CADTH Health Technology Assessment

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Drugs for the management of rheumatoid arthritis: clinical evaluation – project protocol

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This report is prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH) in collaboration with the Canadian Institutes of Health Research (CIHR) Drug Safety and Effectiveness Network (DSEN). This report contains a comprehensive review of existing public literature, studies, materials, and other information and documentation (collectively the "source documentation") available to CADTH at the time it was prepared, and its creation was guided by expert input and advice throughout its preparation.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment in respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this report to ensure that its contents are accurate, complete, and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this report. CADTH takes sole responsibility for the final form and content of this report. The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial or territorial government.

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ABBREVIATIONS AND DEFINITIONS

Abbreviations

DMARD	disease modifying antirheumatic drug
FDA	Food and Drug Administration
F/P/T	Federal, Provincial, Territorial governments
IL	interleukin
JAK	Janus-associated kinase
NMA	network meta-analysis
RA	rheumatoid arthritis
SEB	subsequent entry biologic

Definitions

Moderate rheumatoid arthritis	Patients with moderate disease activity as defined by the American College of Rheumatology guidelines 2015.[1]
Severe rheumatoid arthritis	Patients with high disease activity as defined by the American College of Rheumatology guidelines 2015.[1]
Treatment intolerance	Intolerance to treatment due to an adverse event or contraindication to treatment.
Treatment failure	Less than optimal response to treatment due to a lack of efficacy (i.e., patient does not attain low disease activity).
Inadequate treatment	Patients with treatment intolerance or treatment failure.
Biologic	Biologic disease-modifying anti-rheumatic drug
DMARD	Conventional disease-modifying anti-rheumatic drug
DMARD monotherapy	methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide.
Double DMARD therapy	any two of methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide.
Triple DMARD therapy	methotrexate with sulfasalazine and hydroxychloroquine.
DMARD combination therapy	double or triple DMARD therapy.

1. DRAFTING OF PROTOCOL

Stakeholder Feedback

The policy and research questions and the PICOS items in this protocol were distributed for stakeholder feedback, including CADTH jurisdictional clients, patient groups and industry. Comments received during the feedback process were considered and have been incorporated into the protocol following discussion with the research team and clinical experts advising the review.

Protocol Registration and Peer Review

The protocol is registered in the PROSPERO database: CRD42016041498.

The health technology assessment report will be peer-reviewed by two external clinical experts.

Areas for Potential Amendments

Protocol amendments will be tracked throughout the review, along with reasons for the changes, by the project lead. For amendments that relate to additional outcomes or subgroup analyses that are not identified in the original protocol, consideration will be given to whether the literature search or screening will need to be updated.

Conflict of Interest

2. INTRODUCTION AND POLICY ISSUES

Rheumatoid arthritis (RA) is a chronic, autoimmune condition that affects bone joints.[2] It causes pain, inflammation, stiffness and joint erosion, and consequently joint destruction.[2] RA is associated with premature death, disability, and a decrease in quality of life.[2] Patients with RA are more likely to have comorbid conditions such as cardiovascular disease, infections, and cancer.[2]

The prevalence of RA in Canada has been estimated at 300,000 people living with RA.[3] A recent study of residents of Ontario revealed that the prevalence of RA in that province was approximately 1%.[4] Internationally, the prevalence of RA ranges between 0.4% and 1.3%.[2]

Goals of treatment include symptom relief, reduction in disease activity, reduction in joint damage, and increase in quality of life.[5] Recently, a "treat-to-target" approach has been recommended, in which disease remission is the ultimate target and treatment strategies are maximized until the target is achieved. Low disease activity is an appropriate alternative goal.[6] Early and aggressive treatment has been shown to alter the course of disease and slow or stop radiographic progression.[7, 8]

The *2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis* recommends monotherapy with a disease modifying antirheumatic drug (DMARD) as initial therapy in patients with early or established RA; methotrexate is recommended as the DMARD of choice.[1] In patients with moderate or high disease activity despite a DMARD, various treatment strategies are recommended, which include combination therapy using DMARDs and biologics. No recommendations are made prioritizing one treatment strategy over another.[1] One study showed that DMARDs are non-inferior to biologics drugs in established RA.[9] One network meta-analysis showed that combination treatment of a biologic and a DMARD is not superior to dual or triple combination DMARDs.[10]

The most often used DMARDs are methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine. According to the clinical expert consulted for the development of this protocol, intramuscular gold, azathioprine, and cyclosporine are available but rarely used. Biologic DMARDs (biologics) include:

- tumour necrosis factor inhibitors (adalimumab, etanercept, infliximab, golimumab, and certolizumab pegol)
- T cell costimulatory inhibitor (abatacept)
- B lymphocyte-depleting drug (rituximab)
- interleukin (IL)-6 antagonist (tocilizumab)
- IL-1 inhibitor (anakinra; almost never used to treat adult RA according to the clinical expert consulted for this protocol).

