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ORIGINAL RESEARCH

The Economic Impact of Originator-to-Biosimilar Non-medical Switching in the Real-World Setting: A Systematic Literature Review

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ABSTRACT

Introduction: To save costs to the healthcare system, forced non-medical switch (NMS) policies that cut drug coverage for originator biologics and fund only less expensive biosimilars are being implemented. However, costs related to the impact of NMS on healthcare resource utilization (HCRU) must also be considered. This study aims to summarize the evidence on the economic impact of an originator-to-biosimilar NMS.

Methods: A systematic literature review (SLR) was conducted. Publications reporting on HCRU or costs associated with originator-to-biosimilar NMS in the real-world setting were searched in MEDLINE and EMBASE from January 2008 to February 2020. In addition to hand searching the reference lists of relevant publications and SLRs, key conference websites, PubMed, and various government sites were also searched for the 2 years preceding the search (2018–2020).

Results: A total of 1845 citations were identified, of which 49 were retained for data extraction. Most studies reporting on the HCRU associated with NMS reported on post-NMS HCRU alone without a comparison pre-NMS. However, four studies described a difference in HCRU (i.e., investigations pre- vs post-switch or between non-switchers vs switchers), all of which reported a relative increase in HCRU, including laboratory testing, imaging, medical visits, and hospitalizations, amongst patients who underwent an originator-to-biosimilar NMS. Most studies reporting on the costs associated with NMS reported significant savings following NMS on the basis of drug costs alone. However, four studies specifically reporting on the difference of costs following originator-to-biosimilar NMS all demonstrated an increase in HCRU-related costs associated with NMS (increase in HCRU-related costs of 4–37% or 148–2234 2020 Canadian dollars).

Conclusion: Amongst the studies that reported on the difference in HCRU pre- vs post-switch or between non-switchers and switchers, all showed an increase in HCRU and related costs associated with NMS, suggesting that the expected overall savings due to less costly drug prices may be reduced as a result of an increase in HCRU and its associated costs post-switch.

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Nevertheless, more real-world studies that include NMS-related healthcare costs in addition to drug costs are needed.

Keywords: Biologics; Biosimilar; Drug costs; Non-medical switching; Resource utilization; Systematic literature review

Key Summary Points

Why carry out the study?

As a result of the high cost of biologics, there has been a push to move to biosimilars, which are similar to a biologic but sold at a much lower price.

Biologics and biosimilars are not identical in terms of structure, function, quality, clinical efficacy, and clinical safety; therefore, costs other than those associated with drug acquisition need to be considered.

In order to evaluate the true economic impact of introducing originator-to-biosimilar non-medical switching (NMS) policies in Canada, a systematic literature review (SLR) evaluating the healthcare resource utilization (HCRU) and costs associated with originator-to-biosimilar NMS in the real-world setting was performed.

What was learned from the study?

Originator-to-biosimilar NMS may result in an increase in HCRU and HCRU-related costs, such that the expected cost savings associated with originator-to-biosimilar NMS may be greatly reduced.

Future economic evaluations on this topic need to consider the costs associated with additional HCRU, not just drug costs alone, in order to properly inform the decision to adopt a NMS policy.

INTRODUCTION

A biologic drug is any pharmaceutical drug product whose components or precursors are manufactured in, extracted from, or synthesized from, a living organism, or their cells, such as humans, animals, plants, and fungal or microbial organisms [1]. Important biologic drugs include hormones, hematopoietic growth factors, thrombolytic agents, cytokines, therapeutic enzymes, and antibodies [1]. Biologics are used in the treatment of rheumatological diseases, such as rheumatoid arthritis (RA), and gastrointestinal diseases, such as Crohn's disease (CD) and ulcerative colitis (UC) [2–5]; they can also be used to treat patients suffering from other chronic conditions in the areas of dermatology, hepatology, oncology, and growth development [6–9]. For this reason, the discovery of biological therapies have made a substantial clinical impact on the Canadian healthcare system. Canada is known to have a high prevalence of many of these chronic conditions, such as UC, CD, RA, and psoriasis, having some of the highest rates reported worldwide. Additionally, as a result of an aging population, population growth, and increasing life expectancy, the incidence and prevalence of some of these conditions have been increasing in recent years [10–12].

While biologic drugs comprise various vital therapeutic options for patients, they can be very costly to the healthcare system. In 2018, sales of biologic drugs in Canada reached $7.7 billion, placing Canada among the top-ranked countries in terms of per capita spending [13]. Biosimilars, on the other hand, are biologic medicinal products that are highly similar to a reference biologic drug that was already authorized for sale, and often sold at a lower price [1, 14–17]. Specifically in Canada, biosimilar drugs are sold at a reduced price that is, on average, 30% less than the price of the reference biologic [13, 18]. Accordingly, in comparison to Remicade®, biosimilar infliximab drugs are associated with an approximate 30–40% decrease in the listed price [18].

Biosimilars can play a role in limiting the economic burden on the healthcare system and

increasing patient access to biological treatments. Indeed, biosimilars can be offered at lower prices than the reference biologic and, in consequence, lead to price competition amongst biologic drugs [19]. Consequently, the adoption of biosimilars can help to liberate resources that could be used elsewhere by the healthcare system, such as for the reimbursement of innovative medicines [19]. A number of studies have also suggested that switching from a reference biologic to a biosimilar is not associated with any major efficacy, safety, or immunogenicity issues [19, 20]. For these reasons, governments in some jurisdictions have or are planning on implementing forced non-medical switch (NMS) policies by cutting drug coverage for reference biologics and funding only less expensive biosimilars. These NMS policies describe a plan whereby a stable patient's treatment regimen is changed for reasons other than efficacy, side effects, or adherence related to the original treatment [21]. Importantly, there has been ongoing debate as to whether or not the originator-to-biosimilar NMS is a viable option for patients that are successfully being treated with an originator biologic [21, 22]. Health Canada has authorized various biosimilars for sale in Canada and provinces have already introduced reimbursement policies for the utilization of biosimilars instead of the biologic originator for new patients. British Columbia announced in May 2019 a NMS policy that is expected to reduce costs by an estimated $96.6 million over the first 3 years alone [23, 24]. Specifically, while treatment-naïve patients will receive the biosimilar at treatment initiation, the NMS policy will force patients who are currently receiving the reference biologic to switch to the biosimilar drug regardless of disease activity. In December 2019, Alberta also announced the implementation of a similar originator-to-biosimilar NMS policy, while Ontario is taking steps towards realization of a similar policy [25, 26].

Although the introduction of biosimilars is expected to provide cost savings to the healthcare system, the impact of originator-to-biosimilar NMS on healthcare resource utilization (HCRU) and their associated costs is complex to assess. Importantly, biosimilars are often wrongly likened to generic drugs. Biosimilars are not generic drugs; they can never be exactly the same as their originator. Approved biosimilars are biotherapeutics that have been shown to have no clinically meaningful differences compared to their originator products. Therefore, when estimating the economic impact of originator-to-biosimilar NMS, one must consider indirect costs such as costs associated with additional healthcare resources including medical visits, laboratory tests, and phone consultations.

In 2019, Liu et al. published a systematic literature review (SLR) to retrieve studies that assessed the impact of NMS on HCRU and costs and found that the true economic impact of originator-to-biosimilar NMS remains uncertain as the focus of most studies remains on drug costs [27]. Liu et al. also concluded that more real-world studies focused on drug costs as well as the additional costs associated with HCRU are needed in order to accurately evaluate the overall economic impact of originator-to-biosimilar NMS. Considering the rapidly changing regulatory and market access framework for biosimilars, there are potentially several key studies reporting real-world data on originator-to-biosimilar NMS that have recently been published or presented at recent conferences. Consequently, an updated SLR on this topic, specifically in a real-world setting, is needed to provide more current evidence on the economic impact of introducing such NMS policies in Canada. Accordingly, the objective of this SLR was to systematically identify studies evaluating the HCRU or costs associated with originator-to-biosimilar NMS in the real-world setting.

METHODS

Study Identification

The literature search was performed in the MEDLINE and EMBASE databases using relevant keywords to identify published studies and conference proceedings reporting data associated with HCRU or costs associated with originator-to-biosimilar NMS, from January 2008

until the time of the search (March 3, 2020). For MEDLINE and EMBASE, in order to better align with the precise SLR objective, a search filter was developed and based on the Canadian Agency for Drugs and Technologies in Health (CADTH) for economic evaluations/cost/economic models as well as the recent publication by Lui et al. (2019) in the Cochrane database of systematic reviews, entitled "Search strategies to identify observational studies in MEDLINE and Embase" [28]. The developed filter was supplemented with keywords regarding treatments of interest (i.e., biosimilar, originator, etc.), studies in the real-world setting (i.e., cohort, cross-sectional, real-world, longitudinal, retrospective, etc.), various terms related to HCRU and costs (i.e., health resources, economics, cost, etc.), and NMS (i.e., switch, alternative, launch, etc.). Any additional publications were identified by hand searching reference lists of relevant publications and previously published SLRs. Full details of the literature search are presented in Appendix 1 in the electronic supplementary material.

