OUTCOMES OF SWITCHING FROM ANTI-TNF BIOLOGIC DRUGS TO THEIR BIOSIMILARS: A SYSTEMATIC REVIEW
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Review questions

In people of all ages under active treatment for rheumatic disorders, dermatologic diseases, and inflammatory bowel diseases with anti-TNF biologic medicines (etanercept, infliximab, adalimumab) does switching to their biosimilar (e.g., CT-P13, PF-06438179, GP1111, ABP 501, GP2015, MSB11022, GP2017) [OR a switch from a biosimilar to another of the same biologic medicine] compared to non-switching affect the safety, immunogenicity and efficacy of the treatment?

Summary results

In adults, we found consistent evidence from systematic reviews and RCTs that switching from the originators of anti-TNF biologic medicines switching to their biosimilars does not affect safety, immunogenicity and efficacy of the treatment. A substantial amount of evidence from RCTs is available for infliximab, adalimumab: continuing the originator or switching to a biosimilars does not result in differences in response, ADA development or discontinuation. The certainty of these estimate was judged high for all the three outcomes (see Summary of Findings 1 and 2). Open-label long term extensions of the pivotal trials confirmed the equivalence between switching to a biosimilar or continuing with the biologic originator.

The only one RCT assessing the switch between etanercept originator and its biosimilar showed no differences in terms of response, discontinuation, or ADA development in adult patients with psoriasis. The RCTs was judged at moderate risk of bias. Similar results were found by open-label long term extensions.

In the paediatric population, we were able to retrieve only prospective multicentre observational cohort studies that evaluated the switch from infliximab originator to biosimilar in inflammatory bowel disease. In these studies, switching appears to be safe and effective.

We did not find evidence on switching from a biosimilar to another of the same biologic medicine.

Summary of Findings 1: Continuing reference infliximab (IFX) compared to switching to biosimilar

Patient or population: chronic inflammatory diseases
Intervention: continuing ref-IFX
Comparison: switching to biosimilar

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE) *
	Risk with switching to biosimilar	**Risk with continuing ref-IFX**			
response	665 per 1.000	**665 per 1.000** (612 to 718)	**RR 1.00** (0.92 to 1.08)	1112 (5 RCTs)	⊕⊕⊕⊕ HIGH
anti-drug antibodies	306 per 1.000	**331 per 1.000** (279 to 392)	**RR 1.08** (0.91 to 1.28)	863 (3 RCTs)	⊕⊕⊕⊕ HIGH
discontinuation	105 per 1.000	**101 per 1.000** (71 to 144)	**RR 0.96** (0.68 to 1.37)	1054 (4 RCTs)	⊕⊕⊕⊕ HIGH

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio

Summary of Findings 2: Continuing ref-adalimumab (ADMB) compared to switching to biosimilar

Patient or population: chronic inflammatory diseases
Intervention: continuing ref-ADMB
Comparison: switching to biosimilar

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE) *
	Risk with switching to biosimilar	**Risk with continuing ref-ADMB**			
response	831 per 1.000	**839 per 1.000** (781 to 905)	**RR 1.01** (0.94 to 1.09)	584 (3 RCTs)	⊕⊕⊕⊕ HIGH
anti-drug antibodies	495 per 1.000	**500 per 1.000** (441 to 560)	**RR 1.01** (0.89 to 1.13)	764 (4 RCTs)	⊕⊕⊕⊕ HIGH
discontinuation	57 per 1.000	**65 per 1.000** (40 to 107)	**RR 1.13** (0.69 to 1.86)	941 (4 RCTs)	⊕⊕⊕⊕ HIGH

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio

***GRADE Working Group grades of evidence**
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Introduction

The introduction of biological medicines on the market has changed the course of many serious and rare conditions. Over the past few years, the expiry of patents and/or other data protection certificates of biological medicines has fuelled interest in developing biosimilars, i.e. biological agents that are similar to other previously authorized biological medicines. Health systems should benefit from the introduction of biosimilars as they lead to price competition which improves patients' access to safe and effective biological medicines.
Regulatory authorities are responsible for the marketing authorisation of biosimilars. The approach established for generic medicines is not suitable for development, evaluation and licensing of biosimilars, given that biological medicines are relatively large and complex proteins that are produced following different manufacturing processes, which may lead to molecules that are similar but not identical to the originator. The assessment of biosimilarity with respect to the originator slightly differs in the different world regions, but it is basically based on the demonstration of similar analytical, pre-clinical and clinical performance (WHO 2019).

Definition of interchangeability

Interchangeability is the practice of replacing one medicine with another that is expected to achieve the same clinical effect in a given clinical setting. In the case of biosimilars, this could mean replacing a reference product with a biosimilar (or vice versa) or replacing one biosimilar with another. Replacement can be done by:

Switching: the prescriber decides to exchange one medicine with another medicine with the same therapeutic intent.

Substitution (also known as non-medical switching or automatic substitution): the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the prescriber.

Regulatory authorities usually require no specific studies assessing if alternating or switching from the biosimilar and its originator affect safety and/or efficacy in chronic conditions. In other words, biosimilars are expected to produce the same clinical results as their reference products in any patient, providing that biosimilarity has been demonstrated. The FDA represents a notable exception to this general approach. FDA applications for a biosimilar administered more than once to an individual generally include data from a switching study(ies) demonstrating that the risk in terms of safety or diminished efficacy of alternating or switching between use of the proposed interchangeable product and the reference product is not greater than the risk of using the reference product without such alternation or switch (FDA 2019a). The FDA has created a regulatory designation pathway for the scientific evaluation of interchangeability, requiring that the proposed interchangeable product "can be expected to produce the same clinical result as the originator in any given patient; and for a product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the product and its originator is not greater than the risk of using the originator without such alternation or switch" (FDA 2019b). At the time of this report preparation, no biosimilars have been deemed interchangeable by the FDA.
In Europe, the European Medicines Agency is in charge of the licensing of biosimilars while national authorities are usually responsible for the definition of policies regarding switching and interchangeability with the originator (EMA 2019).

Post-marketing studies comparing switchers to non-switchers have the potential to rule out possible difference in the efficacy, safety and immunogenicity.

Anti-tumour necrosis factors for rheumatic, dermatologic and inflammatory bowel conditions

The cytokine tumour-necrosis factor (TNF) is a key mediator of inflammation in several inflammatory disease. Biologic medicines such as etanercept, infliximab, adalimumab, golimumab and certolizumab that are able to antagonise the effect of TNF are widely used in a variety of inflammatory conditions, such as rheumatic disorders (e.g., rheumatoid arthritis), dermatologic diseases (e.g., psoriasis), and inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis). These medicines have shown significant efficacy and are usually used for long periods, increasing the burden on healthcare systems given their high costs. Biosimilars of etanercept, infliximab, and adalimumab are currently available in several world's regions, including the European and North America markets. The first biosimilars of infliximab, etanercept and adalimumab were licensed by the EMA in 2013, 2016, and 2017 respectively (Allocati 2020). The expiration of patents of golimumab and certolizumab is expected in 2021.

Given the chronic prescription of anti-TNF agents in inflammatory diseases and the rather long experience of use of their biosimilars, this drug class is a key case model for assessing the evidence supporting the safety and efficacy maintenance of switching from originators to biosimilars.

General purpose

The general scope of this report is to summarise the evidence to understand issues and barriers to full interchangeability for wider access to affordable biologic medicines and their biosimilars. This effort includes collecting evidence that reduces uncertainties about the use of biosimilars, evidence of strategies focused on potential mandatory interchangeability at procurement and clinical level, and tackling new approaches to develop, license and monitor biosimilars to improve efficiency of market approval and accelerate access.

This report aims to inform the Expert Committee in charge of issuing recommendations on interchangeability of biosimilar products. Guidance provided by WHO and its Expert Committee will support countries in making evidence-based, timely and informed choices when considering the inclusion of biological and biosimilar medicines on their national lists.

Objective

This report includes a comprehensive review of studies that assessed the outcomes of switching between biologics and their biosimilars and focuses on those treatment considered by the Expert Committee of Essential Medicines List (WHO EML 2019).

Evidence was collected across several diseases and considering both pre-marketing trials and post-marketing drug-utilization data helping to consolidate the practice of switching/substituting from reference to biosimilar medicines.

The review question is the following:

In people of all ages under active treatment for rheumatic, dermatologic and inflammatory bowel conditions with anti-TNF biologic medicines does switching to their biosimilar [OR a switch from biosimilar X to biosimilar Y of the same anti-TNF agent] compared to non-switching affect the safety, immunogenicity and efficacy of the treatment?

Methodology

The following sections describes the general methodological approach applied for each dyad class product-indications.

Eligibility criteria
Secondary and tertiary literature

Up-to-date systematic reviews and other types of evidence syntheses (e.g. health technology assessment [HTA] reports, clinical guidelines if developed following a systematic approach) evaluating safety, immunogenicity or efficacy of switching from a biologic medicine to its biosimilars or from different biosimilars of the same biologics. We considered as "up-to-date" those evidence syntheses in which the last date of literature search was conducted after October 2017, e.g. three years from the preparation of this report (October 2020). The reference lists of those evidence syntheses that were considered not up to date were anyway checked to identify possible additional studies.

Primary literature

Switching studies may apply different designs, including transition, single-switch cross over, multiple-switch studies (Figure 1).