In 2010, CADTH published a therapeutic review of drugs used in RA, which focused on biologics. Specifically, the CADTH therapeutic review evaluated the comparative effectiveness, harms, and cost-effectiveness of eight biologics indicated for the treatment of RA in Canada at the time of the therapeutic review. The comparative efficacy and harms were explored through a systematic review and indirect mixed treatment comparison meta-analyses. The clinical and economic evaluations were used to generate recommendations about the optimal use of biologics in the treatment of RA.

Since then, the therapeutic area of RA has continued to evolve. Tofacitinib, a Janus-associated kinase (JAK) inhibitor, received Health Canada approval in April 2014,[11] and another drug of the same class, baricitinib, has been submitted to the US Food and Drug Administration and Health Canada for review and market approval.[12, 13] These are small molecules, which have the advantage of being administered orally. Two biologics, sarilumab and sirukumab, both IL-6 receptor inhibitors, are in late-stage development.[14, 15]

The introduction of subsequent entry biologics (SEBs or biosimilars) to the Canadian market offers the potential to decrease health care expenditures and provide patients with access to additional treatment options**.** Biosimilar infliximab and biosimilar etanercept have been approved in Canada.[16, 17] Biosimilar adalimumab has recently been approved in the United States and the European Union.[18, 19]

The topic of RA is of importance to the federal, provincial, and territorial (F/P/T) drug plans and they have requested that CADTH undertake a review of pharmacologic treatments used in RA. With the recent introduction of oral small molecules and biosimilars, it would be important to determine the relative effectiveness of all drugs used in RA in patients who have failed or are intolerant to methotrexate. Specifically, there is a need to determine the relative efficacy and safety of all drugs. Questions of interest gathered from the F/P/T drug plans included:

- For patients whose response to methotrexate is less than optimal, should a biologic be added to methotrexate, should a biologic be prescribed alone, or should other DMARDs be added or substituted for methotrexate?
- For patients who cannot tolerate methotrexate due to an adverse event or a contraindication, should DMARDs, alone or in combination, be tried ahead of a biologic?
- What is the relative efficacy of dual DMARD therapy compared with triple DMARD therapy?
- For patients who are inadequately treated with a biologic (alone or with methotrexate), what should be tried next?
- What is the place in therapy of tofacitinib and other JAK inhibitors?
- What are the benefits and harms of innovator biologics and subsequent entry biologics?

To make this project manageable, the scope was limited to patients who have failed or are intolerant to methotrexate. This protocol does not include an in-depth analysis of patients with early or mild disease, DMARD-naive patients, patients with comorbidities, or patients with a poor prognosis. Treatments of

interest were identified through consultation with the F/P/T jurisdictions and have either been approved by Health Canada or are advanced in the development process.

3. PROTOCOL DEVELOPMENT

To inform the final scope of the protocol development, a proposed scope was developed with the assistance of clinical experts and CADTH's F/P/T customers. In addition, targeted stakeholder feedback from patient groups and industry was solicited.

This protocol was written a priori and will be followed throughout the review process.

4. DELIVERABLES

This project aims at completing a clinical review that will include a systematic review and network meta-analysis of drugs used in adult patients with moderate to severe RA who have failed or are intolerant to methotrexate. The focus of this review will be on the clinical evidence of benefits and harms.

5. POLICY QUESTION

In patients with moderate to severe rheumatoid arthritis who have failed or are intolerant to methotrexate, what is the optimal drug therapy?

6. RESEARCH QUESTION

What is the comparative efficacy and safety of DMARD therapies (alone or in combination), biologics (including biosimilars), and JAK inhibitors in patients with moderate to severe RA who have failed or are intolerant to methotrexate?

7. METHODS

The CADTH clinical evaluation will bring together, and build upon, existing systematic reviews and network meta-analyses conducted by Cochrane.[20-22] The search criteria for these reviews will be updated and supplemented as needed to address the selection criteria outlined in this protocol.

7.1 Literature Search Strategy

The literature search will be performed by a research information specialist using a peer-reviewed search strategy.

Published literature will be identified by searching the following bibliographic databases: MEDLINE with in-process records & daily updates through Ovid; Embase through Ovid; EBM Reviews — Cochrane Central Register of Controlled Trials through Ovid; Cochrane Library through Wiley; and PubMed. The search strategy will be comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings) and keywords. The main search concepts will be: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, anakinra, tocilizumab, abatacept, rituximab, methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, infliximab SEB, adalimumab SEB, etanercept SEB, tofacitinib, baricitinib, sarilumab, sirukumab, and RA.

