Effectiveness of Tumor Necrosis Factor Inhibitors in Combination with Various csDMARD in the Treatment of Rheumatoid Arthritis: Data from the DREAM Registry

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ABSTRACT. ***Objective.*** To analyze and compare the effectiveness and drug survival in patients with rheumatoid arthritis, as measured by 28-joint Disease Activity Score (DAS28) and Health Assessment Questionnaire–Disability Index (HAQ-DI), of tumor necrosis factor inhibitor (TNFi) monotherapy, TNFi + leflunomide (LEF), TNFi + sulfasalazine (SSZ), TNFi + other conventional synthetic disease-modifying antirheumatic drugs (csDMARD), and TNFi + methotrexate (MTX) therapy, in daily practice.

Methods. Data were collected from the DREAM registry. Patients beginning their first TNFi treatment were included in the study: TNFi monotherapy (n = 320), TNFi + SSZ (n = 103), TNFi + LEF (n = 80), TNFi + other csDMARD (n = 99), TNFi + MTX alone (n = 919), TNFi + MTX + other csDMARD (n = 412). Treatment effectiveness was analyzed using DAS28 and HAQ-DI with linear mixed models and the TNFi drug survival was analyzed using Kaplan-Meier curves and Cox regression. All analyses have been corrected for confounders.

Results. The patients who received TNFi + MTX had significantly better DAS28 and HAQ-DI values over time (both $p < 0.001$) and longer TNFi drug survival than TNFi monotherapy ($p < 0.001$). TNFi + SSZ and TNFi + other csDMARD had significantly better DAS28 values over time ($p = 0.001$) and longer drug survival ($p = 0.001$) versus TNFi monotherapy. TNFi + LEF was not significantly better compared to monotherapy. Adding other csDMARD to the TNFi + MTX combination provided no added value.

Conclusion. Preferably, TNFi should be prescribed together with MTX. If this is not possible, we advise the use of other csDMARD. (First Release August 1 2016; J Rheumatol 2016;43:1787–94; doi:10.3899/jrheum.151014)

Key Indexing Terms:
RHEUMATOID ARTHRITIS — TUMOR NECROSIS FACTOR INHIBITOR
DISEASE-MODIFYING ANTIRHEUMATIC DRUGS — METHOTREXATE

Tumor necrosis factor inhibitor (TNFi) therapy is effective for the treatment of patients with rheumatoid arthritis (RA). However, randomized controlled trials (RCT) have shown that adding methotrexate (MTX) to the TNFi treatment regimen (i.e., TNFi + MTX) is more efficacious than TNFi monotherapy[1,2,3,4,5,6]. TNFi compounds have been registered for use by the European Medicine Agency and the U.S. Food and Drug Administration (FDA) as a combination therapy with MTX or alone for adalimumab (ADA), etanercept (ETN), and certolizumab and only as a combination therapy

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with MTX for infliximab (IFX) and golimumab. TNFi + MTX treatment is recommended by treatment guidelines[7]. However, in clinical practice, TNFi is also prescribed as monotherapy or in combination with a non-MTX conventional synthetic disease-modifying antirheumatic drug (csDMARD)[8,9,10,11,12] when MTX is contraindicated or not tolerated[13]. The effectiveness of TNFi monotherapy and TNFi in combination with csDMARD other than MTX is not proven.

The study by Finckh, *et al* shows that TNFi in combination with leflunomide (LEF) has the same drug survival and the same adverse events as TNFi plus MTX[14], while other studies are inconclusive on the safety of combining LEF with biological agents[15]. The study by Soliman, *et al* shows significant differences in drug survival between TNFi + MTX alone and TNFi monotherapy, TNFi + sulfasalazine (SSZ), and TNFi + LEF[12]. Drug survival is often used as a proxy for effectiveness, but it has the disadvantage that it is a combination of effectiveness, adverse events, and behavior. To our knowledge, there are no studies available that show effectiveness determined by clinical measures of the different combination therapies compared to MTX combination therapy or monotherapy. Therefore there is a lack of evidence to support recommending other csDMARD in combination with TNFi in those patients who cannot be treated with MTX. For that reason the objective of our study was to compare the effectiveness, measured by Disease Activity Score of 28 joints using erythrocyte sedimentation rate (DAS28-ESR) and Health Assessment Questionnaire–Disability Index (HAQ-DI), and drug survival of TNFi + MTX, TNFi + LEF, TNFi + SSZ, TNFi + other csDMARD co-therapy, and TNFi monotherapy. Moreover, we performed subanalyses for the separate TNFi treatments and TNFi + MTX alone, as well as for TNFi + MTX + other csDMARD.

