Drug survival on tumour necrosis factor inhibitors in patients with rheumatoid arthritis in Finland

KJ Aaltonen[1], JT Joensuu[1], L Pirilä[2], M Kauppi[3,4], T Uutela[5], T Varjolahti-Lehtinen[6], T Yli-Kerttula[7], P Isomäki[4,8], D Nordström[9,10], T Sokka[11,12]

[1]Faculty of Pharmacy, University of Helsinki, Helsinki, Finland
[2]Department of Medicine, Turku University Hospital, Turku, Finland
[3]Department of Medicine, Lahti Central Hospital, Lahti, Finland
[4]Faculty of Medicine, University of Tampere, Tampere, Finland
[5]Department of Medicine, Lapland Central Hospital, Rovaniemi, Finland
[6]Department of Medicine, Tampere City Hospital, Tampere, Finland
[7]Department of Medicine, Satakunta Central Hospital, Rauma, Finland
[8]Department of Medicine, Tampere University Hospital, Tampere, Finland
[9]Department of Medicine, Helsinki University Hospital, Helsinki, Finland
[10]Faculty of Medicine, Clinicum, University of Helsinki, Helsinki, Finland
[11]Department of Medicine, Jyväskylä Central Hospital, Jyväskylä, Finland
[12]Faculty of Health Science, University of Eastern Finland, Kuopio, Finland

Objective: A systematic review found lthat an average of 27% of rheumatoid arthritis (RA) patients using tumour necrosis factor (TNF) inhibitors discontinue their treatment within 1 year. The aim of this study was to assess drug survival on TNF inhibitors among patients with RA.
Methods: Patients were identified from the National Register for Biologic Treatment in Finland (ROB-FIN), which is a longitudinal cohort study established to monitor the effectiveness and safety of biologic drugs in rheumatic diseases. Inclusion was limited to TNF-inhibitor treatments started as the patient's first, second, or third biologic treatment between 2004 and 2014. Follow-up was truncated at 36 months. The results of a time-dependent Cox proportional hazards model were reported as adjusted hazard ratios (HRs) with 95% confidence intervals (CIs).
Results: Of the 4200 TNF-inhibitor treatment periods identified from ROB-FIN, 3443 periods from 2687 patients met the inclusion criteria. Twenty-seven per cent of the patients discontinued their treatment within 12 months. Infliximab (HR 1.8, 95% CI 1.3–2.5) and certolizumab pegol (HR 1.7, 95% CI 1.2–2.3) had lower drug survival compared to golimumab. A similar trend was seen with adalimumab (HR 1.2, 95% CI 0.90–1.7) and etanercept (HR 1.2, 95% CI 0.87–1.6). Concomitant use of methotrexate (MTX) was associated with improved drug survival (HR 0.76, 95% CI 0.64–0.90) in comparison with TNF-inhibitor monotherapy.
Conclusions: Golimumab was better in terms of drug survival than infliximab or certolizumab pegol and at least as good as adalimumab and etanercept. Concomitant use of MTX improved drug survival on TNF inhibitors.

Treatment with tumour necrosis factor (TNF) inhibitors may have to be discontinued for various reasons, of which the most common are adverse events and lack of effectiveness (1, 2). A systematic review in 2016 found that an average of 27% and 37% of rheumatoid arthritis (RA) patients on TNF inhibitors discontinue their treatment within 1 and 2 years, respectively (2). Another systematic review including 26 randomized controlled trials (RCTs) found that etanercept may have to be discontinued owing to adverse events less frequently than other TNF inhibitors, except for golimumab (1). Many, but not all, previous observational studies have found the drug survival on infliximab to be inferior to that on either etanercept or adalimumab (2–8). As far as we know, only one prior study has compared golimumab and certolizumab pegol in an observational setting (9).