Methodological filters will be applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval will be limited to the human population and English language. Due to the use of previous publications,[20-22] searches and retrieval will be limited by various publication years (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, anakinra, tocilizumab, abatacept, rituximab published between January 1, 2015 to present; methotrexate published between January 1, 2014 to present; hydroxychloroquine, sulfasalazine, leflunomide, infliximab SEB, adalimumab SEB, etanercept SEB, tofacitinib, baricitinib, sarilumab, sirukumab no publication date limit). Conference abstracts will be excluded from the search results. See Appendix 1 for draft literature search strategies.

Regular alerts will be established to update the search until the publication of the final report. Regular search updates will be performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) will be identified by searching the *Grey Matters* checklist (https://www.cadth.ca/grey-matters), which includes the websites of regulatory agencies, health technology assessment agencies, clinical guideline repositories, and professional associations. Google and other Internet search engines will be used to search for additional web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers and through contact with appropriate experts and industry.

7.2 Selection Criteria

Two reviewers will independently screen titles and abstracts for relevance to the clinical research questions. Full texts of potentially relevant articles will be retrieved and independently assessed for possible inclusion based on the predetermined selection criteria (Table 1). The two reviewers will then compare their chosen included and excluded studies; disagreements will be discussed until consensus is reached or resolved by a third reviewer, if necessary. The study selection process will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

Table 1: Study Selection Criteria

Selection Criteria	
Population	**Inclusion**: • Adults with moderate to severe, active RA who have failed or are intolerant to methotrexate (inadequate responders) • Patients who are inadequate responders to one or more DMARDs that may include methotrexate[a] **Exclusion**: • Patients who are methotrexate naive • Patients who are treatment experienced, but only inadequate responders to sulfasalazine • Patients who are treatment experienced, but only inadequate responders to leflunomide • Patients who are treatment experienced, but only inadequate responders to hydroxychloroquine • Patients who are inadequate responders to a biologic DMARD (biologic) • Patients who are in clinical remission, have low disease activity, or early RA
Interventions	**Inclusion**: • Conventional DMARD monotherapy, dual therapy or triple therapy (eligible DMARDs: methotrexate, hydroxychloroquine, sulfasalazine, leflunomide)

	• Any of the nine biologics alone or in combination with conventional DMARDs (i.e., adalimumab, certolizumab pegol, etanercept, anakinra[b], golimumab, infliximab, tocilizumab, abatacept, and rituximab) • Oral inhibitors of Janus kinases (i.e., tofacitinib and baricitinib) alone or in combination with conventional DMARDs • Biosimilars (i.e., biosimilars of etanercept, infliximab, and adalimumab) alone or in combination with conventional DMARDs **Exclusion**: • Doses of any of the eligible drugs that are above or below the standard dose approved by Health Canada[c] • Methotrexate compared to itself, placebo, or a drug that is not of interest • Older conventional DMARDs (i.e., auranofin, intramuscular gold, azathioprine, cyclosporine, and chloroquine) • Combination biologics (i.e., two or more biologics given concurrently)
Comparators	**Inclusion**: • Any of the drugs of interest or placebo **Exclusion**: • Studies with only one arm that is eligible • Studies comparing multiple doses of the same drug without a comparator • Studies comparing different routes of administration of the same drug without a comparator
Outcomes	**Inclusion**: <u>Efficacy</u> • ACR 20, 50, 70[d] • Disease Activity Score (DAS/DAS 28) • Function (Health Assessment Questionnaire Disability Index [HAQ-DI]) • Remission (DAS 28 remission [<2.6]) • Radiographic progression • Health-related quality of life (SF-36 Physical and Mental Component Scores) • Fatigue • Pain <u>Harms</u> • Serious adverse events • Withdrawal due to adverse events • Mortality <u>Notable harms</u> • Serious infections • Tuberculosis • Cancer • Leukemia • Lymphoma • Congestive heart failure • Major adverse cardiac events • Herpes zoster **Exclusion** <u>Efficacy</u> • Withdrawal due to lack of efficacy • Time to withdrawal due to lack of efficacy
Study Design	**Inclusion**: <u>Efficacy</u> • Randomized controlled trials <u>Safety</u>

	• Randomized controlled trials • Controlled clinical trials • Clinical trial registries • US Food and Drug Administration (FDA), Health Canada, European Medicines Agency reports, labels and warnings **Exclusion**: • Non-controlled studies (i.e., observational designs) • Single arm studies • Trials with a randomization phase of <12 weeks' duration
Exclusion Criteria	
Other Exclusions	• Non-English publications • Conference abstracts

ACR = American College of Rheumatology; DMARD = disease modifying antirheumatic drug; RA = rheumatoid arthritis; SF-36 = 36-Item Short-Form Health Survey.
[a]These studies will be included in the base case and removed from sensitivity analysis since not all participants were necessarily inadequate responders to methotrexate
[b]Studies of anakinra will be included, but results of comparisons with anakinra will not be made in the review, since it is almost never used to treat adult RA according to our clinical expert
[c]All doses will be considered for drugs that are under development at the time of the review
[d]ACR 50 will be the primary ACR response outcome reported