MATERIALS AND METHODS

Design. For this observational study, we used data collected from the DREAM biologic registry[16]. The registry includes patients with RA who received their first TNFi treatment in one of 13 participating treatment centers in the Netherlands from February 2003 until July 2012. Data collection continued even if the patient changed medication or stopped using biological agents. The choice to either change or stop medication was at the discretion of the treating rheumatologist. According to Dutch regulations, the DREAM registry does not require ethics approval because no additional data — other than data used for monitoring daily practice — are collected. The regional ethics committee Arnhem-Nijmegen confirmed this. All included patients provided written informed consent for the use of their data for scientific purposes.

Inclusion criteria. All included patients had been diagnosed with RA in accordance with the 1987 American College of Rheumatology classification criteria[17]; had moderate to high disease activity (defined as DAS28 > 3.2); received prior treatment with at least 2 csDMARD, including MTX; and had no contraindication for receiving a TNFi (e.g., pregnancy, presence of a serious infection). These inclusion criteria for the DREAM registry were based on the Dutch regulations for providing reimbursement for TNFi therapy. In the Netherlands, all patients with RA have access to TNFi through the Dutch national health insurance system, while all outpatient rheumatology care is provided within a hospital setting.

Patients were included in our study who were starting TNFi therapy in combination with MTX (TNFi + MTX), TNFi therapy in combination with a non-MTX csDMARD [SSZ, LEF, hydroxychloroquine (HCQ), azathioprine (AZA), or parenteral gold/auranofin], and who were only starting with TNFi monotherapy.

Measurements. Patients were assessed at the start of the TNFi treatment (baseline). The following baseline data were collected: age, sex, rheumatoid factor (RF) positivity, disease duration (since the time of diagnosis), presence of erosive disease, previous and/or current antirheumatic treatment, comorbidity (e.g., cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, or malignancy), DAS28-ESR[18], HAQ-DI[19], and medication use. The clinical assessments used to determine the DAS28 scores were performed by trained nurses, and the HAQ-DI was completed by the patients themselves. DAS28, HAQ-DI, medication history, and the presence of comorbidities were reassessed at the scheduled clinical visits, usually once every 3 months.

Statistical analysis. The results were analyzed based on an intention-to-treat approach. For that reason, patients were allowed to change treatment during the studied period, yet they were still analyzed in the group in which they originally started: TNFi monotherapy, TNFi + LEF, TNFi + SSZ, TNFi + other csDMARD, TNFi + MTX alone, and TNFi + MTX + other csDMARD. Univariate analysis of baseline variables was performed using ANOVA, the Kruskal-Wallis test, and the chi-square test, depending on distribution and type of data, to detect baseline differences in age, sex, RF positivity, presence of erosions, disease duration, type of TNF blocking agent, amount of previous DMARD, DAS28 at baseline, and HAQ at baseline. ANOVA and chi-square analyses were used to compare the collected baseline data, mentioned in the measurement section, between the groups. The repeated measures for the primary effectiveness (DAS28) and secondary effectiveness (HAQ-DI) were analyzed with linear mixed models. The advantage of using the mixed model approach for the repeated measures within the patients was that all available data could be used, irrespective of some data missing at random[20]. For the mixed model analyses, the autoregression of order 1 covariance structure was used. This structure turned out to be the best fit for these outcome measures when we looked at the -2 restricted log likelihood of the various covariance structures. Kaplan-Meier survival curves and Cox regression were used to analyze differences in drug survival between the 3 treatment groups. Patients were coded as "stopped" when their initial TNFi treatment discontinued. If they restarted the same TNFi treatment within 3 months, this was not seen as a discontinuation. We controlled for potential confounders by factoring the following baseline measurements into our survival and effectiveness analyses: DAS28 and HAQ-DI, age, sex, disease duration, RF, the presence of erosions, the number of previous DMARD, the specific TNFi medication (IFX, ETN, or ADA), and the year of starting TNFi treatment.