Concomitant treatment with methotrexate (MTX) or other conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) has been shown to reduce the risk of discontinuing TNF-inhibitor therapy in both RA and ankylosing spondylitis in a number of previous studies (2–5, 7, 10). This effect may be mediated by both improved effectiveness and a decreased risk of developing anti-drug

Kalle Jyri Aaltonen, Faculty of Pharmacy, University of Helsinki, PO Box 56, Viikinkaari 5, FI-00014, Helsinki, Finland.
E-mail: kalle.jm.aaltonen@helsinki.fi

Accepted 6 September 2016

DOI: 10.1080/03009742.2016.1234641

antibodies (ADAs). Besides concomitant csDMARD therapy, age, gender, comorbidity, baseline disease activity, presence of rheumatoid factor (RF), and prior csDMARD therapy have been identified as possible predictors of drug survival (2–6, 8, 11).

The aim of this study was to assess the drug survival on TNF inhibitors including golimumab and certolizumab pegol among patients with RA. We sought also to analyse the effect of concomitant non-biologic treatment on the treatment persistence.

Material and methods

Patients

Patients were identified from the National Register for Biologic Treatment in Finland (ROB-FIN), which is a longitudinal cohort study with data dating back to 1999 and was established to monitor the effectiveness and safety of biologic disease-modifying anti-rheumatic drugs (bDMARDs) in rheumatic diseases. Inclusion for this study was limited to TNF-inhibitor treatments started as the patient's first, second, or third bDMARD treatment between 2004 and 2014. Follow-up data were available until the end of 2015; however, follow-up of individual treatment periods was truncated at 36 months. The primary endpoint of this study was the discontinuation of TNF-inhibitor therapy for any reason within the follow-up time. Patients lost to follow-up were censored from the survival analyses. The number of hospital days for any cause and outpatient visits for reasons outside the International Classification of Diseases, 10th revision (ICD-10) M-class in the 24 months before treatment onset were calculated based on data from the Finnish Hospital Discharge Register.

Statistical methods

Missing baseline data were imputed by multiple imputation with predictive mean matching and 10 imputed data

Table 1. Baseline characteristics of the patients included in the study.

Variable	1st bDMARD users (n = 2221) (64%)	2nd/3rd bDMARD users (n = 1222) (36%)	Total (n = 3443)	Missing data (%)
Age (years)	55 (45–62)	55 (46–62)	55 (46–62)	0
Men	604 (27)	283 (23)	887 (26)	0
Patient Global (VAS 0–100)	50 (25–67)	45 (21–65)	48 (24–67)	7.9
Pain (VAS 0–100)	50 (27–70)	47 (22–67)	49 (25–69)	6.4
Investigator Global (VAS 0–100)	36 (19–56)	26 (12–45)	32 (15–52)	15
HAQ	0.94 (0.40–1.4)	1.0 (0.50–1.5)	1.0 (0.50–1.4)	11
ESR	17 (8.0–32)	17 (8.0–32)	17 (8.0–32)	8.4
CRP (mg/L)	9.0 (5.0–24)	7.0 (4.0–20)	8.0 (4.0–22)	7.3
RF	1766 (80)	966 (79)	2732 (79)	16
Time since diagnosis (years)	8.2 (2.4–17)	11 (5.5–19)	9.5 (3.3–18)	0
Erosions in hands and feet	1516 (68)	775 (63)	2291 (67)	31
SJC (0–54)	5.0 (1.0–10)	2.0 (0–7.0)	4.0 (1.0–9.0)	12
TJC (0–53)	4.0 (1.0–11)	3.0 (1.0–7.8)	4.0 (1.0–10)	12
TJC (0–28)	3.0 (0–7.0)	2.0 (0–5.0)	2.0 (0–6.0)	9.2
SJC (0–28)	2.0 (0–6.0)	2.0 (0–4.0)	2.0 (0–6.0)	9.4
DAS28	4.0 (2.6–5.2)	3.6 (2.4–4.7)	3.8 (2.6–5.1)	27
Year of biologic treatment onset	2008 (2006–2011)	2008 (2006–2011)	2008 (2006–2011)	0
Outpatient visits in the past 2 years	1.0 (0–4.0)	2.0 (0–5.0)	1.0 (0–5.0)	0
Hospital days in the past 2 years	1.0 (0–8.0)	2.0 (0–11)	2.0 (0–9.0)	0
Methotrexate	1301 (59)	648 (53)	1949 (57)	0
Hydroxychloroquine	788 (35)	312 (26)	1100 (32)	0
Sulfasalazine	646 (29)	232 (19)	878 (26)	0
Leflunomide	362 (16)	170 (14)	532 (15)	0
Intramuscular Gold	82 (3.7)	47 (3.8)	129 (3.7)	0
Ciclosporin	93 (4.2)	51 (4.2)	144 (4.2)	0
Azathioprine	85 (3.8)	61 (5.0)	146 (4.2)	0
Any concomitant csDMARD	1934 (87)	1025 (84)	2959 (86)	0
Glucocorticoids	1568 (71)	807 (66)	2375 (69)	0
Adalimumab	869 (39)	484 (40)	1353 (39)	0
Etanercept	877 (39)	482 (39)	1359 (39)	0
Infliximab	256 (12)	80 (6.5)	336 (9.8)	0
Golimumab	109 (4.9)	91 (7.4)	200 (5.8)	0
Certolizumab pegol	110 (5.0)	85 (7.0)	195 (5.7)	0