Transition design: patients switch only from one biologic to another (e.g., from originator to biosimilar).

Single-switch cross over: patients starting on the originator are switched to biosimilar and those starting on biosimilar are switched to originator.

Multiple-switch studies: patients undergo a series of switches alternating originator and biosimilar.
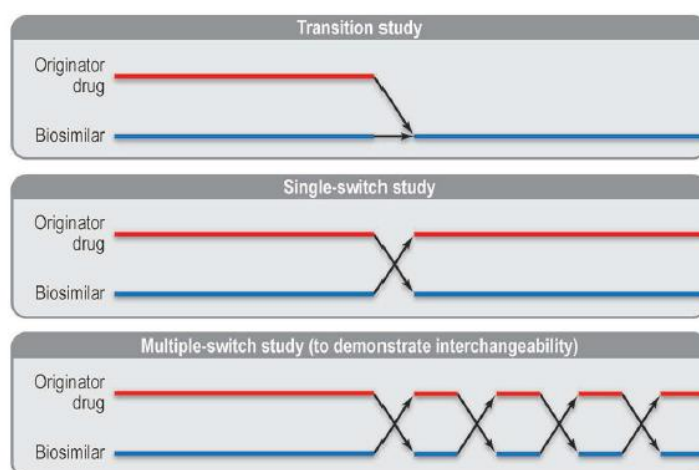
Figure 1: study design for exploring switch between originator biological drugs and biosimilars. Source: Faccin et al 2016.

For the purpose of this review, we applied a hierarchal approach to inclusion of primary studies, focusing on the most robust designs, i.e., randomised design with appropriate control arms, whenever available.

We included randomised controlled trials (RCTs) and prospective controlled cohort studies not included in the previously mentioned secondary and tertiary literature. Retrospective cohort studies, uncontrolled and controlled transition studies, cross over studies are considered eligible only if no evidence from prospective controlled studies are available.

Search strategies
To retrieve the evidence, we searched MedLine, EMBASE, and The Cochrane Library applying the search strategies reported in Appendix 1. The reference lists of the eligible reviews (included and excluded at the full text screening stage) have been checked. To retrieve information on ongoing or

unpublished studies, we searched the main trial registries and the International Clinical Trials Registry Platform.

Study selection

Two reviewers independently screened titles and abstracts of the retrieved records to exclude any clearly irrelevant records. The full publications of possibly eligible records were retrieved and checked by two reviewers to confirm eligibility. Any discrepancies were resolved by discussion.

Data extraction and synthesis

The key feature of each review or study were summarised in a tabular format by one reviewer and checked by a second one. The effect of switching on the three clinical areas of drug efficacy, safety, and immunogenicity was noted for each published study. Whenever possible and appropriate, we extracted numeric information on the results and performed meta-analysis. We estimated treatment effects from each study by using odds ratio (OR) with 95% confidence intervals (95% CIs). We presented results from pairwise meta-analysis as summary relative effect sizes.

Risk of bias assessment

We assessed the risk of bias of included evidence synthesis reports by using the AMSTAR-2 tool (Shea 2017 and AMSTAR-2 2017) and that of primary studies by using the criteria of The Cochrane Collaboration: Risk of bias tool for RCT (Higgins 2011) and ROBINS-I for cohort studies (Sterne 2016). Two review authors independently assessed the risk of bias of each study and resolved disagreements by discussion to reach consensus.
The risk of bias assessment was integrated with the other factors affecting the certainty of evidence (inconsistency, indirectness, imprecision and publication bias) as defined by the GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) methodology (GRADE 2019).

Summary of findings

Whenever possible, we prepared a summary of findings for each dyad class product-indications, considering the following outcomes: measure of clinical efficacy (e.g., clinical remission, response, biomarker levels), persistence in treatment (discontinuation), rate of adverse event, any measure of immunogenicity (e.g., anti-drug antibody levels).

Results

Study selection

The systematic searches launched on December 5th, 2019 and updated on October 2nd, 2020 resulted in 570 records, after duplicates were discarded. Five records were retrieved from other sources. As shown in Figure 2, after applying the eligibility criteria 56 records were selected for the full text reading. We identified 18 systematic reviews published in the period 2017-2020. Two were excluded as focused on slightly different topics: one only compared double-blind vs open label studies to explore the so-called "nocebo effect", i.e. the alleged increased rate of adverse events due to the awareness of switching (Odinet 2018) and one assessed the switch among different biologic agents in clinical practice conditions (Luttropp 2020). Three were excluded as narrative reviews (Kay 2020, Solitano 2020, Numan 2018) and six because their last date for search were older than October 2018 (Gisbert 2018, CADTH 2017, Komaki 2017, Cohen 2018a, Inotai 2017, Moots 2017). The reference lists of the excluded reviews were checked to identify studies not retrieved by our literature searches.

We identified 14 RCTs (seven on infliximab, six on adalimumab, one on etanercept) and 11 open-label extensions (five on infliximab, two on adalimumab, four on etanercept). We also identified two

ongoing with no results at the time of this report (ADA-SWITCH_ NCT04131322 and ACTRN 12618000279224)

Moreover, we included three single-arm cohort studies (Gervais 2018, Sieczkowska 2016, Kang 2018) involving paediatric populations.
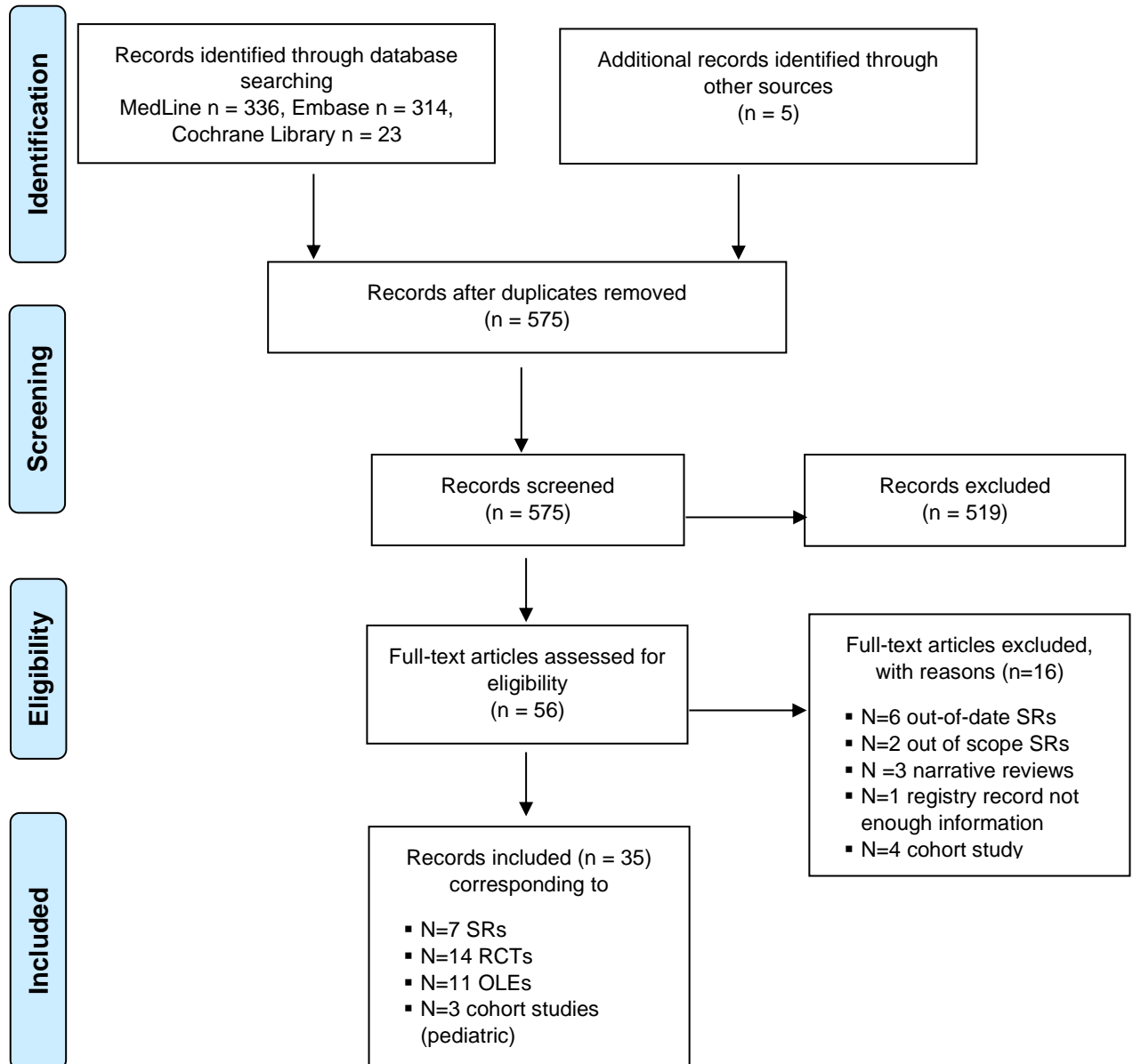

Figure 2: Flow chart (SR: systematic review, RCT: randomised controlled trial, OLE: open-label extension)

Included studies
Adults

Systematic review (N=7)

We identified seven up-to-date reviews, published between 2018-2020, summarising studies on switching from originators to biosimilars of anti-TNF agents (Barbier 2020, Bernard 2020, Queiroz 2020, Mezones-Holguin 2019, Bakalos 2019, Ebbers 2019, Feagan 2018).

