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ABSTRACT (250/250 words)

Objective. Evaluate long-term drug survival (proportion of patients still receiving treatment) and discontinuation of etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab using observational data from patients with rheumatoid arthritis.

Methods. Following a systematic literature review, drug survival at 12 and 12–24 months of follow-up was estimated by summing proportions of patients remaining on treatment and dividing by number of studies. Drug survival at ≥36 months of follow-up was estimated via Metaprop.

Results. 170 publications were included. In the first-line setting, drug survival at 12 months with etanercept, infliximab, or adalimumab was 71%, 69%, and 70%, respectively, while at 12–24 months the corresponding rates were 63%, 57%, and 59%. In the second-line setting, drug survival at 12 months with etanercept, infliximab, or adalimumab was 61%, 69%, and 55%, respectively, while at 12–24 months the corresponding rates were 53%, 39%, and 43%. Drug survival at ≥36 months with etanercept, infliximab, or adalimumab in the first-line setting was 59% (95% confidence interval [CI]: 46–72%), 49% (95% CI: 43–54%), and 51% (95% CI: 41–60%), respectively, while in the second-line setting the corresponding rates were 56% (95% CI: 52–61%), 48% (95% CI: 40–55%), and 41% (95% CI: 36–47%). Discontinuation of etanercept, infliximab, and adalimumab at 36 months of follow-up was 38–48%, 42–62%, and 38–59%, respectively. Data on certolizumab pegol and golimumab were scarce.

Conclusion. After >12 months of follow-up, more patients with rheumatoid arthritis receiving etanercept remain on treatment compared with other TNFi.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent inflammation of the joints that negatively impacts a patient's physical functioning and quality of life [1,2]. The direct and indirect costs associated with RA are considerable and long term, with continued treatment being crucial for maintaining disease remission and maximizing the cost-effectiveness of therapy [3]. Treatment of RA is predominantly focused on controlling inflammation and pain, as well as slowing the progression of joint destruction and disability. A range of therapeutic agents have been approved for treating RA, including: corticosteroids (e.g. methylprednisolone, prednisone, and prednisolone); conventional synthetic disease-modifying antirheumatic drugs (csDMARDs, e.g. methotrexate, hydroxychloroquine, leflunomide, and sulfasalazine); biologic agents that inhibit tumor necrosis factor (TNF) or other important mediators of the inflammatory pathway, such as the IL-6 receptor (e.g. tocilizumab and sarilumab), CD20 (e.g. rituximab), and CTLA-4 (e.g. abatacept); targeted synthetic DMARDs (tsDMARDs; tofacitinib, baricitinib); and biosimilar versions of some of these agents.

The introduction of TNF inhibitors (TNFi) led to a profound improvement in outcomes for patients with RA [4]. The first TNFi to be approved for treating RA was etanercept in 1998, and this was followed by the approvals of infliximab, adalimumab, certolizumab pegol, and golimumab. Discontinuation of TNFi treatment is usually reported to be due to a loss or lack of efficacy or incident adverse events (AEs) [5,6]. The evaluation of survival times and discontinuation rates associated with each of the specific TNFi agents is necessary when evaluating their real-world effectiveness and cost-effectiveness [7,8]. Randomized controlled trials are relatively short compared with the chronic course of RA and therefore real-world studies and clinical registries with longer patient follow-up can be very useful for assessing health care resource utilization in the long-term management of the disease.

Previous studies that compared the drug survival (i.e. the proportion of patients still receiving treatment at a specific time point) of etanercept, infliximab, and adalimumab in patients with RA reported conflicting results. Two US studies that utilized data from the CORRONA registry and a US insurance database for the years 2000–2005 showed that infliximab had the highest drug survival [9,10]. Several European studies, however, reported a shorter drug survival for infliximab compared with etanercept and adalimumab, while other studies have reported no difference among these 3 TNFi [6,11-17]. To the authors' knowledge, there has been no previous analysis that compared drug survival for all 5 currently approved TNFi. Therefore, we conducted a systematic literature review and meta-analysis with the aim of: 1) identifying all publications reporting the long-term drug survival of etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab in observational studies of patients with RA; and 2) evaluating the rates of drug survival and discontinuation in patients with RA after ≥12 months of follow-up.

MATERIALS AND METHODS

Literature search

Relevant publications were identified using an approach that followed the Cochrane dual-reviewer methodology and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol (PRISMA-P) guidelines [18]. The search was conducted in November 2017 using Embase®, MEDLINE®, the Cochrane Central Trials Register and Database of Systematic Reviews, other Cochrane Library databases, and PubMed, with no restrictions on language or the year of publication. Abstracts presented at the annual meetings of the American College of Rheumatology and European League Against Rheumatism in 2016 and 2017 were also searched. The search terms included, but were not restricted to: rheumatoid arthritis, cohort, longitudinal, etanercept, infliximab, adalimumab, certolizumab pegol,

golimumab, Flixabi®, Renflexis®, Inflectra®, Remsima®, Amjevita®, Cyltezo®, Imraldi®, Benepali®, and Erelzi®. The reference lists of relevant review articles were also searched.

