CADTH

ENVIRONMENTAL SCAN

Comparative Assessment of Coverage Criteria for Biologic Disease-Modifying Antirheumatic Drugs Across Canadian Public Drug Plans: An Environmental Scan

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Authors: Sirjana Pant, Mirhad Lončar

Acknowledgements: Kim Baird, Tarry Ahuja, Trevor Richter, Christine Perras

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Abbreviations

ACR	American College of Rheumatology
CAF	Canadian Armed Forces
CSC	Correctional Service Canada
csDMARD	conventional synthetic disease-modifying antirheumatic drug
DMARDs	disease-modifying antirheumatic drugs
EAP	Exceptional Access Program
EDS	Exceptional Drug Status
ES	environmental scan
FWG-HTA	Formulary Working Group for Health Technology Assessments
NIHB	Non-Insured Health Benefits
P/T	provincial and territorial
RA	rheumatoid arthritis
TNF	tumour necrosis factor
VAC	Veterans Affairs Canada

Context

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. According to the Canadian Chronic Disease Surveillance System, RA affected 1.25% of the Canadian population aged 16 and older in 2016. [4] Although RA affects persons of all ages, more than half of all new cases are diagnosed in persons between the ages of 40 and 70 years, and the prevalence of disease is approximately two times higher among women than among men.[4,5]

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] These include 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).[6,7] Several biosimilar drugs are also currently marketed in Canada, including etanercept, infliximab, and rituximab biosimilars; the biosimilar adalimumab has been approved by Health Canada but is not yet marketed.[8] Health Canada approved the biologics to be used in combination with one or more conventional synthetic DMARDs (usually methotrexate); all biologics except infliximab, golimumab, and rituximab are approved for use as monotherapy.[6,7]

In Canada, provincial and territorial (P/T) public drug plans generally provide prescription drug coverage for specific segments of the population such as seniors (persons aged older than 65 years), individuals with low income, or those with high drug costs relative to their income; public coverage is therefore determined based on predefined eligibility criteria for the general population. Additionally, federal public drug plans provide coverage for veterans, First Nations and Inuit individuals, federally incarcerated offenders, the Royal Canadian Mounted Police, and the military. Public drug plans list prescription medicines according to specific coverage categories that can be broadly classified as restricted benefits or unrestricted benefits. "Unrestricted benefit" refers to drugs whose usage is not limited by clinical criteria requiring authorization. Depending on the P/T drug plans, this type of formulary benefit status (coverage category) is referred to as open benefit, full benefit, or regular benefit. "Restricted benefit" refers to drugs whose usage is limited by specific clinical criteria or to a defined patient subgroup. Depending on the jurisdictional plan, this type of formulary benefit status is categorized under Special Authorization, Exceptional Access Program (EAP), Exceptional Drug Status (EDS), Limited Use, Limited Coverage Drug, Prior Authorization. An active approval process is often assumed for drugs within the restricted benefit category; that is, there is a requirement to submit an application for reimbursement, with the required clinical details by the authorized prescriber using established processes (e.g., use of specific authorization

forms). Submitted requests for restricted benefit drugs are often subject to a medication review by the P/T drug plan prior to approval for coverage.[9]

Advances in therapy for patients with RA in the last 20 years have led to better disease management strategies and improved patient outcomes.[3,10] The introduction of new therapies over time has resulted in increased public drug program spending on RA treatment.[11] In light of budget constraints, public health care payers have implemented criteria to restrict the use of pharmacotherapies for RA, including biologic DMARDs, to particular patient subgroups.[12]

An environmental scan (ES) was conducted to better understand the similarities and differences between the current public drug program access criteria for biologic drugs used to treat RA in Canada. This ES is intended to inform a CADTH multicomponent Technology Review that aims to address a broader policy question regarding the harmonization of public coverage policies for biologic drugs for patients with RA in Canada.[13]

Objectives

The objective of this ES was to identify and to compare existing criteria for reimbursing biologic drugs in RA across Canadian public formularies. This ES did not include an assessment of the comparative clinical effectiveness or the relative cost-effectiveness of biologic drugs used to treat RA. Therefore, any conclusions or recommendations about the value of these medications or their place in therapy were outside of the scope of this report.

Methods

The findings of this ES are based on information obtained from formulary databases (drug benefit lists) accessed through Canadian public drug plan formulary websites. No bibliographic literature searches were performed. Online formularies were searched between April 16, 2020 and April 30, 2020. Members of the CADTH Pharmaceutical Advisory Committee Formulary Working Group for Health Technology Assessments (FWG-HTA)[14] — which includes representatives from the federal, provincial, and territorial health ministries, and related health organizations — were consulted to validate the information gathered from the formulary databases and provide feedback on the report findings. The consultation period ended on July 9, 2020; therefore, the information summarized in this report is up-to-date as of July 9, 2020.

This report includes relevant formulary coverage policies regarding all publicly reimbursed biologics and biosimilar DMARDs used in the treatment of RA. Only policies relevant to biologic drugs used in the treatment of adult patients with RA were included. Hence, anakinra, an interleuken-1 inhibitor, was excluded from this report, as this drug is rarely used to treat RA in adults.[15] Private payer policies were also excluded from this report given the focus on the Canadian publicly funded health care system. It should be noted that biologic DMARDs included in this ES are also indicated for other medical conditions; however, this report presents the coverage criteria specific to the RA indication. Some information presented in this report was not available in the public domain and was obtained through personal communication with members of the CADTH FWG-HTA. When this occurred, permission was obtained to publish this information in this report and all details obtained through personal communication were referenced accordingly.

Table 1 presents information on the components of the information presented in this ES: a list of the 14 drugs (nine originator biologics and five biosimilars) and the 14 publicly funded drug

plans of interest (nine provincial, one territorial and four federal drug plans), and the type of information gathered. The term "drugs" is used throughout this report to refer to the originator biologics and their biosimilar variants (if available) used in the management of RA, as listed in Table 1; "originator biologics" are also commonly referred to as reference biologics or innovator biologics. Canadian provincial and territorial abbreviations were used to refer to the respective jurisdictional drug plan formularies. Information on four federal public drug plans was also included: Non-Insured Health Benefits (NIHB), Correctional Services Canada (CSC), Veterans Affairs Canada (VAC), and the Canadian Armed Forces (CAF). It should be noted that publicly reimbursed medications for residents of Nunavut and the Northwest Territories follow the coverage category and reimbursement criteria of the NIHB program.[16,17] The Quebec public drug program — Régie de l'assurance maladie du Québec — was not included in this report.

Synthesis Approach

A qualitative comparison using a systematic approach was adopted to identify the similarities and differences between the reimbursement criteria. Information regarding coverage criteria was presented for each drug according to specific requirements reported by individual drug plans and the relevant coverage categories. Other policies that may be relevant for reimbursing biologic DMARDs were also presented in this report, such as policies on the use of biosimilar drugs and biosimilar switching.

Table 1: Components for Information Gathering

Population	**Adults (> 18 years old) with moderate or severe active RA**
Intervention	Biologic DMARDs (and biosimilars, if available): 1. abatacept (Orencia) 2. adalimumab (Humira) 3. certolizumab pegol (Cimzia) 4. etanercept (Enbrel) 5. etanercept (Brenzys, biosimilar) 6. etanercept (Erelzi, biosimilar) 7. golimumab (Simponi) 8. infliximab (Remicade) 9. infliximab (Inflectra, biosimilar) 10. infliximab (Renflexis, biosimilar) 11. rituximab (Rituxan) 12. rituximab (Truxima, biosimilar) 13. sarilumab (Kevzara) 14. tocilizumab (Actemra)
Settings	Canadian publicly funded drug plans: Provincial/territorial plans — 1. Alberta Drug Benefit List 2. British Columbia Pharmacare Formulary 3. Manitoba Pharmacare Drug Formulary 4. New Brunswick Drug Plan Formulary 5. Newfoundland and Labrador Prescription Drug Program Formulary 6. Nova Scotia Pharmacare Formulary 7. Ontario Drug Benefit Formulary 8. PEI Pharmacare Formulary 9. Saskatchewan Formulary 10. Yukon Drug Formulary Federal plans — 11. Canadian Armed Forces Drug Benefit List 12. Correctional Services Canada National Formulary 13. Non-Insured Health Benefits Drug Benefit List (also applicable to Nunavut and the Northwest Territories) 14. Veterans Affairs Canada Drug Formulary

Types of Information	**Coverage Categories:** Special Authorization, Exceptional Access Program, Exceptional Drug Status, Limited Use, Limited Coverage Drug, Prior Authorization **Coverage Criteria:** clinical criteria; approved dosage, approved duration of coverage including initial approval and renewal policy; criteria for renewal; prescriber requirements; and relevant biosimilar switching policies

DMARDs = disease-modifying antirheumatic drug; PEI = Prince Edward Island; RA = rheumatoid arthritis.

