Maintenance of Sustained Low Disease Activity or Remission in Patients With Rheumatoid Arthritis Treated With Etanercept Monotherapy: Results from the Corrona Registry

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Objective. The purpose of this study was to evaluate maintenance of remission/low disease activity (LDA) in patients with rheumatoid arthritis (RA) who achieved remission/LDA with etanercept (ETN) plus a conventional synthetic disease-modifying antirheumatic drug (csDMARD) and to compare patients who discontinued csDMARD to receive ETN monotherapy (Mono) with those remaining on combination therapy (Combo).

Methods. Patients from the Corrona RA registry between October 1, 2001, and August 31, 2017, were eligible. The index date for the Mono cohort was the csDMARD discontinuation date; the index visit for the Combo cohort was estimated from time between ETN initiation and csDMARD discontinuation in the Mono cohort. The main outcome calculated was maintenance of remission/LDA. Patients were censored if they switched to or added a biologic DMARD, discontinued ETN, when a csDMARD was reintroduced (Mono), or if methotrexate increased more than 5 mg/d (Combo). Trimming was used to balance demographic and clinical characteristics between groups. Cox regression models were adjusted for the remaining differences across groups.

Results. We identified 182 Mono and 403 Combo patients; 120 Mono and 207 Combo patients remained after trimming. Most patients (approximately 80%) were biologic medication–naive before initiating ETN. At 24 months postindex, modeled percentages of patients remaining in remission/LDA were 75% for Mono and 86% for Combo (overall adjusted P = 0.057). More patients were censored for therapy change in Mono than in Combo groups (37% versus 5%), largely due to reintroduction of csDMARDs in the Mono group.

Conclusion. Many patients with RA who achieved remission/LDA on combination therapy maintained remission/LDA with ETN monotherapy for 2 years after csDMARD discontinuation. ETN monotherapy may be a viable option for patients who discontinue csDMARDS after achieving LDA/remission.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease that is characterized by inflammation of diarthrodial joints...
impacts health care systems because of its high prevalence and associated long-term disability (3).

The discovery of biologic agents that target mediators of RA pathogenesis made the achievement of remission or low disease activity (LDA) a realistic goal for treat-to-target strategies as recommended by the American College of Rheumatology (ACR) (4) and the European League Against Rheumatism (EULAR) (5). The first biologic to receive approval for the treatment of RA, etanercept (ETN), is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75-kilodalton tumor necrosis factor receptor linked to the Fc portion of human immunoglobulin G1, which is indicated for the treatment of moderate to severe RA (6). In pivotal, randomized controlled trials, ETN was shown to provide rapid, significant, and sustained benefit to patients with RA as monotherapy (7), in combination with methotrexate (MTX) (8), and in patients with early RA (9) or long-standing RA (10). Data from RA registries have confirmed the effectiveness of ETN for the treatment of RA in real-world practice (11-14).

Most frequently, the initial therapy for RA is conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and if the disease is not controlled, a biologic DMARD (bDMARD) is added. However, patient medication adherence may be compromised by the use of multiple therapies (15), and adverse events may hamper therapy success. Thus, the option of monotherapy with bDMARDs has attracted considerable research interest (16). The efficacy of monotherapy with RA medications has typically been investigated by analyzing patients who initiate a biologic as combination therapy with methotrexate and then discontinue methotrexate (see for example, COMET study design) (17). Questions remain as to whether monotherapy is a viable option after achieving remission/LDA on combination therapy with a bDMARD + csDMARD. For patients in sustained remission, ACR (4) and EULAR (5) guidelines recommend against discontinuation of all RA medications and suggest tapering medications but provide no guidance as to how this should be done.

The objective of this study is to compare the maintenance of remission/LDA among patients who first achieved remission/LDA while on ETN + csDMARD combination therapy and then either discontinued the csDMARD to receive ETN monotherapy or continued on combination therapy. The study was based on data from the Corrona registry, representing real-world clinical practice in the United States.

