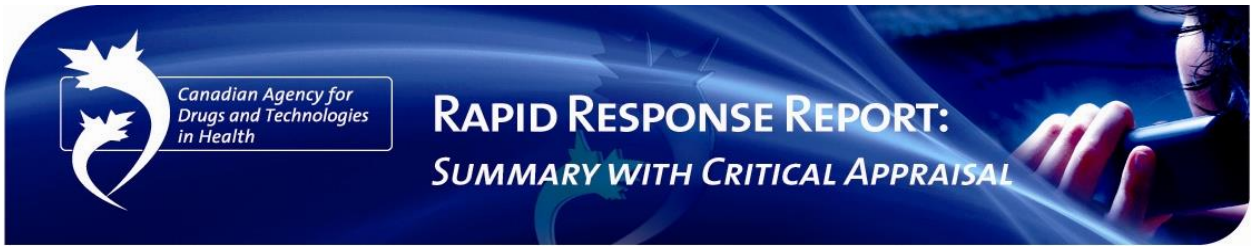

TITLE: Biologic Switching for Patients with Rheumatoid Arthritis: A Review of Clinical Effectiveness, Safety, and Guidelines

DATE: 14 December 2015

CONTEXT AND POLICY ISSUES

Rheumatoid arthritis (RA) is a chronic autoimmune disease, characterized by inflammation, pain, stiffness, and progressive joint destruction.[1] If left untreated, RA can lead to the loss of shape and alignment in the joint, ultimately destroying it.[2] In Canada, about 300,000 individuals have RA.[1]

Earlier and more aggressive treatment strategies with disease-modifying anti-rheumatic drugs (DMARDs) that target specific mechanisms of inflammation have been shown to alter the clinical course of RA and slow or halt radiographic progression.[1,3] DMARDs can be synthetic (i.e., small molecules), suppressing many aspects of the body's immune response at once,[2] or biologic (i.e., products of recombinant DNA technology),[1] targeting specific aspects of the abnormal immune response that happens in RA.[2] The most commonly-prescribed synthetic DMARDs include methotrexate, leflunomide, and sulfasalazine.[1] Biologic DMARDs currently approved for use in Canada include tumor necrosis factor-alpha (TNF-α) inhibitors (i.e., adalimumab, certolizumab pegol, etanercept, infliximab, and golimumab), beta (β)-cell depletors (i.e., rituximab), interleukin-1 inhibitors (i.e., anakinra), interleukin-6 inhibitors (i.e., tocilizumab), and T-cell co-stimulatory inhibitors (i.e., abatacept).[1] A Janus kinase inhibitor known as tofacitinib is a synthetic, small molecule[3,4] that targets cytokine signaling;[3] its synthetic origin but biologic target render it into a unique class of DMARDs.[4] For the purposes of this report, tofacitinib was classified as a biologic.

For patients with RA, it is generally recommended that: 1) methotrexate be part of the first treatment strategy; and 2) in patients responding insufficiently to synthetic DMARDs, biologic DMARDs be commenced, first with a TNF-α inhibitor.[1,4] However, approximately 30% to 40% of patients who start on a TNF-α inhibitor subsequently develop an inadequate response to the drug[5] – defined as moderate-to-high disease activity despite treatment after three months[1,6] or loss of initial response after three months.[6] For patients who fail to respond to an initial TNF-α inhibitor, another TNF-α inhibitor (i.e., within-class switching) or a non-TNF biologic (i.e., out-of-class switching) may be used.[7]

The purpose of this report is to identify and summarize any evidence for clinical effectiveness and safety, as well as evidence-based clinical guidelines, on the practice of switching biologics, both within class and out of class, for adult patients with RA.

RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of switching biologics for adult patients with rheumatoid arthritis (RA)?

2. What are the evidence-based guidelines associated with switching biologics for adult patients with RA?

KEY FINDINGS

Five systematic reviews (SRs) and two randomized controlled trials (RCTs) on adult patients with RA reported significant improvement in various measures of clinical effectiveness, without significant increase in safety issues, associated with switching from one or more tumor necrosis factor-alpha (TNF-α) inhibitors to another biologic, whether a TNF-α inhibitor or non-TNF inhibitor, over placebo or no other treatment. Two SRs reported greater improvement with switching to the non-TNF biologic tocilizumab (i.e., out-of-class switching), compared to another TNF-α inhibitor, golimumab (i.e., within-class switching), while only one SR reported statistically significant greater improvement with switching to the non-TNF biologics abatacept or rituximab compared to golimumab. One RCT reported greater improvement in treatment response with switching to golimumab from etanercept or infliximab, compared to from adalimumab, and also from one previous TNF-α inhibitor, compared to two or three previous TNF-α inhibitors. All intervention and control groups were administered with concurrent synthetic disease-modifying anti-rheumatic drugs (DMARDs). The five SRs were of variable quality, and two RCTs were of poor quality. Recommendations from ten evidence-based guidelines, and the strength of those recommendations, were mixed: three guidelines recommended both within-class and out-of-class switching after failing one TNF-α inhibitor (with moderate to high levels of strength) and only out-of-class switching after failing two TNF-α inhibitors (with a low level of strength); three guidelines recommended switching first to rituximab before switching to other TNF-α inhibitors after failing one or more TNF-α inhibitors (with no level of strength provided); and two guidelines recommended only switching to non-TNF inhibitors after failing one or more TNF-α inhibitors (at low to very-low levels of strength or no level of strength provided). Evidence and recommendations were limited for tofacitinib and lacking on anakinra.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources, including PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, and Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and November 10, 2015.

Selection Criteria and Methods

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

Table 1: Selection Criteria

Population	Adult patients with RA
Intervention	Biologics: • TNF-α inhibitors (i.e., adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) • β-cell depletors (i.e., rituximab) • Interleukin-1 inhibitors (i.e., anakinra) • Interleukin-6 inhibitors (i.e., tocilizumab) • Janus kinase inhibitors (i.e., tofacitinib) • T-cell co-stimulation inhibitors (i.e., abatacept)
Comparator	Biologics (i.e., switching within class and switching out of class)
Outcomes	Q1: Clinical effectiveness and safety Q2: Evidence-based guidelines
Study Designs	Health technology assessments (HTAs), SRs, meta-analyses (MAs), RCTs, and evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, if they were duplicate publications, or if they were published prior to 2010. Primary studies that were reviewed in the included SRs were excluded.

Critical Appraisal of Individual Studies

The included SRs, RCTs, and evidence-based guidelines were critically appraised, using the Assessment of Multiple Systematic Reviews (AMSTAR) tool,[8] Downs and Black instrument,[9] and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument,[10] respectively. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 392 citations were identified in the literature search. Following screening of titles and abstracts, 355 citations were excluded, and 37 potentially relevant reports from the electronic search were retrieved for full-text review. Ten potentially relevant publications were retrieved from the grey literature search. Of these 47 potentially relevant articles, 30 publications were excluded for various reasons, while 17 publications met the inclusion criteria and were included in this report.

The 17 publications comprised five SRs,[7,11-14] two RCTs,[6,15] and eight evidence-based guidelines (with relevant details reported in ten publications).[1,4,16-23] Specifically, two guidelines by the American College of Rheumatology (ACR)[16,17] and Brazilian Society of Rheumatology American College of Rheumatology (BSR)[18,19] are represented by two publications each.

Appendix 1 describes the PRISMA flowchart of the study selection. Additional references of potential interest that did not meet the selection criteria are provided in Appendix 5.

Summary of Study Characteristics

A summary of the characteristics of the included SRs, RCTs, and evidence-based guidelines is presented in Appendix 2.

Clinical effectiveness and safety of switching biologics for adult patients with RA

A total of five SRs[7,11-14] and two RCTs[6,15] provided information on the clinical effectiveness and safety of switching biologics for adult patients with RA.

Study Design

Four SRs[7,11,13,14] included only RCTs, ranging from three to seven primary studies, some of which were included in more than one SR. One SR[12] included RCTs, as well as controlled and uncontrolled observational studies; however, the results of the non-controlled studies are not discussed in this report. Two of the SRs[7,11] conducted indirect pairwise comparisons between biologics, using the results of placebo-controlled trials, considering the lack of head-to-head trials. The five SRs were published in 2014,[7] 2012,[11] 2011,[12] and 2010.[13,14]

Two multi-site, double-blind RCTs were published in 2014.[6,15] In one RCT,[6] due to highly-significant effects of the intervention, study inclusion was terminated early; it was followed by an open-label extension. The other publication[15] presented a post-hoc analysis of an RCT.[24]

Country of Origin

Three SRs were conducted in Korea,[7] the United Kingdom (UK),[12] and Canada.[13] One SR[11] was conducted in collaboration between Austria and the United States (US); and another SR[14] was conducted in collaboration among Austria, Czech Republic, Italy, the Netherlands, Sweden, the UK, and the US.

One RCT[6] was conducted in collaboration between Switzerland and the US; and another RCT[15] was conducted in collaboration among Austria, the Netherlands, and the US.

Patient Population

Five SRs included adult patients with RA who previously had an inadequate response[7,11,12,14] or an exposure[13] to one or more TNF-α inhibitors.

Two RCTs included adult patients with RA who had discontinued one or more TNF-α inhibitors for lack of efficacy,[6,15] intolerance,[6,15] or other reasons (e.g., cost or insurance coverage issues).[15]

Interventions and Comparators

Five SRs[7,11-14] compared switching from one or more TNF-α inhibitors to another biologic, whether a TNF-α inhibitor (i.e., within-class) or non-TNF biologic (i.e., out-of-class), versus switching to placebo,[7,11-13] no other treatment,[12,14] or another biologic.[12] Two SRs[7,11] made indirect pairwise comparisons between biologics, using the results of placebo-controlled trials, considering the lack of head-to-head trials. All intervention and control groups were administered with concurrent synthetic DMARDs.[7,11-14]

Two RCTs[6,15] compared switching from one or more TNF-α inhibitors to another TNF-α inhibitor (i.e., within-class), specifically certolizumab pegol[6] or golimumab,[15] versus switching to placebo. All intervention and control groups were administered with concurrent synthetic DMARDs.[6,15]

Outcomes

Five SRs[7,11-14] reported on the ACR 20/50/70 responses (i.e., measuring 20%, 50%, or 70% improvement in tender and swollen joints and improvement in three of the following five variables: observer evaluation of overall disease activity; patient evaluation of overall disease activity; patient evaluation of pain; a score of physical disability; and improvements in blood acute phase responses[12]). Four SRs[7,12-14] reported on the Health Assessment Questionnaire Disability Index (HAQ-DI) scores (i.e., measuring physical function[7]). Three SRs[12-14] reported on the Sharp-Genant scores[12] or unidentified measures of radiographic progression[13,14] (i.e., measuring joint damage[12]). Two SRs[12,14] reported on disease activity[14] and the Disease Activity Score (DAS) 28 scores[12,14] (i.e., measuring general health and blood acute phase response from counts for tenderness and swelling on 28 joints[12]). One SR[12] reported on the European League Against Rheumatism (EULAR) responses (i.e., measuring patient response[12]), Short Form (SF)-36 mental and physical health scores (i.e., measuring quality of life[12]), and treatment withdrawal rates. Two SRs[11,12] reported on the incidences of adverse events and infections. One SR[12] reported on injection site reactions or infusion reactions.

Two RCTs[6,15] reported on the ACR 20/50/70 responses, DAS 28 scores, HAQ-DI scores, and the incidence of adverse events. One RCT[6] reported on the Clinical Disease Activity Index (CDAI) scores (i.e., measuring disease activity[6]).

Evidence-based guidelines associated with switching biologics for adult patients with RA

Eight evidence-based guidelines[1,4,16-23] provided recommendations on switching biologics for adult patients with RA and were published in 2015,[16,17] 2013,[4,18] 2012,[19,20] 2011,[1,21] and 2010.[22,23]

Country of Origin

One guideline[16,17] was developed in the US by the ACR. One guideline[18,19] was developed in Brazil by the BSR. One guideline[4] was developed in Europe by the European League Against Rheumatoid Arthritis (EULAR). Three guidelines[20,21,23] were developed in the UK by the National Institute for Health and Care Excellence (NICE), as a result of its technology appraisals. One guideline[1] was developed in Canada by the Canadian Rheumatology Association (CRA). One guideline[22] was developed in Spain by the Spanish Society of Rheumatology (SSR).

