two reports, addressing third-line anti-TNF therapy (n = 20
and n = 10), again showed response rates more favourable than
our results [16, 23]. This may be due to differences in patient
selection, but the limited numbers in all studies—including ours—
preclude firm conclusions regarding response rates in these
therapy-refractory and severely affected patients.

The abilities of baseline HAQ and DAS28 scores to predict
treatment response in first-time anti-TNF switchers were found to
vary, depending on the outcome measure studied. 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 and

### Table 3. Treatment response rates at 3 months of therapy

<table>
<thead>
<tr>
<th>Response rates</th>
<th>All (n = 337)</th>
<th>Previous adverse events (n = 138)</th>
<th>Previous inefficacy (n = 137)</th>
<th>Second-time switchers (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 responders, % (95% CI)</td>
<td>51 (45, 56)</td>
<td>57 (48, 65)</td>
<td>46 (38, 55)</td>
<td>35 (18, 52)</td>
</tr>
<tr>
<td>ACR50 responders, % (95% CI)</td>
<td>27 (22, 31)</td>
<td>32 (24, 40)</td>
<td>21* (14, 28)</td>
<td>18 (4, 31)</td>
</tr>
<tr>
<td>ACR70 responders, % (95% CI)</td>
<td>7 (4, 10)</td>
<td>7 (2, 11)</td>
<td>6 (2, 10)</td>
<td>3 (0, 9)</td>
</tr>
<tr>
<td>Missing ACR data, n (% of total)</td>
<td>13 (3.9)</td>
<td>2 (1.4)</td>
<td>5 (3.6)</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>EULAR overall responders, % (95% CI)</td>
<td>71 (66, 76)</td>
<td>77 (70, 84)</td>
<td>64* (55, 73)</td>
<td>58 (40, 75)</td>
</tr>
<tr>
<td>EULAR good responders, % (95% CI)</td>
<td>25 (21, 30)</td>
<td>32 (24, 40)</td>
<td>19* (12, 26)</td>
<td>9 (0, 19)</td>
</tr>
<tr>
<td>Missing EULAR data, n (% of total)</td>
<td>30 (8.9)</td>
<td>8 (5.8)</td>
<td>12 (8.8)</td>
<td>3 (8.3)</td>
</tr>
<tr>
<td>DAS28low, % (95% CI)</td>
<td>30 (25, 35)</td>
<td>38 (30, 46)</td>
<td>25* (18, 32)</td>
<td>9 (18, 32)</td>
</tr>
<tr>
<td>DAS28low responders, % (95% CI)</td>
<td>16 (12.0)</td>
<td>19 (13.26)</td>
<td>12 (6.18)</td>
<td>6 (6.14)</td>
</tr>
<tr>
<td>Missing DAS28 data, n (% of total)</td>
<td>10 (3.0)</td>
<td>4 (2.9)</td>
<td>5 (3.6)</td>
<td>1 (2.8)</td>
</tr>
</tbody>
</table>

### Table 4. Predictors of various treatment response criteria at 3 months of therapy

<table>
<thead>
<tr>
<th>Response criteria</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 response (n = 313 in analysis)</td>
<td>0.92 (0.84, 1.01)</td>
<td>0.068</td>
</tr>
<tr>
<td>EULAR overall response (n = 324 in analysis)</td>
<td>0.90 (0.78, 0.95)</td>
<td>0.004</td>
</tr>
<tr>
<td>ACR50 response (n = 310 in analysis)</td>
<td>0.90 (0.81, 1.00)</td>
<td>0.052</td>
</tr>
<tr>
<td>EULAR good response (n = 304 in analysis)</td>
<td>0.95 (0.47, 1.90)</td>
<td>0.876</td>
</tr>
</tbody>
</table>

Demographics
- Age (per 5-yr increase) 0.92 (0.84, 1.01) 0.068
- Male (vs female) 0.64 (0.35, 1.18) 0.151

Disease characteristics
- Baseline DAS28 (per unit) 1.44 (1.19, 1.75) <0.001
- Baseline HAQ score (per unit) 0.90 (0.67, 1.50) 0.001

Treatment characteristics
- Concurrent NSAID use 0.94 (0.54, 1.49) 0.794
- Concurrent corticosteroids (yes/no) 0.90 (0.54, 1.49) 0.678
- Anti-TNF monotherapy or concurrent DMARDS 0.90 (0.52, 1.59) 0.730
- Previous MTX1 type (yes/no) 1.75 (0.97, 3.18) 0.064

Notes:
- Analysed in separate regression models not including DAS28, as described in the text.
- *P<0.05 as compared with first-time switchers with previous adverse events; valid percent used except when specified.
EULAR overall criteria, and the same trend is seen for the somewhat more stringent ACR50 response. For EULAR good, however, with its inherent requirement to reach a DAS28 level beneath 3.2, the OR falls below 1, suggesting lower baseline DAS28 values to predict response to this criteria set. Similarly, lower baseline DAS28 scores predict achievement of DAS28 remission during first-line anti-TNF therapy [29].