Research Questions

This following research question was addressed:

What are the similarities and differences between the reimbursement criteria issued by Canadian publicly funded drug plans for currently available biologic DMARDs used in the treatment of adult patients with RA?

Findings

A summary of findings relating to jurisdictional coverage policies for biologic DMARDs used in the treatment of patients with RA is presented in the sections that follow. Available information was presented to showcase the similarities and differences in the coverage status and the reimbursement criteria for drugs within and between public drug plans.

1. Jurisdictional drug coverage

Most jurisdictional drug plans provided coverage for almost all the drugs included in this report. Namely, nine out of 14 drug plans (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Newfoundland and Labrador, Prince Edward Island, NIHB) provided coverage for all originator biologic drugs. Two originator biologics were not publicly reimbursed by some jurisdictions:

- Certolizumab pegol was not eligible for reimbursement by CSC, VAC, CAF.
- Sarilumab was not eligible for reimbursement by Nova Scotia, Yukon, and CSC.

All jurisdictions except VAC provided coverage for etanercept and infliximab biosimilars; coverage may be provided by VAC in exceptional cases while these drugs are under review and case-by-case assessment follows the originator biologic criteria for RA. (Anne Bastarache, Veterans Affairs Canada: personal communication, Jul 2020). It should be noted that while all jurisdictions provided coverage for all available etanercept and infliximab biosimilars, one infliximab biosimilar, Renflexis, was not eligible for reimbursement by Yukon. Conversely, three jurisdictions (Alberta, Ontario, and Yukon) provided coverage for Truxima, a rituximab biosimilar. Of note, Truxima was approved by Health Canada in December 2019 and the pan-Canadian Pharmaceutical Alliance negotiation process for Truxima concluded in February 2020. Hence, the coverage status of Truxima by the drug plans may change in the near future.[18,19]

2. Coverage categories

All the drugs were listed under "restricted benefit" categories such as Special Authorization, EAP, EDS, Limited Coverage Drug, Limited Use, and Prior Authorization, with the following exceptions:[8,20-36]

- The biosimilar versions of etanercept, infliximab, and rituximab were listed as a Limited Use benefit by Ontario.
- All drugs were listed as a "benefit with criteria medications" by CSC.

Of note, requests for the biosimilar versions of etanercept and infliximab for patients with RA covered by VAC are assessed on a case-by-case basis, as per the originator biologic criteria. (Anne Bastarache: personal communication, Jul 2020).

As a restricted benefit, all the drugs across all public drug plans were reimbursed under specific medical circumstances because these drugs are effective within certain patient subgroups or are more costly than other, equally safe and effective, drug treatments. In general, the plans required individuals to meet specific clinical criteria for drugs to be eligible for reimbursement. These clinical criteria are typically established by each plan's formulary review committee. For biologic DMARDs (and their biosimilars) used to treat patients with RA, these criteria included a requirement for failure to respond to a first- or a second-line of therapy. Initial or continued coverage was provided for a specific period or indefinitely, depending on the drug and the jurisdictional drug plan.

The restricted benefit categories can be further classified by the following reimbursement processes: restricted benefit-active and restricted benefit-passive.

Restricted Benefit – Active was applicable to the following coverage categories for biologic DMARDs for RA: Special Authorization/Limited Coverage Drug (British Columbia), Special Authorization (Alberta, New Brunswick, Newfoundland and Labrador, Prince Edward Island, Veterans Affairs Canada, Canadian Armed Forces), EAP (Ontario), EDS (Saskatchewan, Manitoba, Nova Scotia, Yukon), or limited use/prior authorization (NIHB). Application for public reimbursement with the required clinical details must be made by the authorized prescriber using established processes (e.g., use of specific authorization forms). Each request is subject to a medication review by staff responsible for claims adjudication at the public drug plan. [8,20-36]

Restricted Benefit – Passive was applicable to the following coverage categories for biologic DMARDs for RA: Limited Use (Ontario), and benefit with criteria medications (CSC). As opposed to "Restricted Benefit – Active," the use of specific authorization forms and a medication review is not a requirement. Rather, a Limited Use code (Ontario) or a Reason for Use code (CSC) must be specified in the prescription. Of note, in Ontario, biosimilars are listed as Limited Use, while the originator biologics are listed as EAP. [8,20-36]

Table 2 presents information on the coverage category (grouped as restricted benefit-active and restricted benefit-passive) for each drug according to each public drug plan. Appendix 1 provides a detailed overview of the specific coverage category — that is, the formulary benefit status terminology used by jurisdictions — and Appendix 2 provides web links for detailed descriptions of each of the jurisdiction-specific coverage categories.

Table 2: Coverage Categories

Generic name (Brand name)	BC	AB	SK	MB	ON	NB	NS	NL	PE	YT	NIHB[a]	CSC	VAC	CAF
abatacept (Orencia)	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	PAS	RES	RES
adalimumab (Humira)	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	PAS	RES	RES
certolizumab pegol (Cimzia)	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	PAS	NAB	NAB
etanercept (Enbrel)	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	PAS	RES	RES
etanercept (Brenzys)[b]	RES	RES	RES	RES	PAS	RES	RES	RES	RES	RES	RES	PAS	UR[c]	RES
etanercept (Erelzi)[b]	RES	RES	RES	RES	PAS	RES	RES	RES	RES	RES	RES	PAS	UR[c]	RES
golimumab (Simponi)	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	PAS	RES	RES
infliximab (Remicade)	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	PAS	RES	RES
infliximab (Inflectra)[b]	RES	RES	RES	RES	PAS	RES	RES	RES	RES	RES	RES	PAS	UR[c]	RES
infliximab (Renflexis)[b]	RES	RES	RES	RES	PAS	RES	RES	RES	RES	NAB	RES	PAS	UR[c]	RES
rituximab (Rituxan)	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	PAS	RES	RES
rituximab (Truxima)[b]	UR	RES	UR	NAB	PAS	NAB	NAB	NAB	NAB	RES	NAB	PAS	NAB	NAB
sarilumab (Kevzara®)	RES	RES	RES	RES	RES	RES	NAB	RES	RES	NAB	RES	PAS	RES	RES
tocilizumab (Actemra)	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	RES	PAS	RES	RES

AB = Alberta; BC = British Columbia; CAF = Canadian Armed Forces; CSC = Correctional Services Canada; MB = Manitoba; NAB = not a benefit; NB = New Brunswick; NIHB = Non-Insured Health Benefits; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PAS = restricted listing – passive (e.g., Limited Use benefit for Ontario); PE = Prince Edward Island; RES = restricted benefit with specified criteria (e.g., Special Authorization, exception drug status, Limited Use benefit for NIHB); SK = Saskatchewan; UR = under review; VAC = Veterans Affairs Canada; YT = Yukon.

[a] Also applicable to Nunavut and the Northwest Territories.

[b] Biosimilar version.

[c] Overage may be provided in exceptional cases while the drug is under review and case-by-case assessment follows the originator biologic criteria for rheumatoid arthritis. Information is based on a personal communication with the jurisdictional representative (Anne Bastarache: personal communication, Jul 2020).

Source: Canadian public drug plan formularies [8,20-36]

3. Clinical Criteria

The following section summarizes the clinical requirements for patients with RA to be approved for coverage for a biologic DMARD. Biosimilar related policies which may impact access to originator biologics are also discussed. [37-39]

a) Diagnosis and prescriber requirements

The drugs were generally eligible for coverage for patients with moderate to severely active RA; some variation was noted in the diagnosis definitions used (Table 3). Ontario explicitly defined the disease activity.[8] However, other drug plans such as British Columbia required that details of the disease activity be specified in the application forms.[25,26] Of note, Manitoba stated that the initial application information must include information on disease activity such as the number of tender and swollen joints, the erythrocyte sedimentation rate, and the C-reactive protein value for certolizumab pegol, etanercept, golimumab, infliximab, sarilumab, and tocilizumab.[40]

Table 3: Details on Diagnosis

Diagnosis	Public drug plans	Notes
Drugs: abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, sarilumab, and tocilizumab		
Active RA	SK, CSC	SK: not applicable to sarilumab and tocilizumab CSC: not applicable to tocilizumab
Moderate to severely active RA	BC, MB, SK, NB, CSC, VAC, CAF	SK: only applicable to sarilumab and tocilizumab CSC: only applicable to tocilizumab
Severely active RA	AB, NS, NL, PE, YT, NIHB	
Severely active RA (≥ 5 swollen joints and rheumatoid factor-positive and/or anti-CCP – positive and/or radiographic evidence of RA)	ON	
Drug: rituximab		
RA	VAC	
Severely active RA	BC, AB, SK, MB, NB, NS, NL, PE, YT, NIHB, CSC, CAF	
Severely active RA (≥ 5 swollen joints and rheumatoid factor-positive and/or radiographic evidence of RA)	ON	

AB = Alberta; BC = British Columbia; CAF =Canadian Armed Forces; CCP = cyclic citrullinated peptide; CSC = Correctional Services Canada; MB = Manitoba; NB =New Brunswick; NIHB = Non-Insured Health Benefit; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PE = Prince Edward Island; RA = rheumatoid arthritis; SK = Saskatchewan; VAC = Veterans Affairs Canada; YT = Yukon.

