

Comparative effectiveness of treatments for rheumatoid arthritis in clinical practice: A systematic review

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ARTICLE INFO

KEYWORDS:

Rheumatoid Arthritis
Biologic DMARD (bDMARD)
targeted-synthetic DMARD (tsDMARD)
Systematic Review
Comparative Effectiveness
Real-World Data

ABSTRACT

Objective: To assess real-world comparative effectiveness studies of biologic (b) and targeted synthetic (ts) disease-modifying antirheumatic drugs (DMARDs) in adults with rheumatoid arthritis (RA) through a systematic review.

Methods: We searched Medline for journal articles (2001–2021) and Embase® for abstracts presented at the European Alliance of Associations for Rheumatology and American College of Rheumatology (ACR) 2020 and 2021 annual meetings on non-randomized studies comparing the effectiveness of b/tsDMARDs using ACR-recommended disease activity measures, measures of functional status, and patient-reported outcomes (HAQ, PROMIS PF, patient pain, Patient and Physician Global Assessment of disease activity). Methodological heterogeneity between studies precluded meta-analyses. Risk of bias was assessed using the Cochrane Risk Of Bias In Non-randomized Studies of Interventions-I tool.

Results: Of 1283 records screened, 68 were selected for data extraction, of which 1 was excluded due to critical risk of bias. Most studies were multicenter observational cohort/registry studies ($n = 60$) and were published between 2011 and 2021 ($n = 60$). Mean or median reported RA duration was between 6 and 15 years. Disease Activity Score in 28 joints (46 studies), Clinical Disease Activity Index (37 studies), and Health Assessment Questionnaire-Disability Index (32 studies) were the most common outcomes used in clinical practice, with regional differences identified. The most common comparison was between tumor necrosis factor inhibitors (TNFis) and non-TNFi bDMARDs (35 studies). There were no evident differences between b/tsDMARDs in clinical effectiveness.

Conclusion: This systematic review summarizing real-world evidence from a very large number of global studies found there are many effective options for the treatment of RA, but relatively less evidence to support the use of any one b/tsDMARD or drug class over another. Treatment for patients with RA should be tailored to suit individual clinical profiles. Further research is needed to identify whether specific patient subgroups may benefit from specific drug classes.

Introduction

Rheumatoid arthritis (RA) is a debilitating inflammatory autoimmune disorder that is associated with progressive, irreversible joint

damage and functional disability, extra-articular manifestations, and systemic complications, with a cumulative worsening of patients' quality of life and an increased risk of early death [1,2].

A changing treatment landscape over the past 20 years has led to the

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<https://doi.org/10.1016/j.semarthrit.2023.152249>

Available online 6 August 2023

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availability of a wide array of therapeutic agents with varying targets. The European Alliance of Associations for Rheumatology (EULAR) and American College of Rheumatology (ACR) guidelines recommend a treat-to-target strategy with attaining low disease activity or remission as the main therapeutic goal [3,4]. The availability of multiple drugs with different mechanisms of action (MOAs) makes such a targeted and dynamic strategy possible.

A wealth of data on the efficacy and safety of conventional synthetic (cs), biologic (b), and targeted synthetic (ts) disease-modifying antirheumatic drugs (DMARDs) in patients with RA are available from published randomized controlled trials (RCTs) and real-world data from studies conducted in clinical practice. RCTs evaluating the efficacy and safety of b/tsDMARDs in patients with RA rarely include direct head-to-head trials between different agents. Additionally, prior studies have shown that 84–93% of patients with RA seen in clinical practice would not be eligible for inclusion in RCTs [5,6]. Thus, participants of RCTs are not representative of the general clinical RA population. While non-randomized studies conducted in real-life clinical settings are at risk of bias through sample selection, data collection, and analysis, such real-world data can nevertheless provide valuable insights, augmenting data from RCTs and providing important information from routine clinical practice [7].

The present study assessed real-world comparative effectiveness studies of bDMARDs and tsDMARDs in adults with RA by systematic review.

Methods

Data source and search strategy

A systematic review was performed following The Cochrane Handbook for Systematic Reviews of Interventions, version 6.3 [8]. The systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [9]. Searches for published journal articles and conference abstracts were carried out using the Medline and Embase® databases, respectively, using pre-specified search terms (**Supplementary Tables S1 and S2**); terms included free text and Medical Subject Heading terms. At the time the literature search was carried out, the only tsDMARDs licensed for use in RA were Janus kinase inhibitors (JAKi) [10]; this is reflected in the chosen search terms (**Supplementary Table S1**).

The date range used for the Medline database search was from January 1, 2001, up to and including November 11, 2021, (at the time the searches were carried out, Bird P, et al. Clin Rheumatol 2022 [11] and Curtis JR, et al. ACR Open Rheumatol 2022 [12] had been published online ahead of print). The start date of the search was chosen to represent the previous 20 years of research and coincided with the introduction of bDMARDs to the market in the late 1990s and allowed enough time to capture real-world data comparing drugs with different MOAs beyond tumor necrosis factor inhibitors (TNFi). Systematic reviews reporting data from real-world studies in RA that met protocol inclusion criteria and were included in the full text review stage were hand searched for relevant studies. The Embase® database was used to search abstracts from the 2020 and 2021 ACR and EULAR annual meetings.

Eligibility

Study eligibility criteria were created using the Population, Intervention, Comparator(s), Outcomes, and Study design process (**Supplementary Table S3**). Studies of interest were prospective or retrospective real-world studies (including observational [cohort and case report] and longitudinal studies) and studies based on data from national disease and bDMARD registries that compared the treatment effectiveness of b/tsDMARDs in adult patients (≥ 18 years of age) with RA. Only studies published in English with a sample size ≥ 100 subjects were included.

Interventions of interest included bDMARDs (including within-class comparisons), their biosimilars by MOA, and tsDMARDs with an indication in RA as outlined in the search terms (**Supplementary Tables S1 and S2**). Interventions of interest could be administered as monotherapy or in combination with csDMARDs. Original research (full manuscripts, brief reports, and congress abstracts), systematic reviews, and network meta-analyses were all considered for inclusion.