As a marker of physical disability, HAQ scores also reflect the degree of irreversible joint damage [39]. Thus, the finding that variations in baseline HAQ scores affect chances to achieve the more stringent ACR50 and EULAR good responses, is not surprising. Similar results have been seen in anti-TNF naïves [29, 30], and also regarding response to non-biological DMARDs [40]. Interestingly though, HAQ scores did not predict responses to the less stringent ACR20 or EULAR overall criteria.

The negative impact of higher age is probably also based on more long-standing and thus more refractory disease. Again, corresponding results have been found in anti-TNF naïves [29, 30], and also regarding response to non-biological DMARDs [40]. Interestingly though, HAQ scores did not predict responses to the less stringent ACR20 or EULAR overall criteria.

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FIG. 1. Predictive potentials of baseline age, HAQ and DAS28 scores and of having ceased the initial anti-TNF treatment due to inefficacy rather than adverse events. ORs are presented as ORs (bold dots) with 95% CI (bold lines). Predictive potentials of having ceased the initial treatment due to inefficacy rather than adverse events were assessed in separate sub-analyses (n = 261), as described in the text.

Our results suggest a better response, having switched therapy because of side-effects, rather than inefficacy. This is supported by an earlier study, restricted to patients having switched therapy following adverse events [24], which shows response rates clearly superior to those of the present and other previous studies including subjects having switched due to both inefficacy and adverse events. The certainty and clinical implications of this finding should not be overestimated though. The reason for treatment termination is not always clear-cut, but the design of the SSATG register protocol only allows one reason to be stated. Thus, potential bias exists regarding the classification of termination reasons [30, 41]. Furthermore, inter-observer variance in classification among scoring physicians cannot be disregarded. The absence of pre-defined washout periods in the current observational study can weaken the power of our results, since disease activity measures of patients switching due to adverse events may be influenced by remaining drug activity from the previous remedy (‘carry over’ effect). Moreover, the current undefined effect of the first treatment course, or with differing response rates to the second treatment unrelated to the prior experience, or indeed both. Also, the uneven distribution of the three agents in the first- and second-line treatment arms (Table 2), render interpretations even more complicated.

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analyses did not differentiate between escape phenomena and primary inefficacies, with the risk that some relevant information was missed. The recent finding that the causes for stopping a second treatment are related to the reasons leading to discontinuation of the first [26], is well compatible with our results, since we only studied response after 3 months.

In switchers, concurrent MTX use did not yield better response as compared with monotherapy according to our data. This is in contrast to the situation in anti-TNF naïves [29, 30]. 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.

The open, non-randomized nature 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 [42]. Furthermore, the relatively high rate of dropouts is also a result of the observational setting, as also reported by others [38]. On the other hand, patient inclusion is not limited by any pre-defined level of disease activity, by rigid treatment guidelines or economical aspects. Decisions to start or stop therapies with a certain agent rest solely with treating physicians. Moreover, the centralized, prospective collection and entry of data optimizes uniformity of interpretation of forms and results.

Treatments with infliximab, etanercept and adalimumab were pooled to investigate response and predictors of response in the entire switcher group. While all are potent blockers of TNF bioactivity, there is increasing knowledge about the various ways in which the three agents differ [43]. Furthermore, agents were not equally distributed in any of the first-, second- or third-line treatment groups (Table 2). These differences, however, were mostly driven by varying drug availability on the Swedish market during the study period [30], thus reducing possible selection bias. These circumstances, and the possible implications they entail, should be born in mind when interpreting the results.

In conclusion, when switching to a second TNF-inhibitor a better response is predicted by lower baseline age and HAQ scores, elevated baseline DAS28 values and having ceased the former treatment due to adverse events rather than inefficacy. No variable, however, was significantly predictive according to all response criteria, probably reflecting different criteria constructions [44]. Benefits of first-time switching of anti-TNF therapy are well supported by available evidence, whereas having previously discontinued one receptor and one antibody-type agent, our results suggest other therapeutic options to be considered.

Rheumatology key messages

- First-time switchers’ response rates are somewhat below that of naïve patients, whereas second-time switchers respond poorly.
- Low age, low HAQ scores, elevated DAS28 values and first anti-TNF withdrawal following side-effects predict good response in first-time switchers.

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