7.3 Data Extraction

All information will be extracted using a standardized web-based data abstraction form, which will be developed, piloted and modified as necessary. Abstraction will include: characteristics of trial participants, including inclusion and exclusion criteria; type of interventions, including dose, duration and co-medication; and results of the clinical safety and efficacy/effectiveness outcomes of the intervention. All data will be extracted by one review author and independently checked for accuracy by a second review author. The original, primary publication for each unique study included will be used for data extraction, except where multiple publications for a single primary study are found. Multiple publications for a unique study (e.g., supplemental online appendices, erratums, companion publications of specific outcomes or populations from the original study) will be handled by extracting the most recently adjudicated data for each outcome specified a priori. Data from the end of the study will be extracted.

Adaptive design trials have been used in RA more recently to allow for planned modifications to participant treatment in the study at a pre-defined interim analysis.[23] In this report, we distinguish between four major types of adaptive designs: 1) early escape trials, 2) rescue therapy trials, 3) treatment switching trials based on non-response criteria; and 4) planned treatment switching trials (Table 2). In the event a study used an adaptive design, analysis will be performed, where possible, on the end of study data using rate ratios adjusted for the length of exposure of participants to treatment who had an adaptation to their treatment course.

Table 2: Definition of Adaptive Design Trials

Adaptive Design	Description
Early escape trial	After a pre-determined period (e.g. 12 or 16 weeks) receiving treatment, patients who do not attain a pre-defined level of disease response are withdrawn from the trial and may enter an open-label extension phase.
Rescue therapy trial	After a pre-determined period of receiving treatment, patients who do not attain a pre-defined level of disease response are permitted to receive rescue therapy (e.g. dose adjustment or addition of a DMARD or corticosteroid, receipt of one or

	more doses of active treatment for those in the comparator arm, increased dose of active drug).
Treatment switching trial (based on non-response)	After a pre-determined period (e.g. 12 or 16 weeks) receiving treatment, patients who do not attain a pre-defined level of disease response are switched to another treatment arm for the remainder of the study.
Treatment switching trial (planned)	Investigators plan a priori to have patients (e.g. in a control group) either switch to another arm or re-randomize patients to switch to one of a few possible treatment arms. The planned treatment switch could occur either: a) as the only adaptation in the study duration, or b) as the second adaptation after an initial adaptation (typically involving patients who had an inadequate response).

7.4 Critical Appraisal of Clinical Studies

Quality assessment will be considered using the Cochrane Collaboration's tool for assessing risk of bias.[24] Two reviewers will independently assess each of the domains and rate the quality of each study as high or low quality. Disagreements will be resolved through discussion or the decision of a third reviewer, if necessary.

Reporting bias will be assessed by constructing funnel plots for each outcome. An asymmetric plot would imply publication bias; and in the absence of bias, the plot should resemble an inverted funnel.

7.5 Data Analysis and Synthesis

Network Meta-Analysis

When it is appropriate, Bayesian network meta-analyses (NMAs) will be conducted for outcomes pre-specified in the protocol, following careful assessment of heterogeneity across trials in terms of patient characteristics, trial methodologies, and treatment protocols. The effect estimate will depend on the outcome of interest and type of data provided in the primary studies. Both fixed and random-effects models will be conducted; model selection will be based on the Deviance Information Criterion (DIC) and residual deviance. R (R Foundation for Statistical Computing, Vienna, Austria) and WinBUGS (MRC Biostatistics Unit, Cambridge, UK) will be used for Bayesian NMA according to the routing that accommodates evidence structures, which may consist of multi-arm trials as developed at the Universities of Bristol and Leicester (www.bris.ac.uk/cobm/research/mpes/).

Methotrexate or another DMARD in combination with placebo (i.e., that is identical in formulation and appearance to an active biologic) will be identified as the reference group for all Bayesian NMAs. Treatment nodes in the evidence network will consist of the standard approved dose(s) of each drug or all doses for drugs that have not yet been approved. Biosimilars of the same drug will be analysed as separate interventions (e.g., all biosimilars of infliximab having a unique treatment node) since they may not be identical. The specific DMARD administered in combination with a biologic, JAK inhibitor or biosimilar will be identified in the treatment node. Treatment nodes of single interventions and of combination therapies for biologics, JAK inhibitors or biosimilars will be separate. Similarly, dual and triple DMARD therapies will be in separate treatment nodes for the evidence network, if possible.

