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Adalimumab for Adult Patients with Rheumatological Disorders: A Review of Clinical Effectiveness

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Abbreviations

ABA	Abatacept
ACR	American College of Rheumatology
ADA	Adalimumab
AE	Adverse Events
AS	Ankylosing Spondylitis
ASAS	Assessment in SpondyloArthritis International Society
ASQoL	Ankylosis Spondylitis Quality of Life
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
CTZ	Certolizumab pegol
DMARD	Disease Modifying Anti Rheumatoid Drugs
bDMARD	biological DMARD
cDMARD	conventional DMARD
ETN	Etanercept
EULAR	European League Against Rheumatism
GOL	Golimumab
HRQoL	Health Related Quality of Life
INF	Infliximab
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IXE	Ixekizumab
NMA	Network Meta-analysis
PASI	psoriasis area severity index
PsA	Psoriatic Arthritis
RA	Rheumatoid Arthritis
SAR	Sarilumab
SEC	Secukinumab
TOC	Tocilizumab
TNF-α	Tumor Necrosis Factor -alpha
TOF	Tofacitinib

Context and Policy Issues

Immune mediated immunological disorders comprise of a group of common conditions that affects the immunomodulatory pathways resulting in lasting and disabling inflammatory conditions.[1] Rheumatological disorders such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) are chronic inflammatory conditions that affect predominantly the musculoskeletal system leading to pain, disability, functional impairment and lowered health related quality of life (HrQoL).[1,2] Treatment of these disorders aim at symptom management and to prevent and control joint and organ damage.[3] They include corticosteroids, non-steroidal anti-inflammatory agents and disease-modifying antirheumatic drugs (DMARDs). Conventional DMARDs (cDMARDs) like methotrexate, sulfasalazine and hydroxychloroquine target the immune pathways, and have been used in early and long-term management of rheumatological disorders. Biologic DMARDs (bDMARDs) and janus kinase inhibitors target the molecules in the inflammatory pathway, thereby suppressing inflammation in RA, PsA and AS among other conditions.[4] The clinical superiority of bDMARDs compared to placebo in rheumatological disorders have been established.[5,6].

Among bDMARDs, tumor necrosis factor-alpha (TNF-α) inhibitors like adalimumab (ADA), infliximab (INF), etanercept (ETN), golimumab (GOL), and certolizumab pegol (CTZ) are approved for used in RA, PsA and AS.[7,8] In addition, interleukin-6 inhibitors like tocilizumab

(TOC) and sarilumab (SAR) and T-cell stimulation blocker, abatacept (ABA) are used for RA,[8] In PsA, secukinumab (SEC) is approved for use, and in AS ixekizumab (IXE) and SEC are also approved.[5,7] A janus kinase inhibitor, tofacitinib (TOF), is also approved for use in patients with RA.[7] There is a scarcity of head-to-head trials comparing the clinical effectiveness of bDMARDs with each other. bDMARDs and targeted DMARDs being expensive, long term treatments with these agents will result in increased healthcare expenditure.[9,10] Thus, in the absence of comparative evidence, cost is a major determinant factor in the choice of bDMARDs.

The objective of this report is to summarize the evidence regarding the comparative efficacy of ADA compared with other bDMARDs and tofacitinib in patients with rheumatological disorders.

Research Question

What is the clinical effectiveness of adalimumab versus other bDMARDs and tofacitinib in adult patients with rheumatological disorders?

Key Findings

Eight systematic reviews (SRs) provided direct and indirect comparative evidence of the clinical effectiveness of adalimumab compared to other biological Disease modifying Anti Rheumatic Drugs (DMARDs) and tofacitinib in adults with rheumatological disorders Among them, four SRs considered patients with rheumatoid arthritis, three SRs considered patients with ankylosing spondylitis (AS) and one SR considered patients with psoriatic arthritis (PsA). No primary randomized controlled studies directly comparing adalimumab with other bDMARDs were identified.

In patients with RA, who were intolerant or inadequately responding to conventional DMARDS, the direct comparative evidence suggested that adalimumab was not superior to tocilizumab and sarilumab. The indirect comparison evidence suggested that adalimumab was no different in clinical efficacy when compared to etanercept, certolizumab pegol, and tofacitinib, but was less favoured when compared to tocilizumab and sarilumab. No evidence was found comparing the clinical efficacy of adalimumab compared to infliximab, golimumab and abatacept. Adalimumab was also found to have a similar safety profile compared to the other biological DMARDs.

In patients with PsA, no direct comparative evidence was found. Evidence from indirect comparisons suggested that adalimumab was superior to ixekizumab in achieving clinical response measured using American College of Rheumatology response, but no differences were found in Psoriatic Area severity index between the two drugs. No differences in clinical effectiveness were found between adalimumab and infliximab, etanercept, certolizumab pegol, secukinumab and golimumab. Adalimumab was also found to have fewer adverse events, but similar serious adverse events compared to the other bDMARDs.

In patients with AS, no direct comparative evidence was found between adalimumab and bDMARDs. Evidence from the indirect comparisons suggested that secukinumab was favoured over adalimumab in achieving clinical response. No differences in clinical effectiveness were found between adalimumab and infliximab, etanercept, certolizumab pegol and golimumab. Adalimumab was also found to have no differences in serious adverse events compared to infliximab, etanercept, certolizumab pegol and golimumab.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE All via Ovid, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were adalimumab and arthritis. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses and randomized controlled trials or controlled clinical trials. Where possible, retrieval was limited to the human population. The search was limited to English language documents published between January 1, 2010 and April 11, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or ankylosing spondylitis (AS)
Intervention	Adalimumab
Comparator	RA: Infliximab, etanercept, certolizumab pegol, golimumab, tocilizumab, sarilumab, abatacept, or tofacitinib PsA: Infliximab, etanercept, certolizumab pegol, golimumab, secukinumab or ixekizumab AS: Infliximab, etanercept, certolizumab pegol, golimumab or secukinumab
Outcomes	Clinical effectiveness: • Health-related quality of life • Remission • Clinical or therapeutic response (e.g., clinical scores) • Disease activity and recurrence • Morbidity (e.g., disability) • Disease progression Adverse Events: (e.g., infection, mortality, hypersensitivity, discontinuation or failure rate of therapy etc.)
Study Designs	Health technology assessments, systematic reviews and randomized controlled trials.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications. Based on the large number of citations identified in the literature search, the search was narrowed to those published from January 1, 2015 to April 11, 2020. Studies that evaluated bDMARD and cDMARD combination therapy were excluded.

Critical Appraisal of Individual Studies

The included SRs[11-18] were critically appraised using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2),[19] the network meta-analyses[11-13,15,16,18] were critically appraised using the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) checklist[20] and the matching adjusted indirect comparison (MAIC)[14] was critically appraised using criteria from the National Institute for Health and Care Excellence (NICE) population-adjusted indirect comparison technical support document[21] by one reviewer. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 292 citations were identified in the literature search. Following screening of titles and abstracts, 254 citations were excluded and 38 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search for full text review. Of these potentially relevant articles, 31 publications were excluded for various reasons, and 8 publications met the inclusion criteria and were included in this report. These comprised 8 SRs[11-18] including seven network meta analyses,[11-13,15-18] and one MAIC.[14] Appendix 1 presents the PRISMA[22] flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Eight publications were identified to be included in this report. All of them were SRs.[11-18] The characteristics of included publications are provided in Appendix 2, Table 2.

The included eight SRs[11-18] had a broader scope and selection criteria than the current report. The results from the seven relevant indirect comparisons [11-15,17,18] and three direct comparisons from primary RCTs[23-25] in four of the included SRs[11,12,16,18] are described in this report.

Study Design

Eight SRs[11-18] were included in this report. All of them[11-18] included indirect comparative evidence of ADA versus other bDMARDs.

The SR with NMA by Camean-Castillo et al. (2019),[11] searched for clinical trials published until June 2017. Twenty-seven RCTs were identified, among which one[24] was a relevant direct comparison study of ADA versus TOC. The NMA was done using a Bayesian approach. The 2019 SR with NMA (Bayesian approach) by Choy et al.,[12] searched RCTs above phase I published without any time limit, identified 9 primary studies with one[23] RCT

involving direct comparison of ADA with SAR. The SR with NMA by Lu et al. (2019)[13] searched for primary studies published until October 2018, identified 18 primary studies. No direct comparison studies were identified. The NMA was done using a frequentist approach. Maksymowych et al. (2018)[14] conducted a matching-adjusted indirect comparison (MAIC) to assess the comparative effectiveness up to one year of the two biologic agents in biologic-naïve ankylosing spondylitis patients with active disease. They did not report their search strategy, but included three RCTs in the MAIC. The SR and NMA by Ollendorf et al.[18] published in 2017 searched for RCTs and comparative observational studies published from 2010 to 2016. This search was done to update a previously published report.[26] The authors identified 137 studies (67 RCTs and 17 observational studies) among which two[23,24] relevant direct comparison RCTs were included of ADA compared to SAR and ADA compared to TOC in the SR The NMA of RCTs was conducted using Bayesian approach. The 2016 SR, NMA and economic evaluation by Corbett et al.[15] searched for primary studies published until July 2014. The authors included 24 primary studies among which there were no relevant direct comparisons. The NMA was conducted using Bayesian approach. The SR and NMA using Bayesian approach by Stevenson and colleagues (2016),[16] searched for articles published until July 2013 and included 60 primary studies among which two[24,25] direct comparisons of ADA with bDMARDs were relevant to the current report (TOC and ETN). cDMARDs were considered as the common reference treatment in the NMA.[16] Lastly, the 2016 SR and NMA by Wang et al.[17] searched for primary studies published until 2015 and included 25 primary studies. No direct comparison studies were identified. It was unclear whether the authors used a Bayesian or frequentist approach.

Country of Origin

The SRs were conducted in Spain,[11] USA,[13,18] UK[15,16] and China.[17] Two SRs were conducted by a multinational team, led by authors from Canada[14] and UK.[12]

Two[23,24] of the primary RCTs included in the SRs were multinational multicentre trials and one[25] was conducted in Japan.

Patient Population

Among the included SRs, four SRs included studies of RA,[11,12,16,18] three of AS[14,15,17] and one of PsA.[13]

Camean-Castillo and colleagues[11] included studies of RA patients with inadequate responses to previous cDMARDs and not previously treated with bDMARDs. They included 11,482 patients in the NMA. The SR by Choy et al.[12] included studies of adult patients with moderate to severe active RA, who had an inadequate response to at least one cDMARD or to at least one TNF-α inhibitor. The number of patients in the NMA was not reported. The SR by Ollendorf et al.[18] included studies of adult patients with moderate to severe RA who had an intolerance or inadequate response to previous cDMARDs therapy and included over 28,000 patients in the NMA. The SR by Stevenson and colleagues[16] included studies of adult patients with severe active RA who were naïve to methotrexate treatment and those with severe or moderate to severe RA previously treated with cDMARDs only. To summarize, four SRs[11,12,16,18] included patients who were inadequate responders to cDMARDs; one[16] also included studies evaluating patients who were naïve to cDMARDs treatment, one SR[11] included patients who were naïve to bDMARD treatment, and one[12] included patients who inadequately responded to at least one TNF-α inhibitor.

Lu et al.[13] included studies involving adult PsA patients who were previously treated with cDMARDs, and the NMA included 10,204 patients.

The SR by Maksymowych et al.[14] included studies of adult AS patients with active or severe active disease, those with inadequate response or intolerance to previous treatments, or those who were naïve to TNF-α inhibitors and had inadequate response or intolerance to conventional treatments. Altogether, 328 patients were included in the MAIC. Corbett et al.[15] included studies involving all adult patients with severe active AS and included 3,755 patients in the NMA. Wang et al.[17] included studies involving patients with AS or active AS. They included 3405 patients in the NMA.