One review (Barbier 2020) synthesized the switch data for biologicals of every therapeutic class for which a European market authorization has been granted but we reported only the data on anti-TNF agents. Another one focused on monoclonal antibodies but had actually retrieved only studies on infliximab (Bakalos 2019); The other reviews evaluated anti-TNF agents in gastrointestinal, rheumatic, and dermatologic chronic conditions. Four reviews focused only on infliximab (Bernard 2020, Queiroz 2020, Mezones-Holguin 2019, Feagan 2018), one on etanercept (Ebbers 2019).

Four reviews included both RCTs and observational studies (Barbier 2020, Bernard 2020, Mezones-Holguin 2019, Feagan 2018). Three reviews only included prospective and retrospective cohort studies as their primary aim was to assess the effect of switching in clinical practice, in particular discontinuation (Queiroz 2020, Bakalos 2019, Ebbers 2019) starting from the assumption that switching may be associated to higher-than-expected discontinuation rates that may occur for subjective reasons, potentially indicative of nocebo responses.

Table 1 summarises the main features of the included reviews. None of the included reviews but Queiroz 2020 performed meta-analyses. None met all the AMSTAR 2 critical domains (see Appendix 2).

Most of the data summarised by the included reviews refer to switching the infliximab originator to CT-P13. Overall, these reviews failed to show any significant differences between biosimilars and originators. Switching was not associated with an increase in safety signals or immunogenic reactions, nor with a decreased efficacy of treatments. Efficacy, safety, and immunogenicity of biosimilars of infliximab have been confirmed in several RCTs an well-conducted observational study. Less studies are available on the biosimilars of adalimumab and etanercept, but data appears to support the similarity with the originators.

Some reviews, based on many uncontrolled studies and case series, reported large variation in post switch discontinuation rate across studies. For example, discontinuation rates of the biosimilar mAb reported in real-world switching studies ranged from 2.8% to 28.2%, which are higher than those reported in the double blind, randomised study NOR-SWITCH study (Jorgensen 2017) and in studies of long-term originator infliximab use (Bakalos 2019). The review by Queiroz et al included 30 observational for a total of 3,594 patients with IBD and reported discontinuation rates of 8%, 14%, and 21% at 6, 12, and 24 months after switch. The main reasons for drug discontinuation and their respective risks were disease worsening (2%), remission (4%), loss of adherence (4%), adverse events (5%), and loss of response (7%). The quality of the evidence ranged from low to very low.

Discontinuation rate is suggested as meaningful marker of treatment efficacy and tolerability that can also provide insight into clinical and patient-reported consequences of non-medical switching (Souto 2016). While this high level of variation may be concerning, especially for patients with chronic diseases who may have been in long-term disease remission before the switch, it should be noted that the robustness of discontinuation rate estimates, especially in single-arm observational studies, is limited by several factors, i.e. its cumulative nature and the possibility of the nocebo effect.

Given the limitations of the included reviews and their important methodological deficiencies (Appendix 2), we analysed the evidence coming from RCTs and long-term extension of RCTs for each anti-TNF.

Non-randomised studies may be helpful for clinical and policy decision making, as they can be conducted on larger samples and in clinical practice settings. However, there are several challenges regarding their study design, the source of data, bias control and the approach to data analysis (Desai 2019).

Table 1: included up-to-date reviews

1st author (year)	Date of last research	Authors' affiliation	Indications	Biologic(s)	Outcomes	Design of included studies	Number of included studies	Total participants	Main results (efficacy)	Main results (safety)	Main results (Immunogenicity)
Barbier 2020*	December 2019	University of Leuven, MEB Agency, The Netherlands	Chronic, inflammatory conditions	Infliximab, adalimumab, etanercept	Efficacy, safety, immunogenicity	RCTs, OLEs, prospective and retrospective observational, registries, case series	Infliximab RCTs and OLEs: 21; other study design: 91 Adalimumab: RCTs and OLEs: 7; other study design: 0 Etanercept: RCTs and OLEs: 5; other study design: 20	Overall, approximately 20,000	Infliximab and etanercept RCTs and OLEs: switch did not negatively affect efficacy; other study design showed some differences, in discontinuations probably because of nocebo effects Adalimumab: RCTs and OLEs: the switch did not negatively affect efficacy	the switch did not negatively affect efficacy, with the exception of some observational studies on infliximab Short study duration precludes the assessment of rare AEs	Apparently, the switch did not negatively affect the immunogenicity profile (less data available)
Queiroz 2020	June 2018	San Paulo University, Brazil	IBD	Infliximab, adalimumab?	Discontinuation at 6-24 months and reasons for discontinuation	(before and after) observational studies, case series	30	3954	Risk of discontinuation at 6 months 8%, 12 months 14%, 24 months 21% Remission 4%; disease worsening 2%, loss of response 7%, loss of adherence 4%, AEs 5% (quality from very low to low)	NA	NA
Bernard 2020	April 2018	University Montreal, Canada	IBD (CD, UC)	Infliximab/CT-P13	Efficacy, effectiveness, response, safety (disease worsening, loss of response, sustained remission)	RCTs and observational studies, case series	3 RCTs, 40 observational studies, 1 case series	NR	Most studies revealed no efficacy concerns	Most studies revealed no safety concerns (however, short FU precludes the correct evaluation)	Most studies revealed no immunogenicity concerns

Mezones-Holguin 2019	June 2018	University, HTA Agency, Peru	Chronic, inflammatory conditions	infliximab	Efficacy, safety (+financial analysis)	Controlled studies	2 RCTs, 3 OLEs	1723	No difference between maintenance and switching groups	No difference between maintenance and switching groups	NA
Ebbers 2019	January 2019	Biogen Intern, UK	RA, PsA or AxSpA, AS, PsO	etanercept (originator vs SB4)	acceptance, effectiveness, safety	prospective and retrospective observational, registries	6 full publications, 23 congress abstracts, 2 letters	13552 (11053 switching)	3 studies: DANBIO registry, BIO-SPAN, Pescitelli: no differences in DAS28 and PASI scores, and other disease index - A higher rate of methotrexate use was also observed in switchers vs. nonswitchers in both the DANBIO registry and the Swedish Rheumatology Quality register	DANBIO registry: no major safety signals,	no data available (low rate of ADAs for etanercept)
Bakalos 2019	May 2018	Hoffmanne La Roche Ltd	rheumatic diseases and IBD	mAbs (all studies on infliximab)	discontinuation rate	observational	14 full publications (2 national registries, 11 prospective control cohort studies, 1 retrospective)	NR	discontinuation rate: range from 2.8% to 28.2%	NR	NR
Feagan 2018	January 2018	Janssen	rheumatic diseases psoriasis, IBD	Infliximab	efficacy, safety	transition study (controlled and uncontrolled), RCTs, observational	6 RCTs, 53 observational studies (molti uncontrolled)	NR	no clinically important efficacy or safety signals associated with switching	no clinically important efficacy or safety signals associated with switching	NR

AS: ankylosing spondylitis; AxSpA: axial spondyloarthritis; DAS28: disease activity score; IBD: inflammatory bowel disease; mAbs: monoclonal antibodies; NR: not reported; PASI: Psoriasis Area and Severity Index; PsA: psoriatic arthritis; PsO: plaque psoriasis; RA: rheumatoid arthritis; RCT: randomised controlled trial.

* the reviews assessed the efficacy, safety and immunogenicity of switching in several classes of biologics; data are reported only for anti-TNF agents.

INFLIXIMAB
RCTs (N=7)

Table 2 summarises the main characteristics of the included RCTs on infliximab.

Six RCTs evaluated the switching from originator to biosimilar, in which patients treated with the originator were randomised to switch to the biosimilar or continue the originator (single transition studies).

- Alten 2019 and Cohen 2020 (REFLECTIONS B537-02): patients with moderate-to-severe, active rheumatoid arthritis were initially randomised to infliximab (biosimilar or originator) for 30 weeks (treatment period 1). During weeks 30–54 (treatment period 2), the patients in the biosimilar group continued their assigned treatment, while the patients in the originator group (n=286) were re-randomised (1:1) to continue the originator or switch to the biosimilar for a further 24-week period. During the treatment period 2, patients in all the three treatment groups maintained comparable treatment response. There were no clinically meaningful differences in the safety profiles between groups and the percentage of patients who were antidrug antibody-positive was generally stable through the treatment period. During the treatment period 3 (week 54-78) all patients received the biosimilar and efficacy was sustained and comparable across groups. The incidence of treatment-emergent adverse events and patients who were ADA positive and neutralizing antibody positive was stable and comparable across groups.
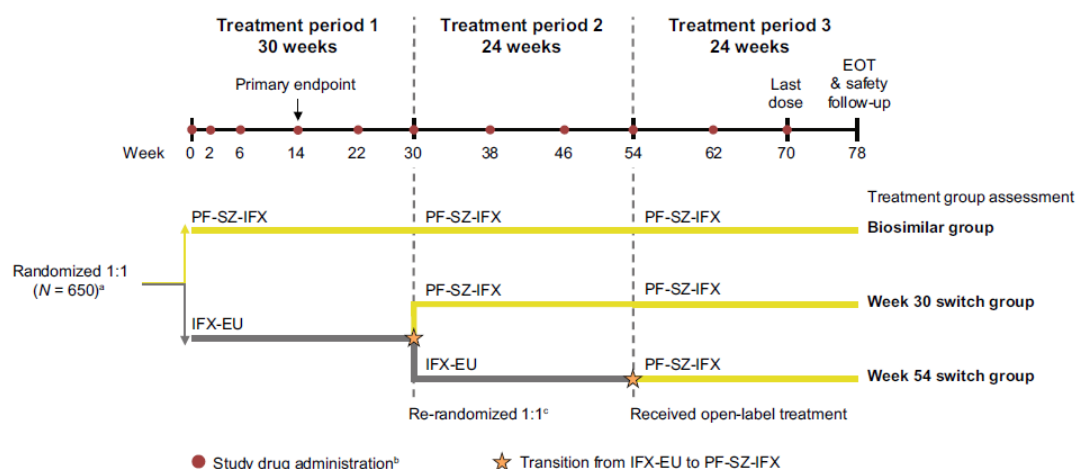
Figure 3: REFLECTIONS B537-02 Study design (Cohen 2020)

