Remission in rheumatoid arthritis patients treated with etanercept monotherapy: clinical practice and clinical trial experience

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Abstract

Objective

To assess, in a randomised controlled trial (RCT) and in clinical practice, an association of time to remission and baseline disease activity with both induction of remission and sustained remission in etanercept-treated patients with rheumatoid arthritis (RA).

Methods

Data from an RCT (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes [TEMPO]; n=682) and an observational registry (Rheumatoid Arthritis DMARD Intervention and Utilization Study [RADIUS II]; n=4341) were used to evaluate disease activity (Clinical Disease Activity Index [CDAI] score) over time in patients initiating etanercept (monotherapy or with methotrexate). CDAI remission (CDAI≤2.8) and sustained remission (≥6 months) were determined through year 3 by treatment group, study, time to remission, and disease severity.

Results

Patients from TEMPO and RADIUS II who received etanercept monotherapy showed similar CDAI remission rates (39% and 35%, respectively, at 3 years). Among patients who received etanercept with methotrexate, remission rates were 54% and 36%, respectively. Remission occurred more rapidly in TEMPO than RADIUS II perhaps from differences in compliance, patient populations, or sequence of combination therapy initiation. Generally, more patients with lower baseline CDAI scores achieved remission than those with higher scores. Continued remission appeared more likely in patients achieving remission earlier in the course of their therapy (0-6 months).

Conclusion

Remission by year 3 in etanercept-treated (with and without methotrexate) patients with RA occurred in ≥35% of patients in both an RCT (TEMPO) and a clinical practice setting (RADIUS II), and more frequently in those with lower baseline disease severity. Patients with lower RA disease activity were more likely to reach remission. Continued remission may be more likely in patients who achieved remission earlier.

Key words

rheumatoid arthritis, remission, etanercept, TEMPO, RADIUS

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G.W. Cannon has received research grant support from Amgen as an investigator in the RADIUS II study;
B.C. Wang, G.S. Park, and D.H. Collier are employees and own Amgen stock;
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Introduction

Rheumatoid arthritis (RA) affects approximately 0.5% to 1% of the overall population (1). Chronic inflammation due to RA is associated with loss of function, joint damage, and increased mortality in patients (2-5). Treatment guidelines for RA currently focus on controlling disease activity and striving to achieve clinical remission (or low disease activity if clinical remission is not feasible), in addition to recommending preservation of function and prevention of long-term joint damage with earlier intervention (6-8). The newest evolution of the clinical goals is to use the absolute number of tender/swollen joints as well as acute phase reactants ≤1 to assess outcomes, underlining the desire to push for the lowest level of clinical disease activity using the Clinical Disease Activity Index (CDAI) or Boolean American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) remission definitions.

Etanercept is a fully human dimeric fusion protein of tumour necrosis factor receptor and the Fc domain of immunoglobulin G (IgG1) (9). The tolerability and efficacy of etanercept, alone and in combination with the disease-modifying anti-rheumatic drug (DMARD) methotrexate, have been demonstrated in randomised clinical trials of patients with RA (10-14), including the double-blind, randomised, controlled Trial of Etanercept and Methotrexate With Radiographic Patient Outcomes (TEMPO) (12). Additionally, the long-term effectiveness of etanercept was described in the Rheumatoid Arthritis Disease-Modifying Anti-rheumatic Drug Intervention and Utilization Study (RADIUS), comprised of 2 prospective, 5-year, multicentre, observational registries that enrolled >10,000 patients with RA and assessed use patterns, effectiveness, and safety of DMARDs and biologics (15, 16).

In this analysis, we examined the influence of etanercept on the induction of clinical remission and time to remission in patients with RA who initiated etanercept either as monotherapy (without other background DMARD therapy) or in combination with concurrent existing or new methotrexate therapy in a clinical trial and routine clinical practice settings. Patients in the RADIUS II observational registry initiated etanercept either as monotherapy (without other background DMARD therapy) or in combination with concurrent existing or new DMARD therapy (15, 16). Patients in the TEMPO study initiated etanercept either as monotherapy or in combination with methotrexate therapy, which was newly initiated in the majority of enrolled patients (12).