RESULTS

Our study included 320 patients who started TNFi monotherapy, 103 SSZ, 80 LEF, 99 csDMARD other than MTX, SSZ, or LEF (42 HCQ, 32 AZA, 9 other csDMARD, 16 a combination of these csDMARD), 919 MTX alone, and 412 MTX + csDMARD (132 SSZ, 198 HCQ, 38 other csDMARD, and 44 > 1 csDMARD). The 6 patient groups differed statistically ($p < 0.05$) in sex, disease duration, age, DAS28 at baseline, HAQ-DI at baseline, and the specific TNFi medications used. These variables were included as a confounding factor in the survival and effectiveness analyses. The patient characteristics at baseline are summarized in Table 1.

Treatment effectiveness. Patients in the TNFi + MTX group had significantly lower DAS28 scores over time versus the

Table 1. Patient characteristics at baseline.

	TNFi Monotherapy, n = 320	TNFi + SSZ, n = 103	TNFi + LEF, n = 80	TNFi + Other csDMARD, n = 99	TNFi + MTX, n = 919	TNFi + MTX + csDMARD, n = 412	p*
Female (%)	74.4	76.7	70.0	69.7	68.6	63.1	0.015
Mean age, yrs (SD)	56.7 (13.0)	56.4 (15.2)	55.2 (12.1)	57.1 (13.2)	55.0 (13.0)	54.7 (12.8)	0.167
Median disease duration, yrs (IQR)	8.01 (2.35–15.4)	5.85 (2.10–11.97)	6.67 (2.08–11.97)	4.83 (1.78–12.22)	4.90 (1.82–11.63)	4.04 (1.11–9.17)	< 0.001
Mean DAS28 (SD)	5.23 (1.32)	5.02 (1.32)	4.91 (1.29)	4.77 (1.40)	4.89 (1.34)	4.79 (1.26)	0.001
Mean HAQ-DI (SD)	1.48 (0.64)	1.41 (0.66)	1.35 (0.67)	1.49 (1.09)	1.30 (0.69)	1.27 (0.64)	< 0.001
RF positivity (%)	67.0	71.8	77.9	70.2	70.7	65.2	0.163
Erosive disease (%)	68.4	59.4	57.4	63.8	66.1	53.1	0.003
No. previous DMARD† (%)							< 0.001
1	7.8	3.9	1.2	6.1	11.4	1.5	
2	25.6	38.8	16.2	21.2	48.4	59.2	
3	23.4	35.0	33.8	24.2	26.0	24.8	
4	21.6	15.5	26.2	20.2	9.1	9.2	
> 4	21.6	6.8	22.5	28.3	5.0	5.3	
TNFi (%)							< 0.001
ADA	33.4	42.7	37.5	35.4	44.6	35.6	
ETN	57.4	50.5	46.2	48.5	41.7	57.3	
IFX	9.1	6.8	16.2	16.2	13.7	7.2	

* p value was the result of ANOVA, Kruskal-Wallis, and chi-squared analyses. † No. csDMARD tried before the start of TNFi treatment. DAS28: Disease Activity Score of 28 joints; HAQ-DI: Health Assessment Questionnaire–Disability Index; IQR: interquartile range; csDMARD: conventional synthetic disease-modifying antirheumatic drug; MTX: methotrexate; TNFi: tumor necrosis factor inhibitor; SSZ: sulfasalazine; LEF: leflunomide; RF: rheumatoid factor.

patients in the TNFi monotherapy group and the TNFi + LEF group (data not shown). Also, after correcting for confounders, the patients in the TNFi + MTX group had significantly lower DAS28 scores over time compared to the patients in the TNFi monotherapy group (β = 0.572; 95% CI 0.411–0.734; p < 0.001) and the TNFi + LEF group (β = 0.297; 95% CI 0.004–0.589; p = 0.047). The DAS28 over time between TNFi + MTX alone and TNFi + MTX + csDMARD (β = 0.089; 95% CI –0.056 to 0.234; p = 0.230) are not significantly different, and neither is the difference between TNFi + MTX and TNFi + SSZ and TNFi + other csDMARD. Moreover, the DAS28 scores in the TNFi monotherapy group differed significantly from the TNFi + SSZ, TNFi + other csDMARD, and TNFi + MTX alone, but not from TNFi + LEF (Figure 1 and Table 2).

The HAQ-DI scores over time also differed significantly between TNFi + MTX and TNFi + LEF for the uncorrected analyses (β = 0.111; 95% CI = 0.005–0.217; p = 0.039), yet they were not significantly different after correction for confounders (β = 0.061; 95% CI –0.104 to 0.225; p = 0.472). TNFi mono and TNFi + MTX did, however, differ significantly with and without correction for confounders (Table 3).

