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CURRENT OPINION

Policy Options for Infliximab Biosimilars in Inflammatory Bowel Disease Given Emerging Evidence for Switching

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Abstract Biosimilars are becoming increasingly available internationally as patents expire on the originator biologic drugs they are intended to copy. Although substitution policies seen with generic drugs are being considered as a means to reduce expenditures on biologics, some biosimilars pose particular challenges in that the act of substitution may eventually lead to increased rates of therapeutic failure. As evidence requirements from regulators do not directly address this challenge, switch trials of biosimilars have emerged that may provide further answers. Using infliximab in inflammatory bowel disease as an example, we critically examine emerging evidence from two key switch trials (NOR-SWITCH and NCT020968610) and discuss the clinical and economic implications of these and what policy options may be most reasonable for payers. Options include reimbursing biosimilars for only newly diagnosed patients, using product-listing agreements to manage uncertainty, or using tiered co-payments or other incentives to promote biosimilar use.

Key Points for Decision Makers

The unique characteristics of some biosimilars require payers and formulary managers to revisit traditional approaches to pricing and reimbursement applied to generic drugs.

Evidence requirements demanded by regulators, in some cases, may be insufficient for payers to implement policies of automatic substitution.

Evidence emerging from switch trials of infliximab in inflammatory bowel disease may appear to provide additional needed evidence for payers, but will likely have little impact on policy decisions until evidence of interchangeability becomes available.

1 Introduction

Biosimilars are becoming increasingly available internationally as patents expire on the originator biologic drugs they are intended to copy [1]. Analogous to generic versions of small molecule drugs, biosimilars represent opportunities to reduce spend on drugs [2]. However, while payers have an opportunity to reduce drug acquisition costs by paying for biosimilars, they must still develop pricing and reimbursement policies that consider the evidence available along with other important factors, like feasibility of implementation and the values of patients and other interested parties.

Like other pharmaceuticals, the evidence to inform reimbursement and pricing policy for biosimilars is largely driven by regulatory requirements; emerging regulatory

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requirements for biosimilars largely focus on in vitro evidence of similarity, pharmacology, immunogenicity, and manufacturing standards [3]. While such data may give payers confidence that similar health outcomes are achievable, there is a notable lack of evidence to support the critical concepts of allowable switching and substitution. Policies that dictate when an original product can be switched to an alternative product generally make distinctions between those that require prescriber direction and supervision and those that do not (e.g., automatic substitution at a pharmacy level deemed allowable by a formulary manager) [4]. Automatic substitution, coupled with preferred pricing and listing arrangements, have become common policy approaches for small molecule generics in particular, as a means of controlling drug expenditures.

Consideration of evidence to support substitution policies is not a new challenge for formulary managers, who have also implemented policies of substitution for other drugs with direct or indirect evidence of similar outcomes. These policies include approaches to substitution between different formulations, drugs within the same class ('therapeutic substitution'), and drugs between classes ('therapeutic interchange'), often with little or no direct evidence to support them [4]. Policy development typically considers the benefit-harm to patients, as well as costs and the need for physician involvement. Uncertainties regarding the impact of substitution have led to the need for indirect evidence [5] and more robust policy approaches, including greater engagement with prescribers and patients, the use of appeals mechanisms and rules of exception, and ongoing monitoring of therapeutic use and impact through special authorization procedures [4].

Substitution policies can be a particular challenge for drugs with a narrow therapeutic window, or where outcomes associated with the policies are highly variable, cannot be immediately monitored, or are hard to predict across different patient populations. These concerns also apply to some biosimilars, specifically larger more complex molecules (e.g., monoclonal antibodies) and introduce a new challenge for payers. Biosimilar antibodies are not structurally identical to the originator molecule, raising the concern that substitution in stable patients whose immune systems have been tolerized to the originator may become sensitized and develop drug-neutralizing antibodies (or anti-drug antibodies; ADAs) [6].