Methods

Patient populations

TEMPO

Methodologic details of TEMPO have been described previously (12). Briefly, eligible patients (aged ≥18 years) in this multicentre, double-blind, randomised clinical trial were enrolled between October 2000 and July 2001 in Europe, Australia, and Israel (17). Patients had disease durations of 4 months to 26 years; adult-onset RA (American College of Rheumatology functional class I–III), defined as ≥10 swollen joints, ≥12 tender joints, and ≥1 of the following: erythrocyte sedimentation rate ≥28 mm/h, plasma C-reactive protein ≥20 mg/L, or morning stiffness for ≥45 minutes; had previous treatment failure with ≥1 DMARD other than methotrexate; and had not received therapy with methotrexate within the 6 months before enrollment (prior methotrexate must have been stopped for reasons other than treatment failure based on efficacy or safety). Patients were randomised to monotherapy with etanercept 25 mg twice weekly, monotherapy with methotrexate 7.5 mg weekly forced escalated to 20 mg weekly (unless adverse events occurred), or combination therapy with these 2 agents, and remained on their treatment regimen throughout the rest of the study (up to 3 years). The majority of patients receiving combination therapy with etanercept and methotrexate initiated therapy with both agents simultaneously.

RADIUS II

The design details for the prospective, multicentre, observational registry

study RADIUS II have been described previously (15, 16). Patients aged ≥18 years with moderate to severe RA (1987 American Rheumatism Criteria) were enrolled at clinical rheumatology practices in the United States from October 2002 to June 2003 with a goal to follow patients for 5 years and record concurrent therapies, clinical outcomes, and adverse events (15). At entry to RADIUS II, patients initiated twice-weekly etanercept 25 mg alone or in combination with ongoing therapy (*e.g.* patients added etanercept therapy to their established DMARD therapy). The RADIUS II patient population of this analysis thus included patients initiating etanercept monotherapy as well as patients receiving combination therapy with etanercept added to existing methotrexate. Patients continued etanercept monotherapy or etanercept combination therapy through the first 3 months, after which time they could change treatments (in the full RADIUS II population 20% of etanercept monotherapy and 9% of combination therapy patients switched off of etanercept at month 3). The current analysis used data only from those patients who stayed on the initial treatment regimen throughout the study.

Data Collection and Outcome Measures

Demographics and baseline characteristics were collected for patients in TEMPO and RADIUS II who initiated etanercept monotherapy or etanercept plus methotrexate, and patients were evaluated for disease activity over time, remission status, and time to initial and sustained remission. For the current analysis, disease activity was defined by the CDAI score with remission defined as a CDAI score ≤2.8. Although other measures of remission are available from TEMPO, Disease Activity Score including 28-joint count (DAS28), Simple Disease Activity Index (SDAI), ACR 20/50/70 are unavailable in RADIUS II. Further, the lack of laboratory measurements including C-reactive protein in RADIUS II prevented the use of ACR/EULAR, Boolean, or SDAI definitions of remission. Thus CDAI was used as it was the only common measure between TEMPO and RADIUS II. When calculating the time to and probability of CDAI remission, only the first remission for each patient was used, and patients were considered censored at time of last follow-up. The percentage of patients achieving remission (CDAI ≤2.8) by year 3 at any point during continued etanercept therapy and the percentage of patients with sustained remission (CDAI ≤2.8 for at least 6 months with at least 2 observations within a continuous observation period) were calculated. Additionally, the time from baseline to sustained remission was determined. The sustained remission analysis was limited to patients who were followed up on their respective study for at least 6 months and continued on etanercept.

Table I. Baseline disease and demographic characteristics in TEMPO and RADIUS II.

