

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

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## **CONTEXT AND POLICY ISSUES**

Anti-tumour necrosis factor alphas (anti-TNFs) such as infliximab (e.g., Remicade©) are biologics that are proven effective against autoimmune inflammatory diseases.<sup>1</sup> Biologics are large, protein-based agents used to block inflammation for a variety of serious diseases. Infliximab can be used for a variety of chronic inflammatory conditions including rheumatoid arthritis (RA), ankylosing spondylitis (AS), inflammatory bowel disease (IBD) including ulcerative colitis (UC) and Crohn's disease (CD), psoriatic arthritis (PA), and plaque psoriasis (PP).<sup>2-4</sup> More recently, subsequent entry biosimilar drugs for infliximab have been introduced to the market due to the patent expiry of the originator (or innovator) drug.<sup>5</sup> Biosimilar drugs are therapeutically and biologically similar to originators, appearing in general when exclusivity rights are lost.<sup>6</sup> 'Biosimilar infliximab' is used interchangeably with subsequent entry infliximab in this review.

The potential cost savings of switching to biosimilars without compromising on clinical effectiveness or safety makes investigation into the interchangeability of these drugs informative. Biosimilar drugs can potentially result in price discounts of 20% to 70%,<sup>7</sup> while biosimilars were estimated to save \$44.2 billion in direct spending on biologic drugs in the US market from 2014 to 2024.<sup>8</sup> In 2015, CADTH reviewed the clinical and cost effectiveness of infliximab biosimilars,<sup>9</sup> but found only five reports, none of which were primary studies on comparability. The lack of evidence at the time prevented conclusions on the efficacy, safety and cost-effectiveness of switching from originator to biosimilar infliximab.

Several agencies such as the Food and Drug Administration (FDA) and Health Canada have now recommended biosimilar infliximab for all the indications of originator infliximab by extrapolation,<sup>10,11</sup> and a stronger evidence base comparing the biologics has been formed since CADTH's last review. Due to the sustained healthcare policy interest in the potential of infliximab biosimilars, and new research, this review updates the 2015 CADTH report on the clinical and cost-effectiveness of infliximab biosimilars for the treatment of RA, AS, CD, UC, PA and PP.<sup>9</sup>

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## 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 spondylitis?
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

Findings from observational studies on patients with rheumatoid arthritis, ankylosing spondylitis, plaque psoriasis, Crohn's Disease, or ulcerative colitis suggest that switching from infliximab treatment to infliximab biosimilar may be possible without compromising efficacy or safety. However the findings need to be interpreted with caution as for most conditions the findings were from single studies, some of which were small in size. No relevant studies on patients with psoriatic arthritis were identified.

Two budget impact studies and a systematic review highlight potential for cost savings after the introduction of biosimilars to the market.

No evidence-based guidelines regarding switching from innovator infliximab to subsequent entry infliximab were identified.

## METHODS

### Literature Search Methods

This report makes use of a literature search strategy developed for a previous CADTH report.<sup>9</sup> For the current report, a limited literature search was conducted on key resources including PubMed, OVID Medline and Embase, The Cochrane Library, 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

retrieval by study type. Where possible, retrieval was limited to the human population. The search was limited to English-language documents published between November 17, 2015 and November 30, 2016 to capture any articles published since the previous report. The grey literature was also searched for additional reports and guidelines.

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

**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. Conference abstracts were also screened, and the citations of relevant abstracts are included in Appendix 5.

<b>Table 1: Selection Criteria</b>	
<b>Population</b>	Patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn's disease, and ulcerative colitis being treated with innovator infliximab
<b>Intervention</b>	Switching to biosimilar infliximab
<b>Comparator</b>	Continuous innovator infliximab use
<b>Outcomes</b>	Q1 to Q6: clinical-effectiveness (e.g., clinical response, disease activity), safety (adverse events) Q7: cost-effectiveness Q8: evidence-based guidelines
<b>Study Designs</b>	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines, conference abstracts (for inclusion in appendix)

**Exclusion Criteria**

Articles were excluded if they did not meet the population, intervention, outcomes and study designs outlined in Table 1. Articles were also excluded if they were duplicate publications, or were published prior to 2015. In the absence of literature comparing patients continuing with innovator infliximab with those switching to a biosimilar, studies that reported on findings for switching to a biosimilar infliximab were considered for inclusion.

**Critical Appraisal of Individual Studies**

Critical appraisal was conducted based on accepted checklists. It was summarized in the form of a list of strengths and weaknesses in each study, available in Appendix 3. Systematic reviews were critically appraised using the AMSTAR checklist<sup>12</sup> and clinical studies were appraised using the Downs and Black checklist.<sup>13</sup> The Drummond checklist<sup>14</sup> was used for economic studies. Conference abstracts were not appraised or summarized, and were included for reference only.