The presence of ADAs, a challenge with large complex proteins, has been strongly associated with loss of response [7, 8]. One factor strongly associated with the development of ADAs and loss of response is episodic treatment [9], which has in turn made adherence and persistence to biologic therapy, in order to avoid progression, a clinical priority. At least one observational study of switching led to a hypothesis that switching from one agent to another may lead to a similar loss of response as seen with episodic treatment [10]; further to this, it is theorized that some patients may not have an immediate loss of response but could be potentially harmed if there is a need to switch back to the first product [10]. This flags a potential concern in an era of formulary management through preferred listings and tendering arrangements for specific products [11].

Although regulator demands for immunogenicity testing with biologics may provide some indirect evidence to address this concern [12], current regulatory frameworks allow immunogenicity to be tested in healthy volunteers and patient populations who may have different immunogenic responses, such as those on anti-cancer drugs or on immunosuppressant therapy. Different immune responses from the use of immune modulator drugs such as methotrexate, for example, was a key factor in changes in efficacy with tumor necrosis factor (TNF) inhibitors in rheumatoid arthritis. This also supported an understanding that better outcomes could be achieved by eliminating ADAs through use of an add-on immune modulator in inflammatory bowel disease [13, 14].

The purpose of this commentary is to explore the policy considerations and options available to payers for substitution policies with biosimilars when therapeutic failure is less desirable and affected by immunogenicity. We have chosen infliximab in the treatment of inflammatory bowel disease (IBD) as an illustrative case specifically because there is now a large amount of experience and study, and it also illustrates where the health of patients may be most sensitive to substitution policy. Policy options proposed will be based on a consideration of the clinical and economic implications of currently available evidence for switching patients with different infliximab products in IBD. Although we have created generic policy options that may be useful to those responsible for pricing and reimbursement of drugs generally, we recognize there may be distinct solutions available to certain payers, given the differences in the underlying structure of financing and delivery of services.

2 Defining the Problem: The Introduction of Infliximab Biosimilars

Biosimilar infliximab (CT-P13, also known as Remsima™ and Inflectra™; SB2, also known as Flixabi™) is a large molecule (monoclonal antibody) that has gained marketing authorization in several jurisdictions for multiple indications including rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), Crohn's disease (CD) and ulcerative colitis (UC) [15]. Evidence provided to

regulators included in vitro assay activity as well as comparative pharmacokinetics in patients with AS and comparative pharmacodynamic properties in patients with active RA treated with the originator product [15]. Assessments of safety and the development of neutralizing antibodies in RA and AS patients were also conducted [15].

The Canadian regulator, Health Canada, in contrast with counterparts in the USA and Europe, did not originally support using evidence from patients with RA and AS to support an indication in CD and UC, citing uncertainty surrounding evidence from in vitro assay activity and a lack of safety data [6]. Although additional evidence was subsequently provided to support its use in IBD indications (CD, fistulizing CD, and UC), as well as safety data available from post-marketing surveillance studies, the question of safety and the development of neutralizing antibodies when patients are switched from the originator product to the biosimilar and vice-versa (i.e., multiple switching) remained mostly unaddressed [6].

This left an important evidence gap for payers considering opportunities for substitution in patients with IBD. While it seemed providing access to those with IBD who were treatment-naïve may be a plausible option, payers were still given no direct evidence to evaluate the impact of substitution in patients with inflammatory bowel disease who have achieved stable remission with originator infliximab therapy. The effect of substitution and switching is a particularly important concept in IBD, where durability of response to infliximab therapy in high-risk patients is considered a valuable outcome. High rates of remission have been achieved with the originator drug through careful patient selection and treatment optimization [16].

