CADTH
ACMTS

Proposed Project Plan

Comparison of triple conventional synthetic disease-modifying anti-rheumatic drugs and biologic drugs or Janus-associated kinase inhibitors for rheumatoid arthritis

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BACKGROUND AND RATIONALE

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease characterized by inflammation of the synovial lining of the joints, tendons and periarticular structures.[1] RA affects 0.5% to 1.0% of the population in Western countries.[2] Untreated, RA leads to joint destruction, functional limitation and severe disability, and has a significant impact on health-related quality of life.[3-6]

Definitive treatments that have disease-modifying potential include glucocorticoids, conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs, such as methotrexate, sulfasalazine, hydroxychloroquine and leflunomide), biologic DMARDs [tumor necrosis factor (TNF) inhibitors and non-TNF inhibitors], or targeted synthetic DMARDs [tsDMARDs, such as the Janus associated kinase (JAK) inhibitors tofacitinib and baricitinib]. The use of DMARDs leads to an improvement in pain and function for patients with RA, as well as more long-term outcomes such as less disease progression and disability.[7-10]

Monotherapy conventional synthetic DMARD (methotrexate preferred) is the drug of choice for treatment-naive patients with early or established RA for any level of disease activity according to the American College of Rheumatology 2015 Guidelines.[11,12] When monotherapy with a csDMARD has been ineffective or partially effective (disease activity remains moderate or high) or have had associated side effects, treatment options include other csDMARDs alone or in combination, biologics (including biosimilars) and JAK inhibitors.[11,12]

This proposed project will evaluate the effectiveness and safety of triple csDMARDs compared with TNF inhibitors (and biosimilars), non-TNF inhibitors, and JAK inhibitors.

Table 1: Policy Question

Is it appropriate to require triple conventional synthetic disease-modifying anti-rheumatic drug therapy for treating rheumatoid arthritis?

Tables 2 and 3 describe the drugs available in Canada that are relevant to this CADTH project.

Table 2: Conventional Synthetic Disease-modifying Anti-rheumatic Drugs used as Triple Therapy[a]

Drug Class	Drug	Brand Name	Manufacturer
antimalarial, immunosuppressant	hydroxychloroquine	Plaquenil, generics	Sanofi-Aventis Canada Inc., others
folate analog metabolic Inhibitor, immunosuppressant	methotrexate	Metoject, generics	Medexus Inc., others
anti-inflammatory, immunomodulator	sulfasalazine	Salazopyrin, PMS-Sulfasalazine	Pfizer Canada Inc., Pharmascience Inc.

[a] combination recommended by the American College of Rheumatology 2015 guidelines

Table 3: Biologic Drugs and Janus-associated Kinase Inhibitors

Drug Class	Generic Name	Brand Name	Manufacturer
TNF Inhibitors			
TNF inhibitors	Etanercept	Enbrel	Immunex Corporation
	Infliximab	Remicade	Janssen

	Adalimumab	Humira	AbbVie Corporation
	Certolizumab pegol	Cimzia	UCB
	Golimumab	Simponi	Janssen
Non-TNF Inhibitors			
B lymphocyte-depleting drug (anti-CD20 therapy)	Rituximab	Rituxan	Roche
T cell costimulatory inhibitor	Abatacept	Orencia	Bristol Myers Squibb
IL-6 inhibitor	Tocilizumab	Actemra	Roche
	Sarilumab	Kevzara	Sanofi Genzyme
Targeted Synthetic DMARDs			
Janus-associated kinase inhibitor	Tofacitinib	Xeljanz	Pfizer
	Baricitinib	Olumiant	Eli Lilly
Biosimilars			
Biosimilar of infliximab	CT-P13	Inflectra, Remsima[a]	Celltrion Healthcare Co. Ltd
	SB2	Renflexis, Flixabi[a]	Samsung Bioepis Co. Ltd
Biosimilar of etanercept	HD203	Davictrel[a]	Hanwha Chemical
	GP2015	Erelzi	Sandoz Canada Inc.
	SB4	Brenzys, Benepali[a]	Samsung Bioepis Co. Ltd
	Unknown	AnBaiNuo[a]	Zhejang Hisun Pharmaceutical Co.
Biosimilar of adalimumab	ABP 501	Amjevita[a], Amgevita[a], Solymbic[a]	Amgen
	ZRC-3197	Exemptia[a]	Zydus Cadila
	SB5	Hadlima[b], Imraldi[a]	Samsung Bioepis Co. Ltd

DMARDs = disease-modifying anti-rheumatic drugs; TNF = tumour necrosis factor
[a] brand name not available in Canada
[b] approved but not marketed in Canada

PROJECT DESCRIPTION

The project will compare the clinical effectiveness, safety and cost-effectiveness of triple csDMARDs with biologic drugs and JAK inhibitors. The selection criteria for this project are described in Table 4.