In order to identify relevant study results that might not have been indexed by EMBASE or MEDLINE at the time of the search, key conference proceedings of disease areas that may be treated with biologics/biosimilars were consulted for the 2 years preceding the search (2018–2020). In parallel, PubMed and government sites, namely National Institute for Health and Care Excellence (NICE), CADTH, and Canadian provincial sites (ex. Institut national d'excellence en santé et en services sociaux, Ontario Health Technology Advisory Committee, etc.) were searched for relevant reports for the same period (2018–2020). For conference proceedings, PubMed, and government sites, simple search terms (e.g., biosimilar, originator, switch) were used independently. A complete list of the conference websites is presented in Appendix 2 in the electronic supplementary material.

Study Eligibility Criteria

This SLR was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [29]. The review question was established using the PICOS framework (Population, Interventions, Comparators, Outcomes, Study Design). Specifically, the study population consisted of patients who underwent an originator-to-biosimilar switch for non-medical, or presumably non-medical, reasons (i.e., patient choice, all patients switched, patients switched irrespective of disease activity, patients with stable disease switched, financial reason), with no restrictions pertaining to patient age, gender, or disease area. Interventions included any biosimilar following treatment with the reference biologic. There was no restriction on the study comparator. The outcomes of interest included HCRU and any costs associated with originator-to-biosimilar NMS. This SLR was restricted to interviews, surveys, cohort studies, database studies, and patient-reported outcomes (PRO) studies in the real-world setting. Lastly, this SLR was limited to English publications, except when searching Québec provincial sites, namely Institut national d'excellence en santé et en services sociaux, for which French publications were also included. The SLR is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Study Selection

Two reviewers independently screened titles and abstracts for relevance. Any citation/abstract deemed relevant by either reviewer was obtained in full-text form. Full-text articles and conference abstracts were then reviewed by both reviewers independently. Any publication failing to meet the eligibility criteria was excluded. In the case of duplicated publications on the same study, the most up-to-date publication was used. Discrepancies in study selection were resolved by consensus or with the help of a third reviewer.

Data Extraction

Using a predefined extraction form, one reviewer extracted information from each eligible study, which was subsequently validated by a second reviewer to ensure accuracy. Data extracted from each publication and conference proceeding, if available, are shown in Table S1 in the electronic supplementary material. All costs were converted and inflated to 2020 Canadian dollars ($C) using the general annual consumer price index [30].

Study Quality Assessment

The risk of bias of each individual selected study available in full-text form was assessed using the Cochrane Collaboration Risk of Bias in Non-Randomized Studies-of Interventions (ROBINS-I) [31].

RESULTS

Search Results

A flowchart of the selection process for the included studies is illustrated in Fig. 1. A total of 1845 studies were initially identified from the MEDLINE and EMBASE databases. After the exclusion of duplicates, 1720 studies were evaluated on the basis of title and abstract. Of them, 1242 were excluded on the basis of title selection and 425 were excluded on the basis of abstract selection. Of the 53 studies remaining, six were excluded for the following reasons: not real-world data ($n = 1$), not originator-to-biosimilar NMS ($n = 1$), no HCRU or costing data ($n = 4$). The search of conference websites and handsearching the reference lists of relevant publications resulted in two additional studies, namely one conference proceeding from each reference source. In total, 18 full-text publications and 31 abstracts were selected for data extraction.

Description of Included Studies

The study characteristics are described in Table 1. The majority were center-based cohort studies ($n = 41$); other study types comprised interviews ($n = 2$), physician surveys as part of a simulation or decision tree model ($n = 2$), post-marketing ($n = 1$), and database ($n = 3$) studies. Most of the studies were from various countries in Europe ($n = 43$). Of note, only one study was based in North America, specifically the USA.

The disease areas identified were primarily in rheumatology ($n = 19$) and gastroenterology ($n = 21$). Infliximab was the sole biosimilar drug investigated in gastroenterology, while studies in rheumatology included infliximab ($n = 5$), rituximab ($n = 1$), and etanercept ($n = 13$). The patient populations and patient follow-ups varied considerably between studies. In gastroenterology studies, the mean number of patients studied was 92.6 (range 5–313) with a mean follow-up time of 13.6 months (range 6–60 months). In studies investigating rheumatology populations, the mean number of patients studied was 170.9 (range 25–1259) with a mean follow-up time of 9.2 months (range 4–15.8 months). Moreover, one study each was performed in dermatology (etanercept, 17 patients, 3-month follow-up), growth development (somatropin, 98 patients, follow-up not reported [NR]), hepatology (erythropoiesis-stimulating agent [ESA], 163 patients, 24 week follow-up), and oncology (filgrastim, 37 patients, follow-up NR). There were five included studies that either focused on multiple disease areas or did not specify the disease area. Lastly, amongst the 49 identified, eight citations reported on the costs associated with the implementation of a switch program at their center in addition to HCRU and/or costs post-NMS.

Healthcare Resource Utilization (HCRU)

Nineteen studies reported on real-world HCRU associated with originator-to-biosimilar NMS (Table 2). Among them, 11 studies investigated gastroenterology patients, four investigated rheumatology, two investigated multiple

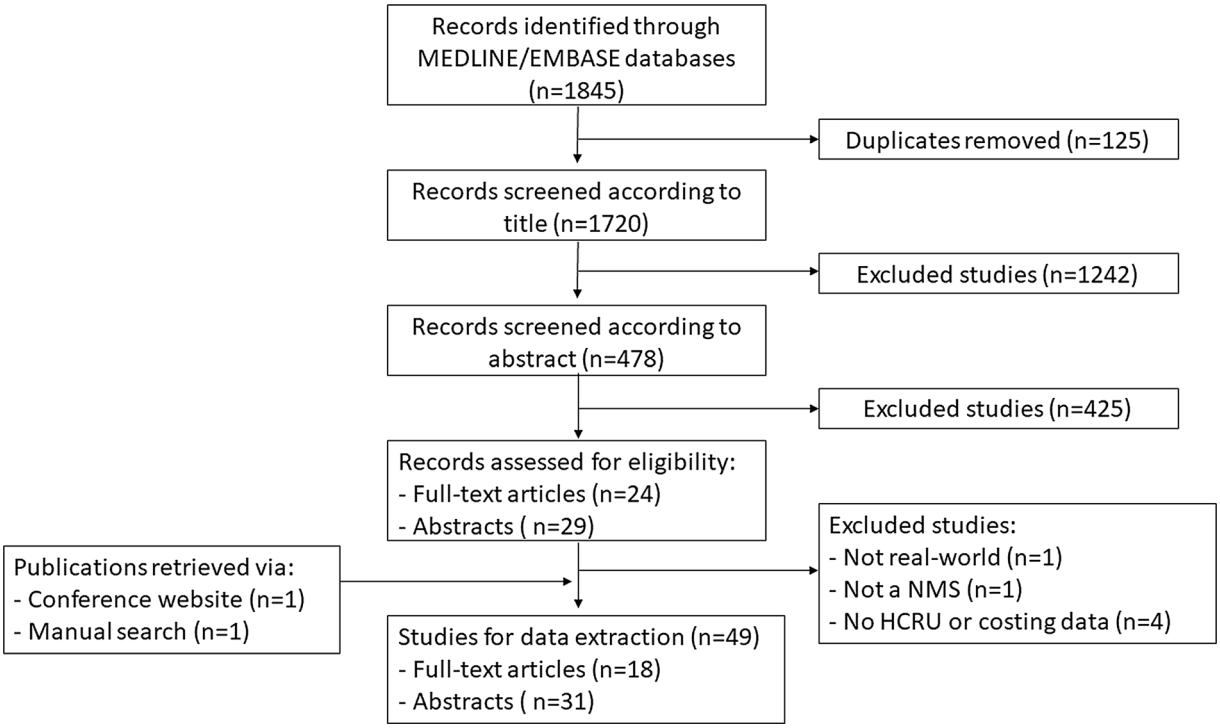


Fig. 1 Flow diagram of included studies

disease or unspecified areas, and there was one study each on oncology and growth development. The majority of these studies (n = 15) reported on HCRU during the follow-up period after NMS only; therefore, as there was no comparison to a study period or patient population without NMS, it cannot be concluded whether or not the reported utilization of healthcare resources was likely due to NMS in these studies. The 11 studies investigating gastroenterology patients demonstrated that hospitalizations and surgeries were common among patients following originator-to-biosimilar NMS; however, these studies did not show that these events were more, equally, or less likely to occur following NMS as there was no comparison to a pre-switch or non-switch population.