The systematic review protocol excluded studies conducted in autoimmune diseases other than RA and studies that were designed to assess RA and a specific comorbidity (e.g., malignancy or lung disease). Where studies included patients with RA and other autoimmune diseases, those studies were only included if outcomes data were reported separately for each indication and could be extracted. In addition, studies in pediatric patients, studies that included only csDMARDs, and studies that only reported safety outcomes were also excluded (**Supplementary Table S3**). RCTs, non-human studies, cross-sectional studies, and case series were also excluded, as were non-original science articles (narrative reviews, opinions, commentaries, diagnostic or treatment guidelines, consensus statements, and letters to editors). Finally, any study that presented with a critical risk of bias (see the Assessment of Bias section) was also excluded from further analysis.

Outcome measures for comparing effectiveness

The following 11 measures of disease activity, which were reviewed by the ACR and fulfilled a “minimum standard” for regular use in most clinic settings [13], were included in the protocol for comparing the effectiveness of agents in real-world studies (**Supplementary Table S3**): Clinical Disease Activity Index (CDAI); Disease Activity Score (DAS); DAS in 28 joints using erythrocyte sedimentation rate or C-reactive protein (DAS28 [ESR] or DAS28 [CRP]); patient-derived DAS28; Hospital Universitario La Princesa Index (HUPI); Multi Biomarker Disease Activity (MBDA) score; Rheumatoid Arthritis Disease Activity Index (RADAI); RADAI-5; Routine Assessment of Patient Index Data 3 (RAPID-3); RAPID-5; and Simplified Disease Activity Index (SDAI). Of these, DAS28 (ESR or CRP), CDAI, SDAI, and RAPID-3 were recommended by the ACR [13].

In addition, the following measures of functional status and patient-reported outcome (PRO) measures were included: Health Assessment Questionnaire (HAQ; all formats, including modified HAQ, multidimensional HAQ, HAQ-Disability Index, and HAQ-II), Patient-Reported Outcomes Measurement Information System for Physical Function (PROMIS PF), Patient Global Assessment of pain, Physician Global Assessment of disease activity (PhGA), and Patient Global Assessment of disease activity (PGA; **Supplementary Table S3**).

The high degree of heterogeneity between studies (e.g., in population, study design, methods of data collection, and line of therapy reported) made it difficult to directly compare outcomes data and meant that meta-analyses or network analyses could not be conducted.

Screening and data extraction

Duplicates were removed before screening of titles and abstracts by one reviewer to determine eligibility according to the predefined inclusion and exclusion criteria. The remaining full text articles were evaluated independently by two reviewers. Differences of opinion were discussed and reconciled by the two reviewers to decide the final inclusion and exclusion of citations. Studies where data could not be accurately extracted from manuscript figures were excluded from the systematic review.

In accordance with Cochrane methodology, data extraction commenced after all articles for data extraction were sourced. Data from each of the relevant publications were extracted by one reviewer before verification against the source publications by a second reviewer. The following information was extracted from each publication: citation details, type of study, study design characteristics, patient numbers,

demographics and selected baseline characteristics, disease activity outcomes, measures of functional status, and PROs. Data relating to baseline confounders (required for completing the assessment of bias; see the Assessment of Bias section) were also extracted. All results that were compatible with each protocol-defined outcome were extracted for each study, where possible. Data for continuous (e.g., mean scores and standard deviations, medians and ranges, absolute mean/median changes from baseline, standardized mean differences, and standard errors) and categorical (e.g., the proportion of patients and/or relative risk of achieving disease remission or low disease activity [LDA] or minimal clinically important difference [MCID]) variables were extracted. Studies were categorized to assess comparative effectiveness by MOA comparison (TNFi versus other MOA bDMARDs, TNFi versus TNFi, JAKi versus TNFi/non-TNFi bDMARDs, non-TNFi bDMARDs versus other non-TNFi bDMARDs, or JAKi versus JAKi), disease measure (as previously listed), previous drug exposure status (b/tsDMARD naive/experienced), and serostatus (rheumatoid factor [RF]/anti-citrullinated protein antibody [ACPA] +/–). Extracted data were tabulated and assessed according to MOA comparison. Histograms were used to assess publications categorized by MOA comparison, outcome measures for comparing effectiveness, and geographical distribution of outcome measures used. Study data were also tabulated and assessed by previous drug exposure status (b/tsDMARD naive/experienced). Studies with some missing summary statistics were included for data extraction but only analyzed in reference to the data that were presented in the article. No manipulation of extracted data was performed. Where reported results were statistically significant, *P* values and 95% confidence intervals were recorded.

Assessment of bias

Risk of bias was assessed within individual studies using the Cochrane Risk Of Bias In Non-randomized Studies of Interventions (ROBINS)-I tool [7]. ROBINS-I offers a robust methodology that compares each individual study selected for the systematic review with a hypothetical ‘target’ RCT (i.e., the gold standard in terms of study design). The tool assesses seven distinct domains (two pre-intervention domains, one at intervention, and four post-intervention) through which bias might be introduced. Overall risk of bias for each study was designated as low, moderate, serious, or critical. Studies that scored low, moderate, or serious were retained in the analysis; any studies scored as critical were excluded. The risk of bias assessment for each paper was performed by one reviewer.

During protocol development (ROBINS-I tool, Stage I), baseline confounders considered likely to be common to intervention studies in RA and possible co-interventions likely to be used in these patients were identified. Possible baseline confounders included: age, sex, disease duration, previous treatment (line of therapy), concomitant medications including csDMARDs such as methotrexate (MTX) and glucocorticoids, disease activity (e.g., CDAI, SDAI, DAS28, total/swollen joint count, PGA, PhGA, patient pain), RF/ACPA serostatus, functional disability (e.g., ACR functional class, HAQ/mHAQ), and comorbidities. Possible co-interventions included: concomitant oral/injectable steroids, concomitant MTX, concomitant csDMARDs, joint surgery, and lifestyle (weight loss, smoking cessation).