## SUMMARY OF EVIDENCE

### Quantity of Research Available

A total of 273 citations were identified in the literature search. Following screening of titles and abstracts, 236 citations were excluded and 37 potentially relevant reports from the electronic search were retrieved for full-text review. Twenty-two potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, fifty one publications were excluded for various reasons, while eight were included in this report. These eight reports comprised of five observational study reports<sup>15-19</sup> and three reports on economic evaluation.<sup>7,20,21</sup> Of the five observational study reports, three reports<sup>15-17</sup> were on extension studies of previously conducted RCTs and henceforth will be referred to as extension studies. Appendix 1 describes the PRISMA flowchart of the study selection.

In addition, 69 conference abstracts met the inclusion criteria, and are provided in Appendix 5, and other publications of potential interest are provided in Appendix 6.

### Summary of Study Characteristics

Detailed characteristics of included studies are provided in Appendix 2.

#### 1. Clinical effectiveness and safety of switching from innovator infliximab to subsequent entry infliximab for patients with rheumatoid arthritis

*Study Design:* Two observational studies addressed this research question.<sup>16,17</sup> These two studies were single-arm extensions of two previously conducted RCTs

*Country of Origin:* One extension study was conducted across 16 countries in Europe, Asia, Latin America and Middle East, respectively<sup>17</sup> while the other extension study took place in Japan.<sup>16</sup>

*Patient population:* The extension studies included adult patients under age 75, diagnosed with RA for at least a year.<sup>16,17</sup> Additionally these extension studies required that the patients had completed their assigned treatment during the main RCT.

*Intervention and Comparators:* The extension studies compared maintaining treatment with the biosimilar, with switching patients, to the biosimilar depending on their initial treatment assignment.<sup>16,17</sup>

*Outcomes:* For all studies, efficacy was based on well-known clinical markers for RA such as American College of Rheumatology's (ACR) ACR20, ACR50, ACR70 response rates. Safety was based on the frequency of adverse events.

#### 2. Clinical effectiveness and safety of switching from innovator infliximab to subsequent entry infliximab for patients with ankylosing spondylitis

*Study Design:* One observational study addressed this research question.<sup>15</sup> This was a single-arm extension study of a previously conducted RCT.

*Country of Origin:* The extension study was conducted across 8 countries.<sup>15</sup>

*Patient Population:* Patients aged 18 to 75 years diagnosed with AS for  $\geq 3$  months prior to screening were eligible for the extension study.<sup>15</sup> The extension study additionally required that patients completed their assigned therapy during the main RCT.

*Intervention and Comparators:* The extension study maintained treatment with the biosimilar, or switched patients to the biosimilar depending on their initial treatment assignment.<sup>15</sup>

*Outcomes:* Commonly accepted clinical markers for AS were used for efficacy endpoints, including the SpondyloArthritis International Society's (ASAS) ASAS20 and ASAS40 response rates, and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Safety was based on the frequency of adverse events.

### **3. Clinical effectiveness and safety of switching from innovator infliximab to subsequent entry infliximab for patients with plaque psoriasis**

*Study Design:* One prospective cohort study included PP patients.<sup>18</sup>

*Country of Origin:* The study took place in Turin, Italy.<sup>18</sup>

*Patient Population:* Eligible patients were diagnosed with moderate to severe PP.<sup>18</sup>

*Intervention and Comparators:* All patients were switched from infliximab to infliximab biosimilar at a similar dose/interval.<sup>18</sup>

*Outcomes:* Psoriasis Area and Severity Index and visual analogue scale score for arthritic pain, as well as adverse events, were used to measure effectiveness and safety.

### **4. Clinical effectiveness and safety of switching from innovator infliximab to subsequent entry infliximab for patients with Crohn's Disease or ulcerative colitis. [Note that Research Questions 4 and 5 are presented together]**

*Study Design:* One observational retrospective cohort study addressed this research question.<sup>19</sup>

*Country of Origin:* The observational cohort study took place in Slovakia.<sup>19</sup>

*Patient Population:* The study included adult CD or UC patients.

*Intervention and Comparators:* In the observational study, the intervention involved switching all patients from innovator infliximab to biosimilar infliximab.<sup>19</sup>

*Outcomes:* Commonly accepted disease activity scales such as the Harvey–Bradshaw Index for CD and the partial Mayo index for UC, and C-Reactive protein levels, were used to determine clinical effectiveness. The frequency of adverse events was used to determine safety.

### **5. Clinical effectiveness and safety of switching from innovator infliximab to subsequent entry infliximab for patients with ulcerative colitis**

The study addressing this question also included patients with Crohn's disease and is already described in the section above for Question 4.

## 6. Clinical effectiveness and safety of switching from innovator infliximab to subsequent entry infliximab for patients with psoriatic arthritis

No relevant studies were identified.