Articles and conference abstracts published in English and reporting data from observational studies in humans were included, while reports on studies with ≤10 participants or with a follow-up duration <12 months were excluded. Publications reporting data from preclinical studies or randomized or non-randomized clinical trials were excluded, as were reviews, guidelines, expert opinions, and case reports. Studies that only reported discontinuations due to treatment switching were also excluded. The publications used a variety of alternative terms to describe drug survival (i.e. the proportion of patients still receiving treatment at a specific time point), including 'retention', 'persistence', and 'continuation', and these were considered equivalent for the present analysis. The term 'drug adherence' was not considered equivalent and data on adherence were not included.

Screening and quality assessment of published studies

Publications identified in the literature search were screened by 2 reviewers in a 2-step process: titles and abstracts were first screened against the pre-specified inclusion and exclusion criteria to identify eligible publications, and then the same reviewers used the same pre-specified criteria to screen the full text of each of the eligible publications. The opinion of a third reviewer was obtained in the event of any disagreement between the 2 reviewers.

The included publications all described non-randomized, observational studies and therefore their quality was assessed using the Newcastle–Ottawa instrument [19]. The quality of conference abstracts was assessed using the modified Downs and Black instrument [20].

Data extraction and synthesis

Data were extracted from the publications by 1 reviewer and validated by a second reviewer. Drug survival was defined as the average proportion of patients still receiving treatment at 12 and 24 months of follow-up, and was estimated for each TNFi by summing the percentages reported by each publication and dividing this by the number of studies reporting data. Drug survival at ≥36 months of follow-up was estimated via meta-analysis using Metaprop (Stata/IC 15.1 for Windows, StataCorp, College Station, TX, USA). Briefly, the Metaprop procedure pools values that are proportions and then presents weighted-subgroup and overall-pooled estimates with inverse-variance weights obtained from a random-effects model.

An exploratory analysis of the survival rates of TNFi monotherapy versus TNFi with concomitant DMARD was also conducted. Data from studies reporting that TNFi treatment was concomitant with methotrexate were pooled with those from studies in which the concomitant DMARD was not reported. Data from any treatment arm that had >85% concomitant DMARD use were included if they were reported for a time point of interest. The estimates at each time point were made regardless of TNFi treatment line in order to include the maximum number of studies possible.

RESULTS

Identification of publications

The initial search yielded a total of 4412 publications (**Figure 1**). Subsequent screening resulted in 170 publications being included in the analysis: 133 full articles and 37 conference abstracts (see **Supplementary Table 1** for a complete reference list). The key characteristics of the studies described in the 170 publications are summarized in **Table 1**. Of the 133 full articles identified, the quality of all except 4 was rated as either ‘excellent’ or ‘good’, with the remaining 4 rated as ‘fair’. Among the 37

conference abstracts, the quality of the majority (26) was rated as 'fair', with 6 rated as 'good' and 5 rated as 'poor'.

Clearly overlapping patient data derived from 6 data sources were reported in 14 of the 170 publications. It was clear from 3 of these 6 sources that identical patient groups were described in the associated publications and therefore only 1 of the publications based on each of these 3 sources was included in the analysis of drug survival and discontinuations. For the remaining 3 sources, all associated publications were included because the results from the overlapping patients could not be separated from the other patients in those studies. There were 64 publications originating from 25 data sources for which the extent of overlap between patient groups within the reported results was unclear. These 64 publications were treated as separate data sets for the analysis of drug survival and discontinuations.

There were only 2 of the 170 identified publications that reported data on biosimilar forms of TNFi. These two publications were both abstracts from 2017, with one describing data obtained following switching of patients from originator to biosimilar forms of etanercept and infliximab [21] and the other reporting data on a biosimilar form of etanercept evaluated in the DANBIO study [22].

Baseline characteristics of the patient populations

The size of the patient populations described in the 170 publications identified in the literature search ranged from 18 to 17,405 patients, with a mean or median follow-up time ranging from 12 months to 12 years. The majority of the studies included a greater proportion of women than men (typically 70–90% women), and the majority reported a baseline mean or median age in the range of 50–60 years. Data on patient race and/or ethnicity were reported in 9 publications. The mean or median duration of disease at baseline ranged from 2.4 to 18.5 years. The majority of publications (96/170) did not report previous

DMARD use. There was 1 publication that reported all patients (100%) were DMARD-naïve, while 4 publications reported prior DMARD use in 1–50% of participants, 19 publications reported prior DMARD use in 51–90% of participants, and 50 publications reported that 90–100% of the patients involved were DMARD-experienced. Approximately half of the publications that reported prior biologic DMARD experience (48/104) stated that 100% of the patients were naïve to treatment with biologic DMARDs.