Note: Certolizumab pegol was not eligible for reimbursement by CSC, VAC, CAF. Renflexis, an infliximab biosimilar, was not eligible for reimbursement by YT. Sarilumab was not eligible for reimbursement by NS, YT and CSC. Truxima, a rituximab biosimilar, was only eligible for reimbursement by AB, ON and YT. Coverage for etanercept and infliximab biosimilars may be provided in exceptional cases by VAC while the drugs are under review (Anne Bastarache: personal communication, Jul 2020).

Source: Canadian public drug plan formularies [8,20-36]

As noted in Table 4, most of the public drug plans explicitly stated that the drug must be prescribed by a "rheumatologist" or a "prescriber with a specialty in rheumatology." In addition to these prescribers, VAC also allowed an "internal medicine specialist" to prescribe these drugs.

Table 4: Prescriber Requirement

Drugs	Public drug plans
abatacept	BC, AB, MB, NB, NS, NL, PE, YT, NIHB, CSC, VAC,[a] CAF
adalimumab	BC, AB, SK, MB, NB, NS, NL, PE, YT, NIHB, CSC, VAC,[a] CAF
certolizumab pegol	BC, AB, SK, MB, NB, NS, NL, PE, YT, NIHB
etanercept	BC, AB, SK, MB, ON, NB, NS, NL, PE, YT, NIHB, CSC, VAC,[a] CAF
golimumab	BC, AB, SK, MB, NB, NS, NL, PE, YT, NIHB, CSC, VAC,[a] CAF
infliximab	BC, AB, SK, MB, ON, NB, NS, NL, PE, YT, NIHB, CSC, VAC,[a] CAF
sarilumab	BC, AB, SK, MB, NB, NL, PE, NIHB, VAC,[a] CAF
tocilizumab	BC, AB, SK, MB, NB, NS, NL, PE, YT, NIHB, VAC,[a] CAF
rituximab	BC, AB, MB, ON, NS, YT, NIHB, CSC

AB = Alberta; BC = British Columbia; CAF = Canadian Armed Forces; CSC = Correctional Services Canada; MB = Manitoba; NB = New Brunswick; NIHB = Non-Insured Health Benefits; NL= Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PE = Prince Edward Island; SK = Saskatchewan; VAC = Veterans Affairs Canada; YT = Yukon.

[a] Or internal medicine specialist.

Note: Certolizumab pegol was not eligible for reimbursement by CSC, VAC, CAF. Renflexis, an infliximab biosimilar, was not eligible for reimbursement by YT. Sarilumab was not eligible for reimbursement by NS, YT, and CSC. Truxima, a rituximab biosimilar, was only eligible for reimbursement by AB, ON, and YT. Coverage for etanercept and infliximab biosimilars may be provided in exceptional cases by VAC while the drugs are under review (Anne Bastarache: personal communication, Jul 2020).

Source: Canadian public drug plan formularies [8,20-36]

b) Prior Therapy

None of the drugs were eligible for coverage as a first line of therapy. In general, patients seeking reimbursement for biologic DMARDs must have experienced failure on an initial treatment such as a conventional synthetic disease-modifying antirheumatic drug (csDMARD) — or in some cases, an anti-TNF agent — or to have experienced intolerance or serious adverse effects with initial therapy to be eligible for coverage.[8,20-36]

Table 5 presents the details on the requirements for prior therapy for each drug or group of drugs. The drugs were only reimbursed if patients were "refractory," "intolerant," or failed to respond to previous therapy with csDMARDs. "Refractory" was defined as a lack of effect at the recommended doses and for a specified duration of treatment. "Intolerant" was defined as demonstrating serious adverse effects or contraindications to treatments, as defined in the product monographs. Previous therapy that included methotrexate alone or in combination with other DMARDs was applicable to all public drug plans, and for all drugs unless contraindicated or not tolerated. These clinical criteria varied between the drug plans, especially regarding the number and the sequence of csDMARDs (or csDMARD combination regimens) that needed to be tried before requesting reimbursement for the biologic DMARDs. Three out of 14 drug plans (Alberta, Manitoba, and Yukon) required failure to at least three lines of prior therapy, including at least one line of methotrexate monotherapy (unless contraindicated or not tolerated) and at least one subsequent line of combination therapy with csDMARDs, before being eligible for coverage with biologic DMARDs. Seven out of 14 drug plans (Saskatchewan New Brunswick, Nova Scotia, Prince Edward Island, CSC, VAC, and CAF) required failure to at least two lines of prior therapy, including one line of methotrexate monotherapy (unless contraindicated or not tolerated) and/or therapy with one or more csDMARDs before being eligible for coverage with biologic DMARDs. British Columbia, Ontario, Newfoundland and Labrador, and NIHB specified an option for access to biologic DMARDs after only one line of dual or triple therapy with csDMARDs. The duration

of monotherapy or combination therapy with csDMARDs ranged from 8 weeks to 4 months. CSC and CAF required failure on at least one anti-TNF therapy, in addition to csDMARDs, to be eligible for coverage for tocilizumab. Yukon and NIHB required failure on at least one anti-TNF therapy, in addition to csDMARDs, to be eligible for coverage for abatacept. Prior therapy criteria for rituximab were the same across all drug plans; that is, a failure to respond to an adequate trial of at least one anti-TNF agent, in addition to jurisdictional requirements for prior therapy with csDMARDs.[8,20-36]

Patients covered by Alberta were permitted to switch from one biologic DMARD to another following an adequate trial of the first biologic agent if patients were unresponsive to initial therapy, or due to serious adverse effects or contraindications. An adequate trial was defined as a minimum completion of induction dosing (e.g., initial coverage period). However, patients were not permitted to switch back to a previously trialled biologic drug if they were deemed unresponsive to that treatment.[8,20-36] CSC required evidence of failure or intolerance with a subcutaneous biologic (e.g., adalimumab) prior to initiating treatment with an IV biologic (e.g., infliximab, abatacept, tocilizumab).[22]

Table 5: Requirement for Failure to Prior Line of Therapy

Refractory,[a] intolerant,[a] or failure to respond to…	Public drug plans	Notes
Drugs: abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, sarilumab, and tocilizumab		
• MTX + ≥ 1of the following (not including HCQ): LEF, SSZ, azathioprine, tacrolimus, cyclosporine, gold, doxycycline **OR** • ≥ 1 DMARD combination	BC	**BC:** >8 weeks trial of MTX (parenteral), ≥ 25 mg/week (≥ 15 mg/week if patient is ≥ 65 years of age) > 10 weeks trial of LEF, 20 mg/day > 3 months trial of SSZ, > 2 gm/day > 3 months trial of azathioprine, 2 mg /kg/day to 3 mg/kg/day DMARD combination: > 4 months trial MTX + HCQ + SSZ (O'Dell protocol) > 10 weeks trial MTX + LEF Note: Antimalarial in combination with one other DMARD is not acceptable. Expectation for adequate dose/duration of DMARD trials; if a medication must be discontinued due to intolerance(s) prior to the expected duration of the trial, an alternate DMARD trial is required. Exceptions are considered when additional DMARD trials cannot be attempted (supporting information must be provided for consideration).
• MTX **AND** • MTX + other DMARDs **AND** • LEF	AB[b]	**AB:** > 12 weeks trial of MTX ≥20 mg/week (p.o., SC, or IM) (≥ 15 mg/week if patient is ≥ 65 years of age) > 4 months trial of MTX + other DMARDs; e.g., MTX with HCQ or MTX with SSZ > 10 weeks trial of LEF 20 mg/day
• MTX, **AND** • LEF	SK	**SK:** *For sarilumab and tocilizumab ONLY:* adequate trial of DMARDs