## 7. Cost-effectiveness of switching from innovator infliximab to subsequent entry infliximab

*Study Design:* One systematic review<sup>20</sup> including six budget impact analysis studies of which two studies were published as full text articles and four studies as conference abstracts was identified. Two budget impact analyses were also identified.<sup>7,21</sup>

*Country of Origin:* The systematic review<sup>20</sup> of budget impact analysis studies included studies from various European countries. Both budget impact studies were European, one focusing on Hungary, Czech Republic, Poland, Romania and Slovakia,<sup>7</sup> and the other in the Netherlands.<sup>21</sup>

*Patient population:* The systematic review<sup>20</sup> of budget impact analysis studies included patients with CD, UC, RA, AS and PA. One budget impact analysis study targeted CD patients,<sup>7</sup> while the other included both CD and UC patients.<sup>21</sup>

*Intervention and Comparators:* The baseline scenario was having no biosimilar introduced.

*Outcomes:* All studies considered cost-savings.

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

No evidence-based guidelines were identified.

### Summary of Critical Appraisal

A detailed summary of the critical appraisal of each included study is provided in Appendix 3.

The three extension studies<sup>15-17</sup> for RA and AS were extensions of multi-centre, multi-country, double-blinded RCTs, benefitting from the initial random assignment of recruits which should have ensured balanced patient characteristics. Selection bias may have occurred however because the studies required patients to have completed their assigned treatment in the main RCT, potentially excluding more severe patients. The two observational studies<sup>18,19</sup> had small sample sizes of less than 50 patients. One study did not describe reasons for the loss of four (33%) patients.<sup>19</sup> No loss to follow up was reported in one study.<sup>18</sup>

The systematic review<sup>20</sup> of economic studies conducted a comprehensive literature search. Details of the included studies were lacking. However, they conducted quality assessment of the two studies that were published as full text articles and reported them to be of good quality. The remaining four studies included in the systematic review were reported as conference abstracts and quality assessment was not undertaken. The two economic studies were of relatively high quality. The modelling approach and perspective was appropriately described and assumptions were justified in the Dutch budget impact analysis for UC and CD patients.<sup>21</sup> The Eastern European budget impact study for CD patients' treatment similarly described its modelling

approach and perspective, though it lacked description on their analysis and assumption justification.<sup>7</sup>

## Summary of Findings

Tables A5 and A6 in Appendix 4 provide a detailed summary of all findings.

### 1. *Clinical effectiveness and safety of switching from innovator infliximab to subsequent entry infliximab for patients with rheumatoid arthritis*

Two single-arm extension studies of RCTs in Europe and Japan suggested similar effectiveness and safety for RA patients who were on maintained biosimilar or who had switched to biosimilar. The studies further demonstrated that clinical response and safety profile were maintained long term on the subsequent-entry biosimilar, with a 102 week follow up.<sup>16,17</sup>

### 2. *Clinical effectiveness and safety of switching from innovator infliximab to subsequent entry infliximab for patients with ankylosing spondylitis*

A single-arm one year extension study showed that switching from infliximab originator treatment to infliximab biosimilar is possible without compromising efficacy or safety in AS patients.<sup>15</sup>

### 3. *Clinical effectiveness and safety of switching from innovator infliximab to subsequent entry infliximab for patients with plaque psoriasis*

Only one single-centre cohort study<sup>18</sup> found no significant differences in the Psoriasis Area and Severity Index (PASI) and visual analog scale for arthritic pain score after all patients in the cohort were switched to biosimilar infliximab. The study compared baseline scores to scores at a median of 23 weeks follow up. There were no adverse events resulting in discontinuation; only one patient experienced a herpes zoster infection that resolved after treatment.<sup>18</sup>

### 4. *Clinical effectiveness and safety of switching from innovator infliximab to subsequent entry infliximab for patients with Crohn's disease*

Note the included study included both CD and UC patients.

A one year observational cohort study included 12 patients who switched from infliximab to biosimilar infliximab to reduce costs. At week 48, 87.5% of 8 remaining patients had a sustained clinical response while the mean Short Inflammatory Bowel Disease Questionnaire score did not change significantly. Two patients (25%) in this study discontinued treatment with biosimilar infliximab due to psoriasiform dermatitis and loss of response.<sup>19</sup>

### 5. *Clinical effectiveness and safety of switching from innovator infliximab to subsequent entry infliximab for patients with ulcerative colitis*

The included study<sup>19</sup> considered both CD and UC patients and findings are described above while addressing question 4.

6. *Clinical effectiveness and safety of switching from innovator infliximab to subsequent entry infliximab for patients with psoriatic arthritis*

No relevant studies were identified.