Interventions and Comparators

All eight SRs[11-18] in this report included studies that compared a range of bDMARDs with each other, cDMARDs (methotrexate), or placebo. The interventions and comparators relevant to this report are summarized below.

The SRs of RA studies[11,12,16,18] included ADA, INF, GOL, ETN, or CTZ in any dosage or administration as interventions. Additionally, three SRs[11,16,18] included TOC, two[12,18] with SAR and one included TOF.[11]

The SR of PsA[13] included ADA, INF, GOL, ETN, CTZ, SEC, IXE or ABA in any dosage or administration as interventions.

The three SRs[14,15,17] which included studies of AS included ADA, INF, GOL, ETN, CTZ or SEC.

All eight SRs[11-18] considered placebo controlled and direct comparison studies as eligible for inclusion. Four SRs[11,12,16,18] identified and included direct comparison studies relevant to this report.

The three primary RCTs[23-25] identified in the SRs[11,12,16,18] were direct head to head comparisons between ADA and a relevant comparator. In the MONARCH trial,[23] 369 RA patients each were randomized to receive ADA 40mg subcutaneously (s.c) every 2 weeks (q2w) (n = 185) or SAR 200 mg s.c q2w (n = 184) for 24 weeks. The 2013 ADACTA trial[24] randomized 326 RA patients each to receive either 40 mg ADA q2w plus placebo q4w (n=162) or TOC 8mg/kg q4w plus placebo q2w(n=163) for 24 weeks. In the open label RCT by Kume et al.[25] RA patients were randomized to receive ADA 40 mg s.c q2w(n = 21) or ETN 25mg s.c twice a week (n = 21), for 24 weeks.

Outcomes

The SRs included in this report described several outcomes related to clinical effectiveness, which are relevant to this report. Clinical response to the treatment was measured using validated and accepted clinical scores, by the percentage of responders to treatment in each study arm. American College of Rheumatology (ACR)[15] scores were reported in five of the included SRs,[11-13,16,18] by using the percentage of ACR20, ACR50 and ACR70 responders (the number indicating the level of improvement required to be denoted as a responder).[27] European League Against Rheumatism (EULAR)[15] response scores were reported by one SR[16] using percentage of patients with “good” and “moderate good” response to treatment. The 75% improvement in the Psoriasis Area Severity Index (PASI75) response was reported in one SR[13]. In three SRs[14,15,17] involving AS patients, clinical response was measured using Assessment in SpondyloArthritis International Society (ASAS) scores, which is a composite score of 4-6 domains.[28] Percentage of

responders in each improvement criteria were reported as ASAS20 (20% improvement), ASAS40 (40% improvement) ASAS5/6 (20% improvement in five of six domains) and ASAS PR (partial remission).

Disease related disability of the patients was measured using Health Assessment Questionnaire - Disability Index (HAQ-DI), and was reported in three SRs.[12,14,16,18] HAQ-DI is a validated measure in RA, with score range from 0 - 3 with a minimal clinical important difference of 0.22.[29]

Disease activity measured using 28 joint Disease Activity Score (DAS28) was reported in three SRs.[12,16,18] One SR reported Patient reported Global Assessment (PtGA).[14] Patient reported disease activity and functional outcomes in AS patients were measured the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Metrology Index (BASMI) indices,[28] which were reported in two of the included SRs.[13,14] Health Related Quality of Life (HRQoL) was measured using the Ankylosis Spondylitis Quality of life (ASQoL) questionnaire and the Short Form 36 (SF-36); the results were reported in three of the included SRs.[14-16] SF-36 is a validated 36 item HRQoL questionnaire that has a physical component score and a mental component score.[30,31] The MCID of SF-36 has been estimated as 2.5 to 5.[29] Safety of ADA compared to the relevant bDMARDs was evaluated in four of the included SRs[12,13,16,17], including reported adverse events (AE), serious adverse events (SAE), discontinuation of treatment, infections and mortality.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3, Table 3.

Systematic Reviews

The eight included SRs[11-18] had clearly defined objectives with a description of the eligibility criteria for the review including population, interventions, comparators and outcomes. Six SRs were conducted based on PRISMA guidelines.[12-16,18]Two SRs[15,16] were registered in PROSPERO, with a pre-established protocol. Seven of the included SRs[11-13,15-18] searched for eligible studies in multiple databases and described their search strategies. Seven SRs[11-13,15-18] reported their study selection process, and the a list of excluded studies along with the reason to exclude was reported in four SRs.[11,12,14,16]

As for the limitations of the included SRs, there were several. Most SRs[11-14,17,18] were not conducted using an a priori protocol. The SR by Maksymowych et al.[14] did not report their search strategies and a PRISMA diagram of study selection was not reported. A risk of bias assessment for the included studies was not reported in four of the included SRs,[11,12,14,17] making the internal validity and quality of the studies included in SRs unclear. Some SRs[11,14,16] did not conduct study selection and data extraction in duplicate which could lead to risk of errors and evidence selection bias. Publication bias was assessed in only one of the SRs.[17] Lastly, two SRs[12,14] were funded by pharmaceutical companies, and poses a possible conflict of interest.

Network Meta-Analyses

This report included seven published NMAs[11-13,15-18] that were appraised using criteria from the ISPOR checklist.[20] Five[11,12,15,16,18] of the NMAS were done using Bayesian network models with likelihood distribution. One NMA[13] used a frequentist framework. Outcome

measures used were validated and accepted in clinical and research settings. Comparative results of the validated outcome measures were reported using effect sizes and 95%CI or 95%CrI. A network diagram of the included primary RCTs were reported in the NMAs as appropriate.[11-13,16,17] All of the included NMAs[11-13,15-18] described the fitted models and the method of model selection. Model selection was done based on Deviance Information Criteria in Bayesian NMAs[11,12,15,16,18] The NMA by Choy et al. used a non informed prior distribution of models. Testing for inconsistency was done in three of the NMAs[11,12,18] and the results between direct and indirect comparisons were consistent. Possible effect modifiers were considered in five NMAs.[12,13,15,16,18] The Choy et al. NMA found that only weight was an effect modifier. Prior treatment with cDMARDs and the response to previous DMARDs were other effect modifiers considered.[13,18] Stevenson and colleagues considered duration of disease as an effect modifier. However, adjusted results were not reported because duration of disease was not found to be an effect modifier as per the deviance information criteria[16] A meta regression analysis was done in Corbett and colleagues to evaluate possible effect modifiers.[15]

The included NMAs had several limitations. It was unclear whether one of the NMAs used Bayesian or frequentist approach.[17] Two[11,12] of the NMAs used a fixed effect model which could affect the estimates of the results due to presence of heterogeneity. Individual study characteristics were not reported in one[12] NMA. A sensitivity analysis was not done in three of the NMAs.[11,13,17] It was unclear if the NMA by Camean-Castillo and colleagues evaluated and addressed heterogeneity.[11] In two NMAs, it was unclear whether prior distributions were used.[15,18] In the NMA by Stevenson and colleagues, the reporting of effect size estimates were unclear.[16] Studies conducted among patients who were previously treated with bDMARDs were excluded. However, additional sensitivity analyses were conducted including a proportion of patients who were previously treated with bDMARDs. Validity of such sensitivity analysis were low, considering the authors did not systematically search for studies involving prior bDMARDs. The NMA assumed that all cDMARDs had the same efficacy and that having failed at one cDMARD was equivalent to failed methotrexate. These assumptions were made based on clinical expert opinion and not based on evidence from systematic reviews. Lastly it was unclear whether testing for inconsistences were done.[16] The generalizability of the results and its implications on target audience were not clearly reported in five of the NMAs.[11,15-18]

Matching adjusted indirect comparison

The authors conducted a systematic search for literature in multiple databases to identify relevant studies. The eligibility criteria and the list of identified trials were provided, along with reasons for exclusion from the MAIC. However, it was unknown if the study selection and data extraction were performed independently by two or more reviewers to reduce the potential bias and validate data accuracy.

Individual patient data (IPD) pooled from two studies – MEASURE 1 and MEASURE 2 (MEASURE 1/2), provided data for secukinumab 150 mg, whereas one study (the ATLAS trial) provided aggregate data for adalimumab 40 mg. All the studies were placebo-controlled randomized trials, and the primary endpoint of the MEASURE 1/2 studies was the proportion of patients with ≥ 20% improvement in the ASAS20 response criteria at week 16, whereas the primary endpoint for the ATLAS study was the proportion of patients with ≥ ASAS20 at week 12. In critically appraising this MAIC, the index and the comparator trials were not retrieved to evaluate sources of between-study heterogeneity independently.

The authors presented the before and after matching baseline characteristics for the ATLAS study and the pooled MEASURE 1/2 trials. The investigators considered age, sex, mean BASFI, score, mean C-reactive protein (CRP) level, mean BASDAI, score and prior exposure to TNF-α inhibitors as treatment effect modifiers. They were identified through a review of clinical literature and advice from clinical experts in the treatment of ankylosing spondylitis. Although plausible, without independent input from a clinical expert on this report, it could not be confirmed if the effect modifiers were all appropriate or exhaustively covered.

The inter-study imbalances between for the ATLAS study and the pooled MEASURE 1/2 trials were statistically significant ($p< 0.05$) for three effect modifiers (sex, BASFI, and previous therapy with TNF-α inhibitors). However, the imbalances did not reach the level of statistical significance for three other effect modifiers (age, BASDAI, and CRP level). A best practice recommendation requires a priori evidence of effect modifier status along with evidence of substantial imbalance;[21] however, it is unclear the impact of including effect modifiers without a statistically significant between-study difference in the MAIC under review.

Before matching, the sources of heterogeneity between MEASURE 1/2 and the ATLAS studies included demographic characteristics and prior TNF-α inhibitor exposure. Notably, 31.0% of patients randomized to secukinumab were TNF-α inhibitor-inadequate responders, whereas all patients receiving adalimumab were TNF-α inhibitor -naïve. A regression model was used to weight the IPD from MEASURE 1/2, and they were matched to the published aggregate data in the ATLAS trial, using the propensity score matching approach. The authors did not report how the regression parameters were estimated. Thus, it is unclear if the weights exactly balanced the mean covariate values between the weighted pooled IPD for MEASURE 1/2 with the ATLAS trial data. However, the propensity score method adjusted for all the specified effect modifiers.

All patients providing data for the secukinumab 150 arm of the analysis were TNF-α inhibitor-naïve after matching, and there was no difference in effect modifiers between the populations of MEASURE 1/2 and the ATLAS trials. After matching, the effective sample size (ESS) for MEASURE 1/2 was 120 (i.e., 60.9% of the before matching sample size) for secukinumab 150 mg and 120 (i.e., 61.2% of the before matching sample size) for placebo. Although it has been reported in the literature that a small ESS indicates that the resulting estimate may be unstable,[21] a defined limit of what constitutes a small ESS has not been established. Therefore, the impact of the reduced ESS in this study is unclear.

Anchored (placebo adjusted) MAIC analysis was possible with data of up to week 12 of study, after which patients randomized to placebo could receive active treatment in the ATLAS trial. Odds ratios (ORs) and corresponding standard errors were calculated using the Bucher method. The differences in mean scores between adalimumab or secukinumab and placebo were calculated, along with 95% confidence intervals and p values based on a normal approximation. A sensitivity analysis was also performed, matching for previous use of TNF-α inhibitor therapy, and all other effect modifiers.

