Comparison of drug retention rates and causes of drug discontinuation between anti-tumor necrosis factor agents in rheumatoid arthritis

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Abstract

OBJECTIVE: Tumor necrosis factor (TNF) inhibitors have revolutionized the treatment of severe rheumatoid arthritis (RA), yet drug discontinuation is common. The aim of this study was to compare treatment retention rates and specific causes of anti-TNF discontinuation in a population-based RA cohort. METHODS: All patients treated with etanercept, infliximab, or adalimumab within the Swiss Clinical Quality Management RA cohort between 1997 and 2006 were included in the study. Causes of treatment discontinuation were broadly categorized as adverse events (AEs) or nontoxic causes, and further subdivided into specific categories. Specific causes of treatment interruption were analyzed using a Cox proportional hazards model and adjusted for potential confounders. RESULTS: A total of 2,364 anti-TNF treatment courses met the inclusion criteria. Treatment discontinuation was reported 803 times: 309 with etanercept, 249 with infliximab, and 245 with adalimumab. Drug inefficacy represented the largest single cause of treatment discontinuation (55.8% of cases). The median time of receiving anti-TNF therapy was 37 months, but discontinuation rates differed between the 3 anti-TNF agents (P < 0.001), with shorter retention rates for infliximab (hazard ratio [HR] 1.24, 99% confidence interval [99% CI] 1.01-1.51). The specific causes of treatment discontinuation revealed an increased risk of AEs with infliximab (HR 1.4, 99% CI 1.003-1.96), mostly due to an increased risk of infusion or allergic reactions (HR 2.11, 99% CI 1.23-3.62). Other discontinuation causes were equally distributed between the anti-TNF agents. CONCLUSION: In this population, infliximab was associated with higher overall discontinuation rates compared with etanercept and adalimumab, which is mainly due to an increased risk of infusion or allergic reactions.
Comparison of Drug Retention Rates and Causes of Drug Discontinuation Between Anti-TNF Agents in Rheumatoid Arthritis

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ABSTRACT

**Background:** Tumour Necrosis Factor inhibitors (anti-TNF) have revolutionized the treatment of severe rheumatoid arthritis (RA), yet drug discontinuation is common.

**Objective:** Compare treatment retention rates and specific causes of anti-TNF discontinuation in a population-based RA cohort.

**Methods:** All patients treated with etanercept (ETA), infliximab (INF) or adalimumab (ADA) within the Swiss RA cohort (SCQM-RA) between 1997 and 2006 were included. Causes of treatment discontinuation were broadly categorized as ‘adverse events’ (AEs) or as ‘non-toxic causes’, and further sub-divided into specific categories. Specific causes of treatment interruption were analysed using a Cox proportional hazards model and adjusted for potential confounders.

**Results:** A total of 2364 anti-TNF treatment courses met the inclusion criteria. Treatment discontinuation was reported 803 times, 325 with ETN, 258 with INF and 221 with ADA. Drug inefficacy represented the largest single cause of treatment discontinuation (50 % of the cases). The median time on anti-TNF therapy was 37 months, but discontinuation rates differed between the 3 anti-TNF agents (ANOVA, $p < 0.001$), with shorter retention rates for INF (Hazard Rate (HR) 1.24 [99% CI 1.01-1.51]). The specific causes of treatment discontinuation revealed an increased risk of AEs with INF (HR 1.4 [99% CI 1.003-1.96]), mostly due to an increased risk of infusion or allergic reactions (HR 2.11 [99% 1.23-3.62]). Other discontinuation causes were equally distributed between the anti-TNF agents.

**Conclusion:** In this population, INF was associated with higher overall discontinuation rates compared to the other anti-TNF agents, which is mainly due to an increased risk of infusion or allergic reactions.
The prognosis of RA has improved over the last decades, due to its prompt recognition, the systematic introduction of disease modifying antirheumatic drugs (DMARDs) at an early stage of the disease, the use of DMARD combinations and the availability of more effective anti-rheumatic agents. (1-4)

