ABSTRACT

Introduction: In the last 20 years, biologic and targeted synthetic disease-modifying antirheumatic drugs (DMARDs) have become available for treating rheumatoid arthritis (RA), and a treat-to-target strategy has been introduced. We hypothesise that these advances should have resulted in changes to the characteristics of patients with RA participating in clinical trials of the newest therapies. This study determined whether the baseline characteristics of patients with RA enrolled in clinical trials have changed in the past decade versus patients participating in earlier RA studies.

Methods: This secondary analysis was based on randomised controlled trials (RCTs) identified in a systematic literature review. Baseline characteristics of patients with RA with inadequate response to conventional synthetic DMARDs were compared between RCTs published in 1999–2009 and those published in 2010–2017 using random-effects meta-analyses.

Results: Forty RCTs were analysed: 22 from 1999–2009 and 18 from 2010–2017. No significant difference between the two timeframes and no obvious trend over time were observed for age, gender, disease duration, rheumatoid factor status, tender and swollen joint counts, physician and patient global assessments of disease activity, and pain scores. Variability between RCTs was high. Similar results were observed for Disease Activity Scores and Health Assessment Questionnaire-Disability Index scores, but with low variability between RCTs.

Conclusion: The baseline characteristics of patients with RA participating in RCTs do not appear to have changed in the last decade despite the availability of new treatments and a different treatment approach. Further research should determine the impact of baseline patient
characteristics on patients’ response to RA treatments.

PLAIN LANGUAGE SUMMARY

In the last 20 years, new treatments and a new treatment approach (called treat-to-target) have been introduced for rheumatoid arthritis (RA). Consequently, the characteristics of patients with RA participating in clinical trials of the newest therapies should have changed compared with those of patients who participated in clinical trials of older therapies. This is important as patient characteristics may influence patients’ response to drug treatment. To determine whether characteristics of patients with RA have changed over time, we compared the baseline characteristics (e.g. age, gender, disease duration, measures of disease activity, and pain scores) of patients with RA between 22 clinical trials published in 1999–2009 and 18 published in 2010–2017. No significant difference between the two timeframes and no obvious trend over time were observed for any baseline characteristic of patients with RA, including physician and patient assessments of disease activity, and Health Assessment Questionnaire-Disability Index and pain scores. The baseline characteristics of patients with RA participating in clinical trials do not appear to have changed in the last decade despite the introduction of new treatments and the treat-to-target approach. Further research is needed to determine the impact of baseline patient characteristics on patients’ response to RA treatments.

Keywords: Disease-modifying antirheumatic drugs; Patient characteristics; Randomised controlled clinical trials; Rheumatoid arthritis; Rheumatology; Systematic review

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, autoimmune, inflammatory arthritis associated with pain, disability and an increased risk of mortality [1–3]. Globally, the prevalence of the
disease is in the range 0.5–1.1% [4, 5]. Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), such as methotrexate, leflunomide and sulfasalazine, provided the standard of care for RA for many years. However, the choice of treatments for the disease has expanded over the last 20 years with the introduction of biologic DMARDs (bDMARDs), such as abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, sarilumab and tocilizumab, and, more recently, targeted synthetic (ts)DMARDs, such as baricitinib and tofacitinib.

Guidelines for the management of RA from the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) recommend early use of DMARDs, with the goal of remission or low disease activity [6, 7]. This treat-to-target approach, first introduced in 2010 [8], has improved the care and outcomes of patients with RA [9, 10]. However, several studies suggest that many patients with RA are not reaping the benefits of this treat-to-target approach or the benefits derived from newer DMARDs because of underuse of these drugs. A review of data from the US National Ambulatory Care Medical Survey over a 12-year period (1996–2007) showed that only 47% of visits to a physician for RA were associated with a DMARD prescription [11], while a later retrospective review of data over a 3-year period (2005–2008) showed that only 63% of 93,143 Medicare enrollees with RA in the USA received a DMARD. Prescribed DMARDs varied with demographic factors, socioeconomic status and geographic location. Cited reasons for the low proportion of DMARD prescriptions included low income, for-profit health plans, patients refusing treatment and increased comorbidities in the elderly resulting in contraindications to available drugs [12].