Data on baseline Disease Activity Score in 28 joints (DAS28) were inconsistent in terms of representing mean or median values, as well as in terms of presenting overall scores for all treatments versus scores separated according to specific TNFi. The minimum reported mean (standard deviation [SD]) DAS28 was 2.5 (0.7) and the maximum mean (SD) DAS28 was 7.3 (1.1). At baseline, the minimum median (interquartile range) Health Assessment Questionnaire (HAQ) score was 0.9 (0.4 to 1.4) and the maximum mean (SD) HAQ score was 2.1 (0.6). Please see Supplemental Materials for additional details on the baseline characteristics of the patient populations and the number of publications that reported these.

Drug survival of TNFi

There were 8 of the 170 publications that did not report sufficient data to be included in the analysis of drug survival and discontinuations, and therefore these endpoints were evaluated from a total of 162 publications. Among these 162 publications, 51 did not report drug survival data, 1 reported the drug survival rate but not the length of follow-up, and 1 reported mortality only. Therefore, there were 109 publications from which drug survival rates could be estimated: 28 that reported follow-up data at 12 months only; 20 that reported a follow-up >12 months but <36 months; and 61 that reported a follow-up ≥36 months (1 study reported a follow-up of 35 months and was included in the ≥36 months group).

In the first-line treatment setting, the survival rates of the 5 TNFi ranged from 62% to 71% at 12 months and 57% to 72% at 12–24 months of follow-up. In the second-line treatment setting, the survival rates ranged from 55% to 69% (no rate was reported for certolizumab pegol) at 12 months and 38% to 57% at 12–24 months of follow-up (**Table 2**).

After excluding publications that did not separate data into specific treatment lines, data from 36 publications were pooled for an exploratory meta-analysis of TNFi survival at ≥36 months. Estimates of drug survival for certolizumab pegol (no publications) and golimumab (1 publication) were not calculated due to a lack of data. The highest rate of drug survival in the first-line treatment setting was in the etanercept group (59%, 95% confidence interval [CI]: 46–72%), followed by adalimumab (51%, 95% CI: 41–60%) and then infliximab (49%, 95% CI: 43–54%) (**Figure 2A**). The etanercept group also displayed the highest rate of drug survival at ≥36 months in the second-line setting (56%, 95% CI: 52–61%), followed by infliximab (48%, 95% CI: 40–55%) and then adalimumab (41%, 95% CI: 36–47%) (**Figure 2B**).

There were 25 publications that reported drug survival rates at 48 months, with the rates reported showing a wide range. Drug survival with etanercept in the first-line setting ranged from 23% to 69% in 15 of the 17 publications reporting data on this agent, with the remaining 2 publications reporting rates of 3% and 95%. First-line drug survival with adalimumab ranged from 27% to 54% in 13 of the 15 publications reporting data on this agent, with the remaining two publications reporting rates of 4% and 100% (the same 2 publications that also reported the much lower and much higher rates for etanercept). Drug survival with infliximab in the first-line setting ranged from 18% to 79% in the 20 publications reporting data on this agent. One publication reported a first-line survival rate of 86% for golimumab. There were 4 studies that reported survival rates at 48 months of follow-up in the second-

line setting, with rates of 42% to 55% for etanercept, 25% to 41% for adalimumab, and 37% to 39% for infliximab.

Exploratory analysis of TNFi survival rates in patients receiving adalimumab, etanercept, or infliximab monotherapy showed that etanercept had the highest survival rate at each time point evaluated (**Table 3**). Drug survival rates in patients receiving TNFi with concomitant DMARD were also highest in those who received etanercept for each time point evaluated, except at 12 months when a slightly higher rate was observed with infliximab and the highest rate was observed in the much smaller number of patients who received golimumab. There was a trend towards improved drug survival in patients who received a TNFi with concomitant DMARD compared with those who received TNFi monotherapy at each time point evaluated, except in the case of adalimumab at 48 months. Drug survival in the 2 groups (TNFi monotherapy and TNFi with concomitant DMARD) at 36 months was investigated via meta-analysis, with the data showing that survival rates, both with or without concomitant DMARD, were higher with etanercept than with adalimumab or infliximab (**Figure 3**). There was a trend towards similar or lower drug survival rates in patients receiving etanercept, infliximab, or adalimumab monotherapy compared with those who received 1 of these TNFi with concomitant DMARD. There was significant heterogeneity among the studies included in the meta-analysis, with the inclusion of data on any TNFi treatment line at each time point being one potentially important contributing factor.