Characteristic*	TEMPO (N = 223)	RADIUS II (N = 1166)
Patient age, y	53.2 (13.8)	52.9 (13.5)
Female, n (%)	171 (76.7)	880 (75.5)
White, n (%)	220 (98.7)	951 (81.6)
Clinical Disease Activity Index score	47.7 (12.4)	36.7 (16.5)
Tender joint count†	18.5 (6.5)	13.5 (8.4)
Swollen joint count†	15.4 (5.8)	11.2 (7.3)
Physician global assessment‡	6.8 (1.5)	6.0 (1.9)
Patient global assessment‡	6.9 (1.7)	6.3 (2.4)
Treatment period, mo	25.1 (13.5)	19.4 (19.9)
Disease duration, y	6.3 (5.1)	9.2 (10.2)
Rheumatoid factor positivity (≥20 IU/mL), n (%)	167 (74.9)	750 (71.9)

*Unless otherwise noted, all data are mean (SD). †Range, 0–28 joints. ‡Global assessment scales from 0–10.

Statistical analysis

Remission status and time to remission were assessed separately by treatment group and individual study (TEMPO or RADIUS II) using Kaplan-Meier estimates. The association between baseline disease activity and remission rate was analysed by comparison of rates of remission among patients stratified by baseline CDAI score. The effect of the time to achieve CDAI remission on duration of first maintained remission (≥6 months) was determined using log-rank tests stratified by treatment group. Baseline demographic and disease characteristics were summarised descriptively with means and standard deviations (SD) for continuous variables and percentages for categorical variables. For baseline comparisons between TEMPO and RADIUS II, continuous variables were compared using 2-sample *t*-tests, and categorical variables using chi-square tests. All analyses were performed using SAS® version 9.2 (SAS Institute, Cary, NC, USA).

Results

Patients

In TEMPO, 223 patients initiated etanercept monotherapy and 231 patients initiated etanercept plus methotrexate combination therapy (initiated simultaneously; 56.3% were methotrexate-naïve) (12). In RADIUS II, 1172 initiated etanercept monotherapy and 2376 added etanercept to existing methotrexate (etanercept was generally added to established methotrexate owing to lack of adequate response to baseline DMARD) (15). Patients in RADIUS II had lower disease activity at baseline (mean [SD] CDAI: 36 (13)) than those in TEMPO (CDAI: 47 (13), $p<0.001$) (Table I). Most other clinical and demographic features (*e.g.* age, rheumatoid factor, sex) were comparable at baseline (Table I). Differences in other demographic features (*e.g.* ethnicity/race) may in part be the result of the different base populations with TEMPO being conducted in Europe, Australia, and Israel, while RADIUS was based in United States.

Efficacy

Patients from TEMPO and RADIUS II who initiated etanercept monotherapy had similar rates of achieving CDAI remission (CDAI ≤2.8) over time (Fig. 1). By year 3, CDAI remis-

sion was achieved by 39% of patients who received etanercept monotherapy in TEMPO and by 35% in RADIUS II (Table II; Fig. 1). CDAI remission was achieved by year 3 in 54% of patients with simultaneous initiation of etanercept and methotrexate in TEMPO and in 36% of patients with etanercept added to established methotrexate in RADIUS II (Table II; Fig. 1).

The proportion of patients achieving a first sustained remission (CDAI ≤2.8 lasting ≥6 months) through year 3 is shown by treatment group for both trials in Figure 2 and Table II. In TEMPO, patients with simultaneous initiation of etanercept and methotrexate achieved first sustained remission sooner and at higher proportions than patients who received etanercept monotherapy in either TEMPO or RADIUS II (Fig. 2; Table II). These patients simultaneously initiating etanercept plus methotrexate in TEMPO also had a higher proportion achieving first sustained remission at all time points compared with the patients in RADIUS II who received etanercept as a sequential add-on to previously initiated methotrexate (Fig. 2; Table II).