Unanchored MAICs (placebo-unadjusted) were used to compare outcomes of the secukinumab 150 arm directly to the adalimumab 40 mg after week 12 of ATLAS. The investigators did not report identifying any effect modifiers and prognostic variables for the unanchored MAIC analysis, and there was no indication that effect modifiers and prognostic variables were adjusted for in subsequent propensity scoring and outcome regression methods. Also, there was no information on the estimate of residual bias due to

unaccounted for covariates. Therefore, the amount of bias is unknown but is likely to be substantial, even exceeding the magnitude of the estimated treatment effects.[21]

Overall, the MAIC approach, as used in the analysis of the short-term (up to week 12) outcomes, appears credible within the inherent limitation that the method cannot adjust for differences in some study parameters, such as treatment administration, co-treatments, or treatment switching. However, the likely substantial amount of bias associated with the unanchored MAIC analysis of data after week 12 was a source of substantial uncertainty about its findings. As a result, it did not provide conclusive evidence for the comparative effectiveness of secukinumab 150 mg versus adalimumab 40 mg in biologic-naïve patients with active ankylosing spondylitis over ≤1 year.

Summary of Findings

Eight SRs[11-18] and three primary RCTs[23-25] identified in the SRs were included in this report. An overall summary of the relevant findings is presented below grouped by condition. Appendix 4 presents a detailed table of the main study findings and authors' conclusions.

Clinical Effectiveness of Adalimumab Compared to Other bDMARDs and tofacitinib in Adults with Rheumatological Disorders

Rheumatoid Arthritis

Health Related Quality of Life

No relevant indirect comparative evidence regarding HRQoL outcomes in ADA and other bDMARDs in RA was identified; therefore, no summary can be provided

Direct Comparison in Primary Studies:

One included SR[16] reported direct comparison results of HRQoL outcomes of ADA vs TOC measured using SF-36. Results were reported from one primary RCT.[24] At 24 weeks, patients from both groups reported clinically important improvements in HRQoL as measured by SF-36. Patients who received ADA reported less improvement in the mental component summary score compared to patients who received TOC (P<0.05). There was no difference in the change from baseline of the physical component summary scores between ADA and TOC at 24 weeks.

Clinical or Therapeutic Response

Direct Comparisons in Primary Studies:

Two primary studies[23,24] included in four SRs[11,16,18] directly compared the clinical response of ADA vs other bDMARDs. Results were reported from two primary RCTs.[23,24] At 24 weeks, patients who received ADA had lower clinical response (ACR20, ACR50, ACR70 and EULAR good response) compared to those who received TOC (P<0.005 for all).[24] Patients who received ADA also had lower clinical response (ACR20, ACR50, ACR70) compared to SAR (P<0.05 for all).[23]

Indirect Comparisons in NMAs:

Four SRs with NMAs[11,12,16,18] provided indirect comparative evidence of clinical response of ADA vs bDMARDs. In patients who had intolerance or inadequate response to previous cDMARD therapy, TOC[11] and SAR[12] were favoured over ADA in achieving ACR20, ACR50 and ACR70 . TOC was also favoured over ADA in achieving ACR response among patients with moderate-to-severe and severe RA (previously treated with cDMARDs).[16] No treatment was favoured between ADA and ETN, TOF or CTZ.

Remission and Disease Activity

Direct Comparisons in Primary Studies:

Direct comparison results of remission and disease activity outcomes from three primary RCTs[23-25] were reported in two SRs.[16,18] At 24 weeks, TOC and SAR were superior to ADA in lowering DAS28 scores. These findings were statistically significant. There was no difference between ADA and ETN.

Indirect Comparisons in NMA:

One SR with NMA[12] reported indirect comparative results of ADA versus other bDMARDs. In patients who had intolerance or inadequate response to previous cDMARD therapy, SAR was favoured over ADA in lowering DAS28 scores.

Disability

Direct Comparisons in Primary Studies:

Direct comparison results of disability measured using HAQ-DI from three primary RCTs[23-25] were reported in two SRs.[16,18] SAR was superior to ADA in lowering the HAQ-DI scores ($P<0.005$). The percentage of patients achieving an improvement meeting the MCID threshold was higher in SAR group compared to ADA group ($P<0.01$). There were no differences between ADA and TOC or ETN.

Indirect Comparisons in NMA:

One SR with NMA[12] reported indirect comparative results of ADA versus other bDMARDs. In patients who had intolerance or inadequate response to previous cDMARD therapy, SAR was favoured over ADA in lowering HAQ-DI scores ($P<0.05$). The difference in HAQ-DI (change from baseline = -0.18(-0.32 to -0.04) was not clinically important, having not met the MCID threshold.

Adverse Events and Safety

Direct Comparisons in Primary Studies:

Two SRs[16,18] reported on safety outcomes from two primary RCTs.[23,24] The ADACTA trial[24] reported that 5.5% of patients who received TOC and 6.1% of patients who received ADA discontinued treatments due to AEs. Forty-two percent of ADA patients and 47.5% of TOC patients had an infection and approximately 3% of patients had a serious infection in each group. There was one death in the TOC group. In the MONARCH trial,[23] rates of serious infection in patients who received ADA and SAR were both 1.1% in each group. While 7.1% of ADA patients discontinued treatment compared to 6% of SAR patients, 6.5% of ADA patients and 4.9% of SAR patients had a SAE. There was one death in the SAR group.

Indirect Comparisons in NMA:

One SR with NMA[12] reported indirect comparative results of ADA versus other bDMARDs. In patients who had intolerance or an inadequate response to previous cDMARD therapy, neither ADA or SAR were favoured in terms of serious infections and SAEs.

Psoriatic Arthritis

Health Related Quality of Life

No relevant direct or indirect comparative evidence regarding ADA and other bDMARDs in PsA was identified; therefore, no summary can be provided.

Clinical or Therapeutic Response

No relevant direct comparative evidence regarding ADA and other bDMARDs in PsA was identified; therefore, no summary can be provided.

Indirect Comparisons in NMA:

One SR with NMA[13] reported indirect comparative evidence of ADA and other bDMARDs. In PsA patients who were previously treated with cDMARDs, patients who received ADA were more likely to achieve ACR20 responses compared t IXE and ABA. Patients who received ADA were also more likely to achieve PASI response when compared to patients who received ABA. These findings were statistically significant. No differences in clinical response was found between ADA and INF, ETN, CTZ, GOL or SEC.

Remission and Disease Activity

No relevant direct or indirect comparative evidence regarding ADA and other bDMARDs in PsA was identified; therefore, no summary can be provided.

Disability

No relevant direct or indirect comparative evidence regarding ADA and other bDMARDs in PsA was identified; therefore, no summary can be provided.

Adverse Events and Safety

No relevant direct comparative evidence regarding ADA and other bDMARDs in PsA was identified; therefore, no summary can be provided.

Indirect Comparisons in NMA:

One SR with NMA[13] reported indirect comparative evidence of ADA and other bDMARDs. In PsA patients who were previously treated with cDMARDs, ADA was found to have lower odds of having AEs compared to INF, CTZ, SEC, GOL, IXE, and ABA. These findings were statistically significant. As to SAEs, no differences were observed between ADA and INF, CTZ, SEC, GOL, IXE, and ABA.

Ankylosing Spondylitis

Health Related Quality of Life

No relevant direct comparative evidence regarding ADA and other bDMARDs in AS was identified; therefore, no summary can be provided.

Indirect Comparisons in NMA and MAIC:

Two SRs, one with MAIC[14,15] reported indirect comparative evidence of ADA and other bDMARDs on HRQoL. When comparing ADA to SEC, no treatment was favoured in terms of improving HRQoL measured using the ASQoL. In addition, when HRQoL was evaluated using the SF-36, neither ADA, CTZ or GOL were favoured in terms of HRQoL of AS patients.

Clinical or Therapeutic Response

No relevant direct comparative evidence regarding ADA and other bDMARDs in AS was identified; therefore, no summary can be provided.

Indirect Comparisons in NMAs and MAIC:

Three SRs, one with MAIC[14,15,17] reported indirect comparative evidence of ADA and other bDMARDs on clinical or therapeutic response. In short term (until week 12), in comparing ADA to SEC, neither treatment was favoured in achieving clinical response. After 12 weeks, the non-placebo adjusted results showed that patients receiving ADA were less likely to achieve ASAS20 and ASAS40 responses compared to SEC. This finding was statistically significant. The likelihood of achievement of ASAS5/6 was not statistically different in ADA and SEC groups at any timepoints in treatment.[14] When comparing ADA to INF, ETN, CTZ or GOL, no treatment was favoured in terms of achieving clinical responses[15,17] (measured using ASAS20, ASA40, ASAS 5/6 and ASAS-PR scores).

Remission and Disease Activity

No relevant direct comparative evidence regarding ADA and other bDMARDs in AS was identified; therefore, no summary can be provided.

Indirect Comparisons in NMA and MAIC:

Two SRs, one with MAIC[14,15] reported indirect comparative evidence of ADA and other bDMARDs on remission and disease activity. Change from baseline of the disease activity outcome measure BASDAI suggests that there is no difference between ADA and SEC. At 12 week, ADA patients had less improvement in PtGA compared to SEC ($P<0.001$). No differences were found at 24 weeks.[14] When comparing ADA to INF, ETN, CTZ of GOL, no treatment was favoured in terms of disease activity outcomes measured using BASDAI, BASFI and BASMI.[15]

Disability

No relevant direct or indirect comparative evidence regarding ADA and other bDMARDs in AS was identified; therefore, no summary can be provided.

Adverse events and safety

Direct Comparisons in Primary Studies:

No relevant direct comparative evidence regarding ADA and other bDMARDs in AS was identified; therefore, no summary can be provided.

Indirect Comparisons in NMA:

One SR with NMA[17] reported indirect comparative evidence of ADA and other bDMARDs regarding safety and adverse events. When comparing ADA to INF, ETN, CTZ or GOL, no treatment was favoured in terms of odds of experiencing an SAE.

Limitations

Overall, the included SR and NMAs were of moderate to good quality. Though not free from limitations, appropriate research questions, methodology and analysis wad conducted. A scarcity of head to head trials that directly compare ADA with other bDMARDs were identified in the literature search. The direct comparative evidence included in this report, from three primary studies[23-25] included in the SRs.[11,12,16,18] were conducted in patients with RA. No direct comparison studies were identified for patients with AS or PsA. Four[11,12,14,17] of the included SRs did not assess the risk of bias of primary studies, thus the quality the studies within these SRs remain unclear. It was unclear how many studies were conducted in Canada, therefore the generalizability to the Canadian setting remains unknown.

Conclusions and Implications for Decision or Policy Making

Eight SRs[11-18] (seven [11-13,15-18] of them with NMAs and one MAIC[14]) and the three primary studies[23-25] included in four of the SRs[11,12,16,18] were identified for this report. While, this report focuses on ADA monotherapy for RA, PSA and AS, a previous CADTH report[8] on the drugs for the management of RA provided comparative evidence on the clinical effectiveness of combination therapies with methotrexate and other cDMARDs.

In patients with RA, direct comparative evidence from two primary studies included in three SRs [11,16,18] suggested that TOC and SAR were superior to ADA in regards to clinical or therapeutic response, remission, and disease activity among patients with RA. While ADA and TOC improved HRQoL in patients that was clinically important, differences between groups were significant only for the mental component score. ADA was not superior to TOC in improving disease activity in RA patients, there were no differences in the safety profile of ADA compared to SAR and TOC. TOC and SAR were favoured over ADA for achieving clinical response. SAR was also favoured over ADA in lowering disease activity and disability. No intervention was favoured between ADA and ETN, CTZ or TOF. ADA was also found to have a similar safety profile compared to the other bDMARDs.

In patients with PsA, no direct comparative studies were identified. Evidence from indirect comparison[13] suggested that ADA was superior to IXE in achieving clinical response, but no differences were found in psoriatic area severity index scores between the two agents. No differences in clinical effectiveness were found between ADA and INF, ETN, CTZ, SEC, and GOL. Adalimumab was also found to have fewer adverse events, but a similar SAEs profile compared to INF, ETN, CTZ, SEC, and GOL.