**Patients and Methods**

**Data source.** This was a retrospective cohort study based on data from the Corrona registry. The Corrona registry is an independent, prospective, observational cohort of patients with RA. Patients are recruited from 174 private practices and academic sites with 712 participating rheumatologists across 41 US states. As of June 30, 2018, data for 49,162 patients with RA have been collected. The Corrona database includes information about 373,064 patient visits and 173,389 patient-years of follow-up. The mean duration of patient follow-up is 4.4 years (median 3.3 years). Information is collected in every registry visit from both the physician and the patient. Detailed medication history, disease activity, and patient-reported outcomes are available for analysis in intervals of approximately every 6 months.

All participating investigators were required to obtain full institutional review board (IRB) approval for conducting research involving human subjects. Sponsor approval and continuing review were obtained through a central IRB (New England Independent Review Board, NEIRB No. 120160610). For academic investigative sites that did not receive a waiver to use the central IRB, full board approval was obtained from the respective local governing IRBs, and documentation of approval was submitted to the sponsor before initiating any study procedures. All registry participants provided written informed consent before participation.

**Patient eligibility.** This study was based on data from the Corrona registry from October 1, 2001, through August 31, 2017. Eligible patients were adults (aged ≥18 years) with RA who initiated ETN in combination with a csDMARD (ETN could be added to an existing csDMARD or could be started concurrently with a csDMARD). After initiation of combination therapy, patients had to achieve remission or LDA (Clinical Disease Activity Index [CDAI] score ≤10). Patients were categorized into two groups on the basis of changes in their therapy at a subsequent visit following the initial achievement of remission/LDA: patients who discontinued the csDMARD and continued on ETN monotherapy were eligible for inclusion in the monotherapy (Mono) group, and patients who continued on combination therapy were eligible for inclusion in the combination (Combo) group. There were no criteria for the length of time a patient was required to be in remission/LDA before discontinuation of the csDMARD.

**Study design and statistical analysis.** The index date was defined as the date that an eligible patient on ETN + csDMARD combination therapy with remission/LDA discontinued the csDMARD and continued on ETN monotherapy. Because the comparator Combo group could not have an index date defined in a similar way (ie, did not discontinue csDMARD therapy), the index date was selected as the date that the patients in the Combo group were in remission/LDA. Patients in the Mono group were matched to patients in the Combo group on a 1:2 basis; for matched patients in the Combo group, their index data had a similar time interval from the ETN initiation visit as for the Mono group. Patients in both groups had to have one or more follow-up visit after the index date to be included in the analysis.

The intent of the analyses was to compare the maintenance of remission/LDA among patients changing to ETN monotherapy with those who remained on combination therapy. Two techniques
were used in sequence. First, patients in both Mono and Combo groups had to have similar exposure to their combination therapy regimen before the index date (Figure 1). Patients were matched without replacement using 3-month intervals of exposure. Second, trimming of patients without overlapping regions of propensity scores for both groups was used to balance differences in patient demographic and clinical characteristics at the index date, and for any variables considered to be of clinical importance. The propensity score construction included the following a priori selected variables: baseline CDAI score, duration of RA, and time in remission/LDA before index date in addition to the patient demographic (age, sex, race), body mass index (BMI), and clinical characteristics (alcohol use, rheumatoid factor status, history of diabetes, number of prior biologics, number of prior csDMARDs). No imputation for missing data was undertaken.

Maintenance of sustained remission/LDA was calculated for both groups and was compared. Cox regression was used to compare maintenance of remission/LDA between the Mono and Combo groups, overall, and at specific time points, adjusted for baseline CDAI score, time in remission/LDA before the index date, age, white race, BMI category, alcohol use, history of diabetes, number of previous biologics used, and number of previous csDMARDs used. Kaplan-Meier survival analysis was used to estimate the maintenance of remission/LDA for the patients on ETN monotherapy who had previous ETN combination therapy for more than 3 years and could not be matched.

Patients were censored if ETN was discontinued, if a csDMARD was restarted in the Mono group, or if the MTX dose was increased by more than 5 mg/d in the Combo group. A disease activity increase to moderate or severe was considered a failure event for the main analysis of maintenance of remission/LDA. No imputation for missing data was undertaken.