- Kaltsonoudis 2019 assessed the long-term effect of switching from infliximab originator to biosimilar in patients with ankylosing spondylitis naïve to other biologics. Patients who were in clinical remission were asked to switch and then randomly allocated to the switch and the maintenance group. After 18 months of treatment, all patients in both groups remained in clinical remission. No significant adverse events were noted between groups.
- Smolen 2018: patients with moderate to severe rheumatoid arthritis despite methotrexate treatment were randomised (1:1) to receive infliximab biosimilar or originator and at week 54 patients receiving the originator were re-randomised (1:1) to switch to biosimilar (n=94) or to continue on the originator (n=101) up to week 70. The efficacy, safety and

immunogenicity profiles remained comparable among the groups up to week 78, with no treatment-emergent issues or clinically relevant immunogenicity after switching.

- NOR-SWITCH study (Jorgensen 2017, Jorgensen 2020) was the first government-funded randomised study to explore switching from infliximab originator to biosimilar in six relevant disease groups. Adult patients with a diagnosis of Crohn's disease, ulcerative colitis, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, or chronic plaque psoriasis on stable treatment with infliximab originator treated in a hospital setting for at least 6 months were randomised (1:1) to either continued the originator or to switch to biosimilar (CT-P13). The study demonstrated that switching was not inferior to continuing treatment with infliximab originator according to a prespecified non-inferiority margin of 15%. As a subgroup analyses of participants with Crohn's and ulcerative colitis displayed a close to significant difference favouring originator infliximab, the authors provided further analysis of the efficacy, safety and immunogenicity in these subgroups. Both in the main and extension part of the study no significant concerns related to switching from originator infliximab to CT-P13 were shown.
- Roder 2018 reported - only in a poster presentation --a single-centre study in patients with Crohn's disease and ulcerative colitis switching from the originator infliximab to the biosimilar CT-P13. 11% more patients in the switching group lost response or had to stop therapy due to side effects as compared to patients who remained on the originator infliximab, although this difference did not reach the significance level.
- Volkers 2017 reported - only in a poster presentation – the preliminary data from a double-blind, phase IV, non-inferiority RCT in patients with Crohn's disease and ulcerative colitis. A total of 47 patients (of whom 21 completed the 30-week follow-up) were randomised to switch CT-P13 or continue infliximab originator. The authors concluded that switching from infliximab to the biosimilar is feasible and safe.

Ye 2019 assessed the switch from biosimilar to originator and vice versa. 220 patients with active Crohn's were randomly assigned (1:1:1:1) to receive CT-P13 then CT-P13, CT-P13 then infliximab, infliximab then infliximab, or infliximab then CT-P13, with switching occurring at week 30. 111 were randomly assigned to initiate CT-P13 (56 to the CT-P13–CT-P13 group and 55 to the CT-P13–infliximab group) and 109 to initiate infliximab (54 to the infliximab–infliximab group and 55 to the infliximab–CT-P13 group). Efficacy was well maintained and similar between groups after switching.

Long-term extensions (N=5)

Additional evidence on the switching from the infliximab originator to the biosimilar CT-P13 are available from the open-label long term extensions of the pivotal trials PLANETAS, PLANETRA and Japan-PLANETRA.

- The PLANETAS trial assessed the efficacy and safety of CT-P13 (biosimilar infliximab) in patients with ankylosing spondylitis. Among the participants who had completed the 54-week of the randomised phase 174 were included in the long-term extension (88 in the maintenance group; and 86 in the switch group) (Park 2017). All the participants received six infusions of CT-P13 from week 62 to week 102. The proportion of patients achieving a clinical response (ASAS20, ASAS40 criteria, ASAS PR rates) was maintained at similar levels to those in the main study in both the maintenance and switch groups and was comparable between groups. The proportion of patients with ADAs was similar in the maintenance and the switch groups at any time point. A lower proportion of patients in the maintenance group than the switch group experienced one or more treatment-emergent

adverse events during the extension. Most of treatment-emergent adverse events in the switch group were generally mild to moderate in severity.

- The PLANETRA trial assessed the efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis. Among the participants who had completed the 54-week of the randomised phase 302 were included in the long-term extension (158 in the maintenance group and 144 in the switch group) (Yoo 2017). All the participants received six infusions of CT-P13 from week 62 to week 102. ACR20, ACR50 and ACR70 response rates were maintained with no differences between the maintenance and switch groups at weeks 78 and 102. The proportion of patients with ADAs was comparable between groups as well as the rate of treatment-emergent adverse events.
- Tanaka 2016: The open-label long term extension of a Japanese trial with a design similar to the PLANETRA trial enrolled 38 patients in the maintenance group and 33 in the switch group. The safety and immunogenicity were similar in two groups.
- Goll 2019: The open-label long term extension of the NORSWITCH study described above compared the maintenance group (patients treated with CT-P13 for 72 weeks) and the switch group (patients treated with the originator for 52 weeks in the double-blind phase then treated with CTP13 for 26 weeks in the open-label phase). Disease worsening during the extension phase occurred at a similar rate in the two groups, with no significant difference amongst those switched at main study baseline and those switched at extension study baseline.

Another RCT conducted in India and published only as poster assessed the efficacy and safety of the infliximab biosimilar BOW015 compared to the originator (Kay 2015). In the open-label phase, responders to the allocated treatment (n=157) received BOW015 every 8 weeks at weeks 22, 30, 38 and 46, with follow-up at week 54. There was no significant difference in the proportion of subjects achieving ACR20, 50, or 70 responses between treatment groups in the randomised phase as well as in the extension after the switch.

ADALIMUMAB

RCTs (N=6)

Table 3 summarises the main characteristics of the included RCTs on adalimumab. Four RCTs evaluated the switching from originator to four different adalimumab biosimilars (single transition studies):

- AURIEL-PsO (Hercogova 2019) was a double-blind randomised controlled equivalence trial, in which patients with moderate-to-severe chronic plaque-type psoriasis were randomised (1:1) to biosimilar adalimumab (MSB11022) or originator. Patients with a ≥50% improvement in PASI at week 16 were eligible to enter a double-blind extension period: patients receiving biosimilar continued treatment, and patients receiving reference adalimumab were re-randomised 1:1 to continue either the originator or switch. Following treatment switch at week 16, no clinically meaningful differences in safety or immunogenicity were seen between treatment arms through the end of the observation period.
- The VOLTAIRE-RA (Cohen 2018b) study involved patients with active rheumatoid arthritis on stable methotrexate who were randomised to biosimilar adalimumab (BI 695501) or originator. At week 24, patients were re-randomised to continue their assigned treatment or switch from originator to biosimilar. Switch from originator to BI 695501 had no impact on efficacy, safety and immunogenicity.
- Weinblatt 2018: patients with moderate-to-severe rheumatoid arthritis were initially randomised (1:1) to receive SB5 or originator (40 mg subcutaneously every other week). At

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24 weeks, patients receiving the originator were re-randomised 1:1 to continue the treatment or switch to SB5 up to week 52; patients receiving SB5 continued with SB5 for 52 weeks. Switching from originator to SB5 had no treatment-emergent issues such as increased adverse events, increased immunogenicity, or loss of efficacy.

- Papp 2017: patients with moderate-to-severe plaque psoriasis were randomised (1:1) to receive biosimilar adalimumab (ABP 501) or originator 40 mg every 2 weeks for 16 weeks. At week 16, patients with ≥ 50% improvement from baseline in Psoriasis Area and Severity Index (PASI) score were eligible to continue to week 52. Patients receiving ABP 501 continued while adalimumab originator patients were re-randomised (1:1) to continue adalimumab or undergo a single transition to ABP 501. PASI percentage improvements from baseline were similar across groups at weeks 16, 32 and 50 as well as changes from baseline in percentage body surface area affected. No new safety signals were detected. AEs were balanced between groups and percentages of patients with binding and neutralizing ADAs were similar across treatments.