A systematic review of 127 studies of patients with RA highlighted significant differences in certain patient characteristics, including age, disease duration, number of DMARDs previously used and Disease Activity Score for 28-joint count (DAS28), between patients enrolled in randomised controlled clinical trials (RCTs) and those enrolled in registries [13]. In addition, baseline DAS28 and Health Assessment Questionnaire-Disability Index (HAQ-DI) scores for patients with RA prescribed bDMARDs (etanercept, rituximab or tocilizumab) decreased over time for RCTs and observational studies published between 2004 and 2014 [13], probably owing to the introduction of the treat-to-target strategy during this period [14]. This trend was consistent with the results of an observational study conducted in the Netherlands, in which symptom duration and inflammatory activity at presentation were found to have decreased over a 23-year period (1993–2015) among patients with RA attending a local rheumatology department. Paradoxically, however, patient-reported outcomes (pain, fatigue, disease activity and global health) worsened over this time period, possibly as a result of increased societal and patient expectations [10].

Given the change in treatment strategy and the introduction of new DMARDs with different mechanisms of action in recent years (e.g. the Janus kinase inhibitors baricitinib and tofacitinib, and the interleukin-6 inhibitor sarilumab), the characteristics of patients participating in RA clinical trials might be expected to have changed over time. This is important as patient characteristics may influence the effects of drug treatment [13]. According to data from the systematic literature reviews (SLRs) conducted by Kilcher et al. [13], the characteristics of patients with RA enrolled in RCTs who show an inadequate response to csDMARDs might be expected to change over time, and this may influence the rate of response to new treatments as well as making it difficult to compare drugs evaluated during different time periods. To date, however, no such analysis has been published. To address this important issue and inform the design of future RCTs evaluating new RA treatments, we conducted a study to determine whether the baseline characteristics of patients with RA with an inadequate response to csDMARDs participating in RCTs between 1999 and 2017 have changed over time.
METHODS

Objective

This study aimed to compare the characteristics of patients with an inadequate response to csDMARDs participating in RA RCTs between two different, predefined timeframes—an earlier timeframe (1999–2009) when bDMARDs were first introduced, and a later timeframe (2010–2017) after the introduction of treatments with different mechanisms of action and adoption of the treat-to-target strategy.

Systematic Literature Review

This secondary analysis was based on the results of a previously conducted SLR [15]. The SLR aimed to identify evidence for the efficacy and safety of treatments for moderately to severely active RA in adults. Searches of Medline, Medline in Process, Embase, Biosciences Information Service and the Cochrane Library were performed to identify RCTs published between 1 January 1999 and 11 December 2017 using search terms related to RA, associated interventions and RCTs (Table S1 in the supplementary material). The original searches were performed on 17 June 2015 and updated searches were performed on 10 August 2016 and 11 December 2017. There were no language limits on the database searches. Conference abstracts (2013–2017), grey literature and the bibliographies of key articles were also reviewed. Data were extracted from relevant full-text publications and quality-checked by an independent reviewer. The quality of each study was also assessed using National Institute for Health and Care Excellence (NICE) guidelines [16]. The SLR was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17].

Current Analysis

The analysis reported here focused on studies from the SLR involving patients with an inadequate response to csDMARDs, including methotrexate, hydroxychloroquine, leflunomide and sulfasalazine. As such, the main analysis study pool only included studies that did not allow prior bDMARD use. The following baseline patient characteristics of interest extracted from the studies were analysed: age, gender, disease duration, rheumatoid factor status, DAS28 based on erythrocyte sedimentation rate (DAS28-ESR) or C-reactive protein (DAS28-CRP), HAQ-DI score, swollen joint count (SJC), tender joint count (TJC), Physician’s Global Assessment of Disease Activity (PGA), Patient’s Global Assessment of Disease Activity (PtGA), pain visual analogue scale (VAS) score, previous use of non-steroidal anti-inflammatory drugs (NSAIDs) and number of previously used csDMARDs.

Additional baseline characteristics that were extracted from the studies but could not be analysed because of lack of or limited data availability included weight, comorbidities, smoking status, Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) scores, Routine Assessment of Patient Index Data-3 (RAPID-3) score, erosion score, joint space narrowing score, van der Heijde modified total Sharp score (mTSS) and Euro-QoL-5 Dimensions (EQ-5D) questionnaire score.

The analysis reported in this article is based on previously conducted studies and does not involve any studies with human participants or animals performed by any of the authors.