Patients. A total of 585 eligible patients were identified, including 182 patients in the Mono group and 403 in the Combo group. After matching, performed on the basis of the duration of combination therapy before the index date, 137 patients in the Mono group and 234 in the Combo group remained in the analysis set; 54 patients (39.4%) in the Mono group and 96 patients (41.0%) in the Combo group were in remission at the index date, and the remainder had LDA. After propensity score trimming—which adjusted for age, race (white), BMI categories, alcohol use, rheumatoid factor status, history of diabetes, number of prior biologics, number of previous csDMARDs used, CDAI, duration of RA, and time in remission/LDA—120 patients in the Mono group and 207 in the Combo group were included in the analyses.

The characteristics of patients after propensity score trimming are shown in Table 1. For the Mono and Combo groups, respectively, the mean ages (SD) were 54.6 (12.6) years and 55.7 (12.4) years, mean durations (SD) of RA were 8.2 (8.7) years and 8.3 (8.6) years, mean CDAI scores (SD) were 4.2 (3.0) and 4.0 (2.9), mean physician global assessment (PGA) scores (SD) were 8.8 (8.5) and 8.5 (8.3), and current prednisone use was reported as 15.8% and 16.9%. Characteristics at the index visit were similar between groups except for prednisone dose (standardized difference: 0.488), receipt of only MTX as the previous csDMARD (standardized difference: −0.775), and receipt of more than one previous non-MTX csDMARD (standardized difference: 0.821) (Table 1).

The mean (SD) duration of remission/LDA before stopping the csDMARD in the Mono group was 5.7 (7.0) months; in the matched Combo group, the mean duration of remission/LDA before the

Figure 1. Study schema. Abbreviations: csDMARD, conventional synthetic disease-modifying antirheumatic drug; ETN, etanercept; LDA, low disease activity; RA, rheumatoid arthritis. *Time in remission/LDA prior to index visit at the discretion of the clinician.
### TABLE 1. Demographic and clinical characteristics at index date before and after propensity score matching

|                         | Before Propensity Score Matching | After Propensity Score Matching |
|-------------------------|----------------------------------|---------------------------------|
|                         | All patients (N = 371)           | Mono group (n = 137)            |
|                         | Combo group (n = 234)            | Difference†                    |
| Age (y), mean (SD)      | 55.1 (12.8)                      | 54.0 (13.0)                     | 55.8 (12.6) | -0.144 |
| Sex, female n (%)       | 278 (74.9)                       | 100 (73.0)                      | 178 (76.1) | -0.070 |
| Race, white n (%)       | 306 (82.5)                       | 119 (86.9)                      | 187 (79.9) | 0.187 |
| Duration of RA, mean years (SD) | 8.4 (8.8)                      | 8.2 (8.8)                      | 8.5 (8.8) | -0.034 |
| RF positive, n/N1 (%)    | 186/248 (75.0)                   | 58/83 (69.9)                     | 128/165 (77.6) | -0.175 |
| Anti-CCP antibody positive, n/N1 (%) | 119/177 (67.2)                   | 30/56 (53.6)                     | 89/121 (73.6) | -0.422 |
| mHAQ, mean score (SD)   | 0.2 (0.4)                        | 0.2 (0.4)                        | 0.2 (0.4) | 0.003 |
| CDAL mean score (SD)    | 4.2 (2.9)                        | 4.2 (3.0)                        | 4.2 (2.9) | 0.021 |
| CDAI categories, n (%)  | Remission (score ≤2.8)           | 150 (40.4)                       | 54 (39.4) | 96 (41.0) | -0.033 |
|                         | LDA (score >2.8 to ≤10)          | 221 (59.6)                       | 83 (60.6) | 138 (59.0) | 0.033 |
| PGA, mean score (SD)    | 8.7 (8.3)                        | 8.7 (8.4)                        | 8.7 (8.3) | 0.001 |
| Number of previous bDMARDs, n (%) | 284 (76.5)                       | 109 (79.6)                       | 175 (74.8) | 0.114 |
|                         | 73 (19.7)                        | 25 (18.2)                        | 48 (20.5) | -0.057 |
|                         | 14 (3.8)                         | 3 (2.2)                          | 11 (4.7) | -0.138 |
| Previous csDMARDs, n (%) | MTFX only                        | 250 (67.4)                       | 60 (42.8) | 190 (81.2) | -0.383 |
|                         | 1 non-MTX csDMARD                | 19 (5.1)                         | 6 (4.4)  | 13 (5.6) | -0.054 |
|                         | Current prednisone use, n (%)     | 64 (17.3)                        | 21 (15.3) | 43 (18.4) | -0.081 |
| Dose, mean mg/d (SD)    | 5.1 (3.0)                        | 5.9 (2.8)                        | 4.6 (3.0) | 0.437 |
| Time in remission/LDA, mean months (SD) | 5.6 (6.7)                      | 5.9 (7.2)                        | 5.4 (6.5) | 0.076 |