One study (Blauvelt 2018) assessed the impact of multiple switches between biosimilar adalimumab (GP2017) and originator in adult patients with moderate-to-severe plaque psoriasis. The study consisted of four periods: screening, treatment period 1 (TP1, randomisation to week 17), treatment period 2 (TP2, weeks 17–35) and an extension period (weeks 35–51). In TP1, eligible patients were randomised (1:1) to receive an initial dose of 80 mg subcutaneous GP2017 or originator, followed by 40 mg every other week, starting 1 week after the initial dose until week 15. Patients achieving ≥ 50% improvement in PASI 50 at week 16 were eligible for re-randomisation (2:1) to continue their originally assigned treatment until week 35 or to receive either GP2017 or originator during three alternating 6-week periods (TP2). During the extension period (weeks 35–51), all patients received the treatment originally assigned at randomisation. Switching up to four times between GP2017 and reference adalimumab had no impact on the incidence of adverse events or injection-site reactions. The frequency of ADA development was similar between the switching and continuing treatment groups, and there was no impact on efficacy.

Hodge 2017 reported - only in a poster presentation – the data from a double-blind, phase III comparing the adalimumab biosimilar CHS-1420 to the originator in people with moderator-severe psoriasis. After 16 weeks from randomisation, half the participants in the originator arm were switched to CHS-1420 and half continued the originator. All participants receiving CHS-1420 continued their treatment for 8 weeks. Patients who switched had similar efficacy and safety results at week 24 compared to non-switchers.

Long-term extensions (N=2)

We retrieved one-label extension study assessing the switch from adalimumab originator to the biosimilar ABP 501 (Cohen 2019). Among the participants who had completed the 26 weeks of the randomised phase 466 were included in the long-term extension (229 in the maintenance group and 237 in the switch group). The percentages of patients who reported treatment-emerging adverse events and efficacy were similar in the group that transitioned from originator to ABP 501 and the group that continued on ABP 501. The single switch from originator to ABP 501 did not impact immunogenicity.

We also retrieved a one-label extension study assessing the switch from adalimumab originator to the biosimilar FKB327 and vice versa. The participants who had completed the 22 weeks of treatment in the main study (Genovese 2019) were rerandomized as follows:

- participants treated with FKB327 (n=366) to continue FKB327 (n=216) or switch to the originator (n=108)

-participants treated with the originator (n=362) to continue the originator (n=213) or switch to FKB327 (n=108)

At week 30, all the participants were treated with FKB327 up to week 76, thus in this third period, 108 patients experienced a double switch (biosimilar-originator-biosimilar), 321 a single switch (either originator-biosimilar-biosimilar or originator-originator-biosimilar). Efficacy, safety and immunogenicity were similar for up to 2 years, and were not affected by single- or double-switching treatment (Genovese 2020, Alten 2020).

Table 2: RCTs (infliximab)

Study, year, (name)	Design&setting	Follow up	Population	Total randomised	Intervention	Control	Main outcomes
Alten 2019 (REFLECTIONS B537-02) and Cohen 2020	multicenter, double blind, 174 centers, 28 countries	24 weeks (up to 78 OLE)	RA, adults aged ≥18 years	286 (treatment period 2) 505 (treatment period 3)	PF-06438179/GP1111 (n=143)	infliximab EU (Remicade) (n=143)	ACR 20 (primary), ACR >20,50,70; DAS28-CPR, HAQ-DI, TEAES; % of ADAs e NAB
Ye 2019	multicenter, non-inferiority, 58 centres, 16 countries	54 weeks	Crohn's disease, adults 18-75 years	110 (switch groups)	CT-P13–infliximab (n=55 of the 110 firstly randomised to CTP13)	infliximab–CT-P13 (n=55 of the 109 firstly randomised to infliximab)	CDAI 70 response at week 6 (primary), CDAI 70 response at week 14 (after switch), clinical remission week 6/14 SIBDQ, incidence causality severity of AE, PO2
Kaltsonoudis 2019	open label, prospective observational cohort study, single centre (Greece) with random allocation (not clear)	18 months	ankylosing spondylitis, adults	88	Inflectra/Remsima (n=45)	reference infliximab (Remicade?) (n=43)	efficacy and safety: BASDAI, ASDAS, ESR (mm/h), CRP (mg/l)
Smolen 2018	double-blind, parallel group (transition study), 11 countries from Europe and Africa	78 weeks	moderate to severe RA, 18-75 year	195 (re-random)	SB2 (n=94)	Remicade (n=101)	ACR20, DAS28, AEs, immunogenicity
Roder 2018*	double-blind, IBD centre (Munich, Germany)	52 weeks	Crohn's disease, ulcerative colitis adults	200	CT-P13 (n=111)	infliximab originator (Remicade?) n=89	clinical remission (CAI and CDAI)
Jorgensen 2017 (NORSWITCH)	double-blind, parallel group, non-inferiority, comparative, phase IV - 24 Norwegian hospitals (17 gastroenterology,12 rheumatology, 5 dermatology hospital departments)	52 weeks	Crohn's disease, ulcerative colitis, spondyloarthritis, RA, psoriatic arthritis, chronic plaque psoriasis, adults	482	CT-P13 (n=241)	infliximab originator (Remicade?) (n=241)	disease worsening, safety (AEs), ADA
Volkers 2017* [ongoing?]	randomized, controlled, double-blind, phase IV, non-inferiority	30 weeks	CD and UC	47	CT-P13 (n=15)	Infliximab (n=6)	remission

* Volkers 2017 and Roder 2018 published only as poster.

ACR: American college of rheumatology; ADA: anti-drug antibody; AE: adverse event; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CAI: cytokine activity index; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28: disease activity score; ESR: erythrocyte sedimentation rate; EU: European union; HAQ-DI: Health Assessment Questionnaire Disability Index; IBD: inflammatory bowel disease; mAbs: monoclonal antibodies; NAB: neutralising antibody; NR: not reported; PASI: Psoriasis Area and Severity Index; RA: rheumatoid arthritis; RCT: randomised controlled trial, SIBDQ: Short Inflammatory Bowel Disease Questionnaire TEAE: treatment-emergent adverse event.

Table 3: RCTs (adalimumab)

Study, year, (name)	Design&setting	Follow up	Population	Total randomised	Intervention	Control	Main outcomes
Hercogova 2019	double-blind phase III equivalence trial, North and South America, Europe	50 weeks	moderate-to-severe chronic plaque-type psoriasis	202 (re-random reference adalimumab)	Switch to MSB11022 (n=101)	Continued reference adalimumab (n = 101)	PASI 75 (primary), mean change PASI -16, PGA, QOL TEAES-SAFETY, ADA
Blauvelt 2018	double-blind, Europe and US	51 weeks	active, clinically stable, moderate-to-severe chronic plaque psoriasis, adults	379	multiple switch GP 2017/originator (n=126)	continue treatment GP 2017/originator (n=253)	PASI 75-week 16, (primary) PASI 50/75/90/100 response rate, PGA disease activity, PK, immunogenicity, tolerability
Cohen 2018b (VOLTAIRE-RA)	double-blind, parallel-group, equivalence trial, 15 countries	58 weeks	moderate to severe RA, adults	645	BI695501 (n=324)	Humira (n=321)	ACR20, DAS28, AEs, immunogenicity
Weinblatt 2018	phase III, double-blind, parallel group (transition study), 7 countries (Bosnia and Herzegovina, Bulgaria, Czech Republic, Lithuania, Poland, Republic of Korea and Ukraine	52 weeks	moderate to severe RA, adults 18-75 years	254 (re-random)	SB5 (n=125)	adalimumab originator (Humira?) (n=129)	ACR20, DAS28, AEs, immunogenicity
Papp 2017	phase III, double-blind, active-controlled (single transition), Australia, Canada, Hungary	52 weeks	severe plaque psoriasis, adults 18-75 years	156	ABP501 (n=79)	adalimumab originator (Humira?) (n=77)	PASI, AE, immunogenicity
Hodge 2017	Phase III, double blind, multicentric (global)	24 weeks	Moderate to severe plaque psoriasis	545	Switch to CHS 1420 (n=124)	CHS 1420/CHS 1420 (n=250) Originator/originator (n=129)	PASI, TEAE, ADA

ACR: American college of rheumatology; ADA: anti-drug antibody; AE: adverse event; DAS28: disease activity score; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment; PK: pharmacokinetics; QoL: quality of life; RA: rheumatoid arthritis; RCT: randomised controlled trial; TEAE: treatment-emergent adverse event

ETANERCEPT

RCT (N=1)