The development of biologic agents, in particular inhibitors of the tumour necrosis factor (anti-TNF) during the last decade, represents a major breakthrough for the treatment of severe forms of RA (5-8). As it is the case for most active therapies, highly effective interventions raise concerns about adverse effects. Controversial data have been published on increased rates of bacterial infections and malignancies associated with anti-TNF agents (9-13). Available anti-TNF agents neutralize the TNF in different ways: etanercept (ETA) (Enbrel®, Amgen Inc., Thousand Oaks, CA) is a soluble TNF receptor (humanized protein) acting as a competitive inhibitor, while infliximab (INF) (Remicade®, Centocor INC., Malvern, PA) or adalimumab (ADA) (Humira®, Abbott Laboratories, Illinois, USA) are monoclonal antibodies (chimeric (human IgGκ / mouse Fv) for INF and fully human for ADA) (14, 15). Given these differences, distinct safety profiles and efficacy figures might be expected between these agents. Post marketing data have indeed suggested an increased risk of reactivation of latent tuberculosis with monoclonal antibodies compared to soluble receptors (16) and suggested that certain anti-TNF agents work better in specific chronic inflammatory diseases than others (17, 18). However, it remains unclear how the differences affect these agents’ long-term therapeutic effectiveness and their overall tolerability.

In clinical practice, drug-related side effects, primary non-response or secondary drug resistance to anti-TNF agents are common problems (4, 19). Comparative analyses of anti-TNF discontinuation rates have generally found no difference between available agents (4). However,
comparative studies are sparse, have limited follow-up time and relatively low numbers of
treatment interruptions.

The aims of this population-based cohort study are thus 1) to compare the treatment retention
rates between ETA, INF and ADA and 2) to compare the specific causes of treatment
discontinuation.

METHODOLOGY

METHODS AND PATIENTS

Study Population: This is a longitudinal, observational, population-based cohort study based on
the Swiss RA registry (SCQM-RA, Swiss Clinical Quality Management for Rheumatoid
Arthritis). SCQM-RA is a national program designed by the Swiss Society for Rheumatology
aiming at following longitudinally patients with RA. Patients are assessed at least yearly for
disease activity, radiographic joint damage, function, quality of life and other patient
characteristics. Information on current treatment, changes in medication, withdrawal and side
effects are also reported. An estimated 70-80% of all RA patients on biologic agents of
Switzerland are included in the registry (4). Approximately half of the patients come from private
rheumatology practices, 30% from non-academic hospital centres and 20% from academic
centres. We included all patients of the database treated with an anti-TNF agent between January
1997 and December 2006. When the reason for anti-TNF discontinuation was unclear or the dates
of initiation or discontinuation uncertain in the database, we contacted the treating physician to
ascertain this information. If he or she did not answer the first mail, a second was sent. Currently,
no compelling guidelines or administrative restrictions exist in Switzerland, which would favour
the use of one anti-TNF agent over another or limit dose adjustments of these agents, if needed. A
study previously published in the same population demonstrated a clinically significant dose
escalation for INF (4).
Primary outcome: The primary endpoints of this study were the time to anti-TNF discontinuation and the specific causes for drug discontinuation. We first examined the time until drug discontinuation independently of the reason that led to drug interruption. Drug discontinuation rates or ‘drug survival rates’ indicate both the patients’ and doctors’ satisfaction with the therapy and provide a useful summary measure of the overall treatment effectiveness and tolerability (20, 21). Drug interruption was defined as the discontinuation of the current anti-TNF agent for more than 6 months. Temporary interruptions (less than 6 months) were not considered a drug discontinuation. We categorized causes of drug discontinuation into adverse events (AEs) (acute systemic reaction including acute infusion or systemic allergic reactions, dermatologic reactions, infectious complications, malignancies and other miscellaneous reasons) and ‘non-toxic causes’ (including treatment ineffectiveness, patient preferences, pregnancy wish and remission). Adverse events and other causes of treatment interruptions were attributed to the current anti-TNF agent, independently to the previous biologic agent. In order to minimize reporting bias by physicians, we chose a priori to consider only AEs severe enough to cause treatment discontinuation. Physicians were allowed to cite more than one reason for interrupting the anti-TNF agent.

Exposure of interest: The exposure of interest for this analysis was the type of anti-TNF agent received, thus all observations were categorized as ADA, INF or ETA.

Statistical analysis: Baseline disease characteristics were compared across the three anti-TNF agents. For continuous variables, the significance of differences in mean values was assessed with one-way analysis of variance (ANOVA) for normally distributed variables and with the Kruskal-Wallis test for non-normally distributed variables. For binary variables, Pearson’s Chi-square test was used to evaluate the significance of differences in proportions. All statistical tests
were two-sided and evaluated at the 0.05 significance level. The statistical analysis was performed with Stata v. 9.2 for Windows (Stata Statistical Software, Texas, USA).