Four studies reported on real-world HCRU associated with originator-to-biosimilar NMS by describing the difference between patients pre- and post-switch or between patients who switched and those who remained on the reference biologic (i.e., switchers and non-switchers, respectively). Interestingly, all four of these studies reported an increase in HCRU with originator-to-biosimilar NMS, three of which were focused on rheumatology and the other on oncology. More specifically, they found that NMS can be associated with increased medical visits, medical services such as imaging, phone consultations, and emergency room (ER) visits, in addition to hospitalizations [6, 32–34].

In rheumatology, Tarallo et al. (2019) reported an increase in HCRU for rheumatology patients following NMS [32]. In this study, rheumatology specialists were surveyed and reported on a total of 1259 patients who switched from the etanercept reference biologic to an etanercept biosimilar. It was found that, in comparison to non-switchers, patients who switched to the biosimilar experienced an increase in the number of various services at both 0–3 months and 4–6 months post-switch, which included blood tests, x-rays, ultrasounds, ER visits, specialist visits, and hospitalizations [32]. In line with these results, the studies by Gibofsky et al. (2019) and Glintborg et al. (2018) also found an increase, although marginal, in the number of outpatient visits post-

Table 1 Characteristics of the included studies

Disease	Citation	Publication type	Country	Drug	Study type	Patient follow-up	Cohort size	Switch program
Dermatology								
Psoriasis	Szlumper [9]	Abstract	UK	Etanercept	Center-based cohort study	3 months	17	NS
Gastroenterology								
CD	Ala [50]	Abstract	UK	Infliximab	Center-based cohort study	6 months	20	NS
CD	Plevris [45]	Journal article	UK	Infliximab	Center-based cohort study (prospective)	12 months	110	Yes
IBD	O'Brien [84]	Abstract	Ireland	Infliximab	Center-based cohort study	NR	20	NS
CD, UC	Bergqvist [51]	Journal article	Sweden	Infliximab	Center-based cohort study (prospective)	12 months	313	NS
CD, UC	Diaz Hernandez [52]	Abstract	Spain	Infliximab	Center-based cohort study (retrospective)	6 months	72	NS
CD, UC	Fischer [53]	Abstract	Germany	Infliximab	Center-based cohort study (prospective)	6 months	114	NS
CD, UC	Geccherle [85]	Abstract	Italy	Infliximab	Center-based cohort study	6 months	5	NS
CD, UC	Guerra Veloz [54]	Journal article	Spain	Infliximab	Center-based cohort study (prospective)	24 months	100	NS
CD, UC	Hoivik [55]	Journal article	Norway	Infliximab	Center-based cohort study (prospective)	18 months	143	NS
CD, UC	Kim [86]	Journal article	Korea	Infliximab	Center-based cohort study (retrospective)	60 months	101	NS

Table 1 continued

Disease	Citation	Publication type	Country	Drug	Study type	Patient follow-up	Cohort size	Switch program
CD, UC	Rahmany [38]	Abstract	UK	Infliximab	Center-based cohort study	NR	78	Yes
CD, UC	Rodriguez Glez [56]	Abstract	Spain	Infliximab	Center-based cohort study (retrospective)	12 months	72	NS
CD, UC	Sieczkowska [57]	Journal article	Poland	Infliximab	Center-based cohort study (prospective)	11 months	39	NS
CD, UC	St Clair Jones [39]	Abstract	UK	Infliximab	Center-based cohort study	6 months	71	Yes
Pediatric CD, UC	Kang [58]	Abstract	South Korea	Infliximab	Center-based cohort study (prospective)	1 year	38	NS
CD, UC, IBDU	Huoponen [35]	Journal article	Finland	Infliximab	Center-based cohort study (prospective)	12 months	54	NS
CD, UC, IBDU	Smits [59]	Journal article	Netherlands	Infliximab	Center-based cohort study (prospective)	12 months	83	NS
CD, UC, IBDU	Razanskaite [44]	Journal article	UK	Infliximab	Center-based cohort study	12 months	143	Yes
CD, FCD, UC	Park [60]	Journal article	South Korea	Infliximab	Post-marketing study	30 weeks	60	NS
LCD, FCD, UC, IBDU	Ratnakumaran [61]	Journal article	UK	Infliximab	Center-based cohort study	12 months	191	NS
NS	Gervais [62]	Journal article	UK	Infliximab	Center-based cohort study (prospective)	12 months	33	NS
Rheumatology								
RA	Dyball [63]	Abstract	UK	Etanercept	Center-based cohort study (retrospective)	N/A	38	NS

Table 1 continued

Disease	Citation	Publication type	Country	Drug	Study type	Patient follow-up	Cohort size	Switch program
RA	Peral [37]	Abstract	Spain	Etanercept	Decision tree model with physician survey	NR	NS	NS
RA	Shah [43]	Abstract	UK	Etanercept	Center-based cohort study (prospective)	4 months	151	Yes
RA	Tarallo [32]	Journal article	UK	Etanercept	Simulation model with physician survey	NR	1,259	NS
RA	Nisar [64]	Abstract	UK	Rituximab	Center-based cohort study	NR	40	NS
RA, PsA, AS	Alkoky [71]	Abstract	UK	Etanercept	Center-based cohort study (prospective)	6 months	158	NS
RA, PsA, AS	Barnes [40]	Abstract	UK	Etanercept	Interview	NR	149–180/center, 4 centers	Yes
RA, PsA, AS	Chan [41]	Journal article	UK	Etanercept	Center-based cohort study	NR	113	Yes
RA, PsA, AS	Dayer [87]	Abstract	Spain	Etanercept	Center-based cohort study (retrospective)	NR	31	NS
RA, PsA, AS	Ma [65]	Abstract	UK	Etanercept	Center-based cohort study	6 months	160	NS
RA, PsA, AS	Gibofsky [34]	Abstract	UK, Germany	Infliximab	Database (retrospective)	12 months	119	NS
RA, PsA, AS	Glintborg [33]	Journal article	Denmark	Infliximab	Center-based cohort study	6 months	769	NS
RA, PsA, AS	Nascimento Junior [66]	Abstract	Brazil	Infliximab	Center-based cohort study (prospective)	NR	78	NS

Table 1 continued

Disease	Citation	Publication type	Country	Drug	Study type	Patient follow-up	Cohort size	Switch program
RA, PsA, AS, JIA	Nisar [42]	Abstract	UK	Etanercept	Center-based cohort study	1 year	82	Yes
RA, PsA, SpA	Uke [72]	Abstract	UK	Etanercept	Database	min 3 months	157	NS
RA, PsA, SpA	Valido [67]	Abstract	Portugal	Infliximab	Center-based cohort study (prospective)	median 15 months	60	NS
NS	Ahmad [68]	Abstract	UK	Etanercept	Interview	NR	104	NS
NS	Moron [88]	Abstract	Spain	Etanercept	Center-based cohort study (retrospective)	9 months	30[a]	NS
NS	Sheppard [73]	Abstract	UK	Infliximab	Center-based cohort study	12 months	25	NS
Hepatology								
Chronic kidney disease	Minutolo [8]	Journal article	Italy	ESA	Center-based cohort study (retrospective)	24 weeks	163	NS
Oncology								
Solid tumors, hematological malignancy	Al Rabayah [6]	Abstract	Jordan	Filgrastim	Center-based cohort study (retrospective)	NR	37	NS
Growth development								
GHD, TS, CRI, PWS, children born small for gestational age	Flodmark [7]	Journal article	Sweden	Somatropin	Center-based cohort study	NR	98	NS
Unspecified or multiple disease areas								
IBD, RA, PsA, AS	Abdalla [69]	Journal article	UK	Infliximab	Center-based cohort study (prospective and retrospective)	Mean 15.8 months	34	NS

Table 1 continued

Disease	Citation	Publication type	Country	Drug	Study type	Patient follow-up	Cohort size	Switch program
NS (areas include rheumatology, gastroentology, internal medicine)	Gutermann [70]	Abstract	France	Infliximab	Center-based cohort study	10 months	267	NS
CD, UC, RA, AS	Ramos Rodriguez [74]	Abstract	Spain	Infliximab	Center-based cohort study (retrospective)	11 months	48	NS
NS (RA, AS most common)	Phillips [36]	Abstract	Turkey	Infliximab	Database	NR	136	NS
NS	Zahorian [89]	Abstract	USA	Infliximab	Center-based cohort study	NR	100	NS