Drug survival. Figure 2 shows Kaplan-Meier drug survival curves for the 3 treatment groups, depicting the time until TNFi therapy was discontinued. Median drug survival for TNFi was 1.5 years in the TNFi monotherapy group, 2.7 years in the TNFi + SSZ group, 2.1 years in the TNFi + LEF group, 3.2 years in the TNFi + other csDMARD, 6.0 years in the TNFi + MTX group, and 5.3 years in the TNFi + MTX + csDMARD group. Using Cox proportional hazard modeling for confounder correction, monotherapy has a significantly worse TNFi drug survival than just MTX (HR 0.467, 95% CI 0.364-0.600, p < 0.001), SSZ (HR 0.647, 95% CI 0.424-0.988, p = 0.044), and other csDMARD (HR 0.451, 95% CI 0.262-0.776, p = 0.004). TNFi + LEF does not differ significantly from TNFi monotherapy (HR 0.643, 95% CI 0.403-1.026, p = 0.064). There were no significant differences in drug survival between TNFi + MTX alone and TNFi + MTX + csDMARD (HR 1.211, 95% CI 0.933-1.572, p = 0.150).

Table 4 presents reasons for a discontinuation of the TNFi treatment. There are no major differences in reasons for stopping TNFi treatment among the various groups. Patients who did stop their TNFi treatment within 4 years were less erosion-positive. The DAS28 and HAQ-DI scores at baseline were higher in the patients who stopped their TNFi treatment within 4 years and on average they used more csDMARD in the past. Age, sex, disease duration, and RF positivity were not significantly different among the groups.

DISCUSSION

The objective of this study was to compare the effectiveness, measured by DAS28 and HAQ-DI, and drug survival of TNFi + various csDMARD combinations. The results showed that combining TNFi with MTX for treating RA resulted in longer improved DAS28 and HAQ-DI scores over time and longer drug survival compared to TNFi monotherapy and TNFi + LEF. TNFi + LEF was not significantly

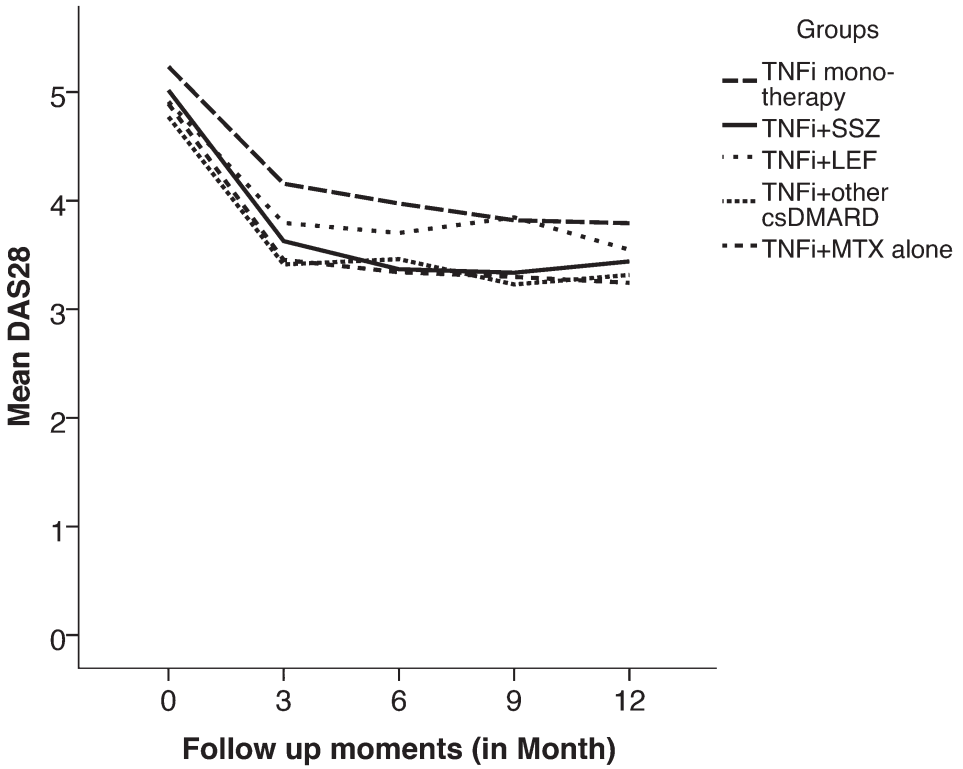

Figure 1. Comparison of the DAS28 levels of the various treatment groups over time. DAS28: 28-joint Disease Activity Score; TNFi: tumor necrosis factor inhibitor; SSZ: sulfasalazine; LEF: leflunomide; csDMARD: conventional synthetic disease-modifying antirheumatic drugs; MTX: methotrexate.