One response to the need for further evidence by prescribers and payers has been examination of registries and identifiable cohorts (observational studies) to demonstrate the impact of switching [17, 18]. These include data from numerous observational studies in Europe and Asia as well as BIO SWITCH, a Netherlands-initiated before-after study in RA/AS/PsA. Other observational studies have been identified in an updated systematic review used to inform the European Crohn's and Colitis Organisation (ECCO) position statement on the use of biosimilars [19, 20]. While potentially informative, registry studies of this kind can be difficult to interpret and lead to questions of credibility and reliability of results primarily because, unlike randomized controlled trials, they cannot adequately control for confounders which can introduce potential bias. Furthermore, these studies highlight difficulties in obtaining the blood samples that are critical for assessment of drug concentrations and ADAs.

Accordingly, data from well-controlled comparative effectiveness studies has become essential. Switching trials that have enrolled IBD patients and identified from a systematic review [19] include the NOR-SWITCH trial [21, 22]; (NCT02096861), a 54-week US-based non-inferiority trial intended to demonstrate the impact of switching to CT-P13 in patients with active CD [23]; and SIMILAR trial (NCT02452151), a 12-week trial in UC and CD patients in remission [24]. As no results have been reported to date from SIMILAR, we will describe available results from the first two trials below and their implications for decision-making. Following this, we will analyze the economic implications of this evidence and present policy options that might be considered.

3 Evidence to Support Substitution

3.1 Clinical Evidence from RCTs

NOR-SWITCH [22] was a non-inferiority trial in which 482 patients with one of five different inflammatory diseases receiving stable doses of originator infliximab were randomized to continue originator infliximab or to switch to CT-P13. At the end of 52 weeks of treatment, 408 patients were included in a per-protocol analysis, 202 in the originator infliximab arm and 206 in the CT-P13 group. The primary endpoint of disease worsening, defined differently for each disease, occurred in 53 (26%) patients in the infliximab originator group and 61 (30%) patients in the CT-P13 group (per-protocol set; adjusted treatment difference − 4.4%, 95% CI − 12.7 to 3.9), which fell within the pre-defined non-inferiority margin of 15% (Fig. 1). No difference in serious adverse event rates was noted between groups (10 and 9% in the originator and CT-P13 groups, respectively).

The authors concluded that switching to CT-P13 was non-inferior to continuation of originator infliximab. However, NOR-SWITCH has several important limitations for decision-making. Firstly, NOR-SWITCH was not statistically powered or intended to demonstrate non-inferiority for individual diseases. Rather, the point estimate for the risk difference of non-inferiority was based on the aggregation of five different disease populations. This led to understandable variation due to random error around the collective point estimate for individual diseases. In CD, for example, the risk difference for switching to biosimilar product was − 14.3% (95% CI − 29.3 to 0.7).

Although this finding from an underpowered sub-group analysis does not provide evidence of inferiority for this disease group, it is still a best estimate for decision-makers, who must consider the chances of making good decisions from the best evidence without concern for statistical significance testing [25]. Embodied in this decisional uncertainty is the possibility that CT-P13 may be less effective for this indication than originator infliximab. This