AS axial spondylarthritis, *CD* Crohn's disease, *CRI* chronic renal insufficiency, *FCD* fistulizing Crohn's disease, *GHD* growth hormone deficiency, *IBD* inflammatory bowel disease, *IBDU* inflammatory bowel disease unclassified, *JIA* juvenile idiopathic arthritis, *LCD* luminal Crohn's disease, *NMS* non-medical switch, *NR* not reported, *NS* not specified, *PsA* psoriatic arthritis, *PWS* Prader–Willi Syndrome, *RA* rheumatoid arthritis, *SpA* spondylarthritis, *TS* Turner syndrome, *UC* ulcerative colitis, *UK* United Kingdom, *USA* United States of America

[a]The selected cohort of 30 patients included all patients treated with etanercept biosimilar since its incorporation into the pharmacotherapeutic guide of the hospital. The number of patients switched from the reference biologic is not specified

Table 2 Reported healthcare resource utilization (HCRU)

Disease	Citation	Publication type	Drug	Cohort size	Data source	Reported HCRU
Gastroenterology						
CD	Plevris [45]	Journal article	Infliximab	110	IBD centers data	Surgery: 1
CD, UC	Diaz Hernandez [52]	Abstract	Infliximab	72	Hospital data	Surgery: 2
CD, UC	Fischer [53]	Abstract	Infliximab	114	Hospital data	Surgery: 1
CD, UC	Guerra Veloz [54]	Journal article	Infliximab	100	Hospital data	Hospitalization: 6 Surgery: 3
CD, UC	Hoivik [55]	Journal article	Infliximab	143	Hospital data	Hospitalization: 1 ER visit: 3 CT Imaging: 1
CD, UC	Kim [86]	Journal article	Infliximab	101	Hospital data	Surgery: 18 1–2 Hospitalizations: CD: 16 (20.5%); UC: 0 (0.0%) $\geq$ 3 Hospitalizations: CD: 10 (12.8%); UC: 5 (21.7%)
CD, UC	Rodriguez Glez [56]	Abstract	Infliximab	72	Hospital data	Surgery: 8
CD, UC	Sieczkowska [57]	Journal article	Infliximab	39	Center data	Surgery: 3
CD, UC	St Clair Jones [39]	Abstract	Infliximab	71	Hospital data	Surgery: 2

Table 2 continued

Disease	Citation	Publication type	Drug	Cohort size	Data source	Reported HCRU
CD, UC, IBDU	Huoponen [35]	Journal article	Infliximab	54	Hospital data	Medical visits: no significant difference
LCD, FCD, UC, IBDU	Ratnakumaran [61]	Journal article	Infliximab	191	Trust data	Surgery: 6/191 (switch) 1/19 (no-switch)
Rheumatology						
RA	Tarallo [32]	Journal article	Etanercept	1259	Survey	*In comparison to non-switchers, 0–3 and 4–6 months post-switch* Blood tests: + 0.38; + 0.40 X-rays: + 0.18; + 0.22 Ultrasounds: + 0.26; + 0.29 ER visits: + 0.46; + 0.54 Hospitalization: + 0.47; + 0.52 *Visit with*: Rheumatologist: + 0.65; + 0.70 Rheumatology nurse: + 0.64; + 0.51 Physiotherapist: + 0.53; + 0.57 Occupational therapist: + 0.33; + 0.37 Podiatrist: + 0.18; + 0.33
RA	Nisar [64]	Abstract	Rituximab	40	Hospital data	Hospitalization: 2 ER visit: 2
RA, PsA, AS	Gibofsky [34]	Abstract	Infliximab	119	Medical records	*Non-switchers vs switchers* Frequency of outpatient visit: 76.4% vs 89.1% Number of outpatient visits: 1.8 vs 2.0

Table 2 continued

Disease	Citation	Publication type	Drug	Cohort size	Data source	Reported HCRU
RA, PsA, AS	Glintborg [33]	Journal article	Infliximab	769	Registry	*6 months pre- vs 6 months post-switch* *Mean days with services per patient* 5.4 vs 5.8 ($p < 0.01$) *Mean rate of service per patient* Ultrasound: Shoulder, elbow, hand: 0.09; 0.07 Hip, knee, foot: 0.08; 0.10 Phone consultation: 1.03; 1.17 ($p = 0.03$) Medical visit: 3.86; 3.95. Outpatient visit: 1.44; 1.45 Nurse activity: 0.61; 0.58 Treatment consultation: 0.09; 0.07 Patient guidance: 0.35; 0.49 ($p < 0.01$) Clinical investigations: 0.31; 0.47 [32] ($p < 0.01$) Clinical control: 2.08; 2.26 ($p < 0.01$) Observation: 0.17; 0.22 ($p < 0.01$) BP measurement: 0.61; 0.60
Oncology						
Solid tumors, hematological malignancy	Al Rabayah [6]	Abstract	Filgrastim	37	NR	*Switchers vs non-switchers* Frequency of hospitalization: 15.6% vs 12.6% Hospital duration: 7 days vs 6.4 days
Growth development						
GHD, TS, CRI, PWS, children born small for gestational age	Flodmark [7]	Journal article	Somatropin	98	Hospital data	Medical visit: 3 patients required extra visit during follow-up Phone consultation: 10 patients required extra phone consultation with physician or nurse during follow-up
Unspecified or multiple disease areas						
IBD, RA, PsA, AS	Abdalla [69]	Journal article	Infliximab	34	Hospital data	Hospitalization: 1 patient pre-switch MRI Imaging: 1 patient post-switch

Table 2 continued

Disease	Citation	Publication type	Drug	Cohort size	Data source	Reported HCRU
NS	Zahorian [89]	Abstract	Infliximab	100	NR	Phone consultation: 5–10 min per patient with pharmacist

AS axial spondylarthritis, *BP* blood pressure, *CD* Crohn's disease, *CRI* chronic renal insufficiency, *CT* computerized tomography, *ER* emergency room, *FCD* fistulizing Crohn's disease, *GHD* growth hormone deficiency, *HCRU* healthcare resource utilization, *IBD* inflammatory bowel disease, *IBDU* inflammatory bowel disease unclassified, *JIA* juvenile idiopathic arthritis, *LCD* luminal Crohn's disease, *MRI* magnetic resonance imaging, *NR* not reported, *NS* not specified, *PsA* psoriatic arthritis, *PWS* Prader–Willi syndrome, *RA* rheumatoid arthritis, *SpA* spondylarthritis, *TS* Turner syndrome, *UC* ulcerative colitis

NMS for rheumatology patients, including RA, psoriatic arthritis, and axial spondylarthritis [33, 34]. The difference in outpatient visits for patients with rheumatic disease associated with NMS was greater in the study by Tarallo et al. (an increase ranging from 0.18 to 0.70 over 3 months) in comparison to both Gibofsky et al. and Glintborg et al. (an increase of 0.2 over 3 months and 0.01 at 6 months post-switch vs 6 months pre-switch, respectively) [32–34]. Once again similar to Tarallo et al., the study by Glintborg et al. (2018) reported a significant increase in the utilization of various healthcare resources, albeit different resources than those reported in Tarallo et al. (2019), following infliximab NMS [33]. In comparison to 6 months pre-switch, Glintborg and colleagues found a significant increase in the total number of days with healthcare services 6 months post-NMS, with a mean of 5.4 days (standard deviation [SD] 2.8) versus 5.8 days (SD 2.8), respectively ($p < 0.01$). With regards to the specific services, patients had more phone consultations (1.17 vs 1.03, $p = 0.03$), patient guidance (0.49 vs 0.35, $p < 0.01$), clinical investigation (0.47 vs 0.31, $p < 0.01$), clinical control (2.26 vs 2.08, $p < 0.01$), and observation (0.22 vs 0.17, $p < 0.01$) within 6 months following NMS in comparison to 6 months pre-switch, respectively [33]. Together, these studies demonstrated that while some healthcare resources may remain unchanged, other healthcare resources may significantly increase following originator-to-biosimilar NMS in rheumatic patients.

In an oncology study, Al Rabayah et al. (2018) also found an increase in both the frequency and duration of hospitalizations among patients who switched to a biosimilar in comparison to those who remained on the reference biologic (15.6% vs 12.6% and 7 days vs 6.4 days, respectively, follow-up period not specified) [6].

