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Review

The challenge of indication extrapolation for infliximab biosimilars

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ABSTRACT

A biosimilar is intended to be highly similar to a reference biologic such that any differences in quality attributes (i.e., molecular characteristics) do not affect safety or efficacy. Achieving this benchmark for biologics, especially large glycoproteins such as monoclonal antibodies, is challenging given their complex structure and manufacturing. Regulatory guidance on biosimilars issued by the U.S. Food and Drug Administration, Health Canada and European Medicines Agency indicates that, in addition to a demonstration of a high degree of similarity in quality attributes, a reduced number of nonclinical and clinical comparative studies can be sufficient for approval. Following a tiered approach, clinical studies are required to address concerns about possible clinically significant differences that remain after laboratory and nonclinical evaluations. Consequently, a critical question arises: can clinical studies that satisfy concerns regarding safety and efficacy in one condition support "indication extrapolation" to other conditions? This question will be addressed by reviewing the case of a biosimilar to infliximab that was approved recently in South Korea, Europe, and Canada for multiple indications through extrapolation. The principles discussed should also apply to biosimilars of other monoclonal antibodies that are approved to treat multiple distinct conditions.

1. Introduction

As innovator biologics lose patent protection, biopharmaceutical companies have sought to develop biosimilar versions of these agents. Several biosimilars have been approved, particularly in Europe. These include molecules such as epoetin, filgrastim and growth hormone which have relatively low molecular weights in distinction to monoclonal antibodies [1].

Biologics are difficult to copy exactly due to their structural complexity and the nature of the cell culture systems used in their manufacture. Thus, biosimilars, particularly larger proteins with post-translational modifications, can be engineered to be highly similar but not identical to their reference biologics. Requirements for approval of a biosimilar by the U.S. Food and Drug Administration (FDA), Health Canada and European Medicines Agency (EMA) include extensive *in vitro* studies demonstrating similarity to a reference biologic in terms of quality attributes, as well as nonclinical and clinical studies demonstrating comparable pharmacokinetics (PK), efficacy, safety, and immunogenicity [2–4]. Given that the clinical performance of the innovator biologic has already been established, the nonclinical and clinical studies required for approval of a biosimilar may be reduced compared with the studies required for approval of the innovator biologic. The appeal of developing a biosimilar is further enhanced by the possibility of gaining approval for all indications held by the reference product based on less extensive nonclinical data, and minimal clinical data in only a subset of indications. The impact of such indication

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extrapolation will vary from one agent to another as some have few approved uses while others have many. FDA, Health Canada and EMA have directed sponsors to justify requests for indication extrapolation based on a number of considerations (Table 1) [2–4]. Providing a global perspective, the World Health Organization (WHO) has also laid out guidelines for indication extrapolation [5].

Indication extrapolation may depend on a limited number of issues for biologics when a single molecular target, mechanism of action, and site of action exists across different indications and a well-described pharmacokinetic–pharmacodynamic relationship has been established, preferably on the basis of a biomarker rather than clinical outcomes (e.g., recombinant human insulin and serum glucose). In contrast, extrapolation for monoclonal antibodies (mAbs) can be more challenging. A biosimilar to infliximab known as CT-P13 was recently approved in South Korea, Europe, and Canada for multiple indications through extrapolation [6–10].

The innovator molecule infliximab, a mAb directed against tumor necrosis factor alpha (TNFα), is approved in many regions around the world for use in adult patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), Crohn's disease (CD), ulcerative colitis (UC), and plaque psoriasis (Pso), as well as in pediatric patients with CD, and UC [11–13]. While TNFα is implicated in the pathophysiology of all these conditions, their clinical manifestations are distinct. Furthermore, the respective mechanisms of action, sites of action, PK, concomitant medications, immunogenicity risk, and safety profile of infliximab are different, or may be different. This article will address factors to consider when evaluating indication extrapolation for biosimilars with a special focus on infliximab.

2. Regulatory basis for indication extrapolation

To date, CT-P13 and REMICADE® (Janssen Biotech, Inc. Horsham, PA, United States) have been studied in comparative clinical trials in RA and AS. In 2013, following endorsement by the Committee for Medicinal Products for Human Use (CHMP) in Europe, CT-P13, also known as REMSIMA™ (Celltron, Inc., Incheon, Republic of Korea) and INFLECTRA™ (Hospira, Inc. Lake Forest, IL, United States), was approved by EMA for all indications held by infliximab including RA, AS, PsA, CD, UC, Pso, and pediatric CD and UC [7,8,14,15]. In 2014, the products were approved by Health Canada for RA, AS, PsA and Pso but not CD or UC [9,10,16,17].