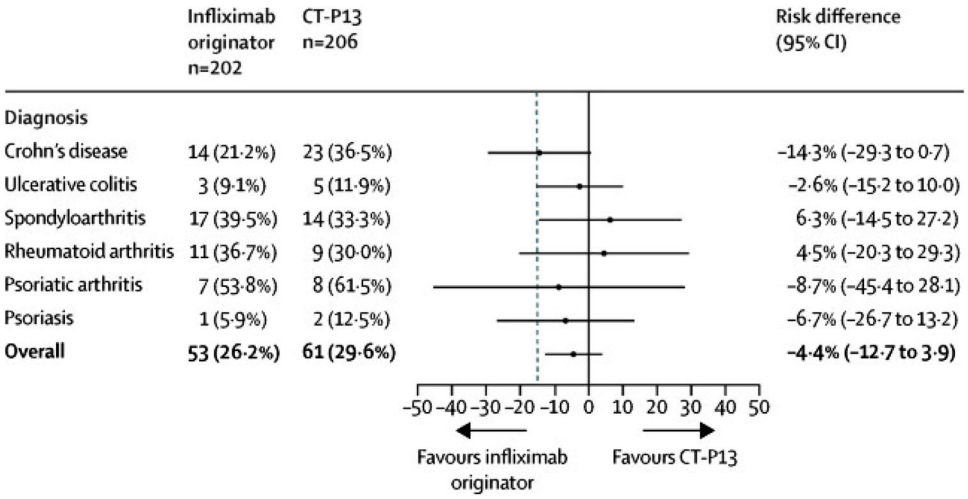

Fig. 1 Forest plot of infliximab originator versus biosimilar from NOR-SWITCH indicating improvement or worsening in disease according to disease-specific instruments

possibility is also supported by observations that anti-TNF drugs may have different mechanisms of action across different autoimmune diseases [26]. Another challenge with the non-inferiority margin of 15% used is that many IBD trials specialists would consider it too large—a difference of 12% has already been interpreted as a clinically meaningful improvement in the key superiority trial that supported immune modulator add-on therapy [13].

Finally, the NOR-SWITCH results tell us nothing about the risks of sensitization in a formulary setting where patients undergo multiple switches between originator and biosimilar(s) due to preferential listing or tendering arrangements with multiple available products. If selection of a TNF antagonist has the potential to be decided exclusively on the basis of drug cost, chronic sequential exposure to different similar but non-structurally identical products raises the real concern of higher rates of sensitization, ADA formation, and reduced rates of responsiveness.

Although the full results of the NCT02096861 non-inferiority trial have not been reported yet, preliminary results have been reported [27]. The multicenter trial evaluated the effects of multiple switching CT-P13 and originator infliximab in 220 patients with active CD who were naïve to previous anti-TNF treatment. The primary outcome is the rate of >70-point worsening of CDAI (CDAI-70). Secondary outcomes include remission rates, health-related quality-of-life and safety assessments, including drug concentrations and ADA titers. The trial features a four-arm design with two arms randomized to the originator and two others randomized to a biosimilar, with one originator and biosimilar arm switched.

Switch data are not available; however, an abstract presentation reported remission rates from the groups that did not switch as similar for originator and biosimilar recipients (45 vs. 43%, $p = 0.8$) [27]. Even when switch information is reported, an important drawback of this trial for payers is enrolment of anti-TNF-naïve participants, which will likely leave unanswered questions regarding substitution in treatment-experienced populations. Results of the non-inferiority analysis have also not been reported.

Additional limitations exist with this trial as have been described with NOR-SWITCH. Again, the choice of non-inferiority margin in NCT02096861 may or may nor be informative but is not yet published to make this interpretation. For example, if a large margin of inferiority (e.g., 15%) is chosen and statistical endpoints are met, clinicians and patients may still interpret the results as showing there is a meaningful chance of a clinically significant worsening or lack of effect.

For practicing IBD specialists, the majority (89.8%) of whom still have concerns about automatic substitution with biosimilars [28], the results of these trials may prove unlikely to provide additional confidence to support policies that lack direct physician involvement. The lack of precision of the estimates provided for IBD patients, failure to incorporate multiple switches, and other design flaws are all-important limitations for clinical decision-making.

Specifically, for payers and prescribers, neither trial addresses important concerns raised about the potentially negative impact of switching back again to the originator product or to a different biosimilar after an initial switch. Immunogenicity is a critical issue that needs to be addressed by obtaining high quality clinical data. While both trials provide prescribers and policymakers with some information about the consequences of one-time switching (in either treatment-naïve or -experienced populations), larger clinical questions related to multiple switching remain. In partial recognition of these concerns the US Food and Drug Administration (FDA) has provided draft guidance specifying the requirements needed to demonstrate interchangeability, which includes assessment of the

immunogenicity risk in well-designed trials that expose patients to multiple cross-overs between originator and biosimilar [29].