Refractory,[a] intolerant,[a] or failure to respond to…	Public drug plans	Notes
• ≥ 3 DMARDs (one of which is MTX and/or LEF) **AND** • One combination of DMARDs	MB	**MB:** Unless intolerance or contraindications to these drugs is documented.
• MTX **AND** • LEF **AND** • 1 DMARD combination **OR** • MTX **AND** • MTX +LEF **OR** • MTX, SSZ, and HCQ	ON[c]	**ON:** > 3months trial of each therapy. MTX (20 mg/week), LEF (20 mg/day), SSZ (2 mg/day), and HCQ (400 mg/day, based by weight up to 400 mg per day). If the patient could not receive adequate trial(s) of MTX and/or LEF due to contraindication(s) or intolerance(s), the nature of the contraindication(s) or intolerance(s) must be provided, together with details of trials of other DMARDs or a clear rationale as to why other DMARDs cannot be considered. If the patient could not receive an adequate trial of MTX, SSZ, and HCQ due to intolerance, then the DMARD trial criteria must be met.
• MTX or MTX + DMARD **AND** • MTX + ≥ 2 DMARDs	NB[b] NS[b] PE[b] CSC[b]	**NB, NS, PE:** > 12 weeks trial of MTX ≥ 20 mg/week (p.o., SC or IM) (≥ 15 mg if patient is ≥ 65 years of age). > 3 months trial of MTX + other DMARDs; e.g., MTX with HCQ and SSZ. Optimal treatment response to DMARDs may take up to 24 weeks; however, coverage of a biologic therapy can be considered if no improvement is seen after 12 weeks of triple DMARD use. If patient factors (e.g., intolerance) prevent the use of triple DMARD therapy, these must be described and dual therapy with DMARDs must be tried. **CSC:** If a patient could not receive an adequate trial of MTX, SSZ, or HCQ due to a contraindication(s) or intolerance(s), the nature of such must be provided, together with the details of the trial of other DMARDs or a clear rationale as to why other DMARDs cannot be considered. *FOR abatacept and infliximab ONLY:* Failure or intolerance with an SC biologic (e.g., adalimumab) should be assessed prior to starting an IV biologic (e.g., infliximab, abatacept, tocilizumab). *FOR tocilizumab ONLY:* An adequate trial will have documented intolerance to or a contraindication to both DMARDs and anti-TNF agents. Failure or intolerance with an SC biologic (e.g., adalimumab) should be assessed prior to starting an IV biologic (e.g., infliximab, abatacept, tocilizumab).
• MTX AND • MTX + ≥ 2 DMARDs **OR** • MTX+ ≥ 2 DMARDs	NL[b]	**NL:** > 12 weeks trial of MTX ≥ 20 mg/week (p.o., SC or IM) (≥ 15 mg if patient is ≥ 65 years of age) > 3 months trial of MTX + other DMARDs; e.g., MTX with HCQ and SSZ Optimal treatment response to DMARDs may take up to 24 weeks; however, coverage of a biologic therapy can be considered if no improvement is seen after 12 weeks of triple DMARD use. If patient factors (e.g., intolerance) prevent the use of triple DMARD therapy, these must be described and dual therapy with DMARDs must be tried

Refractory,[a] intolerant,[a] or failure to respond to…	Public drug plans	Notes
• Parenteral MTX **AND** • ≥ 2 of the following: LEF, SSZ, azathioprine; **AND** • ≥ 1 DMARD combination	YT	**YT:** > 12 weeks trial for each course of therapy. DMARD combination; e.g., MTX with cyclosporine, MTX with HCQ and SSZ, MTX with LEF *FOR abatacept ONLY:* Must have failed adequate trial of an anti-TNF agent
• MTX **AND** • MTX + ≥ 2 DMARDs (SSZ and HCQ) **OR** • ≥ 2 DMARDs combination (SSZ, HCQ, azathioprine, LEF, cyclosporine); if the patient has a contraindication, failure, or intolerance to MTX	NIHB[b]	**NIHB:** > 12 weeks trial for each course of therapy. MTX ≥ 20 mg/week (p.o., SC or IM) (≥ 15 mg if patient is ≥ 65 years of age) *FOR abatacept IV ONLY:* Must have failed (FOR IV FORMULATION ONLY): > 12 weeks trial of etanercept (SC) ***OR*** adalimumab (SC) *OR* golimumab (SC) ***OR*** certolizumab pegol (SC) ***OR*** abatacept (SC) ***OR*** tocilizumab ***OR*** tofacitinib (p.o.) or infliximab biosimilars (IV)
• ≥ 2 DMARDs used as monotherapy or as combination therapy (must include MTX unless contraindicated or not tolerated)	VAC, CAF[b]	**VAC:** > 12 weeks trial for each course of therapy **CAF:** > 12 weeks trial of MTX ≥ 20 mg/week (p.o., SC or IM); 10 weeks trial of LEF 20 mg daily; 20 weeks trial of Gold weekly injections; 3 months trial of SSZ ≥ 2gm daily; 3 months trial of azathioprine 2 mg/kg/day to 3 mg/kg/day FOR tocilizumab ONLY: An adequate trial, have documented intolerance to or a contraindication to both DMARDs and anti-TNF agents.
Drug: rituximab		
• Adequate trial of ≥ 1 anti-TNF agent	BC, AB, ON, SK, MB, NB, NS, NL, PE, YT, NIHB, CSC, VAC, CAF	**BC, ON, VAC:** including intolerance/contraindication to anti-TNF agent **AB:** > 12-week trial of one anti-TNF agent

AB = Alberta; BC =British Columbia; CAF = Canadian Armed Forces; CSC = Correctional Services Canada; DMARDs = disease-modifying antirheumatic drugs; HAQ = Health Assessment Questionnaire; HCQ = hydroxychloroquine; IM = intramuscular; LEF= leflunomide; MB = Manitoba; MTX = methotrexate; NB = New Brunswick; NIHB = Non-Insured Health Benefit; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PE = Prince Edward Island; p.o. = orally; SC= subcutaneous; SK = Saskatchewan; SSZ = sulfasalazine; TNF= tumour necrosis factor; VAC = Veterans Affairs Canada; YT = Yukon.

[a] "Refractory" is defined as lack of effect at the recommended doses and for the duration of treatments specified in the table. "Intolerant" is defined as demonstrating serious adverse effects or contraindications to treatments as defined in product monographs.

[b] Patients who do not exhibit a clinical response or experience gastrointestinal intolerance to p.o. MTX may have a trial of parenteral MTX before being accepted as refractory.

[c] Actemra (tocilizumab), Brenzys (etanercept), Cimzia (certolizumab pegol), Erelzi (etanercept), Inflectra (infliximab), Kevzara (sarilumab), Orencia (abatacept), Renflexis (infliximab), Simponi (golimumab), Xeljanz (tofacitinib).

Note: Certolizumab pegol was not eligible for reimbursement by CSC, VAC, CAF. Renflexis, an infliximab biosimilar, was not eligible for reimbursement by Yukon. Sarilumab was not eligible for reimbursement by Nova Scotia, Yukon, and CSC. Truxima, a rituximab biosimilar, was only eligible for reimbursement by Alberta, Ontario, and Yukon. Coverage for etanercept and infliximab biosimilars may be provided in exceptional cases by VAC while the drugs are under review. (Anne Bastarache: personal communication, Jul 2020).