Confounding was a concern in this analysis, because the choice of an anti-TNF could be associated with disease severity or treatment tolerability. Because such an association would substantially influence drug discontinuation and the incidence of AEs, we used multivariate adjustments to correct for such confounding effects. The time to discontinuation of anti-TNF agents was analyzed using a Cox proportional hazards model (22). We then analyzed the proportion of treatment discontinuations explained by specific causes. We first examined the numbers of events by anti-TNF agent and evaluated the statistical significance of differences in proportions using the Pearson’s Chi-square test or the Fisher exact test, when adequate (unadjusted analysis). We then analyzed the time to event using Cox proportional hazards model and adjusted for potential confounders (adjusted analysis). Survival curves of the time to discontinuation (‘drug survival’) or time to event were produced with the Kaplan-Meier product-limit method (22).

We identified a priori sex, age, disease duration, baseline disease activity, (DAS28 score), baseline functional disability (HAQ score), presence of rheumatoid factor (RF), concomitant DMARDs (leflunomide, methotrexate (MTX) or other DMARDs), co-therapy with low dose glucocorticoids, failure to a previous anti-TNF and year of anti-TNF introduction (<2001, 2001-2003, > 2004) as potential confounding factors and corrected for these in the adjusted model.

Pair-wise comparisons between the 3 treatment groups were planned a priori, but were considered only if the overall comparison indicated a significant difference (ANOVA, p < 0.05). To maintain a Type I error at 5%, pair-wise comparisons and confidence intervals of therapeutic groups were corrected with Bonferroni’s adjustment procedure.
RESULTS

The total person time on anti-TNF agents was 3867 patient-years. Of the 2364 anti-TNF treatment courses 78% were on a first course; 882 patients received ADA, 887 ETA, and 595 INF. The baseline characteristics were consistent between the three anti-TNF groups (table 1), but for previous anti-TNF failure (lower in patient on ETA, p<0.001) and concomitant MTX use (higher in patients on INF, p<0.001). These differences were expected as ETA was the first anti-TNF agent on the market in Switzerland and concomitant MTX is generally used in combination with INF. Eight hundred and three anti-TNF discontinuation were reported; of which 245 for ADA, 309 for ETA and 249 for INF. In about half of the anti-TNF discontinuations the specific motive for interrupting therapy was unclear from the database (448 out of 803), but in 298 cases (298 out of 448) the motive for anti-TNF discontinuation could be elucidated after contacting the treating rheumatologist, but in 19% of cases (150 out of 803; ETA: 72, ADA, 32, INF: 47) the exact reason remained unclear (patient lost to follow-up, no answer from the physician to several mailings). Ultimately, 81% of the causes of treatment discontinuation (653 out of 803) could be retrieved and included in the analysis. The baseline characteristics of patients without specific cause of anti-TNF interruption did not differ from the others and was mainly related to the physician in charge Mean age was 53 ±14 years (p=0.36), disease duration 10.8 ± 9.6 years (p=0.51), baseline DAS score 4.38 ±4.4 (p=0.88), baseline HAQ 1.35 ±0.71 (p=0.61), concomitant Methotrexate 46%(p=0.16), concomitant Leflunomide 21% (p=0.09), other DMARD 21% (p=0.7).