3.2 Economic Evidence to Support Substitution

In Canada, the current list price of the originator infliximab, Remicade®, for CD is $987.56 [30] in Ontario compared to a list price of $525.00 for the biosimilar infliximab [31]. Using the best estimate available from NOR-SWITCH regarding the relative effectiveness of switching to the biosimilar (and disregarding *p* value significance testing for policy decision making [32]), and assuming a switch after 6 months of stability on the originator product, we calculated an incremental cost-effectiveness ratio of $176,695 of switching from Remicade™ to a potentially less costly, less effective biosimilar in Crohn's disease (Box 1). In other words, for every quality-adjusted life-year (QALY) lost by switching to the biosimilar, the payer would reduce costs by $176,695. This is based on an average loss of 0.27 QALYs per patient switched and $47,257 in reduced costs. It also assumes uncertainty given the uncertain results of NOR-SWITCH and given potential changes to key assumptions such as price.

This analysis also assumes that payers are willing to fund products that are potentially less costly and less effective (i.e., appear in the southwest quadrant of the cost-effectiveness plane), which may not always be true [33]. Typically, payers are willing to preferentially pay for products with evidence of potentially inferior outcomes only if adopted first and until decisions are revisited, typically a slower process than adoption decisions. If they choose a policy to adopt a product that may be inferior, it has been suggested that what a payer is willing to accept for a potential loss of health may be much more than what they are willing to pay for similar gains, creating a 'kink' in the acceptability curve [34, 35].

While originator infliximab was adopted at an incremental cost-effective ratio (ICER) of roughly $100,000 per QALY, the willingness to accept a loss by payers might be at least 1.9 times (and as much as 6.4 times) this threshold [34], meaning a payer will require a further price reduction for the biosimilar to achieve more than $190,000 in reduced costs to compensate for the expected loss of one QALY. However, cost reductions achieved through reductions in biosimilar prices will also be offset by any rebates already provided by originators. The implication of adopting less effective, less costly technologies is that every $1 in total cost reductions offered by the producer of the originator product through price agreements must be matched by at least 1.9–6.4 times the reduction in costs through rebates by the biosimilar manufacturer.

4 Policy Options for Pricing and Reimbursement

Assuming payers are interested in policy options that provide access to biosimilars when supported by evidence [36], while recognizing physician and patient autonomy and quality of care delivery within fiscal constraints, several relevant options arise when considering the clinical and economic implications from emerging evidence:

1. *Watch and wait*—payers may want to wait for more evidence to have additional confidence in funding switches. This will avoid any perceptions of paying for products with potentially inferior outcomes, but it may not reduce expenditures, unless a listing agreement is made (see below). This option may be unattractive for patients and clinicians who are willing to switch, but are unable to if a product is not listed. It may also not be possible, for some payers, who are obligated to list a product. Payers may additionally reimburse the biosimilar product only for newly diagnosed patients.
2. *Use product listing agreements to manage uncertainty*—in addition to watching and waiting, payers may want to manage the uncertainty from the availability of current and emerging infliximab biosimilars in IBD through product listing agreements with the innovator, biosimilar manufacturer, or both. These agreements could reflect the downward pressure on price reflected by the existence of one (and eventually more) competing products coupled with a consideration of price based on the economic value using currently available evidence (see Box 1). They may also allow a broader choice of biosimilars to be listed while allowing for physician involvement and responsibility in switching.
3. *Provide access for one-time informed substitution with biosimilar infliximab in any patient*—while emerging evidence on switching may be interpreted as showing a one-time switch will not lead to significant worsening for patients overall, it still provides the basis for an informed decision between clinicians and patients. Switching informed by physician–patient interaction may be more desirable but could lead to resistance or confusion where physicians or patients are less supportive or knowledgeable of the use of biosimilars in IBD. This may also be difficult for some health systems with multiple insurers or health jurisdictions to track switching, which makes the notion of enforcing and administrating a one-time switch difficult. Given current evidence, it will also likely lead to lower switch rates and expenditure reductions than with mandated non-medical substitution policies.
4. *Provide access to either treatment using tiered or co-payments to incent use of less costly products*—if

allowable, payers may consider reducing expenditures through a tiered formulary arrangement or charging a co-payment or top-up payment to patients for non-referred products. This may be either the biosimilar or originator product. This may be viewed as less desirable for some patients who view co-payment as a factor leading to less medication adherence in a chronic and severe condition where sustained responses are important [37]. Co-pay top-up programs offered by either the originator or biosimilar producer could also negate incentives to switch.