Discontinuation of TNFi treatment

Among the 162 publications included in the analysis of outcomes, there were 134 that reported data on a measure of treatment discontinuation. Of these 134 publications, 37 did not report data suitable for the analysis because they presented either a combined group of all TNFi, treatment switching only,

deaths only, discontinuations according to treatment courses only and not according to individual patients, or data for which the time frame of the discontinuations was not clear.

At 36 months of follow-up, infliximab treatment was associated with the highest rate of total discontinuations (42% to 62%), followed by adalimumab (38% to 59%), and then by etanercept (38% to 48%) and golimumab (35%, derived from a single study involving 109 patients). With regard to discontinuations due to AEs at 36 months of follow-up, patients receiving etanercept displayed a lower rate of discontinuation (8% to 16%; 3 publications) than those who received adalimumab (8% to 26%; 7 publications) or infliximab (15% to 27%; 7 publications). Six publications (1 for etanercept and 5 for infliximab) reported the proportion of patients experiencing an infection that resulted in TNFi discontinuation, across any treatment line, for follow-up times ≥36 months. Follow-up times varied considerably among these 6 publications (36–120 months), which limited formal comparison. There were 10 publications that reported discontinuations due to inefficacy at 36 months of follow-up, and these ranged from 12% to 15% for etanercept, 5% to 24% for infliximab, and 11% to 33% for adalimumab.

DISCUSSION

The present analysis of 133 full publications and 37 conference abstracts included a total of 270,000 patients with RA and shows that treatment with etanercept is associated with the highest rate of drug survival among the 5 TNFi agents currently approved for treating the disease. Etanercept was also associated with the lowest rate of treatment discontinuation. The results from the present analysis are consistent with data published in recent systematic reviews by Aroro et al and Souto et al [23,24], although the present analysis goes further than these studies by reporting data from both first- and second-line treatment settings, and by including data on certolizumab pegol and golimumab albeit to a

limited extent due to a lack of published data on these 2 agents. Evidence-based insight into the drug survival and discontinuation rates associated with each of the specific TNFi agents is key when evaluating the real-world effectiveness and cost-effectiveness of these agents when used in long-term dosing paradigms for chronic conditions such as RA [7,8]. Within an environment of increasing pressure on health care budgets, data on drug survival can help inform decision-making aimed at achieving optimal disease outcomes while limiting costs, and this is especially important in countries that limit the number of biologic DMARDs reimbursed.

Discontinuation of TNFi treatment in patients with RA is most commonly reported to be due to a loss or lack of treatment efficacy and/or due to incident AEs, although it can also occur due to patients achieving remission and wishing to reduce their drug exposure, as well as potentially being part of the preparation for receiving surgery or a live vaccine. The higher rates of drug survival with etanercept demonstrated in the present analysis may be explained, at least in part, by the lower reported incidence of anti-drug antibody development when compared with infliximab and adalimumab [25], and/or the potentially lower incidence of serious infections in patients treated with etanercept [26], although data on rates of infection with the various TNFi are complex to interpret and compare [27]. It is possible that the underlying cause of the variability in the safety profiles of the currently approved TNFi agents is due to fundamental differences in their biochemistry, which may result in each of them modifying TNF-mediated signaling in a subtly different way as well as conferring on each a slightly different pharmacokinetic and pharmacodynamic profile.

The key strengths of the present analysis are the large number of publications that were reviewed and the systematic and broad approach that was adopted in order to obtain the data, which were derived entirely from long-term observational studies of TNFi in patients with RA. As well as being a strength of

the analysis, the observational nature of the data was also a limitation in that a comparison of the clinical outcomes achieved with the 5 different TNFi was not possible. Another limitation is the possibility that some of the patients may have been double-counted when identical or similar data were reported within multiple publications included in the analysis. A final limitation is that there were very few data available for either certolizumab pegol or golimumab for some of the variables evaluated despite both of these agents having received regulatory approval from the US FDA 9 years ago.

In conclusion, patients with RA who receive etanercept are more likely to remain on treatment and less likely to discontinue treatment after >12 months of follow-up when compared with those receiving other TNFi.

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FIGURE LEGENDS

Figure 1. Identification of relevant published articles via systematic literature review.

RA: rheumatoid arthritis; TNFi: tumor necrosis factor inhibitor.

Figure 2. Exploratory meta-analysis of drug survival at ≥36 months for first-line (A) and second-line (B) TNFi treatment in patients with RA.

The vertical, broken line represents the mean of the pooled treatment effect from the random-effect analysis, across all studies and regardless of treatment. Diamonds represent the upper and lower 95% confidence interval around the pooled treatment effect. RA: rheumatoid arthritis; TNFi: tumor necrosis factor inhibitor.