For domain 3 (bias due to classification of interventions), very few studies in the systematic review reported either dose or route of administration of medications. However, because these studies were conducted using licensed b/tsDMARDs in clinical practice, it seemed likely that most would be used according to label; as such, most studies were rated as having moderate risk in this domain. For domain 6 (bias in measurement of outcomes), although investigators and patients were likely to have been aware of the medication that a patient was taking, most studies/analyses used measures of disease activity/disability that are well-validated and routinely used to assess patients with RA and were, therefore, rated as having a moderate rather than serious risk of

bias.

Results

Search results

A total of 1276 records were identified in the searches: 786 full publications listed on Medline and 490 conference abstracts (Fig. 1). An additional 7 records were identified through hand searches of systematic reviews that included non-randomized clinical trials that were not already captured by the automated searches. Overall, 68 records were selected following full-text screening for data extraction [10–12,14–75]. Citations for the 43 publications that were excluded based on review of the full text article are listed in **Supplementary Table S4**. Based on the assessment of critical bias, one paper [14] was excluded from further discussion, leaving a total of 67 papers included in the final review (Fig. 1 and **Supplementary Figure 1**).

Characteristics of studies included in the systematic review

Most studies (*n* = 60) were published within the last decade (2011–2021); only 6 studies were published between 2001 and 2010, of which none were published earlier than 2006. The majority of studies (*n* = 60) were multicenter observational cohort or registry studies, while 7 were conducted in a single center (**Supplementary Table S5 and Supplementary results**). There were no case-control studies or studies of other designs (e.g., self-controlled). Overall, 35 studies were reported as prospective longitudinal cohort studies, 21 were retrospective in design, and 3 included both prospective and retrospectively collected data. A further 9 studies reported data from national patient registries and are presumed to have collected data prospectively from the time of patient enrollment, but this was not specified in the publications.

There was considerable heterogeneity between the studies in terms of inclusion/exclusion criteria, study design, data collection, line of therapy, and statistical methods (**Supplementary Table S5**). The sizes of study population varied from 100 to 11,505 patients. Most studies reported clinical effectiveness data at follow-up time points of 6 and/or 12 months after b/tsDMARD initiation. Twelve studies captured data at 3 months and/or reported longer-term data at 18 or 24 months. Most studies did not report data stratified by line of therapy; however, most did specify that patients had previous exposure to ≥ 1 prior b/tsDMARDs. A total of 11 studies reported outcomes data for patients who were b/tsDMARD-naïve [15,17,21,26,39,40,52,53,56,62,76] and 24 studies reported data for patients who were b/tsDMARD-experienced [10,12,15,18,23,24,29,30,32,33,38,40,42–45,50,52,55,63,64,68,71,72]; 3 studies overlapped, reporting outcomes data that were stratified by b/tsDMARD-naïve/experienced status [15,40,52]. Additionally, 23 further studies did not stratify outcomes data by line of therapy but had mixed populations that included patients who were b/tsDMARD-naïve or -experienced, with the proportion of patients who were bDMARD-naïve ranging from 1.9–97.3% [20,25,27,28,34,35,37,41,46–49,54,57,59,61,65–67,73–75,77]. Ten studies did not clearly report the composition of the population [16,19,22,31,36,51,58,60,69,70,78].

Six studies included an analysis of disease activity, functional status, or PROs by patients’ RF/ACPA seropositive and seronegative status [27, 29,41,50,65,74] (**Supplementary Results**).

Assessment of bias

Of the 68 papers that underwent assessment of bias, 3 records had a moderate overall risk of bias and 64 had a serious risk (**Supplementary Figure 1 and Supplementary Results**). One paper was given an overall risk score of ‘critical’ because 43% of patients in the baricitinib arm were excluded for reasons that were not stated in the original paper [14].