5. *Mandate producers to provide evidence of interchangeability*—not meeting the evidentiary needs of payers leads to uncertainty that can delay or prohibit access to biosimilars by insurers. Setting a higher regulatory or health technology assessment (HTA) bar for evidence may discourage biosimilar developers, ultimately delaying or prohibiting more affordable therapies [38]. However, it may still encourage some producers, given the size of current markets. In economic terms, jurisdictions need to decide whether the potential loss of value due to lack of information is outweighed by potential losses due to lack of biosimilar development. Aligning evidence needs imposed by regulators more closely with payer requirements may still be desirable, as it reduces the inherent tension caused by different regulatory requirements [39].

Box 1: Calculating the value-based price based on the incremental cost-effectiveness of originator versus biosimilar infliximab in patients with Crohn's disease based on the NOR-SWITCH trial

Methods

We modelled a one-time switch to biosimilar infliximab after 6- onths of Remicade™ therapy in Crohn's disease patients with clinical characteristics seen in NOR-SWITCH (average age of 39 years, 41% female and with an average disease duration at time of enrolment of 13.5 years and previous average duration of treatment with originator product (Remicade™) of 5.5 years). Seventy-eight per cent (121/155) of patients enrolled had no prior treatment with an anti-tumor necrosis factor (TNF) drug.

Using a time horizon, discount rate, health outcome, and perspective as per new Canadian guidelines [40] (10-year time horizon, 1.5% discount rate for health and costs, quality-adjusted life-years, and Canadian third-party payer perspective), and a Markov model that accounts for dose escalation, progression of disease during separate induction and maintenance phases of treatment estimated from a network meta-analysis and calibration to real-world evidence post 1 year of clinical trial data, the costs and health outcomes associated with the use of originator and biosimilar infliximab could be calculated. The model assumes patients are switched at a given point in time, and potential benefits from early treatment are not taken into consideration. It also does not consider specific populations at high risk for relapse but provides a mean overall estimate.

Results

At a list price of $987.56 per vial for the originator product and $525 per vial for a biosimilar, the 10-year costs associated with Remicade™ are $168,210 versus $120,753 for the biosimilar product. However, data from NOR-SWITCH suggests the reduction in cost would be associated with decreased benefits (6.02 vs. 5.76 QALYs). In this scenario, a loss of 0.27 QALYs for $47,457 of expenditures avoided would lead to an ICER in the southwest quadrant of $176,695 (see Fig. 2 below).

5 Discussion

Our goal was to call attention to the evidence-based policy options available for providing access to biosimilars through switching in cases where direct evidence is lacking. Using infliximab in IBD as an example, our intent was to highlight the strengths and limitations of IBD single-switch trials for drug insurers and pharmacy benefits managers and outline what options might be most feasible for IBD patients. Central to thinking about these policy options is the idea that current switch trials can provide some evidence for payers but are likely insufficient for mandating automatic substitution policies [41]. However, we also wanted to highlight the difficulties in using single switch trial data, especially where sufficient power is lacking to predict outcomes in special populations. Some viable options that will impact patient welfare or healthcare spending positively are to wait for more data to become available, allow informed switching, or renew or implement listing agreements to manage uncertainty in therapeutic areas where evidence is lacking.