7. *Cost-effectiveness of switching from innovator infliximab to subsequent entry infliximab*

One systematic review<sup>20</sup> and two budget impact analyses<sup>7,21</sup> suggest cost savings by switching from innovator to biosimilar infliximab. The systematic review<sup>20</sup> found that cost savings would be substantial, though the exact amount depends on the rate of interchangeability, patient number, eligibility, and the actual cost of the biosimilar. Two primary studies<sup>7,21</sup> also suggest cost savings by switching to biosimilar infliximab in Eastern Europe and in the Netherlands. The first found €8.0 million in cost savings by year 3 if the biosimilar was only offered to anti-TNF naïve patients, and €16.9 million if interchanging was allowed; the amount was mainly sensitive to the price of the biosimilar.<sup>7</sup> The Netherlands budget impact study found total health care savings of €493 million over the total 5 simulated years, accounting for more costs than in the first study. The savings were mostly driven by price reductions due to competition and physician prescribing behavior.<sup>21</sup>

8. *Evidence-based guidelines regarding switching from innovator infliximab to subsequent entry infliximab*

No relevant evidence-based guidelines regarding switching from innovator infliximab to biosimilar infliximab were found.

### **Limitations**

The evidence is limited to observational cohort studies, which are not designed to assess comparative effectiveness and safety. For most conditions, the findings were from single studies, some of which were small in size. Further, the methodology employed in these studies usually failed to adequately adjust for possible confounders and address biases. Though the included studies reported on findings for switching to biosimilars, studies comparing outcomes in patients continuing with innovator infliximab with those switching to biosimilar would have been ideal. We also cannot extrapolate the budget impact for Canada as the studies on cost-savings were European; actual cost-effectiveness was also not the subject of any study, so this research question could not be directly answered. Also, the included economic studies examined the impact of the introduction of biosimilars and not specifically on switching from infliximab to biosimilar. Finally, there were not any evidence-based guidelines published over the study period.



## CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Five observational studies were identified of which two studies included RA patients, one study included AS patients, one study included PP patients and one study included both CD and UC patients. No studies on PA patients were identified. There is a suggestion that switching from infliximab treatment to infliximab biosimilar may be possible without compromising efficacy or safety. However the findings need to be interpreted with caution as for most conditions the findings were from single studies, some of which were small in size. There was also a lack of cost-effectiveness studies, and while the budget impact studies were not in Canada, they consistently demonstrated the potential for cost savings after the introduction of the infliximab biosimilar. While the evidence is relatively consistent to date, higher quality trials, and studies specific to Canada, would aid policy decision making.

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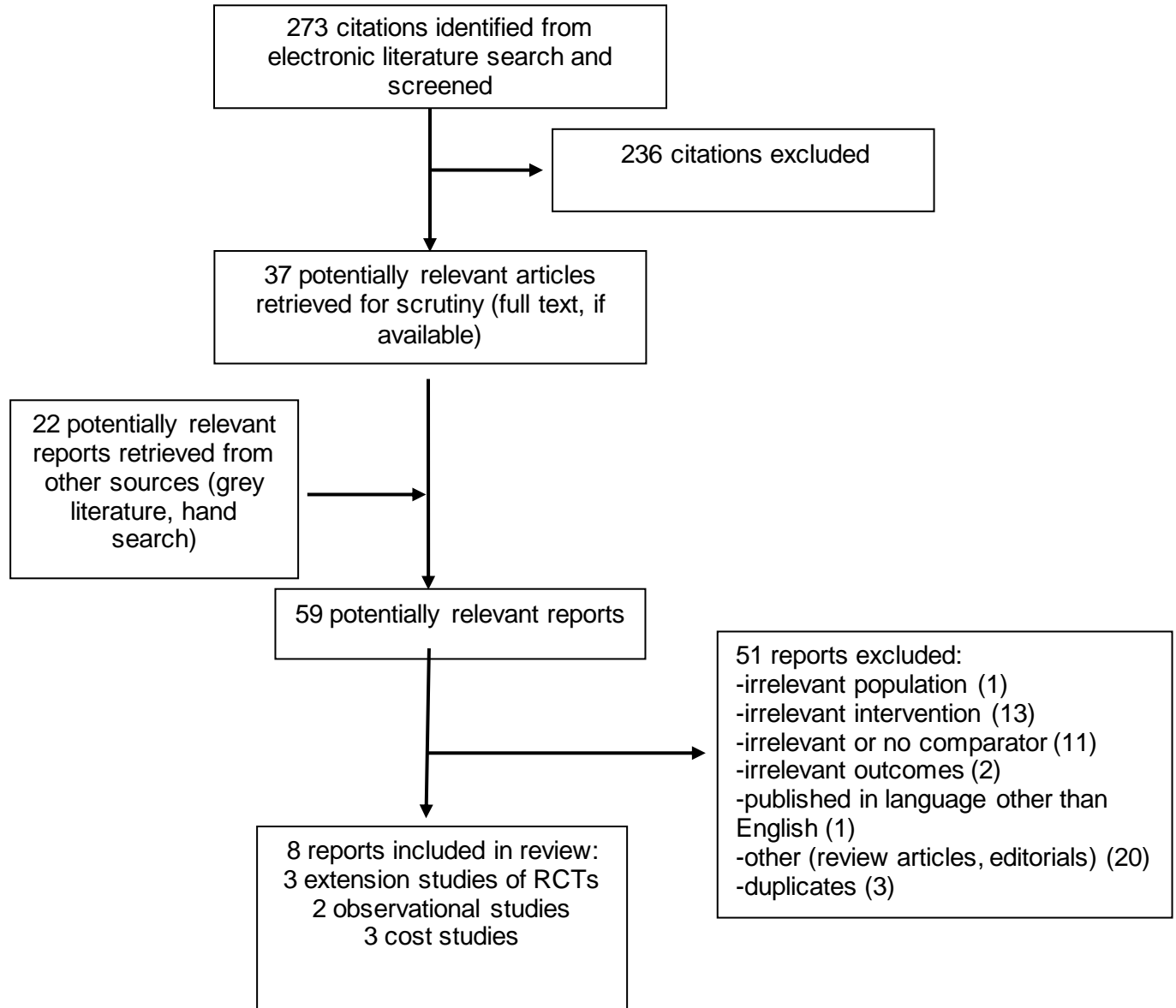
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**APPENDIX 1: Selection of Included Studies**