Data are shown as median (interquartile range) or n (%).
VAS, visual analogue scale; HAQ, Health Assessment Questionnaire; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count; DAS28, Disease Activity Score based on 28-joint count; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug.

sets. Discontinuation proportions and their 95% confidence intervals (95% CIs) were estimated using Kaplan–Meier survival analysis. A Cox proportional hazards model with age as well as csDMARD and glucocorticoid use as time-updated confounders was carried out to compare the survival of individual TNF inhibitors and to study the effects of comedication on TNF drug survival. The best model in terms of Akaike information criteria was used to account for the confounding. We explored possible effect modification by including interaction terms in the model. The proportional hazards assumption was tested, and to comply with this assumption, the model was stratified by the medians of age and investigators' global assessment. The results of the Cox proportional hazards model were reported as adjusted hazard ratios (HRs) with 95% CIs. All data processing and analyses were conducted in R 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

An ethical board statement was acquired from the coordinating ethical committee of Helsinki and Uusimaa Hospital District (73/13/03/00/14).

Results

Of the 4200 TNF-inhibitor treatment periods identified from ROB-FIN, 3443 periods from 2687 patients met the inclusion criteria, accumulating a total of 5695 patient-years. Baseline characteristics of the patients in the study are shown in Table 1. Etanercept, adalimumab, infliximab, golimumab, and certolizumab pegol were used by 1359 (39%), 1353 (39%), 336 (9.8%), 200 (5.8%), and 195 (5.7%) patients, respectively. MTX (57%), hydroxychloroquine (32%), and sulfasalazine (26%) were the most commonly used csDMARDs at the baseline of TNF-inhibitor treatment, while at least one concomitant cDMARD was used by 86%. Glucocorticoids were used by 69%, with a median prednisolone equivalent daily dose of 5.0 mg (interquartile range 5.0–7.5). Median baseline age and Disease Activity Score based on 28-joint count (DAS28) score were 55 years and 3.8, respectively, and 74% of the included patients were women. The amount of missing data varied from 0% to 31% across the variables in the data set. The proportion of patients lost to follow-up within 3, 6, 12, 24, and 36 months was 8.7%, 12%, 16%, 25%, and 30%, respectively.

Based on Kaplan–Meier survival analysis, the probability of discontinuing the treatment within 6, 12, 24, and 36 months was 16%, 27%, 37%, and 43%, respectively. Drug survival was better among the patients with no prior bDMARD therapy than among those using TNF inhibitors as their second or third bDMARD. Certolizumab pegol (41%) and infliximab (38%) were associated with higher probability of treatment discontinuation within 12 months compared to adalimumab (25%), etanercept (25%), and golimumab (25%) (Table 2).

Table 2. Discontinuation probabilities (%) of tumour necrosis factor (TNF) inhibitors based on Kaplan–Meier survival analysis.