Patient Population

Seven guidelines were developed for adult patients diagnosed with RA[1,4,16,17,20-23] or suspected of having RA.[1] The BSR guideline[18,19] provided recommendations for patients with RA, without stating applicable age groups.

Interventions and Comparators

The eight guidelines[1,4,16-23] provided recommendations on switching from one or more TNF-α inhibitors to another TNF-α inhibitor (i.e., within-class)[1,4,21-23] or a non-TNF biologic (i.e., out-of-class).[1,4,16-20,22,23]

Outcomes

Five guidelines[1,4,16-19,22] rated the quality of evidence supporting their recommendations on the type of evidence (i.e., SRs, MAs, RCTs, observational studies, or expert opinions); however, only four guidelines[1,4,16,17,22] graded their recommendations with levels of strength.

Summary of Critical Appraisal

A summary of the critical appraisal of the included SRs, RCTs, and evidence-based guidelines is presented in Appendix 3.

Clinical effectiveness and safety of switching biologics for adult patients with RA

Five SRs[7,11-14] were of variable quality. While one SR[12] stated using an "a priori" design, it was not clear whether an "a priori" design was used in the other four SRs.[7,11,13,14] Duplicate study selection and data extraction was conducted in three SRs.[7,12,14] A comprehensive literature search was conducted in three SRs,[12-14] including grey literature,[13] whereas no detailed search strategy was provided in two SRs.[7,11] Four SRs[7,11-13] provided a list of the included studies and their characteristics, but only one SR[12] provided a list of the excluded studies. All five SRs included a limited number of studies, ranging from three to seven primary studies. The scientific quality of the included studies was assessed in all five SRs but not explicitly described in two SRs[7,14] and not used in formulating conclusions in one SR.[7] None of the five SRs assessed the likelihood of publication bias. While two SRs[7,14] declared no conflict of interest, one SR[13] made no statement, and two SRs[11,12] declared previous involvement with pharmaceutical companies[11,12] and technology assessments.[12]

Two RCTs[6,15] were generally of poor quality. Both RCTs described the aim of their studies, interventions, and main outcomes and findings, blinded both study subjects and staff, and used appropriate outcome measures. However, few statistical tests were conducted in both RCTs, which were generally descriptive. It was unclear whether study subjects were representative of the entire population of interest: one RCT[6] did not describe recruitment methods, while the post-hoc analysis only included a subset of the original sample.[15] While one RCT[6] took into account study subjects lost to follow-up, the other RCT[15] did not. It was unclear whether the RCTs[6,15] were adequately powered to detect meaningful differences. One RCT[6] provided sample size calculations but terminated study enrolment early based on the high level of treatment effects, including only 37 study subjects; it was unclear whether the early termination (e.g., stopping rule) had been planned a priori. The post-hoc analysis[15] did not provide sample size calculations of the original RCT.[24]

Evidence-based guidelines associated with switching biologics for adult patients with RA

Eight evidence-based guidelines[1,4,16-23] were of variable quality. While five guidelines[1,4,16-19,22] explicitly stated their scope and purpose, three guidelines[20,21,23] did not. Six guidelines[4,16,17,20,21,23] were developed by individuals from various relevant groups (e.g., clinicians, methodologists, and patients), whereas it was unclear who developed two guidelines.[18,19,22] Four guidelines[1,4,16-19] explicitly stated the methods for formulating recommendations, and four guidelines[1,4,16,17,20] explicitly stated considering benefits, harms, and/or costs in their recommendations. While five guidelines[1,4,16-19,22] appraised the quality of the included evidence and provided graded recommendations, only four guidelines[1,4,16,17,22] graded their recommendations with levels of strength; three guidelines did not provide any appraisals.[20,21,23] Four guidelines[1,4,18,19,22] were not externally reviewed by experts prior to publication. No procedure for updating was described in four guidelines;[4,16-19,22] three guidelines,[1,1,20,23] published in 2011 or 2010, had proposed updates in 2013, but no updates were identified. While three guidelines[20,21,23] declared no conflict of interest, five guidelines[1,4,16-19,22] declared previous or current involvement with entities with commercial interest in RA guidelines.

Summary of Findings

A summary of the findings of the included SRs, RCTs, and evidence-based guidelines is presented in Appendix 4.

What is the clinical effectiveness and safety of switching biologics for adult patients with RA?

ACR 20/50/70 Responses

Five SRs[7,11-14] and two RCTs[6,15] reported that switching from one or more TNF-α inhibitors to another biologic, whether a TNF-α inhibitor (i.e., certolizumab pegol, golimumab, or unspecified TNF-α inhibitors as a class) or non-TNF inhibitor (i.e., abatacept, rituximab, or tocilizumab), provided significant improvement in treatment response over placebo or no other treatment, when taken in combinations with synthetic DMARDs. For example, the odd ratios (ORs), with the 95% confidence intervals (CIs), of achieving the ACR 20 response at 24 weeks, comparing biologics to placebo, fell in the following ranges, presented as the OR (95% CI):

- Between 2.577 (1.518 to 4.496)[7] and 3.325 (1.71 to 6.47)[11] for golimumab
- Between 4.180 (2.55 to 6.85)[11] and 4.226 (2.606 to 7.023)[7] for abatacept
- Between 4.736 (3.10 to 7.25)[11] and 4.822 (3.176 to 7.492)[7] for rituximab
- Between 8.901 (4.86 to 16.31)[11] and 9.060 (5.064 to 17.000)[7] for tocilizumab

Using indirect pairwise comparisons, two SRs[7,11] reported greater improvement in treatment response with switching to tocilizumab compared to another TNF-α inhibitor (i.e., golimumab), but only one SR[11] demonstrated statistically significant differences with switching to abatacept or rituximab compared to golimumab (Appendix 4)

One RCT[15] reported greater improvement in treatment response with switching to golimumab from etanercept or infliximab, compared to from adalimumab, with 46.8%, 50.9%, and 30.3% of patients achieving the ACR 20 response at 24 weeks, respectively. The RCT[15] also reported greater improvement in treatment response with switching to golimumab from one previous TNF-α inhibitor, compared to two or three TNF-α inhibitors, with 44.5%, 36.2%, and 23.5% of

patients achieving the ACR 20 response at 24 weeks, respectively. However, the numbers of patients who had received two (n=47) and three (n=17) prior TNF-α inhibitors were limited. No statistical test results were provided.

HAQ-DI Scores

Four SRs[7,12-14] and two RCTs[6,15] reported that switching from one or more TNF-α inhibitors to another biologic, whether a TNF-α inhibitor (i.e., certolizumab pegol, golimumab, or unspecified TNF-α inhibitors as a class) or non-TNF inhibitor (i.e., abatacept, rituximab, or tocilizumab), provided significant improvement in physical function over placebo or no other treatment, when taken in combinations with synthetic DMARDs. For example, the mean differences (MDs), with the 95% CIs, in reductions in the HAQ-DI scores at 24 weeks, comparing biologics to placebo, were as follows, presented as the MD (95% CI):

- -0.140 (-0.255 to -0.026)[7] for golimumab
- -0.400 (-0.499 to -0.299)[7] for abatacept
- -0.300 (-0.397 to -0.203)[7] for rituximab
- -0.340 (-0.453 to -0.227)[7] for tocilizumab

Using indirect pairwise comparisons, one SR[7] reported greater improvement in physical function with switching to non-TNF biologics (i.e., abatacept, rituximab, or tocilizumab), compared to another TNF-α inhibitor (i.e., golimumab). For example, the MDs, with the 95% CIs, in reductions in the HAQ-DI scores at 24 weeks, comparing biologics to golimumab, were as follows, presented as the MD (95% CI):

- -0.260 (-0.411 to -0.107)[7] for abatacept
- -0.160 (-0.310 to -0.010)[7] for rituximab
- -0.200 (-0.360 to -0.039)[7] for tocilizumab

One RCT[15] reported greater improvement in physical function with switching to golimumab from etanercept or infliximab, compared to from adalimumab, with 53.2%, 56.1%, and 48.5% of patients achieving > 0.25-unit improvement in the HAQ-DI scores at 24 weeks, respectively. The RCT[15] also reported greater improvement in treatment response with switching to golimumab from one previous TNF-α inhibitor, compared to two or three TNF-α inhibitors, with 53.3%, 46.8%, and 41.2% of patients achieving > 0.25-unit improvement in the HAQ-DI scores at 24 weeks, respectively. However, the numbers of patients who had received two (n=47) and three (n=17) prior TNF-α inhibitors were limited. No statistical test results were provided.

Sharp-Genant Scores and Unidentified Measures of Radiographic Progression

Three SRs[12-14] reported that switching from one or more TNF-α inhibitors to a non-TNF inhibitor (i.e., abatacept or rituximab) provided significant improvement in joint damage over placebo or no other treatment, when taken in combinations with synthetic DMARDs. For example, when comparing rituximab versus placebo, changes included an MD of -1.12, with the 95% CI -2.13 to -0.11, in the Sharp-Genant scores at 56 weeks,[12] and an MD of -1.31, with a *p*-value 0.005, in a unidentified measure of radiographic progression at 52 weeks.[13]

Disease Activity and DAS 28 and CDAI Scores

Two SRs[12,14] and two RCTs[6,15] reported that switching from one or more TNF-α inhibitors to another biologic, whether a TNF-α inhibitor (i.e., certolizumab pegol or golimumab) or non-TNF

inhibitor (i.e., abatacept, rituximab, or tocilizumab), provided significant improvement in disease activity over placebo or no other treatment, when taken in combinations with synthetic DMARDs. For example, the risk ratio (RR) for achieving low disease activity for switching to abatacept, rituximab, or tocilizumab, compared to the control at six months, after TNF-α inhibitor failure, was 6.59, with the 95% CI 4.01 to 10.82.[14] The RR for the DAS 28 remission for tocilizumab was 10.02, with the 95% CI 3.20 to 31.42.[14] The CDAI low disease activity (i.e., CDAI < 10) was significantly higher in the patients treated with certolizumab pegol after 12 weeks, compared to the patients treated with placebo (no effect sizes were provided, with a *p*-value = 0.046).[6]

One RCT[15] reported greater improvement in disease activity with switching to golimumab from etanercept or infliximab compared to from adalimumab, with 61.7%, 59.6%, and 48.5% of patients achieving the good or moderate DAS 28 scores at 24 weeks, determined using C reactive protein (CRP). The RCT[15] also reported greater improvement in disease activity with switching to golimumab from one previous TNF-α inhibitor compared to two TNF-α inhibitors, with 58.4% and 51.1% of patients achieving the good or moderate DAS 28 scores at 24 weeks, determined using CRP. However, the numbers of patients who had received two (n=47) prior TNF-α inhibitors were limited. No statistical test results were provided.

EULAR Response

One SR[12] reported that switching from one or more TNF-α inhibitors to a non-TNF inhibitor (i.e., rituximab) provided significant improvement in patient response over placebo or no other treatment, when taken in combinations with synthetic DMARDs. The RR for achieving the good or moderate EULAR response was 2.96, with the 95% CI 2.25 to 3.89.[12]

SF-36 Scores

One SR[12] reported that that switching from one or more TNF-α inhibitors to a non-TNF inhibitor (i.e., abatacept or rituximab), provided significant improvement in quality of life over placebo or no other treatment, when taken in combinations with synthetic DMARDs. The MD between the intervention and control groups in the SF-36 mental and health scores, respectively, was 3.70, with the 95% CI 1.45 to 5.95, and 5.50, with the 95% CI 3.74 to 7.26, for abatacept and 3.07 and 5.16, with the 95% CI not reported, for rituximab.[12]

Incidences of Adverse Events, Infections, and Injection Site or Infusion Reactions

Two SRs[11,12] and two RCTs[6,15] reported that the risk of adverse events[6,11,12,15] or infections[11,12] associated with switching from one or more TNF-α inhibitors to another biologic, whether a TNF-α inhibitor (i.e., certolizumab pegol, golimumab, or unspecified TNF-α inhibitors as a class) or non-TNF inhibitor (i.e., abatacept, rituximab, or tocilizumab), was comparable to placebo or no other treatment, when taken in combinations with synthetic DMARDs. One SR[12] reported no differences in the risk of injection site reactions or infusion reactions for abatacept or rituximab versus placebo.