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Dapavo; 2016; Italy <sup>18</sup>	Single-centre prospective observational open-label study	Diagnosis of moderate to severe plaque psoriasis	Switch from infliximab originator to biosimilar	Treatment with biosimilar infliximab at same dose/interval	Efficacy (PASI and visual analog scale scores)
Tanaka; 2016; Japan <sup>16</sup>	Multi-centre, open-label, single-arm extension study	RA patients who already completed a 54-week treatment with infliximab or biosimilar, and were judged as suitable for extension of treatment with CT-P13	2-h intravenous infusion of 3 mg/kg CT-P13 at Week 62 and eight weekly doses thereafter up to the study termination	Switch from infliximab	Safety and efficacy (ACR20, ACR50, ACR70, ASAS response rates, adverse events)
Park; 2016; Europe; 102-week data from the PLANETAS extension study <sup>15</sup>	Extension of multi-centre, multi-country, double-blind, randomized trial	Patients aged 18–75 years diagnose with AS for ≥3 months prior to screening, and who agreed to participate in 1 year extension study	Six infusions of CT-P13 given every 8 weeks from week 62 to week 102. CT-P13 was administered via 2 h intravenous infusion at 5 mg/kg.	Switch from infliximab	Safety and efficacy (ASAS20, ASAS40 and ASAS-PR response rates, and adverse events)
Hlavaty; 2016; Slovakia <sup>19</sup>	Retrospective, single-centre cohort study	All consecutive adult (≥ 18 years old) patients with CD or UC who were treated with CT-P13 in the IBD centre of the Department of Internal Medicine, University Hospital Bratislava	5 mg/kg CT-P13 infusions administered every eight weeks	Switch from infliximab	Safety and efficacy (Clinical response, SIBDQ scores and adverse events)
Yoo; 2016; Europe; PLANETRA	Open-label, single arm extension of	Patients aged 18–75 years with active RA	Six 2hr, 3 mg/kg infusions of	Switch from infliximab	Safety and efficacy (Achievement

**Table A1: Characteristics of Included Clinical Studies**

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
<i>extension study</i> <sup>17</sup>	multi-centre, multi-country, double-blind, randomized trial	for ≥ 1 year, did not respond adequately to ≥3 months of treatment with methotrexate (MTX), received a stable MTX dose (12.5–25mg/week) for ≥ 4 weeks before screening, and completed the main 54-week study	CT-P13 from week 62 to week 102		of ACR20, ACR50, and ACR70, adverse events)

ACR = American College of Rheumatology; AS = ankylosing spondylitis; ASAS = Assessment in SpondyloArthritis International Society; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CD = Crohn's disease; CDAI = Clinical Disease Activity Index; CRP = C-Reactive protein; DAS = Disease Activity Score; ESR = erythrocyte sedimentation rate; FCP = fecal calprotectin; HBI = Harvey Bradshaw Index; IBD = inflammatory bow el disease; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; PA = psoriatic arthritis; PASI = Psoriasis Area and Severity Index; PCDAI = Pediatric Crohn's Disease Activity Index; PP = plaque psoriasis; RA = rheumatoid arthritis; PUCAI = Pediatric Ulcerative Colitis Activity Index; SCCAI = Simple Clinical Colitis Activity Index; SDAI = Simple Disease Activity Index; sIBDQ = Short Inflammatory Bow el Disease Questionnaire; UC= ulcerative colitis