Figure 3. Exploratory meta-analysis of drug survival at 36 months in patients with RA and receiving either TNFi monotherapy or TNFi with concomitant DMARD.

The vertical, broken line represents the mean of the pooled treatment effect from the random-effect analysis, across all studies and regardless of treatment. Diamonds represent the upper and lower 95% confidence interval around the pooled treatment effect. DMARD: disease-modifying antirheumatic drug; RA: rheumatoid arthritis; TNFi: tumor necrosis factor inhibitor.

Table 1. Key characteristics of published studies included after the screening process.

Study characteristic	Number of included publications, n (%) [N=170]
Geographic region	
Asia	27 (16)
Australia	2 (1)
Europe	99 (58)
North America	37 (22)
South America	5 (3)
Study design	
Registry	58 (34)
Local registry	4 (2)
Retrospective cohort	33 (19)
Prospective cohort	30 (18)
Prospective and retrospective cohort	1 (1)
Cohort (design not reported)	3 (2)
Claims database	25 (15)
Chart review	7 (4)
Clinical records	6 (4)
Not reported	3 (2)
Biologic DMARD intervention	
Adalimumab	111 (65)
Certolizumab pegol	18 (11)

Etanercept	118 (69)
Golimumab	37 (22)
Infliximab	118 (69)
Biologic DMARD treatment line*	
1st only	88 (52)
1st or later line**	9 (5)
2nd only	26 (15)
2nd and 3rd	3 (2)
2nd or later line†	5 (3)
3rd only	2 (1)
3rd or later line†	2 (1)
4th, 5th, and 6th	1 (<1)
Continuing†	1 (<1)
Mixed lines	27 (16)
Not specified‡	51 (30)
Endpoints of interest reported	
Drug survival	119 (70)
Discontinuation	134 (79)
Anti-drug antibodies	12 (7)
Economic evaluation	20 (12)
*Total number of publications sums to >170 and percentages do not sum to 100% because some publications report data for >1 biologic treatment line and are counted twice.	

**Publications in which data are reported as 1st–2nd, 1st–3rd, or 1st–4th line.

†The number of subsequent treatment lines was not reported in some publications.

‡Three publications reported a treatment line, the number of which was not specified, followed by a subsequent line (not specified+1).

DMARD: disease-modifying antirheumatic drug.

Table 2. Unweighted average TNFi survival rates in patients with RA.

TNFi	1st treatment line, % survival		2nd treatment line, % survival	
	12 months follow-up	12–24 months follow-up	12 months follow-up	12–24 months follow-up
Adalimumab	70 [n = 17,783]	59 [n = 11,616]	55 [n = 1341]	43 [n = 1061]
Certolizumab pegol	62 [n = 26]	72 [n = 628]	Not reported	38 [n = 253]
Etanercept	71 [n = 25,344]	63 [n= 15,587]	61 [n = 1005]	53 [n = 810]
Golimumab	63 [n = 85]	68 [n = 339]	66 [n = 51]	57 [n = 282]
Infliximab	69 [n = 15,685]	57 [n = 12,796]	69 [n = 723]	39 [n = 349]

TNFi: tumor necrosis factor inhibitor.

Table 3. Unweighted average TNFi survival rates according to concomitant DMARD use (all treatment lines included).

Treatment regimen	12 months follow-up, % survival	24 months follow-up, % survival	48 months follow-up, % survival
TNFi monotherapy			
Adalimumab	59 [n = 2631]	48 [n = 2751]	44 [n = 2661]
Etanercept	72 [n = 4662]	55 [n = 4886]	46 [n = 4637]
Infliximab	56 [n = 3211]	37 [n = 3272]	30 [n = 3127]
Combination therapy			
Adalimumab + concomitant DMARD	68 [n = 1389]	59 [n = 903]	42 [n=525]
Etanercept + concomitant DMARD	73 [n = 6105]	66 [n = 1806]	51 [n = 1129]
Golimumab + concomitant DMARD	88 [n = 139]	Not reported	Not reported
Infliximab + concomitant DMARD	76 [n = 4468]	56 [n = 3551]	38 [n = 2854]
DMARD: disease-modifying antirheumatic drug; TNFi: tumor necrosis factor inhibitor.			