The median drug survival time for anti-TNF was of 37 months [IQR 13- 57]. Treatment discontinuation due to AEs occurred on average after 11 months [IQR 4-19], which is significantly shorter than for non-toxic causes of treatment discontinuation, occurring after 18
months [IQR 6-24] (p<0.001). A statistical significant difference was noted in the discontinuation rates between the three anti-TNF agents (crude p=0.04, adjusted p<0.001, Figure 1). INF was associated with the highest treatment discontinuation rate (crude hazard ratio (HR): 1.19 [99% confidence interval (CI): 0.98-1.45]), adjusted HR 1.24 [99% CI: 1.01-1.51]), Figure 1). Time to anti-TNF discontinuation because of an AE was significantly different between the three anti-TNF agents in disfavour of INF (ANOVA p=0.02, Figure 2, HR 1.4 [99%CI: 1.003-1.96]), while no differences existed in treatment discontinuation for the non toxic causes (ANOVA p=0.38, Figure 3). Strong confounders of the overall discontinuation rate proved to be a history of previous failure on anti-TNF and the year of treatment initiation. Median drug survival was the longest for the first anti-TNF agent (37 months [IQR 13-57]) and decreased with subsequent anti-TNF agents (21 months (IQR 11-40) for the second anti-TNF agent, 13 months (IQR 6-29) for the third anti-TNF agent). Anti-TNF agents started before 2000 had a median survival time of 43 months, compared to 37 months in the years 2001-2004 and 26 months after 2005. Other significant predictors for treatment discontinuation included absence of concomitant glucocorticoids (HR 1.69 [95% CI 1.46-1.95] and high baseline DAS28 levels (HR 1.09 [95% CI: 1.02-1.16]). We also found a trend in favour of a lower risk of anti-TNF discontinuation for anti-TNFs in combination with MTX (HR 0.85 [95% CI 0.70-1.02]). After adjusting for these variables in the multivariate analysis, the relative risk for treatment discontinuation of ADA compared to INF was significantly modified (crude HR 0.87 [99% CI: 0.70-1.10], adjusted HR 0.74 [99% CI 0.59-0.92]), suggesting that a history of previous anti-TNF failure and the year of treatment initiation particularly affected ADA treatment maintenance. After one year of anti-TNF initiation, 78% of the patients were still on INF, 82% on ETA and 84% on ADA. At two years, 58% were on INF, 65% on ETA and 66% on ADA (Figure 1).
Overall, AEs were responsible for treatment discontinuation in 47% of cases (318 of 653 cases): 16% for acute systemic reactions (105 cases), 10% for a dermatological complication (65 cases), 14% for infections (89 cases), 2% for malignancies (15 cases), and 24% for other miscellaneous complications (neurological, ophthalmological, cardiovascular, pulmonary, gastroenterological, renal, haematological and osteoarticular) (157 cases). Non-toxic causes were responsible for treatment discontinuation in 61% of cases (397 out of 653 cases). Treatment inefficacy represented the largest single cause for anti-TNF treatment discontinuation: 50% (327 cases). At the time of treatment interruption, the mean DAS28 level in this group was of 4.37 [95% CI 4.21-4.53], compared to 3.78 [95% CI 3.66-3.90] for patients with other causes of treatment discontinuation (p<0.001). Other non-toxic causes included patient preference in 8.8% (58 cases), followed by remission in 2.9% (19 cases) and finally, pregnancy (wish) in 1.1% (8 cases). Of note, physicians could motivate anti-TNF discontinuation by more than one reason, explaining why the total exceeds 100%.

The proportion of overall AEs causing treatment discontinuation did not differ significantly between the three anti-TNFs (p=0.093, table 2), although slightly more AEs were reported as cause for treatment discontinuation with INF (52%) compared to the other two agents (~43 and 49%). Similar results were seen when taking into account the time to AE and adjusting for differences in baseline risk factors (table 3), with an increased overall risk of AEs with INF (HR 1.4 [99% CI 1.00-1.96]) compared to the other two agents. An analysis of the specific types of AEs revealed significantly more acute systemic reactions with INF (crude p<0.001, adjusted p=0.018, HR for INF 2.11 [99% IC 1.23-3.62]). No significant difference between the three anti-TNF agents existed for dermatological AEs (adjusted p=0.81), infectious AEs (adjusted p=0.18) or malignancies (adjusted p=0.21). The types of infections causing treatment discontinuation
were diverse and included: respiratory tract infections (12 of which 6 pneumonias), urogenital tract infections (8), osteomyelitis (4), viral infections (2 herpes simplex 1, one chicken pox), cutaneous infections (3), gastrointestinal infections (3), septicaemia (2), ENT infections (2), lymphangitis (2), pneumocystis jirovecii (2) and other rare infections. Four cases of mycobacterial infections were reported, two with Mycobacteria (MB) tuberculosis, one with MB kanzasii, and one with MB fortuitum, and no MB infection was associated with ETA. In certain cases, the recurrence of infectious AEs (cystitis, respiratory tract infections) more than the severity of the disease was the cause of treatment discontinuation. Fifteen cases of malignancies led to anti-TNF discontinuation. The most common malignancies were: breast cancers (2 cases with ETA and ADA), lymphomas (2 cases with ETA and ADA), and uro-genital malignancies (2 cases with ETA and INF).

