CADTH

CADTH PROPOSED PROJECT SCOPE

Harmonization of Public Coverage Policies for Biologic Drugs in the Treatment of Rheumatoid Arthritis

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Background and Rationale

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disease.[1,2] It is characterized by the infiltration of T cells, B cells, and monocytes into the synovial membranes of multiple joints, which is thought to play an important role in the pathophysiology of RA.[2,3] RA is a debilitating disease that affects physical functioning, work productivity, and health-related quality of life.[3] If left untreated or insufficiently treated, 80% of patients will develop joint deformity and 40% will be unable to work within 10 years of disease onset.[3] The cause of RA is not known and there is no cure. It was reported that RA affected 0.9% of the Canadian population in 2010 (approximately 272,299 persons), and that the prevalence of this condition is expected to increase to an estimated 1.3% of the Canadian population by 2040 (approximately 549,218 persons).[4] Although RA affects persons of all ages, more than half of all new cases are diagnosed in persons between ages 40 and 70, and the prevalence of disease is approximately two times higher among women than among men.[4]

Disease-modifying antirheumatic drugs (DMARDs) are a class of medications used to treat the signs and symptoms associated with RA, to slow the progression of disease, and to improve physical function.[3] There are synthetic DMARDs and biologic DMARDs.[3] Synthetic DMARDs are small molecules, whereas biologic DMARDs are large proteins that target specific components of the immune response and are administered parenterally. Biologic DMARDs are further classified into tumour necrosis factor (TNF) inhibitors and non-TNF inhibitors.[2,3] The majority of biologic DMARDs currently approved for use in Canada are TNF inhibitor drugs and include adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab. Other available biologic DMARDs include the following non-TNF inhibitors: abatacept (T cell co-stimulatory inhibitor), anakinra (interleukin-1 receptor antagonist), rituximab (B lymphocyte-depleting drug), sarilumab and tocilizumab (interleukin-6 receptor antagonists). Several biosimilar drugs are also currently marketed in Canada, including biosimilars etanercept and infliximab;[5,6] adalimumab and rituximab biosimilars have been approved by Health Canada but are not yet marketed. All biologic drugs are approved for use in combination with one or more conventional synthetic DMARDs (usually methotrexate), and all biologics except infliximab, golimumab, and rituximab are approved for use as monotherapy.[5,6] Appendix 1 provides a summary of the approved doses of biological drugs and small molecules available for the treatment of RA in Canada.

Modern therapeutic approaches including biologic DMARDs have significantly improved the ability to achieve disease control and to avoid joint damage and deformity in patients with RA. Optimal management of RA requires early diagnosis and intervention coupled with a treat-to-target (T2T) strategy in clinical practice where the therapeutic target for most patients is defined as clinical remission (i.e., the absence of signs and symptoms of substantial inflammatory disease activity) or low disease activity for some individuals with long-standing disease in whom remission is unattainable.[3,7,8] In addition to identifying an appropriate target and choosing how and when to assess if the target has been achieved, a T2T approach entails timely decisions to switch therapies if the treatment target is not reached.[8] T2T has been adopted as a guiding principle of care for RA in Canada by the Canadian Rheumatology Association national clinical practice guidelines,[9] and it has also been jointly endorsed by the American College of Rheumatology and EULAR — the European League Against Rheumatism.[3,7] Timely and targeted care consistent with the T2T approach has been shown to produce superior clinical outcomes compared to standard care in RA, including improvements in health-related quality of life and an increased likelihood of disease remission at one year.[10,11]

Policy Issue

Advances in therapy for RA in the last 20 years have led to better disease management strategies and improved patient outcomes.[3,7] The introduction of newer and often more costly therapies over time has also resulted in increased public drug program spending.[12] In light of budget constraints, public health care payers have implemented criteria for the use of pharmacotherapies for RA, including biologic DMARDs for particular patient subgroups. Although these strategies may have been adopted with the goal of maximizing population health within constrained budgets, they have been applied differently across provinces and territories.[13] This has resulted in considerable variation in public coverage for biologic DMARDs and varying timing of access to medications for patients with similar disease status but living in different geographic locations.