Comparisons of CT-P13 and infliximab have been presented at the European League Against Rheumatism Congress in 2013 [18], in two publications [19,20], in two European Public Assessment Reports (EPARs) for CT-P13 [7,8], the Product Monographs of REMSIMA™ and INFLECTRA™ in Canada [9,10], and in the Summary Basis of Decision documents for REMSIMA™ and INFLECTRA™ issued by Health Canada [16,17]. According to these sources, CT-P13 and infliximab exhibited similarity in most but not all of the biochemical and bioactivity assays employed. The molecules also exhibited similar PK, safety and efficacy in AS, as well as similar safety and efficacy in RA [7,8,16,17,19,20] to the limited extent that small to moderately sized trials are able to exclude differences.

The EPARs provide insight into the regulatory basis for the indication extrapolation in Europe [7,8]. Even though differences between CT-P13 and infliximab were noted in certain sensitive *in vitro* assays, EMA assigned more weight to other assays that it considered more clinically relevant [7,8], and which demonstrated similarity between CT-P13 and infliximab. (These assays will be described in more detail below.) EMA also judged RA to be a sufficiently sensitive clinical model in which to detect potential differences between CT-P13 and infliximab [7,8]. Overall, EMA concluded that the sponsor provided convincing evidence and adequate scientific justification to allow indication extrapolation [7,8].

Health Canada had a different view of the sponsor's proposed justification, as extrapolation was allowed for PsA and Pso but not CD or UC [9,10,16,17]. According to Health Canada, approval of CD or UC could not be recommended due to the differences between CT-

Table 1
Regulatory considerations for indication extrapolation for biosimilars.

Health Canada [3]	• In some cases, comparative pharmacokinetic/pharmacodynamic (PK/PD) data to bridge two or more indications may be sufficient for extrapolation. • It may also be possible to extrapolate clinical data to other indications where rationales are sufficiently persuasive. • The extrapolation should be justified based on: mechanism(s) of action; pathophysiological mechanism(s) of the disease(s) or conditions involved; safety profile in the respective conditions and/or populations; and clinical experience with the reference biologic drug.
European Medicines Agency [2]	• Extrapolation is possible based on the overall evidence of comparability provided from the comparability exercise and with adequate justification. • If pivotal evidence for comparability is based on PD and for the claimed indications different mechanisms of action are relevant (or uncertainty exists), then applicants should provide relevant data to support extrapolation to all claimed clinical indications. • Applicants should support such extrapolations with a comprehensive discussion of available literature including the involved antigen receptor(s) and mechanism(s) of action.
U.S. Food and Drug Administration (draft) [4]	• Scientific justification for extrapolation should address, for example, the following issues for the tested and extrapolated conditions of use: ○ The MOA(s) in each condition of use for which licensure is sought. This may include the following: ▪ The target/receptor(s) for each relevant activity/function of the product; ▪ The binding, dose/concentration response, and pattern of molecular signaling upon engagement of target/receptor(s); ▪ The relationship between product structure and target/receptor interactions; ▪ The location and expression of the target/receptor(s); ○ The PK and bio-distribution of the product in different patient populations; PD measures may provide important information on the MOA; ○ Differences in expected toxicities in each condition of use and patient population (including whether expected toxicities are related to the pharmacological activity of the product or to off-target activities); ○ Any other factor that may affect the safety or effectiveness of the product in each condition of use and patient population for which licensure is sought.

P13 and infliximab observed *in vitro*, potential differences in the mechanism of action of infliximab in the conditions, and the absence of clinical studies [16,17]. Meanwhile, debate continues in the medical community about whether the data in RA and AS provide an adequate foundation for extrapolation to other indications [21–27].

3. Clinical considerations

When planning for indication extrapolation, FDA recommends that sponsors "consider whether the tested condition of use is the most sensitive in which to detect clinically meaningful differences in safety (including immunogenicity) and effectiveness" [4]. The following sections will discuss the sensitivity of RA and AS studies comparing CT-P13 and infliximab, and address the residual uncertainty about safety and efficacy in other conditions.