	Follow-up time				
	3 months	6 months	12 months	24 months	36 months
TNF inhibitors used as the 1st bDMARD					
Adalimumab	5.5 (3.9–7.0)	14 (11–16)	24 (21–27)	33 (30–37)	38 (35–42)
Certolizumab pegol	5.2 (0.80–9.4)	19 (11–27)	34 (24–43)	44 (33–54)	48 (36–57)
Etanercept	6.9 (5.1–8.6)	16 (13–18)	25 (22–28)	34 (30–37)	39 (36–43)
Golimumab	5.9 (1.2–10)	18 (10–26)	24 (15–32)	32 (21–41)	35 (24–45)
Infliximab	7.8 (4.3–11)	19 (14–24)	38 (32–44)	49 (42–56)	56 (48–62)
Total	6.3 (5.2–7.3)	16 (14–17)	26 (24–28)	36 (33–38)	41 (39–43)
TNF inhibitors used as the 2nd or 3rd bDMARD					
Adalimumab	6.5 (4.2–8.8)	18 (14–21)	28 (23–32)	38 (33–42)	46 (41–51)
Certolizumab pegol	15 (6.9–23)	24 (14–33)	49 (36–60)	68 (54–77)	70 (56–79)
Etanercept	7.0 (4.6–9.3)	16 (13–20)	25 (21–29)	36 (31–40)	44 (39–49)
Golimumab	2.7 (0–6.5)	9.9 (2.7–17)	26 (15–36)	34 (21–45)	40 (25–53)
Infliximab	10 (3.2–17)	23 (13–32)	37 (25–47)	49 (36–60)	59 (44–69)
Total	7.2 (5.7–8.7)	17 (15–20)	29 (26–31)	39 (36–42)	48 (44–51)
TNF inhibitors used as the 1st, 2nd, or 3rd bDMARD					
Adalimumab	5.8 (4.5–7.1)	15 (13–17)	25 (23–28)	35 (32–37)	41 (38–44)
Certolizumab pegol	9.3 (4.9–13)	21 (15–27)	41 (33–48)	54 (46–62)	57 (48–65)
Etanercept	6.9 (5.5–8.3)	16 (14–18)	25 (23–28)	34 (32–37)	41 (38–44)
Golimumab	4.2 (1.2–7.2)	15 (9.3–20)	25 (18–31)	33 (25–40)	37 (28–45)
Infliximab	8.4 (5.3–11)	20 (16–25)	38 (32–43)	49 (43–55)	56 (50–62)
Total	6.6 (5.7–7.5)	16 (15–18)	27 (26–29)	37 (35–39)	43 (41–45)

Data are shown as % (95% confidence interval).
bDMARD, biologic disease-modifying anti-rheumatic drug.

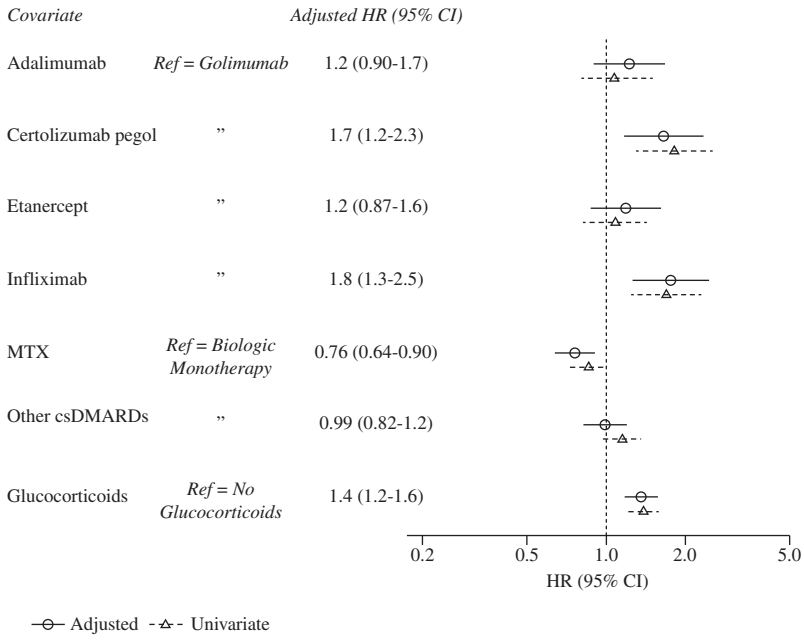

Figure 1. Results of the Cox proportional hazards model on drug survival on tumour necrosis factor inhibitors. MTX, methotrexate; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; HR, hazard ratio; CI, confidence interval.