Statistical Analysis

If not already presented as such, baseline patient characteristics from different treatment arms within a given study were combined into an overall study result. Where necessary, medians and ranges from each study were converted to means and standard deviations using the methods of Wan et al. [18]. For binary data, the variance estimate (v) for proportions (p) was used to derive the standard error using the formula \( v = p(1 - p) \). The results from the various studies were compared between the two study publication timeframes (1999–2009 vs 2010–2017) using random-effects meta-analyses. Between-study variance was assessed using restricted maximum-likelihood estimation and was presented as an \( I^2 \) value, showing the
proportion of the observed variance that reflects real difference between studies (i.e. it is not due to random error), where higher percentages represent higher variance; and a Tau-squared value, showing between-study variation, where higher values represent higher variation. The level of significance was taken as \( p \leq 0.05 \) (unadjusted for multiple testing). Missing data were not imputed for this analysis. Forest plots were generated for all analyses, with study results ordered by year of publication to provide a visual display of potential changes over time. Analyses were conducted using SAS version 9.4, R studio version 3.4, and metafor package version 2.0 [19].

Sensitivity Analyses

Two sensitivity analyses were performed to assess the effect of changing the patient population on results. One sensitivity analysis excluded Asia–Pacific studies, since patients from these countries (mainly Japanese) were likely to have been treated with a low dose of methotrexate (<7.5 mg/week), which could potentially impact the extent of methotrexate failure among trial populations. In addition to studies included in the main analysis, the second sensitivity analysis included studies that allowed prior bDMARD use in up to 20% of patients, since patients receiving bDMARDs were more likely to be further advanced in the RA treatment algorithm. The value of 20% was selected as many studies allowing some prior use of bDMARDs cited this value as the cut-off.

RESULTS

Study Numbers

A total of 147 primary studies including patients with an inadequate response to csDMARDs were identified in the SLR, of which 94 were excluded (Fig. 1). Of the remaining 53 studies, 13 allowed prior use of bDMARDs in up to 20% of patients and were consequently excluded from the main analysis. Thus, the main analysis included a total of 40 studies. Of these, 22 were published in the earlier timeframe and 18 in the later timeframe. The 13 studies allowing prior use of bDMARDs in up to 20% of patients were combined with the 40 studies from the main analysis into a sensitivity analysis; details of these 53 studies are provided in Table S2 in the supplementary material [20–72]. Treatments evaluated in the studies included csDMARDs (hydroxychloroquine, methotrexate, sulfasalazine), bDMARDs (abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, sarilumab, tocilizumab), and tsDMARDs (baricitinib, tofacitinib). Not all identified studies were included in each specific characteristic analysis as some did not report relevant information or reported data in a manner that did not allow data to be converted (e.g. to means and standard deviations).

Main Analysis

There was no statistically significant difference between the two timeframes and no obvious trend over time for age, gender, disease duration (mean difference between timeframes approximately 1 year), rheumatoid factor status, PGA, PtGA and pain VAS scores (Figs. 2 and S1). However, there was high variability (heterogeneity) between studies. Similarly, there was no statistically significant difference between timeframes and no obvious trend over time for DAS28-ESR, DAS28-CRP and HAQ-DI scores; in these cases, heterogeneity was low (Fig. 3). SJC (score range 0–66) and TJC (score range 0–68) were not significantly different between timeframes and there was no obvious trend over time; heterogeneity was also high. Different inclusion criteria were observed between studies for the minimum number of swollen or tender joints. We therefore conducted further analyses focusing on the minimum number of swollen or tender joints used as the inclusion criterion in each study, and on the most common inclusion criteria for minimum number of swollen and tender joints (≤6 for SJC, ≤6 and ≥8 for TJC). However, this did not change the results to any great extent (Figs. 4 and S2).

Information on the number of csDMARDs previously used was not reported in a unified manner, with very few studies (\( n = 3 \) in
Fig. 1 PRISMA diagram for study identification. bDMARD, biologic DMARD; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate
1999–2009; \( n = 5 \) in 2010–2017) providing means and standard deviations. For studies providing the latter, a statistically significant difference between timeframes was observed with low to moderate heterogeneity \( (I^2 33\%, \text{ Tau}^2 0.06, p < 0.001; \text{ Fig. S3}) \). The remaining studies either did not report this information or reported categories, which could not be converted into means and standard deviations. For prior NSAID exposure, most studies (24 out of 28; 86\%) reported NSAID use in 100\% of patients; therefore, no meta-analysis was run.

**Sensitivity Analyses**

The sensitivity analysis excluding Asia–Pacific studies included 28 studies: 16 from the earlier timeframe and 12 from the later timeframe. The results of this analysis were consistent with those of the main analysis (Fig. S4).