Posterior densities for unknown parameters will be estimated using Markov Chain Monte Carlo (MCMC) methods. Basic parameters will be assigned non-informative or vague prior distributions; more informative priors will be considered; for example, an informative prior for the between-study variance will be considered following Turner et al.[25] Point estimates and 95% credible intervals will be used to summarize findings. The probability of a comparator being optimal will be estimated for each outcome based on the

proportion of MCMC simulations in which its relative measure of effect was best. Consistency between direct and indirect evidence will be formally assessed using back-calculation and node splitting techniques. Graphical methods and numerical summaries will be developed for presenting results from NMAs. Model diagnostics will also include trace plots and the Gelman-Rubin-Brooks statistic to assess and ensure model convergence. Three chains will be fit in WinBUGS for each analysis, each usually employing approximately 20,000 iterations, with a burn in of approximately 20,000 iterations.

Estimated relative and absolute differences in the benefits and harms, absolute mean difference, and relative per cent change from baseline will be included in the summary of findings table.

Meta-Analysis

Meta-analyses will be considered for outcomes when a NMA is not possible. The data will first be summarized descriptively. A meta-analysis will be undertaken using a fixed or random-effects model when data are available, sufficiently similar and of sufficient quality. The effect sizes for the identified dichotomous outcomes will be expressed in terms of the risk ratio or odds ratio (OR). In cases when events are rare, the Peto OR will be used. Estimated relative and absolute differences in the important benefits and harms, absolute mean difference, and relative per cent change from baseline will be included in the summary of findings table.

Results will be assessed for both clinical and methodological diversity. Clinical diversity will be assessed by checking that the populations, interventions, and comparators are not too different from each other, such that combining them would be inappropriate. Methodological diversity will be assessed by checking that the studies are similar in terms of study design and risk of bias. Once satisfied that the studies are minimally diverse and that it makes sense to pool them together in a meta-analysis, an assessment of the statistical heterogeneity will be undertaken by examining the forest plot and result of the I^2 statistic; the forest plots providing a visual sense of heterogeneity and the I^2 statistic indicating the presence of statistical heterogeneity. If the effects observed across trials are inconsistent, and vary to a large extent (e.g., $I^2 > 50\%$), the results will again be explored to assess whether the differences can be explained by some clinical or methodological feature. Inconsistency that cannot be reduced by pre-specified subgroup or meta-regression analyses will lead to an overall estimate with less confidence when interpreting the inference from the meta-analysis. In this case, a more conservative random-effects model approach would be used so that the uncertainty of the single effect estimate is reflected in wider confidence intervals.

Descriptive Analysis

A descriptive analysis will be completed for any outcomes for which it would not be appropriate to conduct a NMA or a meta-analysis.

Subgroup and Sensitivity Analyses

Results may be influenced by publication, with more recent studies tailoring eligibility criteria for study participants to increase the likelihood that participants will achieve low disease activity or remission with the intervention than when biologics were first being developed. Based on consultation with a clinical expert, the year 2007 has been selected a priori as the cut-off date (i.e. older studies are defined as published before 2007 and newer studies are those published from 2007 onward).

Sensitivity analyses will be conducted based on aspects of the PICOS statement and study methodology to examine the robustness of the results to the risk of bias and the influence of other variables. In particular, a sensitivity analysis excluding high-risk-of-bias-studies (i.e., studies of low overall quality as

identified by two independent reviewers) will be compared to the reference case in which all studies of low- and higher-risk-of-bias were included; if the results differ, the conclusions of the review will be based on analyses of low-risk-of-bias studies only (i.e., studies of high overall quality as identified by two independent reviewers).

ACR50 and withdrawals due to adverse events have been selected *a priori* as the outcomes for which to conduct the subgroup and sensitivity analyses. If no differences are observed for these key outcomes, it will be considered that there are no differences in results for the remaining outcomes.

7.6 Data Availability

The primary source of data is in the public domain. All stakeholders will be given the option of identifying and providing unpublished data on the condition that, if used, it would be included in publicly available reports and documents, related to the clinical review.

8. REFERENCES

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APPENDIX 1: DRAFT LITERATURE SEARCH STRATEGY

Embase, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

#	**Searches**
1	exp Arthritis, Rheumatoid/ use pmez
2	exp rheumatoid arthritis/ use oemezd
3	(rheumatic* or rheumatoid* or rheumatis*).ti,ab,kf,kw.
4	((Caplan* or Felty* or Sjogren* or Sicca*) adj3 syndrome*).ti,ab,kf,kw.
5	Still* Disease*.ti,ab,kf,kw.
6	or/1-5
7	Adalimumab/
8	Certolizumab Pegol/
9	Etanercept/
10	golimumab/ use oemezd
11	Infliximab/
12	tocilizumab/ use oemezd
13	Abatacept/
14	Rituximab/
15	(adalimumab or Humira or Trudexa or certolizumab pegol or Cimzia or Perstymab or etanercept or Enbrel or golimumab or Simponi or infliximab or Inflectra or Remicade or Remsima or Reemsima or Remmicade or Remykeyd or Revellex or anakinra or Kineret or Antril or tocilizumab or Actemra or Aktemra or RoActemra or atlizumab or abatacept or Orencia or Belatacept or Nulojix or rituximab or Rituxan or Mabtera or Mabthera or Reditux or Relito or Rituxim).ti,ab,kw,kf.
16	Methotrexate/
17	(abitrexate or amethopterin* or amethpterin* or ametopterin* or antifolan or Artrait or Atrexal or Bertanel or Biotrexate or brimexate or canceren or cytotrex or ebetrex or ebetrexat* or emtexate or emthexat* or Emthrxate or emtrexate or enthexate or farmitrexat*