Non-medical Switching-Related Costs

Thirty-three studies reported on real-world HCRU-related and drug-related costs associated with NMS (Table 3). Among them, 13 studies investigated gastroenterology patients, 15

Table 3 Reported drug and healthcare resource utilization costs

Disease	Citation	Publication type	Drug	Cohort size	Data source	Switch programme	Drug-related costs and savings (2020 $C)	Overall costs and savings (2020 $C)	Inputs for overall cost and savings
Dermatology									
Psoriasis	Szlumper [9]	Abstract	Etanercept	17	Registry data	NS	NR	Savings: £10,080 ($C18,383) over 3 months Projected savings: £131,040/year ($C238,984/year)	NR
Gastroenterology									
CD	Ala [50]	Abstract	Infliximab	20	Hospital data	NS	NR	Savings: £220, 000/year ($C441,613)	NR
CD	Plevris [45]	Journal Article	Infliximab	110	IBD Centers data	Yes	For 756 infusions, total cost: Remicade: £1,135,134 ($C1,974,759) CT-P13: £608,315 ($C1,058,267) cost savings of 46.4%	NR	NA
IBD	O'Brien [84]	Abstract	Infliximab	20	Hospital data	NS	NR	15% discount: €76,638 savings ($C118,850) 45% discount: €180,099 savings ($C279,296) No discount rate: 25% savings	NR
CD, UC	Diaz Hernandez [52]	Abstract	Infliximab	72	Hospital data	NS	NR	Savings: 26% over 6 months	NR
CD, UC	Fischer [53]	Abstract	Infliximab	114	Hospital data	NS	Savings: €354,137.88/ 6 months ($C549,194)	NR	NA

Table 3 continued

Disease	Citation	Publication type	Drug	Cohort size	Data source	Switch programme	Drug-related costs and savings (2020 $C)	Overall costs and savings (2020 $C)	Inputs for overall cost and savings
CD, UC	Geccherle [85]	Abstract	Infliximab	5	NR	NS	NR	Savings: €79,125 ($C125,502) in 6 months, not specific to post-NMS	NR
CD, UC	Rahmany [38]	Abstract	Infliximab	78	Trust data	Yes	NR	Savings: £232,576.52/ 6 months ($C466,858) Staff costs: £90,000 ($C180,660)	NR
CD, UC	Rodriguez Glez [56]	Abstract	Infliximab	72	Hospital data	NS	Savings: €248,716/year ($C394,493)	NR	NA
CD, UC	St Clair Jones [39]	Abstract	Infliximab	71	Hospital data	Yes	Savings: £224,000/year ($C355,291)	Savings: £300,000/year ($C475,836) Switch Programme: funding of £1250/patient was required ($C1,983)	Drug costs including cost of treatment discontinuation, treatment switch, dose (de)escalation, and lab tests
CD, UC, IBDU	Huoponen [35]	Journal Article	Infliximab	54	Hospital data	NS	*Pre- vs post-switch annual drug costs* CD: €11,784 vs €4163 ($C18,691 vs $C6603) UC/IBDU: €8978 vs €3568 ($C14,240 vs ($C5659)	*Pre- vs post-switch* *Total annual secondary healthcare costs* CD: €3202 vs €3898 ($C5079 vs $C6183) UC/IBDU: €2648 vs €2763 ($C4200 vs $C4382)	Drug costs Costs related to the secondary healthcare provider (intervention, ward, ambulatory visits, laboratory, radiology, pathology, outpatient visits)
CD, UC, IBDU	Razanskaite [44]	Journal Article	Infliximab	143	Hospital data	Yes	Savings to hospital of £40,000–£60,000/month ($C72950–$C109425)	NR	NA
LCD, FCD, UC, IBDU	Ratnakumaran [61]	Journal Article	Infliximab	191	Trust data	NS	NR	Savings: £1 million/year ($C1.77 million)	NR

Table 3 continued

Disease	Citation	Publication type	Drug	Cohort size	Data source	Switch programme	Drug-related costs and savings (2020 $C)	Overall costs and savings (2020 $C)	Inputs for overall cost and savings
NS	Gervais [62]	Journal Article	Infliximab	33	Medical records, case reports	NS	Savings: £1500/patient/year ($C2660)	NR	NA
Rheumatology									
RA	Dyball [63]	Abstract	Etanercept	38	Hospital data	NS	NR	Savings: £26,400/year ($C48,147)	NR
RA	Peral [37]	Abstract	Etanercept	NR	Survey and Registry	NS	NR	*Switcher vs non-switcher annual costs*[a] €11,478.90 ($C17,801) vs €10,251.14 ($C15,897)	Drug costs Monitoring Hospitalization Other healthcare costs (no specified)
RA	Shah [43]	Abstract	Etanercept	151	Clinic data	Yes	Savings: £500,000/year ($C886,788)	NR	NA
RA	Tarallo [32]	Journal Article	Etanercept	1259	Survey	NS	Annual drug costs per patient: SB4: £8528 ($C14,836) GP2015: £8365 ($C14,552) Originator: £9295 ($C16,170)	*Switcher vs non-switcher annual HCRU costs per patient:* Originator to GP2015: + £1120 ($C1948) Originator to SB4: + £1283 ($C2232)	HCRU cost inputs: Specialist visit (rheumatologist, physiotherapist, occupational therapist, and podiatrist) Rheumatology nurse visit Imaging (X-rays, ultrasounds) Blood tests Hospitalization Emergency visits
RA	Nisar [64]	Abstract	Rituximab	40	Hospital data	NS	NR	Savings: approx. £140,000/year ($C240,415)	NR
RA, PsA, AS	Alkoky [71]	Abstract	Etanercept	158	Center data	NS	NR	Savings: approx. £370,000/year ($C656,223)	NR

Table 3 continued

Disease	Citation	Publication type	Drug	Cohort size	Data source	Switch programme	Drug-related costs and savings (2020 $C)	Overall costs and savings (2020 $C)	Inputs for overall cost and savings
RA, PsA, AS	Barnes [40]	Abstract	Etanercept	149–180 center (4 centers)	Center data	Yes	NR	Switch programme costs: Staff time: £12,638–£16,679 ($C22,414–$C29,581) Implementation: £1615–£30,033 ($C2864–$C53,266) Follow-up costs: £4686–£31,352 ($C8311–$C55,605)	Switch implementation and follow-up activities: Routine outpatient clinics Time spent auditing and reporting about switch Post-switch clinic appointments
RA, PsA, AS	Chan [41]	Journal Article	Etanercept	113	Hospital data	Yes	Savings: £95,017/8 months ($C173,287)	Overall savings in prescribing costs: £186,000 using switch programme ($C339,217)	Drug costs Implementation costs Pharmacist costs Administration costs
RA, PsA, AS	Dayer [87]	Abstract	Etanercept	31	Hospital data	NS	Annual savings: €3047.72/patient ($C4630)	NR	NA
RA, PsA, AS	Ma [65]	Abstract	Etanercept	160	Hospital data, medical records	NS	NR	Savings: £660, 000/year ($C1,170,561)	NR
RA, PsA, AS	Nascimento Junior [66]	Abstract	Infliximab	78	NR	NS	Savings: R$1.75 million/ 1689 vials ($C0.63 million/1689 vials)	NR	NA
RA, PsA, AS, JIA	Nisar [42, 67]	Abstract	Etanercept	82	Hospital data	Yes	NR	Savings: approx. £100,000/year ($C171,725)	NR

Table 3 continued

Disease	Citation	Publication type	Drug	Cohort size	Data source	Switch programme	Drug-related costs and savings (2020 $C)	Overall costs and savings (2020 $C)	Inputs for overall cost and savings
RA, PsA, SpA	Valido [67]	Abstract	Infliximab	60	Center data	NS	NR	26.4% cost reduction	NR
NS	Moron [88]	Abstract	Etanercept	30[b]	Hospital data	NS	Savings: €44,713.37/ 9 months ($C67,922)	NR	NA
NS	Sheppard [73]	Abstract	Infliximab	25	Hospital data	NS	NR	Savings: £70,000/year ($C140,513)	NR
Growth development									
GHD, TS, CRI, PWS, children born small for gestational age	Flodmark [7]	Journal Article	Somatropin	98	Hospital data	NS	Savings: €650,000/year ($C975,480)	NR	NA
Unspecified or multiple disease areas									
NS (areas include rheumatology, gastroentology, internal medicine)	Gutermann [70]	Abstract	Infliximab	267	Hospital data	NS	NR	Savings: €599,540/ 10 months ($C950,942)	NR
CD, UC, RA, AS	Ramos Rodriguez [74]	Abstract	Infliximab	48	Medical records	NS	Savings: €72,237 (33%) ($C112,025)	NR	NA