Source: Canadian public drug plan formularies [8,20-36]

c) Use of Concomitant Drugs

Seven out of 14 drug plans stated that concomitant treatment with methotrexate (MTX) or another csDMARD was mandatory for all drugs. Where MTX is contraindicated or not tolerated, Alberta, Saskatchewan, and Ontario permitted the use of specific biologic DMARDs as monotherapy, including: adalimumab (Alberta, Saskatchewan), certolizumab pegol (Saskatchewan), etanercept (Saskatchewan), infliximab (Saskatchewan), golimumab (Saskatchewan), sarilumab (Alberta, Ontario) or tocilizumab (Alberta). Of note, (Alberta, Saskatchewan, New Brunswick, Nova Scotia, Newfoundland and Labrador, and Prince Edward Island explicitly stated that patients were limited to receiving one immunosuppressive biologic drug at a time, regardless of the condition for which it was being prescribed[8,20-36]

Table 6 provides details on use of concomitant drugs. [8,20-36]

Table 6: Concomitant Drugs

Use of concomitant drugs	Public drug plans
Treatment should be combined with methotrexate or other csDMARDS	For ALL drugs: BC, AB, NB, NS, NL, PE, NIHB For specific drugs, ONLY • YT: abatacept, rituximab[a] • SK: adalimumab, certolizumab pegol, etanercept, infliximab, golimumab and rituximab • MB: rituximab[a] • CSC: rituximab[a] • VAC: rituximab[a] • CAF: rituximab[a] • ON: sarilumab
Monotherapy permitted (if MTX is contraindicated and/or for those patients who have experienced serious adverse effects)	For specific drugs, ONLY • AB: adalimumab, sarilumab, and tocilizumab • ON: sarilumab • SK: adalimumab, certolizumab pegol, etanercept, infliximab, and golimumab
Should not be used concomitantly with other biologic DMARDs including anti-TNF agents	For ALL drugs: AB, SK, NB, NS, NL, PE For specific drugs, ONLY • YT: abatacept and sarilumab • MB: rituximab • ON: rituximab • NIHB: rituximab • CSC: rituximab • VAC: rituximab • CAF: rituximab

AB = Alberta; BC = British Columbia; CAF = Canadian Armed Forces; CSC = Correctional Services Canada; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs DMARDs = disease-modifying antirheumatic drugs; MB = Manitoba; MTX = methotrexate; NB = New Brunswick; NIHB = Non-Insured Health Benefit; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PE = Prince Edward Island; SK =Saskatchewan; TNF= tumour necrosis factor; VAC = Veterans Affairs Canada; YT=Yukon.

[a] To be combined with MTX.

Note: Certolizumab pegol was not eligible for reimbursement by CSC, VAC, CAF. Renflexis, an infliximab biosimilar, was not eligible for reimbursement by Yukon. Sarilumab was not eligible for reimbursement by Nova Scotia, Yukon, and CSC. Truxima, a rituximab biosimilar, was only eligible for reimbursement by Alberta, Ontario, and Yukon. Coverage for etanercept and infliximab biosimilars may be provided in exceptional cases by VAC while the drugs are under review (Anne Bastarache: personal communication, Jul 2020)

Source: Canadian public drug plan formularies. [8,20-36]

d) Approved Dose, Duration, and Supply Limits

There were considerable differences across jurisdictions regarding the approved duration of initial therapy and requirements for treatment renewal for the drugs. Alberta had the shortest duration for the initial approval period for all drugs. A six-month or annual initial duration of approval and a renewal at every 12 months thereafter was most reported. However, Ontario allowed a one-year period for first renewal, with subsequent renewals at every five years for all drugs. British Columbia allowed indefinite renewal for most of the drugs. NIHB allowed indefinite approval for the biosimilar version of etanercept and infliximab. Although renewals of rituximab were not possible across drug plans, many drug plans allowed a second course of therapy for this drug. Table 7 provides details about the duration of initial approval and renewal periods. [8,20-36]

Nine out of 14 drug plans required confirmation of a clinical response to the drug for renewal of coverage; in most cases, this was a minimum improvement in the American College of Rheumatology (ACR) criteria — the ACR 20 response. Table 7 provides the specific details relating to renewal criteria for the drugs across all drug plans.[8,20-36]

Dose limits were highly similar between drug plans. Ontario required a planned dosing regimen to be submitted with the request for coverage. Ontario, New Brunswick, Nova Scotia, Newfoundland and Labrador, and Prince Edward Island explicitly stated that dose escalation was not permitted for one or more drugs. Table 9 provides the specific details of the dose limits for the drugs across all drug plans. [8,20-36]

Information on supply limits for one or more drugs was available for British Columbia, Alberta, Saskatchewan, and the Yukon (Table 10).[20,25,26,32]

Table 7: Approval Duration for Initial Therapy and Treatment Renewal

Approval period		Public drug plans	Additional notes
Drugs: abatacept, adalimumab, etanercept			
Initial approval	8 weeks (adalimumab, etanercept) 12 weeks (abatacept)	AB	NIHB: Coverage for etanercept biosimilars will be approved indefinitely.
	6 months	MB, NB, NS, NL, PE, CSC	
	1 year	BC, ON, YT, NIHB	
	3 years	SK	
Renewal	1 year	AB, MB, NB, NS, NL, PE, CSC	
	1 year to indefinite	BC	
	2 years	YT	
	3 years	SK	
	First renewal: 1 year Subsequent renewals: 5 years	ON	

Approval period		Public drug plans	Additional notes
Drug: certolizumab pegol			
Initial approval	12 weeks	AB	
	16 weeks	NL	
	6 months	MB, NB, NS, PE,	
	1 year	BC, ON, YT, NIHB	
	3 years	SK	
Renewal	1 year	AB, MB, NB, NS, NL, PE	
	2 years	YT	
	3 years	SK	
	1 year to indefinite	BC	
	First renewal: 1 year Subsequent renewals: 5 years	ON	
Drug: golimumab			
Initial approval	4 months	AB, CSC	
	6 months	MB, NB, NS, NL, PE	
	1 year	BC, ON, YT, NIHB	
	3 years	SK	
Renewal	1 year	BC, AB, MB, NB, NS, NL, PE, CSC	
	2 years	YT	
	3 years	SK	
	First renewal: 1 year Subsequent renewals: 5 years	ON	
Drug: infliximab			
Initial approval	6 weeks	AB, NIHB	NIHB: Coverage of infliximab biosimilars will be approved indefinitely.
	3 months	CSC	
	6 months	MB, NB, NS, NL, PE	
	1 year	BC, ON, YT	
	3 years	SK	
Renewal	1 year	AB, MB, NB, NS, NL, PE, CSC	
	2 years	YT	
	3 years	SK	
	1 year to indefinite	BC	
	First renewal: 1 year Subsequent renewals: 5 years	ON	
	Indefinitely (only for Inflectra)	NIHB	

Approval period		Public drug plans	Additional notes
Drug: sarilumab			
Initial approval	12 weeks	AB	
	16 weeks	NB, NL	
	6 months	MB, PE	
	1 year	BC, ON, NIHB	
	3 years	SK	
Renewal	1 year	BC, AB, MB, NB, NL, PE	
	3 years	SK	
	First renewal: 1 year Subsequent renewals: 5 years	ON	
Drug: tocilizumab			
Initial approval	16 weeks	AB, SK, NB, NS, NIHB	
	6 months	MB, NL, PE	
	1 year	BC, ON, YT, NIHB (for SC), CSC	
Renewal	1 year	AB, MB, NB, NS, NL, PE, CSC	
	1 year to indefinite	BC	
	2 years	YT	
	3 years	SK	
	First renewal: 1 year Subsequent renewals: 5 years	ON	
Drug: rituximab [re-treatment ONLY]			
Initial approval	1 course	AB, PE, NIHB	One (1) course is two (2) doses of 1,000 mg at 0 weeks and 2 weeks.
	2 courses, minimum of 24 weeks apart	BC	
	3 months or 90 days	CSC, ON, SK	
	6 months	MB,	
Renewal	1 course (cannot be considered prior to 24 weeks elapsing from the initial dose of the previous course of therapy)	AB	
	3 months or 90 days	ON, SK	
	2 courses, to be administered within 1 year; or indefinite coverage (one course every 24 weeks)	BC	
	1 year	MB, CSC	

AB = Alberta; BC = British Columbia; CSC = Correctional Services Canada; MB = Manitoba; NB = New Brunswick; NIHB =Non-Insured Health Benefits; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PE = Prince Edward Island; SK = Saskatchewan; VAC = Veterans Affairs Canada; YT = Yukon.

Note: Certolizumab pegol was not eligible for reimbursement by CSC, VAC, CAF. Renflexis, an infliximab biosimilar, was not eligible for reimbursement by YT. Sarilumab was not eligible for reimbursement by NS, YT, and CSC. Truxima, a rituximab biosimilar, was only eligible for reimbursement by AB, ON and YT.