Using indirect pairwise comparisons, one SR[11] reported significantly fewer adverse events for switching to golimumab compared to abatacept, rituximab, or tocilizumab. The risk differences (RD), comparing biologics to golimumab, were 0.13 for abatacept, 0.18 for rituximab, and 0.18 for tocilizumab, with the 95% CI not reported.[11]

Treatment Withdrawals

One SR[12] reported that switching from one or more TNF-α inhibitors to a non-TNF inhibitor (i.e., abatacept or rituximab) provides significant reduction in treatment withdrawals over placebo or no other treatment, when taken in combinations with synthetic DMARDs. The RR between the intervention and control groups in treatment withdrawals was 0.53, with the 95% CI 0.35 to 0.81, for abatacept and 0.39, with the 95% CI 0.29 to 0.51, for rituximab.[12]

What are the evidence-based guidelines associated with switching biologics for adult patients with RA?

The EULAR,[4] CRA,[1] and SSR[22] guidelines included the following recommendations on switching biologics for adult patients with RA:

- In patients who have failed treatment with one TNF-α inhibitor due to lack of efficacy or toxicity, the following options are recommended:
    - Switch to another TNF-α inhibitor (the EULAR, CRA, and SSR assigned moderate to high levels of strength to this recommendation);[1,4,22]
    - Switch to another biologic with a different mechanism of action (i.e., abatacept, rituximab, or tocilizumab) (the EULAR, CRA, and SSR assigned moderate to high levels of strength to this recommendation);[1,4,22] or
    - Add methotrexate or another synthetic DMARD if the TNF-α inhibitor was used in monotherapy (the SSR provided no grading of this recommendation).[22]
- In patients who have failed treatment with two TNF-α inhibitors, a switch to another biologic with a different mechanism of action (i.e., abatacept, rituximab, or tocilizumab) is recommended (the CRA assigned low strength to this recommendation).[1]
- In the absence of data on therapeutic strategies after failure of abatacept, rituximab, or tocilizumab, the following options can be considered (the CRA assigned very-low strength to these recommendations):
    - Switch to any biologic not previously tried and failed;[1]
    - Add or switch to a synthetic DMARD not previously tried and failed;[1] or
    - Enroll the patient in a clinical trial with a new drug.[1]

The NICE guidelines[20,21,23] recommended switching first to rituximab and then to adalimumab,[23] etanercept,[23] infliximab,[23] abatacept,[23] golimumab,[21] or tocilizumab,[20] in cases of a contraindication or adverse event to rituximab, after the failure of one or more TNF-α inhibitors. No grading of these recommendations was provided.

The ACR[16,17] and BSR[18,19] guidelines recommended only switching to non-TNF inhibitors after the failure of one or more TNF-α inhibitors (i.e., out-of class switching). The ACR assigned low to very-low strength to these recommendations; the BSR provided no grading of these recommendations. The ACR[16,17] and EULAR[4] guidelines recommended switching to abatacept, rituximab, or tocilizumab over tofacitinib since tofacitinib is a newer drug, with limited long-term experience and safety data. The ACR assigned low to very-low strength to this recommendation; the EULAR assigned high strength to this recommendation.

Limitations

A limited number of SRs and RCTs met the inclusion criteria for this report. The SRs included in this report identified a limited number of relevant studies, ranging from three to seven primary studies, none of which were head-to-head RCTs directly comparing one biologic to another

biologic (instead of placebo or no treatment). Therefore, high-quality controlled studies on switching biologics for patients with RA appeared generally lacking.

Only five[1,4,16-19,22] of the eight evidence-based guidelines included in this report appraised the quality of the included evidence, and only four of them[1,4,16,17,22] graded their recommendations with levels of strength. The strength of the recommendations was generally graded as being low, with inconsistencies among the guidelines on some recommendations. Therefore, high-quality recommendations on switching biologics for patients with RA appeared generally lacking.

Across the SRs, RCTs, and evidence-based guidelines included in this report, evidence and recommendations were limited on tofacitinib and lacking on anakinra, as the two drugs are newer than the other drugs included in this report and have limited data.[16,17]

The BSR guideline[18,19] included in this report was developed specifically for the Brazilian population and did not state applicable age groups and may not be directly applicable to Canadian adults.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Five SRs and two RCTs on adult patients with RA reported significant improvement in various measures of clinical effectiveness (i.e., treatment response, physical function, joint damage, disease activity, quality of life, or treatment withdrawals), without significant increase in safety issues (i.e., adverse events, infections, or injection site or infusion reactions), associated with switching from one or more TNF-α inhibitors to another biologic, whether a TNF-α inhibitor (i.e., certolizumab pegol, golimumab, or unspecified TNF-α inhibitors as a class) or non-TNF inhibitor (i.e., abatacept, rituximab, or tocilizumab), over placebo or no other treatment. Two SRs reported greater improvement with switching to the non-TNF biologic tocilizumab (i.e., out-of-class switching), compared to another TNF-α inhibitor, golimumab (i.e., within-class switching), while only one SR reported statistically significant greater improvement with switching to the non-TNF biologics abatacept or rituximab compared to golimumab. One RCT reported greater improvement in treatment response with switching to golimumab from etanercept or infliximab, compared to from adalimumab, and also from one previous TNF-α inhibitor, compared to two or three previous TNF-α inhibitors. All intervention and control groups were administered with concurrent synthetic DMARDs. The five SRs were of variable quality, and two RCTs were of poor quality. Therefore, the evidence presented in this report should be interpreted with caution.

Recommendations from ten evidence-based guidelines, and the strength of those recommendations, were mixed: three guidelines recommended both within-class and out-of-class switching after failing one TNF-α inhibitor (with moderate to high levels of strength) and only out-of-class switching after failing two TNF-α inhibitors (with a low level of strength); three guidelines recommended switching first to rituximab before switching to other TNF-α inhibitors after failing one or more TNF-α inhibitors (with no level of strength provided); and two guidelines recommended only switching to non-TNF inhibitors after failing one or more TNF-α inhibitors (at low to very-low levels of strength or no level of strength provided).

Evidence and recommendations were limited on tofacitinib and lacking on anakinra.

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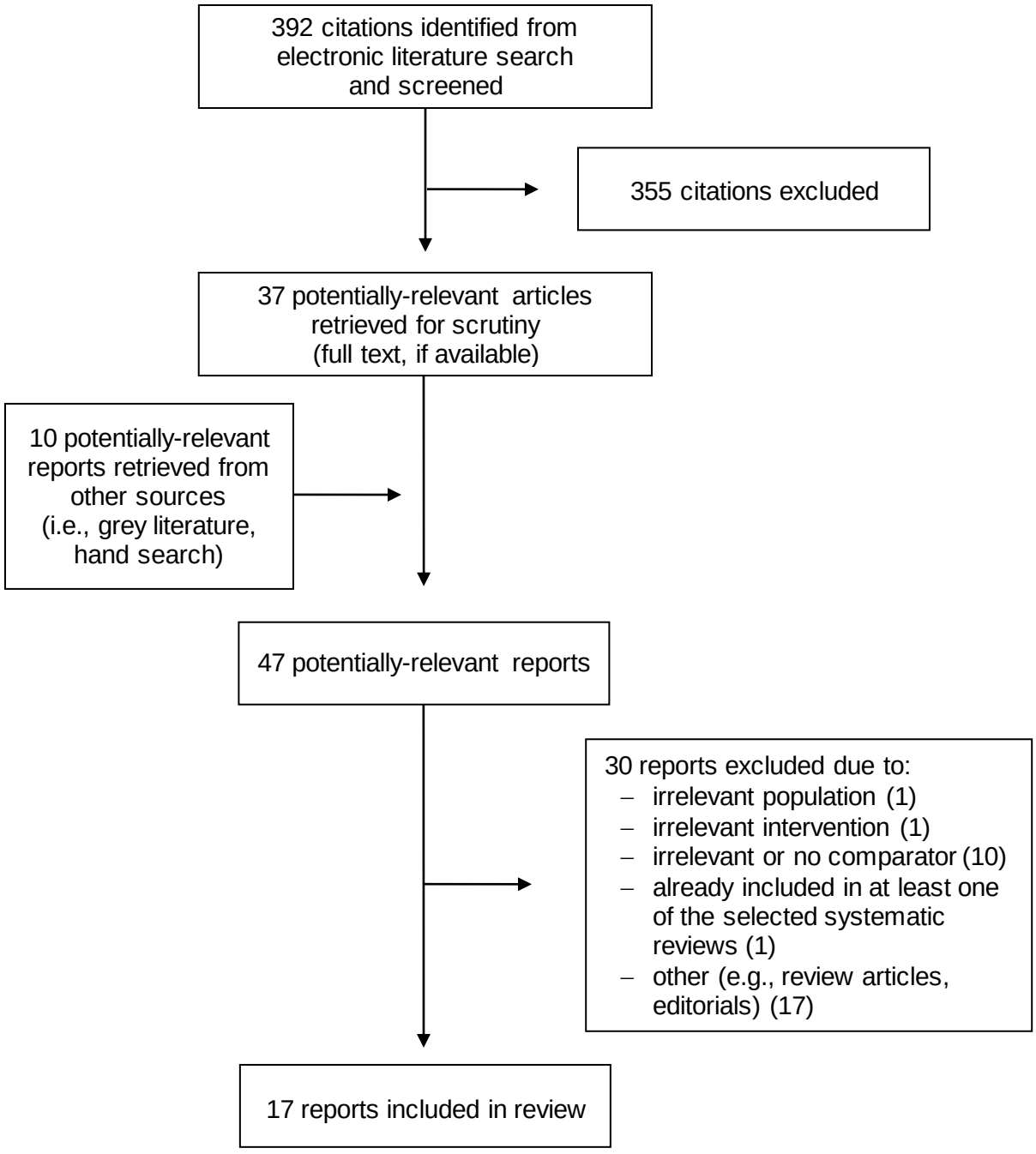
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included SRs

First Author, Publication Year, Country	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Follow-Up Length
Kim[7] 2014 Korea	SR of 6 RCTs, published between 2005 and 2012, including ATTAIN, GO-AFTER, and RADIATE studies Data were analyzed in indirect comparisons, using a Bayesian approach and fixed-effect models.	Adult RA patients, with an inadequate response to TNF-α inhibitors	Another TNF-α inhibitor (i.e., golimumab) or another non-TNF biologic (i.e., abatacept, rituximab, and tocilizumab), in combination with synthetic DMARDs	Placebo, in combination with synthetic DMARDs	Outcomes: ACR 20/50/70 responses and HAQ-DI scores Follow-up length: 6 months
Schoels[11] 2012 Austria and US	SR of 4 RCTs, published between 2005 and 2009, including ATTAIN, GO-AFTER, RADIATE, and REFLEX studies Data were analyzed in indirect comparisons, using random-effect models.	Adult RA patients, with an inadequate response to TNF-α inhibitors	Another biologic (i.e., abatacept, golimumab, rituximab, and tocilizumab), in combination with synthetic DMARDs	Placebo, in combination with synthetic DMARDs	Outcomes: ACR 20/50/70 responses and incidence of adverse events Follow-up length: 24 weeks
Malottki[12] 2011 UK	SR of 3 RCTs and 1 non-randomized controlled cohort study, published between 2005 and 2010, including	Adult RA patients, with an inadequate response to a first TNF-α inhibitor	Abatacept, adalimumab, etanercept, infliximab, and rituximab, with or without supportive care*	Placebo or another biologic,** with or without supportive care,*** or supportive care alone	Outcomes: ACR 20/50/70 responses, DAS 28 scores, EULAR response, HAQ-DI scores, SF-36 scores, Sharp-Genant scores, incidences

