Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

TITLE: **Switching from Innovator to Biosimilar (Subsequent Entry) Infliximab: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines**

DATE: 26 February 2015

CONTEXT AND POLICY ISSUES

Infliximab (INX) is a chimeric murine monoclonal antibody that acts against tumour necrosis factor alpha (TNF-alpha).[1] TNF inhibition with biologic agents, including INX, play a major role in contemporary management of autoimmune diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), plaque psoriasis and inflammatory bowel disease (IBD) including ulcerative colitis (UC) and Crohn's disease (CD).[2-4] INX has been available since the late 1990s and is indicated for the treatment of CD, PsA, RA, AS, plaque psoriasis and UC.[4,5] Despite almost 20 years of experience using INX in clinical practice, concerns remain regarding harms associated with infection, specifically tuberculosis (TB) and fungal infections, and potential for increased risk of developing a malignancy.[4] Immunogenicity and the development of anti-drug antibodies (ADA) are also cited as concerns in the literature with respect to their impact on long-term efficacy of INX.[6,7]

As patents expire on innovator products, there is increasing interest in developing biosimilar products globally. The term biosimilar has been defined by the World Health Organization as a biotherapeutic product that is similar in efficacy, safety and quality to the reference product.[4] In the fall of 2013, the European Medicines Agency (EMA) approved a biosimilar formulation of INX, known as CT-P13, which is marketed under the trade names Remsima[8,9] and Inflectra.[10] Within this report the term biosimilar INX is used synonymously with subsequent entry INX, CT-P13, Remsima or Inflectra.[10] Biological products are large molecules manufactured using recombinant DNA technology, through a process that is unique to the manufacturer. As a result, there is variability in manufacturing processes across manufacturers, leading to some concerns regarding adequate duplication of the process to ensure similar safety and efficacy of a biosimilar agent.[6,11] For this reason, biosimilar agents are not considered generic versions of the innovator and are considered under a unique regulatory framework at both the EMA and Health Canada.[6,12]

The EMA approved biosimilar INX for all therapeutic areas which innovator INX is indicated including RA, CD, UC, AS, PsA and plaque psoriasis.[8] Approval was based on the outcomes of a Phase III Randomized Controlled Trial (RCT) comparing CT-P13 with INX in patients with RA and a Phase I RCT comparing CT-P13 with INX in patients with AS.[10,13,14] According to the EMA, CT-P13 demonstrated comparable efficacy and safety compared to innovator INX.[10] In the fall of 2014, Health Canada approved both Remsima and Inflectra for treatment of active RA (in combination with methotrexate), for treatment of AS in patients who have failed conventional treatment, and for treatment of PsA and plaque psoriasis.[15-17] Approval was based on the same two trials in patients with RA and AS that provided the basis of approval by the EMA.[13-16] According to Health Canada's guidance of submission of subsequent entry biologics, if the manufacturer is able to demonstrate sufficient similarity with the reference product and that no differences in product quality exist that may affect the safety or efficacy of the biosimilar product,

extrapolation may be made to other indications for which the innovator is approved.[12,15,16] It is important to note that Health Canada does not consider biosimilar INX to be interchangeable with innovator INX.[7] Presently, the Canadian Rheumatology Association and the Canadian Association of Gastroenterology recommend against interchanging or substituting innovator and biosimilar agents in clinical practice.[2,18]

The availability of biosimilar INX has been postulated to offer cost savings compared to innovator INX, which could lead to patients being switched between products.[19] The purpose of this report is to summarize the comparative clinical and cost effectiveness of switching from innovator to biosimilar INX compared to continued use of innovator INX over a broad range of indications.

RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of switching from innovator infliximab to subsequent entry infliximab for patients with rheumatoid arthritis?

2. What is the clinical effectiveness and safety of switching from innovator infliximab to subsequent entry infliximab for patients with ankylosing sponsylitis?

3. What is the clinical effectiveness and safety of switching from innovator infliximab to subsequent entry infliximab for patients with plaque psoriasis?

4. What is the clinical effectiveness and safety of switching from innovator infliximab to subsequent entry infliximab for patients with Crohn's Disease?

5. What is the clinical effectiveness and safety of switching from innovator infliximab to subsequent entry infliximab for patients with ulcerative colitis?

6. What is the clinical effectiveness and safety of switching from innovator infliximab to subsequent entry infliximab for patients with psoriatic arthritis?

7. What is the cost-effectiveness of switching from innovator infliximab to subsequent entry infliximab?

8. What are the evidence-based guidelines regarding switching from innovator infliximab to subsequent entry infliximab?

KEY FINDINGS

Limited evidence from conference abstracts of open-label extension studies suggests that switching from innovator infliximab to subsequent entry (biosimilar) infliximab is associated with similar clinical efficacy in patients with rheumatoid arthritis or ankylosing spondylitis. Clinical safety and development of antidrug antibodies appeared similar in patients with rheumatoid arthritis who switched from innovator to biosimilar infliximab compared to patients who continued on biosimilar infliximab. In patients with ankylosing spondylitis, there were numerically more patients who experienced a treatment emergent adverse effect, infection or developed antidrug antibodies in the group who switched from innovator to biosimilar infliximab.

One retrospective cohort study, published as a conference abstract, evaluated switching from innovator to biosimlar infliximab in patients with inflammatory bowel disease. Based on small sample size, no conclusions regarding the clinical safety or effectiveness can be drawn from the study findings.

No clinical evidence addressing switching between innovator and biosimilar infliximab in patients with psoriasis or psoriatic arthritis was identified.

A budget impact analysis conducted in Eastern Europe found that availability of biosimilar infliximab represents an opportunity for cost savings over strict innovator infliximab use when switching is allowed or when switching was disallowed but new patients could receive biosimilar infliximab.