Source: Canadian public drug plan formularies [8,20-36]

Table 8: Renewal Criteria

Renewal/ re-treatment criteria	Public drug plans	Notes
Drugs: abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, sarilumab, tocilizumab		
Patient must be assessed after initial therapy, and a written confirmation of response is required for renewal	BC, AB, ON, NIHB, NB, NS, NL, PE, CSC	**AB:** Minimum ACR20[a] response *OR* improvement of 1.2 units in the DAS28[b] score *AND* improvement of 0.22 in HAQ score[b] *For etanercept ONLY* — Patient must be assessed after 8 weeks, but no longer than 12 weeks, after the initial coverage period to determine response *For tocilizumab ONLY* — Patient must be assessed after 16 weeks, but no longer than 20 weeks, after treatment to determine response **BC, ON, NL, NIHB:** Minimum ACR20[a] response **AB, ON:** Evidence of maintenance of response required for ongoing (subsequent) coverage; i.e., after the first renewal **NS:** *For tocilizumab IV ONLY* — Minimum 20% improvement in symptoms **NL:** *For certolizumab pegol ONLY* — Response to be assessed after 16 weeks of treatment and therapy continued only if there is clinical response **CSC:** Minimum 20% improvement in symptoms. Number of swollen joints, DAS28 score, HAQ scores, C-reactive protein level, or ACR20[a] response may be used to demonstrate improvement
Drug: rituximab [re-treatment ONLY]		
Re-treatment considered after an interval of at least 6 months since previous course of therapy	AB, ON, NB, NS, NL, PE, YT	**ON, NB, NS, NL, PE, YT:** Re-treatment considered for patients who have achieved a response, followed by loss of effect
Patent must be assessed after initial therapy, and a written confirmation of response is required	BC, AB, ON, NIHB, CSC	**BC:** Minimum ACR20[a] response compared to pre-rituximab status. HAQ must be submitted with the Special Authority request. **AB:** Minimum ACR20[a] response *OR* improvement of 1.2 units in the DAS28[b] score *AND* improvement of 0.22 in HAQ score[b] **ON:** A joint count at 3 to 4 months indicating at least a 20% reduction in swollen joint count and a minimum of improvement in 2 swollen joints **NL:** Minimum ACR20[a] response *OR* improvement of 1.2 units in the DAS28[b] **NIHB and CSC:** An assessment after the 20th to 24th week of therapy and indicating an ACR20[a] response

AB = Alberta; ACR = American College of Rheumatology; BC = British Columbia; CSC = Correctional Services Canada; DAS = disease activity score; HAQ = Health Assessment Questionnaire; NB = New Brunswick; NIHB = Non-Insured Health Benefits; NL =Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PE=Prince Edward Island.

[a] The ACR 20 response is a 20% reduction in tender joint count and swollen joint count, and 20% improvement in at least three (3) of the following: patient's assessment of pain, patient's global assessment, physician's global assessment, patient's assessment of disability, and acute phase reactant measures — that is, erythrocyte sedimentation rate or C-reactive protein.

[b] The DAS28 score is reported to one decimal place. The HAQ score is reported to two decimal places. The initial score for the DAS28 or HAQ score will be rounded to the correct number of decimal places.

Note: Certolizumab pegol was not eligible for reimbursement by CSC, VAC, or CAF. Renflexis, an infliximab biosimilar, was not eligible for reimbursement by Yukon. Sarilumab was not eligible for reimbursement by Nova Scotia, Yukon, and CSC. Truxima, a rituximab biosimilar, was only eligible for reimbursement by Alberta, Ontario, and Yukon.

Source: Canadian public drug plan formularies [8,20-36]

Table 9: Dose Limits

Drug and dose limits	Public drug plans	Additional notes
abatacept SC: 125 mg weekly IV: by weight < 60 kg: 500 mg, 60 kg to 100 kg: 750 mg, > 100 kg: 1,000 mg at 0, 2, and 4 weeks, then every 4 weeks.	BC, AB, ON, NB, NS, NL, PE, NIHB	**ON:** Dose escalation not permitted **ON, NB, NS, NL, PE, NIHB:** loading dose allowed **ON:** max single IV loading dose prior to SC is 750 mg **AB, NB, NS, NL, PE:** max single IV loading dose prior to SC is 1,000 mg **NIHB:** weight-based loading dose
adalimumab 40 mg every 2 weeks	BC, AB, ON, NB, NS, NL, PE, NIHB, CSC	**ON:** The planned dosing regimen for the requested biologic should be provided **NS, NL:** Dose escalation not permitted
Certolizumab pegol 400 mg (2 SC injections of 200 mg each) at 0, 2, and 4 weeks, followed by maintenance 200 mg every other week or 400 mg every 4 weeks	BC, AB, ON, NB, NS, NL, PE, NIHB	**ON:** The planned dosing regimen for the requested biologic should be provided. **NS:** Dose escalation not permitted
etanercept 25 mg, 50 mg — total dose of 50 mg weekly	BC, AB, ON, NB, NS, NL, PE, NIHB, CSC	**ON:** The planned dosing regimen for the requested biologic should be provided. **NS, NL:** Dose escalation not permitted
golimumab 50 mg once a month	BC, AB, ON, NB, NS, NL, PE, NIHB, CSC	**ON:** Planned dosing regimen required **NS, NL:** Dose escalation not permitted **AB:** Should continued coverage criteria be met, coverage will only be granted for 12 doses per a 12-month period
infliximab 3mg/kg/dose at 0, 2, and 6 weeks followed by maintenance therapy of 3mg/kg/dose every 8 weeks	BC, AB, ON, NB, NS, NL, PE, NIHB, CSC	**ON:** Planned dosing regimen required **ON:** Only a maximum of six maintenance doses per year **AB:** For patients with incomplete response, dose up to 10 mg/kg and/or treating as often as every 4 weeks can be considered
sarilumab 200 mg (SC) every 2 week	BC, AB, ON, NB, NL, PE, NIHB,	**BC, ON, NIHB:** ON and NIHB recommend a reduced dose of 150 mg once every two weeks for patients with neutropenia, thrombocytopenia, or with elevated liver enzymes. BC permits reduced dose of 150 mg once every two weeks
tocilizumab IV: 4mg/kg/dose every 4 weeks followed by up to 8mg/kg/dose based on clinical response; up to 800 mg even for individuals > 100 kg SC: < 100 kg — starting dose of 162 mg every other week, followed by an increase to weekly based on clinical response; > 100 kg — 162 mg weekly	BC, AB, ON, NB, NS, NL, PE, NIHB	**ON:** The planned dosing regimen should be provided **NB, NS, NL, PE:** Dose escalation not permitted

Drug and dose limits	Public drug plans	Additional notes
rituximab 2 courses — one course is two doses of 1,000 mg	BC, AB, ON, PE, NL, NIHB	**BC:** Courses must be a minimum of 24 weeks apart **ON:** Two courses will be approved each year (courses should be at least 6 months apart, with second course being given only AFTER loss of effect as per the re-treatment guidelines). Second course is not approved for "maintenance" therapy. For renewal, repeated courses are not approved for maintenance therapy. **AB:** For coverage for an additional two-dose course of therapy, the patient must be assessed by an RA specialist after each course of therapy, between 16 weeks and 24 weeks after receiving the initial dose of each course of therapy, to determine response. Subsequent courses of therapy cannot be considered prior to 24 weeks elapsing from the initial dose of the previous course of therapy

AB = Alberta; BC = British Columbia; CSC = Correctional Services Canada; IV = Intravenous; NB = New Brunswick; NIHB = Non-Insured Health Benefits; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PE = Prince Edward Island; RA = rheumatoid arthritis; SC = subcutaneous.

Note: Certolizumab pegol was not eligible for reimbursement by CSC, Veterans Affairs Canada, or the Canadian Armed Forces. Renflexis, an infliximab biosimilar, was not eligible for reimbursement by Yukon. Sarilumab was not eligible for reimbursement by NS, Yukon, and CSC. Truxima, a rituximab biosimilar, was only eligible for reimbursement by AB, ON, and Yukon.

Source: Canadian public drug plan formularies [8,20-36]

Table 10: Supply Limits

Drugs	Information on supply limits
abatacept	**BC:** 28 days per prescription **AB:** One dose of abatacept IV per prescription. One-month supply of abatacept SC injection per prescription
adalimumab and etanercept	**BC:** 28 days per prescription **AB:** One month per prescription
certolizumab pegol	**BC:** 28 days per prescription **AB:** One month per prescription. **YT**: One dose per month for the first four months
golimumab	**BC:** One month per prescription **AB:** One month per prescription. If continued coverage criteria is met, 12 doses every 12 months **YT:** One dose per month for the first four months
infliximab	**BC:** 56 days[a] per prescription **AB:** One dose per prescription
sarilumab	**BC:** 28 days per prescription **AB:** One month per prescription
tocilizumab	**BC:** 28 days per prescription for tocilizumab IV. Up to 56 days per prescription for tocilizumab SC[b] **AB:** One dose of tocilizumab IV per prescription, and one-month supply of tocilizumab SC per prescription **YT:** One dose per month for the first four months

Drugs	Information on supply limits
rituximab	**BC:** One dose per prescription. **AB:** One dose per prescription

AB = Alberta; BC = British Columbia; SC = subcutaneous; YT = Yukon.

[a] One infusion (dose) usually provides treatment for 56 days or less.

[b] When dosed at 14-day intervals.