Table A1: Characteristics of Included SRs

First Author, Publication Year, Country	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention	Comparator(s)	Clinical Outcomes, Follow-Up Length
	ATTAIN, REFLEX, and SUNRISE studies		*Supportive care included synthetic DMARDS and corticosteroids.	**One of the included studies compared two biologics (i.e., TNF-α inhibitors as a class and rituximab) head-to-head. ***Supportive care included synthetic DMARDS and corticosteroids.	of adverse events, infections, or injection site or infusion reactions, and treatment withdrawals Follow-up length: 24 to >48 weeks
CADTH[13] 2010 Canada	SR of 3 RCTs, published between 2005 and 2009, including ATTAIN, GO-AFTER, and REFLEX studies	Adult RA patients, with exposure to TNF-α inhibitors	Biologics (i.e., abatacept, golimumab, and rituximab), in combination with synthetic DMARDs	Placebo, in combination with synthetic DMARDs	Outcomes: ACR 50 response, HAQ-DI scores, and radiographic progression Follow-up length: 24 to 54 weeks
Nam[14] 2010 Austria, Czech Republic, Italy, the Netherlands, Sweden, UK, and US	SR of seven* RCTs, published between 1998 and 2008, including GO-AFTER study *The exact number was not reported and only described as "several".	Adult RA patients, with an inadequate response to TNF-α inhibitors	Another biologic (i.e., abatacept, golimumab, rituximab, and tocilizumab), in combination with methotrexate	Methotrexate alone	Outcomes: ACR 20 response, disease activity, DAS 28 scores, HAQ-DI scores, and radiographic progression Follow-up length: 6 months

ACR = American College of Rheumatology; CADTH = Canadian Agency for Drugs and Technologies in Health; DAS = disease activity score; DMARD = disease-modifying anti-rheumatic drug; EULAR = European League Against Rheumatism; HAQ-DI = health assessment questionnaire disability index; RA = rheumatoid arthritis; RCT = randomized controlled trial; SF = short form; SR = systematic review; TNF-α = tumor necrosis factor-alpha; UK = United Kingdom; US = United States

Table A2: Characteristics of Included RCTs

First Author, Publication Year, Country	Study Design, Study Name (if reported)	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Follow-Up Length
Schiff[6] 2014 Switzerland and US	Multi-site, double-blind RCT, followed by an open-label extension	37* RA patients,** who had discontinued an initially-effective TNF-α inhibitor, other than certolizumab pegol, for lack of efficacy or intolerance *Due to highly-significant effects of the intervention, study inclusion was terminated after entry of 36.3% of the originally-planned 102 patients. **Eligible patients had RA for > 6 months, with ≥ 6 tender and swollen joints, an elevated C-reactive protein, or a CDAI ≥ 12.	Certolizumab pegol,*** in combination with synthetic DMARDs (n=27) ***400 mg were administered subcutaneously at Weeks 0, 2, and 4, followed by 200 mg every 2 weeks until 12 weeks. The intervention was repeated at 12 weeks for the open-label extension.	Placebo,**** in combination with synthetic DMARDs (n=10) ****After 12 weeks, the intervention was administered for the open-label extension.	Primary outcomes: ACR 20 response Secondary outcomes: ACR 50/70 responses, CDAI scores, DAS 28 scores, HAQ-DI scores, and incidence of adverse events Follow-up length: 12 weeks since treatment start plus 12 weeks for open-label
Smolen[15] 2014 Austria, the Netherlands, and US	Post-hoc analysis of a multi-site, double-blind RCT, GO-AFTER	304 RA patients,* who had received one or more doses of adalimumab, etanercept, or infliximab but discontinued for any reason, including lack of efficacy, intolerance, or other reasons (e.g., cost or insurance coverage issues) *Eligible patients had RA for ≥ 3 months, with ≥ 4 swollen and ≥ 4 tender joints.	Golimumab at low (n=101) or high (n=100) doses,** with methotrexate **50 or 100 mg were administered subcutaneously every 4 weeks. Patients in the low dose group with < 20% improvement in both tender and swollen join counts at Week 16 escaped early to receive 100 mg at Weeks 16 and 20.	Placebo,*** with methotrexate (n=103) ***Patients with < 20% improvement in both tender and swollen join counts at Week 16 escaped early to receive 50 mg at Weeks 16 and 20.	Outcomes: ACR 20/50/70 responses, DAS 28 scores, HAQ-DI scores, incidence of adverse events Follow-up length: 24 weeks since treatment start

ACR = American College of Rheumatology; CDAI = clinical disease activity index; DAS = disease activity score; DMARD = disease-modifying anti-rheumatic drug; HAQ-DI = health assessment questionnaire disability index; RA = rheumatoid arthritis; RCT = randomized controlled trial; TNF-α = tumor necrosis factor-alpha; US = United States

Table A3: Characteristics of Included Evidence-Based Guidelines

Objectives			Methodology			
Intended Users, Target Population, Development Country	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence Collection, Selection, and Synthesis**	**Evidence Quality and Strength**	**Recommendations Development and Evaluation**	**Guideline Validation**
Singh, 2015[16,17] – ACR						
Intended users: clinicians and patients with RA Target population: adult patients with early (<6 months) and established (≥6 months) RA Development country: US	Pharmacological treatment of RA with synthetic and biologic DMARDs, tofacitinib, and glucocorticoids	Therapy strategies after failure of: Single or multiple TNF-α inhibitors Non-TNF biologics	Systematic search of peer-reviewed literature for SRs, RCTs, and observational studies, published in English between 2009 and 2014 Selection of literature using inclusion/exclusion criteria Syntheses by pooling data and analyzing with random-effects models Grading of included recommendations, using the GRADE criteria	Quality of evidence was rated on levels including: High: evidence from MA of RCTs or at least 1 RCT Moderate: evidence from at least 1 well-designed controlled study without randomization or quasi-experimental study or extrapolated from Grade A evidence Low: evidence from well-designed non-experimental descriptive studies or extrapolated from Grade A or B evidence Very low: evidence from expert committee reports or opinions or extrapolated from Grade A, B, or C evidence	Recommendations were developed by multiple teams and panels of clinicians, methodologists, and patients, with consideration of the balance of relative benefits and harms of the treatment options and using a group consensus building technique.	A draft guideline was subject to the ACR review and comment as well as peer-review by two journals.

Table A3: Characteristics of Included Evidence-Based Guidelines

Objectives			Methodology			
Intended Users, Target Population, Development Country	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence Collection, Selection, and Synthesis**	**Evidence Quality and Strength**	**Recommendations Development and Evaluation**	**Guideline Validation**
da Mota, 2013[18,19] – BSR						
Intended users: Brazilian rheumatologists Target population: patients with RA Development country: Brazil	Treatment of RA in Brazil	Therapy strategies after failure one or more biologics	Systematic search of peer-reviewed literature for real clinical scenarios, published up to 2011 Grading of included recommendations on strengths	Quality of evidence was rated on strengths including: A: evidence from most consistent experimental and observational studies B: evidence from less consistent experimental and observational studies C: evidence from case reports (i.e., uncontrolled studies) D: evidence from opinions	Recommendations were developed, with opinions of the BSR RA Committee expert members and using a group consensus building technique.	Not reported (although a draft guideline was likely subject to peer-review by the publishing journal)
Smolen, 2013[4] – EULAR						
Intended users: rheumatologists, patients with RA, hospital managers, national rheumatology societies, social security agencies, regulatory	Management of RA with synthetic and biologic DMARDs	Therapy strategies after failure of one or more biologics	Systematic search of peer-reviewed literature for SRs, MAs, RCTs, and observational studies, published up to 2009 Categorizations of evidence and grading of included recommendations, using the standards of the	Quality of evidence was rated on levels and strengths. Levels included: 1a: evidence from SRs of RCTs 1b: evidence from an individual RCT 2a: evidence from SRs of cohort studies	Recommendations were developed by an international task force and a steering group of clinicians, methodologists, and patients, with considerations for risks, benefits, and costs and using a	Not reported (although a draft guideline was likely subject to peer-review by the publishing journal)

Table A3: Characteristics of Included Evidence-Based Guidelines						
Objectives			Methodology			
Intended Users, Target Population, Development Country	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality and Strength	Recommendations Development and Evaluation	Guideline Validation
authorities, government officials Target population: adult patients with RA Development country: Europe			Oxford Centre for Evidence-Based Medicine	2b: evidence from an individual cohort study 3a: evidence from SRs of case-control studies 3b: evidence from an individual case-control study 4: evidence from case-series studies or poor-quality cohort and case-control studies 5: evidence from expert opinions Strengths included: A: consistent Level 1 studies B: consistent Level 2 or 3 studies or extrapolated from Level 1 studies C: evidence from Level 4 studies or extrapolated from Level 2 or 3 studies D: evidence from Level 5 or troublingly-inconsistent or inconclusive studies of any level	consensus-finding and voting process.	

Table A3: Characteristics of Included Evidence-Based Guidelines

Objectives			Methodology			
Intended Users, Target Population, Development Country	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence Collection, Selection, and Synthesis**	**Evidence Quality and Strength**	**Recommendations Development and Evaluation**	**Guideline Validation**
NICE, 2012[20] – NICE						
Intended users: health care professionals Target population: adult patients with RA Development country: UK	Pharmacological treatment of RA with tocilizumab	Therapy strategies after failure of one or more biologics	Evidence review (no details reported) Consideration of additional data submitted to NICE by drug manufacturers	Not reported	Recommendations were developed by an appraisal committee of clinicians, methodologists, and lay members, with considerations for benefits and costs.	Drug manufacturers, professional, patient, and carer groups, and consultees were invited to comment on the final recommendation.
Bykerk, 2011[1] – CRA						
Intended users: rheumatologists, other primary prescribers of RA drug therapies, and patients with RA Target population: adult patients diagnosed or suspected of having RA Development country: Canada	Pharmacological treatment of RA with synthetic and biologic DMARDs	Therapy strategies after failure of: 1 or 2 TNF-α inhibitors Abatacept, rituximab, or tocilizumab	Systematic search of peer-reviewed and grey literature for international RA guidelines and consensus statements, published in English or French between 2000 and 2010 Selection of literature using inclusion/exclusion criteria Appraisals of included guidelines and consensus statements, using the AGREE checklist	Quality of evidence was rated on levels and strengths. Levels included: I: evidence from MAs or SRs of RCTs or individual RCTs II: evidence from MAs or SRs of observational studies or individual observational studies III: evidence from non-analytic studies (e.g., case reports, case series) IV: evidence from	Recommendations were developed by a working group of clinicians, methodologists, and patients, with considerations for costs and using a modified Delphi consensus technique.	A draft guideline was subject to the CRA review and comment.

Table A3: Characteristics of Included Evidence-Based Guidelines						
Objectives			Methodology			
Intended Users, Target Population, Development Country	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality and Strength	Recommendations Development and Evaluation	Guideline Validation
			Grading of included recommendations on levels and strengths, using a customized SIGN checklist Adaptation of included recommendations for use in the Canadian health care context (i.e., DMARDs currently approved for use in Canada for adult RA patients)	expert opinions Strengths included: A: strong with direct Level I evidence B: moderate with direct Level II or extrapolated Level I evidence C: weak with direct Level III or extrapolated Level II evidence D: consensus with Level IV evidence		
NICE, 2011[21] – NICE						
Intended users: health care professionals Target population: adult patients with RA Development country: UK	Pharmacological treatment of RA with golimumab	Therapy strategies after failure of a TNF-α inhibitor	Systematic search of literature (no details reported) Consideration of additional data submitted to NICE by drug manufacturers	Not reported	Recommendations were developed by an appraisal committee of clinicians, methodologists, and lay members, with considerations for benefits and costs.	Drug manufacturers, professional, patient, and carer groups, and consultees were invited to comment on the final recommendation.
Molina, 2010[22] – SSR						
Intended users: rheumatologists and others	Treatment of RA with biologic therapies	Therapy strategies after failure	Systematic search of peer-reviewed for all new RCTs, published between	Quality of evidence was rated on levels and strengths.	Recommendations were developed by a panel of experts	Not reported (although a draft guideline was

Table A3: Characteristics of Included Evidence-Based Guidelines						
Objectives			Methodology			
Intended Users, Target Population, Development Country	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality and Strength	Recommendations Development and Evaluation	Guideline Validation
involved in treatment of RA Target population: adult patients with RA Development country: Spain		of one or more biologics	2006 and 2008 Categorizations of evidence and grading of included recommendations, using the standards of the Oxford Centre for Evidence-Based Medicine	Levels included: 1a: evidence from SRs of RCTs 1b: evidence from an individual RCT 2a: evidence from SRs of cohort studies 2b: evidence from an individual cohort study 3a: evidence from SRs of case-control studies 3b: evidence from an individual case-control study 4: evidence from case-series studies or poor-quality cohort and case-control studies 5: evidence from expert opinions Strengths included: A: consistent Level 1 studies B: consistent Level 2 or 3 studies or extrapolated from Level 1 studies C: evidence from Level	who had published articles on RA, using a Delphi consensus technique.	likely subject to peer-review by the publishing journal)

Table A3: Characteristics of Included Evidence-Based Guidelines

Objectives			Methodology			
Intended Users, Target Population, Development Country	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence Collection, Selection, and Synthesis**	**Evidence Quality and Strength**	**Recommendations Development and Evaluation**	**Guideline Validation**
				4 studies or extrapolated from Level 2 or 3 studies D: evidence from Level 5 or troublingly-inconsistent or inconclusive studies of any level		
NICE, 2010[23] – NICE						
Intended users: health care professionals Target population: adult patients with RA Development country: UK	Pharmacological treatment of RA with adalimumab, etanercept, infliximab, rituximab, and abatacept	Therapy strategies after failure of one or more TNF-α inhibitors	Systematic search of peer-reviewed literature for primary studies, excluding non-randomized studies with < 20 patients in a treatment arm, published up to 2009 Selection of literature using inclusion/exclusion criteria Consideration of additional data submitted to NICE by drug manufacturers	Not reported	Recommendations were developed by an appraisal committee of clinicians, methodologists, and lay members, with considerations for benefits and costs.	Drug manufacturers and professional, patient, and carer groups were invited to comment on the final recommendations .

