

Comparison of Drug Retention Rates and Causes of Drug Discontinuation Between Anti-Tumor Necrosis Factor Agents in Rheumatoid Arthritis

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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.

INTRODUCTION

The prognosis of rheumatoid arthritis (RA) has improved over the last few 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 antirheumatic agents (1–4).

The development of biologic agents during the last decade, in particular tumor necrosis factor (TNF) inhibitors, represents a major breakthrough for the treatment of severe

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forms of RA (5–8). Similar to most active therapies, highly effective interventions raise concerns about adverse effects. Conflicting 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 is a soluble TNF receptor (humanized protein) acting as a competitive inhibitor, whereas infliximab and adalimumab are monoclonal antibodies (chimeric [human IgGκ/murine Fv] for infliximab and fully human for adalimumab) (14,15). Given these differences, distinct safety profiles and efficacy figures might be expected between these agents. Post-marketing data have suggested an increased risk of reactivation of latent tuberculosis with monoclonal antibodies compared with soluble receptors (16), and suggested that certain anti-TNF agents work better in specific chronic inflammatory diseases than in others (17,18). However, it remains unclear how the differences affect the long-term therapeutic effectiveness and overall tolerability of the agents.

In clinical practice, drug-related side effects, primary nonresponse, 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 and have limited followup time and relatively low numbers of treatment interruptions. The aims of this population-based cohort study were to 1) compare the treatment retention rates between etanercept, infliximab, and adalimumab and 2) compare the specific causes of treatment discontinuation.

PATIENTS AND METHODS

Study population. We conducted a longitudinal, observational, population-based cohort study using data from the Swiss Clinical Quality Management for Rheumatoid Arthritis (SCQM-RA) registry. The SCQM-RA is a national program designed by the Swiss Society for Rheumatology aimed at longitudinally following 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 from Switzerland receiving biologic agents are included in the registry (4). Approximately half of the patients come from private rheumatology practices, 30% come from non-academic hospital centers, and 20% come from academic centers. We included all patients in 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 were uncertain in the database, we contacted the treating physician to ascertain this information. If he or she did not answer the first request, a second was sent. Currently, no compelling guidelines or administrative restrictions exist in Switzerland that would favor the use of one anti-TNF agent over another or limit dose adjustments of these agents if needed. One previous study published in the

same population demonstrated a clinically significant dose escalation for infliximab (4).

Primary outcome. The primary end points 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 indicated both the patient's and doctor's satisfaction with the therapy and provided 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; including acute systemic reactions consisting of acute infusion or systemic allergic reactions, dermatologic reactions, infectious complications, malignancies, and other miscellaneous reasons) and nontoxic causes (including treatment ineffectiveness, patient preferences, desire for pregnancy, and remission). AEs and other causes of treatment interruption were attributed to the current anti-TNF agent independently of 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.

The exposure of interest for this analysis was the type of anti-TNF agent received; therefore, all observations were categorized as adalimumab, infliximab, or etanercept.

Statistical analysis. Baseline disease characteristics were compared across the 3 anti-TNF agents. For continuous variables, the significance of differences in mean values was assessed with a one-way analysis of variance 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 2-sided and evaluated at the 0.05 significance level. The statistical analysis was performed with Stata, version 9.2 for Windows (StataCorp, College Station, TX).

Confounding was a concern in this analysis because the choice of an anti-TNF agent 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 Pearson's chi-square test or Fisher's exact test, when adequate (unadjusted analysis). We then adjusted the model for potential confounders (adjusted analysis). Survival curves for

Table 1. Baseline characteristics of the study population*

	Infliximab (n = 595)	Etanercept (n = 887)	Adalimumab (n = 882)	P†
Age, years	53 ± 13	54 ± 14	55 ± 13	0.16
Men, %	24	22	21	0.42
Disease duration, years	10 ± 9	10 ± 9	10 ± 9	0.2
Rheumatoid factor positivity, %	77	74	75	0.88
Failure of previous anti-TNF agent, %	23	19	27	< 0.001
DAS28‡	4.27 ± 1.52	4.23 ± 1.53	4.14 ± 1.42	0.066
RADAI‡	4.29 ± 2.14	4.31 ± 2.24	4.16 ± 2.15	0.37
HAQ score‡	1.32 ± 0.72	1.25 ± 0.76	1.17 ± 0.71	0.117
DMARDs, no. (%)‡				
Methotrexate	439 (74)	486 (55)	541 (61)	< 0.001
Leflunomide	99 (17)	151 (17)	160 (18)	0.765
Other	101 (17)	164 (19)	181 (20)	0.246
No DMARDs	67 (11)	252 (29)	195 (22)	< 0.001
Glucocorticoids, no. (%)	312 (52)	460 (52)	439 (49)	0.409