3.1. Clinical sensitivity

In the pivotal clinical comparability study, 606 patients with RA who previously failed MTX were randomized to receive CT-P13 or infliximab at a single-dose level of 3 mg/kg at weeks 0, 2 and 6 and only at an interval of every 8 weeks thereafter in combination with MTX (12.5–25 mg/week) [20]. Methotrexate itself has clinical activity in RA, and potentiates the activity of infliximab [28] and other TNF antagonists by reducing immunogenicity, increasing drug concentrations and affecting mechanisms not targeted by the biologics. Accordingly, it remains a challenge to attribute levels of response to one agent or the other when the agents are used in combination. For this reason, the use of concomitant MTX, while required for the treatment of RA, may confound a conclusion that CT-P13 and infliximab have similar potency and/or efficacy. Hence, a demonstration of comparability in RA may not reflect outcomes in PsA, CD, UC, or Pso which are often treated with infliximab monotherapy or in combination with drugs other than MTX (Table 2). (Concomitant MTX may be used in PsA, but its use is not required.) While similar efficacy in AS was observed when CT-P13 and infliximab were given as monotherapy ($n = 250$; efficacy endpoints were secondary to PK endpoints) [19], the approval of CT-P13 in AS should not imply that extrapolation from RA to AS for future biosimilars is appropriate.

Other questions remain as to whether RA is a sensitive indication for evaluating the clinical impact of differences between products. In a recent publication, Lee proposed that indications with the highest placebo-adjusted response rate are most appropriate for detecting differences between drugs [26]. This position is based on the principle that sensitivity for detecting small differences between agents is optimized in situations where the signal-to-noise ratio is highest. RA has been identified as having the lowest placebo-adjusted response to infliximab (for ACR20/50/70 endpoints), and Pso the highest (for PASI75) [26]. Taken together, these considerations raise questions about extrapolation from RA (least sensitive clinical endpoint; treated with infliximab and MTX) to other indications. Perhaps recognizing some of these considerations, at least two developers are conducting biosimilar studies for adalimumab in Pso [29,30].

3.2. Mechanisms of action

Whether a single indication can support broad extrapolation for mAbs relies on, among other things, the commonality of mechanisms of action across indications. Cytokines and hormones such as epoetin, filgrastim, insulin, and growth hormone typically have a single binding site, molecular target and mechanism of action as well as an easily assessed biological readout. In contrast, mAbs have Fc and Fab regions (the latter include the antigen-binding regions) which participate in various biological activities (Table 3) [31–33]. For example, antigen neutralization requires only binding through the Fab region, whereas antibody-dependent cell-mediated cytotoxicity (ADCC) requires binding to antigen through the Fab region along with binding to Fcγ receptors on effector cells through the Fc region. Considerable uncertainty exists regarding the extent to

Table 2
Indications and dosing guidelines for TNFα antagonists according to the product monographs in Canada.

Indication	Infliximab [13]	Golimumab [56]	Adalimumab [41]	Etanercept [37]	Certolizumab pegol [57]
RA	3 mg/kg at wk 0, 2, 6 → q8wk (up to 10 mg/kg and/or q4wk) (+MTX)	50 mg/month (+MTX)	40 mg q2wk (±MTX)	50 mg/wk (±MTX)	400 mg at wk 0, 2, 4 → 200 mg q2wk (or 400 mg q4wk) (±MTX)
JIA	(not approved)	(not approved)	Up to 40 mg q2wk[a] (±MTX)	Up to 50 mg/wk[a]	(not approved)
AS	5 mg/kg at wk 0, 2, 6 → q6-8wk	50 mg/month	40 mg q2wk	50 mg/wk	400 mg at wk 0, 2, 4 → 200 mg q2wk (or 400 mg q4wk)
PsA	5 mg/kg at wk 0, 2, 6 → q8wk (±MTX)	50 mg/month (±MTX)	40 mg q2wk (±MTX)	50 mg/wk (±MTX)	400 mg at wk 0, 2, 4 → 200 mg q2wk (or 400 mg q4wk) (±MTX)
CD	5 mg/kg at wk 0, 2, 6 → q8wk (up to 10 mg/kg) (±conventional therapy)	(not approved)	160 mg at wk 0 → 80 mg at wk 2 → 40 mg at wk 4, q2wk	(not approved)	(not approved; approved in US with dosing 400 mg at wk 0, 2, 4 → 400 mg q4wk)
Pediatric CD (≥9 y)	5 mg/kg at wk 0, 2, 6 → q8wk	(not approved)	160 mg at wk 0 → 80 mg at wk 2 → 20 mg at wk 4, q2wk	(not approved)	(not approved)
UC	5 mg/kg at wk 0, 2, 6 → q8wk (up to 10 mg/kg)	200 mg wk 0 → 100 mg at wk 2 → 50 mg at wk 6, q4wk (up to 100 mg q4wk)	160 mg at wk 0 → 80 mg at wk 2 → 40 mg at wk 4, q2wk	(not approved)	(not approved)
Pediatric UC (≥6 y)	5 mg/kg at wk 0, 2, 6 → q8wk	(not approved)	(not approved)	(not approved)	(not approved)
Pso	5 mg/kg at wk 0, 2, 6 → q8wk	(not approved)	80 mg at wk 0 → 40 mg at wk 1, q2wk	50 mg 2×/wk for 3 months → 50 mg/wk	(not approved)