ACR = American College of Rheumatology; AGREE = Appraisal of Guidelines Research and Evaluation; BSR = Brazilian Society of Rheumatology; CRA = Canadian Rheumatology Association; DMARD = disease-modifying anti-rheumatic drug; EULAR = European League Against Rheumatism; GRADE = Grading of Recommendations Assessment, Development and Evaluation; MA = meta-analysis; NICE = National Institute for Health and Care Excellence; RA = rheumatoid arthritis; RCT = randomized controlled trial; SIGN = Scottish Intercollegiate Guideline Network; SR = systematic review; SSR = Spanish Society of Rheumatology; TNF-α = tumor necrosis factor-alpha; UK = United Kingdom; US = United States

APPENDIX 3: Critical Appraisal of Included Publications

Table A4: Strengths and Limitations of Included SRs Using AMSTAR[6] link to AMSTAR checklist

Strengths	Limitations
Kim, 2014[7]	
• There was duplicate study selection and data extraction. • A list of the included studies and their characteristics were provided. • The methods used to combine the findings of studies were appropriate. • No conflict of interest was declared.	• It is unclear whether an "a priori" design was used. • It is unclear whether a comprehensive literature search was conducted. Although a flow diagram for the search results was provided, the status or type of publication (e.g., grey literature) was not used as an inclusion criterion, and no detailed search strategy was provided. • A list of the excluded studies was not provided. • A small number of studies – six in total – were included. • Although Cochrane's risk of bias table was completed, the scientific quality of the included studies was not explicitly described or used in formulating conclusions. • The likelihood of publication bias was not assessed.
Schoels, 2012[11]	
• A list of the included studies and their characteristics were provided. • The scientific quality of the included studies was assessed and documented, using the five-point Jadad score, and used appropriately in formulating conclusions.	• It is unclear whether an "a priori" design was used. • There was no duplicate study selection and data extraction. • It is unclear whether a comprehensive literature search was conducted. Although a flow diagram for the search results was provided, the status or type of publication (e.g., grey literature) was not used as an inclusion criterion, and no detailed search strategy was provided. • A list of the excluded studies was not provided. • A small number of studies – four in total – were included. • Although the methods used to combine the findings of studies were appropriate, data were often presented in qualitative terms (e.g., in figures), with no quantitative details. • The likelihood of publication bias was not assessed. • Conflicts of interest were declared and included honoraria or grants received from, as well as board involvement with, pharmaceutical companies.

Table A4: Strengths and Limitations of Included SRs Using AMSTAR[8] link to AMSTAR checklist	
Strengths	**Limitations**
Malottki, 2011[12]	
• An "a priori" design was used. • There was duplicate study selection and data extraction. • A comprehensive literature search was performed. A detailed search strategy and a flow diagram for the search results were provided. • A list of the included and excluded studies was provided. • The characteristics of the included studies were provided. • The scientific quality of the included studies was assessed and documented, using criteria on the methods used for randomization, allocation concealment, and blinding among others, and used appropriately in formulating conclusions. • The methods used to combine the findings of studies were appropriate.	• The status or type of publication (e.g., grey literature) was not used as an inclusion criterion in the search strategy. • A small number of the included studies – four in total – were relevant to this report. • The number of the included studies for each biologic assessed was too small to formally assess the likelihood of publication bias. Therefore, the likelihood of publication bias was not assessed. • Conflicts of interest were declared and included previous involvement in technology assessments and supports received from, as well as board involvement with, pharmaceutical companies.
CADTH, 2010[13]	
• A comprehensive literature search was performed, using the status or type of publication (e.g., grey literature) as an inclusion criterion. A detailed search strategy and a flow diagram for the search results were provided. • A list of the included studies and their characteristics were provided. • The scientific quality of the included studies was assessed and documented, using criteria on the methods used for allocation concealment, blinding, and approach to analysis among others, and used appropriately in formulating conclusions.	• It is unclear whether an "a priori" design was used. • There was no duplicate study selection and data extraction. • A list of the excluded studies was not provided. • No statement was made on any conflict of interest. • Although the possibility of publication bias was noted, the likelihood of publication bias was not assessed.
Nam, 2010[14]	
• There was duplicate study selection and data extraction. • A comprehensive literature search was performed. A detailed search strategy and a flow diagram for the search results were provided. • A list of the included studies and their characteristics were provided. • No conflict of interest was declared.	• It is unclear whether an "a priori" design was used. • The status or type of publication (e.g., grey literature) was not used as an inclusion criterion in the search strategy. • A list of the excluded studies was not provided. • Although the scientific quality of the included studies was documented for the conclusions, it is unclear what approach was used. • The likelihood of publication bias was not assessed.

CADTH = Canadian Agency for Drugs and Technologies in Health; SR = systematic review

Table A5: Strengths and Limitations of Included RCTs Using Downs and Black[9] link to Downs and Black	
Strengths	**Limitations**
Schiff, 2014[6]	
Reporting • The hypothesis/aim/objective of the study was described. • The main outcomes for the study were described. • The characteristics of the study subjects were described. • The interventions were described. • The distributions of principal confounders in each intervention group of study subjects were described. • The main findings were described. • Important adverse events were reported. • The characteristics of study subjects lost to follow-up were described. *External validity* • The trial design was representative of the care setting. *Bias* • Attempts were made to blind the study subjects to the intervention they received and blind the staff measuring the main outcomes. • Results of any post-hoc analyses were described. • The statistical tests used to assess the main outcomes were appropriate. • Compliance with the interventions was reliable. • The main outcome measures were accurate (i.e., valid and reliable). *Confounding* • The study subjects were randomized to intervention groups. • Intervention assignment was concealed from both study subjects and staff until recruitment was complete and irrevocable. • Although no adjustment was made for confounding in the analysis for the main findings, characteristics of the study subjects were similar between the intervention groups. • Losses of study subjects to follow-up were taken into account.	*Reporting* • Actual probability values were not always reported. *External validity* • No details were provided on how the study participants were recruited. Therefore, it is unclear whether the subjects asked to participate or included in the study were representative of the entire population of interest. *Confounding* • No details were provided on how the study participants were randomized other than the 2:1 ratio used. Therefore, it is unclear whether the study subjects in different intervention groups were recruited from the same population over the same period of time. *Power* • Although the study provided sample size calculations, it did not have sufficient power to detect a clinically important effect, due to the early termination of study enrolment based on the high level of treatment effects.

Table A5: Strengths and Limitations of Included RCTs Using Downs and Black[9] link to Downs and Black	
Strengths	**Limitations**
Smolen, 2014[15]	
Reporting • The hypothesis/aim/objective of the study was described. • The main outcomes for the study were described. • The characteristics of the study subjects were described. • The interventions were described. • The distributions of principal confounders in each intervention group of study subjects were described. • The main findings were described. • Estimates of the random variability in the data for the main outcomes were provided. • Important adverse events were reported. • The characteristics of the study subjects lost to follow-up were described. • Actual probability values were reported. *External validity* • The trial design was representative of the care setting. *Bias* • Attempts were made to blind the study subjects to the intervention they received and blind the staff measuring the main outcomes. • Results of post-hoc analyses were described. • Compliance with the interventions was reliable. • The main outcome measures were accurate (i.e., valid and reliable). *Confounding* • The study subjects in different intervention groups were recruited from the same population over the same period of time. • The study subjects were randomized to intervention groups. • Intervention assignment was concealed from both study subjects and staff until recruitment was complete and irrevocable.	*External validity* • It is unclear whether the subjects asked to participate or included in the study were representative of the entire population of interest. *Bias* • For this post-hoc, descriptive analysis of an RCT, no formal statistical tests were conducted. *Confounding* • There was no adjustment for confounding in the analysis for the main findings. • Losses of study subjects to follow-up were not taken into account. *Power* • It is unclear whether the study had sufficient power to detect a clinically important effect.

RCT = randomized controlled trial

Table A6: Strengths and Limitations of Included Evidence-Based Guidelines Using AGREE II[10] link to checklist

Strengths	Limitations
Singh, 2015[16,17] – ACR	
Scope and Purpose • Objectives were described. • Health questions were described. • Target populations were described. *Stakeholder Involvement* • The guideline was developed by individuals from all relevant professional groups, including clinicians, methodologists, and patients. • Target population input was sought. • Targets users were described. *Rigour of Development* • Evidence selection criteria were described. • Appraisals on the quality of included evidence were provided. • Methods for formulating recommendations were described. • Recommendations considered benefits, harms, costs, and quality of evidence, and their links to supporting evidence tables were explicit. • The guideline was peer-reviewed by two journals prior to its publication. *Clarity of Presentation* • Recommendations were unambiguous, specific for different types of conditions or issues, and easily identifiable. *Editorial Independence* • Funding sources were disclosed and included no entities with commercial interest in RA guidelines.	*Rigour of Development* • Although systematic search methods were used, only peer-reviewed literature, and not grey literature, was searched. • A procedure for updating the guideline was not described. *Applicability* • Barriers to implementing the guideline were not described. • Aside from a summary document, the guideline provided no links to tools and resources. • The guideline did not consider resource implications. • The guideline did not provide monitoring or auditing criteria. *Editorial Independence* • Conflicts of interest were disclosed and included research funding and honoraria received from entities with commercial interest in RA guidelines and owning stocks in those entities.
da Mota, 2013[18,19] – BSR	
Scope and Purpose • Objectives were described. • Health questions were described. • Target populations were described. *Stakeholder Involvement* • Targets users were described. *Rigour of Development*	*Stakeholder Involvement* • It is unclear who developed the guideline. • It is unclear whether target population input was sought. *Rigour of Development* • Although systematic search methods were used, only peer-reviewed literature, and not grey literature, was searched. • Evidence selection criteria were not described.