**Table A2: Characteristics of Included Cost Studies**

First author, Publication Year, Country	Type of Analysis, Perspective	Intervention, Comparator	Study Population	Time Horizon	Main Assumptions
Jacob; 2016; several European countries, UK, Ireland <sup>20</sup>	Systematic review of six budget impact studies (results from 2 studies reported in full text publications and 4 studies reported in conference abstracts)	Infliximab, biosimilar, other treatments	Patients with CD, UC, RA, AS or PA	3 to 5 years	NR
Brodzky; 2015; Czech Republic, Hungary, Poland, Romania, and Slovakia <sup>7</sup>	Prevalence-based and country-specific budget impact assessment to estimate total direct costs of each scenario, and potential number of new patients treatable in case of all savings was put back into the healthcare budget to	Infliximab, biosimilar, other biological treatments	CD patients receiving originator therapy	3 years	-Scenario 1: interchanging between originator infliximab and biosimilar infliximab was not allowed -Scenario 2: 80% of the patients could interchange between originator and biosimilar infliximab and new biological

**Table A2: Characteristics of Included Cost Studies**

First author, Publication Year, Country	Type of Analysis, Perspective	Intervention, Comparator	Study Population	Time Horizon	Main Assumptions
	finance additional biosimilar therapy for CD patients				treatments -biologic market yearly growth rate of 10%; retail price of biosimilar infliximab 75% of originator infliximab in all six countries
Severs; 2016; Netherlands <sup>21</sup>	Stochastic economic probabilistic model using Monte Carlo simulation to assess the impact of the introduction of anti-TNF biosimilars on annual IBD-specific health care costs	Anti-TNF biosimilars versus no biosimilar introduction	UC and CD patients naïve to anti-TNFs, or who switch	5 years	-Use of anti-TNF compounds increases 1% annually -Hospitalization costs assume to decrease by a maximum of 10% over time -Biosimilar price decreases to a minimum of 30% and a maximum of 60% of the originator price, while originator price decreases to between 40% and 90% respectively -A 50% price reduction necessary to induce a switch to biosimilars in anti-TNF users in 80 to 85% of users -20% of new anti-TNF users start on infliximab; 80% on biosimilar

Anti-TNF – anti-tumor necrosis factor; CD= Crohn’s Disease; IBD = inflammatory bow el disease; UC = ulcerative colitis, NR = not reported



**APPENDIX 3: Critical Appraisal of Included Publications**

<b>Table A3: Strengths and Limitations of Clinical studies using the Downs and Black checklist<sup>13</sup></b>	
<b>Strengths</b>	<b>Limitations</b>
<b>Extensions of Randomized Controlled Trials</b>	
Tanaka 2016 <sup>16</sup>	
<ul style="list-style-type: none"> <li>Multi-centre study that was an extension of a longer 5 year trial</li> <li>Imputation for missing outcome values</li> </ul>	<ul style="list-style-type: none"> <li>Non-randomized, open-label</li> <li>Different baseline characteristics in maintenance and switch group</li> <li>Much higher loss to follow up in switch group (33% versus 16%)</li> <li>No uncertainty measures, especially with regards to imputations</li> </ul>
Park 2016 <sup>15</sup>	
<ul style="list-style-type: none"> <li>Multi-centre, multi-national study that was extension of a longer randomized trial</li> <li>Low and comparable loss to follow up across arms</li> <li>Large sample size</li> <li>Appropriate statistical analyses and modelling</li> </ul>	<ul style="list-style-type: none"> <li>Partially-blinded, non-randomized</li> </ul>
Yoo 2016 <sup>17</sup>	
<ul style="list-style-type: none"> <li>Multi-centre, multi-national study that was extension of a longer randomized trial</li> <li>Non-responder imputation for missing values</li> <li>Population comprised ITT population of the initial trial</li> <li>Large sample size, similar discontinuation rates</li> </ul>	<ul style="list-style-type: none"> <li>Partially blinded, non-randomized</li> </ul>
<b>Observational Cohort Studies</b>	
Dapavo 2016 <sup>18</sup>	
<ul style="list-style-type: none"> <li>No reported loss to follow up</li> <li>Controlled intervention involving entire patient population</li> </ul>	<ul style="list-style-type: none"> <li>Non-randomized, open-label</li> <li>Generalizability unclear</li> <li>Small sample size, further stratified by treatment history</li> <li>Sample with known long-lasting response to infliximab</li> </ul>
Hlavaty 2016 <sup>19</sup>	
<ul style="list-style-type: none"> <li>Controlled intervention including all patients at a single centre with one year follow up</li> </ul>	<ul style="list-style-type: none"> <li>Multiple testing issues for significance test</li> <li>Non-randomized, open-label</li> <li>Small sample size</li> <li>No patient characteristics across groups described</li> <li>Reason for loss of follow up of 4/12 patients not clear</li> </ul>