RA, rheumatoid arthritis; JIA, juvenile idiopathic arthritis; AS, ankylosing spondylitis; PsA, psoriatic arthritis; CD, Crohn's disease; UC, ulcerative colitis; Pso, psoriasis. Reasons for nonapproval of specific indications may include the following: studies not performed; studies yielded negative outcome; studies not accepted by regulatory authorities.
[a] Weight-based dosing.

Table 3
Fab-mediated and Fc-mediated interactions of monoclonal antibodies [31–33].

Antibody domain	Molecular target	Biological activities[a]
Fab	Soluble antigen	Neutralization (inhibition of receptor binding)
	Transmembrane antigen	Neutralization (inhibition of receptor binding) Inhibition of extracellular domain shedding Reverse signaling (apoptosis)
Fc	FcγRI FcγRII FcγRIII	*Activating functions*: ADCC Endocytosis of immune complexes (and antigen presentation for RI and RIII) Phagocytosis Clearance
		Inhibitory functions: Inhibiting activation of B lymphocytes, monocytes, mast cells, and basophils
	FcRn	Turnover
	C1q complement	CDC

[a] Each biological activity may be relevant to only a subset of molecular targets shown.

which the Fc domain of infliximab contributes to mechanism of action in different indications. In RA, infliximab is thought to act predominantly through the neutralization of soluble and transmembrane TNFα, whereas in other conditions such as CD, signaling through membrane-associated forms of TNFα and Fcγ receptor (triggering apoptosis or ADCC) may play a more important role [7,8,16,17,32,34,35]. EMA acknowledged such a separation of function, stating in its guidance that ADCC appears to be more important in some indications than in others [2]. While the apoptotic effects of CT-P13 and infliximab were reportedly comparable, differences between CT-P13 and infliximab were observed in a sensitive ADCC assay [7,8,16,17]. Accordingly, the comparative data generated in RA may not support the assumption of comparable efficacy in all indications.

Signaling through the Fc region of mAbs also depends on the nature of their Fc receptor targets. Binding of mAbs to FcγRIIIa is affected by the valine (V)/phenylalanine (F) polymorphism of FcγRIIIa amino acid 158, which in turn affects ADCC. The 158V form of the receptor has higher affinity for IgG1-Fc than the 158F form [36]. Compared with infliximab, CT-P13 exhibited reduced binding *in vitro* to FcγRIIIa (V and F allotypes) as well as to NK cells isolated from healthy donors and CD patients (dependent on FcγRIIIa genotype V/V and V/F; no difference was observed with F/F genotype) [7,8,18]. Differences in ADCC were observed when NK cells from CD patients were used, according to donor genotype (as above) [7,8,18]. These results suggest that pivotal studies beyond RA as well as studies in patients with FcγRIIIa polymorphisms may be warranted.