better than monotherapy, as opposed to TNFi + SSZ and TNFi + MTX alone, which were significantly better. TNFi + MTX alone had the same DAS28 score over time and the same drug survival as TNFi + MTX + another csDMARD.

Our findings regarding drug survival are partly consistent with earlier studies[12,21]. In the study by Finckh, *et al,* TNFi + LEF has the same drug survival and frequency of adverse events as TNFi + MTX and TNFi + other csDMARD[14], while other studies are inconclusive about the safety of combining LEF and biological agents[15]. Soliman, *et al* showed significant differences in drug survival between TNFi + MTX alone and TNFi monotherapy, TNFi + SSZ, and TNFi + LEF[12].

Our results about the effectiveness of using TNFi monotherapy, TNFi + various csDMARD, and TNFi + MTX have never been studied before in the daily clinical practice setting and can therefore only be compared with clinical trials. However, the TNFi + various csDMARD groups have not been studied in the original clinical trials. In the original trials, TNFi monotherapy yielded a poorer outcome than TNFi combined with MTX[2,4]. The only study of the effectiveness of IFX and ETN in combination with various csDMARD in daily practice was that of Hyrich, *et al*[11]. They compared 3 groups (TNFi monotherapy, TNFi + csDMARD, and TNFi + MTX). However, ADA was not included, and results at only 1 followup point were presented (6 mos after the start). The study did not consider csDMARD separately. This observational study revealed that IFX and ETN monotherapies are less efficacious than when these drugs are combined with MTX at 6 months after TNFi start, and reported higher effectiveness of TNFi when combined with a non-MTX csDMARD compared to TNFi monotherapy, in terms of the European League Against Rheumatism response criteria[11].

Our study did not show significant differences in longterm drug survival or effectiveness between TNFi + MTX alone compared to TNFi + MTX + csDMARD, while Soliman, *et al* concluded that TNFi with MTX and another csDMARD showed better treatment persistence than TNFi + MTX alone[12]. For that reason, we advise caution when drawing conclusions from these subanalyses. Moreover, further studies from registries or preferably from randomized clinical trials are needed.

Our study had some limitations that warrant discussion. The first limitation is that there is no randomization and therefore possible confounding by indication. We corrected for all measured confounders, but other factors might also have differed between the groups and could have been confounders that we could not correct for. Unfortunately, owing to sample size limitations, no further subanalyses

Table 2. DAS28 over time with and without confounders with linear mixed models and DAS28 baseline as covariate.

	β	95% CI	p
Model without confounder correction			
Intercept	1.538	1.294–1.781	< 0.001
TNFi mono (ref)			
TNFi + SSZ	–0.375	–0.601 to –0.149	0.001
TNFi + LEF	–0.043	–0.290 to 0.204	0.731
TNFi + other csDMARD	–0.372	–0.605 to –0.138	0.002
TNFi + MTX	–0.510	–0.606 to –0.343	< 0.001
Time	–0.029	–0.039 to –0.019	< 0.001
DAS28 at baseline	0.503	0.464–0.543	< 0.001
Model with confounder correction			
Intercept			< 0.001
TNFi mono (ref)			
TNFi + SSZ	–0.420	–0.696 to –0.144	0.003
TNFi + LEF	–0.275	–0.584 to 0.033	0.080
TNFi + other csDMARD	–0.502	–0.806 to –0.198	0.001
TNFi + MTX	–0.572	–0.734 to –0.411	< 0.001
Time	–0.032	–0.041 to –0.022	< 0.001
DAS28 at baseline	0.415	0.359–0.471	< 0.001
Erosive disease negative	0.217	0.071–0.362	0.004
HAQ baseline	0.192	0.074–0.309	0.001
Age	0.016	0.011–0.021	< 0.001
Disease duration	–0.009	–0.017 to –0.000	0.041
Medication: Infliximab (ref)			
Adalimumab	–0.678	–0.869 to –0.488	< 0.001
Etanercept	–0.704	–0.891 to –0.517	< 0.001
Male sex	–0.069	–0.206 to 0.068	0.326
RF-negative	0.103	–0.042 to 0.249	0.164
No. previous DMARD > 4 (ref)			
1	–0.048	–0.336 to 0.239	0.741
2	–0.008	–0.238 to 0.221	0.944
3	0.136	–0.088 to 0.361	0.234
4	0.079	–0.162 to 0.320	0.518
Year of starting TNFi	0.734	0.678 to 0.795	< 0.001