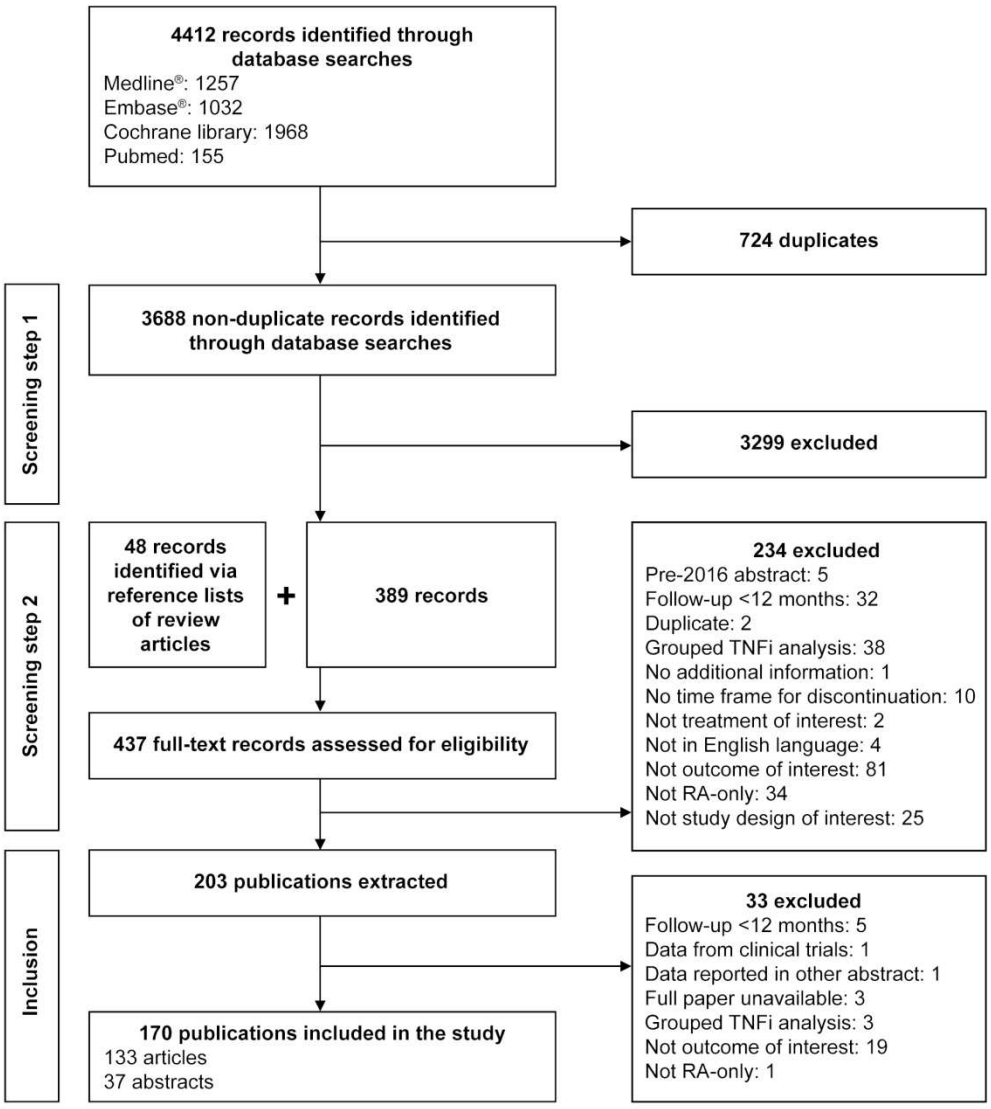

Figure 1. Identification of relevant published articles via systematic literature review. RA: rheumatoid arthritis; TNFi: tumor necrosis factor inhibitor.