Abbreviations: bDMARD, biologic disease-modifying antirheumatic drug; CCP, cyclic citrullinated peptide; CDAL, Clinical Disease Activity Index; Combo, combination therapy with etanercept and csDMARD; csDMARD, conventional synthetic disease-modifying antirheumatic drug; LDA, low disease activity; mHAQ, modified Health Assessment Questionnaire; Mono, etanercept monotherapy; MTFX, methotrexate; N1, number of patients with data available; PGA, physician global assessment; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation.  
† Standardized difference, used to measure effect size, to quantify the difference between the two groups.
Maintenance of remission/LDA. Maintenance of remission/LDA is shown in Table 2. At 24 months postindex, the percentages of patients remaining in remission/LDA were 75% for Mono and 86% for Combo (overall adjusted hazard ratio [95% CI] for the Combo group versus the Mono group, 0.635 [0.399, 1.013], \( P = 0.057 \)). No other variables (ie, 10-year age categories, sex, race [white], prior csDMARD therapy) were associated with a significant increase in hazard ratios in Cox regression analysis. The distribution of reasons for censoring over the 24 months postindex is shown in Table 3. More patients were censored in the Mono group than in the Combo group.

As mentioned above, we also investigated the 45 patients who could not be matched because of their long duration of combination therapy before the index date. The estimated percentages of these 45 patients who remained in remission/LDA were 92% at 6 months and 79% at 12 months, 18 months, and 24 months postindex.

Across all patients, 120 (52.4%) were in remission at the end of the study period.

### DISCUSSION

In our study, we investigated the maintenance of remission/LDA in patients who switched from ETN combination therapy to ETN monotherapy after LDA was achieved. We found that it was not significantly different compared with continuation of ETN + csDMARD (most commonly MTX) combination therapy.

Although bDMARDs are recommended for use as combination therapy with csDMARDs, studies have consistently shown that approximately 30% of patients with RA are prescribed bDMARDs as monotherapy in the real world (16,18,19). Many patients do not tolerate symptoms related to csDMARD therapy, and many are nonadherent. In a recent survey of patients with RA, 42% of respondents indicated that they had not taken their MTX in accordance with physician instructions, including not taking the drug at all, taking smaller doses than prescribed, or skipping doses (20); reasons for nonadherence included forgetting to take it (33%), not needing it when feeling well (24%), and concerns about long-term safety (24%).

Patients who do well on combination therapy and achieve remission/LDA pose a challenge regarding how best to manage therapies and maintain remission/LDA. The level of evidence is low for strategies to maintain disease control in patients with RA.

### TABLE 2. Maintenance of time in remission/LDAa

| Time After Index Date | ETN Mono Group (n = 120) | ETN + csDMARD Combo Group (n = 207) |
|-----------------------|--------------------------|-------------------------------------|
| 6 mo                  | 106 (88)                 | 199 (96)                            |
| 12 mo                 | 92 (77)                  | 190 (92)                            |
| 18 mo                 | 90 (75)                  | 184 (89)                            |
| 24 mo                 | 90 (75)                  | 178 (86)                            |

Note. Values are presented as n (%). Abbreviations: CCP, cyclic citrullinated peptide; csDMARD, conventional synthetic disease-modifying antirheumatic drug; ETN, etanercept; LDA, low disease activity.

a Models were adjusted for sex, race, age group, insurance type, anti-CCP antibody status, and previous csDMARD use.