* Values are the mean ± SD unless otherwise indicated. Anti-TNF = anti-tumor necrosis factor; DAS28 = 28-joint Disease Activity Score; RADAI = Rheumatoid Arthritis Disease Activity Index; HAQ = Stanford Health Assessment Questionnaire; DMARDs = disease-modifying antirheumatic drugs.
† One-way analysis of variance of means for continuous variables.
‡ Patients could be receiving >1 concomitant DMARD; therefore, the total could exceed 100%.

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 (Disease Activity Score in 28 joints [DAS28]), baseline functional disability (Health Assessment Questionnaire [HAQ] score), presence of rheumatoid factor, concomitant DMARDs (leflunomide, methotrexate [MTX], or other DMARDs), cotherapy with low-dose glucocorticoids, failure of a previous anti-TNF agent, and year of anti-TNF agent introduction (before 2001, 2001–2003, or after 2004) as potential confounding factors and corrected for these in the adjusted model. Pairwise comparisons between the 3 treatment groups were planned a priori, but were considered only if the overall comparison indicated a significant difference between anti-TNF agents ($P < 0.05$). To maintain a Type I error at 5%, pairwise comparisons and confidence intervals of therapeutic groups were corrected with Bonferroni adjustment procedure.

RESULTS

The total person-time of receiving anti-TNF agents was 3,867 patient-years. Of the 2,364 anti-TNF treatment courses, 78% were on a first course; 882 patients received adalimumab, 887 received etanercept, and 595 received infliximab. The baseline characteristics were consistent between the 3 anti-TNF groups (Table 1) except for previous failure of an anti-TNF agent (lower in patients receiving etanercept; $P < 0.001$) and concomitant MTX use (higher in patients receiving infliximab; $P < 0.001$). These differences were expected because etanercept was the first anti-TNF agent on the market in Switzerland and concomitant MTX is generally used in combination with infliximab. A total of 803 anti-TNF discontinuations were reported: 245 for adalimumab, 309 for etanercept, and 249 for infliximab. In ~55.8% of the anti-TNF discontinua-

tions (448 of 803), the specific motive for interrupting therapy was unclear from the database; in 298 of 448 cases, the motive for anti-TNF discontinuation could be elucidated after contacting the treating rheumatologist, but in 19% of cases (151 of 803: 72 etanercept, 32 adalimumab, and 47 infliximab) the exact reason remained unclear (patients lost to followup, no answer from the physician after several requests). Ultimately, 81% (653 of 803) of the causes of treatment discontinuation could be retrieved and included in the analysis.

The baseline characteristics of the patients without a specific cause of anti-TNF interruption did not differ from the others and was mainly related to the physician in charge. Mean ± SD age was 53 ± 14 years ($P = 0.36$), mean ± SD disease duration was 10.8 ± 9.6 years ($P = 0.51$), mean ± SD baseline DAS28 score was 4.38 ± 4.4 ($P = 0.88$), mean ± SD baseline HAQ score was 1.35 ± 0.71 ($P = 0.61$), concomitant MTX use was 46% ($P = 0.16$), concomitant leflunomide use was 21% ($P = 0.09$), and other DMARD use was 21% ($P = 0.7$).

The median drug survival time for anti-TNF agents was 37 months (interquartile range [IQR] 13–57). Treatment discontinuation due to AEs occurred on average after 11 months (IQR 4–19), which is significantly shorter than nontoxic causes of treatment discontinuation occurring after 18 months (IQR 6–24; $P < 0.001$). A statistically significant difference was noted in the discontinuation rates between the 3 anti-TNF agents (crude $P = 0.04$, adjusted $P < 0.001$) (Figure 1). Infliximab was associated with the highest treatment discontinuation rate (crude hazard ratio [HR] 1.19, 99% confidence interval [99% 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 3 anti-TNF agents in disfavor of infliximab (HR 1.4, 99% CI 1.003–1.96; Cox proportional hazards model $P = 0.02$) (Figure 2), whereas no differences existed in treatment discontinuation due to nontoxic causes (Cox proportional hazards model $P =$