Evidence based guidance was limited to a systematic review of international position papers which recommended switching be allowed after 6 month use of the innovator product based on the decision of the physician with consent of the patient. The authors caution that switching should be done for economic reasons only. The evidence supporting these recommendations is unclear.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including Medline, Embase, PubMed, The Cochrane Library (2015, Issue 01), University of York Centre for Reviews and Dissemination (CRD) databases, 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 January 28, 2015.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to the selection criteria in table 1.

Table 1: Selection Criteria

Population	Patients with RA, AS, PsA, plaque psoriasis, CD, and UC being treated with innovator INX (Remicade)
Intervention	Switching to biosimilar INX (may be called Inflectra, Remsima, CT-P13)
Comparator	Continuous innovator INX use
Outcomes	Clinical effectiveness, safety, cost-effectiveness, evidence-based guidelines
Study Designs	Health Technology Assessment / Systematic review / Meta-analysis Evidence-based Guidelines

	Randomized controlled trials Non-randomized studies Economic evaluations Conference abstracts

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications, or were published prior to 2010. Articles were also excluded if they were reported as part of an included HTA or systematic review. Abstracts were excluded if they were subsequently published and available in full text format.

Critical Appraisal of Individual Studies

Critical appraisal of a study was conducted based on an assessment tool appropriate for the particular study design. Based on the systematic review methodology used by the authors of the position statement, the AMSTAR checklist[20] was used to critically appraise the position statement. The Drummond Checklist was used to appraise the economic study.[21]

For critical appraisal, a numeric score was not calculated. Instead, the strengths and limitations of the study were described.

A formal quality assessment of conference abstracts was not conducted since they provide limited information for appraisal. The quality of these studies is discussed in the limitations section.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 153 articles were identified from the literature search and 14 articles from the grey literature search for a total of 167 articles; after screening of titles and abstracts, 53 were selected for full-text screening. Five of the references screened met the inclusion criteria.

Three conference abstracts were identified that addressed switching from innovator INX to biosimilar INX in patients with RA[22], AS[23] and IBD.[24] One economic evaluation was identified which addressed switching in patients with RA.[25] There was one position paper that was based on a systematic review methodology and addressed switching from innovator to biosimilar INX in patients with rheumatic diseases.[11] There were no studies identified which addressed clinical effectiveness or safety in patients with plaque psoriasis or psoriatic arthritis.

Appendix 1 describes the PRISMA flowchart of the included studies in the report.

Summary of Study Characteristics

Characteristics of the included conference abstracts, economic study and position statement are summarized below and details are provided in Appendix 2, 3 and 4.

Conference Abstracts

Three conference abstracts that addressed switching between innovator INX and biosimilar INX were identified.[22-24] Yoo and colleagues[22] presented in 2013 an open label extension study of the PLANETRA randomized controlled trial (RCT).[5] The PLANETRA trial was a Phase III RCT that randomized patients with active RA from 19 countries (including Europe, Asia, Latin America and the Middle East) to receive 3mg/kg of INX or CT-P13 at 0, 2 and 6 weeks, then every 8 weeks, both combined with methotrexate and folic acid and followed them over 54 weeks. The open label extension of PLANETRA included 302 of the 455 patients who completed the initial 54 weeks and followed them for an additional 48 weeks. Two groups of patients were compared: the maintenance group (n=158) continued to receive CT-P13 and the switch group (n=144) transitioned from INX to CT-P13 at week 54. Follow-up was for a total of 102 weeks. The second conference abstract was an open label extension study of the PLANETAS RCT.[23] The PLANETAS RCT was a Phase I RCT that randomized patients with active AS from 10 countries in Europe, Asia and Latin America to 5mg/kg of either INX or CT-P13 over 2 hours at 0, 2, and 6 weeks and then every 8 weeks. Patients were followed for 54 weeks. Park and colleagues[23] published an open label extension of PLANETAS that included 174 of the 210 patients who completed the initial 54-week treatment period and followed them for an additional 48 weeks. Two groups of patients were compared: the maintenance group (n=88) continued to receive CT-P13 and the switch group (n=86) transitioned from INX to CT-P13 at week 54. Follow-up was for a total of 102 weeks. Both Yoo[22] and Park[23] report on measures of disease activity and adverse effects. Lastly, Kang and colleagues[24] in 2014 reported on 17 patients in South Korea with IBD, 9 with UC and 8 with CD. CT-P13 was initiated in 6 patients. Twelve patients who had previously received maintenance therapy with innovator INX were switched to CT-P13. The authors report on clinical response, remission and adverse effects. The duration of follow-up was not reported.

Economic Study

In 2014, Brodszky and colleagues published a budget impact analysis evaluating the cost savings of introducing biosimilar INX in six Eastern European countries (Bulgaria, Czech Republic, Hungary, Poland, Romania and Slovakia).[25] The perspective was that of the third party payer and the authors specifically considered patients with RA. The number of RA patients receiving biological agents was estimated based on the number treated in the previous quarter and the estimated growth. In this budget impact analysis, the RA population receiving treatment with a biologic was approximately 17,300 patients. Two scenarios in addition to the reference scenario were considered. The reference scenario was no availability of biosimilar INX. The first scenario disallowed switching between innovator and biosimilar INX. Only patients who were newly starting biological therapy were allowed to receive biosimilar INX. The second scenario allowed switching between innovator INX and biosimilar INX after 6 months of treatment with the innovator. Patients newly starting biological therapy were allowed to use the biosimilar agent. The model ran on quarterly time periods over a 3-year time horizon. At the end of each quarter, patients could continue on the same biologic, switch to another biologic or leave the model. Several assumptions were made in the model. For all treatments, a 3-month discontinuation probability was assumed to be 0.049%. When innovator INX was selected as first or second line treatment, it was assumed that biosimilar INX would be prescribed in 65% of cases. When a non-INX TNF inhibitor was selected as first or second line treatment, it was assumed that biosimilar INX would be prescribed in 25% of cases. The rate of switching between innovator INX and biosimilar INX was assumed to be 0% in scenario 1 (switching was disallowed) and 80% in scenario 2 when switching was allowed. Total costs of drug

administration, acquisition, and monitoring were included. The cost of biosimilar INX was assumed to be 75% of the cost of innovator INX. Cost savings were reported in 2013 prices and no discounting was applied.