In patients with AS, no direct comparative evidence was found between adalimumab and bDMARDs. Evidence from the indirect comparisons[14,15,17] suggested that SEC was favoured over ADA. No intervention was favoured in terms of HRQoL, clinical response and disease activity between ADA and INF, ETN, CTZ, or GOL. ADA was also found to have no differences in SAEs when compared to INF, ETN, CTZ, or GOL.

A lack of well-designed head to head trials as well as the identified limitations in the NMA methodology should be considered. Future well designed head to head trials may help reduce uncertainty with the evidence of clinical effectiveness of ADA compared to other bDMARDs in patients with rheumatological disorders.

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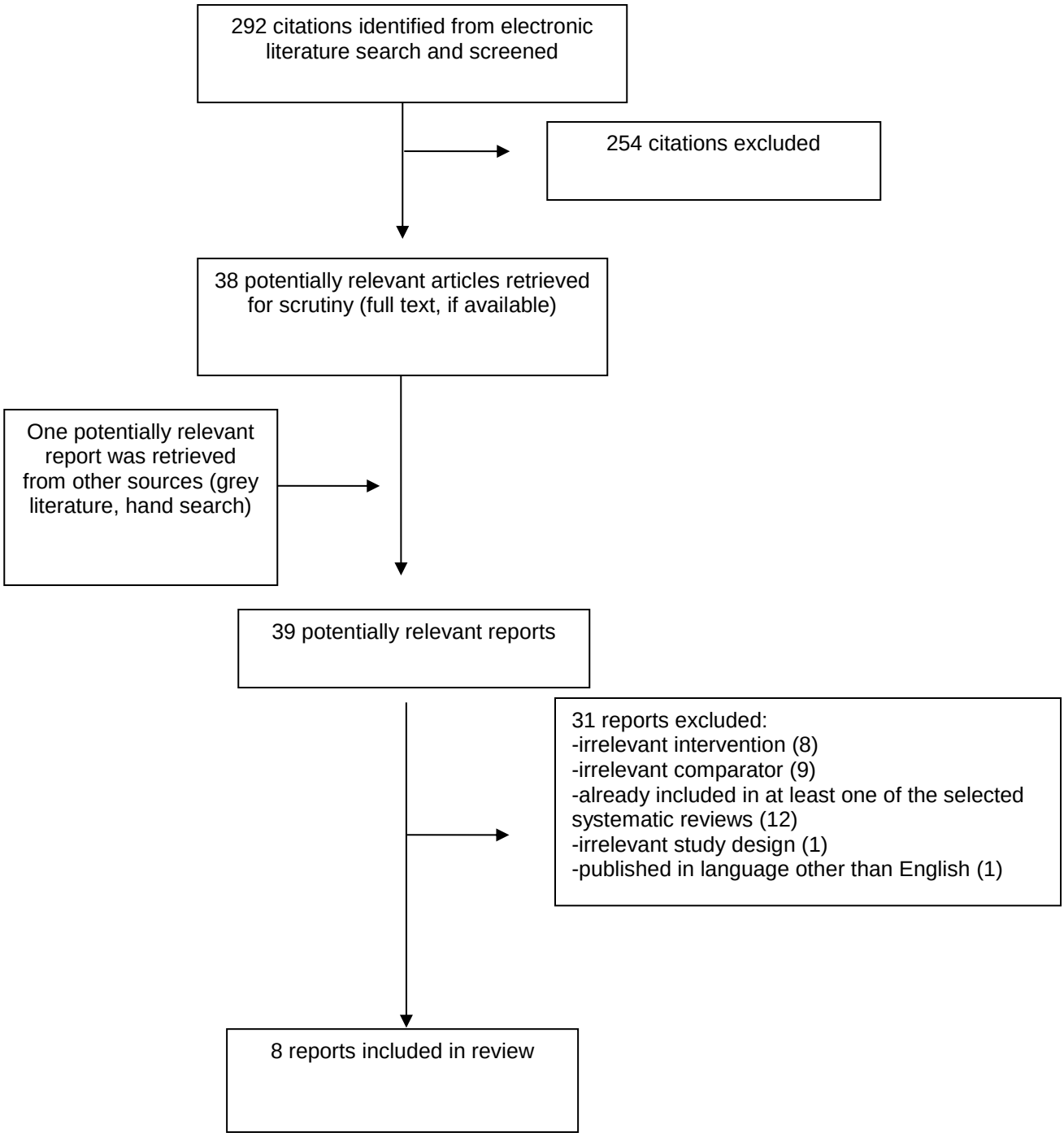
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews, Network Meta-Analyses, and Matching-Adjusted Indirect Comparison

First Author, Publication Year, Country, Funding sources	Study Design, Objective, Search Strategy, Number of Primary Studies Included, Quality Assessment Tool	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Camean-Castillo 2019[11] **Country**: Spain **Funding sources:** Not reported	**Study Design:** Network meta analysis, using Bayesian approach. **Objective:** To determine the efficacy of biological DMARDs including tofacitinib in RA patients naïve to previous biological DMARD therapy. **Search Strategy:** Searched MEDLINE and EMBASE for clinical trials published up to 2017 June. Bibliographies of identified studies were included in the search. **Number of primary RCTs included:** 27. **Number of relevant direct comparative RCTs included: 1** **Quality Assessment tool:** None (quality assessment not done)	RA patients with inadequate responses to previous conventional DMARD and not previously treated with biological DMARD. **Total number of patients included in the NMA**: 11,482	**Relevant Intervention:** Biological DMARDs. Adalimumab, Tocilizumab, tofacitinib, etanercept, certolizumab, Infliximab, golimumab, abatacept. Unapproved doses of biological DMARDs and biosimilar drugs were excluded. **Comparators:** Placebo or any of the drugs in the intervention.	**Primary outcome:** 50% reduction in the ACR score (ACR50) **Length of follow up:** 24 weeks.
Choy 2019[12] Country: UK,US and France Funding sources: Sanofi and Regeneron Pharmaceuticals	**Study Design:** Systematic Review and indirect treatment comparison. **Objective:** To evaluate the comparative efficacy and safety of sarilumab monotherapy versus other approved monotherapies for RA. **Search Strategy:** MEDLINE, EMBASE and Cochrane databases were searched without any time limit. Conference proceedings from 2013 to Dec 2016 were also searched. **Number of relevant direct comparative RCTs included: 1**	- Adult patients with moderately-to-severely active RA who have had inadequate response to at least one conventional DMARDs - Adult patients with moderately-to-severely active RA who have had inadequate response to at least one TNFα-inhibitors **Total number of patients included in the NMA:** Not reported	**Relevant interventions**: Any dosage or administration of Adalimumab, sarilumab, certolizumab, etanercept t, golimumab, Infliximab, abatacept, tocilizumab, tofacitinib. **Comparator:** Placebo or any of the interventions used as monotherapy.	**Clinical Outcomes:** - Clinical response: ACR20, ACR50, ACR70. - Disability index change from baseline: HAQ-DI. - Safety outcomes; Serious infection, serious adverse event. **Follow up time:** 24 weeks and 52 weeks.

First Author, Publication Year, Country, Funding sources	Study Design, Objective, Search Strategy, Number of Primary Studies Included, Quality Assessment Tool	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Quality Assessment tool: None (quality assessment not done)			
Lu, 2019[13] **Country:** USA **Funding sources:** China Scholarship council.	**Study Design:** Systematic review and network meta analysis using a frequentist framework. **Objective:** To assess the safety and efficacy of targeted therapies currently considered for the management of active PsA. **Search strategy**: Pubmed, Embase, web of science and Cochrane library, from inception until October 1, 2018. **Number of primary RCTs included**:29 **Number of relevant direct comparative RCTs included: 0** **Quality assessment tool:** Cochrane collaboration's tool.	- Adult PsA patients fulfilling the CASPAR criteria, and had previous treatment with conventional DMARDS. **Total number of patients in the NMA:** 10,204.	**Relevant interventions:** Any dosage or administration of adalimumab, tofacitinib, secukinumab, ixekizumab, abatacept, etanercept, infliximab, certolizumab pegol and golimumab. **Comparators:** placebo or conventional DMARDs and biological DMARDs used as monotherapy or in combination.	**Clinical outcomes:** - ACR20. - PASI75 Safety outcomes: count of all reported AE and SAE. **Length of follow up**: Induction period (defined as ≤ 24 weeks).
Maksymowych, 2018[14] **Country:** Multinational team including Canada, US, Australia, Germany, UK, Netherlands, Switzerland **Funding sources:** Novartis Pharma AG.	**Study design:** Matching adjusted indirect comparison. **Objective:** comparative effectiveness of medium-term biologic therapy for biologic naïve patients with active AS. **Search strategy**: not reported. **Number of primary studies:** Three clinical trials, of which one study involved adalimumab as intervention. **Number of relevant direct comparative RCTs included: 0** **Quality Assessment tool:** None (quality assessment not done)	- Adult patients with active or severe active AS - AS patients who had inadequate response to previous treatments - AS patients who were intolerant to previous treatments - AS patients who were TNFi-naïve and had demonstrated previous intolerance or inadequate response to conventional treatments.	**Interventions:** Any dosage or administration of adalimumab, secukinumab, certolizumab pegol, etanercept, infliximab, golimumab. **Comparators:** Placebo or any of the drugs in the intervention.	**Relevant clinical outcomes**: Efficacy: -ASAS scores -global assessment of disease activity -BASDAI score -BASMI score -BASFI score - Health related quality of life assessed by ASQoL, SF-36, HAQ Safety: Mortality, discontinuation, individual safety outcomes.

First Author, Publication Year, Country, Funding sources	Study Design, Objective, Search Strategy, Number of Primary Studies Included, Quality Assessment Tool	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		Total number of patients in the MAIC: 328.		**Length of follow up:** 8-52 weeks
Ollendorf, 2017[18] **Country:** US **Funding sources:** The report was prepared by the Institute for Clinical and Economic Review. for the New England Comparative Effectiveness Public Advisory Council	**Study Design:** Systematic review and network meta-analysis **Objective:** to determine the comparative clinical effectiveness potential harms of the major targeted immunomodulators in RA. **Search strategy:** Embase, Medline, and Cochrane indexed articles were searched for studies (RCTs and comparative observational studies) published from Jan 2010 to September 2016. Search was to update a AHRQ report[26] References of SRs were searched for additional studies. **Number of primary studies in SR:** 137 studies. (67 RCTs and 17 observational studies) **Number of relevant direct comparative RCTs included: 2**	Adult patients with moderately to severe RA and inadequate response or intolerance to previous cDMARD therapy. **Total number of patients in the NMA:** > 28,000	**Interventions:** Adalimumab, certolizumab pegol, etanercept, infliximab, golimumab, abatacept, tocilizumab, sarilumab and tofacitinib. **Comparator:** Any of the drugs in the intervention. Studies that had only placebo as the comparator was excluded.	**Relevant clinical outcomes**: -Standardized criteria for RA treatments response (ACR scores**)** **-**Disease activity and remission (DAS28) -Disability (HAQ-DI) - Safety: Adverse events (serious infection), mortality) **Length of follow up**: 6 months for clinical effectiveness outcomes and 3 months for safety outcomes
Corbett 2016[15] **Country:** UK **Funding sources:** funded by the HTA program on behalf of NICE as project number 13/46/01**.** This study was registered as PROSPERO CRD42014010182.	**Study design:** Systematic review and economic evaluation **Objective:** to determine the clinical effectiveness and safety of TNFα inhibitors for the treatment of severe AS. **Search strategy:** Multiple databases including MEDLINE, EMBASE, CINAHL, clinicaltrials.gov, Cochrane library, PROSPERO, HTA database, conference proceedings, National guidelines clearinghouse. Searched until July 2014.	- Adult patients with severe active AS. Total number of patients in the NMA:3,755 .	**Intervention:** Adalimumab, certolizumab pegol, etanercept, golimumab, infliximab or any of their biosimilars. **Comparators**: Conventional management strategies, placebo or TNF-α inhibitors listed above	**Clinical outcomes:** - ASAS score -disease activity (BASDAI score) -functional capacity (BASFI score) -HRQOL, -treatment discontinuation and withdrawal -adverse events. **Length of follow up:** 10-16 weeks.