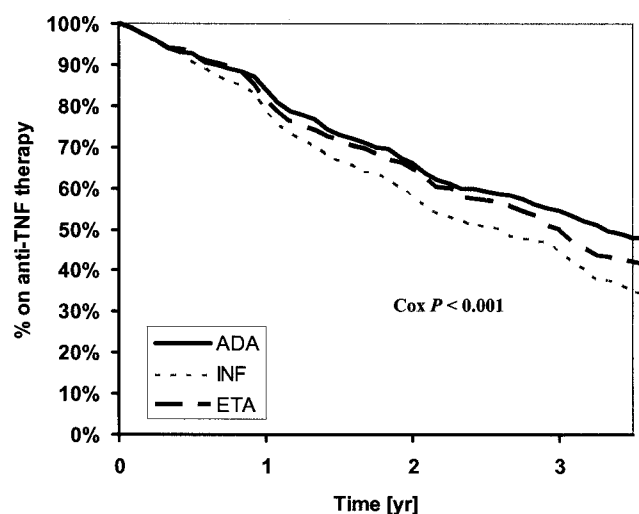


Figure 1. Kaplan-Meier curve for time to anti-tumor necrosis factor (anti-TNF) agent discontinuation (drug survival). All causes of discontinuation were analyzed together. The survivor curve was adjusted for rheumatoid factor positivity, baseline disease activity scores (Disease Activity Score in 28 joints), baseline levels of functional disability (Health Assessment Questionnaire), year of treatment initiation, and failure of previous anti-TNF agents. ADA = adalimumab; INF = infliximab; ETA = etanercept.

0.38) (Figure 3). Strong confounders of the overall discontinuation rate proved to be previous failure of an anti-TNF agent 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 with 37 months from 2001–2004 and 26 months after 2005. Other significant

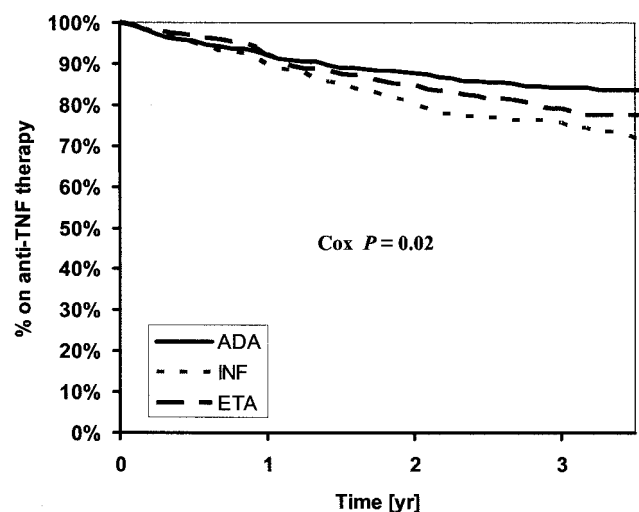


Figure 2. Kaplan-Meier curve for time to anti-tumor necrosis factor (anti-TNF) agent discontinuation (drug survival) due to adverse events. The survivor curve was adjusted for rheumatoid factor positivity, baseline disease activity scores (Disease Activity Score in 28 joints), baseline levels of functional disability (Health Assessment Questionnaire), year of treatment initiation, and failure of previous anti-TNF agents. ADA = adalimumab; INF = infliximab; ETA = etanercept.

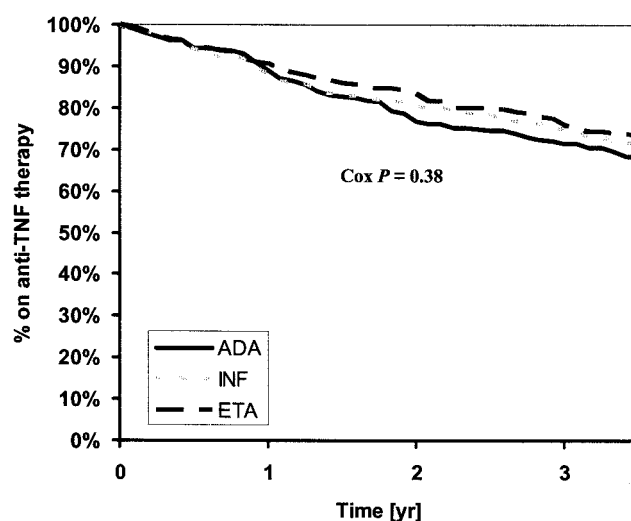


Figure 3. Kaplan-Meier curve for time to anti-tumor necrosis factor (anti-TNF) agent discontinuation (drug survival) due to nontoxic causes, including ineffectiveness, remission, desire for pregnancy, and patient preference. The survivor curve was adjusted for rheumatoid factor positivity, baseline disease activity scores (Disease Activity Score in 28 joints), baseline levels of functional disability (Health Assessment Questionnaire), year of treatment initiation, and failure of previous anti-TNF agents. ADA = adalimumab; INF = infliximab; ETA = etanercept.