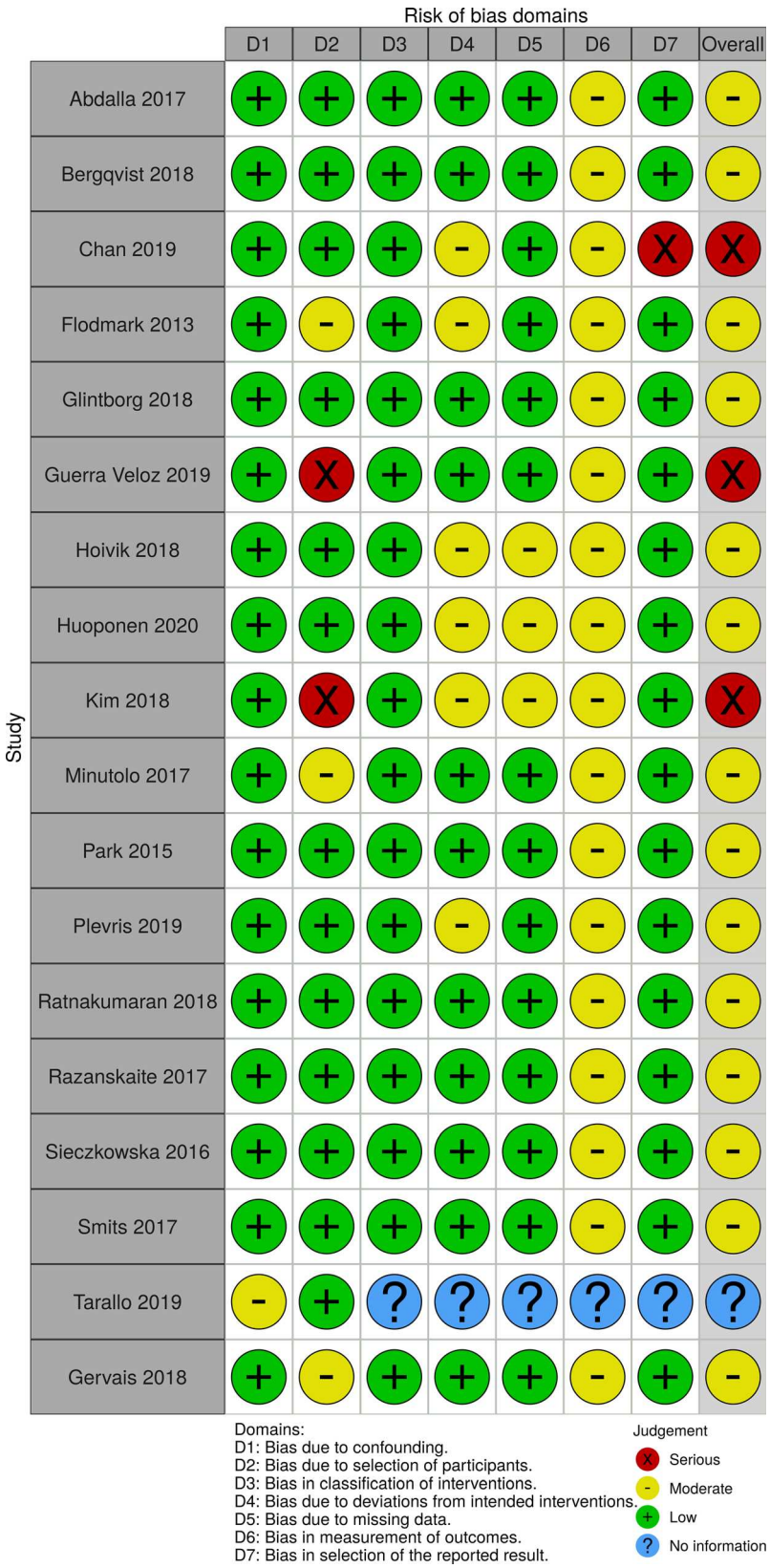
Table 3 continued

Disease	Citation	Publication type	Drug	Cohort size	Data source	Switch programme	Drug-related costs and savings (2020 $C)	Overall costs and savings (2020 $C)	Inputs for overall cost and savings
NS (RA, AS most common)	Phillips [36]	Abstract	Infliximab	136	National database	NS	Pharmacy costs: TL 1473 vs TL 1329 ($C590 vs $C533)	*Switchers vs non-switchers* Outpatient costs: TL 269 vs TL 181 ($C108 vs $C73) Inpatient costs: TL 64 vs TL 29 ($C26 vs $C12) Total healthcare costs: TL 2009 vs TL 1640 ($C805 vs $C657)	Outpatient costs Inpatient costs Pharmacy costs

AS axial spondylarthritis, *CD* Crohn's disease, *CRI* chronic renal insufficiency, *FCD* fistulizing Crohn's disease, *GHD* growth hormone deficiency, *HCRU* healthcare resource utilization; *IBD* inflammatory bowel disease, *IBDU* inflammatory bowel disease unclassified, *JIA* juvenile idiopathic arthritis, *LCD* luminal Crohn's disease, *NMS* non-medical switch, *NR* not reported, *NS* not specified, *PsA* psoriatic arthritis, *PWS* Prader–Willi Syndrome, *R* Brazilian Real, *RA* rheumatoid arthritis, *SpA* spondylarthritis, *TL* Turkish lira, *TS* Turner Syndrome, *UC* ulcerative colitis: *$C* 2020 Canadian dollars

[a]Annual cost-per-patient was estimated using the patient journey scenario of the decision tree model for which inputs were based on survey and registry data

[b]The selected cohort of 30 patients included all patients treated with etanercept biosimilar since its incorporation into the pharmacotherapeutic guide of the hospital. The number of patients switched from the reference biologic is not specified


Risk of bias domains
D1
D2
D3
D4
D5
D6
D7
Overall
Study
Abdalla 2017
Bergqvist 2018
Chan 2019
Flodmark 2013
Glintborg 2018
Guerra Veloz 2019
Hoivik 2018
Huoponen 2020
Kim 2018
Minutolo 2017
Park 2015
Plevris 2019
Ratnakumaran 2018
Razanskaite 2017
Sieczkowska 2016
Smits 2017
Tarallo 2019
Gervais 2018
Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.
Judgement
Serious
Moderate
Low
No information

◀**Fig. 2** Risk of bias assessment

nvestigated rheumatology, three investigated unspecified or multiple disease areas, and there was one study each on dermatology and growth development. The majority of these studies reported on the savings associated with drug costs alone or the overall savings following NMS without specifying the inputs used for the calculations; however, four of these studies reported on the difference in costs between patients pre- and post-switch (n = 1) or between patients who switched and those who remained on the reference biologic (i.e., switchers and non-switchers, respectively, n = 3) [32, 35–37].

With regards to infliximab originator-to-biosimilar NMS, a recent publication by Huoponen et al. (2020) assessed the economic impact of the switch among gastroenterology patients by comparing costs pre- and post-switch [35]. While Huoponen et al. (2020) found substantial cost savings when taking into account drug costs alone for either CD (pre-switch = €11,784 [$C18,691]/year vs post-switch = €4163 [$C6603]/year, a 65% reduction in drug cost) or UC and inflammatory bowel disease unclassified (IBDU) (pre-switch = €8978 [$C14,240]/year vs post-switch = €3568 [$C5659]/year, a 60% reduction in drug cost), the HCRU-related costs were numerically greater in patients following NMS. While not as significant as the savings gained as a result of reduced biosimilar drug costs, the total annual secondary healthcare costs following NMS in patients with CD and UC/IBDU were €3898 ($C6183) and €2763 ($C4382), respectively, in comparison to €3202 ($C5079) and €2648 ($C4200), respectively, prior to NMS, amounting to an increase in total healthcare costs ranging from 4% to 22% [35]. Phillips et al. (2017) used the Turkish healthcare database to investigate the difference in costs for infliximab originator-to-biosimilar switchers versus non-switchers, which mostly included patients with ankylosing spondylitis or RA [36]. They found a greater overall healthcare cost associated with patients who switched to the infliximab biosimilar in comparison to those who remained on the reference biologic (Turkish lira [TL] 2009 vs TL 1640 [$C805 vs $C657], respectively), amounting to an overall increase in healthcare costs of 23%, which was determined on the basis of an increase in outpatient costs, inpatient costs, and overall pharmacy costs (TL 269 [$C108] vs TL 181 [$C73], TL 64 [$C26] vs TL 29 [$C12], and TL 1473 [$C590] vs TL 1329 [$C533], respectively) [36]. With regards to etanercept originator-to-biosimilar NMS, Peral et al. (2018) found that, using a decision-tree model with physician survey input, switching from etanercept to the biosimilar leads to a higher annual cost per patient (+ €1227.75 [$C1904], + 12.0%) in comparison to those remaining on the reference biologic to treat RA [37]. These results were corroborated by the findings of Tarallo et al. (2019), who published results of a physician survey of 1259 patients with RA who switched from etanercept to the biosimilar [32]. Tarallo et al. (2019) found that the difference in drug costs alone led to an annual drug costs savings of 8.2% (£767 [$C1334]) to 10.0% (£930 [$C1618]) per patient following NMS to etanercept biosimilar, but that the switch generated an increase in annual HCRU-related costs of £1120 ($C1948) to £1283 ($C2232) per patient, amounting to an increase of 32% to 37% in total costs per patient following NMS, which is greater than the savings attributed to drug costs alone [32]. Although biosimilars are expected to provide savings to healthcare systems, these studies suggested that, when taking into account HCRU-related costs in addition to drug costs, the overall savings associated with originator-to-biosimilar NMS are either reduced or eliminated resulting in an increase, rather than decrease, in the annual costs per patient.