First Author, Publication Year, Country, Funding sources	Study Design, Objective, Search Strategy, Number of Primary Studies Included, Quality Assessment Tool	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Number of primary studies included: 24. **Number of relevant direct comparative RCTs included: 0** . **Quality assessment tool:** Cochrane risk of bias tool.			
Stevenson, 2016[16] **Country**: UK **Funding sources:** funded by the HTA program on behalf of NICE as project number 11/74/01. This study is registered as PROSPERO CRD42012003386.	**Study design:** Systematic review and network meta-analysis **Objective:** to determine the clinical effectiveness of TNFα inhibitors for the treatment of RA not previously treated with DMARDs. **Search strategy**: Multiple databases including MEDLINE, EMBASE, CINAHL, Cochrane library, PROSPERO, HTA database and Toxicology Literature. Searched until July 2013. **Number of primary studies included in the SR,** n=60. **Number of relevant direct comparative RCTs included: 2** **Quality assessment tool**: Cochrane risk of bias tool, and NHS center for reviews and dissemination report.	- Population1: Adults patients with severe active RA (DAS≥5.1) previously not treated with methotrexate. - Population 2: Adults with severe active RA (DAS≥5.1) who had been previously treated with CDSMARDs only. - Population 3: Adults with moderate to severe RS (DAS 3.2 to 5.1) who had been treated with cDMARDs only. Excluded: patients with a DA 0df <3.2, patients who had been previously treated with one or more biologics, patients with DAS of <5.2 who had not been previously treated with methotrexate.	**Intervention:** Population 1: Adalimumab, etanercept, golimumab, infliximab. Population 2 and 3: Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab. **Comparator:** biologic interventions compared with each other.	**Clinical outcomes:** - Disease activity (ACR, EULAR responses, tender and swollen joint count) - physical function (HAQ-DI) - Disease progression -HRQoL -mortality **Length of follow up:** 22-30 weeks
Wang, 2016[17] **Country:** China	**Study design:** systematic review and network meta analysis. **Objective:** to compare the TNFα inhibitors in AS and to determine the optimal TNFα inhibitor.	-patients with AS or active AS according to modified New York Criteria. **Total number of patients in the NMA:** 3405	**Intervention:** Adalimumab, etanercept, certolizumab pegol, golimumab or infliximab	**Clinical outcomes**: ASAS score - ASAS20, ASAS40, ASAS70 or ASAS 5/6, and

First Author, Publication Year, Country, Funding sources	Study Design, Objective, Search Strategy, Number of Primary Studies Included, Quality Assessment Tool	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Funding sources: Not reported	**Search strategy**: Pubmed, Embase and Cochrane register for controlled trial, searched until April 2015. Hand searching for references was also done. **Number of relevant primary studies included:** 25, **Number of relevant direct comparative RCTs included: 0** **Quality Assessment tool:** None (quality assessment not done)		**Comparators**: Placebo or any of the drugs in the intervention	ASAS partial remission - Serious adverse events **Follow up**:6- 30 weeks

ACR: American College of Rheumatology; AS: Ankylosing Spondyltis; ASAS: Assessment in SpondyloArthritis International Society; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; DMARD: Disease Modifying Anti Rheumatoid Drugs; cDMARD: Conventional DMARD; DAS: Disease Activity Index; EULAR: European League Against Rheumatism; HAQ-DI: Health Assessment Questionnaire- Disease Activity; HRQoL: Health related Quality of Life; HTA: Health Technology Assessment; NMA: Network metaanalysis; PsA: Psoriatic Arthritis; RA: Rheumatoid Arthritis, RCT = Randomized Controlled Trial, TNFα:Tumor Necrosis Factor alpha;

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using ISPOR checklist,[20] AMSTAR 2,[19] and NICE technical support document[21]

Strengths	Limitations
Camean-Castillo,2019[11]	
• The study rationale and objectives are described clearly and included a description of the eligibility criteria for population, intervention, comparators and outcome. • Multiple databases (MEDLINE and Embase) were searched for eligible studies. Bibliographies of identified studies were searched for additional studies. • The study selection process was reported in detail, including justification for excluding studies. • Outcome measures were described. • Models were fitted using Deviance Information Criteria (DIC) and the NMA was conducted using Bayesian approach, and a posterior distribution model was obtained. • Fixed effects model was used as it resulted in better DIC values and narrower CIs. • Direct and indirect comparative findings were compared to evaluate consistency. • Characteristics and results of individual primary studies are presented clearly in a table. • A justification of the model fit was reported. • The network of studies was presented in a figure. •	• It was not reported whether the review methods were established in the form of a protocol. • It was unclear whether the study selection and data extraction was done in duplicate. • Quality assessment of the individual studies were not reported. • It was unclear if heterogeneity was addressed. • The results were not analyzed using a priori random effects model. • Unclear if effect modifiers were considered. • A sensitivity analysis was not done. • Internal validity of the study was not discussed by means of reporting publication bias and the risk of bias in the individual primary studies. • External validity of the results and the implications of results for a target audience were not discussed. • Funding source of the NMA was not reported • There was no interpretation of results from a biological and clinical perspective.
Choy, 2019[12]	
• The study rationale and objectives are described clearly. • The methods section included a description of the eligibility criteria for the review including population, interventions, comparators and outcomes and study design were described in detail. • MEDLINE, EMBASE and Cochrane databases were searched for eligible studies without a time limit. Conference proceedings were also searched. • The study selection process was reported in detail, including justification for excluding studies. • Study selection and data extraction was done independently by two reviewers. • Outcome measures were described in detail. • The statistical methods used to conduct the indirect comparison was clearly reported. (Bayesian NMA with likelihood distribution. Non informative prior distribution of model parameters in the Bayesian Network were done. • A feasibility assessment was conducted a priori. A scenario analysis was done based on effect modifiers found in feasibility analysis.	• Characteristics of each included studies were not reported. • Quality assessment of the individual studies were not reported. • Internal validity of the study was not discussed by means of reporting publication bias and the risk of bias in the individual primary studies. • There was no interpretation of results from a biological and clinical perspective.

Strengths	Limitations
• Random and fixed effects model were fitted and decided using DIC A fixed effects model was used based on the result of feasibility assessment showing less variability with adalimumab as the common comparator. • The network of studies were presented in a figure. • Indirect comparative results were reported as Odds Ratio, Risk Difference or change from baseline along with 95%CrI • A discussion of external validity was done.	
Lu, 2019[13]	
• The study rationale and objectives are described clearly • The methods section included a description of the eligibility criteria for the review including population, interventions, comparators and outcomes and study design were described in detail • A systematic review of literature was conducted according to the PRISMA guidelines. • MEDLINE, EMBASE, web of science and Cochrane databases were searched for eligible studies. The search strategy was reported for all databases. • Study selection and data extraction was done independently by two reviewers. • Quality assessment of included studies was done by three reviewers using the Cochrane collaboration's risk of bias tool. • Outcome measures of interest were described in detail. • The data analysis method and models used were described in the methods section. The authors used a frequentist framework with a random effects model. • Quantitative assessment of inconsistency was done using loop specific consistency plots and side-splitting test • Heterogeneity was assessed using I2 statistic and p value. • A sub-group analysis based on possible effect modifiers (prior exposure to bDMARDs) • Characteristics and results of individual primary studies are presented clearly in a table • The network of studies were presented in a figure. • The results of the NMA were presented clearly, using Odds Ratios and 95 % CI. • The discussion section contained a summary of results and a discussion on internal and external validity of the results.	• It was unclear whether a sensitivity analysis was performed. • Likelihood of publication bias was not assessed. • Interpretation of results from a biological perspective was not done. • Included studies were funded by pharmaceutical companies.
Maksymowych, 2018[14]	
• A systematic search for literature in multiple databases • Well-defined eligibility criteria describing relevant PICO elements	• Unknown if study selection and data extraction were performed in duplicate to reduce the potential for bias and validate data accuracy.

Strengths	Limitations
• Study inclusion criteria with reasons for exclusion • Provision of a list of included and excluded studies • Identification of treatment effect modifiers for anchored MAIC • Adjustments for all effect modifiers in anchored MAIC analysis • Matching achieved homogeneity in the effect modifiers in patients who contributed data for the MAIC analysis	• Unclear if the effect modifiers in anchored MAIC were all appropriate or exhaustively covered • Unknown impact of including effect modifiers without a statistically significant between-study difference in the MAIC under review • Unclear how the unidentified method of estimating regression parameters impacted the balancing of the mean covariate values between the index and comparator trials. • Unknown if the reduction in the ESS after matching to achieve homogeneity was large enough to affect the precision of the resulting estimates • Lack of identification of effect modifiers and prognostic variables for the unanchored MAIC resulted in significant uncertainty about its findings
Ollendorf, 2017[18]	
• The study rationale and objectives were described clearly • The methods section included a description of the eligibility criteria for the review including population, interventions, comparators and outcomes and study design were described in detail. • A systematic review of literature was conducted according to the PRISMA guidelines. • MEDLINE, EMBASE, and Cochrane databases were searched for eligible studies. The search strategy was reported for all databases • The characteristics of included studies were reported in detail and clearly. • Quality assessment of the included studies were done using the US Preventive Services Task Force checklist. • Outcome measures were described in detail. • The data analysis method and models used were described in the methods section. The network meta-analysis was done using a Bayesian framework. • A sensitivity analysis was conducted, and the results were reported. • An a priori random effects model was used. • An adjusted model was specified as a control for confounding and heterogeneity. • Effect modifiers (cDMARD response) were considered and tested for. • A network diagram was included for each of the outcomes in NMA. • Competing models (adjusted and unadjusted) were compared, but no effect modification was found. Thus, an unadjusted model was used. • The results of the NMA were presented clearly, using Odds Ratios and 95 % CrI. • The discussion section contained a summary of results ad discussion on the internal validity of the results.	• Study selection was done by a single reviewer. • It was unclear whether the data extraction was done in duplicate. • It was unclear inconsistency was evaluated. • Interpretation of results from a biological perspective was not done. • Generalizability of the findings and implications for the target audience were not clearly discussed

Strengths	Limitations
Corbett, 2016[15]	
• The study rationale and objectives are described clearly • The review methods were established prior to the review and registered in PROSPERO. • The methods section included a description of the eligibility criteria for the review including population, interventions, comparators and outcomes and study design were described in detail • Multiple databases were searched for eligible studies. Search strategies for all databases were reported. • Study selection was done independently by two reviewers. Data extraction was done by one reviewer and independently checked for accuracy by a second reviewer. • Quality assessment of included extraction was done by one reviewer and independently checked for accuracy by a second reviewer using the Cochrane collaboration's risk of bias tool. • Outcome measures of interest were described in detail. • Multiple treatment meta-analysis was conducted using a random effects model in Bayesian framework. Sensitivity analyses was done. • Possible effect modifiers were considered and evaluated using meta regression. • Model selection was reported, and the best model was adequately justified. • Characteristics and results of individual primary studies were reported clearly. • The results of the indirect comparisons were presented clearly, using Odds Ratios, relative risks and change from baselines and 95 % CrI as appropriate. • Discussion section had a summary of findings.	• It was unclear whether inconsistencies were evaluated and the method used. • It was unclear whether an uninformed prior was used. • A network diagram of included studies was not reported. • It was unclear whether publication bias was assessed • The probability to reflect decision uncertainty was not reported. • The external validity and generalizability of the results were not discussed. • Interpretation of results from a biological perspective was not done.
Stevenson, 2019[16]	
• The objectives of the systematic review were clearly described. The inclusion and exclusion criteria for the review were described in detail and included components of population, intervention, comparators and outcomes. • The review methods were established prior to the review and registered in PROSPERO. • The study designs eligible and rationale for including were reported. • A comprehensive search of multiple databases including (MEDLINE, Embase, CINAHL, Cochrane Library, and toxicology literature) and clinical trial registries was done, without imposing a date restriction. Hand searching for additional publications in references was also done. Grey literature was searched using CADTH toolkit. • A list of excluded studies along with the reason for exclusion was reported.	• Study selection was done by one reviewer. • Data extraction from selected studies was not done in duplicate. It was mentioned in the protocol that a second reviewer would check 10% of results for accuracy. However, this was not done. • Assumptions considered for the NMA were not substantiated using a SR, but were based on clinical expert opinions • It was unclear how the relative effect estimates and results of the NMA were reported. • Primary studies beyond the scope of the SR were included in the sensitivity analysis, • Interpretation of results from a biological perspective was not done. • It was unclear whether inconsistencies were assessed. • It was unclear whether publication bias was assessed.