The sensitivity analysis allowing prior use of bDMARDs in up to 20\% of patients included 53 studies: 26 from the earlier timeframe and 27 from the later timeframe. Again, the results of this analysis were consistent with those of the main analysis (Fig. S5).

**DISCUSSION**

With the introduction of the treat-to-target strategy in RA and the availability of new treatments, the inclusion criteria for RA clinical trials might be expected to have changed in the past decade. However, the results of our analysis suggest that this is not the case: the characteristics of patients participating in recent clinical trials do not appear to have changed compared with those of patients participating in RCTs 10–20 years ago.

Patient characteristics are an important consideration in clinical trials as they may influence the effects of treatment. For example, older age is associated with decreased response rates in patients treated with etanercept or tocilizumab \([73, 74]\), while male sex, being rheumatoid factor-positive, having a low HAQ-DI score and being a non-smoker predict a better response to various bDMARDs \([73, 75, 76]\). In addition, a study comparing the baseline characteristics of patients with RA between RCTs and observational studies showed that patients participating in RCTs had better prognostic factors than those participating in observational studies, which could result in overestimation of the treatment effect \([13]\).

In this analysis, the lack of a change in DAS28 and HAQ-DI scores at baseline between the two timeframes was surprising given that real-world data from registries or observational studies suggest that baseline disease activity among patients with RA has decreased over time \([77–79]\). In addition, the aforementioned study by Kilcher et al. \([13]\) comparing the baseline characteristics of patients with RA between RCTs and observational studies showed that baseline DAS28, HAQ-DI, ESR and CRP significantly decreased in patients participating in RCTs over the time period 1999–2015. An SLR of patients with RA receiving anti-tumour necrosis factor treatment in clinical trials over a 16-year period (1993–2008) showed a similar decrease in baseline CRP over time among patients previously treated with methotrexate but not among those with no experience of this drug \([80]\). However, the current analysis suggests that baseline disease activity among patients with RA participating in RCTs has not decreased over time, possibly because patients participating in RCTs tend to have more severe disease at baseline than those in routine clinical practice \([13, 81]\). The lack of change in disease activity in the current analysis may also be due to barriers in adopting the treat-to-target strategy in clinical practice compared with clinical trials, such as a lack of physician understanding of this treatment strategy, the feeling that the disease activity score may be falsely high due to symptoms or inflammation unrelated to RA, physician resistance to algorithm-based treatment, or a lack of time at clinic visits \([82–84]\). The lack of change in baseline disease activity over time likely reflects a lack of change in the strict inclusion criteria for patients participating in an RCT. In view of this, different methodology to that used in our analysis and measurement of different clinical/laboratory parameters might be necessary to detect any change over time in patient...
characteristics; this could be a subject for future research.

This analysis suggests that the mean number of previously used csDMARDs in patients participating in RCTs has decreased over time, possibly reflecting adoption of the treat-to-target approach. However, this result was based on only a few studies and was not observed in the sensitivity analysis that included studies allowing prior bDMARD use in up to 20% of patients.

Fig. 2 Forest plots showing means and 95% confidence intervals (CI; box and whisker plots) for the different studies according to year of publication for (a) Physician's Global Assessment of Disease Activity score, (b) Patient's Global Assessment of Disease Activity score and (c) Pain Visual Analogue Scale score. If studies reported pain on a scale of 0–10, values were multiplied by 10. $I^2$ and $\tau^2$ values indicate a high degree of heterogeneity between studies, while $p$ values indicate no significant difference in mean values between studies published from 1999 to 2009 (studies above dashed line) and those published from 2010 to 2017 (studies below dashed line).
This suggests that it was either a ‘chance finding’ based on a small number of studies or that the inclusion of patients with prior bDMARD use corresponded to the inclusion of patients with more severe disease and hence a higher number of previously used csDMARDs, which would have diluted the effect over time. Very few studies reported the mean number of previously used csDMARDs: most reported previously used csDMARDs as the percentage of patients
using a certain number (e.g. 1, ≥ 1, ≥ 2, etc.), which could not be used in the current analysis. Thus, no definitive conclusions about previous csDMARD use can be drawn.