Note: Certolizumab pegol was not eligible for reimbursement by Correctional Services Canada (CSC), Veterans Affairs Canada, Canadian Armed Forces. Renflexis, an infliximab biosimilar, was not eligible for reimbursement by YT. Sarilumab was not eligible for reimbursement by Nova Scotia, YT, and CSC. Truxima, a rituximab biosimilar, was only eligible for reimbursement by AB, Ontario, and YT.

Source: Canadian public drug plan formularies [20,25,26,32]

e) Biosimilar Policies

Of the 14 publicly reimbursed drugs for patients with RA, five were biosimilars; there were two etanercept biosimilars (Brenzys, Erelzi), two infliximab biosimilars (Inflectra, Renflexis), and one rituximab biosimilar (Truxima).[8,20-36] Etanercept and infliximab biosimilars were reimbursed by all drug plans except VAC, where coverage is currently determined on a case-by-case basis. Although the rituximab biosimilar was reimbursed by Ontario, Alberta, and Yukon,[8,20-36] its coverage status may changes in the future, as this drug was recently approved by Health Canada (in December 2019); the pan-Canadian Pharmaceutical Alliance negotiation process concluded in February 2020.[18,19]

Findings regarding biosimilar policies revealed that, in most cases, jurisdictions provided coverage for biosimilars for biologic-naive patients only, and that patients who were stable on an originator biologic were permitted to continue their treatment, with an option to switch to a biosimilar. Conversely, biosimilar policies in British Columbia and Alberta mandate that all patients be administered biosimilar versions of etanercept and infliximab if they were treatment-naive, or switch to these biosimilars if they were already taking the originator biologics; the Alberta biosimilar policy will be effective as of January 15, 2021. Although no other drug plans had controlled switching policies that required existing originator biologic users to switch to a biosimilar, Newfoundland and Labrador and Manitoba specified that switching between originator biologics and biosimilar products was not permitted for infliximab and etanercept (Manitoba, only) if a patient was previously trialled on the originator drug or biosimilar and was deemed unresponsive to therapy. Table 11 provides details of biosimilars-related policies.

Manitoba, CSC, and VAC stated that the biosimilar version of etanercept and infliximab was the preferred option for all etanercept-naive and infliximab-naive patients, respectively. However, Manitoba implemented a tiered biologics policy that is applicable to etanercept- and infliximab-naive patients and existing patients who have previously been trialled and deemed unresponsive to biologic therapy. According to this policy, biosimilars fall under Tier 1 and their corresponding originator biologic falls under Tier 2 drugs. Patients must fail to respond to more than two Tier 1 drugs to be eligible for coverage for Tier 2 drugs. [8,20-36]

Table 11: Policies Related to Biosimilars

Relevant biosimilar policy	Public drug plan
Controlled switch policy of **ALL** patients to biosimilar version of etanercept and infliximab	BC,[a] AB[b]
Etanercept-naive patients were approved for coverage of biosimilar versions, only. Patients stable on the reference biologics continue to be approved for the coverage of the originator biologic, with the option to switch to a biosimilar version.	SK, ON, NB, NS, NL, PE, YT, CAF
Infliximab-naive patients were approved for coverage of biosimilar versions. Patients stable on the reference biologics continue to be approved for the coverage of the originator biologic, with the option to switch to a biosimilar version.	ON, NB, NS, NL, PE[c], YT, CAF NIHB
Rituximab-naive patients were approved for coverage of biosimilar versions. Patients stable on the reference biologics continue to be approved for the coverage of the originator biologic, with the option to switch to a biosimilar version.	ON, YT
A biosimilar version of etanercept and infliximab is the preferred option for all etanercept-naive and infliximab-naive patients, respectively.	MB, VAC, CSC

AB = Alberta; BC = British Columbia; CAF = Canadian Armed Forces; CSC = Correctional Services Canada; MB = Manitoba; NB = New Brunswick; NIHB = Non-Insured Health Benefits; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PE = Prince Edward Island; SK = Saskatchewan; VAC = Veterans Affairs Canada; YT = Yukon.

[a] Originator biologics covered for patients who are medically unable to switch products. A new Special Authorization request for exceptional coverage is required, which will be reviewed by Special Authority on a case-by-case basis. This request had to be submitted before November 26, 2019 to ensure continued coverage. [b] Patients who are taking an originator biologic must switch to its biosimilar version by January 15, 2021. Only the biosimilar versions of the drugs will be covered after January 15, 2021.

[c] Remicade (infliximab originator biologics) can be approved for infliximab-naive patients

Note: Renflexis, an infliximab biosimilar, was not eligible for reimbursement by YT. Truxima, a rituximab biosimilar, was only eligible for reimbursement by AB, ON, and YT. Coverage for etanercept and infliximab biosimilars may be provided in exceptional cases by VAC while the drugs are under review. (Anne Bastarache: personal communication, Jul 2020)

Source: Canadian public drug plan formularies [8,20-36]

Limitations

Formulary policies presented in this report are current up to the date of the final search of drug plans' formulary databases and validation by the FWG-HTA members (July 9, 2020). These policies may change in the future, especially regarding the use of biosimilars as more biosimilar version of the originator biologic DMARDs enter the market. These findings are relevant to the Canadian federal (excluding the Royal Canadian Mounted Police health benefits program and the Immigration, Refugees and Citizenship Canada Federal Health Program), provincial (excluding Quebec), and territorial public drug plans, and did not include information about private payers or any international jurisdictions.

There were some gaps in information, as elements of coverage criteria were not available for one or more drugs. These included missing information on: initial and renewal periods (VAC, CAF, CSC, and NIHB), renewal criteria (Saskatchewan, Manitoba, VAC, CAF, and NIHB), or dose limits (Saskatchewan, Manitoba, VAC, CAF, CSC, and Yukon). Information on supply limits for one or more drugs was available for British Columbia, Alberta and Yukon, but not specified for other plans.

Conclusions and Implications for Decision- or Policy-Making

This ES sought to identify and to compare criteria for reimbursing 14 biologic DMARDs used to treat patients with RA across 14 federal, provincial, and territorial public drug programs in Canada. The information in this report was collected from the public domain — namely, the online formulary databases or drug benefit lists — and subsequently validated by drug plan representatives who were members of the CADTH FWG-HTA Committee.

Most jurisdictional drug plans provided coverage for almost all the drugs included in this report; exceptions included certolizumab pegol; sarilumab; and biosimilar versions of infliximab, etanercept, and rituximab, which were not reimbursed by one or more drug plans. Of note, infliximab biosimilars and etanercept biosimilars are under review by VAC, and Truxima, a rituximab biosimilar, is under review by British Columbia and Saskatchewan; therefore, these biosimilars may be reimbursed in the future by these drug plans. Biologic DMARDs and their biosimilars were listed as "restricted benefit" for RA (for example, as Special Authority, EAP, EDS, Limited Use, Limited Coverage Drug, or Prior Authorization benefit listing); that is, drugs that are reimbursed according to specific criteria and often requiring the use of specific authorization forms. Twelve out of 14 drug plans required an "active" approval process to access originator biologics and their biosimilar versions; that is, there is a requirement to submit an application for reimbursement and each request is subject to a medication review at the public drug plan prior to approval for coverage. The use of specific authorization forms and a medication review was not a requirement for drugs covered by CSC or for biosimilars in Ontario; instead, the reimbursement of these drugs follows as "passive" approval process through the use of Limited Use (by Ontario) or Reason for Use (by CSC) codes specified by prescribers in the prescription.

In general, biologic DMARDs were restricted to patients with moderate to severely active RA and had to be prescribed by a rheumatologist. Nine out of 14 drug plans (British Columbia, Alberta, Manitoba, Nova Scotia, New Brunswick, Newfoundland and Labrador, Prince Edward Island, and VAC) had similar prior therapy requirements for all of the drugs except for rituximab, while six plans (Saskatchewan, Ontario, Yukon, NIHB, CSC, and CAF) had discrete prior therapy requirements for abatacept, sarilumab or tocilizumab, in addition to rituximab.