Strengths	Limitations
• The characteristics of included studies were described clearly. • Quality assessment of the included studies were done using validated instruments. • Source of funding for the individual studies were reported when available. • NMA was conducted using Bayesian approach, and effect sizes were reported on a probit scale using prior distributions. Statistical model was described in detail. • Sensitivity analyses were done and rationales for them were described. • Results of the NMA were presented using effect sizes and 95% CrI. • A network diagram was included for each of the outcomes in NMA. • Heterogeneity was evaluated using between studies SD • Effect modifiers (duration of the disease) were considered and evaluated using DIC. Funding sources and potential conflicts of interest for the authors were reported.	
Wang, 2016[17]	
• The study rationale and objectives are described clearly. • The methods section included a description of the eligibility criteria for the review including population, interventions, comparators and outcomes and study design were described. • Multiple databases were searched for eligible studies. Search strategies were reported. • Study selection and data extraction was done independently by two reviewers. • Outcome measures of interest were described in detail. • The statistical methods and models for analysis were described • Testing for heterogeneity and inconsistency was done, and models were fit based on heterogeneity and consistency. • Heterogeneity was low as measured using I2 values. • The results of the indirect comparisons were presented, using Odds Ratios, relative risks and change from baselines and 95 % CI as appropriate. • Funnel plots of small sample size bias was reported. • Discussion section had summary of findings • Interpretation of results from a biological perspective was done in detail.	• It was unclear if the NMA was conducted using Bayesian or frequentist approach. • Quality assessment of included studies was not done. • Individual study characteristics like demographics and study results were not reported. • It was unclear whether a sensitivity analysis was done. As the study characteristics are not reported, it is difficult to assess such analyses are warranted. • Possible effect modifiers like previous or concurrent use of other medications, duration of illness were not considered. • It was unclear whether publication bias was assessed. • The external validity and generalizability of the results were not discussed.

AMSTAR = A MeaSurement Tool to Assess systematic Reviews; CADTH: Canadian Agency for Drugs and Technologies in Health; CI: Confidence interval; CINAHL = Cumulative Index to Nursing and Allied Health Literature; CrI: credible interval; DIC: deviance information criterion; EMBASE = Excerpta Medica database; HTA = Health Technology Assessment; MAIC: Matching adjusted indirect comparison; NMA: Network met-analysis; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SD: standard deviation;

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Systematic Reviews, and Network Meta-Analyses, and Matching-Adjusted Indirect Comparison

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Camean-Castillo 2019[11]</td></tr>
<tr><td>This SR and NMA of 25 studies aimed to determine the comparative efficacy of bDMARDs in RA.

Relevant findings are summarized below:

Direct comparison results from primary studies:
One relevant head to head trial was identified in the SR.

<table>
<tr><td>Gabay,2013[24]
(ADACTA trial)

Adalimumab, n=163
Tocilizumab, n=163</td><td>Outcome: ACR
At 24 weeks,
ACR 50 (% achieving ACR50)
➢ Tocilizumab = 47.2; Adalimumab = 27.8
➢ Tocilizumab vs adalimumab, OR = 2.3 (1.5-3.7)
➢ P= 0.0002</td></tr>
</table>

Indirect Comparison results from NMA:

ACR 50 (% achieving ACR50)
- Etanercept vs Adalimumab, OR = 3.79 (0.56 -28)
- Certolizumab pegol vs Adalimumab, OR = 2.48 (0.23-27.8)
- Tocilizumab vs Adalimumab, OR = 2.31 (1.16-4.56)*
- Tofacitinib vs Adalimumab, OR = 1.68 (0.31-9.15)

*indicates results in favour of Tocilizumab</td><td>"Regarding efficacy, certolizumab and tocilizumab with or without methotrexate, and abatacept, infliximab, golimumab, adalimumab, baricitinib and tofacitinib in combination with methotrexate, conformed to the efficacy criteria to consider them as ETA in patients naïve to biological DMARDs."[11] p395</td></tr>
<tr><td colspan="2">Choy,2019[12]</td></tr>
<tr><td>SR and indirect treatment comparison to evaluate the efficacy and safety of sarilumab monotherapy vs other approved monotherapies in RA patients.

Relevant findings are summarized below:

Direct comparison results from primary studies:
One relevant head to head trial was identified in the SR[23]. The MONARCH trial[23] compared the effectiveness of sarilumab 200 mg s.c q2w with adalimumab 40 mg s.c q2w. Direct comparison results were not reported.

Indirect Comparison results from NMA:

ACR20 (OR and 95% CI)
- Sarilumab vs adalimumab, OR = 1.82 (1.18 – 2.83)
ACR50
- Sarilumab vs adalimumab, OR = 1.99 (1.3 – 3.07)
ACR70
- Sarilumab vs adalimumab, OR = 2.28 (1.31 – 4.06)

EULAR good
- Sarilumab vs adalimumab, RD = 0.268 (0.173 – 0.363)</td><td>"In csDMARD-IR patients, sarilumab 200mg monotherapy has superior efficacy and similar safety versus csDMARDs, superior efficacy and similar safety versus adalimumab, and similar efficacy and safety versus bDMARDs and tsDMARDS." [12] (p 825)</td></tr>
</table>

Main Study Findings	Authors' Conclusion
EULAR mod-good - Sarilumab vs adalimumab, RD = 0.135 (0.05 – 0.219) DAS28 remission score: - Sarilumab vs adalimumab, RD = 0.196 (0.123 – 0.269)* HAQ-DI - Sarilumab vs adalimumab, CFB = -0.181 (-0.319 – -0.041)* Serious infection - Sarilumab vs adalimumab, RI = 0 (-0.021 – -0.021) SAE - Sarilumab vs adalimumab, RD = -0.016 (-0.064 – -0.031) *indicates results in favour of Sarilumab	
Lu,2019[13]	
SR and NMA of 29 trials assessing the comparative efficacy of targeted therapies in PsA. Relevant findings are summarized below: **Direct comparison results from primary studies:** No studies were identified directly comparing adalimumab with any of the relevant comparators. **Indirect Comparison results from NMA:** ACR20 (OR and 95 % CI) - Adalimumab vs infliximab, OR = 0.52 (0.24 – 1.11) - Adalimumab vs etanercept, OR = 0.72(0.34 – 1.56) - Adalimumab vs certolizumab pegol, OR = 1.75(0.91 – 3.39) - Adalimumab vs secukinumab 150mg, OR = 1.64 (0.98 – 2.77) - Adalimumab vs secukinumab 300mg, OR = 1.35 (0.78 – 2.32) - Adalimumab vs golimumab, OR = 0.64 (0.35 – 1.16) - Adalimumab vs ixekizumab every 2 weeks, OR = 1.99 (1.07 – 3.69)* - Adalimumab vs ixekizumab every 4 weeks, OR = 2.02 (1.09 – 3.74)* PASI75 (OR and 95 % CI) - Adalimumab vs infliximab, OR = 0.28 (0.05 – 1.79) - Adalimumab vs etanercept, OR = 2.17(0.33 – 14.29) - Adalimumab vs certolizumab pegol, OR = 3.91(0.92 – 16.59) - Adalimumab vs secukinumab 150mg, OR = 2.12 (0.57 – 7.92) - Adalimumab vs secukinumab 300mg, OR = 1.59 (0.41– 6.12) - Adalimumab vs golimumab, OR = 1.96 (0.49 – 7.69) - Adalimumab vs ixekizumab every 2 weeks, OR = 1.14 (0.27 – 4.85) - Adalimumab vs ixekizumab every 4 weeks, OR = 1.11 (0.26 – 4.69) Adverse events(OR and 95 % CI) - Adalimumab vs infliximab, OR = 0.26 (0.10 – 0.70)* - Adalimumab vs etanercept, NR - Adalimumab vs certolizumab pegol, OR = 0.26 (0.10 – 0.71)*	"Our network meta-analysis suggests that infliximab, golimumab, guselkumab, adalimumab, secukinumab and ustekinumab may be the safest and most efficacious targeted therapies for inducing remission among patients with active PsA." [13] (p 387)

Main Study Findings	Authors' Conclusion
- Adalimumab vs secukinumab 150mg, OR = 0.27 (0.11 – 0.67)* - Adalimumab vs secukinumab 300mg, OR = 0.28 (0.11 – 0.71)* - Adalimumab vs golimumab, OR = 0.22 (0.09 – 0.56)* - Adalimumab vs ixekizumab every 2 weeks, OR = 0.16 (0.06 – 0.42)* Serious adverse events (OR and 95 % CI) - Adalimumab vs infliximab, OR = 0.5 (0.12 – 2.17) - Adalimumab vs etanercept, OR = 0.81 (0.15 – 4.48) - Adalimumab vs certolizumab pegol, OR = 0.38 (0.09 – 1.65) - Adalimumab vs secukinumab 150mg, OR = 0.86 (0.26 – 2.9) - Adalimumab vs secukinumab 300mg, OR = 0.82 (0.22– 2.98) - Adalimumab vs golimumab, OR = 1.2 (0.32 – 4.54) - Adalimumab vs ixekizumab every 2 weeks, OR = 0.36 (0.08 – 1.64) - Adalimumab vs ixekizumab every 4 weeks, OR = 0.43 (0.09 – 2.01) - *indicates statistical significance in favor of adalimumab.	
Maksymowych, 2018[14]	
Systematic review and matching adjusted indirect comparison of adalimumab 40 mg and secukinumab150 mg in AS. Relevant findings are summarized below: **Direct comparison results from primary studies:** No studies were identified directly comparing adalimumab with any of the relevant comparators. **Indirect Comparison results from MAIC:** • ASAS20 (OR and 95 % CI) - Week 8, Secukinumab vs adalimumab, OR = 0.91 (0.44 – 1.89), p=0.795 - Week 12, Secukinumab vs adalimumab, OR = 0.60 (0.28 – 1.28), p=0.185 - Week 16[a], Secukinumab vs adalimumab, OR = 1.60 (1.01 – 2.54), p=0.047* - Week 24[a], Secukinumab vs adalimumab, OR = 1.76 (1.11 – 2.79), p=0.017* - Week 52[a], Secukinumab vs adalimumab, OR = 1.48 (0.98 – 2.22), p=0.062 • ASAS40 (OR and 95 % CI) - Week 8, Secukinumab vs adalimumab, NR - Week 12, Secukinumab vs adalimumab, OR = 0.93 (0.39 – 2.21), p=0.867 - Week 16 [a], Secukinumab vs adalimumab, NR - Week 24 [a], Secukinumab vs adalimumab, OR = 1.79 (1.14 – 2.82), p=0.012* - Week 52 [a], Secukinumab vs adalimumab, OR = 1.54 (1.06 – 2.23), p=0.023* • ASAS5/6 (OR and 95 % CI) - Week 8, Secukinumab vs adalimumab, NR - Week 12, Secukinumab vs adalimumab, OR = 0.50 (0.22– 1.18), p=0.015* - Week 16[a], Secukinumab vs adalimumab, NR - Week 24[a], Secukinumab vs adalimumab, OR = 1.51 0.96 – 2.38), p=0.072 - Week 52[a], Secukinumab vs adalimumab, OR = 1.42 (0.97 – 2.07), p=0.072 • ASQoL(Change from baseline and 95%CI) Week 12 - Adalimumab, CFB = -2.2 (-3.2 – -1.2) - Secukinumab, CFB = -2.0 (-3.0 – -0.9)	"the current MAIC of patients with active AS in the MEASURE 1/2 RCTs receiving secukinumab 150 mg who were matched for treatment effect modifiers to the ATLAS RCT population receiving adalimumab demonstrates comparable placebo-adjusted ASAS 20 and 40 responses up to 12 weeks but suggests a higher probability of achieving both medium-and long-term ASAS-defined responses (ASAS 20 and ASAS 40) in those receiving secukinumab." [14] (p 222)