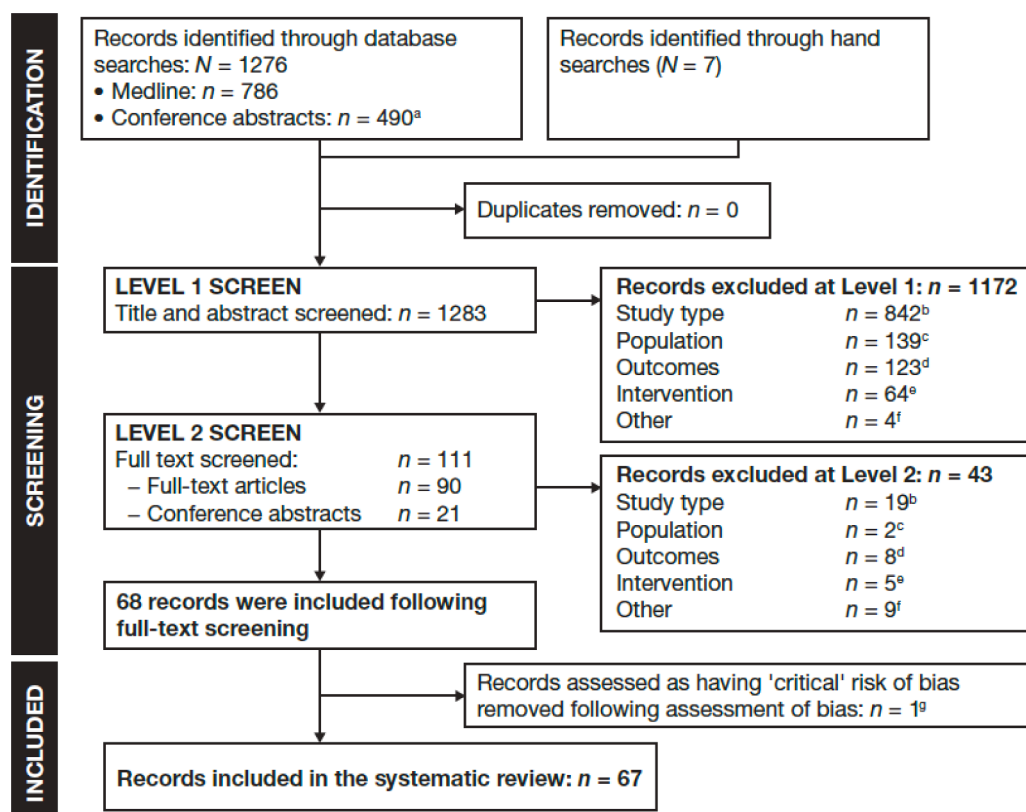


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram

^a EULAR and ACR 2020 and 2021 annual meetings. ^b Reasons for exclusion (combined for Levels 1 and 2) due to study type included: not a comparative efficacy study ($n = 610$); safety study ($n = 103$); randomized controlled trial/systematic review reporting only randomized controlled trials ($n = 104$); narrative review ($n = 22$); cross-sectional study ($n = 8$); immunogenicity study ($n = 6$); phase 1b study ($n = 3$); animal study ($n = 2$); case study ($n = 1$); pharmacokinetic/pharmacodynamic study ($n = 1$); in vitro study ($n = 1$). ^c Reasons for exclusion due to population: sample size < 100 ($n = 40$); indication other than RA ($n = 91$); assessed RA together with a comorbidity ($n = 10$). ^d No systematic review protocol-defined outcomes were included in the study. ^e Reasons for exclusion due to intervention included: intervention not relevant to protocol ($n = 66$) and comparison of originator versus biosimilar of same mechanism of action ($n = 3$). ^f Other reasons for exclusion: data relevant to systematic review protocol outcomes could not be extracted from published figures ($n = 5$); insufficient data in the conference abstract ($n = 2$); conference abstract had later full publication with identical data ($n = 2$); incomplete manuscript abstract, conference abstract not available.

able, later update to study captured in search, ACR 2021 abstract was an encore of EULAR 2021 abstract ($n = 1$ each). ^g One paper was deleted after completion of assessment of bias because it was scored as having a 'critical' overall risk of bias [14]. ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; RA: rheumatoid arthritis.

Patient demographics and baseline characteristics

For most of the studies included, mean or median reported age ranged from 50–65 years and the proportion of patients who were female ranged from 70–90% (Supplementary Table S5). All studies reported data for patients with established RA, with the majority reporting a mean or median disease duration that ranged from 6–15 years. Most studies reported the proportion of patients who were seropositive at baseline as ranging from 40–90%. Of the studies reporting baseline RF/ACPA serostatus, 16 reported RF only and 27 reported RF and/or ACPA.

b/tsDMARD comparisons included in selected studies

When categorized by b/tsDMARD MOA, the most common drug/drug class comparison was between a TNFi and a non-TNFi bDMARD with another MOA (35 studies; Fig. 2). Of these, 11 studies compared TNFi with tocilizumab or an unspecified interleukin (IL)-6 receptor inhibitor (IL-6Ri) [15,26,42,49,52,55,56,63,67,71,76], 9 with rituximab only [24,29,32,33,36,38,44,50,72], 7 with abatacept only [40,41,43,46,53,54,74], and 8 with non-TNFi bDMARDs of multiple MOA [12,17,18,27,30,47,68,75]. Of the 14 studies that compared a TNFi with other TNFis, 12 included adalimumab, etanercept, and infliximab [21–23,25,28,31,34,39,51,65,70,78]; 1 included golimumab [69]; and 1 compared

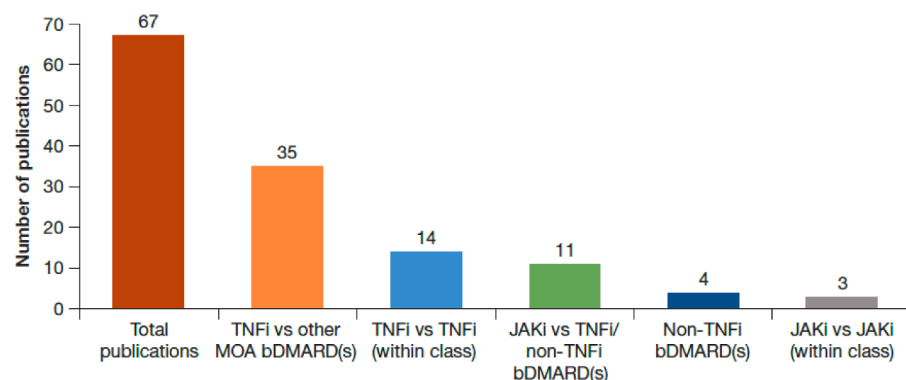


Fig. 2. Number of publications categorized by b/tsDMARD drug/class comparison

At the time of the literature search, the only tsDMARDs licensed for use in patients with RA were JAKis [10], which is reflected in the studies selected for inclusion. The only JAKis included in papers selected for this systematic review were tofacitinib and baricitinib. b: biologic; DMARD: disease-modifying antirheumatic drug; JAKi: Janus kinase inhibitor; MOA: mechanism of action; TNFi: tumor necrosis factor inhibitor; ts: targeted synthetic.

only adalimumab and etanercept [61].

At the time of the literature search, the only tsDMARDs licensed for use in patients with RA were JAKis, which is reflected in the studies selected for inclusion; the only JAKis included in papers selected for this systematic review were tofacitinib and baricitinib (**Supplementary Table S6**). Of the 11 studies that compared a JAKi with a TNFi and/or a non-TNFi bDMARD (**Fig. 2**), 8 included only tofacitinib [10,11,19,58,60,62,66,73], 2 compared baricitinib with other b/tsDMARDs [20,37], and 1 compared both baricitinib and tofacitinib with other bDMARDs [16]. Only 4 studies compared non-TNFi bDMARDs alone, 3 compared abatacept with tocilizumab [45,57,77], and 1 compared abatacept, tocilizumab, and rituximab [64]. All 3 studies comparing only JAKis included baricitinib and tofacitinib [35,48,59].