In each study, likelihood for CDAI remission and time to remission varied with baseline disease activity. Generally, more patients with lower baseline CDAI scores achieved remission by year 3 in both trials compared with those with higher baseline CDAI scores (Table II). The relationship between time to first sustained remission and duration that the patient remained in sustained remission is shown in Figure 3. In both trials, patients with an earlier onset of CDAI remission seemed to have a higher likelihood of sustained remission than patients with a later onset of remission (Table II; Fig. 3). Patients achieving sustained remission early (0–6 months) had a longer duration of remission than those who achieved continued remission >6 months after initiation of therapy (Fig. 3).

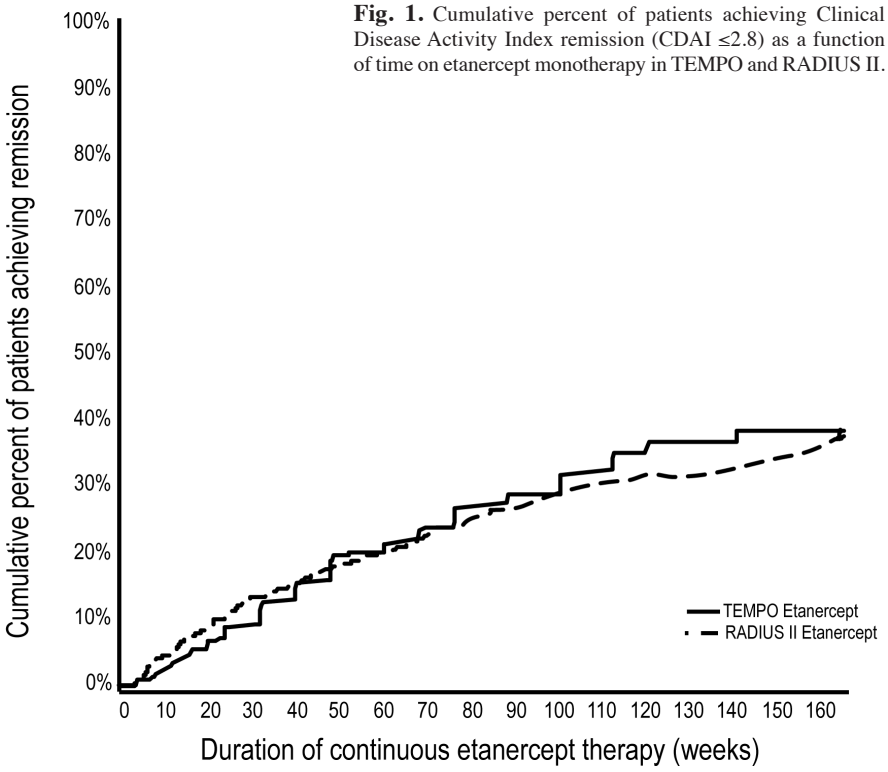

Fig. 1. Cumulative percent of patients achieving Clinical Disease Activity Index remission (CDAI ≤2.8) as a function of time on etanercept monotherapy in TEMPO and RADIUS II.

Table II. Remission and time to remission in patients treated with etanercept with or without methotrexate.

	Etanercept Etanercept monotherapy	
	TEMPO	RADIUS II
Cumulative proportion achieving remission by year 3, % (95% CI)*	n=223 39 (31–47)	n=1172 35 (32–38)
Cumulative proportion achieving remission by year 3 by baseline CDAI score subgroup, %, (95% CI) *		
20–29	n=15 50 (28–78)	n=222 56 (45–66)
30–39	n=47 49 (34–67)	n=241 34 (25–45)
40–49	n=59 37 (24–54)	n=197 17 (10–28)
50–59	n=52 32 (19–50)	n=148 25 (15–40)
Proportion achieving continued remission† by year 3, % (95% CI)*	n=200 11.5 (7–17)	n=659 10.6 (8–13))
Proportion achieving continued remission† by time to initial remission, %		
0-6	2.0	5.2
>6-12	3.5	2.3
>12-24	4.5	2.1
>24-36	1.5	1.1