predictors for treatment discontinuation included absence of concomitant glucocorticoids (HR 1.69, 95% confidence interval [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 favor of a lower risk of discontinuation of anti-TNF agents 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 adalimumab compared with infliximab 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 previous failure of an anti-TNF agent and the year of treatment initiation particularly affected adalimumab treatment maintenance. After 1 year of anti-TNF initiation, 78% of the patients were still receiving infliximab, 82% were receiving etanercept, and 84% were receiving adalimumab. At 2 years, 58% were receiving infliximab, 65% were receiving etanercept, and 66% were receiving adalimumab (Figure 1).

Overall, AEs were responsible for treatment discontinuation in 48.7% of cases (318 of 653): 16% for acute systemic reactions (105 cases), 10% for a dermatologic complication (65 cases), 14% for infections (89 cases), 2% for malignancies (15 cases), and 24% for other miscellaneous complications (157 cases, including neurologic, ophthalmologic, cardiovascular, pulmonary, gastroenterological, renal, hematologic, and osteoarticular). Nontoxic causes were responsible for treatment discontinuation in 61% of cases (397 of 653). 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 cohort was 4.37 (95% CI 4.21–4.53) compared with 3.78 (95% CI 3.66–3.90) for patients with other causes of treatment discontinuation ($P < 0.001$). Other nontoxic causes included patient

Table 2. Causes of treatment discontinuation: number of events by anti-tumor necrosis factor agent (unadjusted analysis)

	Infliximab, no. (%) (n = 209)	Etanercept, no. (%) (n = 237)	Adalimumab, no. (%) (n = 213)	P*
Total person-time receiving medication, patient years	1,042	1,660	1,165	
All adverse events	108 (51.7)	118 (49)	92 (43.2)	0.093
Acute systemic reaction†	50 (23.9)	24 (10)	31 (14.6)	< 0.001
Infections	26 (12.4)	41 (17)	22 (10.3)	0.088
Dermatologic disease	16 (7.6)	20 (8.4)	29 (13.6)	0.09
Malignancy	8 (3.8)	5 (2.1)	2 (0.9)	0.12
Death	2 (1.0)	0	2 (0.9)	0.33
Miscellaneous complications	46 (22.1)	54 (22.8)	57 (26.8)	0.78
General‡	14 (6.7)	13 (5.49)	9 (4.2)	0.46
Neuropsychiatric	15 (7.2)	13 (5.49)	21 (9.9)	0.22
Ophthalmologic	3 (1.4)	7 (2.9)	2 (0.9)	0.29
Ear, nose, throat	2 (1.0)	3 (1.3)	0	0.29
Cardiovascular	7 (3.3)	14 (5.9)	6 (2.8)	0.23
Pulmonary	3 (1.4)	10 (4.21)	5 (2.3)	0.22
Gastroenterological	11 (5.2)	17 (7.2)	16 (7.5)	0.67
Renal disease	4 (1.9)	7 (2.9)	0	0.03
Hematologic	2 (1.0)	4 (1.69)	2 (0.9)	0.75
Osteoarticular	6 (2.9)	4 (1.69)	4 (1.9)	0.63
Nontoxic causes	111 (53)	148 (63)	138 (64.8)	0.11
Ineffectiveness	90 (43)	125 (52)	112 (52.6)	0.17
Desire for pregnancy	3 (1.4)	2 (0.8)	2 (0.9)	0.80
Remission	5 (2.3)	5 (2.1)	12 (5.6)	0.11
Preference	17 (8.1)	23 (9.7)	18 (8.4)	0.90

* Chi-square test or Fisher's exact test when appropriate.

† Including infusion reactions or systemic allergic reactions.

‡ Including fatigue, headaches, and weight changes.

preference in 8.8% (58 cases), remission in 33% (22 cases), and desire for pregnancy in 1.0% (7 cases). Physicians could motivate anti-TNF discontinuation with more than one reason, which explains why the total exceeds 100%.