Data are missing for 53.7% of the patients. Patients with missing DAS28 values are equally divided among the groups TNFi monotherapy, TNFi + LEF, TNFi + SSZ, TNFi + MTX, TNFi + other csDMARD, TNFi + MTX + other csDMARD (p value = 0.365). The missing data per measurement timepoints are equally divided among the groups. TNFi: tumor necrosis factor inhibitor; MTX: methotrexate; SSZ: sulfasalazine; LEF: leflunomide; csDMARD: conventional synthetic disease-modifying antirheumatic drugs; ref: reference; HAQ: Health Assessment Questionnaire; DAS28: 28-joint Disease Activity Score; RF: rheumatoid factor.

could be performed in this study. For example, it would be interesting to study the differences among TNFi + LEF, TNFi + HCQ, and TNFi + SSZ, compared to TNFi monotherapy or TNFi + MTX, etc. in the separate TNFi treatments (ADA, ETN, IFX). Further research will be necessary to draw conclusions about those subgroups.

Based on our results, and in the context of previously published studies, we conclude that combining MTX with a TNFi yields the best outcome in terms of effectiveness and drug survival in patients with RA who are starting their first TNFi treatment. We also conclude that TNFi monotherapy is less efficacious than TNFi + non-MTX csDMARD combination therapy, although for TNFi + LEF the results are inconclusive. We recommend prescribing TNFi in combination with MTX whenever possible. If this is not possible, another csDMARD seems to be a good alternative and preferred over monotherapy, although we have not proven better effectiveness and longer drug survival of TNFi + LEF. Adding other csDMARD to the TNFi + MTX combination does not seem to add to effectiveness and drug survival.

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Table 3. HAQ-DI over time with and without confounders with linear mixed models and HAQ-DI baseline as covariate.

	β	95% CI	p
Model without confounder correction			
Intercept	0.294	0.218–0.370	0.000
TNFi mono (ref)			
TNFi + SSZ	–0.084	–0.187 to 0.019	0.108
TNFi + LEF	–0.024	–0.138 to 0.090	0.680
TNFi + other csDMARD	–0.138	–0.246 to –0.031	0.012
TNFi + MTX	–0.135	–0.195 to –0.076	0.000
Time	–0.004	–0.007 to –0.000	0.038
HAQ-DI at baseline	0.650	0.616–0.683	0.000
Model with confounder correction			
Intercept	–0.018	–0.212 to 0.176	0.856
TNFi mono (ref)			
TNFi + SSZ	–0.050	–0.163 to 0.063	0.385
TNFi + LEF	0.006	–0.119 to 0.130	0.931
TNFi + other csDMARD	–0.096	–0.219 to 0.027	0.125
TNFi + MTX	–0.086	–0.151 to –0.019	0.011
Time	–0.004	–0.008 to 0.000	0.057
HAQ-DI at baseline	0.709	0.661–0.757	0.000
Erosive disease negative	0.081	0.021–0.142	0.008
DAS28 at baseline	–0.027	–0.051 to –0.004	0.022
Age	0.007	0.005–0.009	0.000
Disease duration	0.006	0.002–0.009	0.001
Medication: Infliximab (ref)			
Adalimumab	–0.069	–0.148 to 0.010	0.086
Etanercept	–0.068	–0.145 to 0.010	0.088
Male sex	–0.067	–0.123 to –0.011	0.019
RF-negative	0.048	–0.011 to 0.107	0.112
No. previous DMARD > 4 (ref)			
1	–0.115	–0.232 to 0.002	0.054
2	–0.081	–0.175 to 0.013	0.092
3	–0.070	–0.162 to 0.021	0.133
4	–0.000	–0.099 to 0.098	0.992
Year of start TNFi	–0.001	–0.017 to 0.013	0.811

TNFi: tumor necrosis factor inhibitor; MTX: methotrexate; SSZ: sulfasalazine; LEF: leflunomide; csDMARD: conventional synthetic disease-modifying antirheumatic drugs; ref: reference; HAQ-DI: Health Assessment Questionnaire–Disability Index; DAS28: 28-joint Disease Activity Score; RF: rheumatoid factor.