	or farmotrex or Hytas or Imutrex or ifamet or imeth or fermitrexat* or fauldexato or folex or hdmtx or lantarel or ledertrexate or lumexon or maxtrex or medsatrexate or Meisusheng or merox or metatrexan or metex or Metrex or Methoblastin or methohexate or methotrate or Methox or meticil or Metodik or methotrexat* or Methylaminopterin* or methrotrexate or methopterin* or methpterin* or metopterin* or Metotressato or Metotrexato or Metotreksat or metoject or Metrotex or mexate or MTX or Novatrex or Otrexup or Rasuvo or Rheumatrex or texate or tremetex or trexeron or Trexall or trixilem or Midu or Mtrex or Neotrexat* or Onkomet or Otaxem or Pterin or Quinux or Reumatrex or Sanotrexat* or Texorate or Trexan or Trexate or Trexol or Trexonate or Trexxol or Unitrexates or Viztreksat or Xantromid or Zexate).ti,ab,kw,kf.
18	Hydroxychloroquine/
19	(Hydroxychloroquin* or Oxychlorochin* or Oxychloroquin* or Hydroxychlorochin* or Plaquenil or Idrossiclorochina or Oxichlorochinum or Hydroxyquine or Advaquenil or Arthroquin or Axokine or Chloguin or Diclor or Dimard or Dolquine or Duloc or Duroc or Ercoquin or Evoquin or Fen Le or Geniquin or Haloxin or HCQS or Hydroquin or Hydroquine or Hyquin or Ilinol or Immard or Metirel or Oxcq or Oxiklorin or Plakvenil or Plaquinol or Quensyl or Quinoric or Reconil or Reuquinol or Roquin or Supretic or Winflam or Yuma or Zyq or chloroquinol).ti,ab,kf,kw.
20	Sulfasalazine/ use pmez
21	salazosulfapyridine/ use oemezd
22	(Salicylazosulfapyridin* or salazosulfpyridin* or salazopyrin* or salazopyridin* or Sulphasalazin* or Salazosulfapyridin* or Pleon or azopyrin* or azosulfidin* or benzosulfa or colopleon or Ulcol or Ucine or Azulfidin* or azlufidin* or Azulfadin* or pyralin or Asulfidine or Azulfin or azulfid* or Bomecon or Disalazin or Falazine or Gastropyrin or Lazafin or Lazo or rorasul or Rosulfant or SAAZ or Salazex or Salazine or Salazo or Salazodin or Salivon or salisulf or Salopyr or Salopyrine or Saridin* or Sazo or Sulcolon or Sulfasalazin or Sulfasalizin* or sulfosalazin* or Sulfitis or Sulzin or Zopyrin).ti,ab,kw,kf.
23	leflunomide/
24	(leflunomid* or arava or Airuohua or Arabloc or Arastad or Aravida or Arheuma or Arolef or Arresto* or Artrilab or Cartina or Imaxetil or Inflaxen or Kinetos or Lara or Leflu or Lefluar or Lefluartil or Leflyutab or Lefno or Lefora or Lefra-20 or Motoral or Movelef or Nodia or Repso or Rheufact or Rheumide or Rualba or Synomid or Youtong).ti,ab,kw,kf.
25	tofacitinib/
26	(Tofacitinib* or tasocitinib* or Xeljanz* or Kselyanz*).ti,ab,kw,kf.
27	baricitinib/

28	(Baricitinib* or ISP4442I3Y or LY3009104 or INCB028050 or ISP 4442I3Y or LY 3009104 or INCB 28050 or "INCB 028050").ti,ab,kf,kw.
29	sarilumab/
30	(Sarilumab* or NU90V55F8I or SAR153191 or REGN88 or SAR 153191 or REGN 88).ti,ab,kw,kf.
31	sirukumab/
32	(sirukumab* or 640443FU93 or CNTO136 or CNTO 136).ti,ab,kw,kf.
33	or/7-32
34	Infliximab/ or Adalimumab/ or Etanercept/
35	(adalimumab or Humira or Trudexa or infliximab or Inflectra or Remicade or Remsima or Reemsima or Remmicade or Remykeyd or Revellex or etanercept or Enbrel).ti,ab,kw,kf.
36	(reference or innovator or originator or generic or generics or biosimilar or bio-similar or biosimilars or bio-similars or follow-on or subsequent-entry or SEB or SEBs or biobetter or biobetters or bio-better or bio-betters or biosuperior or biosuperiors or bio-superior or bio-superiors or next generation or second-generation or third-generation or next-gen).ti,ab.
37	(biologic* or biological*).ti,kw,kf.
38	exp *Biological Products/ use pmez
39	exp *biological product/ use oemezd
40	(34 or 35) and (36 or 37 or 38 or 39)
41	6 and (33 or 40)
42	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial).pt.
43	Randomized Controlled Trial/
44	exp Randomized Controlled Trials as Topic/
45	"Randomized Controlled Trial (topic)"/
46	Controlled Clinical Trial/
47	exp Controlled Clinical Trials as Topic/
48	"Controlled Clinical Trial (topic)"/
49	Randomization/