**Table A4: Strengths and Limitations of a Systematic Review including Economic Studies using AMSTAR<sup>12</sup>**

Strengths	Limitations
Jacobs 2016 <sup>20</sup>	
<ul style="list-style-type: none"> <li>• Comprehensive literature search</li> <li>• Division into grey versus empirical papers</li> <li>• Quality assessment of studies conducted</li> <li>• Appropriate conclusions</li> </ul>	<ul style="list-style-type: none"> <li>• Double extraction on only 10% of articles</li> <li>• Potential conflict of interest, and no a priori protocol reported</li> <li>• Lack of detail on study characteristics</li> </ul>

**Table A5: Strengths and Limitations of Economic Studies using Drummond checklist<sup>14</sup>**

Strengths	Limitations
Brodsky 2015 <sup>7</sup>	
<ul style="list-style-type: none"> <li>• Real data to determine initial parameters when available</li> <li>• Appropriate sensitivity analysis for assumed parameters</li> </ul>	<ul style="list-style-type: none"> <li>• Unclear basis for assumptions relating to discontinuation, probabilities of initiating biosimilar or rate of interchanging by physicians or discount of biosimilar</li> <li>• No description of model</li> <li>• Considers limited number of costs</li> </ul>
Severs 2016 <sup>21</sup>	
<ul style="list-style-type: none"> <li>• Dutch prevalence and IBD cost data based on previous study that used detailed cost questionnaires</li> <li>• Assumptions were justified well, based on existing data and expert panel consultation</li> <li>• Appropriate sensitivity analysis for assumed parameters</li> </ul>	<ul style="list-style-type: none"> <li>• Results highly sensitive to assumption around prescribing behavior, which is difficult to predict due to lack of literature</li> </ul>

**APPENDIX 4: Main Study Findings and Author's Conclusions**

<b>Table A6 Summary of Findings of Included Studies</b>	
<b>Main Study Findings</b>	<b>Author's Conclusions</b>
<b>Dapavo 2016<sup>18</sup></b>	
-No difference in PASI (McNemar exact test $p > 0.05$ ) and visual analog scale scores (McNemar exact test $p > 0.05$ ) -No adverse events resulting in discontinuation	Severe plaque psoriasis patients being treated with infliximab originator can switch to the biosimilar without significant change in clinical response or safety profile.
<b>Tanaka; 2016<sup>16</sup></b>	
-Mean changes (+ SD) in ACR20, ACR50, ACR70 from baseline were $2.707 \pm 1.589$ , $2.747 \pm 1.727$ , $2.761 \pm 1.613$ , and $2.036 \pm 1.305$ , $1.940 \pm 1.664$ , and $1.964 \pm 1.711$ , in maintenance and switch group, respectively -Safety: 4 (10.5%) and 8 (24.2%) subjects had AEs resulting in discontinuation in the biosimilar group and switch group, respectively, unchanged from initial therapy. Most commonly, these were infusion related reactions.	CT-P13 demonstrated stable clinical efficacy and was well tolerated in both patients who maintained and switched to CT-P13 in RA patients
<b>Park 2016<sup>15</sup></b>	
-Change in ASAS20 (OR = 1.25 (0.58 to 2.70)), ASAS40 scores (OR = 1.09 (0.57 to 2.07)), and ASAS PR rates (OR = 0.80 (0.37 to 1.72)) similar in maintenance and switch group -Safety: Maintenance and switch groups reported similar AEs resulting in discontinuation from the study (3/90 and 4/84, respectively)	Switching from the originator to CT-P13 is possible without compromising efficacy or safety in AS patients
<b>Hlavaty 2016<sup>19</sup></b>	
-Efficacy: Sustained clinical response maintained in 87% of patients by week 40; no change in SIBDQ scores -Safety: Two AE (25%) resulting in discontinuation post-switch (loss of response and dermatitis)	Switching from infliximab to CT-P13 was largely safe, with similar clinical relapse and adverse event rates in IBD patients
<b>Yoo 2016<sup>17</sup></b>	
-Efficacy: Achievement of ACR20, ACR50, and ACR70 was 77.5%, 50.0% and 23.9% at week 54 (i.e. right before switch) and 71.8%, 51.4% and 26.1% at follow-up end; proportions similar to maintenance group; no notable differences in other efficacy endpoints -Safety: 16 (10.1%) and 8 (5.6%) patients had AE resulting in discontinuation in the maintenance versus switch groups; no noticeable difference in safety profile compared to main study	Patients who switched from infliximab to its biosimilar CT-P13 demonstrated comparable treatment efficacy and tolerability
<b>Brodzky 2015<sup>7</sup></b>	
-Total cost savings achieved in scenario disallowing interchanging, and in scenario allowing interchanging between infliximab and the biosimilar over the 3 years were estimated at 8.0 and 16.9 million Euros, respectively -Results were most sensitive to assumptions around biosimilar infliximab drug costs, population size and patients' average body weight	Considerable budget savings are possible with the introduction of biosimilar infliximab to treat CD