Discordance in reimbursement policies for biologic DMARDs used to treat RA is not unique to government-sponsored drug plans. Indeed, similar variation in access to biologic drugs for RA has been encountered with Canadian private insurers.[14] To address this issue, private insurers (through the CLHIA–the Canadian Life and Health Insurance Association) established a standard reimbursement criterion in 2015 for access to biologic drugs for adult patients with RA in collaboration with professional organizations (CRA–Canadian Rheumatology Association and ORA–Ontario Rheumatology Association) and with input from rheumatologists.[14] However, a national standard for the coverage of biologic DMARDs by Canadian public health care payers is currently lacking.

Continued variation in access to biologic DMARDs and the uneven portability of coverage across Canadian public drug plans may impact patient health outcomes and the expenditures associated with these medications; and, by extension, the inefficient allocation of health care resources. Harmonization of public coverage policies for biologic DMARDs for RA may therefore prove to be beneficial when trying to improve efficiency and equity in the health care system, as well as to support the optimal management of patients with RA.

The primary aim of this project is to determine whether pan-Canadian criteria may be identified and used to align access to biologic DMARDs across jurisdictions. Several research questions are proposed to guide the research process and achieve the policy objective, including a review of the available evidence regarding the clinical effectiveness of biologic DMARDs compared to other biologic drugs. Although this project is focused on the harmonization of coverage criteria for biologic DMARDs, an evidence review relating to targeted synthetic DMARDs (Janus kinase, or JAK, inhibitors) is also proposed, as these small molecule drugs are often part of the treatment paradigm and jurisdictional criteria for RA drugs.

Policy Question

1. Are there criteria that could be adopted to harmonize access of biologic DMARDs across all publicly funded drug plans in Canada for patients with RA?

Research Questions

1. What are the similarities and differences between the reimbursement criteria issued by Canadian public drug plans for currently available biologic DMARDs used in the treatment of RA?
2. What are the evidence-based guideline recommendations for the optimal pharmacologic management of patients with RA in Canada and internationally?
3. What is the clinical effectiveness of JAK inhibitor drugs compared to biologic DMARDs or conventional synthetic DMRARD (csDMARD) therapy alone in patients with moderate-to-severe RA who experience inadequate response to previous methotrexate or other csDMARD therapy?
4. What is the current and prospective utilization[a] of biologic drugs in RA across Canadian public drug plans under existing coverage policies? What are the costs associated with this utilization?
5. What is the budget impact of implementing harmonized criteria for reimbursing biologic DMARDs across all publicly funded drug plans in Canada compared to current coverage policies?

Project Description

The policy question will be addressed through several evidence modules designed to answer one or more research questions. Research for each module may be conducted in sequence or in parallel; in some cases, results from earlier evidence modules may help to inform the design or approach taken in subsequent modules. Consultation with clinical experts or policy-makers may occur at various stages of the research process to ensure the relevance of findings is reflective of real-world practice and policy. High-level details for each evidence module are presented in Table 1 and the scope is delimited in Table 2.

[a] Refers to the forecasting exercise conducted as part of a drug utilization study (e.g., time-series analysis) whereby complex statistical models make predictions about future usage based on historical data trends, often using aggregate data. This is different from the future uptake and costs of medications generated using a budget impact model – a computing framework based on assumptions regarding the financial implications of introducing a new drug to an existing mix of treatments.