The major difference between the drug plans was in the number of lines of prior therapy with csDMARDs that is required to be completed prior to being able to access a biologic DMARD. For most drugs, all drug plans required failure to respond to at least two or three lines of monotherapy or combination therapy with csDMARDs before being eligible for coverage with biologic DMARDs; except for British Columbia, Ontario, Newfoundland and Labrador, and NIHB, which provided an option to access biologic DMARDs after one line of combination therapy (dual or triple therapy) with csDMARDs. Some drug plans required failure to respond to at least one anti-TNF therapy, in addition to csDMARDs, to be eligible for coverage for tocilizumab (CSC and CAF) and abatacept (YT and NIHB). Prior therapy criteria for rituximab were the same across all drug plans; that is, a failure to respond to an adequate trial of at least one anti-TNF agent, which meant that patients also needed to fulfill the prior therapy requirement for csDMARDs according to the respective drug plans. As such, rituximab, abatacept, tocilizumab, and sarilumab required failure to the greatest number of prior lines of therapy before treatment with a biologic DMARD at one or more drug plans. Since the number of lines of prior therapy that RA patients are required to fail prior to accessing a biologic DMARD may affect the length of time it takes for a patient to ultimately access a biologic DMARD, the high degree of

variability among jurisdictions with respect to this parameter represents a potential area for rationalizing access criteria across jurisdictions to better reflect an optimal approach to RA pharmacotherapy.

In addition to variability in the requirements for prior treatments, there was variation among the drug plans regarding several other access criteria. Half of the drug plans included in this scan mandated concomitant treatment with methotrexate or another csDMARD for all biologic DMARDs and their biosimilars. Many drug plans did not allow concomitant use with other biologic DMARDs, especially for rituximab. There were considerable differences regarding the approved duration of initial therapy and the timing of treatment renewal for the drugs between the drug plans. Eight out of 14 drug plans required confirmation of clinical response to the drug for renewal of coverage; in most cases, this was a minimum improvement of an ACR20 response. Dose limits for each drug were generally similar between all drug plans. Other than British Columbia and Alberta, no other drug plans had switching policies that required existing users of originator biologics to switch to a biosimilar. In most jurisdictions, biologic-naive patients were approved for coverage of biosimilar versions only, and patients stable on an originator biologic drug were permitted to continue their treatment, with option to switch to a biosimilar version.

In summary, the results of this ES have revealed that access criteria for biologic DMARDs for RA are broadly similar in terms of being restricted for use in patients with moderate to severe RA, and after failing other, less costly treatments, such as csDMARDs. However, there is considerable heterogeneity in other criteria related to biologic DMARD reimbursement, including requirements for the number of prior treatments; concomitant use of other treatments; and the duration of approval. Better alignment of criteria for biologic DMARDs for RA among public drug plans could promote the optimal use of public health care resources and equity in care.

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Appendix 1: Detailed Coverage Categories

Generic Name (Brand Name)	BC	AB	SK	MB	ON	NB	NS	NL	PE	YT	NIHB[a]	CSC	VAC	CAF
abatacept (Orencia)	SA/LCD	SA	EDS	EDS	EAP	SA	EDS	SA	SA	EDS	LU/PA	CM	SA	SA
adalimumab (Humira)	SA/LCD	SA	EDS	EDS	EAP	SA	EDS	SA	SA	EDS	LU/PA	CM	SA	SA
certolizumab pegol (Cimzia)	SA/LCD	SA	EDS	EDS	EAP	SA	EDS	SA	SA	EDS	LU/PA	NAB	NAB	NAB
etanercept (Enbrel)	SA/LCD	SA	EDS	EDS	EAP	SA	EDS	SA	SA	EDS	LU/PA	CM	SA	SA
etanercept (Brenzys)[b]	SA/LCD	SA	EDS	EDS	LU	SA	EDS	SA	SA	EDS	LU/PA	CM	UR[c]	SA
etanercept (Erelzi)[b]	SA/LCD	SA	EDS	EDS	LU	SA	EDS	SA	SA	EDS	LU/PA	CM	UR[c]	SA
golimumab (Simponi)	SA/LCD	SA	EDS	EDS	EAP	SA	EDS	SA	SA	EDS	LU/PA	CM	SA	SA
infliximab (Remicade)	SA/LCD	SA	EDS	EDS	EAP	SA	EDS	SA	SA	EDS	LU/PA	CM	SA	SA
infliximab (Inflectra)[b]	SA/LCD	SA	EDS	EDS	LU	SA	EDS	SA	SA	EDS	LU/PA	CM	UR[c]	SA
infliximab (Renflexis)[b]	SA/LCD	SA	EDS	EDS	LU	SA	EDS	SA	SA	NAB	LU/PA	CM	UR[c]	SA
rituximab (Rituxan)	SA/LCD	SA	EDS	EDS	EAP	SA	EDS	SA	SA	EDS	LU/PA	CM	SA	SA
rituximab (Truxima)[b]	UR	SA	UR	NAB	LU	NAB	NAB	NAB	NAB	EDS	NAB	NAB	NAB	NAB
sarilumab (Kevzara)	SA/LCD	SA	EDS	EDS	EAP	SA	NAB	SA	SA	NAB	LU/PA	NAB	SA	SA
tocilizumab (Actemra)	SA/LCD	SA	EDS	EDS	EAP	SA	EDS	SA	SA	EDS	LU/PA	CM	SA	SA

AB = Alberta; BC = British Columbia; CAF = Canadian Armed Forces; CM = benefit with criteria medications; CSC = Correctional Services Canada; EAP = Exceptional Access Program; EDS = Exceptional Drug Status; LCD = Limited Coverage Drug; LU = Limited Use; MB = Manitoba; NAB = not a benefit; NB = New Brunswick; NIHB = Non-Insured Health Benefits; NL = Newfoundland and Labrador; NS = Nova Scotia; ON = Ontario; PA = Prior Authorization; PE = Prince Edward Island; SA = Special Authorization; SK = Saskatchewan; UR = Under Review; VAC=Veterans Affairs Canada; YT=Yukon

[a] Also applicable to Nunavut and the Northwest Territories.

[b] Biosimilar version.

[c] Coverage may be provided in exceptional cases while the drug is under review and case-by-case assessment follows the originator biologic criteria for rheumatoid arthritis. (Anne Bastarache: personal communication, Jul 2020).

Source: Canadian public drug plan formularies. [8,20-36]

Appendix 2: Links to Details of Coverage Categories

Public drug plan	Name of program	Links for further details
British Columbia (BC)	Special Authorization[41]	https://www2.gov.bc.ca/gov/content/health/health-drug-coverage/pharmacare-for-bc-residents/what-we-cover/drug-coverage/drugs-requiring-pre-approval
	Limited Coverage Drug[42]	https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/limited-coverage-drug-program
Alberta (AB)	Special Authorization[43]	https://www.ab.bluecross.ca/dbl/pdfs/dbl_sec1_sa.pdf
Saskatchewan (SK)	Exceptional Drug Status[44]	http://formulary.drugplan.ehealthsask.ca/About
Manitoba (MB)	Exceptional Drug Status[40]	https://www.gov.mb.ca/health/mdbif/docs/edsnotice.pdf
Ontario (ON)	Exceptional Access Program[45]	https://www.ontario.ca/page/applying-exceptional-access-program
	Limited Use[46]	https://www.ontario.ca/page/get-coverage-prescription-drugs#section-5
New Brunswick (NB)	Special Authorization[21]	https://www2.gnb.ca/content/gnb/en/departments/health/MedicarePrescriptionDrugPlan/NBDrugPlan/ForHealthCareProfessionals/NewBrunswickDrugPlansFormulary.html
Nova Scotia (NS)	Exceptional Drug Status[47]	https://novascotia.ca/dhw/pharmacare/exception-status-drugs.asp
Newfoundland and Labrador (NL)	Special Authorization[48]	https://www.health.gov.nl.ca/health/prescription/covered_specialauthdrugs.html
Prince Edward Island (PE)	Special Authorization[29]	https://www.princeedwardisland.ca/sites/default/files/publications/pei_pharmacare_formulary.pdf
Yukon (YT)	Exceptional Drug Status[32]	http://apps.gov.yk.ca/drugs/f?p=161:9000:4123039820786828 (See Preamble)
Non-Insured Health Benefit (NIHB)	Limited Use (LU)/ Prior Authorization[30]	https://www.sac-isc.gc.ca/DAM/DAM-ISC-SAC/DAM-HLTH/STAGING/texte-text/nihb_benefits-services_drugs_dbl-index_1573154657223_eng.pdf
Correctional Services Canada (CSC)	Benefit with Criteria Medication	Link to publicly available source not available. (Alka Bhalla, Correctional Service Canada: personal communication, Jul 2020) CSC National Formulary, April 2020, Health Services, Correctional Services Canada,
Veterans Affairs Canada (VAC)	Special Authorization[49]	https://www.veterans.gc.ca/eng/financial-support/medical-costs/treatment-benefits/poc10/poc10a
Canadian Armed Forces (CAF)	Special Authorization[23]	http://www.cmp-cpm.forces.gc.ca/hs/en/drug-benefit-list/index.asp