Table A6: Strengths and Limitations of Included Evidence-Based Guidelines Using AGREE II[10] link to checklist	
Strengths	**Limitations**
• Systematic search methods were used. • Appraisals on the quality of included evidence were provided. • Methods for formulating recommendations were described. • The links between recommendations and supporting evidence tables were explicit. *Clarity of Presentation* • Recommendations were unambiguous, specific for different types of conditions or issues, and easily identifiable.	• It is unclear whether the recommendations considered benefits, harms, costs, and quality of evidence, and their links to supporting evidence tables were not explicit. • The guideline was not externally reviewed by experts prior to its publication. • A procedure for updating the guideline was not described. *Applicability* • Facilitators and barriers to implementing the guideline were not described. • The guideline provided no links to tools and resources. • The guideline did not consider resource implications. • The guideline did not provide monitoring or auditing criteria. *Editorial Independence* • Funding sources were not disclosed. • Conflicts of interest were disclosed and included remuneration for consultation and/or speaking engagement and research funding received from entities with commercial interest in RA guidelines.
Smolen, 2013[4] – EULAR	
Scope and Purpose • Objectives were described. • Health questions were described. • Target populations were described. *Stakeholder Involvement* • The guideline was developed by individuals from all relevant professional groups, including clinicians, methodologists, and patients. • Target population input was sought. • Targets users were described. *Rigour of Development* • Appraisals on the quality of included evidence were provided. • Methods for formulating recommendations were described. • Recommendations considered benefits, harms, costs, and quality of evidence, and their links to supporting evidence tables were explicit.	*Rigour of Development* • Although systematic search methods were used, only peer-reviewed literature, and not grey literature, was searched. The description of the search results was not provided. • Evidence selection criteria were not described. • It is unclear whether the guideline was externally reviewed by experts prior to its publication. • A procedure for updating the guideline was not described. *Applicability* • Facilitators and barriers to implementing the guideline were not described. • The guideline did not provide links to tools and resources. • The guideline did not consider resource implications. • The guideline did not provide monitoring or auditing criteria.

Table A6: Strengths and Limitations of Included Evidence-Based Guidelines Using AGREE II[10] link to checklist	
Strengths	**Limitations**
Clarity of Presentation • Recommendations were unambiguous, specific for different types of conditions or issues, and easily identifiable. *Editorial Independence* • Funding sources were disclosed.	*Editorial Independence* • Conflicts of interest were disclosed and included remuneration for consultation and/or speaking engagement and research funding received from entities with commercial interest in RA guidelines.
NICE, 2011[20] – NICE	
Stakeholder Involvement • The guideline was developed by individuals from all relevant professional groups, including clinicians, methodologists, and patients. • Target population input was sought. *Rigour of Development* • Recommendations considered benefits and costs. • The guideline was externally reviewed by experts prior to its publication. *Clarity of Presentation* • Recommendations were unambiguous, specific for different types of conditions or issues, and easily identifiable. *Applicability* • The guideline provided links to tools and resources, including a summary document. • The guideline considered resource implications. *Editorial Independence* • Anyone with a conflict of interest was excluded from participating in the appraisal.	*Scope and Purpose* • Objectives, health questions, and target populations were not explicitly described. *Stakeholder Involvement* • Targets users were not explicitly described. *Development* • Although systematic search methods were reported to have been used, no details on the methods were provided. • Evidence selection criteria were not described. • Appraisals on the quality of included evidence were not provided. • Methods for formulating recommendations were not described. • It was not clear whether recommendations considered quality of evidence, and their links to supporting evidence tables were not explicit. • Although a procedure for updating the guideline in 2013 was described, no update was identified. *Applicability* • Facilitators and barriers to implementing the guideline were not described. • The guideline did not provide monitoring or auditing criteria. *Editorial Independence* • Funding sources were not disclosed.
Bykerk, 2011[1] – CRA	
Scope and Purpose • Objectives were described. • Health questions were described. • Target populations were described.	*Rigour of Development* • A procedure for updating the guideline after a two-year period was described, but no update was available. • The guideline was not externally reviewed by experts prior to its publication.

Table A6: Strengths and Limitations of Included Evidence-Based Guidelines Using AGREE II[10] link to checklist	
Strengths	**Limitations**
Stakeholder Involvement • The guideline was developed by individuals from all relevant professional groups, including clinicians, methodologists, and patients. • Target population input was sought. • Targets users were described. *Rigour of Development* • Systematic search methods were used. • Evidence selection criteria were described. • Appraisals on the quality of included evidence were provided. • Methods for formulating recommendations were described. • Recommendations considered costs, and their links to supporting evidence tables were explicit. *Clarity of Presentation* • Recommendations were unambiguous, specific for different types of conditions or issues, and easily identifiable. *Applicability* • Barriers to implementing the guideline were described, if identified. *Editorial Independence* • Funding sources were disclosed and included no entities with commercial interest in RA guidelines.	*Applicability* • Aside from a summary document, the guideline provided no links to tools and resources. • The guideline did not consider resource implications. • The guideline did not provide monitoring or auditing criteria. *Editorial Independence* • Conflicts of interest were disclosed and included research funding and honoraria received from entities with commercial interest in RA guidelines.
NICE, 2011[21] – NICE	
Stakeholder Involvement • The guideline was developed by individuals from all relevant professional groups, including clinicians, methodologists, and patients. • Target population input was sought. *Rigour of Development* • Recommendations considered benefits and costs. • The guideline was externally reviewed by experts prior to its publication. *Clarity of Presentation* • Recommendations were unambiguous, specific for different types of conditions or issues, and easily identifiable.	*Scope and Purpose* • Objectives, health questions, and target populations were not explicitly described. *Stakeholder Involvement* • Targets users were not explicitly described. *Development* • Although systematic search methods were reported to have been used, no details on the methods were provided. • Evidence selection criteria were not described. • Appraisals on the quality of included evidence were not provided. • Methods for formulating recommendations were not described.

Table A6: Strengths and Limitations of Included Evidence-Based Guidelines Using AGREE II[10] link to checklist	
Strengths	**Limitations**
Applicability • The guideline provided links to tools and resources, including a summary document. • The guideline considered resource implications. *Editorial Independence* • Anyone with a conflict of interest was excluded from participating in the appraisal.	• It was not clear whether recommendations considered quality of evidence, and their links to supporting evidence tables were not explicit. • Although a procedure for updating the guideline in 2013 was described, no update was identified. *Applicability* • Facilitators and barriers to implementing the guideline were not described. • The guideline did not provide monitoring or auditing criteria. *Editorial Independence* • Funding sources were not disclosed.
Molina, 2010[22] – SSR	
Scope and Purpose • Objectives were described. • Health questions were described. • Target populations were described. *Stakeholder Involvement* • Targets users were described. *Rigour of Development* • Appraisals on the quality of included evidence were provided. • Methods for formulating recommendations were described. • The links between recommendations and supporting evidence were explicit. *Clarity of Presentation* • Recommendations were unambiguous and specific for different types of conditions or issues. *Editorial Independence* • Funding sources were disclosed.	*Stakeholder Involvement* • It is unclear who developed the guideline. • It is unclear whether target population input was sought. *Rigour of Development* • Although systematic search methods were used, only peer-reviewed literature, and not grey literature, was searched. The description of the search results was not provided. • Evidence selection criteria were not described. • It is unclear whether recommendations considered benefits, harms, costs. • It is unclear whether the guideline was externally reviewed by experts prior to its publication. • A procedure for updating the guideline was not described. *Clarity of Presentation* • Recommendations were not easily identifiable. *Applicability* • Facilitators and barriers to implementing the guideline were not described. • The guideline did not provide links to tools and resources. • The guideline did not consider resource implications. • The guideline did not provide monitoring or auditing criteria.

Table A6: Strengths and Limitations of Included Evidence-Based Guidelines Using AGREE II[10] link to checklist	
Strengths	**Limitations**
	Editorial Independence • Conflicts of interest were disclosed and included research funding received from entities with commercial interest in RA guidelines.
NICE, 2010[23] – NICE	
Stakeholder Involvement • The guideline was developed by individuals from all relevant professional groups, including clinicians, methodologists, and patients. • Target population input was sought. *Rigour of Development* • Systematic search methods were used. • Recommendations considered benefits and costs. • The guideline was externally reviewed by experts prior to its publication. *Clarity of Presentation* • Recommendations were unambiguous, specific for different types of conditions or issues, and easily identifiable. *Applicability* • The guideline provided links to tools and resources, including a summary document. • The guideline considered resource implications. *Editorial Independence* • Anyone with a conflict of interest was excluded from participating in the appraisal.	*Scope and Purpose* • Objectives, health questions, and target populations were not explicitly described. *Stakeholder Involvement* • Targets users were not explicitly described. *Rigour of Development* • Evidence selection criteria were not described. • Appraisals on the quality of included evidence were not provided. • Methods for formulating recommendations were not described. • It was not clear whether recommendations considered quality of evidence, and their links to supporting evidence tables were not explicit. • Although a procedure for updating the guideline in 2013 was described, no update was identified. *Applicability* • Facilitators and barriers to implementing the guideline were not described. • The guideline did not provide monitoring or auditing criteria. *Editorial Independence* • Funding sources were not disclosed.

ACR = American College of Rheumatology; AGREE = Appraisal of Guidelines for Research and Evaluation; BSR = Brazilian Society of Rheumatology; CRA = Canadian Rheumatology Association; EULAR = European League Against Rheumatism; NICE = National Institute for Health and Care Excellence; RA = rheumatoid arthritis; SSR = Spanish Society of Rheumatology

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A7: Summary of Findings of Included SRs

Main Study Findings	Author's Conclusions
Kim, 2014[7]	

ACR 20/50/70 Responses
• Direct comparisons showed that compared to placebo, biologics were associated with higher ACR 20/50/70 response rates in adult RA patients who had an inadequate response to TNF-α inhibitors.
  ○ The OR for ACR 20 was:
  ▪ 2.577 for golimumab, with the 95% CI 1.518 to 4.496
  ▪ 4.226 for abatacept, with the 95% CI 2.606 to 7.023
  ▪ 4.822 for rituximab, with the 95% CI 3.176 to 7.492
  ▪ 9.060 for tocilizumab, with the 95% CI 5.064 to 17.000
  ○ The OR for ACR 50 was:
  ▪ 4.254 for golimumab, with the 95% CI 1.947 to 10.550
  ▪ 6.866 for abatacept, with the 95% CI 2.900 to 20.870
  ▪ 7.231 for rituximab, with the 95% CI 3.812 to 15.490
  ▪ 10.83 for tocilizumab, with the 95% CI 4.731 to 29.690
  ○ The OR for ACR 70 was:
  ▪ 4.211 for golimumab, with the 95% CI 1.605 to 13.460
  ▪ 8.574 for abatacept, with the 95% CI 2.312 to 56.850
  ▪ 16.220 for rituximab, with the 95% CI 4.575 to 121.800
  ▪ 12.900 for tocilizumab, with the 95% CI 3.474 to 86.120
• Indirect pairwise comparisons showed that compared to golimumab, tocilizumab was associated with higher ACR 20
  ▪ 3.52 for tocilizumab, with the 95% CI 1.567 to 7.946
• ACR 20/50/70 response rates did not significantly differ for all other indirect pairwise comparisons between golimumab and non-TNF biologics
 	
HAQ-DI Scores
• Direct comparisons showed that compared to placebo, biologics were associated with higher HAQ-DI score change in adult RA patients who had an inadequate response to TNF-α inhibitors. The MDs were:
  ○ -0.140 for golimumab, with the 95% CI -0.255 to -0.026
  ○ -0.400 for abatacept, with the 95% CI -0.499 to -0.299
  ○ -0.300 for rituximab, with the 95% CI -0.397 to -0.203
  ○ -0.340 for tocilizumab, with the 95% CI -0.453 to -0.227
• Indirect pairwise comparisons showed that compared to golimumab, non-TNF biologics were associated with
	• Switching to a non-TNF biologic was more effective than switching to another TNF-α inhibitor in adult RA patients who previously had an inadequate response to TNF-α inhibitors.