None of the policy options we have outlined are mutually exclusive from one another and there may be other options available to policymakers depending on the structure and delivery of drug insurance within individual jurisdictions. For example, unlike their European counterparts, Canadian policymakers have few levers to incent physician prescribing of biosimilars beyond formulary listing coupled with educational programs and prior

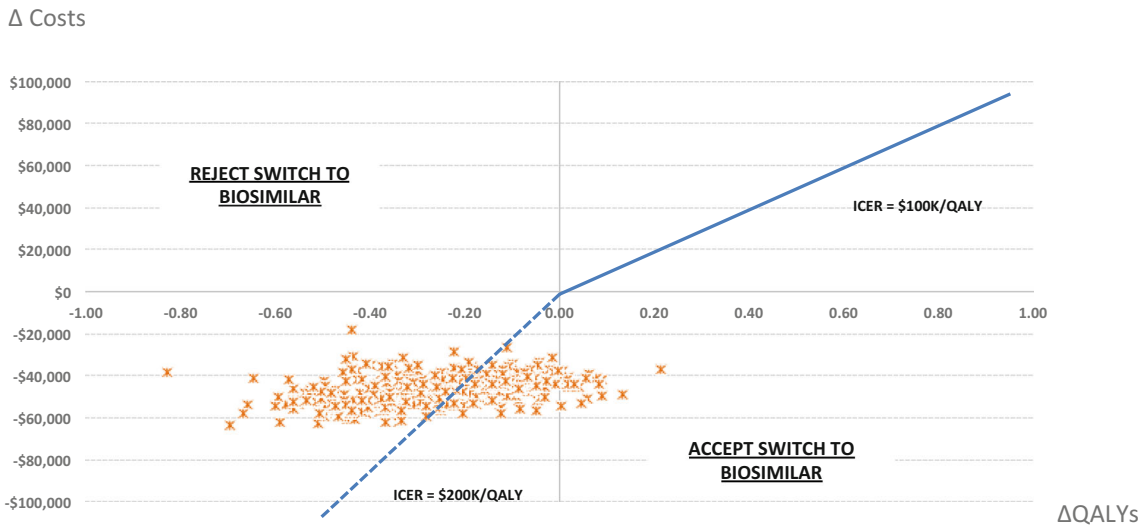

Fig. 2 Probabilistic sensitivity analysis scatterplot for biosimilar versus originator infliximab

authorization procedures or audit [42]. Like the USA, Canada also has a mixture of private and public insurance coverage and until now uptake of biosimilar infliximab has been relatively low [43]. Countries such as Norway and Germany stand in stark contrast, where budgets are held at levels closer to care and providers are given incentives to lower overall costs of care. This leads to situations where clinicians directly benefit from switching through gain-sharing or a diversion of freed resources to improving patient care, which could be a potential cause for concern given some of the uncertainty about the true impact of substitution and need for further study.

With the increasing use of product listing agreements between payers and manufacturers to manage payer uncertainty, coupled with the interests of originator producers to continue to market biologics for other conditions for which biosimilars are not available, it seems there may be opportunities for payers to garner value from the availability of biosimilars. Our calculation of a value-based price using a well-developed model is similar to another study we have identified [44]. Only our interpretation based on the the cost-effectiveness threshold differs.

At the crux of the issue is the potential misalignment of evidence requirements by regulators and HTA bodies for chronic diseases associated with severe burden or relapse where evidence to support automatic substitution (i.e., evidence of interchangeability) plays a more crucial role. This tension between regulator- and payer-important evidence is not a new one, and has also been evident in past reimbursement policy. For example, the advent of generic drugs with narrow therapeutic windows led to regulator-certified copies of patented drugs being available but not preferentially funded by insurers. This has led to a more recent international focus on aligning payer and regulator requirements [45]. It has also led to the increased use of HTA early scientific advice programs and initiatives, including tri-partite dialogue among producers, HTA bodies, and regulators [46].