50	Random Allocation/
51	Double-Blind Method/
52	Double Blind Procedure/
53	Double-Blind Studies/
54	Single-Blind Method/
55	Single Blind Procedure/
56	Single-Blind Studies/
57	Placebos/
58	Placebo/
59	Control Groups/
60	Control Group/
61	(random* or sham or placebo*).ti,ab,hw,kf,kw.
62	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
63	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
64	(control* adj3 (study or studies or trial*)).ti,ab,kf,kw.
65	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.
66	allocated.ti,ab,hw.
67	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
68	or/42-67
69	41 and 68
70	exp animals/
71	exp animal experimentation/ or exp animal experiment/
72	exp models animal/
73	nonhuman/
74	exp vertebrate/ or exp vertebrates/

75	or/70-74
76	exp humans/
77	exp human experimentation/ or exp human experiment/
78	or/76-77
79	75 not 78
80	69 not 79
81	80 not conference abstract.pt.
82	limit 81 to English language

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#6	Search (rheumatic*[tiab] OR rheumatoid*[tiab] OR rheumatis*[tiab])
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#3	Search (Hydroxychloroquin*[tiab] OR Oxychlorochin*[tiab] OR Oxychloroquin*[tiab] OR Hydroxychlorochin*[tiab] OR Plaquenil[tiab] OR Idrossiclorochina[tiab] OR Oxichlorochinum[tiab] OR Hydroxyquine[tiab] OR Advaquenil[tiab] OR Arthroquin[tiab] OR Axokine[tiab] OR Chloguin[tiab] OR Diclor[tiab] OR Dimard[tiab] OR Dolquine[tiab] OR Duloc[tiab] OR Duroc[tiab] OR Ercoquin[tiab] OR Evoquin[tiab] OR Fen Le[tiab] OR Geniquin[tiab] OR Haloxin[tiab] OR HCQS[tiab] OR Hydroquin[tiab] OR Hydroquine[tiab] OR Hyquin[tiab] OR Ilinol[tiab] OR Immard[tiab] OR Metirel[tiab] OR Oxcq[tiab] OR Oxiklorin[tiab] OR Plakvenil[tiab] OR Plaquinol[tiab] OR Quensyl[tiab] OR Quinoric[tiab] OR Reconil[tiab] OR Reuquinol[tiab] OR Roquin[tiab] OR Supretic[tiab] OR Winflam[tiab] OR Yuma[tiab] OR Zyq[tiab] OR chloroquinol[tiab] OR Salicylazosulfapyridin*[tiab] OR salazosulfpyridin*[tiab] OR salazopyrin*[tiab] OR salazopyridin*[tiab] OR Sulphasalazin*[tiab] OR Salazosulfapyridin*[tiab] OR Pleon[tiab] OR azopyrin* [tiab] OR azosulfidin*[tiab] OR benzosulfa [tiab] OR colopleon[tiab] OR Ulcol[tiab] OR Ucine[tiab] OR Azulfidin*[tiab] OR azlufidin*[tiab] OR Azulfadin*[tiab] OR pyralin[tiab] OR Asulfidine[tiab] OR Azulfin[tiab] OR azulfid*[tiab] OR Bomecon[tiab] OR Disalazin[tiab] OR Falazine[tiab] OR Gastropyrin[tiab] OR Lazafin[tiab] OR Lazo[tiab] OR rorasul[tiab] OR Rosulfant[tiab] OR SAAZ[tiab] OR Salazex[tiab] OR Salazine[tiab] OR Salazo[tiab] OR Salazodin[tiab] OR Salivon[tiab] OR salisulf[tiab] OR Salopyr[tiab] OR Salopyrine[tiab] OR Saridin*[tiab] OR Sazo[tiab] OR Sulcolon[tiab] OR Sulfasalazin[tiab] OR Sulfasalizin*[tiab] OR sulfosalazin*[tiab] OR Sulfitis[tiab] OR Sulzin[tiab] OR Zopyrin[tiab] OR leflunomid*[tiab] OR arava[tiab] OR Airuohua[tiab] OR Arabloc[tiab] OR Arastad[tiab] OR Aravida[tiab] OR Arheuma[tiab] OR Arolef[tiab] OR Arresto*[tiab] OR Artrilab[tiab] OR Cartina[tiab] OR Imaxetil[tiab] OR Inflaxen[tiab] OR Kinetos[tiab] OR Lara[tiab] OR Leflu[tiab] OR Lefluar[tiab] OR Lefluartil[tiab] OR Leflyutab[tiab] OR Lefno[tiab] OR Lefora[tiab] OR Lefra-20[tiab] OR Motoral[tiab] OR Movelef[tiab] OR Nodia[tiab] OR Repso[tiab] OR Rheufact[tiab] OR Rheumide[tiab] OR Rualba[tiab] OR Synomid[tiab] OR Youtong[tiab] OR Tofacitinib*[tiab] OR tasocitinib*[tiab] OR Xeljanz*[tiab] OR Kselyanz*[tiab] OR Baricitinib*[tiab] OR ISP4442I3Y[tiab] OR LY3009104[tiab] OR INCB028050[tiab] OR ISP 4442I3Y[tiab] OR LY 3009104[tiab] OR INCB 28050[tiab] OR INCB 028050[tiab] OR Sarilumab*[tiab] OR NU90V55F8I[tiab] OR SAR153191[tiab] OR REGN88[tiab] OR SAR 153191[tiab] OR REGN 88[tiab] OR sirukumab*[tiab] OR 640443FU93[tiab] OR CNTO136[tiab] OR CNTO 136[tiab])
#2	Search (abitrexate[tiab] or amethopterin*[tiab] or amethpterin*[tiab] or ametopterin*[tiab] or antifolan[tiab] or Artrait[tiab] or Atrexal[tiab] or Bertanel[tiab] or Biotrexate[tiab] or brimexate[tiab] or canceren[tiab] or cytotrex[tiab] or ebetrex[tiab] or ebetrexat*[tiab] or emtexate[tiab] or emthexat*[tiab] or Emthrxate[tiab] or emtrexate[tiab] or enthexate[tiab] or farmitrexat*[tiab] or farmotrex[tiab] or Hytas[tiab]