DISCUSSION

This study demonstrates a statistically significant difference in discontinuation rates between the three anti-TNF agents, with shorter drug retention, and an increased risk of AEs in patients treated with INF, mainly due to a higher risk of infusion and systemic allergic reactions. Other discontinuation causes were equally distributed across the three anti-TNF agents. Analyses from the British Biologic Register also suggested a higher discontinuation rate of INF (42%) compared to ADA (30%) and ETA (29%) during a first course of anti-TNF (23). Bocqu et al. also found better retention rates with ETA (p=0.0001) and ADA (p=0.01) than with INF at one year (24). Similarly, Kristenson et al. suggested a difference of anti-TNF retention at five years between ETA (65%) and INF (36%) (p<0.001) when combined with MTX (25). However, other analyses, found similar retention rates of available anti-TNF agents in RA (26, 27). The small number of patients included in these studies probably explains part of these discrepancies. In the literature,
anti-TNF treatment survival was shown to be prolonged when combined with MTX (25, 28). Although we found a trend in favour of a lower risk of anti-TNF discontinuation for anti-TNFs in combination with MTX (HR 0.85 [95% CI 0.70-1.02]), this result did not reach statistical significance ($p=0.08$). In addition, we observed that a relevant predictor of treatment interruption was the absence of concomitant use of glucocorticoids (HR 1.69 [95% CI 1.46-1.95]). While a decreased risk of infusion reactions with low dose glucocorticoids has been described in patients receiving INF (29), a potential increase of anti-TNF maintenance by low-dose glucocorticoids is of practical importance but needs to be confirmed in other patient populations.

The most frequent single cause for anti-TNF discontinuation in our study was treatment ineffectivity, which was not significantly different between the three anti-TNF agents. Which of treatment ineffectiveness or overall AEs is the primary cause of anti-TNF discontinuation remains of debate in the literature (23, 26, 30, 31). Moreover, we noted that drug survival was inversely proportional to previous anti-TNF failure and later year of treatment initiation. The inverse association with calendar year of treatment initiation reflects the greater availability of therapeutic alternatives favouring treatment switches over time and the increasing proportion of patients starting biologics after having failed previous anti-TNF agents (4). Switching once anti-TNF (from a soluble receptor to a monoclonal antibody or vice versa) is supported by the literature (23, 32-34), but switching a second time seems much less effective (32), which is demonstrated in our study by very short treatment retention with a third anti-TNF agent (median retention time of only 13 months (IQR 6-29)).

INF was associated with a higher discontinuation rate due to AEs (HR 1.4 [99% CI 1.003-1.96]) compared to ADA and ETA, which was mainly due to an increased incidence of acute systemic reactions (HR 2.15 [99% CI 1.24-3.7]). No difference between anti-TNF agents was reported.
with regards to infections, malignancies and dermatological complications. Furthermore, no differences were found in the incidence of other non-toxic causes of treatment discontinuation (remission, pregnancy (wish) and patient preference). Baseline characteristics between anti-TNF agents were fairly similar and do not explain the difference in drug discontinuation or incidence of AEs. Overall, these results suggest that available anti-TNF agents do not differ in their effectiveness to control RA, but may differ in their incidence of specific AEs. In particular, acute systemic reactions caused more often treatment interruption with INF, which could be related to the structure (chimeric component) and the IV administration of INF.

In the literature, the risk of acute infusion reactions with INF varies considerably (between 0.8 to 8.8 % per infusion) and affects approximately between 10 to 23% of patients per year (35-40). Cheifetz et al. distinguished acute infusion reactions occurring within 24 hours and delayed infusion reactions occurring between 1 to 14 days after therapy (38). Delayed infusion reactions occur in about 2% of the patients per year (38, 39) and resemble closely a “serum sickness like” reaction. Others have concluded that patients having developed human anti-chimeric antibodies (HACA) are more susceptible to develop acute allergic reactions (41). Moreover, the presence of positive baseline antinuclear antibodies and the absence of concomitant use of MTX have also been demonstrated to increase the risk of infusion reactions (42). Because ETA and ADA are administered subcutaneously, allergic reactions to these two agents are more likely to be categorized as ‘dermatological reaction’ by treating physicians, which could have created some misclassification. In a sensitivity analysis, we combined the dermatological and acute systemic reaction categories, and still found a significant hazard for this combined AE category with INF (HR 1.69 [99% CI 1.05-2.72]), which suggests that overall allergic reactions remain a more common cause of treatment discontinuation for INF.
The risk of infection was similar for the three drugs. The spectrum of infections reported in this study is similar to that found in literature (respiratory tract, skin and soft tissue, bone and joint, urinary tract infections), although we did not see an increased incidence of skin and soft tissue infections, as has been suggested by others (11, 43). A difference in susceptibility to MB infections between the monoclonal antibodies and the soluble receptor has also been described (16). A recent study demonstrated a HR of 10 [95%CI 1.92-52.61] for the risk of tuberculosis reactivation in patients treated with monoclonal antibodies anti-TNF agents as compared to those receiving ETA (44). Although the incidence of MB infections was too low in our population to demonstrate significant differences between these agents, we found no MB infections in the ETA group. Furthermore, no significant difference could be demonstrated in solid or lymphomatous tumours between the anti-TNF agents. These findings are similar to those previously published in the literature (27, 45). The dosages of anti-TNF agents in patients presenting a malignancy were not different from those used in the rest of the study population.