Table 4: Project Scope

Population	▪ treatment-experienced adults with moderate to severe, active RA who have failed or are intolerant to methotrexate (inadequate responders)[a]
Intervention	▪ triple csDMARDs
Comparators	▪ biologic drugs, biosimilars and JAK inhibitors ▪ may include combination therapy with methotrexate
Outcomes	▪ disease severity (ACR 50) ▪ disease activity (DAS/ DAS-28) ▪ remission (DAS-28 remission) ▪ WDAEs ▪ SAEs
Research Questions	
1. What is the clinical effectiveness and safety of triple csDMARDs compared with TNF inhibitors (and biosimilars)? 2. What is the clinical effectiveness and safety of triple csDMARDs compared with non-TNF inhibitors? 3. What is the clinical effectiveness and safety of triple csDMARDs compared with JAK inhibitors? 4. What is the cost-effectiveness of triple csDMARDs compared with biologic drugs or JAK inhibitors?	

ACR = American College of Rheumatology; csDMARDs = conventional synthetic disease-modifying anti-rheumatic drugs; DAS = disease activity score; JAK = Janus-associated kinase; RA = rheumatoid arthritis; SAEs = serious adverse events; TNF = tumour necrosis factor; WDAEs = withdrawal due to adverse events

[a] Definitions

- Moderate rheumatoid arthritis: Patients with moderate disease activity as defined by the American College of Rheumatology guidelines 2015.
  Severe rheumatoid arthritis: Patients with high disease activity as defined by the American College of Rheumatology guidelines 2015.
  Treatment-experienced: Patients previously treated for rheumatoid arthritis.
- 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 responders: Patients with treatment intolerance or treatment failure.

KEY PROJECT COMPONENTS

In order to address the questions described above, this HTA project may include the following key components.

A Science Report:

- A systematic review of the evidence on clinical efficacy and safety. This may include an indirect comparison in the form of a network meta-analysis. The information used for the clinical evaluation will borrow from the data generated in the *Drugs for the Management of Rheumatoid Arthritis* published in March 2018.
- A review of economic studies.
- An economic evaluation (depending on the results of the systematic and economic reviews).

Summary of patient group input: Patient experience, expectations and perspective obtained for the project *Drugs for the Management of Rheumatoid Arthritis* may be of use in the selection of outcomes relevant for patients, and in the contextualization of the evidence.

A Recommendations Report or Policy Options Report: A Recommendation Report or Policy Options Report may be produced based on the Science Report. Determination of whether such recommendations or policy options are developed will be based on CADTH jurisdictional customers' needs.

STATUS OF THE DOCUMENT

This proposed project scope is posted for 10 business days for stakeholder feedback. The feedback will be considered as we finalize the project plan. A list of included studies and a project protocol may be posted on CADTH's website if required.

REFERENCES

1. Lee DM, Weinblatt ME. Rheumatoid arthritis. *Lancet (London, England).* 2001;358(9285):903-911.
2. Wong Rea. *Prevalence of arthritis and rheumatic disease around the world. A growing burdent and implications for health care needs.* University Health Network;2010.
3. Lubeck DP. Patient-reported outcomes and their role in the assessment of rheumatoid arthritis. *PharmacoEconomics.* 2004;22(1):27-38.
4. Odegard S, Finset A, Kvien TK, Mowinckel P, Uhlig T. Work disability in rheumatoid arthritis is predicted by physical and psychological health status: a 7-year study from the Oslo RA register. *Scandinavian journal of rheumatology.* 2005;34(6):441-447.
5. Yelin E. Work disability in rheumatic diseases. *Current opinion in rheumatology.* 2007;19(2):91-96.
6. Kvien TK, Uhlig T. Quality of life in rheumatoid arthritis. *Scandinavian journal of rheumatology.* 2005;34(5):333-341.
7. Cash JM, Klippel JH. Second-line drug therapy for rheumatoid arthritis. *The New England journal of medicine.* 1994;330(19):1368-1375.
8. Finckh A, Liang MH, van Herckenrode CM, de Pablo P. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: A meta-analysis. *Arthritis and rheumatism.* 2006;55(6):864-872.
9. Pincus T, Ferraccioli G, Sokka T, et al. Evidence from clinical trials and long-term observational studies that disease-modifying anti-rheumatic drugs slow radiographic progression in rheumatoid arthritis: updating a 1983 review. *Rheumatology (Oxford, England).* 2002;41(12):1346-1356.
10. Strand V, Singh JA. Improved health-related quality of life with effective disease-modifying antirheumatic drugs: evidence from randomized controlled trials. *The American journal of managed care.* 2008;14(4):234-254.
11. Singh JA, Saag KG, Bridges SL, Jr., et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis & rheumatology (Hoboken, NJ).* 2016;68(1):1-26.
12. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Annals of the rheumatic diseases.* 2014;73(3):492-509.
13. Fleischmann R, Tongbram V, van Vollenhoven R, et al. Systematic review and network meta-analysis of the efficacy and safety of tumour necrosis factor inhibitor-methotrexate combination therapy versus triple therapy in rheumatoid arthritis. *RMD open.* 2017;3(1):e000371.
14. Scott DL, Ibrahim F, Farewell V, et al. Randomised controlled trial of tumour necrosis factor inhibitors against combination intensive therapy with conventional disease-modifying antirheumatic drugs in established rheumatoid arthritis: the TACIT trial and associated systematic reviews. *Health technology assessment (Winchester, England).* 2014;18(66):i-xxiv, 1-164.