Assessment of comparative effectiveness

In terms of the 16 protocol-defined outcomes, DAS28, CDAI, and HAQ were the most common with 46, 37, and 32 studies reporting data for these outcomes, respectively (**Fig. 3**). Less commonly reported were PGA ($n = 13$), SDAI ($n = 10$), patient pain ($n = 9$), PhGA ($n = 6$), RAPID-3 ($n = 4$), and PROMIS PF and RADAI ($n = 1$ each). No study included DAS, patient-derived DAS28, HUPI, MBDA score, RADAI-5, or RAPID-5. When considering geographic region, DAS28 was more commonly used in studies carried out in Europe than in those conducted in the USA and/or Canada. CDAI and HAQ were more frequently used in studies from the USA and/or Canada or the rest of the world than in Europe (**Fig. 4**). **Table 1** and **Supplementary Table S6** show a summary of the number of studies reporting the most common outcomes by drug class comparison and individual drugs studied.

Due to the substantial heterogeneity between the studies, direct comparisons could not be made; however, the sections below describe potential trends (or lack of trends) among similar drug MOAs.

Clinical disease activity outcomes

A total of 11 studies compared DAS28 outcomes in response to treatment with different TNFis and showed no apparent differences between individual agents (**Supplementary Table S7**) [21–23,28,31,34,39,51,65,69,78]. Among the 24 studies that compared TNFi or non-TNFi bDMARDs for DAS28 as the outcome, 18 appeared to show trends favoring agents with an alternative MOA (tocilizumab/IL-6Ri [15,17,26,47,49,52,67,68,75,76], rituximab [24,29,32,33,38,50], and abatacept [44,46]). The 6 studies comparing JAKis with bDMARDs (TNFi, abatacept, anakinra, rituximab, and IL-6Ri) showed no apparent trends in terms of differences between agents for DAS28 [10,11,16,19,58,62]. Three studies compared non-TNFi bDMARDs only (abatacept, rituximab, tocilizumab) [57,64,77] and 2 studies compared JAKis only (baricitinib versus tofacitinib) [35,48], with no differences. Overall,

there were no evident differences between agents in DAS28 outcomes across studies.

Overall, 9 out of 20 studies evaluating CDAI response to treatment reported trends favoring non-TNFi bDMARDs over TNFis (tocilizumab/IL-6Ri [15,26,30,67,68,75], abatacept [40,53], or rituximab [44]; **Supplementary Table S8**). Studies ($n = 10$) comparing JAKis with bDMARDs (TNFis, abatacept, anakinra, rituximab, and IL-6Ri) showed no apparent differences in CDAI response between agents or MOA [10,11,16,19,20,37,60,62,66,73]. Similarly, 3 studies comparing only TNFis [21,39,78], 2 studies comparing only non-TNFi bDMARDs [45,77], and 2 studies comparing only JAKis [48,59] reported no trends. Overall, there were no observable differences between agents in CDAI across studies.

Ten studies included data on SDAI (**Supplementary Table S9**) [11,19,21,48,54,59,67,68,77,78]. In general, for comparisons of bDMARDs, all drug classes performed relatively similarly in terms of the proportion of patients achieving SDAI remission at 6 or 12 months. One of the 2 studies that compared TNFis (adalimumab, etanercept, and infliximab), showed a significantly greater proportion of patients in remission with adalimumab versus infliximab and etanercept [78]. One of the 2 studies comparing JAKis showed a significantly greater mean change from baseline with baricitinib versus tofacitinib [59]. There were no evident differences observed between agents in SDAI.

Functional status and patient-reported outcome (PRO) measures

The majority of studies reported data on mean or median change from baseline in HAQ (**Supplementary Table S10**). There were no trends in terms of differences between agents for studies comparing individual TNFis ($n = 7$) [25,31,51,61,69,70,78], TNFis with non-TNFi bDMARDs ($n = 15$) [24,26,29,40,42–44,52,63,67,68,71,72,75], JAKis with bDMARDs ($n = 6$) [16,20,58,60,62,73], non-TNFi bDMARDs with other non-TNFi bDMARDs ($n = 2$) [45,57], or JAKis with other JAKis ($n = 1$) [59]. Similarly, among the 5 studies reporting HAQ MCID data, there were no differences between any of the agents. Overall, across these studies, there were no evident differences observed between agents in HAQ.

Thirteen studies included data on PGA (**Supplementary Table S11**) [15,20,24,29,30,57,67,68,71,73,76–78]. In terms of mean change from baseline in PGA, all drug classes performed relatively similarly at the different time points represented, with no specific trends for improvement for one class of b/tsDMARD over another. Overall, there were no evident differences observed between agents in PGA.

Nine studies included data on patient pain (**Supplementary Table S12**) [15,20,26,29,30,66,71,73,78]. Of the studies that reported mean change from baseline in patient pain, there was a trend toward greater mean change with non-TNFi bDMARDs (tocilizumab and rituximab) compared with TNFis [15,26,29,30]. For studies that included a

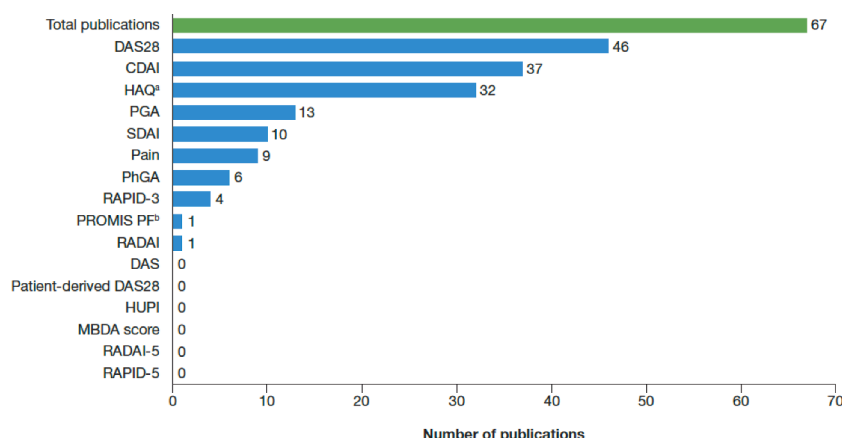


Fig. 3. Number of publications categorized by systematic review protocol-defined outcome