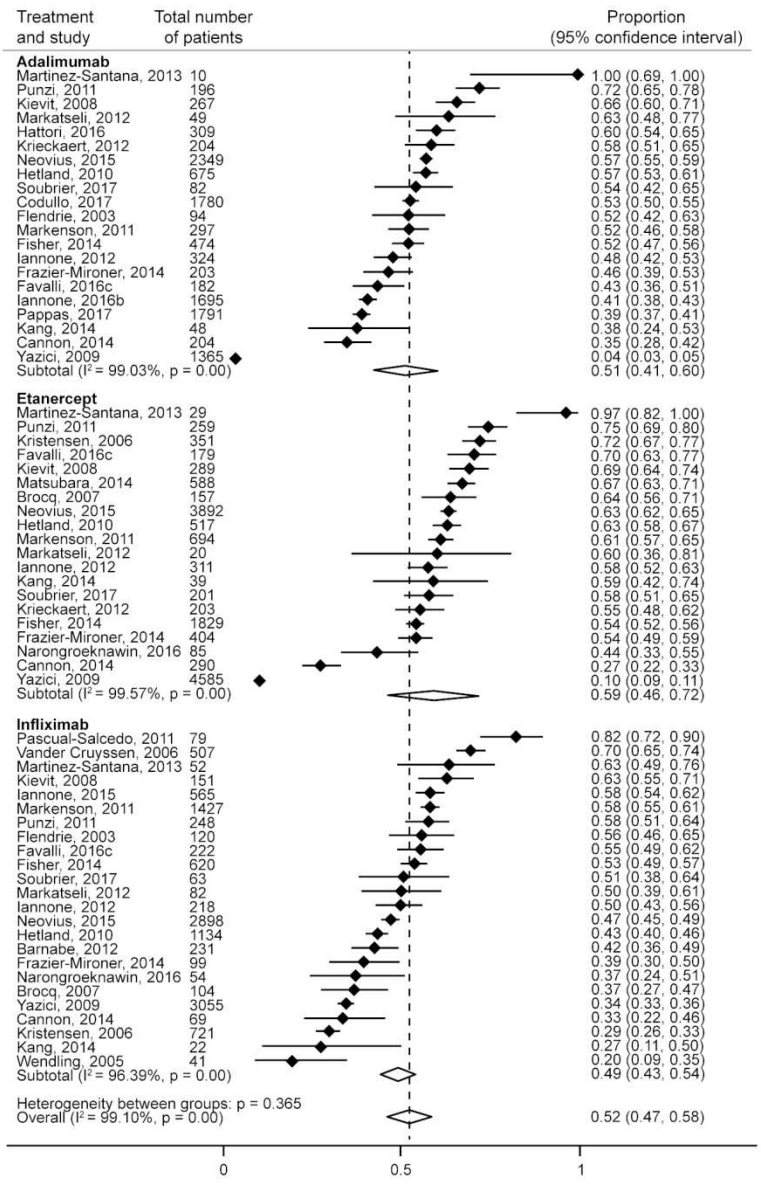

Figure 2A. Exploratory meta-analysis of drug survival at ≥36 months for first-line (A) and second-line (B) TNFi treatment in patients with RA.

The vertical, broken line represents the mean of the pooled treatment effect from the random-effect analysis, across all studies and regardless of treatment. Diamonds represent the upper and lower 95% confidence interval around the pooled treatment effect. RA: rheumatoid arthritis; TNFi: tumor necrosis factor inhibitor.

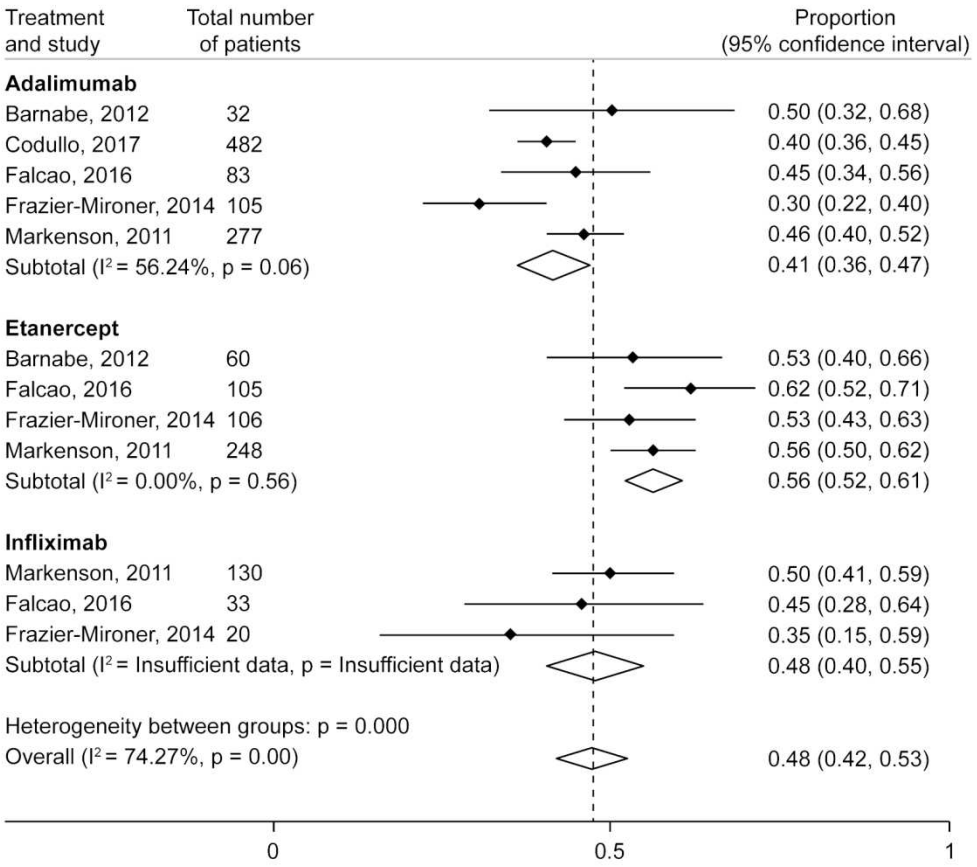

Figure 2B. Exploratory meta-analysis of drug survival at ≥36 months for first-line (A) and second-line (B) TNFi treatment in patients with RA.
The vertical, broken line represents the mean of the pooled treatment effect from the random-effect analysis, across all studies and regardless of treatment. Diamonds represent the upper and lower 95% confidence interval around the pooled treatment effect. RA: rheumatoid arthritis; TNFi: tumor necrosis factor inhibitor.