**Table A6 Summary of Findings of Included Studies**

Main Study Findings	Author's Conclusions
Severs 2016 <sup>21</sup>	
-Total cost savings after the introduction of biosimilars yielded total health care savings of €493 million over 5 simulated years -Results were most sensitive to price reductions of anti-TNF therapy and physician prescribing behaviour; in addition 121 million Euros could be saved if physicians switched to biosimilars amidst only minimal price reductions	Considerable budget savings are possible with the introduction of biosimilar infliximab to treat IBD

ACR = American College of Rheumatology; AE = adverse event; AS = ankylosing spondylitis; ASDAS = Ankylosing Spondylitis Disease Activity Score; ASAS = Assessment in SpondyloArthritis International Society; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CD = Crohn's disease; CDAI = Clinical Disease Activity Index; CRP = C-Reactive protein; DAS = Disease Activity Score; ESR = erythrocyte sedimentation rate; FCP = fecal calprotectin; HAQ-DI = Health Assessment Questionnaire for Rheumatoid Arthritis; HBI = Harvey Bradshaw Index; IBD = inflammatory bowel disease; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; PA = psoriatic arthritis; PASI = Psoriasis Area and Severity Index; PCDAI = Pediatric Crohn's Disease Activity Index; PP = plaque psoriasis; PUCAI = Pediatric Ulcerative Colitis Activity Index; SCCAI = Simple Clinical Colitis Activity Index; RA = rheumatoid arthritis; SCCAI = Simple Clinical Colitis Activity Index; SDAI = Simple Disease Activity Index; sIBDQ = Short Inflammatory Bowel Disease Questionnaire; UC = ulcerative colitis

**APPENDIX 5: Citations for Relevant Conference Abstracts**

Abdalla A, Byrne NE, Conway R, Walsh T, Mannion G, Hanly M, et al. Long term safety and efficacy of biosimilar infliximab among patients with inflammatory arthritis switched from reference product [abstract]. *Annals of the Rheumatic Diseases*. 2016 Jun;75:223. (Presented at Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR 2016;2016 Jun 8-11; London, England).

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Batticciotto A, Parisi S, Li Gobbi F, Antivalle M, Benucci M, Fusaro E, et al. Safety and efficacy of switching from innovator to biosimilar infliximab in patients affected by spondyloarthritis. A 6-month observational study [abstract]. *Annals of the Rheumatic Diseases*. 2016 Jun;75:806. (Presented at Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR 2016;2016 Jun 8-11; London, England).

Betty M, Downey L, Underhill C, Callaghan J, Rush M, Ahmed I, et al. Outcomes of a managed switching programme changing IBD patients established on originator infliximab to biosimilar infliximab [abstract]. *Journal of Crohn's and Colitis*. 2016 Mar;10:S43-44. (Presented at 11th Congress of the European Crohn's and Colitis Organisation, ECCO 2016;2016 Mar 16-19; Amsterdam, Netherlands).

Bocquet F, Degrasat-Théas A, Cordonnier A, Raybaut C, Parent de Curzon O, Fusier I, et al. Biosimilar infliximab: Feedback after a nine months experience of their use in the 37 public hospitals of Paris [abstract]. *Value in Health*. 2016 Nov;19(7):A444. (Presented at ISPOR 19th Annual European Congress;2016 Oct 29-Nov 2; Vienna, Austria).

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Carvalho LL, Anapaz V, Oliveira AM, Branco J, Cardoso M, Graca RC, et al. Biosimilar infliximab in real-life Crohn's disease's anti-TNFalfa naive patients: A comparative observational cohort study (SIMRECRO study) [abstract]. *Journal of Crohn's and Colitis*. 2016 Mar;10:S259. (Presented at 11th Congress of the European Crohn's and Colitis Organisation, ECCO 2016;2016 Mar 16-19; Amsterdam, Netherlands).

Choe JY, Prodanovic N, Niebrzydowski J, Staykov I, Dokoupilova E, Baranauskaite A, et al. A randomised, double-blind, phase III study comparing sb2, an infliximab biosimilar, to the infliximab reference product (remicade) in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy [abstract]. *Annals of the Rheumatic Diseases*. 2015 Jun;74:706-7. (Presented at Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR 2015;2015 Jun 10-13; Rome, Italy).

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**APPENDIX 6: Additional References of Potential Interest****Systematic review, randomized controlled trials, or observational studies not on switching**

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