Discussion

In this analysis, etanercept therapy, either with or without concomitant methotrexate, effectively induced remission, as measured by CDAI in a significant proportion of patients with RA from TEMPO and RADIUS II. Sustained remission of at least 6 months was also seen in many patients but was less frequent. Clinical benefit, as measured by CDAI remission over time, of etanercept monotherapy in the TEMPO clinical trial was similar in the RADIUS II observational study, thus replicating the original findings from TEMPO in a clinical practice setting (12). Results from TEMPO showed that patients in the etanercept plus methotrexate

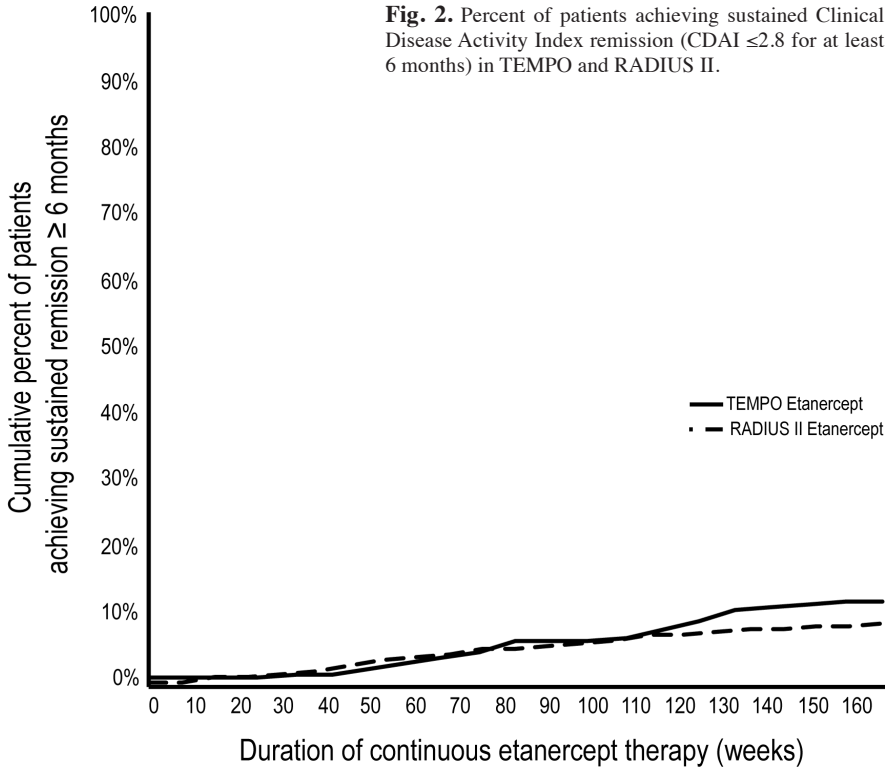

Fig. 2. Percent of patients achieving sustained Clinical Disease Activity Index remission (CDAI ≤2.8 for at least 6 months) in TEMPO and RADIUS II.