Table 1: Project Components

Product Type	Description	Relevant research question
Module 1		
a. Policy Scan	Comparative assessment of existing coverage criteria for available biologic DMARDs reimbursed by Canadian public drug plans for the treatment of RA.	1
b. Review of Guidelines	A critical review of Canadian and international clinical practice guidelines for RA will be conducted to determine current practice recommendations for the optimal pharmacologic management of patients with RA and to explore the extent to which existing criteria for reimbursing biologic DMARDs by Canadian public payers align with current guideline recommendations.	2
Module 2		
a. Focused Critical Appraisal and Scoping Search	A summary and critical appraisal of a recently published, independent evidence review[15] on JAK inhibitors will be performed. The applicability of findings to the Canadian decision-making context will be assessed. Potential gaps in the evidence base will be identified from this report and supplemented by a scoping literature search to inform the need for additional research comparing biologic DMARDs and JAK inhibitors.	3
b. Clinical Evidence Review — Biologics and JAK Inhibitors	If feasible and required, a clinical evidence review will be conducted to determine the comparative clinical effectiveness of biologic DMARDs versus other biologic DMARDs or JAK inhibitors for the management of RA.	
Module 3 *(if feasible)*		
a. Utilization Analysis (With Forecasting)	Current utilization of available biologic DMARDs will be explored. This includes the identification of appropriate data sources (e.g., NPDUIS datasets), collection of claims or user-level data for all biologic DMARDs and linkage with information relating to medical indication, and analysis of total drug volume and total costs over a specified time period (e.g., the last five to 10 years). A drug utilization study may be performed (pending data availability) to explore the prospective utilization and expenditures associated with available biologic DMARDs for RA under existing reimbursement criteria.	4
b. Budget Impact Assessment	A policy-oriented budget impact model may be developed to facilitate consideration of the financial impact of alternative harmonized reimbursement strategies (compared to existing coverage policies) for available biologic DMARDs in the treatment of patients with RA across all publicly funded drug plans in Canada.	5
Module 4		
OU360 Brief	A summary of the available evidence on coverage criteria and practice guidelines, and a discussion of	N/A

Product Type	Description	Relevant research question
	policy implications of any changes to criteria for reimbursing biologic DMARDs by Canadian public formularies will be provided. Possible options and approach to harmonization of current coverage policies for biologic DMARDs in RA will be discussed.	
Module 5 *(if required)*		
Implementation Advice Panel	A panel of Canadian clinical experts and/or policy-makers will be convened to review the various project components and provide enhanced implementation support relating to the development and adoption of pan-Canadian harmonized criteria for the reimbursement of biologic DMARDs for RA. Information generated through this panel will be used to provide advice to Canadian public payers.	N/A

DMARD = disease-modifying antirheumatic drug; JAK = Janus kinase; NPDUIS = National Prescription Drug Utilization Information System; RA = rheumatoid arthritis.

Table 2: Project Scope Limits

Within the scope	Outside the scope

Population/Setting:
• Adults with moderate or severe active RA
 	
Interventions:
• Biologic DMARDs, alone or in combination with conventional DMARDs, including:
  ○ TNF inhibitors (adalimumab and adalimumab biosimilar, etanercept and etanercept biosimilar, infliximab and infliximab biosimilar, golimumab, and certolizumab pegol)
  ○ Non-TNF inhibitors (abatacept, rituximab and rituximab biosimilar, sarilumab, tocilizumab)
• Janus-associated kinase inhibitors, alone or in combination with conventional DMARDs, including: baricitinib, upadacitinib, and tofacitinib
 	
Comparators:
• Any of the drugs of interest or placebo
 	
Outcomes:
• Clinical benefit (e.g., disease severity, disease activity, remission)
• Harms (e.g., withdrawal due to adverse events, serious adverse events)
	Population/Setting:
	• Patients who are treatment-naive
	
	or
	
	• Patients who are in clinical remission or who have low disease activity
	
	Interventions/Comparators:
	• IL-1 inhibitor (anakinra; almost never used to treat adult RA)

DMARD = disease-modifying antirheumatic drug; IL-1 = interleukin-1; RA = rheumatoid arthritis; TNF = tumour necrosis factor.