### TABLE 3. Distribution of censoring at 24 months of follow-up

| Censor reason              | ETN Mono Group (n = 120) | ETN + csDMARD Combo Group (n = 207) | Total (N = 327) |
|----------------------------|--------------------------|-------------------------------------|-----------------|
| Remaining                  | 40 (33.3)                | 148 (71.5)                          | 188 (57.5)      |
| Discontinued/switched      | 11 (9.2)                 | 1 (0.5)                             | 12 (3.7)        |
| Added csDMARD              | 33 (27.5)                | 5 (2.4)                             | 38 (11.6)       |
| Increased MTX dose         | 0                       | 5 (2.4)                             | 5 (1.5)         |
| Lost LDA (event)           | 36 (30.0)                | 48 (23.2)                           | 84 (25.7)       |

Note. Values are presented as n (%). Abbreviations: csDMARD, conventional synthetic disease-modifying antirheumatic drug; ETN, etanercept; LDA, low disease activity; MTX, methotrexate.
who have achieved LDA or remission. For patients in sustained remission, ACR (2015 recommendations) (4) and EULAR (2016 recommendations) (5) allow cautious tapering of current medications but not discontinuation of all RA medications.

Our study sheds new light on the management of such patients. On the basis of our results, patients who achieve LDA on ETN combination therapy may experience a similar duration of maintenance of disease control with the patients who continue combination therapy; indeed, there was a statistically nonsignificant difference in persistency of remission/LDA between patients who stayed on combination therapy and those who went on to ETN monotherapy. However, more patients on ETN monotherapy were censored compared with those on combination. This suggests that there may be a subset of patients for whom switching to monotherapy can still maintain disease control achieved with combination.

A strength of the study was the use of real-world data within one of the largest RA registries in the world with systematic and frequent collection of disease activity, patient-reported outcomes, and medication changes. The large number of patients in the registry allowed for robust matching techniques that reduce biases while maintaining adequate sample sizes.

A limitation of our analysis lies with the nature of any observational study in the context of a registry. Generalizability and residual biases are of concern. Regarding generalizability, Corrona is a large registry that enrolls patients across the United States in both rural and urban areas from both academic and private practices. There are no exclusion criteria that would eliminate patients from both areas. Furthermore, as with any observational registry study, there are some data we cannot capture. For example, we could not capture disease activity at the time of discontinuation when it occurred between visits; this means we may have underestimated failure events in those who discontinued.

These results should be interpreted with appreciation of the study limitations. Interpretation of this analysis is limited to the characteristics describing the matched data sets. We did not specify a minimum duration in remission/LDA before follow-up began, although there was wide variation in therapy before patients transitioned to monotherapy. The maintenance of LDA was also not statistically different between the Mono and Combo groups, although a numerical difference was present. In addition, more patients in the ETN Mono group had to restart a csDMARD or discontinue ETN and/or switch to another biologic compared with the ETN Combo group. However, a subset of patients successfully maintained LDA for long periods of time on continuous ETN monotherapy, indicating a need to identify characteristics that could predict which patients can successfully transition to ETN monotherapy and maintain good disease control.

Twenty-five percent of the patients who switched from combination therapy to monotherapy could not be matched to patients remaining in the Combo group because of the long duration before discontinuing the csDMARD. These patients could not be included in the comparative longitudinal analysis. These unmatched patients in the ETN Mono group also had high maintenance (unadjusted) of remission/LDA over 2 years and perhaps would have altered the results more in favor of ETN monotherapy.

In conclusion, many patients with RA in this study who achieved remission/LDA on combination therapy maintained remission/LDA with ETN monotherapy for 2 years after csDMARD discontinuation. This study provides real-world evidence that ETN monotherapy may be a viable option for some patients with RA who discontinue csDMARDs after achieving LDA/remission.