In 19% of the treatment discontinuations, the specific reason for anti-TNF interruption could not be retrieved, generally due to a lack of response from the physician in charge. We do not think this confounds our results, because missing information is primarily related to the doctor in charge and not to disease characteristics of these patients. Patients missing the specific cause of treatment interruption had similar disease and treatment characteristics than the rest of the population. Since this is an observational study, there is a potential for selection bias between treatment groups. However, the baseline characteristics were relatively homogeneous, but for expected differences (proportion of previous failures to anti-TNF, MTX use). Furthermore, glucocorticoid use is a good proxy for RA disease severity and its prevalence was similar between the 3 treatment groups. The physician’s personal preference seemed to be the most
involved in the selection of a particular anti-TNF agent. We adjusted the analysis for potential confounders (table 1); however we cannot exclude confounding by unmeasured factors. To our knowledge, this is the first cohort study to directly compare the specific causes of treatment discontinuation between the available anti-TNF agents. It is a, population-based study, which minimizes potential selection biases and allowed to adjust the analysis for important confounding factors. The specific causes of treatment discontinuation were reported by the physician in charge of the patient. Inefficacy was the most frequent cause of treatment discontinuation. Definition for inefficacy is ill defined in the literature (46) and remains largely physician –dependant. We did not analyse transitory causes of treatment discontinuation in order to minimize reporting bias, frequent for expected AEs.

This study found a higher discontinuation rate for patients treated with INF than with the other anti-TNF agents. The shorter treatment retention is primarily explained by a higher risk of infusion reactions or acute systemic reactions. Furthermore, with similar rates of treatment discontinuation for inefficacy across all 3 agents, this study suggests no difference in effectiveness between the 3 anti-TNF agents. Given the protective effect of glucocorticoids on infusion reactions with INF (29), and the longer treatment survival of INF if combination with MTX, our results suggest that ETA or ADA may be considered preferentially for patients unwilling or unable to take MTX or glucocorticoid co-therapy.
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<table>
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<tr>
<th>Baseline characteristics</th>
<th>INF (N=595)</th>
<th>ETA (N=887)</th>
<th>ADA (N=882)</th>
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<td>Age§ [years]</td>
<td>53 ±13</td>
<td>54 ±14</td>
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<td>Gender, male [%]</td>
<td>24</td>
<td>22</td>
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<td>Disease duration* [years]</td>
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<td>RF [%]</td>
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<td>74</td>
<td>75</td>
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<td>Failure to previous anti-TNF [%]</td>
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<td>DAS 28*</td>
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<td>N (%)</td>
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<td>99 (17)</td>
<td>151 (17)</td>
<td>160 (18)</td>
<td>0.765</td>
</tr>
<tr>
<td>Other</td>
<td>101 (17)</td>
<td>164 (19)</td>
<td>181 (20)</td>
<td>0.246</td>
</tr>
<tr>
<td>No DMARD</td>
<td>67 (11)</td>
<td>252 (29)</td>
<td>195 (22)</td>
<td>0.000</td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>312 (52)</td>
<td>460 (52)</td>
<td>439 (49)</td>
<td>0.409</td>
</tr>
</tbody>
</table>

**Legend Table 1:**

§ mean ±SD; * one way analysis of variance (ANOVA) of means for continuous variables;

# patients could have more than one concomitant DMARD, therefore the total could exceed
100%. INF = infliximab, ETA = etanercept, ADA = adalimumab, RF = rheumatoid factor; anti-TNF = anti-tumour necrosis factor inhibitor; DAS 28 = 28-joint Disease Activity Score; RADAI = rheumatoid arthritis disease activity index; HAQ = Stanford Health Assessment Questionnaire; DMARDs = disease-modifying antirheumatic drugs;
Table 2: Causes of treatment discontinuation: Number of events by anti-TNF agent (Unadjusted analysis)