The proportion of overall AEs causing treatment discontinuation did not differ significantly between the 3 anti-TNF agents ($P = 0.093$) (Table 2), although slightly more AEs were reported as a cause for treatment discontinuation

with infliximab (52%) compared with adalimumab and etanercept (~43% and 49%, respectively). Similar results were seen when taking into account the time to an AE and adjusting for differences in baseline risk factors (Table 3), with an increased overall risk of AEs with infliximab (HR 1.4, 99% CI 1.00–1.96) compared with etanercept and adalimumab. An analysis of the specific types of AEs revealed significantly more acute systemic reactions with

Table 3. Causes of treatment discontinuation: analysis of the time to event (Cox proportional hazards model, adjusted analysis)*

	Infliximab (reference)	Etanercept, HR (95% CI)	Adalimumab, HR (95% CI)	P
All adverse events	1	0.79 (0.55–1.13)	0.67 (0.45–0.97)	0.02
Acute systemic reaction†	1	0.4 (0.21–0.78)	0.56 (0.29–1.09)	0.018
Dermatologic disease	1	0.85 (0.43–1.70)	1.04 (0.54–2.02)	0.81
Infection	1	1.14 (0.68–1.92)	0.56 (0.30–1.04)	0.18
Malignancy	1	0.54 (0.16–1.85)	0.20 (0.37–1.06)	0.12
Miscellaneous	1	0.81 (0.55–1.19)	0.85 (0.58–1.25)	0.55
All nontoxic causes	1	0.90 (0.64–1.26)	0.82 (0.58–1.18)	0.38
Ineffectiveness	1	0.95 (0.71–1.26)	0.82 (0.61–1.11)	0.42
Remission	1	0.85 (0.22–3.3)	1.10 (0.36–3.44)	0.91
Desire for pregnancy	1	0.75 (0.10–5.55)	1.89 (0.24–14.9)	0.95
Preference	1	0.68 (0.37–1.45)	0.85 (0.41–1.77)	0.68

* Cox proportional hazards model analysis, adjusted for sex, age, disease duration, Disease Activity Score in 28 joints, Stanford Health Assessment Questionnaire, rheumatoid factor, leflunomide, methotrexate, other disease-modifying antirheumatic drugs, and glucocorticoids. HR = hazard ratio; 95% CI = 95% confidence interval.

† Including infusion reaction or systemic allergic reaction.

infliximab (HR 2.11, 99% CI 1.23–3.62; crude $P < 0.001$, adjusted $P = 0.018$). No significant difference between the 3 anti-TNF agents existed for dermatologic AEs (adjusted $P = 0.81$), infectious AEs (adjusted $P = 0.18$), or malignancies (adjusted $P = 0.12$). The types of infections causing treatment discontinuation were diverse and included respiratory tract infections ($n = 12$, 6 of which were pneumonia), urogenital tract infections ($n = 8$), osteomyelitis ($n = 4$), viral infections ($n = 2$ herpes simplex virus type 1, $n = 1$ chickenpox), cutaneous infections ($n = 3$), gastrointestinal infections ($n = 3$), septicemia ($n = 2$), ear, nose, throat infections ($n = 2$), lymphangitis ($n = 2$), *Pneumocystis jiroveci* ($n = 2$), and other rare infections. Four cases of mycobacterial infections were reported: 2 with *Mycobacterium tuberculosis*, 1 with *Mycobacterium kansasii*, and 1 with *Mycobacterium fortuitum*, and no mycobacterial infection was associated with etanercept. 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 cancer (2 cases with etanercept and adalimumab), lymphomas (2 cases with etanercept and adalimumab), and urogenital malignancies (2 cases with etanercept and infliximab).

DISCUSSION

This study demonstrates a statistically significant difference in discontinuation rates between the 3 anti-TNF agents with shorter drug retention and an increased risk of AEs in patients treated with infliximab, mainly due to a higher risk of infusion and systemic allergic reactions. Other discontinuation causes were equally distributed across the 3 anti-TNF agents. Analyses from the British Biologics Register also suggested a higher discontinuation rate of infliximab (42%) compared with adalimumab (30%) and etanercept (29%) during a first course of anti-TNF agents (23). Brocq et al also found better retention rates with etanercept ($P = 0.0001$) and adalimumab ($P = 0.01$) than with infliximab at 1 year (24). Similarly, Kristensen et al suggested a difference of anti-TNF retention at 5 years between etanercept (65%) and infliximab (36%; $P < 0.001$) when combined with MTX (25). However, other analyses found similar retention rates of the 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 favor of a lower risk of anti-TNF discontinuation for anti-TNF agents 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). Although a decreased risk of infusion reactions with low-dose glucocorticoids has been described in patients receiving infliximab (29), a potential increase of anti-TNF maintenance with low-dose glucocorticoids is of practical

importance but needs to be confirmed in other patient populations.