arm had higher CDAI remission rates at all time points than patients in the etanercept-only arm. CDAI remission rates for the etanercept plus methotrexate groups were higher for patients in TEMPO than for patients in RADIUS II. CDAI remission also appeared to occur more rapidly in TEMPO than RADIUS II, even among patients with similar baseline disease activity (data not shown). However, the ability to fully compare efficacy between studies is limited by differences in treatment regimens, inclusion criteria, and potential differences in patient populations due to regional differences between the largely Western European TEMPO study and the US-based RADIUS II study. One critical difference was that methotrexate and etanercept were initiated simultaneously in TEMPO (although some may have had prior exposure in the 6 months prior to entry), whereas in RADIUS II etanercept was added to methotrexate in patients with inadequate response to methotrexate. This discrepancy in the timing of etanercept and methotrexate therapy (simultaneous initiation versus sequential initiation of each agent) makes the comparison of the two etanercept and methotrexate combination groups from the TEMPO and RADIUS II groups problematic. The response to combination therapy appears to be more robust when the patient is naïve to both medications than having failed methotrexate and adding a biologic to this failed DMARD. This is consistent with data reported from previous studies. The response rate to etanercept was similar in two separate studies of patients who had failed prior DMARD and were treated with etanercept monotherapy (10-14) or who required the addition of etanercept to existing methotrexate as combination therapy (10-14). Although these investigations involved two different populations and protocols, the study groups appear comparable, The treatment protocols were generally similar except one group remained on methotrexate when the etanercept was started and the other group did not remain on the prior DMARD. The ACR 20, 50, and 70 responses of these studies were remarkably similar. Thus, in patients with prior methotrexate exposure and failure of response, the percent of patients entering into remission in response to etanercept was the same regardless of whether patients received etanercept monotherapy or combination therapy. This may partially explain the differences observed between the TEMPO and RADIUS II studies in the current analysis. However, differences in study design and patient characteristics (disease severity, comorbidities, treatment adherence), make it difficult to compare the combination therapy groups between the two trials. As a result, data must be interpreted with caution; the intent is not to bridge RCT data to a clinical practice registry or to directly contrast the two, but rather to use each as a foil for the other to find commonalities to answer clinical questions that cannot be answered in one dataset alone. Despite these limitations, there were some consistent observations between the different studies and subgroups analysed.

In both studies, the likelihood for CDAI remission and time to remission paralleled baseline disease severity, suggesting that patients with moderate disease activity have a better response to etanercept therapy than patients with severe disease activity. Data from a large systematic review of predictors for remission in RA support the idea that baseline disease activity is a strong predictor of remission (18). Patients with moderate disease activity, as assessed by baseline CDAI score, were also more likely to achieve remission than patients with more severe disease activity. These results are supported by data from an earlier study that showed that patients from TEMPO and the etanercept Early Rheumatoid Arthritis (ERA) trial (10) with moderate disease activity as assessed by DAS28 achieve better clinical outcomes (DAS28 and radiographic progression) than those with more severe disease activity (19). The small number of patients with early disease (mean disease duration in TEMPO was 6.3 years and in RADIUS II was 9.2 years) did not allow for an assessment of the relationship between earlier treatment and likelihood of remission. However, the analysis did indicate that patients in both trials with a shorter time to remission tended to remain in remission for a longer duration than those with a longer time to remission, suggesting that achievement