Position Statement

In 2014 the Portuguese Society of Rheumatology published a position paper on the use of biosimilar agents in patients with rheumatic disease.[11] Two systematic literature reviews were undertaken and published together. The objective of the first systematic review was to identify clinical trials of biosimilar agents. The objective of the second systematic review of was to identify international position papers addressing the use of biosimilar agents. The first systematic review of biosimilar agents did not identify any trials that addressed switching from innovator to biosimilar products. The second systematic review of international position papers specifically addressed the question of switching between innovator and biosimilar agents. A total of 29 international position papers were included in the review, half from European countries and twenty percent from North America. The majority of papers (58%) were published in the past 2 years. Most were publish by medical societies (31%), non-profit non-governmental organization (13.8%), pharmaceutical organizations (27.6%), governmental departments (13.8%) including Health Canada, and pharmaceutical manufacturers (13.8%). Substitution was addressed by 16 organizations and interchangeability (specifically switching) was addressed by 18 organizations. Results of the systematic reviews were discussed and a position statement was developed during the national meeting of the Portuguese Society of Rheumatology in October 2013.

Summary of Critical Appraisal

Strengths and limitations of the economic study and systematic review position statement are provided in Appendix 5.

Economic Analysis

The budget impact analysis by Brodszky et al.[25] was of good quality. The research question, economic importance and perspective were all well described and justified. The model details and estimates for model inputs were also clearly described. Model estimates such as base population using biologic agents, drug acquisition cost, discontinuation rates and switching between available biological treatments were estimated based on data from published literature. The time horizon was reported although a rationale was not provided. While a sensitivity analysis was undertaken, only certain model parameters were considered and their values were only altered by 10%. Precision of the cost savings is unclear as no confidence intervals were reported. Only direct costs associated with drug administration were considered and clinical effectiveness was not included in the model.

Position Statement

The systematic review of position papers was of poor quality.[11] The research questions and search strategy were developed *a priori.* A list of included position papers was reported based on the original publishing organization. The main limitation of the systematic review was that the quality of the included position papers, potential conflicts of interest, and evidence supporting the recommendations of the various organizations were unclear. Details on selection of included

papers and data abstraction were not described. One electronic medical database was searched and this was supplemented by a hand search of international society websites. Excluded studies were not listed.

Summary of Findings

The overall findings from the conference abstracts, economic analysis and position statement are summarized below and detailed in Tables 2 and 3 and Appendices 6 and 7.

Clinical effectiveness and safety of switching from innovator INX to subsequent entry INX for patients with RA

Conference Abstracts

Measures of disease activity (American College of Rheumatology [ACR]20/50/70, disease activity score [DAS]28, European League Against Rheumatism [EULAR] good and moderate responses) between the maintenance and switch groups at week 78 and 102 appeared numerically similar.[22] ACR20 was achieved by 72% of the maintenance group and 78% of the switch group at week 78. ACR50 was achieved by 48% of the maintenance group and 50% of the switch group at week 78. ACR70 was achieved by 25% of the maintenance group and 30% of the switch group at week 78. The proportion of patients achieving ACR20/50/70 appeared to be maintained at week 102. The change from baseline in the DAS28-CRP and DAS28-ESR varied between -2.4 and -2.8 across groups at week 78 and 102. EULAR-CRP good and moderate responses were achieved by 80% of the maintenance group and 86% of the switch group at week 78, and 82% of the maintenance group and 77% of the switch group at week 102. Findings were similar for the proportion of patients achieving EULAR-ESR good or moderate responses at week 78 and 102. No statistical comparisons between groups were undertaken and no *P*-values were reported at any time point. Approximately 54% of patients in the maintenance and switch groups experienced one or more treatment emergent adverse effect by week 102. Approximately 5% of these were classified as severe. There was one death in the maintenance group but cause of death was not reported. Rates of infection were similar between the two groups at approximately 31%. ADAs were also similar between the two groups with approximately 50% of patients having ADAs at week 54, 78 and 102. The authors concluded that switching from INX to CT-P13 has a similar efficacy and safety profile compared to continued CT-P13 at 102 weeks in patients with RA.

Clinical effectiveness and safety of switching from innovator INX to subsequent entry INX for patients with AS

Conference Abstracts

At week 54, assessment of spondyloarthritis [ASAS]20 and ASAS40 were similar between the CT-P13 and INX groups, 70.5% vs. 75.6% and 58% vs. 53.5%, respectively.[23] ASAS partial remission was achieved in 20.5% of patients who received CT-P13 and 19.8% of patients who received INX at week 54. Change from baseline in ASDAS-CRP was -1.77 in the CT-P13 group compared to -1.74 in the INX group at week 54. Measures of disease activity (ASAS20, ASAS40, ASAS partial remission and ASDAS-CRP) between the maintenance and switch groups at week 78 and 102 appeared numerically similar. At week 78, 70% of the maintenance group and 77% of the switch group achieved an ASAS20. At the same time point, 58% of the

maintenance group and 52% of the switch group achieved ASAS40. ASAS partial remission was reported in 22% of both groups at week 78. Change from baseline in ASDAS-CRP was -1.88 in the maintenance group compared to -1.68 in the switch group at week 78. Similar results were seen at week 102 for all measures of disease activity. No statistical comparisons between groups were undertaken and no *P*-values were reported at any time point. Treatment emergent adverse events were reported in 49% of the maintenance group and 71% of the switch group at week 102. Three patients in the maintenance group and five patients in the switch group had a severe adverse event. The number of deaths was not reported. Rates of infection were 26% in the maintenance group and 35% in the switch group. ADAs were also similar between the two groups at week 54, at 22% of the CT-P13 and 26% of the INX group. At week 78, 24% of the maintenance group and 31% of the switch group were ADA positive. At week 102, 25% of the maintenance group and 31% of the switch group were ADA positive. The authors concluded that switching from INX to CT-P13 had a similar efficacy and safety profile compared to continued CT-P13 at 102 weeks in patients with AS.