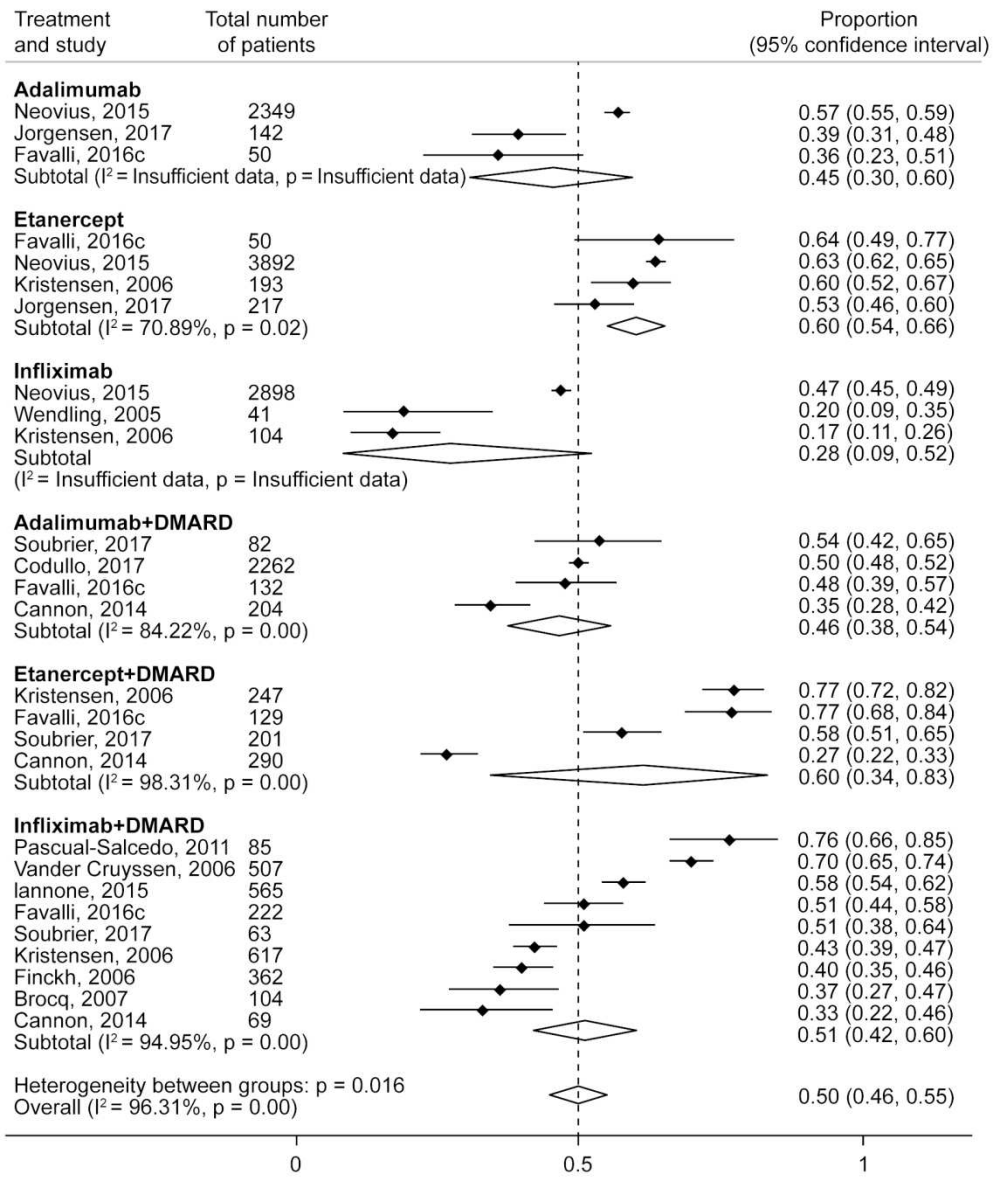

Figure 3. Exploratory meta-analysis of drug survival at 36 months in patients with RA and receiving either TNFi monotherapy or TNFi with concomitant DMARD.
The vertical, broken line represents the mean of the pooled treatment effect from the random-effect analysis, across all studies and regardless of treatment. Diamonds represent the upper and lower 95% confidence interval around the pooled treatment effect. DMARD: disease-modifying antirheumatic drug; RA: rheumatoid arthritis; TNFi: tumor necrosis factor inhibitor.