Another factor that must be considered in the costs associated with originator-to-biosimilar NMS is the establishment of a switch program. Eight studies reported on the costs associated with the implementation of a switch program within their center (Table 1) [38–45]. Four of these studies, namely Razanskaite et al. (2017) [44], Shah et al. (2018) [43], Chan et al. (2019) [41], and Plevris et al. (2019) [45], reported substantial savings that were

calculated using drug costs alone (Table 3). In addition, Nisar et al. (2019) stated an overall annual savings of approximately £100,000 ($C171,725) without specifying the inputs used in the calculations [42]. The three remaining studies reported on the specific costs generated by the switch program. St Clair Jones et al. (2017) found that the savings related to yearly drug costs amounted to £224,000 ($C355,291) and an overall savings of £300,000 ($C475,836); however, in order to fund a specialist IBD nurse, the program also required a one-time fee of £1250 ($C1983) in funding per patient [39]. Rhamany et al. (2016) also reported substantial savings of more than £200,000 ($C343,450) over a 6-month period, though the authors also specified an additional staff cost of £90,000 ($C180,660) over the 6-month period associated with the program [38]. Barnes et al. (2018) reported on various costs associated with different aspects of the switch program, including additional staff time (£12,638 to £16,679 [$C22,414 to $C29,581]), implementation of the program (£1615 to £30,033 [$C2864 to $C53,266]), and patient follow-up (£4686 to £31,352 [$C8311 to $C55,605]) [40]. Therefore, while the implementation of switch programs are expected to provide cost savings to the healthcare system, the calculations are often based on drug costs alone. Accordingly, the inclusion of other factors, such as additional staff time and program funding, reduces the anticipated cost savings associated with originator-to-biosimilar switch programs.

Study Quality

The general risk of bias of the included full-text articles, according to the Cochrane Collaboration ROBINS-I tool, is presented in Fig. 2. Of the 18 published journal articles, the overall risk of bias was rated as moderate for 14 citations, serious for three citations, and unclear for one citation. Of note, each citation, except for Tarallo et al. (2019), which could not be assessed for the domain, was evaluated as a moderate risk of bias for domain 6, which pertains to the measurement of outcomes. As both the patients and physicians were not blinded to treatment allocation (i.e., NMS) in a clinical setting, a moderate risk of bias was considered for most studies as it is possible that outcome measures or answers to survey questions were influenced by the knowledge of the intervention received by the patients. As the overall risk of bias is judged as moderate when a moderate risk is determined for at least one of the domains, the overall risk of bias was, consequently, considered as moderate for the majority of included studies.

DISCUSSION

While the introduction of biosimilars is expected to provide cost savings to the healthcare system, the economic impact of originator-to-biosimilar NMS is complex to assess. While highly similar, Health Canada authorization of biosimilar drugs does not signify equivalence to, or interchangeability with, the reference biologic drug [1]. Consequently, additional costs, such as those related to HCRU, in addition to drug acquisition costs, need to be taken into account when estimating the economic impact of originator-to-biosimilar NMS. In 2019, Liu et al. published a SLR evaluating the economic impact of originator-to-biosimilar NMS [27]. The authors stated that their review retrieved more data on anticipated cost estimates (i.e., generated from simulation studies) than on real-world observed post-NMS HCRU and costs. As a result, this SLR focused on real-world data in order to evaluate the economic impact of originator-to-biosimilar NMS in a real-word setting.

In the current SLR, we found many studies that focussed on savings related to drug costs alone without taking HCRU-related costs into account. Moreover, few studies investigated the difference in HCRU or costs associated with originator-to-biosimilar NMS, where findings were presented for patients both prior to and following the switch or were presented for patients who underwent NMS in comparison to patients that remained on the reference biologic. While these studies were scarce, they provided a better understanding of the savings or costs that were associated with the switch

from the reference biologic to the biosimilar drug. Specifically, three studies reported on HCRU differences [6, 33, 34], three studies reported on cost differences [35–37], and one study reported on differences in both HCRU and overall costs [32]. With regards to HCRU, all studies concluded that NMS was associated with a significant or numerical increase in HCRU among patients who underwent originator-to-biosimilar NMS [6, 32–34]. Interestingly, there was a notable difference between studies in terms of outpatient visits associated with NMS, where this was greater for the study by Tarallo et al. in comparison to both Gibofsky et al. and Glintborg et al. (an increase in outpatient visits per patient of 0.18 to 0.70 versus 0.2 and 0.01, respectively) [32–34]. Study differences that may account for this variation may include study design, where Tarallo et al. reported results of a physician survey whereas Gibofsky et al. and Glintborg et al. obtained medical records and registry data, respectively, or the drug examined, where Tarallo et al. examined etanercept, which is administered subcutaneously, whereas Gibofsky et al. and Glintborg et al. both examined infliximab, which is administered intravenously [32–34]. In contrast, Peral et al. (2018), Tarallo et al. (2019), and Phillips et al. (2017) found that a NMS from originator etanercept or infliximab to the biosimilar in rheumatic patients generated an overall increase in total costs to patients in comparison to remaining on the originator ($p = 0.046$ in Phillips (2017), unreported in Peral (2018) and Tarallo (2019)) [32, 36, 37]. Importantly, Tarallo et al. identified blood and imaging tests, emergency visits, hospitalizations, and visits with various specialists as the primary healthcare costs leading to the increase in total patient costs following NMS [32]. Altogether, these studies suggested that post-NMS costs can, at times, be greater than the savings attributed to drug costs following a switch from the reference biologic to the biosimilar drug, such that NMS can result in an increase, rather than the anticipated decrease, in total costs per patient, at least in the short-term. Total costs per patient in the long-term following an originator-to-biosimilar NMS remain to be elucidated. Accordingly, potential long-term savings generated from an originator-to-biosimilar NMS could increase resources for the reimbursement of innovative drugs, which could be beneficial to patients. Altogether, as the patient populations of interest are dealing with chronic conditions, studies evaluating HCRU and costs in the long-term would provide much needed information. However, these analyses can prove challenging as, particularly in immunologic conditions, patients often lose response and switch to more expensive therapy, which may limit the long-term cost differences associated with NMS to a more finite time horizon.

In Canada, biosimilar drugs are sold at a reduced price that is, on average, 30% less than the price of the reference biologic [13, 18], suggesting that originator-to-biosimilar NMS policies result in savings to the Canadian healthcare system. However, understanding the full economic impact of introducing originator-to-biosimilar NMS policies in Canada requires the consideration of HCRU-related costs associated with NMS as well. In order to better understand the costs associated with originator-to-biosimilar NMS in Canada, HCRU-related costs associated with NMS, based on the HCRU data retrieved from this current SLR, were estimated from a Canadian perspective [46]. Using unit costs from Canadian governmental sources and published literature, it was determined that, over a 6-month period, rheumatic patients who underwent originator-to-biosimilar NMS incurred greater HCRU-related costs, estimated at an additional $1317 per patient, compared to those who stayed on the originator biologic. In this analysis, the main drivers of the difference in costs between switchers and non-switchers were hospitalization costs and productivity loss [46].