The most frequent single cause of anti-TNF discontinuation in our study was treatment inefficacy, which was not significantly different between the 3 anti-TNF agents. Whether treatment ineffectiveness or overall AEs is the primary cause of anti-TNF discontinuation is still debated in the literature (23,26,30,31). Moreover, we noted that drug survival was inversely proportional to previous failure of anti-TNF therapy and later year of treatment initiation. The inverse association with calendar year of treatment initiation reflects the greater availability of therapeutic alternatives favoring treatment switches over time and the increasing proportion of patients starting biologics after having failed with previous anti-TNF agents (4). Switching an anti-TNF agent once (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 a very short treatment retention with a third anti-TNF agent (median retention time 13 months [IQR 6–29]).

Infliximab was associated with a higher discontinuation rate due to AEs (HR 1.4, 99% CI 1.003–1.96) compared with adalimumab and etanercept, which was mainly due to an increased incidence of acute systemic reactions (HR 2.15, 99% CI 1.24–3.7). No differences between anti-TNF agents were reported with regard to infections, malignancies, and dermatologic complications. Furthermore, no differences were found in the incidence of other nontoxic causes of treatment discontinuation (remission, desire for pregnancy, 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 more often caused treatment interruption with infliximab, which could be related to the structure (chimeric component) and the intravenous administration of infliximab.

In the literature, the risk of acute infusion reactions with infliximab varies considerably (between 0.8% and 8.8% per infusion) and affects between approximately 10% and 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 and 14 days after therapy (38). Delayed infusion reactions occur in approximately 2% of patients per year (38,39) and closely resemble a serum sickness–like reaction. Other studies have concluded that patients with human antichimeric antibodies 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 etanercept and adalimumab are administered subcutaneously, allergic reactions to these 2 agents are more likely to be categorized as a dermatologic reaction by treating physicians, which could have created some misclassification. In a sensitivity analysis, we combined the dermatologic and acute systemic reaction categories and still found a

significant hazard for this AE category combined with infliximab (HR 1.69, 99% CI 1.05–2.72), which suggests that overall allergic reactions remain a more common cause of treatment discontinuation for infliximab.

The risk of infection was similar for the 3 medications. The spectrum of infections reported in this study is similar to that found in the 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, which has been suggested in other studies (11,43). A difference in susceptibility to mycobacterial infections between the monoclonal antibodies and the soluble receptor has also been described (16). A recent study demonstrated an HR of 10 (95% CI 1.92–52.61) for the risk of tuberculosis reactivation in patients treated with monoclonal antibody anti-TNF agents as compared with those receiving etanercept (44). Although the incidence of mycobacterial infections was too low in our population to demonstrate significant differences between these agents, we found no mycobacterial infections in the etanercept group. Furthermore, no significant differences could be demonstrated in solid or lymphomatous tumors between the anti-TNF agents. These findings are similar to those previously published in the literature (27,45). The doses of anti-TNF agents in patients with a malignancy were not different from those used in the remainder 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 that 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 to the rest of the population. Because this is an observational study, there is a potential for selection bias between treatment groups. However, the baseline characteristics were relatively homogeneous for expected differences (proportion of previous failures of anti-TNF therapy, 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 prominent factor 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. This is a population-based study, which minimizes potential selection biases and allows adjustment of 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. Inefficacy is not well-defined in the literature (46) and remains largely physician-dependant. We did not analyze transitory causes of treatment discontinuation in order to minimize reporting bias, which is frequent for expected AEs.

In this study, we found a higher discontinuation rate

for patients treated with infliximab than with etanercept and adalimumab. 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 infliximab (29) and the longer treatment survival of infliximab in combination with MTX, our results suggest that etanercept or adalimumab may be considered preferential for patients unwilling or unable to receive MTX or glucocorticoid cotherapy.

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AUTHOR CONTRIBUTIONS

All authors were involved in contributions to study conception and design, acquisition of data, or analysis and interpretation of data, and drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Martin Du Pan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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