<table>
<thead>
<tr>
<th>Causes</th>
<th>INF 1042 N=209</th>
<th>ETA 1660 N=237</th>
<th>ADA1165 N=213</th>
<th>P°</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Adverse Events</td>
<td>108 (51.7)</td>
<td>118 (49)</td>
<td>92 (43.2)</td>
<td>0.093</td>
</tr>
<tr>
<td>Acute Systemic Reaction *</td>
<td>50 (23.9)</td>
<td>24 (10)</td>
<td>31 (14.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infections</td>
<td>26 (12.4)</td>
<td>41 (17)</td>
<td>22 (10.3)</td>
<td>0.088</td>
</tr>
<tr>
<td>Dermatological disease</td>
<td>16 (7.6)</td>
<td>20 (8.4)</td>
<td>29 (13.6)</td>
<td>0.09</td>
</tr>
<tr>
<td>Malignancy</td>
<td>8 (3.8)</td>
<td>5 (2.1)</td>
<td>2 (0.9)</td>
<td>0.12</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0.33</td>
</tr>
<tr>
<td>Miscellaneous complications</td>
<td>46 (22.1)</td>
<td>54 (22.8)</td>
<td>57 (26.8)</td>
<td>0.78</td>
</tr>
<tr>
<td>- General #</td>
<td>14 (6.7)</td>
<td>13 (5.49)</td>
<td>9 (4.2)</td>
<td>0.46</td>
</tr>
<tr>
<td>- Neuropsychiatrical</td>
<td>15 (7.2)</td>
<td>13 (5.49)</td>
<td>21 (9.9)</td>
<td>0.22</td>
</tr>
<tr>
<td>- Ophthalmologic</td>
<td>3 (1.4)</td>
<td>7 (2.9)</td>
<td>2 (0.9)</td>
<td>0.29</td>
</tr>
<tr>
<td>- Ear nose throat</td>
<td>2 (1.0)</td>
<td>3 (1.3)</td>
<td>0</td>
<td>0.29</td>
</tr>
<tr>
<td>- Cardiovascular</td>
<td>7 (3.3)</td>
<td>14 (5.9)</td>
<td>6 (2.8)</td>
<td>0.23</td>
</tr>
<tr>
<td>- Pulmonary</td>
<td>3 (1.4)</td>
<td>10 (4.21)</td>
<td>5 (2.3)</td>
<td>0.22</td>
</tr>
<tr>
<td>- Gastroenterological</td>
<td>11 (5.2)</td>
<td>17 (7.2)</td>
<td>16 (7.5)</td>
<td>0.67</td>
</tr>
<tr>
<td>- Renal disease</td>
<td>4 (1.9)</td>
<td>(2.9)</td>
<td>0</td>
<td>0.03</td>
</tr>
<tr>
<td>- Haematological</td>
<td>2 (1.0)</td>
<td>4 (1.69)</td>
<td>2 (0.9)</td>
<td>0.75</td>
</tr>
<tr>
<td>- Osteoarticular</td>
<td>6 (2.9)</td>
<td>4 (1.69)</td>
<td>4 (1.9)</td>
<td>0.63</td>
</tr>
<tr>
<td>Non toxic causes</td>
<td>111 (53)</td>
<td>148 (63)</td>
<td>138 (64.8)</td>
<td>0.11</td>
</tr>
<tr>
<td>Ineffectiveness</td>
<td>90 (43)</td>
<td>125 (52)</td>
<td>112 (52.6)</td>
<td>0.17</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>3 (1.4)</td>
<td>2 (0.8)</td>
<td>2 (0.9)</td>
<td>0.8</td>
</tr>
<tr>
<td>Remission</td>
<td>5 (2.3)</td>
<td>5 (2.1)</td>
<td>12 (5.6)</td>
<td>0.11</td>
</tr>
<tr>
<td>Preference</td>
<td>17 (8.1)</td>
<td>23 (9.7)</td>
<td>18 (8.4)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Legend table 2
INF = infliximab, ETA = etanercept, ADA = adalimumab, °chi-square or Fisher test when appropriate; * acute systemic reaction included infusion reactions or systemic allergic reactions
general: fatigue, head aches, weight changes…
Table 3: Causes of treatment discontinuation. Analysis of the time to event (Cox proportional hazard model, adjusted analysis)