The EGALITY study (Gerdes 2017, Griffiths 2017) was a multicentre, randomised, double-blind, phase 3, confirmatory efficacy and safety study conducted in 11 European countries and South Africa. Patients older than 18 years, with active but clinically stable chronic plaque psoriasis were randomised (1:1) to etanercept biosimilar (GP2015) or originator twice-weekly until week 12 (treatment period 1). Patients who had achieved at least a 50% improvement in PASI scores from baseline (PASI 50) at week 12 were re-randomised to either continue the same treatment on a once-weekly dosing schedule ('continued GP2015' and 'continued ETN' groups respectively), or undergo a sequence of three treatment switches between GP2015 and ETN at 6-week intervals until week 30 ('switched GP2015' and 'switched ETN' groups, respectively, treatment period 2). Of the 531 randomised patients, 497 were treated in the treatment period 2. Mean (standard deviation [SD]) PASI scores at baseline (before first drug administration) were comparable between patients who underwent multiple switches and those with continued treatments (22.60 [9.540] for pooled switched and 22.29 [8.622] for pooled continued treatment groups). The mean (SD) PASI score and mean percentage change from baseline in PASI score were also comparable between pooled switching and pooled continuing treatment groups at all time points. The median duration of drug exposure was similar in both treatment groups (120 days) as well as the proportion of patients with at least 1 treatment-emergent AE during the treatment period 2 (pooled switching 36.7%; pooled continuing 34.9%). During treatment period 2, discontinuations were similar in the two groups (continued ETN: 9/151, 6.0% vs switched ETN: 5/96, 5.2%). No patient from both treatment groups were positive for ADAs during treatment period 2.
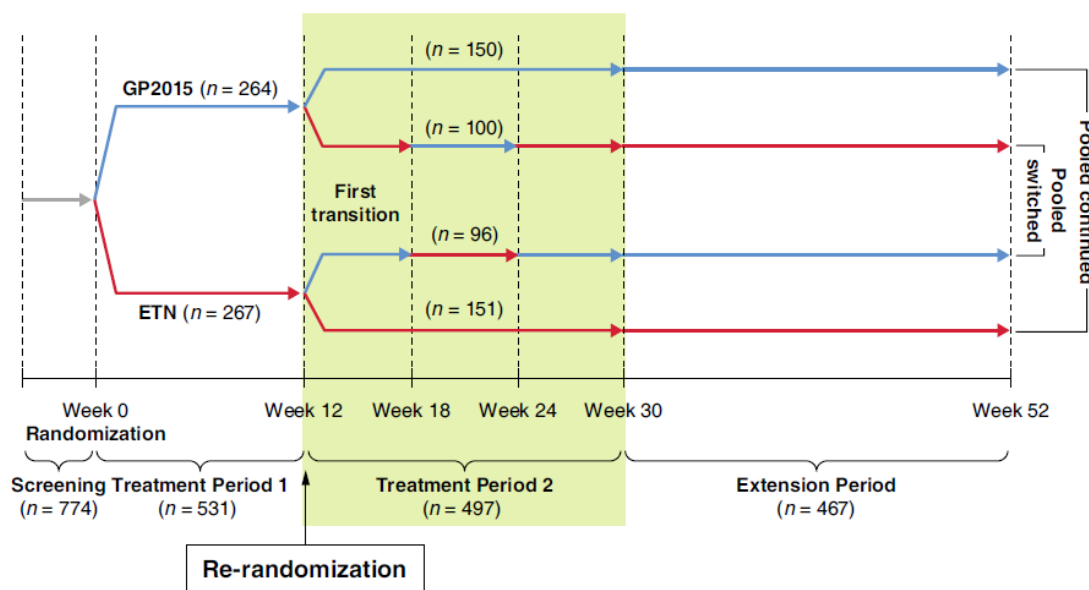
Figure 4: EGALITY Study design (Gerdes 2017).

Long-term extensions (N=4)

Additional evidence on the switching from the etanercept originator to three different biosimilars are available from the open-label long term extensions of RCTs:

- Jaworski 2019: the EQUIRA study was a phase III, double-blind study conducted in patients with moderate-to-severe rheumatoid arthritis and inadequate response to disease-modifying anti-rheumatic drugs. Eligible patients were randomised 1:1 to receive subcutaneous 50 mg etanercept biosimilar (SDZ ETN) or the originator, once-weekly, for 24

20

weeks. Among the participants with at least a moderate EULAR response at week 24, 341 were included in the long-term extension (175 in the maintenance group and 166 in the switch group). Change in DAS28-CRP from baseline up to week 48 was comparable between the "continued SDZ ETN" and "switched to SDZ ETN" groups, as well as the proportion of patients achieving good/moderate EULAR responses. The proportions of patients with at least one treatment-emergent adverse event and serious adverse events were similar the two groups. After week 24, no patient in the switching group developed ADAs, while 4 patients in the maintenance group had single-event, very low titre, non-neutralizing ADAs detected.

- Park 2019: this study is the long-term extension of an RCT comparing etanercept biosimilar (LBEC0101) and originator in patients with rheumatoid arthritis. Among the participants who had completed treatment in the randomised phase at week 52, 148 were included in the extension study (70 in the maintenance group; 78 in the switch group). Improvements in the DAS28-ESR score from week 52 were well maintained throughout the extension phase in both the maintenance and switch groups. The incidence of adverse events and the proportion of patients with newly developed ADAs were similar too.

- Emery 2017: this study is the long-term extension of an RCT comparing subcutaneous SB4 50 mg or etanercept originator once weekly for 52 weeks. 245 patients who completed the scheduled 52-week visit were enrolled in the open-label, single-arm extension period (126 in the maintenance group and 119 in the switch group). Efficacy, safety, and immunogenicity were comparable between the groups, showing no risk associated with switching patients from ETN to SB4.

- O Dell 2017: this study is a long-term extension of etanercept (biosimilar) CHS-0214 and originator inpatients with moderate-severe rheumatoid arthritis. After 24 weeks (Part 1) patients achieving ACR20 and no safety concerns then received CHS-0214 open-label for 24 weeks (Part 2). Over the 52-week study, no clinically meaningful differences in safety, immunogenicity, or efficacy were observed in patients who were switched from etanercept to CHS-0214 in comparison with those who only received CHS-0214.

Paediatric population

We retrieved three prospective multicentre observational cohort studies evaluating the switch from infliximab originator to biosimilar (CT-P13) in paediatric population affected by Crohn's disease, ulcerative colitis and other IBDs (Gervais 2018, Kang 2018, and Sieczkowska 2016). Two were small single-group studies involving 33 and 39 participants respectively (Gervais 2018, Sieczkowska 2016). No clinically significant changes to disease activity, biomarkers, ADA, and trough levels were recorded. A larger study on 74 patients (38 maintained on originator and 36 switched to CT-P13) showed a similar persistence in treatment and persistent remission at 1 year, as well as no statistically significant differences in any measures of disease activity, pharmacokinetics, or immunogenicity between the time of switch and 1-year post-switch in the CT-P13 switch group (Kang 2018).

Summary of the main findings

We were able to retrieve a large body of evidence regarding the switch between anti-TNF (especially infliximab and adalimumab) originators and biosimilars in adults with chronic inflammatory diseases, such as rheumatic disorders, inflammatory bowel diseases and psoriasis. When we pooled the results of the RCTs assessing the switch between infliximab originator and their biosimilars, we did not find any differences in the response, development of ADA or discontinuations (Figure 5).

Figure 5: meta-analyses of RCTs assessing the switch between infliximab and their biosimilars.
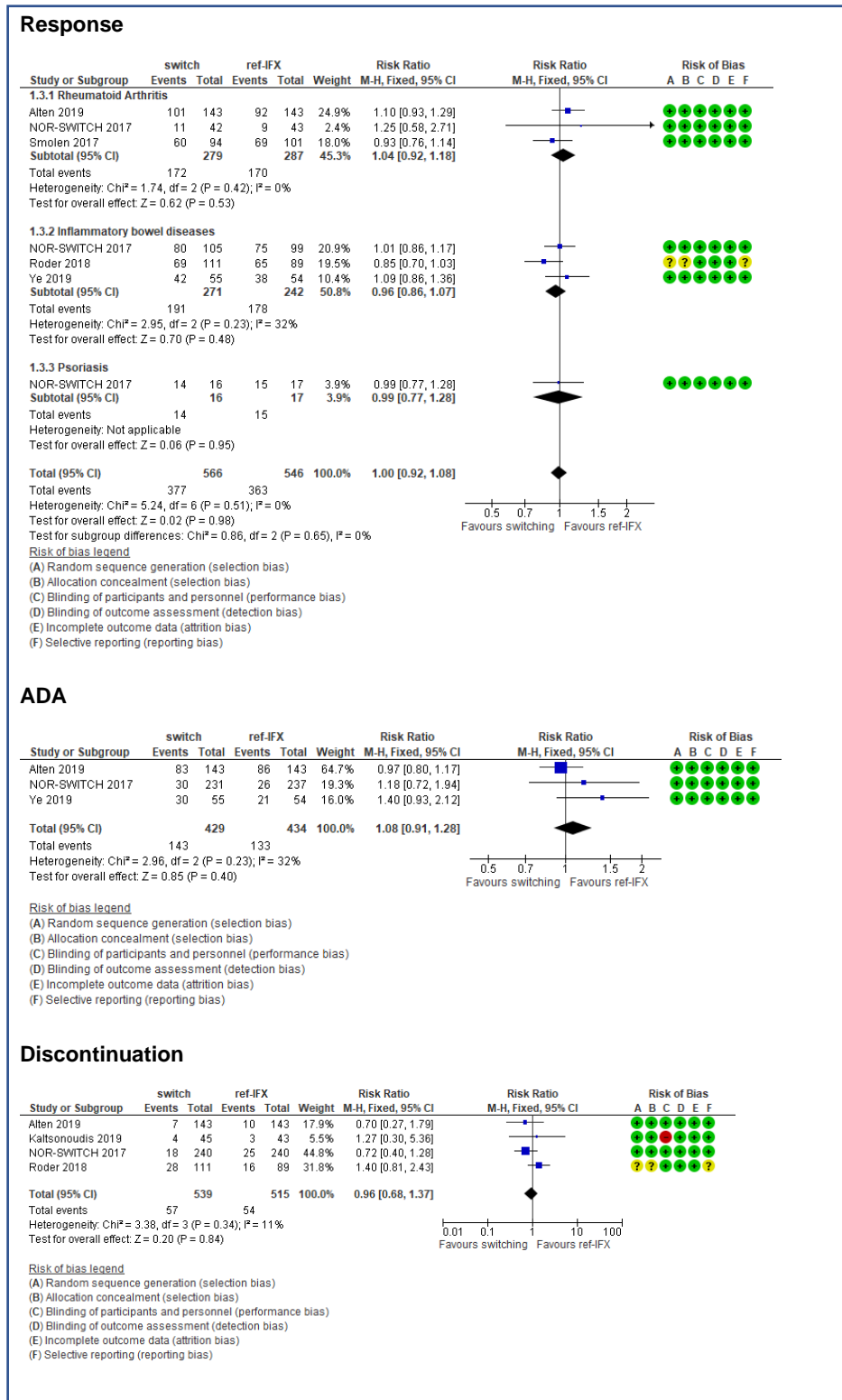
The certainty of these estimate was judged high for all the three outcomes. Open-label long term extensions of the pivotal trials confirmed the equivalence between switching to a biosimilar or continuing with the infliximab originator.