Clinical effectiveness and safety of switching from innovator INX to subsequent entry INX for patients with plaque psoriasis

There were no studies identified that met the inclusion criteria to address this question.

Clinical effectiveness and safety of switching from innovator INX to subsequent entry INX for patients with CD or UC

Conference Abstracts

Of the 6 patients (4 with UC and 2 with CD) who received the induction regimen of CT-P13, clinical response was achieved in 4 patients (3 with UC and 1 with CD) at 8 weeks. Remission at 8 weeks was achieved in 3 patients, all with UC. One patient did not respond and one patient experienced a severe skin reaction. Clinical effectiveness in the 12 patients who were switched from innovator INX to CT-P13 was not reported. Eleven patients who switched did not experience any adverse effects or loss of response. One patient with CD experienced a disease flare when switched from INX to CT-P13. The authors concluded that CT-P13 may be similar to INX in IBD; however, the authors recommend confirmation with a large scale RCT.

Table 2: Main Study Findings and Authors' Conclusions for IBD

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Kang, 2014[24]	Clinical response at 8 weeks: CT-P13: n=4 (n=3 UC and n=1 CD) Switching from INX to CT-P13: NR Clinical Remission at 8 weeks: CT-P13: n=3 (all with UC) Switching from INX to CT-P13: NR Non-response: CT-P13: n=1 (with CD)	Large RCT are required to investigate the interchangeability of CT-P13 with INX

Table 2: Main Study Findings and Authors' Conclusions for IBD		
First Author, Publication Year	**Main Study Findings**	**Authors' Conclusions**
	Switching from INX to CT-P13: NR Safety: CT-P13: 1 patient experienced a severe skin rash and discontinued therapy Switching from INX to CT-P13: NR	
CD=Crohn's Disease; **INX**=infliximab; **NR**=not reported; **RCT**=randomized controlled trial; **UC**=ulcerative colitis		

Clinical effectiveness and safety of switching from innovator INX to subsequent entry INX for patients with PsA

There were no studies identified that met the inclusion criteria to address this question.

Cost-effectiveness of switching from innovator INX to subsequent entry INX

In a budget impact analysis conducted in Eastern Europe in 2014, Brodszky and colleagues found that, compared with the reference case (no availability of biosimilar INX), when switching was disallowed, but patients newly prescribed biologic therapy were permitted to use the biosimilar agent (scenario 1), total cost savings were €15.3 million over the first 3 years after introduction of the biosimilar product. When switching from innovator to biosimilar INX was permitted (scenario 2), cost savings increased to €20.8 million over 3 years. A sensitivity analysis found that the parameters with the largest budget impact were the initial number of patients receiving a biologic, and the price of biosimilar INX relative to innovator INX. The authors postulate that if these savings were used to allow for more patients with RA to receive treatment with biosimilar INX, an additional 1,205 and 1,790 patient could be treated in scenarios 1 and 2, respectively. The authors conclude that allowing innovator INX to be interchanged with biosimilar INX in patients with RA may have a substantial cost savings on the national health care budget in Central and Eastern Europe. The authors caution that the cost savings are sensitive to the number of patients treated with a biologic agent and to the cost of the biosimilar product relative to the innovator.

Table 3: Main Study Findings and Authors' Conclusions in the Economic Analysis

First Author, Publication Year	Main Study Findings
Brodszky, 2014[25]	Results of Scenario Analysis

	Budget Impact (€)			
	Year 1	**Year 2**	**Year 3**	**Total**
Scenario 1: Switching Disallowed	-945,241	-4,782,462	-9,612,331	-15,340,034
Scenario 2: Switching allowed (after 6 months of using innovator)	-2,394,545	-6,968,620	-11,463,059	-20,826,224

Evidence-based guidelines regarding switching from innovator INX to subsequent entry INX

A systematic review conducted by the Portuguese Society of Rheumatology identified 29 international position papers addressing the use of biosimilar agents. Automatic substitution where the pharmacist could provide the biosimilar agent in place of the innovator agent without physician consent was opposed by 13 of the 29 organizations (44.8%). Eighteen organizations (62.1%) supported switching from innovator to biosimilar agents if the attending physician consented. Of these 18 organizations, four indicated that patient consent was also required for switching to occur. The Portuguese Society of Rheumatology recommends against the practice of automatic substitution but supports switching in the context of potential cost savings based on the decision of the prescriber after discussion with the patient. Presently, the Portuguese Society of Rheumatology does not support switching solely on the basis of efficacy or safety. Further recommendations are that switching should only take place after a minimum 6 month use of the innovator agent and subsequent safety and efficacy assessments should be completed and registered in the Rheumatic Disease Portuguese Register (available online at Reuma.pt).

Limitations

No evidence addressing the clinical effectiveness or safety of switching from innovator INX to biosimilar INX in patients with plaque psoriasis or PsA is included in this report. Evidence supporting the use of biosimilar INX in plaque psoriasis is limited to case-series.[26] No conclusions may be drawn from these results because of small sample size and lack of comparator.

Studies addressing clinical effectiveness and safety of switching from innovator INX to biosimilar INX in patients with RA, AS or IBD are limited to conference abstracts.[22-24] Two of these abstracts report on open label extension data of RCT in patients with RA[22] and AS[23]. Selection bias may limit the generalizability of results as patients who tolerate and responded to treatment are more likely to continue in the extension trial. Since the comparator in these trials was

continued biosimilar INX, it is unclear from these results how switching from innovator INX to biosimilar INX would compare to continued use of innovator INX. The small sample sizes and open-label nature of the three conference abstracts limit the conclusions that can be drawn regarding the efficacy, safety, and immunogenicity of switching from innovator INX to biosimilar INX.