RCTs are very different to real-world clinical practice in that patients who are eligible for clinical trials generally have more severe disease [81]. Results of the current analysis suggest that patients currently being enrolled in RA RCTs are not receiving the correct treatment before commencement of the study. Although treat-to-target is the recommended approach for the management of RA [6, 7], RCTs are still being performed in which none of the participating patients have been treated accordingly. This begs the question as to whether RCTs are as informative as they were 15 years ago. In future, it would be interesting to design RCTs that include patients who have been treated according to treat-to-target recommendations.

To our knowledge, this is the first study to investigate changes over time in the characteristics of patients enrolled in RCTs of RA treatments. The main strength of this analysis is that it was based on a comprehensive SLR. However, it should be noted that transformation of median into mean values can introduce bias if the data summarised by a median value are not normally distributed [13]. As it was not the aim of this analysis to evaluate outcomes, the risk of bias was not assessed. Finally, although a highly sensitive search strategy with no language or geographic limits was used, it cannot be guaranteed that all relevant studies have been included.

CONCLUSION

The results of this analysis suggest that the characteristics of patients included in current RA clinical trials do not differ from those of patients included in trials for testing the first bDMARDs 20 years ago, despite current recommendations for a treat-to-target strategy. Further research is needed to determine the impact of patient characteristics on patients’ response to RA treatments in clinical trials. It also appears

Fig. 4 Forest plots showing means and 95% confidence intervals (CI; box and whisker plots) for the different studies according to year of publication for studies providing data on a swollen joint count (score range 0–66), and b tender joint count (score range 0–68). Diamond shapes indicate 95% confidence intervals around the means summarised by timeframe and overall, respectively. $I^2$ and $\tau^2$ values indicate a high degree of heterogeneity between studies, while $p$ values indicate no significant difference in mean scores between studies published from 1999 to 2009 (studies above dashed line) and those published from 2010 to 2017 (studies below dashed line)
that patients currently being enrolled in RCTs of RA treatments are not being treated according to a treat-to-target strategy before the start of the study. Future RCTs of RA treatments should include patients who have been treated using this strategy if RCTs are to remain informative and impactful.

ACKNOWLEDGEMENTS

**Funding.** The SLR was conducted by RTI Health Solutions under the direction of Eli Lilly and Company, Indianapolis, IN, USA. This analysis was also funded by Eli Lilly and Company. Employees of Eli Lilly and Company contributed to the study protocol design, data interpretation, and report development and review. The Rapid Service and Open Access Fees were funded by Eli Lilly and Company.

**Medical Writing Assistance.** The authors would like to acknowledge Dr Sue Chambers and Sue Williamson (Rx Communications, Mold, UK) for medical writing assistance with the preparation of this manuscript, funded by Eli Lilly and Company.

**Authorship.** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

**Disclosures.** Roberto Caporali has nothing to disclose. Walid Fakhouri, Claudia Nicolay, Serena Losi and Veronica Rogai are employees and minor stockholders of Eli Lilly and Company. Harriet Longley is a former employee of Eli Lilly and Company and is now affiliated with the University of Bath.

**Compliance with Ethics Guidelines.** The analysis reported in this article is based on previously conducted studies and does not involve any studies with human participants or animals performed by any of the authors.

**Data Availability.** Data are not publicly available.

**Open Access.** This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit [http://creativecommons.org/licenses/by-nc/4.0/](http://creativecommons.org/licenses/by-nc/4.0/).

**REFERENCES**

1. Verma MK, Sobha K. Understanding the major risk factors in the beginning and the progression of rheumatoid arthritis: current scenario and future prospects. Inflamm Res. 2015;64(9):647–59.

2. Ogdie A, Maliha S, Sin D, et al. Cause-specific mortality in patients with psoriatic arthritis and rheumatoid arthritis. Rheumatology (Oxford). 2017;56(6):907–11.

3. Ometto F, Fedeli U, Schievano E, Botsios C, Punzi L, Corti MC. Cause-specific mortality in a large population-based cohort of patients with rheumatoid arthritis in Italy. Clin Exp Rheumatol. 2018;36(4):636–42.

4. 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(6):1576–82.

5. Tobón GJ, Youinou P, Saraux A. The environment, geo-epidemiology, and autoimmune disease: rheumatoid arthritis. J Autoimmun. 2010;35(1):10–4.
6. Singh JA, Saag KG, Bridges SL, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2016;68(1):1–26.