When we pooled the results of the RCTs assessing the switch between adalimumab and their biosimilars, we did not find any differences in the response, development of ADA or discontinuations (Figure 6). The certainty of these estimate was judged high for all the three outcomes. Similar results were found by open-label long term extensions.

Figure 6: meta-analyses of RCTs assessing the switch between infliximab and their biosimilars

Response

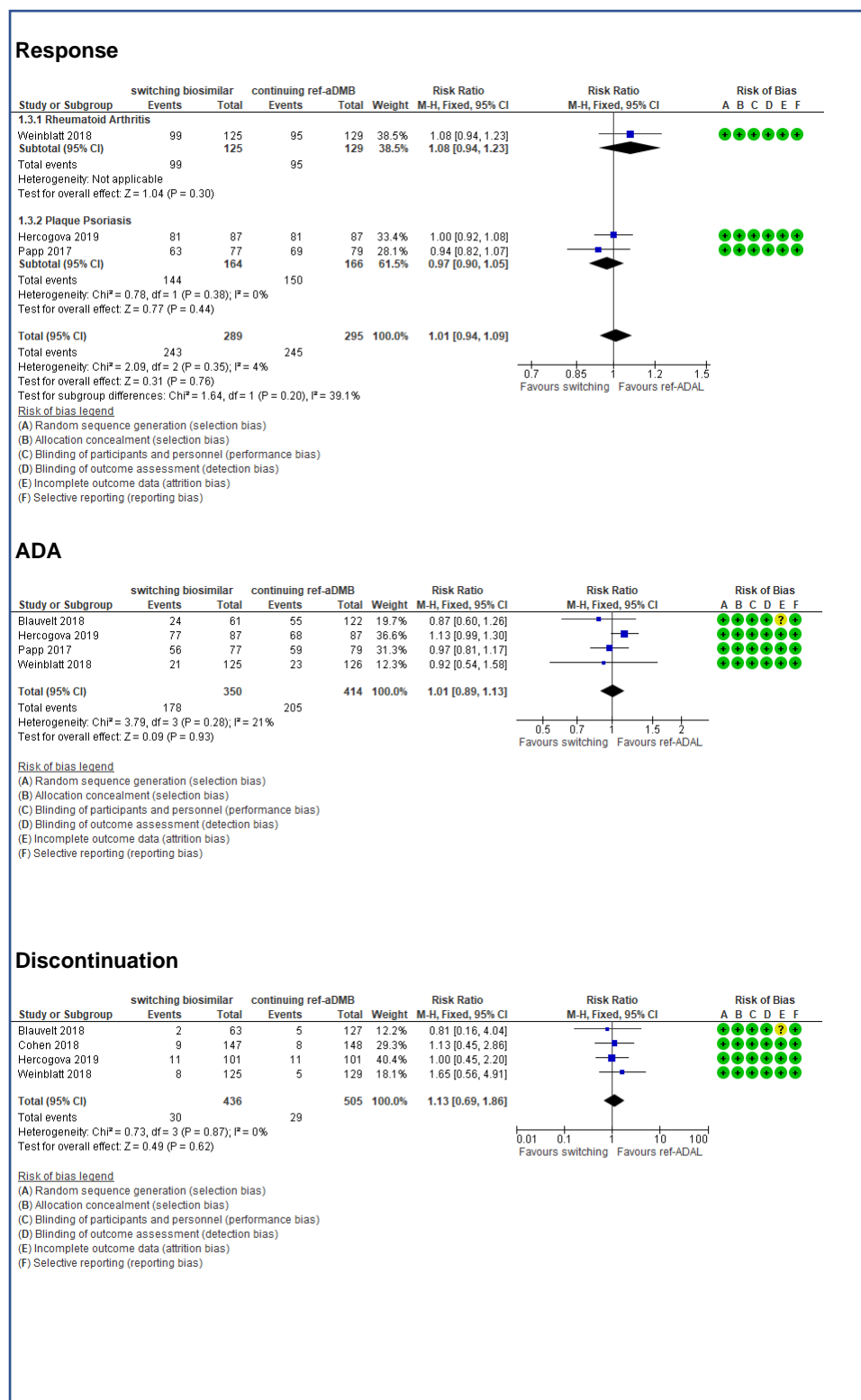| Study or Subgroup	switching biosimilar Events	Total	continuing ref-aDMB Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Rheumatoid Arthritis						
Weinblatt 2018	99	125	95	129	38.5%	1.08 [0.94, 1.23]
Subtotal (95% CI)		125		129	38.5%	1.08 [0.94, 1.23]
Total events	99		95			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
1.3.2 Plaque Psoriasis						
Hercogova 2019	81	87	81	87	33.4%	1.00 [0.92, 1.08]
Papp 2017	63	77	69	79	28.1%	0.94 [0.82, 1.07]
Subtotal (95% CI)		164		166	61.5%	0.97 [0.90, 1.05]
Total events	144		150			
Heterogeneity: Chi² = 0.78, df = 1 (P = 0.38); I² = 0%						
Test for overall effect: Z = 0.77 (P = 0.44)						
Total (95% CI)		289		295	100.0%	1.01 [0.94, 1.09]
Total events	243		245			
Heterogeneity: Chi² = 2.09, df = 2 (P = 0.35); I² = 4%						
Test for overall effect: Z = 0.31 (P = 0.76)						
Test for subgroup differences: Chi² = 1.64, df = 1 (P = 0.20), I² = 39.1%						

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

ADA

Study or Subgroup	switching biosimilar Events	Total	continuing ref-aDMB Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Blauvelt 2018	24	61	55	122	19.7%	0.87 [0.60, 1.26]
Hercogova 2019	77	87	68	87	36.6%	1.13 [0.99, 1.30]
Papp 2017	56	77	59	79	31.3%	0.97 [0.81, 1.17]
Weinblatt 2018	21	125	23	126	12.3%	0.92 [0.54, 1.58]
Total (95% CI)		350		414	100.0%	1.01 [0.89, 1.13]
Total events	178		205			
Heterogeneity: Chi² = 3.79, df = 3 (P = 0.28); I² = 21%						
Test for overall effect: Z = 0.09 (P = 0.93)						

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

Discontinuation

Study or Subgroup	switching biosimilar Events	Total	continuing ref-aDMB Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Blauvelt 2018	2	63	5	127	12.2%	0.81 [0.16, 4.04]
Cohen 2018	9	147	8	148	29.3%	1.13 [0.45, 2.86]
Hercogova 2019	11	101	11	101	40.4%	1.00 [0.45, 2.20]
Weinblatt 2018	8	125	5	129	18.1%	1.65 [0.56, 4.91]
Total (95% CI)		436		505	100.0%	1.13 [0.69, 1.86]
Total events	30		29			
Heterogeneity: Chi² = 0.73, df = 3 (P = 0.87); I² = 0%						
Test for overall effect: Z = 0.49 (P = 0.62)						

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

The only one RCT assessing the switch between etanercept originator and its biosimilar showed no differences in terms of response, discontinuation, or ADA development in adult patients with psoriasis. Similar results were found by open-label long term extensions.

The evidence in the paediatric population is scarce, and limited to infliximab used in Crohn's disease, ulcerative colitis and other IBDs. Data suggest a comparable efficacy and safety profile after switching to biosimilar.