The results of the current SLR are in line with those of Liu et al. [27]. While Liu et al. found that many studies demonstrated a cost reduction associated with NMS, the authors noted that many of these same studies were largely limited to drug costs alone and did not take into consideration the costs related to HCRU. When Liu et al. isolated the real-world studies that reported on NMS-related costs, aside from drug costs alone, the authors found that originator-to-biosimilar NMS was associated with

increased HCRU and HCRU-related costs. More specifically, Liu et al. emphasized three real-world database studies identified in their search, two of which pertained to the same study by Glintborg et al. [33] and the other to the conference abstract by Phillips et al. [36], both of which were also identified and highlighted in the current SLR. Liu et al. concluded by emphasizing the need for more real-world studies that include both drug costs and other NMS-related costs in order to appreciate the full economic impact of NMS in both the short and long term.

Additional factors can also have an impact on the costs associated with originator-to-biosimilar NMS. Indeed, three studies reported on the costs, aside from drug costs alone, associated with a switch program, which highlighted patient funding, program implementation, and the additional staff time required as important costing parameters that should not be overlooked [38–40]. In British Columbia, the Biosimilar Initiative, which supports originator-to-biosimilar NMS, encourages the reimbursement of various fees billable to the Medical Service Plan, including pharmacist and physician visit fees as well as a fee to fund the nursing staff required to support patients with gastrointestinal diseases [47–49]. These fees add to the overall cost of implementing a switch program. While originator-to-biosimilar switch programs may be accompanied by added costs to the healthcare system, it is noteworthy to mention that managed switch programs can be funded through a gain share agreement [44]. Specifically, a gain share agreement is a collaborative arrangement between healthcare commissioners and providers to distribute the resulting cost savings between the stakeholders so that the cost savings can be reinvested by hospitals in patient care [44]. Therefore, the short-term costs associated with a switch program may be outweighed by the long-term benefits to patients if funded through a gain share agreement.

Aside from the costs associated with a switch program, additional factors related to differences in efficacy and safety between originators and biosimilars can also have an impact on the costs associated with originator-to-biosimilar NMS. The manufacturing of biologic drugs is complex, hence the position of Health Canada about the non-interchangeability of an originator biologic to biosimilar [1]. After NMS, an inadequate response can lead to treatment discontinuation, which is another factor that can be associated with increased total costs, particularly when treatment discontinuation is associated with another treatment switch or adverse events (AEs) requiring medical intervention. Accordingly, Tarallo et al. (2019) determined that the total costs associated with patients who, following initial originator-to-biosimilar NMS, switched back to the reference biologic or to an alternative biologic were consistently greater than the total costs for patients who switched just once [32]. The characteristics associated with treatment discontinuation following originator-to-biosimilar NMS are presented in Table S2 in the electronic supplementary material. Biosimilar discontinuation rates were variable between studies and disease areas ranging from 2.6% to 38.5% [32, 35, 36, 39, 42, 44, 45, 50–70]. Switch-back rates (to the reference biologic) ranged from 0.5% to 16% [7, 32, 36, 41–44, 61, 63, 64, 67–73], while the rate of switching to an alternative drug ranged from 0.9% to 18.2% [32, 35, 37, 39, 41, 42, 45, 50, 54, 55, 57, 61, 62, 64, 67–70]. Common reasons for discontinuation resulting in a switch included loss of response (LOR) [39, 44, 52–57, 59, 62, 63, 66, 69, 70], disease activity [41–43, 45, 50, 51, 65, 67–69, 72], and AEs [42–45, 51, 53–55, 57, 59–61, 63–65, 67, 69, 70, 73], all of which could be directly associated with additional treatment costs. Moreover, LOR may be addressed through dose escalation prior to discontinuation. For the studies that reported dose escalation, the rates ranged from 2.1% to 48.5% [8, 39, 45, 51, 54, 56, 58–62, 74]; however, dose reductions were also reported at a frequency of 8–21.5% [8, 39, 51, 59]. In this study, switching and discontinuation rates for biologic originators by disease area were not captured. However, interestingly, a recent study conducted by Fitzgerald et al. indicated that patients switching from originator to biosimilar infliximab were two to three times more likely to switch to another originator biologic compared to those

remaining on originator infliximab [75]. While results are variable between studies, these findings validate that, at the very least, there is the potential that a patient who undergoes NMS may subsequently undergo dose escalation, or be switched to an alternative treatment or back to the reference biologic, where multiple switches may be associated with greater total healthcare costs [32]. Along with additional costs associated with HCRU and switch programs, these added elements must also be considered in the decision to adopt a NMS policy.

Subjective reasons such as negative expectations, often referred to as the nocebo effect, can lead to biosimilar discontinuations and should also be considered as a factor that may impact the overall costs post-NMS. The nocebo effect describes negative outcomes with active treatments in the real-world clinical setting, including new or worsening symptoms and AEs, stemming from a patient's negative expectation rather than the pharmacologic action of the treatment itself [76]. The nocebo effect can reduce adherence to biosimilar treatment, particularly in the setting of NMS [22, 76]. To minimize this risk, additional costs related to the education of both patients and healthcare professionals on biosimilars would be necessary. The implementation of such comprehensive education programs should also be taken into account when considering the implementation costs associated with an originator-to-biosimilar NMS policy.

Some governments have discussed and/or announced the implementation of NMS policies [23–26]. While several experts support NMS policies [77, 78], others have voiced their opposition to such "forced" switches for non-medical reasons [79–81]. Moreover, the Canadian Association of Gastroenterology and Crohn's and Colitis Canada released a joint statement wherein they recommend against infliximab originator-to-biosimilar NMS in patients who have stable CD or UC and who are doing well on the reference biologic [82]. This opinion was formed as a result of data suggesting that switching in this setting leads to an increased risk of LOR, dose escalation, or secondary switching [82]. Importantly, various studies reporting on HCRU and/or costs post-NMS also reported biosimilar dose escalations and listed LOR as a reason behind treatment discontinuation or secondary switching in patients who were stable prior to NMS (Table S2 in the electronic supplementary material). More recently, the Institut national d'excellence en santé et en services sociaux of Québec published a report on the position of various medical societies, associations, and clinicians with regard to biologic-to-biosimilar NMS policies [83]. It was concluded that, while the use of biosimilars in treatment-naïve patients or as a substitution in patients for a medical reason is generally accepted, the implementation of an originator-to-biosimilar switch for non-medical reasons is not accepted. Accordingly, only two Canadian provinces, namely British Columbia and Alberta, have originator-to-biosimilar NMS policies currently in place. Québec clinicians agree that forcing an originator-to-biosimilar NMS in patients comes with a risk of destabilization to the patient, with a possibility of non-response or development of significant adverse events, for whom little treatment options are available [83]. Altogether, the idea of forcing stable patients to switch without a medical reason to a biosimilar drug remains a debatable topic amongst expert groups.

This study is subject to some limitations. First, the studies included in the SLR were limited in number and comprised primarily conference abstracts, highlighting a need for more studies, and subsequent publication of the results, regarding HCRU and/or costs associated with originator-to-biosimilar NMS. Secondly, many of the included studies were funded by pharmaceutical companies, such that the investigated outcomes or results shown may be biased towards the affiliated drug. The variability in the methodologies used by the identified studies may limit the interpretation and generalizability of the synthesized results. Furthermore, the skewed proportion of studies considering infliximab originator-to-biosimilar NMS may limit the generalizability of the current results to other biologics. Similarly, the skewed proportion of studies investigating rheumatological or gastroenterological diseases may also limit the generalizability of the current results to other disease areas. Among the

identified studies, most are conference abstracts. While conference abstracts allow for the inclusion of studies that have yet to be published, it must be noted that publications from conference proceedings have not undergone a thorough peer-review process, as is required for an article published by a journal. Moreover, as conference abstracts follow a strict word limit, there is often a lack of details and information pertaining to the study. While the risk of bias was assessed for all published journal articles, this assessment was not performed for conference abstracts, which represented most of the included studies. It must also be noted that the ROBINS-I tool, which was used for this SLR, was not considered suitable for all included journal articles. While the Newcastle–Ottawa scale is the preferred tool for the assessment of database studies, the ROBINS-I was used as the majority of included journal articles were cohort-based studies. Future research providing more real-world evidence regarding originator-to-biosimilar NMS is warranted.

CONCLUSION

This systematic literature review found that the overall economic impact of originator-to-biosimilar NMS in the real-world setting remains uncertain, as drug costs alone, without consideration of the additional HCRU associated with NMS, continue to be the focus of most economic studies. Nevertheless, among the seven studies that reported on the difference in HCRU or costs with and without NMS, all studies showed an increase in healthcare services used and HCRU-related costs associated with NMS. These findings suggest that the expected overall savings generated by an originator-to-biosimilar switch owing to less costly drug prices may be reduced because of an increase in HCRU and its associated costs post-switch. More real-world studies that include both drug costs and additional NMS-related healthcare costs are needed to better evaluate the full economic impact of NMS.

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