Table A7: Summary of Findings of Included SRs	
Main Study Findings	**Author's Conclusions**
higher HAQ-DI score change in adult RA patients who had an inadequate response to TNF-α inhibitors. The MDs were: ○ -0.260 for abatacept, with the 95% CI -0.411 to -0.107 ○ -0.160 for rituximab, with the 95% CI -0.310 to -0.010 ○ -0.200 for tocilizumab, with the 95% CI -0.360 to -0.039	
Schoels, 2012[11]	
ACR 20/50/70 Responses • Direct comparisons showed that compared to placebo, biologics were associated with higher ACR 20/50/70 response rates in adult RA patients who had an inadequate response to TNF-α inhibitors. ○ The OR for ACR 20 was: ▪ 3.325 for golimumab, with the 95% CI 1.71 to 6.47 ▪ 4.180 for abatacept, with the 95% CI 2.55 to 6.85 ▪ 4.736 for rituximab, with the 95% CI 3.10 to 7.25 ▪ 8.901 for tocilizumab, with the 95% CI 4.86 to 16.31 ○ The OR for ACR 50 was: ▪ 5.541 for golimumab, with the 95% CI 2.01 to 15.27 ▪ 6.393 for abatacept, with the 95% CI 2.51 to 16.30 ▪ 7.027 for rituximab, with the 95% CI 3.55 to 13.93 ▪ 10.240 for tocilizumab, with the 95% CI 4.19 to 25.01 ○ The OR for ACR 70 was: ▪ 4.051 for golimumab, with the 95% CI 1.29 to 12.75 ▪ 7.404 for abatacept, with the 95% CI 1.73 to 31.70 ▪ 13.500 for rituximab, with the 95% CI 3.22 to 56.56 ▪ 10.75 for tocilizumab, with the 95% CI 2.47 to 46.80 • Indirect pairwise comparisons showed that compared to golimumab, non-TNF biologics were associated with higher ACR 20 response rates in adult RA patients who had an inadequate response to TNF-α inhibitors. There was no significant efficacy difference in ACR 50 or ACR 70 response rates. ○ The OR for ACR 20 was: ▪ 0.58 for golimumab compared to abatacept, with the 95% CI 0.36 to 0.92 ▪ 0.56 for golimumab compared to rituximab, with the 95% CI 0.36 to 0.89 ▪ 0.59 for golimumab compared to tocilizumab, with the 95% CI 0.36 to 0.96 • ACR 20/50/70 response rates did not significantly differ among patients with one, two, or three previous treatments with TNF-α inhibitors. Incidences of Adverse Events and Infections • The risk of adverse events, serious adverse events, and serious infections from golimumab, abatacept, rituximab,	• In adult RA patients who were refractory to one or more TNF-α inhibitors, new biologics provide significant improvement with good safety. • Indirect comparisons show that all biologics have similar effects.

Table A7: Summary of Findings of Included SRs	
Main Study Findings	**Author's Conclusions**
and tocilizumab versus placebo was non-significant. Indirect pairwise comparisons showed that compared to abatacept, rituximab, or tocilizumab, golimumab had significantly fewer adverse events. The RD was: ○ 0.13 for golimumab compared to abatacept, with the 95% CI not reported ○ 0.18 for golimumab compared to rituximab, with the 95% CI not reported ○ 0.18 for golimumab compared to tocilizumab, with the 95% CI not reported	
Malottki, 2011[12]	
• One cohort study compared patients who started a new TNF-α inhibitor (i.e., "switchers") to patients who did not start any other biologic (i.e., stoppers) after discontinuing a first TNF-α inhibitor and reported significantly greater improvement in the HAQ-DI score in the switchers compared to the stoppers (adjusted MD -0.11, with the 95% CI -0.18 to -0.04). • One RCT compared patients receiving rituximab versus placebo after an inadequate response or intolerance to one or more TNF-α inhibitors and reported, in the rituximab arm compared to the placebo arm, at 24 weeks, unless otherwise indicated: ○ Fewer treatment withdrawals (RR 0.39, with the 95% CI 0.29 to 0.51); ○ Higher ACR 20 (RR 2.85, with the 95% CI 2.08 to 3.91), ACR 50 (RR 5.40, with the 95% CI 2.87 to 10.16), and ACR 70 (RR 12.14, with the 95% CI 2.96 to 49.86) response rates; ○ Higher EULAR response rates (RR 2.96, with the 95% CI 2.25 to 3.89 for good or moderate response; RR 7.59, with the 95% CI 2.77 to 20.77 for good response); ○ Smaller DAS 28 scores (mean score -1.40, with the 95% CI -1.67 to -1.13), as well as greater reductions in the DAS 28 scores (MD -1.50, with the 95% CI -1.74 to -1.26); ○ Greater reductions in the HAQ-DI scores (MD -0.30, with the 95% CI -0.40 to -0.20); ○ Smaller changes in the Sharp-Genant total scores (MD -1.12, with the 95% CI -2.13 to -0.11 at 56 weeks); and ○ Greater improvement in the SF-36 mental (MD 3.07, with the 95% CI not reported) and physical health scores (MD 5.16, with the 95% CI not reported). No significant differences were reported in the incidence of serious adverse events, infections or serious infections, or injection site reactions or infusion reactions. • One RCT compared patients receiving abatacept versus placebo after an inadequate response to one or two TNF-α inhibitors and reported, in the abatacept arm compared to the placebo arm, at six months: ○ Fewer treatment withdrawals (RR 0.53, with the 95% CI 0.35 to 0.81); ○ Higher ACR 20 (RR 2.56, with the 95% CI 1.77 to 3.69), ACR 50 (RR 5.36, with the 95% CI 2.19 to 13.10), and ACR 70 (RR 6.70, with the 95% CI 1.62 to 27.8) response rates: ○ Greater reductions in the DAS 28 scores (MD -1.27, with the 95% CI -1.62 to -0.93); ○ Greater reductions in the HAQ-DI scores (MD -0.34, with the 95% CI not reported); and ○ Greater improvement in the SF-36 mental (MD 3.70, with the 95% CI 1.45 to 5.95) and physical (MD 5.50,	• Evidence from RCTs suggests that abatacept and rituximab are clinically more effective than placebo or supportive care.

Table A7: Summary of Findings of Included SRs	
Main Study Findings	**Author's Conclusions**
with the 95% CI 3.74 to 7.26) health scores. No significant differences were reported in the incidence of serious adverse events, infections or serious infections, or injection site reactions or infusion reactions. • One prospective cohort study, comparing rituximab to TNF-α inhibitors in patients with an inadequate response to one or more TNF-α inhibitors, reported no significant differences in change in the DAS scores or in the incidence of injection site reactions or infusion reactions.	
CADTH, 2010[13]	
ACR 50 Response • In three RCTs comparing abatacept, golimumab, and rituximab to placebo in adult RA patients with previous exposure to TNF-α inhibitors, ACR 50 response rates in the control group ranged from 4% (versus 20% for abatacept) to 7% (versus 16% for golimumab). The magnitude of the point estimates for ACR 50 response rates were similar in the abatacept (OR 6.53, with the 95% CI 2.54 to 16.77) and rituximab (OR 7.01, with the 95% CI 3.53 to 13.91) placebo-controlled trials but lower for the golimumab placebo-controlled trial (OR 2.83, with the 95% CI 1.31 to 6.12). However, consideration should be given to the overlap in CIs. HAQ-DI Scores • All three RCTs reported statistically significant improvements in the HAQ-DI scores, favouring the biologic agent over placebo. However, improvements were considered clinically relevant only for abatacept (MD -0.30 reported by 47.3% versus 23.3%, with a *p*-value < 0.001) and rituximab (MD -0.30, with the 95% CI -0.40 to -0.20) and not for golimumab (MD -0.14, with the 95% CI not reported but reported to be statistically significant). Radiographic Progression • One RCT reported statistically significant differences in radiographic progression between rituximab and placebo at 52 weeks, with significantly lower radiographic progression for rituximab versus placebo (score 1.00 versus 2.31, with a *p*-value = 0.005).	• The trial evidence was limited by the following factors: lack of head-to-head trials, the small number of trials conducted in patients failing TNF-α inhibitors, a less severe patient population evaluated in the golimumab trial, and limitations of data from trial subgroups.
Nam, 2010[14]	
ACR 20 Response • In several RCTs evaluating biologics after TNF-α inhibitor failure, abatacept, golimumab, rituximab, and tocilizumab have all shown efficacy. The RR for the ACR 20 response at six months, when comparing the addition of any of the four biologics to an existing synthetic DMARD versus continuing a synthetic DMARD alone (i.e., "control"), was 2.78, with 95% CI 2.28 to 3.38. Disease Activity and DAS 28 Scores • The RR for achieving low disease activity for abatacept, rituximab, and tocilizumab compared to the control at six	• Abatacept, golimumab, rituximab, and tocilizumab have demonstrated efficacy compared to the control in the TNF-α inhibitor-resistant

Table A7: Summary of Findings of Included SRs	
Main Study Findings	**Author's Conclusions**
months was 6.59, with 95% CI 4.01 to 10.82. The RR for the DAS 28 remission for tocilizumab was 10.02, with 95% CI 3.20 to 31.42. HAQ-DI Scores • Improvement in the HAQ-DI scores at six months was higher with abatacept, golimumab, rituximab, and tocilizumab compared to the control (no effect sizes or statistical tests were provided). Radiographic Progression • Six-month radiographic progression was lower with rituximab compared to the control (no effect sizes or statistical tests were provided).	patients (level of evidence 1B). • The decision on which agent to switch to after the initial TNF-α inhibitor failure remains unclear, with no head-to-head comparisons undertaken to date.

ACR = American College of Rheumatology; CADTH = Canadian Agency for Drugs and Technologies in Health; CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; EULAR = European League Against Rheumatism; HAQ-DI = health assessment questionnaire disability index; MD = mean difference; OR = odds ratio; RA = rheumatoid arthritis; RCT = randomized controlled trial; RD = risk difference; RR = risk ratio; SF = short form; SR = systematic review; TNF-α = tumor necrosis factor-alpha

Table A8: Summary of Findings of Included RCTs	
Main Study Findings	**Author's Conclusions**
Schiff, 2014[b]	
ACR 20/50/70 Responses • Among RA patients who had discontinued an initially-effective TNF-α inhibitor, the ACR 20 response was observed in a significantly higher proportion of the patients treated with certolizumab pegol, whereas no patients treated with placebo achieved the ACR 20 response (61.5% versus 0%, with a *p*-value < 0.005). The ACR 50 and ACR 70 responses were markedly higher after 12 weeks in the patients treated with certolizumab pegol, compared to patients treated with placebo (no effect sizes or statistical tests were provided). • During the 12 weeks of the open-label extension, the group of patients who switched from placebo to certolizumab pegol demonstrated significant improvement in the ACR 20, ACR 50, and ACR 70 responses (no effect sizes or statistical tests were provided). DAS 28 and CDAI Scores • Among RA patients who had discontinued an initially-effective TNF-α inhibitor, the DAS 28 scores, CDAI low disease activity (i.e., CDAI < 10), and CDAI decrease > 13.9 (as an additional post-hoc analysis) were significantly higher in the patients treated with certolizumab pegol after 12 weeks, compared to the patients treated with placebo (no effect sizes were provided, with a *p*-value = 0.046). • During the 12 weeks of the open-label extension, the group of patients who switched from placebo to certolizumab pegol demonstrated significant improvement in the DAS 28 and CDAI scores (no effect sizes or statistical tests were provided). HAQ-DI Scores • Among RA patients who had discontinued an initially-effective TNF-α inhibitor, the percentage of patients with a decrease in the HAQ-DI scores of ≥ 0.3 was significantly higher in the patients treated with certolizumab pegol (n=18), compared to the patients treated with placebo (n=2) (66.7% versus 20%, with a *p*-value = 0.046). • During the 12 weeks of the open-label extension, the HAQ-DI score improvement was also observed in the group of patients who switched from placebo to certolizumab pegol (no effect sizes or statistical tests were provided). Incidence of Adverse Events • Among RA patients who had discontinued an initially-effective TNF-α inhibitor, treatment-emergent adverse events occurred in 59.3% and 40.0% of patients in the certolizumab pegol and placebo groups, respectively. The treatment-emergent adverse events in both treatment groups were mild (43.8% certolizumab pegol; 75.0% placebo) or moderate (56.3% certolizumab pegol; 25.0% placebo), as no severe events occurred. No statistical test results were provided.	• This study supports the use of certolizumab pegol in RA patients who had discontinued an initially-effective TNF-α inhibitor, other than certolizumab pegol, for lack of efficacy or intolerance.