^a HAQ included all formats, including modified HAQ, multidimensional-HAQ, HAQ-Disability Index and HAQ-II. ^b PROMIS PF: returned papers with 5 scales: SF-10a, -10b, -20a, -4, and computer adaptive test; one paper included a PROMIS PF outcome (EQ-5D-3L) [58]. CDAI: Clinical Disease Activity Index; DAS: Disease Activity Score; DAS28: DAS in 28 joints; EQ-5D-3L: European Quality of Life 5 Dimensions 3 Level Version; HAQ: Health Assessment Questionnaire; HUPI: Hospital Universitario La Princesa Index; MBDA: Multi-Biomarker Disease Activity score; Pain: Patient Global Assessment of pain; PGA: Patient Global Assessment of disease activity; PROMIS PF: Patient-Reported Outcomes Measurement Information System for Physical Function; PhGA: Physician Global Assessment of disease activity; RADAI: Rheumatoid Arthritis Disease Activity Index; RAPID: Routine Assessment of Patient Index Data; SDAI: Simplified Disease Activity Index; SF: Short-Form.

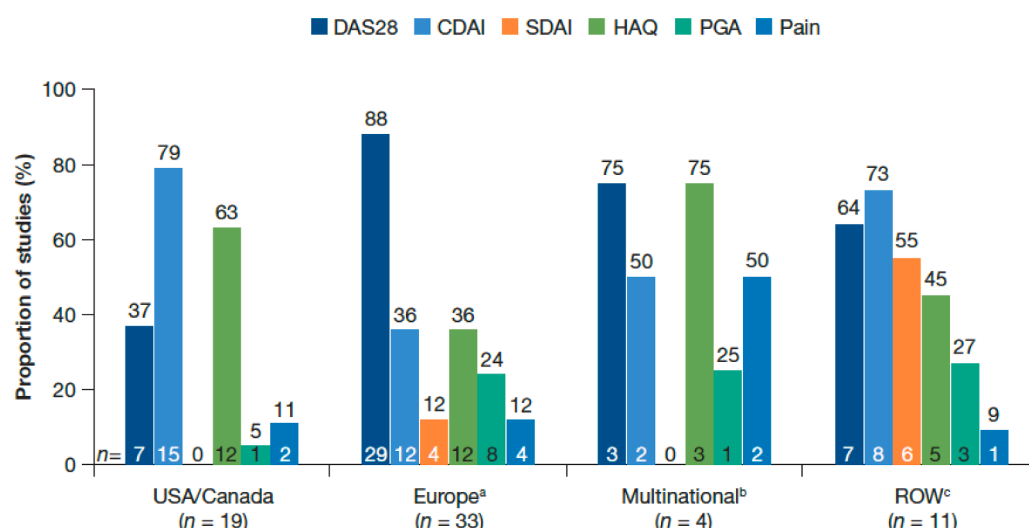


Fig. 4. Frequency of use of systematic review protocol-defined outcomes by geographic region

^a Includes single-country and multinational studies. ^b Studies with data from multiple countries (including pan-European and global studies). ^c Single-country studies from regions other than USA, Canada, or Europe (includes Australia, Colombia, and Japan). CDAI: Clinical Disease Activity Index; DAS28: Disease Activity Score in 28 joints; HAQ: Health Assessment Questionnaire; Pain: Patient Global Assessment of pain; PGA: Patient Global Assessment of disease activity; ROW: rest of world; SDAI: Simplified Disease Activity Index.

Table 1

Summary of number of studies by systematic review protocol outcomes, drug class, and individual treatment^a

Number of studies	DAS28 n = 46	CDAI n = 37	SDAI n = 10	HAQ n = 32	PGA n = 13	Pain n = 9
Studies with 'complete' (i.e., baseline and follow-up) data, n (%)	40 (87)	31 (84)	6 (60)	28 (88)	9 (69)	4 (44)
TNFi vs other MOA bDMARDs	n = 24	n = 20	n = 3	n = 15	n = 8	n = 5
TNFi vs TNFi	n = 11	n = 3	n = 2	n = 7	n = 1	n = 1
JAKi vs TNFi/non-TNFi bDMARD	n = 6	n = 10	n = 2	n = 6	n = 2	n = 3
Non-TNFi bDMARD	n = 3	n = 2	n = 1	n = 3	n = 2	n = 0
JAKi vs JAKi	n = 2	n = 2	n = 2	n = 1	n = 0	n = 0

b: biologic; CDAI: Clinical Disease Activity Index; DAS28: Disease Activity Score in 28 joints; DMARD: disease-modifying antirheumatic drug; HAQ: Health Assessment Questionnaire; JAKi = Janus kinase inhibitor; MOA: mechanism of action; Pain: Patient Global Assessment of pain; PGA: Patient Global Assessment of disease activity; SDAI: Simplified Disease Activity Index; TNFi: tumor necrosis factor inhibitor.

^a Note that this table indicates specific drugs included in the studies, of which many included two or more drugs, therefore the numbers do not tally to the section totals.

JAKi, there was no difference observed in mean change from baseline between baricitinib [20] or tofacitinib [73] and other b/tsDMARDs. As reported for the outcomes above, there were no evident differences observed between agents in patient pain.