Status of the Document

Stakeholder feedback may be requested at the project planning stage for some modules. Reports generated from the multi-module project may also be posted on the CADTH website for stakeholder feedback, if required. As this project is not a Therapeutic Review, no CADTH Canadian Drug Expert Committee recommendations will be made.

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Appendix 1: Biological Drugs and Small Molecules for the Treatment of Rheumatoid Arthritis

Table 3: Approved Doses of Innovator Biologics, Biosimilars, and Small Molecules available for the Treatment of Rheumatoid Arthritis in Canada

Drug class	Non-proprietary name	Brand name	Year approved by Health Canada	Health Canada–approved dosage
TNF inhibitors				
TNF Inhibitors	Etanercept	Enbrel	2000	25 mg SC twice weekly or 50 mg every week
	Infliximab	Remicade	2001	3 mg per kg IV; initial dose at 0 weeks, 2 weeks, and 6 weeks; then every 8 weeks
	Adalimumab	Humira	2004	40 mg SC every 2 weeks
	Certolizumab pegol	Cimzia	2009	400 mg SC (divided into two injections) initially and at week 2 and week 4, then 200 mg every 2 weeks[a]
	Golimumab	Simponi	2011	50 mg SC every 4 weeks (monthly)
				2 mg per kg IV; initial dose at 0 weeks and 4 weeks, then every 8 weeks
Non-TNF inhibitors				
IL-1 inhibitor	Anakinra[b]	Kineret	2002	100 mg SC, every day
B lymphocyte-depleting drug (anti-CD20 therapy)	Rituximab	Rituxan	2006	2 doses of 1,000 mg IV every 2 weeks
T cell co-stimulatory inhibitor	Abatacept	Orencia	IV: 2006	10 mg per kg IV; initial dose at 0 weeks, 2 weeks, and 4 weeks; then every 4 weeks (< 60 kg: 500 mg; 60 kg to 100 kg: 750 mg; > 100 kg: 1,000 mg)
			SC: 2013	125 mg SC initial loading dose; second dose within 1 day, then once weekly
IL-6 inhibitor	Tocilizumab	Actemra	2010	4 mg per kg IV every 4 weeks; increase to 8 mg per kg based on clinical response
				162 mg SC every 2 weeks; increase to every week based on clinical response
	Sarilumab	Kevzara	2017	200 mg every 2 weeks SC; reduction to 150 mg every 2 weeks SC to manage neutropenia, thrombocytopenia, and elevated liver enzymes

Drug class	Non-proprietary name	Brand name	Year approved by Health Canada	Health Canada–approved dosage
Targeted synthetic DMARDs				
Janus-associated kinase inhibitor	Tofacitinib	Xeljanz	2014	5 mg p.o. twice daily
	Baricitinib	Olumiant	2018	2 mg p.o. once daily
	Upadacitinib	Rinvoq	2019	15 mg p.o. once daily
Biosimilars				
Biosimilar of infliximab	CT-P13	Inflectra	2014	3 mg per kg IV; initial dose at 0 weeks, 2 weeks, and 6 weeks; then every 8 weeks
	SB2	Renflexis	2017	3 mg per kg at 0 weeks, 2 weeks, and 6 weeks; then every 8 weeks (IV)
Biosimilar of etanercept	SB4	Brenzys	2016	50 mg per week SC; 25 mg twice weekly SC
	GP2015	Erelzi	2017	50 mg per week SC; 25 mg twice weekly SC
Biosimilar of adalimumab	SB5	Hadlima, Hadlima PushTouch	2018	40 mg SC every 2 weeks
Biosimilar of rituximab	CT-P10	Truxima	2019	2 doses of 1,000 mg IV every 2 weeks

DMARD = disease-modifying antirheumatic drug; IL= interleukin; IV = intravenous; p.o. = orally; SC = subcutaneously; TNF = tumour necrosis factor.

[a] 400 mg every 4 weeks can be used for a maintenance dose.

[b] Almost never used to treat adult rheumatoid arthritis.