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AUTHOR CONTRIBUTIONS

All authors provided critical revision of the manuscript and final approval of submission.

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REFERENCES

1. Spector TD. Rheumatoid arthritis. Rheum Dis Clin North Am 1990;16:513–37.
2. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising?: Results from Olmsted County, Minnesota, 1955–2007. Arthritis Rheum 2010;62:1576–82.
3. Ma VY, Chan L, Carruthers KJ. Incidence, prevalence, costs, and impact on disability of common conditions requiring rehabilitation in the United States: stroke, spinal cord injury, traumatic brain injury, multiple sclerosis, osteoarthritis, rheumatoid arthritis, limb loss, and back pain. Arch Phys Med Rehabil 2014;95:986–95.
4. Singh JA, Saag KG, Bridges SL, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 2016;68:1–26.
5. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960–77.
6. Cwirwa SE, Balasubramanian P, Duffin DJ, Wagstrom CR, Gates CM, Singer SC, et al. Peptide agonist of the thrombopoietin receptor as potent as the natural cytokine. Science 1997;276:1696–9.
7. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med 1999;130:478–86.
8. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 1999;340:253–9.

9. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 2000;343:1586–93.

10. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004;363:675–81.

11. Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, et al. Postmarketing surveillance of safety and effectiveness of etanercept in Japanese patients with rheumatoid arthritis. Mod Rheumatol 2011;21:343–51.

12. Ornbjerg LM, Ostergaard M, Boyesen P, Krogh NS, Thomann A, Tarp U, et al. Impact of tumour necrosis factor inhibitor treatment on radiographic progression in rheumatoid arthritis patients in clinical practice: results from the nationwide Danish DANBIO registry. Ann Rheum Dis 2013;72:57–63.

13. Iannone F, Gremese E, Gallo G, Sarzi-Puttini P, Botsios C, Trotta F, et al. High rate of disease remission in moderate rheumatoid arthritis on etanercept therapy: data from GISEA, the Italian biologics register. Clin Rheumatol 2014;33:31–7.

14. Kotak S, Mardekian J, Horowicz-Mehler N, Shah A, Burgess A, Kim J, et al. Impact of etanercept therapy on disease activity and health-related quality of life in moderate rheumatoid arthritis patients population from a national British observational cohort. Value Health 2015;18:817–23.

15. Grijalva CG, Chung CP, Arbogast PG, Stein CM, Mitchel Jr EF, Griffin MR. Assessment of adherence to and persistence on disease-modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis. Med Care 2007;45:S66–76.

16. Choy E, Aletaha D, Behrens F, Finckh A, Gomez-Reino J, Gotzenberg JE, et al. Monotherapy with biologic disease-modifying anti-rheumatic drugs in rheumatoid arthritis. Rheumatology (Oxford) 2017;56:689–97.

17. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet 2008;372:375–82.

18. Catay E, Bravo M, Rosa J, Soriano ER. Prevalence of biologics monotherapy in a cohort of patients with rheumatoid arthritis in daily clinical practice. BMC Musculoskelet Disord 2016;17:110.

19. Favalli EG, Becciolini A, Biggioggero M, Bertoldi I, Crotti C, Raimondo MG, et al. The role of concomitant methotrexate dosage and maintenance over time in the therapy of rheumatoid arthritis patients treated with adalimumab or etanercept: retrospective analysis of a local registry. Drug Des Devel Ther 2018;12:1421–9.

20. DiBenedetti DB, Zhou X, Reynolds M, Ogale S, Best JH. Assessing methotrexate adherence in rheumatoid arthritis: a cross-sectional survey. Rheumatol Ther 2015;2:73–84.

21. Curtis JR, Chen L, Bharat A, Delzell E, Greenberg JD, Harrold L, et al. Linkage of a de-identified United States rheumatoid arthritis registry with administrative data to facilitate comparative effectiveness research. Arthritis Care Res (Hoboken) 2014;66:1790–8.