<table>
<thead>
<tr>
<th>Causes</th>
<th>INF Ref</th>
<th>ETA HR [95%CI] §</th>
<th>ADA HR [95%CI] §</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Adverse events</td>
<td>1</td>
<td>0.79 [0.55-1.13]</td>
<td>0.67 [0.45-0.97]</td>
<td>0.02</td>
</tr>
<tr>
<td>Acute syst. reaction #</td>
<td>1</td>
<td>0.4 [0.21-0.78]</td>
<td>0.56 [0.29-1.09]</td>
<td>0.018</td>
</tr>
<tr>
<td>Dermatological disease</td>
<td>1</td>
<td>0.85 [0.43-1.70]</td>
<td>1.04 [0.54-2.02]</td>
<td>0.81</td>
</tr>
<tr>
<td>Infection</td>
<td>1</td>
<td>1.14 [0.68-1.92]</td>
<td>0.56 [0.30-1.04]</td>
<td>0.18</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1</td>
<td>0.54 [0.16-1.85]</td>
<td>0.20 [0.37-1.06]</td>
<td>0.12</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1</td>
<td>0.81 [0.55-1.19]</td>
<td>0.85 [0.58-1.25]</td>
<td>0.55</td>
</tr>
<tr>
<td>All non-toxic causes</td>
<td>1</td>
<td>0.90 [0.64-1.26]</td>
<td>0.82 [0.58-1.18]</td>
<td>0.38</td>
</tr>
<tr>
<td>Ineffectiveness</td>
<td>1</td>
<td>0.95 [0.71-1.26]</td>
<td>0.82 [0.61-1.11]</td>
<td>0.42</td>
</tr>
<tr>
<td>Remission</td>
<td>1</td>
<td>0.85 [0.22-3.3 ]</td>
<td>1.10 [0.36-3.44]</td>
<td>0.91</td>
</tr>
<tr>
<td>Pregnancy wish</td>
<td>1</td>
<td>0.75 [0.10-5.55]</td>
<td>1.89 [0.24-14.9 ]</td>
<td>0.95</td>
</tr>
<tr>
<td>Preference</td>
<td>1</td>
<td>0.68 [0.37-1.45]</td>
<td>0.85 [0.41-1.77]</td>
<td>0.68</td>
</tr>
</tbody>
</table>

**Legend table 3**

INF = infliximab, ETA = etanercept, ADA = adalimumab; # acute systemic reaction included infusion reaction or systemic allergic reaction; § values are hazard ratio (HR) with 95% confidence interval (CI), INF (infliximab) = 1 is the reference (REF); * Cox proportional hazard analysis, adjusted for sex, age, disease duration, disease activity score (DAS 28), Standford health assessment questionnaire (HAQ), rheumatoid factor, leflunomide, methotrexate, other disease modifying antirheumatic drugs (DMARDs), and glucocorticoids.
Figure 1: Time to anti-TNF discontinuation

ANOVA $p < 0.001$
Figure 2: Time to anti-TNF discontinuation due to adverse events

ANOVA $p = 0.02$
Figure 3  Time to anti-TNF discontinuation due to non-toxic causes

ANOVA $p = 0.38$
**Legends of figures**

**Figure 1**: The Kaplan-Meier curve for time to anti-TNF discontinuation (‘‘drug survival’’). All causes of discontinuation were analysed together. The survivor curve was adjusted for RF positivity, baseline disease activity scores (DAS28), baseline levels of functional disability (HAQ), year of treatment initiation, and failure of previous anti-TNF agents. ADA = adalimumab; INF = infliximab; ETA = etanercept.

**Figure 2**: The Kaplan-Meier curve for time to anti-TNF discontinuation (‘‘drug survival’’) due to adverse effects (AEs). The survivor curve was adjusted for RF positivity, baseline disease activity scores (DAS28), baseline levels of functional disability (HAQ), year of treatment initiation, and failure to previous anti-TNF agents. ADA = adalimumab; INF = infliximab; ETA = etanercept.

**Figure 3**: The Kaplan-Meier curve for time to anti-TNF agent discontinuation (‘‘drug survival’’) due to non toxic causes. Non toxic causes included ineffectiveness, remission, pregnancy wish, and patient preference. The survivor curve was adjusted for RF positivity, baseline disease activity scores (DAS28), baseline levels of functional disability (HAQ), year of treatment initiation, and failure to previous anti-TNF agents. ADA = adalimumab; INF = infliximab; ETA = etanercept.
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