Main Study Findings	Authors' Conclusion
- P= 0.756 Week 24[a] - Adalimumab, CFB = -3.6 (-5.0 – -2.2) - Secukinumab, CFB = -4.2 (-5.0 – -3.3) - P= 0.478 • BASDAI, 0-100 VAS (Change from baseline and 95%CI) Week 12 - Adalimumab, CFB = -1.8 (-2.4 – -1.2) - Secukinumab, CFB = -1.2 (-1.6 – -0.8) - P= 0.104 Week 24[a] - Adalimumab, CFB = -2.6 (-3.0 – -2.2) - Secukinumab, CFB = -2.9 (-3.2 – -2.6) - P= 0.267 • PtGA,0-100 VAS (Change from baseline and 95%CI) Week 12 - Adalimumab, CFB = -45.6 (-60.9 – -30.3) - Secukinumab, CFB = -15.4(-20.5 – -10.4) - P <0.001 Week 24[a] - Adalimumab, CFB = -37.8 (-47.6 – -28.0) - Secukinumab, CFB = -34.2 (-38.0 – -30.5) - P= 0.503 *indicates statistical significance. [a] Results from week 16, 24 and 52 are non-placebo adjusted.	
Ollendorf, 2017[18]	
SR and NMA to determine the comparative clinical effectiveness of targeted immune modulators for RA . The SR had a broader scope than the current report. Only the findings relevant to this report are summarized below: **Direct comparison results from primary studies:** Two relevant head to head trials were identified.[23,24] Adalimumab monotherapy was less likely to achieve clinical response rates when compared to tocilizumab and sarilumab. Adalimumab resulted in less improvement in HAQ-DI compared to sarilumab. Primary study citation: Gabay 2013[24] (ADACTA trial) Included adult RA patients who were on cDMARD of cannot tolerate methotrexate. All cDMARD were stopped before trial. Adalimumab, n= 163 tocilizumab, n=163 Summary of relevant results: Phase IV RCT of tocilizumab (8mg/kg iv q4w) vs adalimumab (40 mg s.c q2w) in patients with Moderate to severe RA, previously treated with methotrexate. ACR 20 (% achieving ACR20) ➢ Adalimumab = 49.4; Tocilizumab = 65.0 ➢ P<0.005 ACR 50 (% achieving ACR50) ➢ Adalimumab = 27.8; Tocilizumab = 47.2 ➢ P<0.005 ACR 70 (% achieving ACR70) ➢ Adalimumab = 17.9; Tocilizumab = 32.5 ➢ P<0.005	"Adalimumab monotherapy was inferior to monotherapy with tocilizumab and sarilumab in rates of clinical remission achieved and ACR responses across all levels; adalimumab also resulted in significantly less improvement in HAQ-DI compared with sarilumab. In all other head-to-head trials of combination therapy, adalimumab was similar to abatacept, etanercept, tofacitinib, and certolizumab pegol in rates of remission achieved, ACR response across all levels, and

Main Study Findings		Authors' Conclusion
Follow up time- 24 weeks. Funding source: Hoffmann-La Roche Countries: 76 centers in 15 countries in North and South America, Australia, and Europe	EULAR response ➢ % achieving good EULAR response ○ Adalimumab = 19.8; Tocilizumab = 51.5 ○ P<0.0001 DAS28 (mean change form baseline (SD)) ➢ Adalimumab = -1.8(NR); Tocilizumab=-3.3(NR) ○ P<0.0001 HAQ-DI ➢ HAQ-DI, mean change form baseline (SD) ➢ Adalimumab = -0.5; Tocilizumab=-0.7 ➢ P=0.06 Discontinuation due to adverse events (%) ➢ Adalimumab 16 (10); Tocilizumab, 19 (12) Serious Infection (%) ➢ Tocilizumab, 5/162 (3.1); Adalimumab, 5/162 (3.1) Mortality, n ➢ Adalimumab 0; Tocilizumab 1	improvement in HAQ-DI; there was also no statistical difference between abatacept and adalimumab in slowing radiographic progression."[18] (P ES8)
Burmester, 2017[23] (MONARCH trial) Included adult patients with active RA who are intolerant or not responding to previous cDMARD treatment. Adalimumab, n= 185 tocilizumab, n=184 Follow up time- 24 weeks. Funding source: Sanofi Country: 86 centers in Europe, Israel, Russia, South Africa, South Korea, and the USA	Phase III double blinded RCT of adalimumab 40 mg q2w + placebo vs sarilumab 200 mg q2w + placebo. After 16 weeks, dose escalation to weekly adalimumab was done for patients who did not achieve at least ACR20. ACR 20 (% achieving ACR20) ➢ Adalimumab = 58.4; Sarilumab = 71.1 ➢ P<0.05 ACR 50 (% achieving ACR50) ➢ Adalimumab = 29.7; Sarilumab = 45.7 ➢ P<0.005 ACR 70 (% achieving ACR70) ➢ Adalimumab = 11.9; Sarilumab = 23.4 ➢ P<0.005 DAS-28 At 24 weeks, DAS 28, mean change form baseline (SD) ➢ Adalimumab = -2.2; Sarilumab = -3.28 ➢ P<0.0001 HAQ-DI HAQ-DI, mean change form baseline (SD) ➢ Adalimumab = -0.43; Sarilumab = -0.61 ➢ P<0.005 ➢ Percentage of patients achieving an improvement meeting MCID (0.3) threshold- Adalimumab = 47.6%; Sarilumab = 62% (P<0.01) Serious infection (%) ➢ Adalimumab = 2 (1.1) ; Sarilumab = 2 (1.1) Serious adverse events (%) ➢ Adalimumab = 12 (6.5) ; Sarilumab = 9 (4.9) Discontinuation (%) ➢ Adalimumab = 13 (7.1) ; Sarilumab = 11 (6) Mortality	

Main Study Findings	Authors' Conclusion
➢ Adalimumab = 0 ; Sarilumab = 1 **Indirect Comparison results from NMA:** In all RA patients with monotherapy, ACR20 (OR and 95 % CI) - Adalimumab vs tocilizumab, OR = 0.76 (0.59 – 0.90)* - Adalimumab vs etanercept, OR = 0.79(0.55 – 1.05) - Adalimumab vs sarilumab, OR = 0.80(0.67 – 0.91)* ACR50 (OR and 95 % CI) - Adalimumab vs tocilizumab, OR = 0.63 (0.44 – 0.82)* - Adalimumab vs etanercept, OR = 0.66(0.39 – 1.09) - Adalimumab vs sarilumab, OR = 0.68(0.53 – 0.85)* ACR70 (OR and 95 % CI) - Adalimumab vs tocilizumab, OR = 0.52 (0.33 – 0.75)* - Adalimumab vs etanercept, OR = 0.56(0.27 – 1.13) - Adalimumab vs sarilumab, OR = 0.60(0.42 – 0.79)* In RA patients who were biologic naïve, ACR20 (OR and 95 % CI) - Adalimumab vs tocilizumab, OR = 0.8 (0.42 – 1.03) - Adalimumab vs etanercept, OR = 0.84(0.39 – 1.40) - Adalimumab vs sarilumab, OR = 0.84(0.54 – 1.13) ACR50 (OR and 95 % CI) - Adalimumab vs tocilizumab, OR = 0.67 (0.27 – 1.06) - Adalimumab vs etanercept, OR = 0.73(0.23 – 1.75) - Adalimumab vs sarilumab, OR = 0.74(0.40 – 1.23) ACR70 (OR and 95 % CI) - Adalimumab vs tocilizumab, OR = 0.55 (0.17 – 1.11) - Adalimumab vs etanercept, OR = 0.63(0.13 –2.27) - Adalimumab vs sarilumab, OR = 0.63(0.28 – 1.35) *indicates results in favour of the comparator.	
Corbett, 2016[15]	
This HTA aimed to determine the comparative clinical effectiveness of TNFα inhibitors in the patients with AS. The SR had a broader scope than the current report. Only the findings relevant to this report are summarized below: **Direct comparison results from primary studies:** No studies were identified directly comparing adalimumab with any of the relevant comparators. **Indirect Comparison results from NMA:** No treatments were favoured between ADA, CTZ, ETN, GOL or INF. • ASAS20 (OR and 95% CrI)	"In AS, although there is a little variation in treatment effects and it is possible that infliximab may be more effective than other anti-TNFs at 12 weeks, the evidence for this is

Main Study Findings	Authors' Conclusion
- Adalimumab vs certolizumab pegol, OR = 1.74 (0.84 – 3.57) - Adalimumab vs etanercept, OR = 1.07 (0.67 – 1.71) - Adalimumab vs golimumab, OR = 1.18 (0.69 – 2.05) - Adalimumab vs infliximab, OR = 0.82 (0.33 – 1.99) • ASAS40 (OR and 95% CrI) - Adalimumab vs certolizumab pegol, OR = 1.68 (0.69 – 4.04) - Adalimumab vs etanercept, OR = 1.47 (0.71 – 3.02) - Adalimumab vs golimumab, OR = 1.19 (0.60 – 2.38) - Adalimumab vs infliximab, NR • ASAS50 (OR and 95% CrI) - Adalimumab vs certolizumab pegol, NR - Adalimumab vs etanercept, OR = 0.71 (0.20 – 2.49) - Adalimumab vs golimumab, NR - Adalimumab vs infliximab, OR = 0.24 (0.03 – 1.71) • BASDAI (Mean difference of change from baseline (CFB) and 95% CrI) - Adalimumab vs certolizumab pegol, CFB = -0.10 (-0.88 – 0.68) - Adalimumab vs etanercept, CFB = 0.20 (-0.30 – - 0.71) - Adalimumab vs golimumab, NR - Adalimumab vs infliximab, CFB = 0.73 (-0.24 – 1.69) • BASFI (Mean difference of change from baseline (CFB) and 95% CrI) - Adalimumab vs certolizumab pegol, CFB = -0.15 (-0.97 – 0.67) - Adalimumab vs etanercept, CFB = 0.18 (-0.36 – 0.73) - Adalimumab vs golimumab, CFB = 0.20 (-0.35 – 0.75) - Adalimumab vs infliximab, CFB = 0.91 (-0.2 – 2.00) • BASMI (Mean difference of change from baseline (CFB) and 95% CrI) - Adalimumab vs certolizumab pegol, CFB = -0.11 (-0.42– 0.21) - Adalimumab vs etanercept, CFB = 0.00 (-0.31 – 0.32) - Adalimumab vs golimumab, CFB = -0.26 (-0.46 – -0.06) - Adalimumab vs infliximab, NR • SF-36 PCS (Mean difference of change from baseline (CFB) and 95% CrI) - Adalimumab vs certolizumab pegol, CFB = -2.11 (-4.44 – 0.20) - Adalimumab vs etanercept, NR - Adalimumab vs golimumab, CFB = -1.52 (-3.30 – 0.24) - Adalimumab vs infliximab, NR • SF-36 MCS (Mean difference of change from baseline (CFB) and 95% CrI) - Adalimumab vs certolizumab pegol, CFB = 0.15 (-3.53 – 3.83) - Adalimumab vs etanercept, NR - Adalimumab vs golimumab, CFB = -1.33 (-3.63 – 0.98) - Adalimumab vs infliximab, NR	not strong and it is plausible that anti-TNFs may have a common class effect, with the treatments being equally effective." [15] (p 66)
Stevenson, 2019[16]	
This SR and NMA aimed to determine the comparative clinical effectiveness of bDMARDs in defined populations of patients with RA.	"Better evidence on the relative efficacies of bDMARDs and the reduction in efficacy when used after a

Main Study Findings	Authors' Conclusion

The SR had a broader scope than the current report. Only the findings relevant to this report are summarized below:

Direct comparison results from primary studies:
Two[24,25] relevant primary studies were identified in the SR.