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Appendix 1: search strategy anti-TNF (02.10.2020)

PubMed (N= 336)

((((((((((((("Drug Substitution"[Mesh] OR "Switch"[All] OR "switching"[All] OR "switched"[All] OR "switches"[All] OR "substitute"[All] OR "substitutes"[All] OR "substitution"[All] OR "substituted"[All] OR "substituting"[All] OR "interchange"[All] OR "interchanges"[All] OR "interchanged"[All] OR "interchanging"[All] OR "interchangeability"[All] OR "interchangeable"[All] OR "inter-change"[All] OR "inter-changes"[All] OR "inter-changed"[All] OR "inter-changing"[All] OR "inter-changeability"[All] OR "inter-changeable"[All] OR "inter change"[All] OR "inter changes"[All] OR "inter changed"[All] OR "inter changing"[All] OR "inter changeability"[All] OR "inter changeable"[All] OR "switchability"[All])))))

AND ((((("Biosimilar pharmaceuticals"[Mesh] OR "biosimilar"[All] OR "biosimilars"[All] OR "biosimilarity"[All] OR "similar biological medicine"[All] OR "similar biological medicines"[All] OR "similar biological medicinal product"[All] OR "similar biological medicinal products"[All] OR "follow on biologic"[All] OR "follow-on biologic"[All] OR "follow on biologics"[All] OR "follow-on biologics"[All] OR "Subsequent entry biologic"[All] OR "Subsequent-entry biologic"[All] OR "Subsequent entry biologics"[All] OR "Subsequent-entry biologics"[All] OR "follow on biological"[All] OR "follow-on biological"[All] OR "follow on biologicals"[All] OR "follow-on biologicals"[All] OR "Subsequent entry biological"[All] OR "Subsequent-entry biological"[All] OR "Subsequent entry biologicals"[All] OR "Subsequent-entry biologicals"[All]))))))))

AND

(((((((adalimumab) OR "Adalimumab"[Mesh]) OR humira)) OR (((etanercept) OR "Etanercept"[Mesh]) OR enbrel)) OR ((("Infliximab"[Mesh] OR "Infliximab"[All] OR "Jaximab"[All] OR "Remicade"[All] OR "SCH 215596"[All] OR "SCH215596"[All] OR "SCH-215596"[All] OR "TA 650"[All] OR "TA-650"[All] OR "TA650"[All]))))

Embase (N= 314)

No.	Query	Results
#16	#1 AND #2 AND #10 AND #14 AND [embase]/lim	274
#15	#1 AND #2 AND #10 AND #14	282
#14	#6 OR #11 OR #12 OR #13	434160
#13	'psoriasis'/exp/mj	55926
#12	'rheumatic disease'/exp/mj	177854
#11	'inflammatory bowel disease'/exp/mj	93612
#10	#3 OR #4 OR #5 OR #7 OR #8 OR #9	70856
#9	'etanercept'/exp/mj	6607
#8	'adalimumab'/exp/mj	8136
#7	'infliximab'/exp/mj	12737
#6	'inflammatory bowel disease' OR 'crohn disease' OR 'rheumatic disease' OR 'psoriasis'	269428
#5	'etanercept'	31155

No.	Query	Results
#4	'adalimumab'	**32483**
#3	Infliximab	**49562**
#2	'biosimilar agent' OR 'biosimilar drug' OR 'follow on biological'	**4302**
#1	'drug substitution'/exp OR 'drug substitution' OR 'switch' OR 'switching' OR 'interchange' OR 'interchangeability' OR 'switchability'	**203536**

Cochrane Library (N= 23)

#1 ("Drug Substitution" OR "Switch" OR "switching" OR "switched" OR "switches" OR "substitute" OR "substitutes" OR "substitution" OR "substituted" OR "substituting" OR "interchange" OR "interchanges" OR "interchanged" OR "interchanging" OR "interchangeability" OR "interchangeable" OR "inter-change" OR "inter-changes" OR "inter-changed" OR "inter-changing" OR "inter-changeability" OR "inter-changeable" OR "inter change" OR "inter changes" OR "inter changed" OR "inter changing" OR "inter changeability" OR "inter changeable" OR "switchability")

#2 MeSH descriptor: [Drug Substitution] explode all trees

#3 #1 OR #2

#4 ("Biosimilar pharmaceuticals" OR "biosimilar" OR "biosimilars" OR "biosimilarity" OR "similar biological medicine" OR "similar biological medicines" OR "similar biological medicinal product" OR "similar biological medicinal products" OR "follow on biologic" OR "follow on biologics" OR "Subsequent entry biological" OR "Subsequent-entry biological" OR "Subsequent entry biologicals" OR "Subsequent-entry biologicals")

#5 MeSH descriptor: [Biosimilar Pharmaceuticals] explode all trees

#6 #4 OR #5

#7 ("Infliximab" OR "Infliximab" OR "Jaximab" OR "Remicade" OR "SCH 215596" OR "SCH215596" OR "SCH-215596" OR "TA 650" OR "TA-650" OR "TA650")

#8 MeSH descriptor: [Infliximab] explode all trees

#9 #7 OR #8

#10 ("adalimumab"):ti,ab,kw OR ("Humira"):ti,ab,kw

#11 MeSH descriptor: [Adalimumab] explode all trees

#12 #10 OR #11

#13 ("etanercept"):ti,ab,kw OR ("Enbrel"):ti,ab,kw

#14 MeSH descriptor: [Etanercept] explode all trees

#15 #13 OR #14

#16 #9 OR #12 OR #15

#17 #3 AND #6 AND #16

#18 "accession number" near pubmed

#19 "accession number" near EMBASE

#20 #18 OR #19

#21 #17 NOT #20

Appendix 2: risk of bias assessment of included reviews and RCTs

Systematic reviews assessed with AMSTAR 2

Author (year)	1	2*	3	4*	5	6	7*	8	9*	10	11*	12	13*	14	15*	16
Barbier 2020*	yes	no	yes	yes	no	no	no	yes	no	no	No MA	No MA	no	no	No MA	yes
Queiroz 2020	yes	no	yes	part yes	yes	no	no	yes	no	no	no	no	yes	no	No MA	yes
Bernard 2020	yes	no	yes	no	yes	yes	no	yes	no	no	No MA	No MA	no	no	No MA	yes
Mezones-Holguin 2019	yes	no	yes	yes	yes	yes	no	yes	yes (only RCT)	no	No MA	No MA	yes	no	No MA	yes
Ebbers 2019	yes	no	yes	part yes	no	no	no	yes	part yes (only NRSI)	no	No MA	No MA	no	no	No MA	yes
Bakalos 2019	yes	no	yes	part yes	no	no	no	yes	part yes (only NRSI)	no	No MA	No MA	no	no	No MA	yes
Feagan 2018	yes	no	no	no	no	no	no	yes	no	no	No MA	No MA	no	no	No MA	yes

MA: meta-analysis, NRSI: non-randomised studies included

AMSTAR Critical domains (Shea 2017):

2. Protocol registered before commencement of the review
4. Adequacy of the literature search
7. Justification for excluding individual studies
9. Risk of bias from individual studies being included in the review
11. Appropriateness of meta-analytical methods
13. Consideration of risk of bias when interpreting the results of the review
15. Assessment of presence and likely impact of publication bias

RCTs assessed with Cochrane Risk of Bias tool (Higgins 2011)

Study ID	Random sequence generation	Description	Allocation concealment	Description	Blinding of participants and personnel	Description tion	Blinding of outcome assessment	Description	Incomplete outcome data	Description	Selective outcome reporting	Description	RoB Overall
Hercogova, 2019	Low	No info but multicentre, stratified	Low	Centralised, central interactive web response system	Low	Double-blind	Low	Double-blind	Low	Per protocol and ITT-19 patients (8.6%) biosimilar and 30 (13.6) originator excluded from the PPS	Low	Registered	low
Alten, 2019	Low	No info but multicentre, stratified	Low	No info but multicentre, stratified	Low	Double-blind	Low	Double-blind	Low	Not clear type of analysis but 89.4% completed TP2	Low	Registered	Low
Ye, 2018	Low	Randomized, multicentre, computer generation	Low	Sequential allocation	Low	Double-blind	Low	Double-blind	Low	ITT analysis	Low	Registered	Low
Blauvelt, 2018	Low	No info but multicentre, stratified	Low	Performed centrally	Low	Double-blind	Low	Double-blind	Unclear	Full analysis set (study was completed by 301, 64.7% ptz) – not clear if unbalanced	Low	Registered	Moderate
Kaltsonoudis, 2019	Low	Internet based allocation program	Low	Internet based allocation program	High	Open-label	Low	Open-label but objective outcomes	Low	80% patients completed the study – balanced between the two groups	Low	Not registered but seems that the published report includes all expected outcomes	High

Jorgensen	Low	Computer-generated randomised allocation sequence	Low	Central randomisation	Low	Double-blind	Low	Double-blind	Low	Intention-to-treat analysis; full analysis set 481/482	Low	Registered, protocol available	Low
Cohen	Low	No info but multicentre, stratified	Low	Interactive response technology system	Low	Double-blind	Low	Double-blind	Low	Full analysis set (6/645 excluded)	Low	Registered	Low
Weinblatt	Low	No info but multicentre, stratified	Low	Interactive web response system	Low	Double-blind	Low		Low	Full analysis set (2/544 excluded)	Low	Registered	Low
Smolen	Low	Interactive web response system	Low	Interactive web response system	Low	Double-blind	Low	Double-blind	Low	Intention-to treat analysis – full analysis set all patients randomised	Low	Registered	Low
Gerdes, 2017 Griffith, 2017	Low	Randomized	Unclear		Low	Double-blind	Low	Double-blind	Low	Per protocol and full analysis set during TP2	Low	Registered	Moderate
Papp, 2017	Low	Computer generated	Low	Interactive voice and web response system	Low	Double-blind	Low	Double-blind	Low	Full analysis set; 93%-94% completed the study	Low	Registered	Low
Roder	unclear	Randomized (no other info)	unclear	uneven numbers due to simplified random process	low	double-blind	low	double-blind	low	apparently no lost to follow up	Unclear	registration not found – not clear from abstract if all outcomes are reported	moderate