The main limitation of the budget impact analysis is the difficulty applying findings from Eastern European countries to Canada. Cost savings may also be underestimated in geographical regions where the number of patients who are treated with biological therapy is higher, a parameter to which the model was sensitive. Acquisition cost of biosimilar INX was assumed in the budget impact analysis and was found to have the greatest impact on cost savings. This limits the extrapolation of study findings in jurisdictions where the acquisition cost of biosimilar INX is more than 75% of the cost of innovator INX. Furthermore, only costs directly related to drug treatment were considered. This may not be an accurate reflection of all the potential costs associated with biological therapy. Other potential costs include those associated with managing adverse effects of biological agents, or costs associated with absence from work related to lack of efficacy. Lastly, the number of patients who initiate treatment with biosimilar INX rather than innovator INX may affect potential cost savings. It is unclear whether the results of this economic analysis can be extrapolated to indications other than RA.

Guidelines addressing switching from innovator to biosimilar INX are limited to one systematic review of international position papers.[11] The methodology of the systematic review was poor and conclusions that can be drawn from the results are limited. These recommendations are based on position statements of various international organizations; it is unclear what, if any, evidence these recommendations are based on. Position statements of both brand and generic pharmaceutical companies were included in the systematic review and may represent a source of bias in the recommendations. In addition, no conflict of interest statements were included and no quality appraisal was undertaken.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The evidence addressing the clinical effectiveness and safety of switching from innovator INX to biosimilar INX is limited to three conference abstracts. In patients with RA or AS who completed a 54 week RCT and were subsequently switched from innovator INX to biosimilar INX, the effect of disease activity appeared similar to those patients who continued to receive biosimilar INX over an additional 48 weeks of follow-up. Based on the results of 12 patients with IBD who switched from innovator INX to biosimilar INX, no conclusions can be drawn. Potential harms or development of ADA associated with switching from innovator to biosimilar INX appeared to be similar to continued use of biosimilar INX in patients with RA. In patients with AS there were numerically more patients who experienced a treatment emergent adverse effect, infection or developed ADA in the group who switched from innovator to biosimilar INX. No information regarding the clinical effectiveness or safety of switching from innovator INX to biosimilar INX compared to continued use of innovator INX was identified for inclusion in this review. A phase 4 double blind RCT evaluating the clinical safety and efficacy of switching from innovator INX to biosimilar INX compared to continued use of innovator INX in patients with RA, PsA, plaque psoriasis, spondyloarthritis, UC and CD is currently recruiting patients at multiple centers in Norway.[27] The primary study outcome is disease worsening over 52 weeks of follow-up. This trial is projected to be completed in May 2016.

No evidence addressing the clinical effectiveness or safety of switching from innovator INX to biosimilar INX in patients with plaque psoriasis or PsA was identified. Presently, the evidence supporting the use of biosimilar INX in psoriasis is limited to case series.

A budget impact analysis demonstrated the potential for cost savings when switching from innovator to biosimilar INX. The authors did not address any clinical evidence to support the practice of switching. While the methodology of the analysis appears sound, the applicability of the results and the cost savings to Canada is questionable.

Recommendations resulting from a systematic review of international position papers provided little evidence based guidance regarding switching or interchanging between biosimilar products.

Availability of biosimilar INX represents a potential cost savings to the Canadian health care system. Presently, the existing evidence does not adequately address concerns with respect to switching between innovator and biosimilar INX in terms of continued effectiveness, development and impact of ADAs over time, and economic impact.

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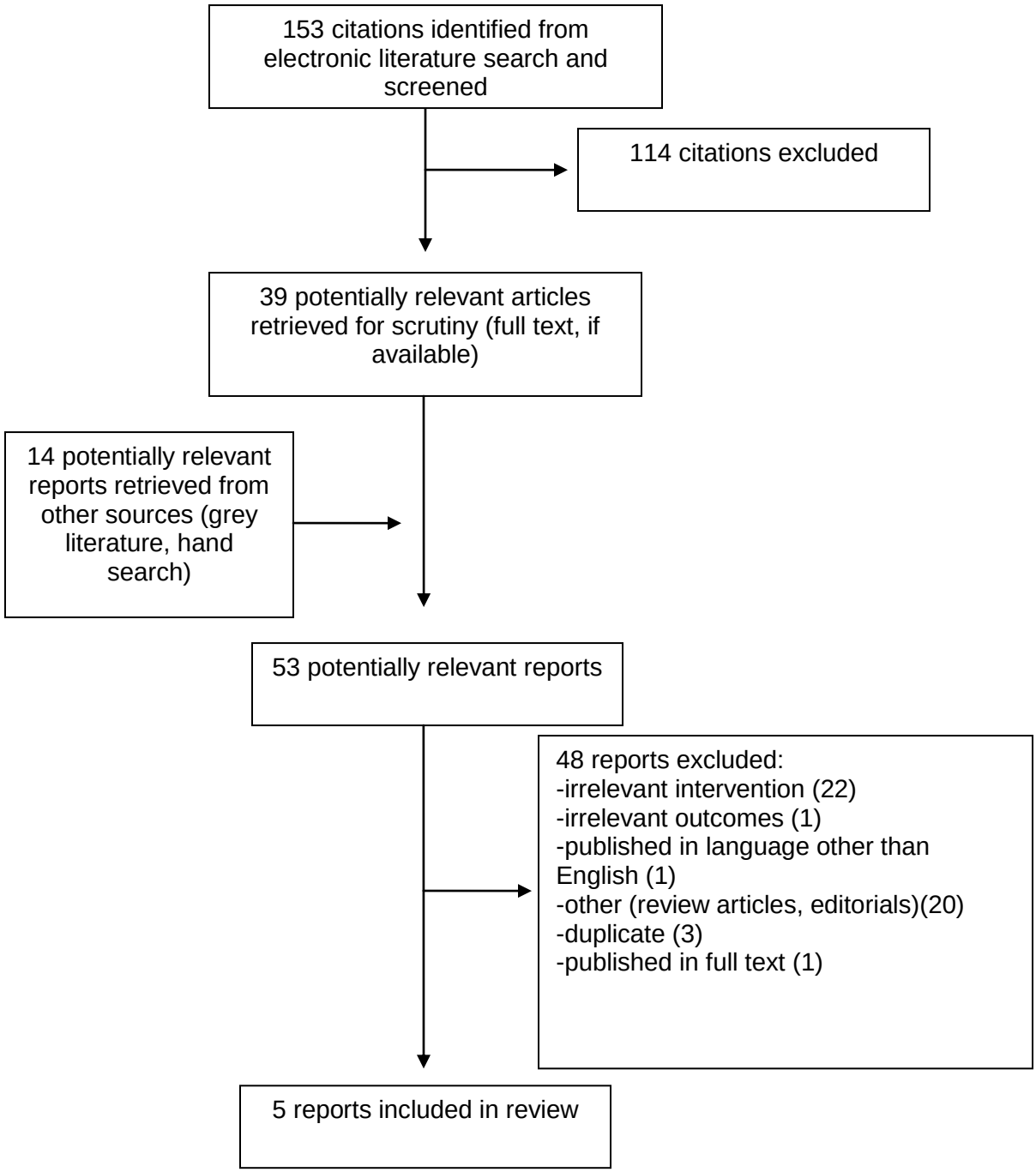
ABBREVIATIONS