7. Smolen JS, Landewé R, Bijlsma J, 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(9):960–77.

8. Smolen JS, Aletaha D, Bijlsma JWJ, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2010;69(4):631–7.

9. Haugeberg G, Boyesen P, Helgetveit K, Proven A. Clinical and radiographic outcomes in patients diagnosed with early rheumatoid arthritis in the first years of the biologic treatment era: a 10-year prospective observational study. J Rheumatol. 2015;42(12):2279–87.

10. Nieuwenhuis WP, de Wit MPT, Boonen A, van der Helm-van Mil AHM. Changes in the clinical presentation of patients with rheumatoid arthritis from the early 1990s to the year 2010: earlier identification but more severe patient reported outcomes. Ann Rheum Dis. 1990s;75(11):2054–6.

11. Solomon DH, Ayanian JZ, Yelin E, Shaykevich T, Brookhart MA, Katz JN. Use of disease-modifying medications for rheumatoid arthritis by race and ethnicity in the National Ambulatory Medical Care Survey. Arthritis Care Res (Hoboken). 2012;64(2):184–9.

12. Schmajuk G, Trivedi AN, Solomon DH, et al. Receipt of disease-modifying antirheumatic drugs among patients with rheumatoid arthritis in Medicare managed care plans. JAMA. 2011;305(5):480–6.

13. Kilcher G, Hummel N, Didden EM, Egger M, Reichenbach S, GetReal Work Package 4. Rheumatoid arthritis patients treated in trial and real world settings: comparison of randomized trials with registries. Rheumatology. 2018;57(2):354–69.

14. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. JAMA. 2018;320(13):1360–72.

15. Hartley L, Ahmedzai O, Bell J, Mitchell S. Systematic literature review of clinical evidence of baricitinib and comparator treatment in rheumatoid arthritis. RTI Health Solutions, Manchester, UK. Data on file, Eli Lilly and Company, 9 May 2018.

16. National Institute for Health and Care Excellence (NICE). The guidelines manual. Chapter 6. Reviewing the evidence. Process and Methods [PMG6]. November 2012. https://www.nice.org.uk/process/pmg6/chapter/reviewing-the-evidence. Accessed 14 May 2019.

17. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264–9.

18. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.

19. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw. 2010;36:1–48.

20. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group Lancet. 1999;354(9194):1932–9.

21. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med. 1999;130(6):478–86.

22. Weinblatt ME, Kremer JM, Bankhurst AD, 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(4):253–9.

23. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. 2003;48(1):35–45.

24. Furst DE, Schiff MH, Fleischmann RM, et al. Adalimumab, a fully human anti tumor necrosis factor alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol. 2003;30(12):2563–71.

25. Edwards JC, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004;350(25):2572–81.

26. Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized,
placebo-controlled, 52-week trial. Arthritis Rheum. 2004;50(5):1400–11.

27. Lan JL, Chou SJ, Chen DY, Chen YH, Hsieh TY, Young M. A comparative study of etanercept plus methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis: a 12-week, double-blind, randomized, placebo-controlled study. J Formos Med Assoc. 2004;103(8):618–23.

28. Nishimoto N, Yoshizaki K, Miyasaka N, et al. Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial. Arthritis Rheum. 2004;50(6):1761–9.

29. Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: a double-blind randomised controlled trial. Lancet. 2004;363(9410):675–81.

30. van de Putte L, Atkins C, Malaise M, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis. 2004;63(5):508–16.

31. Abe T, Takeuchi T, Miyasaka N, et al. A multicenter, double-blind, randomized, placebo controlled trial of infliximab combined with low dose methotrexate in Japanese patients with rheumatoid arthritis. J Rheumatol. 2006;33(1):37–44.

32. Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized study. Ann Intern Med. 2006;144(12):865–76.

33. Combe B, Codreanu C, Fiocco U, et al. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. Ann Rheum Dis. 2006;65(10):1357–62.

34. De Filippis I, Caliri A, Anghelone S, Scibilia G, Lo Gullo R, Bagnato G. Improving outcomes in tumour necrosis factor a treatment: comparison of the efficacy of the tumour necrosis factor a blocking agents etanercept and infliximab in patients with active rheumatoid arthritis. Panminerva Med. 2006;48(2):129–35.

35. Westhovens R, Yocum D, Han J, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum. 2006;54(4):1075–86.

36. Kim HY, Lee SK, Song YW, et al. A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. APLAR J Rheumatol. 2007;10(1):9–16.