Key outcomes by b/tsDMARD-naïve/experienced status

In terms of comparative effectiveness between agents/drug class, there were similar trends in key outcomes data (DAS28, CDAI, and HAQ) in studies that stratified by line of therapy (i.e., in b/tsDMARD-naïve and/or -experienced populations) to those observed in the overall dataset of 67 studies (Supplementary Tables S13 and S14). Only studies that compared TNFis with other non-TNFi bDMARDs demonstrated differences between agents, with a slight trend toward greater response with a non-TNFi bDMARD versus TNFis in 5 studies in patients who were bDMARD-naïve (all comparing tocilizumab/IL-6Ri with TNFis [15,17,26,52,76]) and in 13 studies in patients who were bDMARD-experienced (3 tocilizumab studies [15,30,68], 8 rituximab

studies [24,29,32,33,38,44,50,72], and 2 abatacept studies [40,43]).

Discussion

Using ACR-reviewed disease activity measures [13], measures of functional status, and PROs, this systematic review assessed the comparative effectiveness of currently available b/tsDMARDs in non-randomized interventional studies conducted in real-world settings. This analysis represents one of the largest datasets of its kind, allowing us to build a qualitative picture of real-world comparative research on the relative effectiveness of b/tsDMARDs in RA that has taken place over the last two decades (2001–2021). Overall, reported outcomes data showed there are many effective options for the treatment of RA; however, there were no evident differences between agents in clinical effectiveness and no evidence to support the use of any specific b/tsDMARD or MOA over another. This finding is in agreement with current treatment guidelines which, in terms of clinical efficacy, do not differentiate between b/tsDMARD agents [3,4]. Thus, when it comes to selecting appropriate treatments for individual patients, arguably individual drug or drug class matters less than adopting a personalized treatment approach that focuses on therapy selection and considers an individual patient's clinical profile and preferences.

Heterogeneity in many aspects of the studies included in this systematic review means the following differences observed between treatments should be interpreted with caution. Studies making within-class comparisons for TNFis (largely etanercept, infliximab, and adalimumab) and those that compared a JAKi with bDMARDs showed no apparent difference between individual agents in terms of DAS28, CDAI, or HAQ outcomes. Studies that compared the use of a TNFi with bDMARDs with alternative MOAs did show a trend toward efficacy benefits with non-TNFi (abatacept, rituximab, or tocilizumab) over TNFis in DAS28 and CDAI response. This is not unexpected as most of these studies included a proportion of bDMARD-experienced patients (most commonly treated with prior TNFi), and prior studies have shown better drug persistence and efficacy when switching to a new MOA versus cycling to another TNFi [79,80]. However, this systematic review was not designed to assess treatment differences based on patients treatment status (b/tsDMARD-naïve and -experienced) or line of therapy; thus, the possibility of channeling bias cannot be ruled out.

Variability in methods of disease assessment, together with a high degree of heterogeneity observed in study design (different lengths of follow-up, inclusion/exclusion criteria, primary disease activity measure [e.g., DAS28 (ESR)/(CRP)/not specified]), patient population (concomitant medication, unknown comorbidities), patient numbers (ranged from 100 to 11,505 patients), line of therapy (biologic-naïve/

experienced, monotherapy/combination therapy), data collection and analysis methods (continuous and/or categorical variables, descriptive data/statistical analysis [e.g., mean, median, change from baseline, between-treatment difference, percent LDA/remission, odds ratio, un-adjusted/adjusted]) and interventions studied, make it challenging to directly compare outcomes data captured in this systematic review. Because of these variations, it was not possible to perform network or meta-analyses.

The wide availability of efficacious and well-tolerated therapies with a range of MOAs allows for dynamic, targeted, and effective treatment strategies in patients with RA [3,4] and, in presenting clinicians with certain challenges when deciding on the most appropriate treatment, highlights a need for data comparing the effectiveness of these drugs. While our study focused on real-world data, a few RCTs have been performed that included direct comparisons between b/tsDMARDs [81–86]. Notably, the ORAL-Strategy and Exxcelerate trials concluded that tofacitinib and certolizumab pegol, respectively, were non-inferior to adalimumab [81,85]. The RA-BEAM and Select-Compare studies showed that baricitinib and upadacitinib, respectively, were superior to adalimumab [82,86]. Ultimately, treatment guidelines, influenced by both real-world studies and RCTs, recommend that treatment should be tailored to suit individual patient needs [3,4]. Furthermore, the strict eligibility criteria of RCTs mean that selected patients do not necessarily reflect the heterogeneous populations found in real-world clinical practice [5]. Thus, comparative data from real-world non-randomized interventional trials are both useful and needed.

The drawbacks associated with the broad heterogeneity found in real-world observational trials has led to the concept of ‘target trial emulation’, where investigators pose a research question using observational data as if they were conducting an idealized RCT. A recent systematic review used such a ‘target trial emulation’ framework to evaluate the design limitations of comparative effectiveness research studies in RA [87]. The authors found that 94% of 31 studies included had at least 1 design limitation, the most common of which related to eligibility criteria, causal contrasts, and treatment assignment [87]. We note that few studies considered line of therapy in the study design as either a confounding or stratifying variable. This highlights the importance of considering line of therapy in RA pharmacoepidemiologic studies. In our systematic review, even when patient data were collected prospectively from cohort entry, most studies applied eligibility criteria that included some post-baseline information. Despite this shortcoming, the concept of ‘true prospective recruitment’ has the potential to be highly restrictive for studies conducted in clinical settings. Clinical cohorts are, by their nature, diverse, and evaluating a drug’s effectiveness in such variable populations is what makes observational studies useful in comparison with a more idealized population in RCTs.

The heterogeneity of the studies in this systematic review seems to encapsulate the reality of patient care where physicians are faced with deciding the best treatment regimen for individual patients. Our findings support current treatment guidelines that state there are no appreciable differences between agents, at least in terms of clinical efficacy [3,4]. One might also expect to see fewer obvious treatment differences in real-world studies versus RCTs, given that rheumatologists tend to take a personalized patient-centered approach, choosing treatments that optimize outcomes and rarely keeping a patient on drugs that produce less than favorable responses. This, taken together with the availability of an extensive armamentarium of agents with different MOAs, suggests that perhaps initial choice of agent matters less than implementing an effective treatment strategy.