ACR	American College of Rheumatology
ADA	anti-drug antibodies
AS	ankylosing spondylitis
ASDAS-CRP	ankylosing spondylitis disease activity score C-reactive protein
CD	Crohn's disease
DAS	disease activity score
EMA	European Medicines Agency
EULAR	European League Against Rheumatism
HTA	health technology assessment
IBD	inflammatory bowel disease
INX	infliximab
PsA	psoriatic arthritis
RA	rheumatoid arthritis
RCT	randomized controlled trial
TB	tuberculosis
TNF	tumor necrosis factor
UC	ulcerative colitis

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Conference Abstracts

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
Yoo, 2013, 19 countries in Europe, Asia, Latin America and Middle East[22]	Open-label extension study of PLANETRA RCT[13] Follow-up: 102 weeks total	n=302 patients with RA (of the original 606 randomized) Characteristics of patients enrolled in the extension study were not reported	Switching from INX to CT-P13 (n=144)	Continued CT-P13 (n=158)	Disease activity (ACR20/50/70, DAS28, EULAR good and moderate response) Adverse events
Park, 2013, 10 countries in Europe, Asia and Latin America[23]	Open-label extension study of PLANETAS RCT[14] Follow-up: 102 weeks total	n=174 patients with AS (of the original 250 randomized) Characteristics of patients enrolled in the extension study were not reported	Switching from INX to CT-P13 (n=86)	Continued CT-P13 (n=88)	Disease activity (ASAS20/40) Adverse events
Kang, 2014, South Korea[24]	Retrospective cohort study Follow-up: NR	n=17 patients (n=9 with UC and n=8 with CD)	Switching from INX to CT-P13 (n=12)	CT-P13 (n=6)	Clinical response, remission, Adverse effects

ACR=American college of rheumatology; **AS**=ankylosing spondylitis; **ASAS**=assessment of spondyloarthritis; **CD=**Crohn's disease; **DAS**=disease activity score; **EULAR**=European league against rheumatism; **INX**=infliximab; **NR**=not reported; **RA**=rheumatoid arthritis; **RCT**=randomized controlled trial; **UC**=ulcerative colitis

APPENDIX 3*:* Characteristics of Included Economic Study

First Author, Publication Year, Country	Type of Economic Evaluation, Study Perspective	Patient Population	Intervention (n)	Comparator(s) (n)	Assumptions
Brodszky, 2014, Central and Eastern Europe[25]	Budget impact analysis, Third-party payer	Patients with RA receiving biological agents n=17,300	Scenario 1: Switching Disallowed Scenario 2: Switching allowed (after 6 months of using innovator)	Reference scenario (no biosimilar INX available)	3-month discontinuation probability of 0.049% 65% of cases where MD would have prescribed INX, the MD would select biosimilar INX 25% of cases where MD prescribed a non-INX anti-TNF, the MD would select biosimilar INX Rate of interchanging innovator INX with biosimilar INX is 0% in scenario 1 and 80% in scenario 2
INX=infliximab; **RA**=rheumatoid arthritis					

APPENDIX 4: Organizations Represented in the Portuguese Society of Rheumatology Position Paper[11]

Organization	Country	Publication Year
Medical Societies / Colleges (31%)		
American College of Rheumatology	USA	2010
Colegio Mexicano de Reumatologia	Mexico	2012
American Academy of Dermatology	USA	2012
European Crohn's and Colitis Organization	Europe	2013
Sociedad Espanola de Patologia Digestiva/Sociedad Espanola de Farmacologia	Spain	2013
Austrian Society of Hematology and Oncology	Austria	2008
Italian Society of Hematology	Italy	2011
International Union of Angiology	International	2012
Societe Fraincaise de Nephrologie/Societe Francophone de Dyalise	France	2009
Non-profit Non-Governmental Organizations (13.8%)		
National Psoriasis Foundation	USA	2013
National Comprehensive Cancer Network	USA	2011
National Haemophilia Foundation	USA	2009
Diabetes UK	UK	2013
Pharmaceutical Organizations (27.6%)		
European Biopharmaceutical Enterprises/European Federation of Pharmaceutical Industries and Associations	Europe	2007
Biotechnology Industry Organization Deutschland	Germany	2012
International Federation of Pharmaceutical Manufacturers and Associations	International	2011
Organization of Pharmaceutical Producers of India	India	2012
Belgian Biotechnology Industry Organization	Belgium	2013
Generic Pharmaceutical Association	USA	2013
Association of the British Pharmaceutical Industry	UK	2013
Apifarma	Portugal	2013
Governmental Departments (13.8%)		
Department of Health's Ministerial Industry Strategy Group	UK	2009
Agenzia Italiana del Farmaco	Italy	2013
Scottish Medicines Consortium	UK	2011
Health Canada	Canada	2010
Pharmaceutical Manufacturers (13.8%)		
Merck Sharp & Dohme	USA	2010
Eli Lilly and Company	USA	2010
F. Hoffmann-La Roche AG	Switzerland	2010
Bristol Meyers Squibb	UA	2013