The evidence available to inform substitution will also not be an issue for all biosimilars. This might be the case in some therapeutic areas, where patients are expected to be treatment naïve, and where short courses of therapy are warranted, or where purification and the size of the biosimilar molecule makes the development of immune responses less of an issue. There may also be cases where biosimilars perform better than their originators ("bio-betters"), which could create additional challenges [47]. Substitution would also certainly be considered much less of an issue where therapeutic monitoring and feedback is relatively straightforward and rapid for both patients and clinicians. Biosimilars of insulin and filgastrim fall into this category and their evaluation and ascension to public formularies may be seen as less of a payer problem.

Given the future introduction of additional infliximab biosimilars and the need for formulary managers to consider how to allow access, it appears the focus on automatic substitution and the interchangeability of biologics in some select conditions will only intensify these underlying challenges. While regulators in Europe, Canada, and Japan have not addressed the issue for the time being, the FDA's current focus, with published draft guidance, could renew interest in the area [29]. The FDA draft guidance suggests the number and duration of switches should be "at least three … with each switch crossing over to the alternate product" with duration of exposure "sufficiently long to allow for washout of the reference product" [29]. There may still be issues with the guidance if improved and implemented, including the number of switches meaningful

to practitioners and payers, and the sample sizes and equivalency/non-inferiority margins required to confidently demonstrate interchangeability.

Implementation of this guidance, coupled with increased experience with evaluation of biosimilars, could lead to an increased focus on interchangeability or at the very least heightened awareness of this and other issues facing payers such as extrapolation. In theory, regulators could be more vigilant about picking diseases that truly have the greatest sensitivity to differences in biosimilars functionality and immunogenicity in the reference case. For infliximab, one of us (BF) has argued that ulcerative colitis may have been a more prudent reference population than either RA or AS [6].

Given the large potential market, biosimilar producers themselves may also respond to the need to distinguish themselves by providing additional evidence of switching/interchangeability that goes beyond regulator requirements. Trials such as NCT02096861 in Crohn's disease may prove a value-add to insurers who must decide what biosimilar to fund. Ongoing experience and robust study of biosimilar agents will likely lead to greater confidence in prescribing and switching to these and overcome a large psychological component for care providers and patients, who may perceive less expensive care as less effective. To reduce clinical uncertainty and greatly improve the uptake of biosimilars, future efforts should focus on randomized controlled trials in line with draft FDA guidance [29], trials that demonstrate the effectiveness across multiple switches that include objective outcome measures and state of the art immunogenicity assays.

6 Concluding Remarks

Reimbursement and pricing of biosimilars is an evolving field and undoubtedly regulatory and policy approaches will continue to learn and change. Some of the issues highlighted here may be unique to infliximab in IBD and new issues could arise in other therapeutic areas and with other molecules. At the core of these issues is the need for evidence that is valuable to payers and the HTA bodies that support them. What is clear is that there are no clear or universal pathways to healthcare markets for all biosimilars and that uptake will depend on local healthcare delivery and support for decisions when direct evidence is lacking.

Data Availability The information provided regarding the economic evaluation largely complies with the CHEERS Statement checklist [48], but additional details can be found in descriptions of the original model [49] as well as small modifications that have been published [50]. The dataset including input parameters as well as the mathematical model underpinning this research is privately owned, but details regarding its structure, underlying assumptions, and other information necessary to facilitate its replication will be made upon reasonable request with the corresponding author.

Compliance with Ethical Standards

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Author contributions BF provided the original inspiration and some key content for this work. DH led the writing of the manuscript including the drafting of the outline and manuscript and is the guarantor of this work. All authors approved the outline of the work, helped to write and revise the manuscript, and read and approved the final version of the manuscript.

Conflict of interest All authors have signed conflict of interest forms and read information regarding disclosure of potential conflict of interest at http://www.springer.com/us/authors-editors/journal-author/journal-author-helpdesk/before-you-start and declare the following: accepting consulting fees from medical device and pharmaceutical companies who may have interest in the work (DH, BF, CSH).

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