37. Schiff M, Keiserman M, Coddling C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis. 2008;67(8):1096–103.

38. Miyasaka N. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. Mod Rheumatol. 2008;18(3):252–62.

39. Kay J, Matteson EL, Dasgupta B, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. Arthritis Rheum. 2008;58(4):964–75.

40. Smolen J, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet. 2008;371(9617):987–97.

41. Keystone EC, van der Heijde D, Mason J, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a 52-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum. 2008;58(11):3319–29.

42. Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum. 2008;58(10):2968–80.

43. Keystone EC, Genovese MC, Klareskog L, et al. Golimumab, a human antibody to tumour necrosis factor alpha given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis. 2009;68(6):789–96.

44. Smolen J, Landewe R, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A
randomised controlled trial. Ann Rheum Dis. 2009;68(6):797–804.

45. Nishimoto N, Miyasaka N, Yamamoto K, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol. 2009;19(1):12–9.

46. Jones G, Sebba A, Gu J, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis. 2010;69(1):88–96.

47. Kameda H, Ueki Y, Saito K, et al. Etanercept (ETN) with methotrexate (MTX) is better than ETN monotherapy in patients with active rheumatoid arthritis despite MTX therapy: a randomized trial. Mod Rheumatol. 2010;20(6):531–8.

48. Emery P, Deodhar A, Rigby WF, et al. Efficacy and safety of different doses and retreatment of rituximab (RTX) in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab’s Efficacy in MTX iNadequate rEsponders [SERENE]). Ann Rheum Dis. 2010;69(9):1629–35.

49. Kremer JM, Blanco R, Brzosko M, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. Arthritis Rheum. 2011;63(3):609–21.

50. Kim HY, Hsu PN, Barba M, et al. Randomized comparison of etanercept with usual therapy in an Asian population with active rheumatoid arthritis: the APPEAL trial. Int J Rheum Dis. 2012;15(2):188–96.

51. Tanaka Y, Harigai M, Takeuchi T, et al. Golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis: results of the GO-FORTH study. Ann Rheum Dis. 2012;71(6):817–24.

52. van Vollenhoven R, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med. 2012;367(6):508–19.

53. Weinblatt M, Fleischmann R, Huizinga T, et al. Efficacy and safety of certolizumab pegol in a broad population of patients with active rheumatoid arthritis: results from the REALISTIC phase IIIb study. Rheumatol (Oxford). 2012;51(12):2204–14.

54. Gabay C, Emery P, Van Vollenhoven R, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet. 2013;381(9877):1541–50.

55. Kang YM, Park W, Park YE, et al. Efficacy and safety of certolizumab pegol (CZP) with concomitant methotrexate (MTX) in Korean rheumatoid arthritis (RA) patients (PTS) with an inadequate response to MTX. Ann Rheum Dis. 2013;71(Suppl 3):666.

56. Li Z, Zhang F, Kay J, et al. Safety and efficacy of subcutaneous golimumab in Chinese patients with active rheumatoid arthritis despite MTX therapy: results from a randomized, placebo-controlled, phase 3 trial. Arthritis Rheum. 2013;65(Suppl 10):S598–S59999.

57. van der Heijde D, Tanaka Y, Fleischmann R, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheum. 2013;65(3):559–70.

58. O’Dell JR, Mikuls TR, Taylor TH, et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med. 2013;369(4):307–18.

59. Dougdados M, Kissel K, Conaghan PG, et al. Clinical, radiographic and immunogenic effects after 1 year of tocilizumab-based treatment strategies in rheumatoid arthritis: the ACT-RAY study. Ann Rheum Dis. 2014;73(5):803–9.

60. Schiff M, Weinblatt ME, Valente R, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. Ann Rheum Dis. 2014;73(1):86–94.

61. Kivitz A, Olech E, Borosky M, et al. Subcutaneous tocilizumab versus placebo in combination with disease-modifying antirheumatic drugs in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2014;66(11):1653–61.

62. Yamamoto K, Takeuchi T, Yamanaka H, et al. Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial. Mod Rheumatol. 2014;24(5):715–24.

63. Machado DA, Guzman RM, Xavier RM, et al. Open-label observation of addition of etanercept versus a conventional disease-modifying antirheumatic drug in subjects with active rheumatoid arthritis.
despite methotrexate therapy in the Latin American region. J Clin Rheumatol. 2014;20(1):25–33.