APPENDIX 5: Summary of Critical Appraisal of Individual Studies

First Author, Publication Year	Strengths	Limitations
Economic Studies		
Brodszky[25] 2014	• Research question and economic importance was well established • Perspective was clearly described and justified • The form of economic analysis was described and justified • The primary outcome measure (cost savings) was clearly stated • Number of patients receiving biological therapy (TNF inhibitor or otherwise) were reported separately • Methods for estimating quantities, costs and pricing data were described • Model details were clearly outlined and justified • Time horizon (3 years) was reported • Conclusions were consistent with study findings	• Budget impact analysis does not consider effectiveness data • No discounting was applied and rationale was not provided • Only direct costs of drug treatment were considered (acquisition, administration and monitoring) • Statistical approach was not described • One-way sensitivity analysis was conducted on select model parameters without justification for the parameter variability • Confidence intervals for cost savings were not reported
Position Statement		
Fonseca[11] 2014	• Research question and inclusion criteria were developed *a priori* • A list of included position papers was reported • Included position papers were listed based on the publishing organization	• No details were provided on study selection or data abstraction • Only one electronic database was searched (MEDLINE) which was supplemented by a hand search • Excluded position papers were not reported • The quality of the included position papers was not assessed • The evidence supporting the recommendations was unclear • Conflicts of interest were not reported or discussed

APPENDIX 6: Table of Main Study Findings and Authors' Conclusions in RA

<table>
<tr><th>First Author, Publication Year</th><th>Main Study Findings and Authors' Conclusions</th></tr>
<tr><td>Yoo, 2013[22]</td><td>Efficacy Outcomes
<table>
<tr><th>Outcome</th><th>Follow-up time</th><th>CT-P13 throughout (n=151)</th><th>Switched from INX to CT-P13 in extension phase (n=142)</th></tr>
<tr><td rowspan="3">ACR20, n(%)</td><td>Week 54</td><td>116 (76.8)</td><td>110 (77.5)</td></tr>
<tr><td>Week 78</td><td>108 (71.5)</td><td>111 (78.2)</td></tr>
<tr><td>Week 102</td><td>109 (72.2)</td><td>102 (71.8)</td></tr>
<tr><td rowspan="3">ACR50, n(%)</td><td>Week 54</td><td>69 (45.7)</td><td>71 (50.0)</td></tr>
<tr><td>Week 78</td><td>73 (48.3)</td><td>68 (47.9)</td></tr>
<tr><td>Week 102</td><td>73 (48.3)</td><td>73 (51.4)</td></tr>
<tr><td rowspan="3">ACR70, n(%)</td><td>Week 54</td><td>33 (21.9)</td><td>34 (23.9)</td></tr>
<tr><td>Week 78</td><td>37 (24.5)</td><td>42 (29.6)</td></tr>
<tr><td>Week 102</td><td>37 (24.5)</td><td>37 (26.1)</td></tr>
<tr><td rowspan="4">DAS28-CRP</td><td>Baseline</td><td>5.8</td><td>5.8</td></tr>
<tr><td>Δ BL at wk 54</td><td>-2.4</td><td>-2.4</td></tr>
<tr><td>Δ BL at wk 78</td><td>-2.4</td><td>-2.6</td></tr>
<tr><td>Δ BL at wk 102</td><td>-2.4</td><td>-2.5</td></tr>
<tr><td rowspan="4">DAS28-ESR</td><td>Baseline</td><td>6.6</td><td>6.6</td></tr>
<tr><td>Δ BL at wk 54</td><td>-2.5</td><td>-2.6</td></tr>
<tr><td>Δ BL at wk 78</td><td>-2.6</td><td>-2.8</td></tr>
<tr><td>Δ BL at wk 102</td><td>-2.6</td><td>-2.7</td></tr>
<tr><td rowspan="3">EULAR-CRP good and moderate responses, n(%)</td><td>Week 54</td><td>135 (89.4)</td><td>124 (87.3)</td></tr>
<tr><td>Week 78</td><td>120 (79.5)</td><td>122 (85.9)</td></tr>
<tr><td>Week 102</td><td>123 (81.5)</td><td>109 (76.8)</td></tr>
<tr><td rowspan="3">EULAR-ESR good and moderate responses, n(%)</td><td>Week 54</td><td>136 (90.1)</td><td>122 (85.9)</td></tr>
<tr><td>Week 78</td><td>120 (79.5)</td><td>123 (86.6)</td></tr>
<tr><td>Week 102</td><td>123 (81.5)</td><td>115 (81.0)</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>First Author, Publication Year</th><th>Main Study Findings and Authors' Conclusions</th></tr>
<tr><td></td><td>
Safety Outcomes
<table>
<tr><th>Outcome</th><th>Follow-up time</th><th>CT-P13 throughout (n=151)</th><th>Switched from INX to CT-P13 in extension phase (n=142)</th></tr>
<tr><td colspan="2">TEAEs, n</td><td>226</td><td>180</td></tr>
<tr><td colspan="2">Pts with ≥1 TEAE, n(%)</td><td>85 (53.5)</td><td>77 (53.8)</td></tr>
<tr><td colspan="2">Mild</td><td>37 (23.3)</td><td>38 (26.6)</td></tr>
<tr><td colspan="2">Moderate</td><td>39 (24.5)</td><td>31 (21.7)</td></tr>
<tr><td colspan="2">Severe</td><td>7 (4.4)</td><td>8 (5.6)</td></tr>
<tr><td colspan="2">Life-threatening</td><td>1 (0.6)</td><td>0</td></tr>
<tr><td colspan="2">Death</td><td>1 (0.6)</td><td>0</td></tr>
<tr><td colspan="2">Pts with ≥1 TESAE, n(%)</td><td>12 (7.5)</td><td>13 (9.1)</td></tr>
<tr><td colspan="2">Pts with ≥1 infection, n(%)</td><td>50 (31.4)</td><td>47 (32.9)</td></tr>
<tr><td rowspan="3">ADA positive n(%)</td><td>Week 54</td><td>78 (49.1)</td><td>69 (49.3)</td></tr>
<tr><td>Week 78</td><td>71 (50.4)</td><td>66 (49.6)</td></tr>
<tr><td>Week 102</td><td>64 (46.4)</td><td>64 (49.6)</td></tr>
</table>
Authors' Conclusions
Biosimilar infliximab (CT-P13) had similar efficacy and safety profiles in patients with RA in the maintenance and switch groups over a 48-week extension trial.
</td></tr>
<tr><td colspan="2">ACR=American College of Rheumatology; ADA=antidrug antibodies; DAS=disease activity score; EULAR=European leagues against rheumatism; Pts=patients; TEAE=treatment emergent adverse effects; TESAE=treatment emergent serious adverse effects; wk=week</td></tr>
</table>