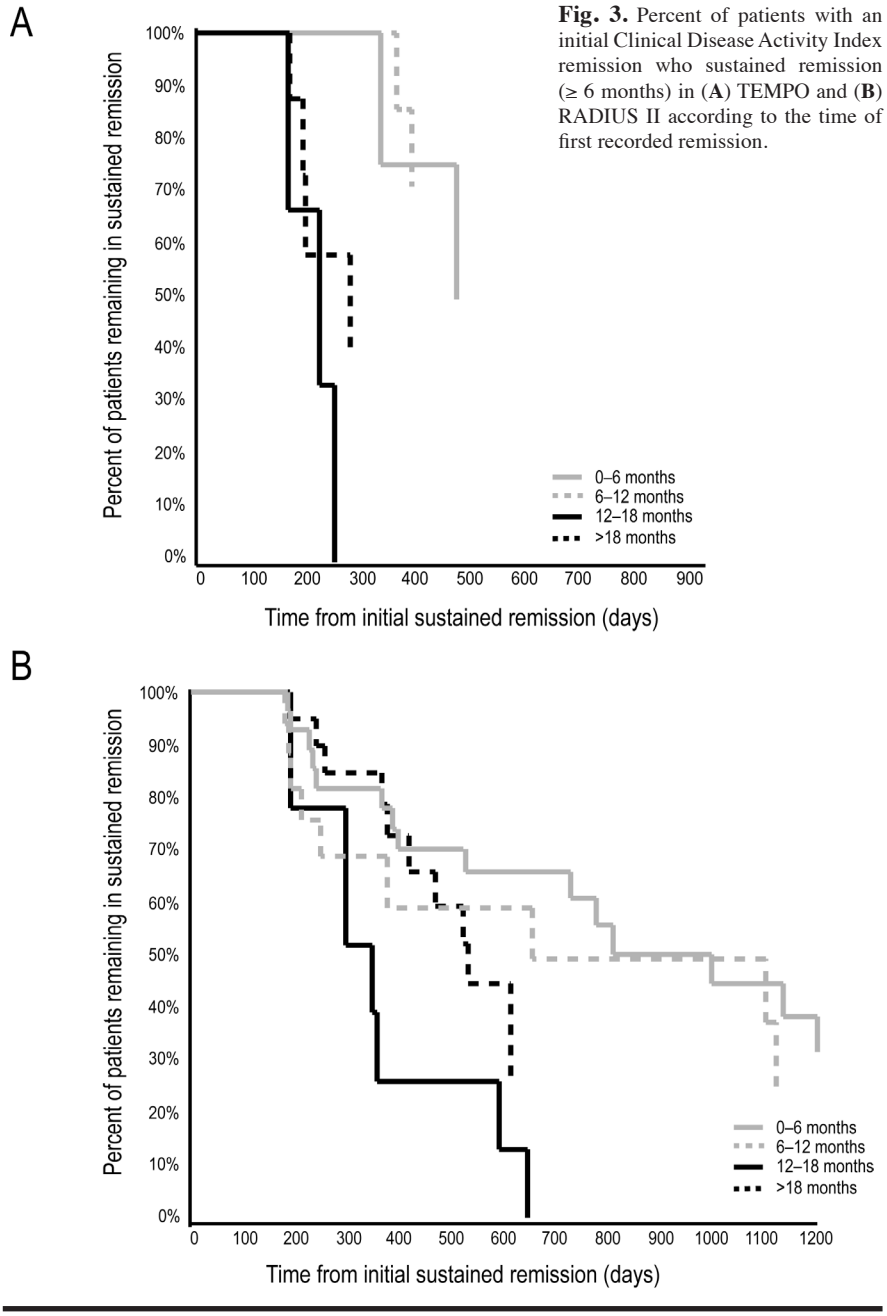

Fig. 3. Percent of patients with an initial Clinical Disease Activity Index remission who sustained remission (≥ 6 months) in (**A**) TEMPO and (**B**) RADIUS II according to the time of first recorded remission.

of earlier remission is associated with a longer duration of remission with etanercept therapy. These results are supported by other analyses showing that earlier onset of remission improves sustainability of remission (20-22).

Biologics registries can yield real-world evidence of safety and effectiveness of treatments, and because of their large size, inclusion of patients with and without significant co-morbidities, and duration of follow-up, registries are well-suited to detecting rare AEs and generally are a more accurate reflection of patients in clinical practices, complementing data from randomised controlled trials (23-27). Indeed, our analysis showed that patients in the etanercept-only arm in the TEMPO clinical trial had similar CDAI remission rates to patients receiving etanercept alone in the RADIUS II observational study. Further, the patients receiving monotherapy in RADIUS II had similar CDAI remission rates to patients receiving etanercept/methotrexate combination therapy. This supports the potential for using etanercept as monotherapy in some patients in clinical practice.

Conclusions

This analysis showed that patients with moderate disease activity are more likely to achieve both remission and sustained remission with etanercept therapy than patients with severe disease activity. The patients who achieve an early remission are more likely to experience a sustained remission in response to etanercept. Our results were consistent in both the TEMPO controlled trial and clinical practice settings of RADIUS II. These findings were consistent across controlled trial and clinical practice settings, regardless of the use of methotrexate in combination with etanercept. This analysis supports the continued use of randomised controlled trials to characterise therapeutic response in a structured clinical setting, but also emphasises the contribution provided by clinical practice data for more generalisable information.

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