Variables included in the adjusted model, along with their respective correlation coefficients and confidence intervals, are presented in Supplementary Table S1. The interaction terms between TNF inhibitors and csDMARD or glucocorticoid use were not statistically significant and were not included in the final model.

The results of the model suggest that infliximab (HR 1.8, 95% CI 1.3–2.5) and certolizumab pegol (HR 1.7, 95% CI 1.2–2.3) had lower drug survival compared with golimumab. Similar although statistically non-significant trends were seen with adalimumab (HR 1.2, 95% CI 0.90–1.7) and etanercept (HR 1.2, 95% CI 0.87–1.6) compared with golimumab. Concomitant use of MTX with or without any additional csDMARDs was associated with improved drug survival (HR 0.76, 95% CI 0.64–0.90) compared with TNF-inhibitor monotherapy. Glucocorticoid use was associated with a worsening of the survival on TNF-inhibitor therapy (HR 1.4, 95% CI 1.2–1.6) (Figure 1).

Discussion

Our results showed that there were notable differences in drug survival on different TNF-inhibiting agents. Golimumab was associated with better drug survival than infliximab and certolizumab pegol, but did not statistically significantly differ from adalimumab and etanercept. Dalén et al found golimumab to be better in treatment persistence compared with etanercept and adalimumab, yet similar to certolizumab pegol (9). Their study did not, however, include information on the patients' disease activity, which may have confounded the results. Nevertheless, the results of RCTs provide some support for these findings (1). The overall rates of treatment discontinuation were similar to those observed in a recent systematic review based on prior drug survival studies (2).

Concomitant use of MTX was associated with improved treatment persistence on TNF inhibitors, which is in accordance with many previous studies (8). This effect is likely to be mediated by improved treatment effectiveness, which in turn encourages both the patient and physician to continue the treatment. Although the formation of ADAs, or the absence thereof, may play a role in drug survival, the fact that MTX also improved the drug survival of etanercept suggests that the bulk of the effect is due to other reasons (12, 13). Despite adjusting for confounding in the regression analysis, the possibility of residual confounding remains. In particular, those patients who are willing to continue using MTX despite its rather common adverse effects may also be more adherent to their treatment with TNF inhibitors. Similarly, it seems plausible that patients who do not require the use of oral glucocorticoids have a better prognosis for reasons other than the glucocorticoid treatment itself.

The formation of ADAs was not routinely monitored during the follow-up period. Regretfully, we were unable to analyse the reasons for TNF-inhibitor discontinuation as this information was too infrequently reported in our data. We do, however, expect the distribution of reasons to be similar to that reported from Sweden, with the possible difference of discontinuing infliximab treatments for financial reasons in favour of the self-injectable TNF inhibitors reimbursed by the Social Insurance Institution instead of the hospital (7). Our data on the patients' comorbidities and general health status were incomplete and, hence, we used hospital treatments and outpatient visits to specialized

healthcare facilities as a substitute. Unlike in the Swedish study (7), neither the number of hospital days nor outpatient visits predicted drug survival at all.

We did not find statistically significant effect modification between individual TNF inhibitors and either concomitant csDMARDs or glucocorticoids, and therefore our results on the effect of concomitant treatment on drug survival apply to all five TNF inhibitors.

In conclusion, we found that golimumab was better in terms of drug survival than infliximab or certolizumab pegol and at least as good as adalimumab and etanercept. Concomitant use of MTX improved drug survival on TNF inhibitors, whereas the opposite was true for glucocorticoids.

Acknowledgements

We wish to thank all rheumatologists who participated in the data collection.

This study was supported in part by a research grant from the Investigator Initiated Studies Program of Merck Sharp & Dohme Corp/MSD. The opinions expressed in this paper are those of the authors and do not necessarily represent those of Merck Sharp & Dohme Corp/MSD. In addition, ROB-FIN has received financial support from the following pharmaceutical companies: Abbvie, BMS, Hospira, and Pfizer.