Table A8: Summary of Findings of Included RCTs	
Main Study Findings	**Author's Conclusions**
Smolen, 2014[15]	
ACR 20/50/70 Responses • Among patients with RA who were previously treated with a TNF-α inhibitor, 40.8% of the patients treated with golimumab and 14.6% of the patients treated with placebo achieved the ACR 20 response at Week 24. The ACR 50 and ACR 70 response rates were also higher among patients who received golimumab (20.9% and 11.4%, respectively) than among those who received placebo (3.9% and 2.9%, respectively). No statistical test results were provided. • Among patients receiving golimumab, 137 had previously received only one TNF-α inhibitor (adalimumab, n=33; etanercept, n=47; infliximab, n=57). The proportion of patients who achieved the ACR 20 and ACR 50 responses, respectively, at Week 24 was 30.3% and 15.2% among those who had been treated only with adalimumab, 46.8% and 25.5% among those who had been treated only with etanercept, and 50.9% and 22.8% among those who had been treated only with infliximab. No ACR 70 response was reported. No statistical test results were provided. • Among patients receiving golimumab, 137, 47, and 17 had previously received one, two, or three TNF-α inhibitors, respectively. The proportion of patients who achieved the ACR 20 and ACR 50 responses, respectively, at Week 24 was 44.5% and 21.9% among those who had been treated with one TNF-α inhibitor, 36.2% and 23.4% among those treated with two, and 23.5% and 5.9% among those treated with three. No ACR 70 response was reported. Therefore, improvement in clinical signs and symptoms and in physical function appeared to be more robust among patients who previously had received fewer TNF-α inhibitors. However, the numbers of patients who had received two (n=47) and three (n=17) prior TNF-α inhibitors were limited. No statistical test results were provided. DAS 28 Scores • Among patients with RA who were previously treated with a TNF-α inhibitor, 56.7% and 57.7% of the patients treated with golimumab and 23.3% and 26.2% of the patients treated with placebo achieved good or moderate DAS 28 scores at Week 24, determined using CRP and ESR, respectively. No statistical test results were provided. • Among patients receiving golimumab, 137 had previously received only one TNF-α inhibitor (adalimumab, n=33; etanercept, n=47; infliximab, n=57). The proportion of patients who achieved the good or moderate DAS 28 scores at Week 24, determined using CRP and ESR, respectively, was 39.4% and 39.4% among those who had been treated only with adalimumab, 61.7% and 59.6% among those who had been treated only with etanercept, and 66.7% and 71.9% among those who had been treated only with infliximab. No statistical test results were provided. • Among patients receiving golimumab, 137, 47, and 17 had previously received one, two, or three TNF-α inhibitors, respectively. The proportion of patients who achieved the good or moderate DAS 28 scores at Week 24, determined using CRP and ESR, respectively, at Week 24 was 58.4% and 59.9% among those who had	• Patients with RA previously treated with one or more TNF-α inhibitors had clinically-relevant improvement with golimumab and methotrexate. This improvement appeared somewhat enhanced among those who received only etanercept or infliximab as their prior TNF-α inhibitor. • Safety with golimumab and methotrexate treatment appeared similar across patients, regardless of TNF-α inhibitor(s) previously used.

Table A8: Summary of Findings of Included RCTs	
Main Study Findings	**Author's Conclusions**
been treated with one TNF-α inhibitor, 51.1% and 51.1% among those treated with two, and 58.8% and 58.5% among those treated with three. Therefore, improvement in clinical signs and symptoms and in physical function appeared to be more robust among patients who previously had received fewer TNF-α inhibitors. However, the numbers of patients who had received two (n=47) and three (n=17) prior TNF-α inhibitors were limited. No statistical test results were provided. HAQ-DI Scores • Among patients with RA who were previously treated with a TNF-α inhibitor, 50.7% of the patients treated with golimumab and 34.0% of the patients treated with placebo achieved ≥ 0.25-unit improvement in the HAQ-DI scores at Week 24. No statistical test results were provided. • Among patients receiving golimumab, 137 had previously received only one TNF-α inhibitor (adalimumab, n=33; etanercept, n=47; infliximab, n=57). The proportion of patients who achieved ≥ 0.25-unit improvement in the HAQ-DI scores at Week 24 was 48.5% among those who had been treated only with adalimumab, 53.2% among those who had been treated only with etanercept, and 56.1% among those who had been treated only with infliximab. No statistical test results were provided. • Among patients receiving golimumab, 137, 47, and 17 had previously received one, two, or three TNF-α inhibitors, respectively. The proportion of patients who achieved ≥ 0.25-unit improvement in the HAQ-DI scores at Week 24 was 53.3% among those who had been treated with one TNF-α inhibitor, 46.8% among those treated with two, and 41.2% among those treated with three. Therefore, improvement in clinical signs and symptoms and in physical function appeared to be more robust among patients who previously had received fewer TNF-α inhibitors. However, the numbers of patients who had received two (n=47) and three (n=17) prior TNF-α inhibitors were limited. No statistical test results were provided. Incidence of Adverse Events • The overall proportions of patients developing adverse events were similar among those treated with either golimumab or placebo, when grouped by number of prior TNF-α inhibitors received, specific prior TNF-α inhibitor received, or reason for discontinuation of that previous agent.	

ACR = American College of Rheumatology; CDAI = clinical disease activity index; CRP = C reactive protein; DAS = disease activity score; ESR = erythrocyte sedimentation rate; HAQ-DI = health assessment questionnaire disability index; RA = rheumatoid arthritis; RCT = randomized controlled trial; RD = risk difference; TNF-α = tumor necrosis factor-alpha

Table A9: Summary of Findings of Included Evidence-Based Guidelines
Relevant Recommendations
Singh, 2015[16,17] – ACR

• If disease activity remains moderate or high, despite use of a single TNF-α inhibitor:
  ○ Use a non-TNF biologic over another TNF-α inhibitor (Grade: Low to Very low); or
  ○ Use a non-TNF biologic over tofacitinib. (Grade: Very low)
• If disease activity remains moderate or high despite use of a single non-TNF biologic, use another non-TNF biologic over tofacitinib. (Grade: Very low)
• If disease activity remains moderate or high despite use of multiple (>2) sequential TNF-α inhibitors, first use a non-TNF biologic over another TNF-α inhibitor or tofacitinib. (Grade: Very low)
• If disease activity remains moderate or high despite use of multiple TNF-α inhibitors, use tofacitinib if use of a non-TNF biologic is not an option. (Grade: Low)

da Mota, 2013[18,19] – BSR
• In RA patients with an inadequate response to methotrexate or other synthetic DMARDs and TNF-α inhibitor therapy, the use of rituximab, primarily in combination with methotrexate, improved clinical, radiological, and functional progress, while increasing the risk of adverse events. • Tocilizumab treatment of RA patients, especially those with an inadequate responses to methotrexate, when combined with methotrexate or synthetic DMARDs or as a monotherapy, produces effective clinical, functional, radiological, and remission responses. Tocilizumab is also effective in patients who are non-responsive to TNF-α inhibitors. There may be an increased risk of adverse events. • In RA patients who are non-responsive to methotrexate or TNF-α inhibitor therapy, the use of abatacept led to increased clinical responses, remission, and functional responses over 6-12 months, and these rates were maintained over a 24-month period. However, there may be an increased risk of adverse events. • There are no direct comparisons that enable an accurate estimate of the differences in benefits between the various biologics. • The choice of the employed treatment sequence remains at the discretion of the physician, depending on the particularities of each case. A minimum of three months and a maximum of six months of clinical evaluation are recommended before proceeding to a change in regimen (e.g., switching between biologics).
Smolen, 2013[4] – EULAR
• If a first biologic has failed, patients should be treated with another biologic. If a first TNF-α inhibitor has failed, patients may receive another TNF-α inhibitor or a biologic with another mode of action. (Level: 1a; Grade: A) • Tofacitinib may be considered after biologic treatment has failed. (Level: 1b; Grade: A) • TNF-α inhibitors (i.e., adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, and biosimilars), abatacept, tocilizumab, and, under certain circumstances, rituximab are essentially considered to have similar efficacy and safety. If the first biologic fails, any other biologic may be used. • Tofacitinib, a targeted synthetic DMARD, is recommended, where licensed, after use of at least one biologic.
NICE, 2011[20] – NICE
• Tocilizumab, in combination with methotrexate, is recommended as an option for the treatment of RA in adults if: ○ The disease has responded inadequately to synthetic DMARDs and a TNF-α inhibitor;

Table A9: Summary of Findings of Included Evidence-Based Guidelines
Relevant Recommendations
○ The person cannot receive rituximab because of a contraindication to rituximab or because rituximab is withdrawn because of an adverse event; and ○ Tocilizumab is used as described in the 2010 NICE technical appraisal guidance.[23]
Bykerk, 2011[1] – CRA
• In patients who have failed treatment with one TNF-α inhibitor due to lack of efficacy or toxicity, the following options are recommended (Level: I, II; Strength: B): ○ Switch to another TNF-α inhibitor (Level: I, II); ○ Switch to another biologic with a different mechanism of action (i.e., abatacept, rituximab, or tocilizumab) (Level: I); or ○ Add methotrexate or another synthetic DMARD if the TNF-α inhibitor was used in monotherapy. (Level: II) • In patients who have failed treatment with two TNF-α inhibitors, a switch to another biologic with a different mechanism of action (i.e., abatacept, rituximab, or tocilizumab) is recommended. (Level: II/IV; Strength: C) • In the absence of data on therapeutic strategies after failure of abatacept, rituximab, or tocilizumab, the following options can be considered (Level: IV; Strength: D): ○ Switch to any biologic not previously tried and failed; ○ Add or switch to a synthetic DMARD not previously tried and failed; or ○ Enroll the patient in a clinical trial with a new drug.
NICE, 2011[21] – NICE
• Golimumab, in combination with methotrexate, is recommended as an option for the treatment of RA in adults whose RA has responded inadequately to other DMARDs, including a TNF-α inhibitor, if it is used as described in the 2010 NICE technical appraisal guidance.[23]
Molina, 2010[22] – SSR
• If the TNF-α inhibitor is being employed as monotherapy, the possibility of adding methotrexate, with a rapid dose increase to the treatment, must be evaluated before switching to another biologic. • If the TNF-α inhibitor is being used in combination with methotrexate, and therapeutic response is not achieved, the following options may be considered, in no particular order of preference: ○ If the patient is being treated with infliximab, the dose may be increased or the administration interval may be shortened (Level: 4; Strength: C). ○ Switch to another TNF-α inhibitor. (Level: 2b; Strength: B) ○ Change the therapeutic target and switch to abatacept, rituximab, or tocilizumab. (Level: 2b; Strength: B) ○ If the patient was in treatment with tocilizumab as a first-line agent, no information is available in order to emit a specific recommendation, although cumulative experience with biologics does not suggest that a different pattern than that seen with other TNF-α inhibitors will be observed. (Level: 5; Strength: D).
NICE, 2010[23] – NICE
• Rituximab, in combination with methotrexate, is recommended as an option for the treatment of adults with severe RA who have had an inadequate response to, or intolerance of, other DMARDs, including at least one TNF-α inhibitor. Treatment with rituximab should be given no more frequently than every six months.

Table A9: Summary of Findings of Included Evidence-Based Guidelines
Relevant Recommendations
• Adalimumab, etanercept, infliximab, and abatacept, each in combination with methotrexate, are recommended as treatment options only for adults with severe RA who: o Have had an inadequate response to, or intolerance of, other DMARDs, including at least one TNF-α inhibitor; and o Cannot receive rituximab because they have a contraindication to rituximab or when rituximab is withdrawn because of an adverse event. • Adalimumab monotherapy and etanercept monotherapy are recommended as treatment options for adults with severe RA who: o Have had an inadequate response to, or intolerance of, other DMARDs, including at least one TNF-α inhibitor; and o Cannot receive rituximab because they have a contraindication to methotrexate or when methotrexate is withdrawn because of an adverse event.

ACR = American College of Rheumatology; BSR = Brazilian Society of Rheumatology; CRA = Canadian Rheumatology Association; DMARD = disease-modifying anti-rheumatic drug; EULAR = European League Against Rheumatism; NICE = National Institute for Health and Care Excellence; RA = rheumatoid arthritis; SSR = Spanish Society of Rheumatology; TNF-α = tumor necrosis factor-alpha

APPENDIX 5: Additional References of Potential Interest

No methods for recommendation development were reported in the following guidelines or consensus statements.

Fonseca JE, Bernardes M, Canhao H, Santos MJ, Quintal A, Malcata A, et al. Portuguese guidelines for the use of biological agents in rheumatoid arthritis – October 2011 update. Acta Reumatol Port [Internet]. 2011 Oct [cited 2015 Nov 17];36(4):385-8. Available from: http://www.actareumatologica.pt/oldsite/conteudo/pdfs/ARP_2011_5__10_-_PC_-_PTGuidelines_ARP2011-115.pdf

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