	or Imutrex[tiab] or ifamet[tiab] or imeth[tiab] or fermitrexat*[tiab] or fauldexato[tiab] or folex[tiab] or hdmtx[tiab] or lantarel[tiab] or ledertrexate[tiab] or lumexon[tiab] or maxtrex[tiab] or medsatrexate[tiab] or Meisusheng[tiab] or merox[tiab] or metatrexan[tiab] or metex[tiab] or Metrex[tiab] or Methoblastin[tiab] or methohexate[tiab] or methotrate[tiab] or Methox[tiab] or meticil[tiab] or Metodik [tiab] or methotrexat*[tiab] or Methylaminopterin*[tiab] or methrotrexate [tiab] or methopterin*[tiab] or methpterin*[tiab] or metopterin* [tiab] or Metotressato[tiab] or Metotrexato[tiab] or Metotreksat [tiab] or metoject[tiab] or Metrotex[tiab] or mexate[tiab] or MTX[tiab] or Novatrex[tiab] or Otrexup[tiab] or Rasuvo[tiab] or Rheumatrex[tiab] or texate[tiab] or tremetex[tiab] or trexeron[tiab] or Trexall[tiab] or trixilem[tiab] or Midu[tiab] or Mtrex[tiab] or Neotrexat*[tiab] or Onkomet[tiab] or Otaxem[tiab] or Pterin[tiab] or Quinux[tiab] or Reumatrex[tiab] or Sanotrexat*[tiab] or Texorate[tiab] or Trexan[tiab] or Trexate[tiab] or Trexol[tiab] or Trexonate[tiab] or Trexxol[tiab] or Unitrexates[tiab] or Viztreksat[tiab] or Xantromid[tiab] or Zexate[tiab])
#1	Search (adalimumab[tiab] or Humira[tiab] or Trudexa[tiab] or certolizumab pegol[tiab] or Cimzia[tiab] or Perstymab[tiab] or etanercept[tiab] or Enbrel[tiab] or golimumab[tiab] or Simponi[tiab] or infliximab[tiab] or Inflectra[tiab] or Remicade[tiab] or Remsima[tiab] or Reemsima[tiab] or Remmicade[tiab] or Remykeyd[tiab] or Revellex[tiab] or anakinra[tiab] or Kineret[tiab] or Antril[tiab] or tocilizumab[tiab] or Actemra[tiab] or Aktemra[tiab] or RoActemra[tiab] or atlizumab[tiab] or abatacept[tiab] or Orencia[tiab] or Belatacept[tiab] or Nulojix[tiab] or rituximab[tiab] or Rituxan[tiab] or Mabtera[tiab] or Mabthera[tiab] or Reditux[tiab] or Relito[tiab] or Rituxim[tiab])