Primary study citation	Summary of relevant results
Gabay 2013[24] (ADACTA trial) Multinational multicentre trial. Adalimumab, n= 163 tocilizumab, n=163 Follow up time- 24 weeks.	Phase IV RCT of Tocilizumab vs adalimumab in patients with Moderate to severe RA, previously treated with methotrexate. ACR 20 (% achieving ACR20) ○ Tocilizumab = 65.0; Adalimumab = 49.4 ○ P <0.05 ACR 50 (% achieving ACR50) ○ Tocilizumab = 47.2; Adalimumab = 27.8 ○ P <0.05 ACR 70 (% achieving ACR70) ○ Tocilizumab = 32.5; Adalimumab = 17.9 ○ P <0.05 EULAR response ○ % achieving good EULAR response ○ Tocilizumab = 51.5 ; Adalimumab = 19.8 ○ P<0.01 ○ % achieving moderate to good EULAR response ○ Tocilizumab = 77.9; Adalimumab = 54.9 ○ Not statistically significant DAS28 (mean change form baseline (SD)) ○ Tocilizumab=-3.3(NR) ; Adalimumab = -1.8(NR) ○ P<0.05 HAQ-DI ○ HAQ-DI, mean change form baseline (SD) ○ Tocilizumab=-0.7 ; Adalimumab = -0.5 ○ Not statistically significant SF-36 ○ SF36, mean change form baseline (SD) ○ PCS: Tocilizumab=9.2 ; Adalimumab = 7.6 (NS) ○ MCS: Tocilizumab=7.9 ; Adalimumab = 5.0, P<0.05 Discontinuation due to adverse events (%) ○ Tocilizumab, 9/163 (5.5); Adalimumab 10/163 (6.1) Infection (%) ○ Tocilizumab, 77/162 (47.5); Adalimumab 68/162 (42) Serious Infection (%) ○ Tocilizumab, 5/162 (3.1); Adalimumab, 5/162 (3.1) Mortality, n ○ Tocilizumab 1; Adalimumab 0
Kume,2011[25] Country: Japan Adalimumab monotherapy n=22	Open label RCT of adalimumab vs etanercept monotherapy in patients with severe RA naïve to previous methotrexate. DAS-28 At 24 weeks, DAS 28, mean change form baseline (SD)

different bDMARD would be beneficial, but it is acknowledged that large RCTs would be required to provide definitive answers."[16] (p lvii)

Main Study Findings	Authors' Conclusion
<table><tr><td>Etanercept monotherapy, n=21</td><td>Etanercept = -2.884 (0.42); Adalimumab = -2.12 (0.38) (NS) HAQ-DI HAQ-DI, mean change form baseline (SD) Etanercept = -0.68 (0.09); Adalimumab = -0.69 (0.11) (NS)</td></tr></table> **Indirect Comparison results from NMA:** • **ACR response**, **Treatment effect on a probit scale (95% CrI)** <u>Patients with severe active RA naïve to previous methotrexate</u> - Etanercept vs adalimumab: –0.41 (–1.08 - 0.27) <u>Patients with moderate-to-severe and severe active RA (previously treated with cDMARDs)</u> - Etanercept vs adalimumab: –0.37 (–0.95 - 0.20) - Tocilizumab vs adalimumab: –0.57 (–1.07 - –0.09) • **EULAR response Treatment effect on a probit scale (95% CrI)** <u>Patients with moderate-to-severe and severe active RA (previously treated with cDMARDs)</u> - Etanercept vs adalimumab: 0.15 (–1.91 - 2.28) - Tocilizumab vs adalimumab: –0.78 (–1.69 - 0.13)	
Wang, 2016[17]	
This systematic review and network meta analysis compared the clinical effectiveness of five TNFα inhibitors. Relevant findings are summarized below: **Direct comparison results from primary studies:** No studies were identified directly comparing adalimumab with any of the relevant comparators. **Indirect Comparison results from NMA:** • ASAS20 - Adalimumab vs etanercept, OR = 0.78 (0.44 – 1.38) - Adalimumab vs golimumab, OR = 1.13 (0.59 – 2.19) - Adalimumab vs infliximab, OR = 1.05 (0.57 – 1.93) - Adalimumab vs certolizumab pegol, OR = 1.75 (0.81 – 3.84) • ASAS40 - Adalimumab vs etanercept, OR = 0.94 (0.46 – 1.90) - Adalimumab vs golimumab, OR = 0.92 (0.37 – 2.32) - Adalimumab vs infliximab, OR = 0.70 (0.31 – 1.57) - Adalimumab vs certolizumab pegol, OR = 1.31 (0.55 – 3.125) • ASAS5/6 - Adalimumab vs etanercept, OR = 1.50 (0.42 – 5.31) - Adalimumab vs golimumab, OR = 1.73 (0.46 – 6.55) - Adalimumab vs infliximab, OR = 1.08 (0.27 – 4.34) - Adalimumab vs certolizumab pegol, OR = 1.47 (0.29 – 7.69) • ASAS-PR - Adalimumab vs etanercept, OR = 1.36 (0.50 – 3.69)	"For summary, the mixed treatment comparison suggested that etanercept, infliximab and adalimumab appeared to be among the top three drug therapies. Although with no substantial distinctions. However, further investigations with larger sample size are still in demand to provide AS patient with optimal clinical therapy." [17] (p 1691)

Main Study Findings	Authors' Conclusion
- Adalimumab vs golimumab, OR = 1.80 (0.54 – 6.00) - Adalimumab vs infliximab, OR = 0.78 (0.20 – 2.97) - Adalimumab vs certolizumab pegol, OR = 0.89 (0.24 – 3.22) • SAE - Adalimumab vs etanercept, OR = 0.41 (0.08 – 2.01) - Adalimumab vs golimumab, OR = 1.07 (0.19 – 5.88) - Adalimumab vs infliximab, OR = 0.51 (0.08 – 3.19) - Adalimumab vs certolizumab pegol, OR = 1.88 (0.35 – 10)	

ACR: American College of Rheumatology; AS: Ankylosing Spondyltis; ASAS: Assessment in SpondyloArthritis International Society; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; DMARD: Disease Modifying Anti Rheumatoid Drugs; cDMARD: Conventional DMARD; DAS: Disease Activity Index; EULAR: European League Against Rheumatism; HAQ-DI: Health Assessment Questionnaire- Disease Activity; HRQoL: Health related Quality of Life; NMA: Network metaanalysis; PsA: Psoriatic Arthritis; PtGA: Patient Reported Global Assessment RA: Rheumatoid Arthritis, RCT = Randomized Controlled Trial, SR: Systematic review ;TNFα:Tumor Necrosis Factor alpha

Appendix 5: Additional References of Potential Interest

Related CADTH reports

Drugs for the management of rheumatoid arthritis: clinical evaluation. *(CADTH Health Technology Assessment).* Ottawa (ON): CADTH; 2018
https://www.cadth.ca/sites/default/files/pdf/HT0010_RA_Report.pdf

Clinical and Economic Overview: Biological Response Modifier Agents for Adults with Rheumatoid Arthritis. *(CADTH Therapeutic Review).* Ottawa (ON): CADTH; 2010:
https://www.cadth.ca/sites/default/files/pdf/TR_RA_Clinical_and_Economic_Overview_e.pdf

Systematic Reviews and Meta-analyses – Alternative Population

Desai RJ, Thaler KJ, Mahlknecht P, et al. Comparative Risk of Harm Associated With the Use of Targeted Immunomodulators: A Systematic Review. *Arthritis Care Res (Hoboken)*. 2016 08;68(8):1078-1088.
PubMed: PM26663412

Systematic Reviews and Meta-analyses – bDMARD combined with cDMARDs

Albert DA. Are All Biologics the Same? Optimal Treatment Strategies for Patients With Early Rheumatoid Arthritis: Systematic Review and Indirect Pairwise Meta-Analysis. *J Clin Rheumatol*. 2015 Dec;21(8):398-404.
PubMed: PM26226612

Systematic Reviews and Meta-analyses – Alternative Comparator

Hou LQ, Jiang GX, Chen YF, et al. The Comparative Safety of TNF Inhibitors in Ankylosing Spondylitis-a Meta-Analysis Update of 14 Randomized Controlled Trials. *Clin Rev Allergy Immunol.* 2018 Apr;54(2):234-243.
PubMed: PM28717941

Tvete IF, Natvig B, Gasemyr J, Meland N, Roine M, Klemp M. Comparing Effects of Biologic Agents in Treating Patients with Rheumatoid Arthritis: A Multiple Treatment Comparison Regression Analysis. *PLoS One.* 2015;10(9):e0137258.
PubMed: PM26356639

Randomized Controlled Trials- Alternate Intervention

Mease PJ, Smolen JS, Behrens F, et al. A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naive patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial. *Ann Rheum Dis*. 2020 Jan;79(1):123-131.
PubMed: PM31563894

Fleischmann R, Weinblatt M, Ahmad H, et al. Efficacy of Abatacept and Adalimumab in Patients with Early Rheumatoid Arthritis With Multiple Poor Prognostic Factors: Post Hoc Analysis of a Randomized Controlled Clinical Trial (AMPLE). *Rheumatol Ther*. 2019 Dec;6(4):559-571.
PubMed: PM31642045

Strand V, de Vlam K, Covarrubias-Cobos JA, et al. Tofacitinib or adalimumab versus placebo: patient-reported outcomes from OPAL Broaden-a phase III study of active psoriatic arthritis in patients with an inadequate response to conventional synthetic disease-modifying antirheumatic drugs. *RMD Open*. 2019;5(1):e000806.
PubMed: PM30713721

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 EXXELERATE study. *Lancet*. 2016 12 03;388(10061):2763-2774.
PubMed: PM27863807

Alternate study design

Yun H, Xie F, Delzell E, et al. The comparative effectiveness of biologics among older adults and disabled rheumatoid arthritis patients in the Medicare population. *Br J Clin Pharmacol*. 2015 Dec;80(6):1447-1457.
PubMed: PM26130274

Correction Notice

The original report, published May 25, 2020, included eight systematic reviews. Of those, six also conducted a network meta-analysis, one conducted a matching-adjusted indirect comparison, and the remaining one did not conduct any indirect comparisons.

However, the review that we indicated did not conduct indirect comparisons did, in fact, conduct a network meta-analysis as well. Evidence from this network meta-analysis (Stevenson et al., 2016)[16] has been added to this corrected report. Thus overall, the quantity of research available comprised eight systematic reviews[11-18] including seven network meta-analyses[11-13,15-18] and one matching-adjusted indirect comparison.[14]