There were several strengths to this study. This was a truly comprehensive, global search of the published literature for real-world comparative effectiveness research on b/tsDMARDs. The protocol was designed to search for studies that included all bDMARDs and tsDMARDs currently licensed for the treatment of RA conducted across the world over the past two decades (i.e., from shortly after release of the first bDMARDs on to the market in 1999). The protocol included a broad

range of ACR-recommended disease activity measures [13], common measures of functional status, and PROs. Finally, assessment of bias was conducted for each publication included using ROBINS-I [7], a tool that has been specifically designed to assess risk of bias in non-randomized intervention trials.

There were also several limitations. First, the initial search results were only screened by one reviewer – a more robust strategy may have consisted of two reviewers screening, with a third to resolve any disputes. Second, minor differences in terms searched for versus those used in published journal articles may have resulted in some papers being overlooked for inclusion. The aforementioned heterogeneous nature of the studies included in the review – in terms of research question, population, study design, data collection, methods of analysis, and intervention and outcomes assessed – made further network or meta-analyses infeasible, which in turn made it hard to directly compare outcomes data for different therapeutic agents. Indeed, previous studies have highlighted the design limitations and inadequacies of comparative effectiveness research studies in RA, which hindered comprehensive interpretation of the data (defining eligibility criteria and covariates for adjustment, accounting for treatment changes and missing data, the number of outcomes explored) [87,88]. Therefore, when designing future comparative effectiveness studies, researchers would be advised to follow the 2022 EULAR recommendations for analyzing and reporting comparative effectiveness research using observational data [89]. It may also be beneficial for experienced practitioners to obtain consistent, systematic, high-quality assessments of patient/disease characteristics and outcome measures at every clinic visit, with the understanding that all drug initiations may be used for future comparisons. Difficulties in determining trends within such a highly variable dataset, or where only a small number of studies show a particular outcome, further limits the generalizability of the data. In addition, few studies stratified data by line of therapy, meaning definitive conclusions on the relative benefits of a particular agent by treatment line could not be made. This also meant that the possibility of channeling bias could not be realistically determined. Reporting of outcomes data by concomitant therapy (use of concomitant csDMARD versus monotherapy) was also limited. Interpretation of the findings was also compounded by a lack of information on dose/dose frequency in most studies; however, for the purpose of assessment of bias, we assumed that b/tsDMARDs were largely used according to their licensed dose. Greater reporting of outcomes data from real-world studies by line of therapy (such as those reported by Gerhold, et al. 2015 [90]) and/or concomitant drug use may improve our understanding of true differences between individual agents or drug classes. Due to the broad scope, we were unable to pursue a systematic review on comparative safety, a factor which may guide many treatment decisions, particularly given that our study suggests similar comparative effectiveness. Finally, our protocol was not designed to search for predictors of response; consequently, only a handful of studies analyzed data by, for example, RF/ACPA serostatus, making it hard to comment on the influence of such prognostic indicators on treatment outcomes. Thus, that holy grail of RA therapy – specific disease and treatment characteristics that facilitate clinical decision making for tailored, precision medicine for the individual patient – remains elusive.

Conclusions

This systematic review represents one of the largest datasets of its kind, summarizing 20 years of studies on the relative effectiveness of b/tsDMARDs in patients with RA conducted in a clinical practice setting, allowing us to start building a qualitative picture of global real-world comparative effectiveness research. We found there are many effective options for the treatment of RA; however, there was relatively less evidence to support the use of any single b/tsDMARD or MOA over another, supporting the consensus of current treatment guidelines that the individual drug or drug class is perhaps less important than tailoring treatment strategies to the individual patient. Future real-world

observational studies may focus on stratifying the relative effectiveness of b/tsDMARDs by specific line of treatment and/or concomitant therapies or identification of specific factors for predicting response to therapy.

Key Messages

- This systematic review summarizes over 20 years of global real-world data on the comparative effectiveness of biologic/targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) in patients with rheumatoid arthritis (RA)
- There was no apparent evidence that a specific b/tsDMARD drug class was more effective than others for the management of RA disease activity and patient-reported outcomes
- These data support the consensus of current RA treatment guidelines, which state that adopting a personalized treatment approach may be more important than specific use of a single b/tsDMARD or mechanism of action

Author Contributions

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication.

Objectives. JAS, LRH, TAS, KW, SK, KL, VK, and KM.

Drafting of manuscript. JAS, LRH, TAS, KW, SK, KL, VK, and KM.

Review of manuscript. JAS, LRH, TAS, KW, SK, KL, VK, and KM.

Data Availability

Bristol Myers Squibb's policy on data sharing may be found at <https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html>.

Declaration of Competing Interest

JAS: supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (grant numbers R01 AR080659, R01 AR077607, P30 AR070253, and P30 AR072577), the R. Bruce and Joan M. Mickey Research Scholar Fund, and the Llura Gund Award funded by the Gordon and Llura Gund Foundation; research support: Bristol Myers Squibb; consultant: AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Gilead, Inova Diagnostics, Janssen, Optum, and Pfizer. LRH: employee and stakeholder: CorEvitas; consultant: AbbVie, Bristol Myers Squibb, and Roche; speakers bureau: Bristol Myers Squibb. TAS: consultant: Bristol Myers Squibb and Janssen. KW, SK, KL, and VK: employees and shareholders: Bristol Myers Squibb. KM: nothing to disclose.

Acknowledgments

Professional medical writing and editorial assistance was provided by Rachel Rankin, PhD, at Caudex and was funded by Bristol Myers Squibb. Caudex designed the systematic review to answer the review questions, drafted the protocol, and provided expert review.

Funding Support

This systematic review was funded by Bristol Myers Squibb.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.semarthrit.2023.152249](https://doi.org/10.1016/j.semarthrit.2023.152249).

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