64. Burmester GR, Rubbert-Roth A, Cantagrel A, et al. A randomised, double-blind, parallel-group study of the safety and efficacy of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with moderate to severe rheumatoid arthritis (SUMMAMCTA study). Ann Rheum Dis. 2014;73(1):69–74.

65. Genovese MC, Fleischmann R, Kivitz AJ, et al. Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a phase III study. Arthritis Rheumatol. 2015;67(6):424–37.

66. Smolen JS, Burmester GR, Combe B, et al. Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELE-RATE study. Lancet. 2016;388(10061):2763–74.

67. Peterfy C, Emery P, Tak PP, et al. MRI assessment of suppression of structural damage in patients with rheumatoid arthritis receiving rituximab: results from the randomised, placebo-controlled, double-blind RA-SCORE study. Ann Rheum Dis. 2016;75(1):170–7.

68. Burmester GR, Lin Y, Patel R, et al. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. Ann Rheum Dis. 2017;76(5):840–7.

69. Fleischmann R, Mysler E, Hall S, et al. Efficacy and safety of tofacitinib mono-therapy versus tofacitinib and methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet. 2017;390(10093):457–68.

70. Taylor PC, Keystone EC, Van Der Heijde D, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med. 2017;376(7):652–62.

71. Dougdas M, van der Heijde D, Chen YC, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. Ann Rheum Dis. 2017;76(1):88–95.

72. Bi L, Li Y, He L, et al. Rapid onset of response observed with certolizumab pegol in rheumatoid arthritis patients with inadequate response to methotrexate: efficacy and safety results of a randomized, double-blind, placebo-controlled phase 3 study. Arthritis Rheumatol. 2017;69:Abstr. 2451.

73. Daïen Cl, Morel J. Predictive factors of response to biological disease modifying antirheumatic drugs: towards personalized medicine. Mediators Inflamm. 2014;2014:386148.

74. Yamanaka H, Tanaka Y, Inoue E, et al. Efficacy and tolerability of tocilizumab in rheumatoid arthritis patients seen in daily clinical practice in Japan: results from a retrospective study (REACTION study). Mod Rheumatol. 2011;21(2):122–33.

75. Leffers HC, Østergaard M, Glintborg B, et al. Efficacy of abatacept and tocilizumab in patients with rheumatoid arthritis treated in clinical practice: results from the nationwide Danish DANBIO registry. Ann Rheum Dis. 2011;70(7):1216–22.

76. Maneiro RJ, Salgado E, Carmona L, Gomez-Reino JJ. Rheumatoid factor as predictor of response to abatacept, rituximab and tocilizumab in rheumatoid arthritis: systematic review and meta-analysis. Semin Arthritis Rheum. 2013;43(1):9–17.

77. Curtis JR, Jain A, Asling J, et al. A comparison of patient characteristics and outcomes in selected European and US rheumatoid arthritis registries. Semin Arthritis Rheum. 2010;40(1):2–14.e1.

78. Diffin JG, Lunt M, Marshall T, Chipping JR, Symmons DP, Verstappen SM. Has the severity of rheumatoid arthritis at presentation diminished over time? J Rheumatol. 2014;41(8):1590–9.

79. Sato E, Tanaka E, Ochiai M, et al. Chronological changes in baseline disease activity of patients with rheumatoid arthritis who received biologic DMARDs between 2003 and 2012. Mod Rheumatol. 2015;25(3):350–7.

80. Rahman MU, Buchanan J, Doyle MK, et al. Changes in patient characteristics in anti-tumour necrosis factor clinical trials for rheumatoid arthritis: results of an analysis of the literature over the past 16 years. Ann Rheum Dis. 2011;70(9):1631–40.

81. Aaltonen KJ, Ylikyla S, Tuulikki J, et al. Efficacy and effectiveness of tumour necrosis factor inhibitors in the treatment of rheumatoid arthritis in randomized controlled trials and routine clinical practice. Rheumatology. 2017;56(5):725–35.

82. Caporali R, Conti F, Covelli M, et al. Treating rheumatoid arthritis to target: an Italian rheumatologists’ survey on the acceptance of the treat-to-
83. Akdemir G, Markusse IM, Goekoop-Ruiterman YP, et al. Rheumatologists' adherence to a disease activity score steered treatment protocol in early arthritis patients is less if the target is remission. Clin Rheumatol. 2017;36(2):317–26.

84. Ford JA, Solomon DH. Challenges in implementing treat-to-target strategies in rheumatology. Rheum Dis Clin North Am. 2019;45(1):101–12.