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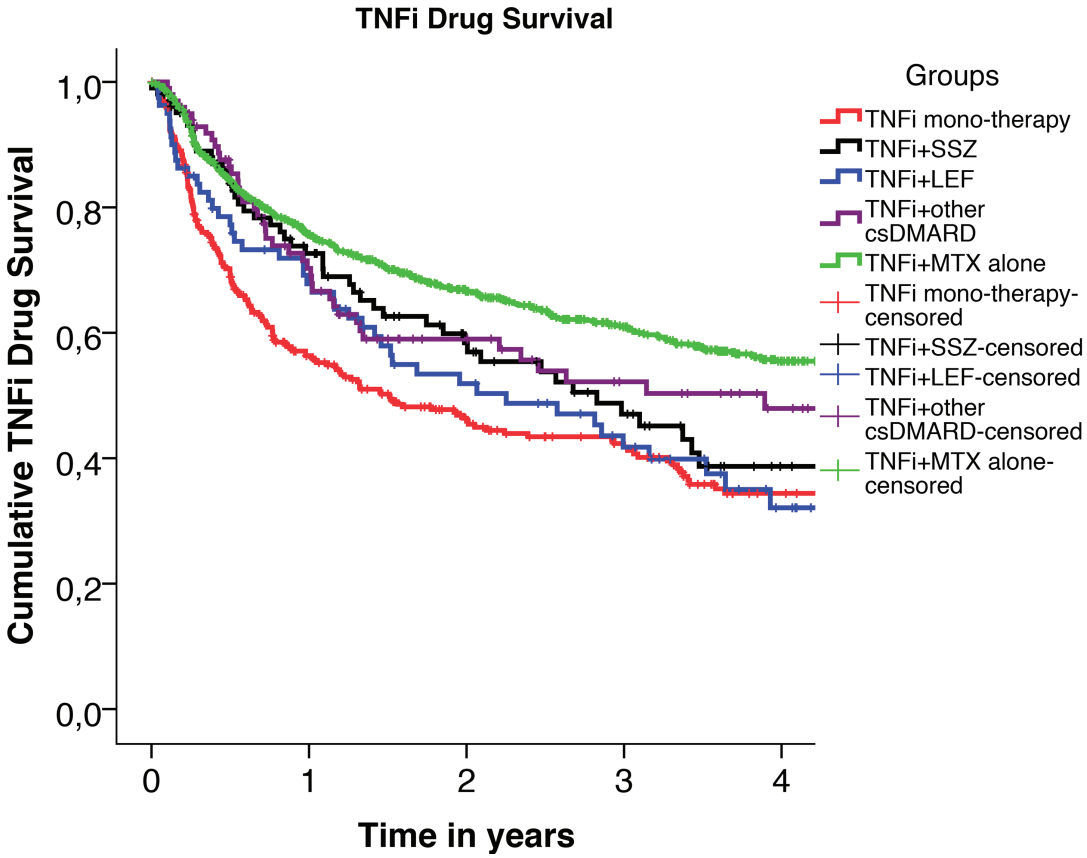

Figure 2. Kaplan-Meier drug survival curves for the 3 treatment groups, depicting the time until tumor necrosis factor inhibitor (TNFi) therapy was discontinued. SSZ: sulfasalazine; LEF: leflunomide; csDMARD: conventional synthetic disease-modifying antirheumatic drugs; MTX: methotrexate.

Table 4. Reasons to discontinue TNFi treatment per treatment group. All data are percentages.

Reasons to Discontinue TNFi	Monotherapy 181/320	SSZ 48/103	LEF 46/80	Other csDMARD 42/99	MTX Alone 347/919	MTX+ csDMARD 159/412
Side effects	42.9	51.4	54.5	48.8	43.4	45.6
Ineffectiveness	50.6	48.6	43.2	46.3	50.6	52.4
Ineffectiveness and side effects	6.5	0.0	2.3	4.9	6.0	2.0

TNFi: tumor necrosis factor inhibitor; MTX: methotrexate; SSZ: sulfasalazine; LEF: leflunomide; csDMARD: conventional synthetic disease-modifying antirheumatic drugs.

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