References

1 Aaltonen KJ, Virkki LM, Malmivaara A, Konttinen YT, Nordström DC, Blom M. Systematic review and meta-analysis of the efficacy and safety of existing TNF blocking agents in treatment of rheumatoid arthritis. PLoS One 2012;7:e30275.
2 Souto A, Maneiro JR, Gómez-Reino JJ. Rate of discontinuation and drug survival of biologic therapies in rheumatoid arthritis: a systematic review and meta-analysis of drug registries and health care databases. Rheumatology (Oxford) 2016;55:523–34.
3 Flouri I, Markatseli TE, Voulgari PV, Boki KA, Papadopoulos I, Settas L, et al. Comparative effectiveness and survival of infliximab, adalimumab, and etanercept for rheumatoid arthritis patients in the hellenic registry of biologics: low rates of remission and 5-year drug survival. Semin Arthritis Rheum 2014;43:447–57.
4 Heiberg MS, Koldingsnes W, Mikkelsen K, Rødevand E, Kaufmann C, Mowinckel P, et al. The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study. Arthritis Rheum 2008;59:234–40.
5 Scirè CA, Caporali R, Sarzi-Puttini P, Frediani B, Di Franco M, Tincani A, et al. Drug survival of the first course of anti-TNF agents in patients with rheumatoid arthritis and seronegative spondyloarthritis: analysis from the MonitorNet database. Clin Exp Rheumatol 2013;31:857–63.
6 Markenson JA, Gibofsky A, Palmer WR, Keystone EC, Schiff MH, Feng J, et al. Persistence with anti-tumor necrosis factor therapies in patients with rheumatoid arthritis: observations from the RADIUS registry. J Rheumatol 2011;38:1273–81.
7 Neovius M, Arkema EV, Olsson H, Eriksson JK, Kristensen LE, Simard JF, et al. Drug survival on TNF inhibitors in patients with rheumatoid arthritis comparison of adalimumab, etanercept and infliximab. Ann Rheum Dis 2015;74:354–60.
8 Lopez-Gonzalez R, Leon L, Loza E, Redondo M, Garcia de Yebenes MJ, Carmona L. Adherence to biologic therapies and associated factors in rheumatoid arthritis, spondyloarthritis and psoriatic arthritis: a systematic literature review. Clin Exp Rheumatol 2015;33:559–69.
9 Dalén J, Svedbom A, Black CM, Lyu R, Ding Q, Sajjan S, et al. Treatment persistence among patients with immune-mediated rheumatic disease newly treated with subcutaneous TNF-alpha inhibitors and costs associated with non-persistence. Rheumatol Int 2016;36:987–95.
10 Heinonen AV, Aaltonen KJ, Joensuu JT, Lahteenmaki JP, Pertovaara MI, Romu MK, et al. Effectiveness and drug survival of TNF inhibitors in the treatment of ankylosing spondylitis: a prospective cohort study. J Rheumatol 2015;42:2339–46.
11 Voulgari PV, Alamanos Y, Nikas SN, Bougias DV, Temekonidis TI, Drosos AA. Infliximab therapy in established rheumatoid arthritis: an observational study. Am J Med 2005;118:515–20.
12 Garcês S, Demengeot J, Benito-Garcia E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. Ann Rheum Dis 2013;72:1947–55.
13 Chen D-Y, Chen Y-M, Hung W-T, Chen -H-H, Hsieh C-W, Chen Y-H, et al. Immunogenicity, drug trough levels and therapeutic response in patients with rheumatoid arthritis or ankylosing spondylitis after 24-week golimumab treatment. Ann Rheum Dis 2015;74:2261–4.

Supporting information

Additional supporting information may be found in the online version of this article.

Supplementary Table S1. The results of the Cox proportional hazards model on drug survival on TNF-inhibitors.

Please note that the editors are not responsible for the content or functionality of any supplementary material supplied by the authors. Any queries should be directed to the corresponding author.