APPENDIX 7: Table of Main Study Findings and Authors' Conclusions in AS

<table>
<tr><th>First Author, Publication Year</th><th>Main Study Findings and Authors' Conclusions</th></tr>
<tr><td>Park, 2013[23]</td><td>
Efficacy Outcomes
<table>
<tr><th>Outcome</th><th>Follow-up time</th><th>CT-P13 throughout (n=88)</th><th>Switched from INX to CT-P13 in extension phase (n=86)</th></tr>
<tr><td rowspan="3">ASAS20, n(%)</td><td>Week 54</td><td>62 (70.5)</td><td>65 (75.6)</td></tr>
<tr><td>Week 78</td><td>61 (70.1)</td><td>64 (77.1)</td></tr>
<tr><td>Week 102</td><td>67 (80.7)</td><td>60 (76.9)</td></tr>
<tr><td rowspan="3">ASAS40, n(%)</td><td>Week 54</td><td>51 (58.0)</td><td>46 (53.5)</td></tr>
<tr><td>Week 78</td><td>50 (57.5)</td><td>43 (51.8)</td></tr>
<tr><td>Week 102</td><td>53 (63.9)</td><td>48 (61.5)</td></tr>
<tr><td rowspan="3">ASAS partial remission, n(%)</td><td>Week 54</td><td>18 (20.5)</td><td>17 (19.8)</td></tr>
<tr><td>Week 78</td><td>19 (21.8)</td><td>18 (21.7)</td></tr>
<tr><td>Week 102</td><td>23 (27.7)</td><td>22 (28.2)</td></tr>
<tr><td rowspan="4">ASDAS-CRP</td><td>Baseline</td><td>3.86</td><td>3.85</td></tr>
<tr><td>Mean Δ from BL at wk 54</td><td>-1.77</td><td>-1.74</td></tr>
<tr><td>Mean Δ from BL at wk 78</td><td>-1.88</td><td>-1.68</td></tr>
<tr><td>Mean Δ from BL at wk 102</td><td>-2.03</td><td>-1.81</td></tr>
</table>
Safety Outcomes
<table>
<tr><th>Outcome</th><th>Follow-up time</th><th>CT-P13 throughout (n=151)</th><th>Switched from INX to CT-P13 in extension phase (n=142)</th></tr>
<tr><td colspan="2">TEAEs, n</td><td>103</td><td>162</td></tr>
<tr><td colspan="2">Pts with ≥1 TEAE, n(%)</td><td>44 (48.9)</td><td>60 (71.4)</td></tr>
<tr><td colspan="2">Mild</td><td>20 (22.2)</td><td>27 (32.1)</td></tr>
<tr><td colspan="2">Moderate</td><td>21 (23.3)</td><td>28 (33.3)</td></tr>
<tr><td colspan="2">Severe</td><td>3 (3.3)</td><td>5 (6.0)</td></tr>
<tr><td colspan="2">Pts with ≥1 TESAE, n(%)</td><td>4 (4.4)</td><td>4 (4.8)</td></tr>
<tr><td colspan="2">Pts with ≥1 infection, n(%)</td><td>23 (25.6)</td><td>29 (34.5)</td></tr>
<tr><td rowspan="3">ADA positive n(%)</td><td>Week 54</td><td>20 (22.2)</td><td>22 (26.2)</td></tr>
<tr><td>Week 78</td><td>21 (24.4)</td><td>25 (31.3)</td></tr>
<tr><td>Week 102</td><td>21 (25.0)</td><td>23 (30.7)</td></tr>
</table>
</td></tr>
</table>

First Author, Publication Year	Main Study Findings and Authors' Conclusions
	Authors' Conclusions Biosimilar infliximab (CT-P13) had similar efficacy and safety profiles in patients with AS in the maintenance and switch groups over a 48-week extension trial.

ADA=antidrug antibody; **ASAS**=assessment of spondyloarthritis; **ASDAS-CRP**=ankylosing spondylitis disease activity score c-reactive protein; **TEAE**=treatment emergent adverse effect; **TESAE**=treatment emergent serious adverse effect