In its justification for extrapolation to inflammatory bowel diseases, EMA questioned the physiological relevance of ADCC assay results using NK cells, and reported on several studies in which similarity between CT-P13 and infliximab was observed [7,8]. For example, the difference in binding to NK cells was abrogated in the presence of diluted CD patient serum. Also, ADCC was comparable when peripheral blood mononuclear cells from CD patients (V/F or F/F genotype), or whole blood from healthy donor or CD patients was used as a source of effector cells. Other supportive data included (but were not limited to) the induction of regulatory macrophages and inhibition of T-cell proliferation (regardless of FcγRIIIa donor cell genotype), wound healing in a colon epithelial cell culture model, inhibition of pro-inflammatory cytokine secretion from human intestinal epithelial cells, and inhibition of soluble TNFα-induced apoptosis of human intestinal epithelial cells. In contrast, Health Canada did not approve CD or UC indications [9,10,16,17], possibly reflecting a more conservative approach to extrapolation in Canada. Health Canada stated that "differences in the ability of [CT-P13 and infliximab] to induce ADCC could not be ruled out" and that "ADCC cannot be ruled out as a mechanism of action in the inflammatory bowel diseases" [16,17].

Finally, differences in clinical activity among TNFα antagonists illustrate that activity in one indication cannot be relied upon to predict activity in other indications (Table 2). For example, etanercept is active in rheumatoid diseases but not inflammatory bowel diseases, and is used at a different dose level in Pso [37,38]. Compared with infliximab, etanercept exhibits a number of differences in biochemical activity, including an inability to bind monomeric TNFα [39], lower avidity binding to transmembrane TNFα as well as less stable binding to both soluble TNFα and transmembrane TNFα [39,40], reduced activity on cells bearing transmembrane TNFα as well as reduced CDC, impaired reverse signaling/apoptosis, and less potent ADCC (in a cell-line dependent manner) [32]. As another example, adalimumab is used at different dose levels in RA, AS and PsA than in CD and UC, as well as Pso [32,41].

Taken together, these findings suggest that the structure–activity relationships of infliximab are key to its range of clinical activities, and that the molecular interactions and mechanisms of action required for activity may not be common across all rheumatoid diseases, inflammatory bowel diseases, and psoriasis.

3.3. Immunogenicity

Given the variety of minor differences in the drug product that can impact immunogenicity, such as formulation, impurities, and packaging, clinically significant differences in immunogenicity between products are arguably impossible to exclude without clinical trials. FDA and WHO recommend that to support indication extrapolation, immunogenicity should be investigated in the patient population that carries the highest risk of an immune response and immune-related adverse events [4,5]. As described above, patients in the RA study comparing CT-P13 and infliximab received concomitant MTX. MTX suppresses the formation of anti-drug antibodies (ADAs) to infliximab [28] which may reduce the sensitivity for detecting differences in immunogenicity between the products as well as potential inhibitory effects of ADAs on clinical response. Patients in the comparative study in AS were treated with infliximab or CT-P13 monotherapy; however, patients with AS (as well as patients with RA treated with MTX) have historically exhibited a lower incidence of ADAs to infliximab than patients with Pso, CD or UC [13,42,43]. Accordingly, AS and RA should not be considered sensitive populations from which to extrapolate immunogenicity data.

3.4. Safety

FDA has guided sponsors to be cautious about extrapolating safety risk profiles of candidate biosimilars across indications because patient populations for different indications may have different co-morbidities and receive different concomitant medications [4]. Health Canada and EMA also identify safety profile as an important consideration for indication extrapolation [2,3]. Depending on the product attribute that accounts for a given safety risk (e.g., impurity, off-target effect, target interaction, or pharmacological effect), potential differences between a biosimilar and the reference biologic may impact some safety risks but not others. Where clinical data are needed to address the possibility that

product differences might impact a specific safety risk, those data should be generated in the clinical setting (e.g., indication, dosing, patient population) where that risk is more commonly manifest.

The terms of marketing authorization for REMICADE® (infliximab) identify specific, albeit infrequent, adverse drug reactions linked to specific indications, comorbid conditions, concomitant therapies, and/or age groups [11–13]. For example, patients with mild heart failure should use REMICADE® with caution based on observed higher mortality and higher incidence of cardiovascular adverse events in patients with moderate/severe heart failure who received doses of 10 mg/kg and 5/10 mg/kg, respectively. Also, rare cases of hepatosplenic T-cell lymphoma have occurred primarily in patients with CD or UC who had received treatment with AZA or 6-MP concomitantly with or immediately prior to REMICADE®. The majority of cases involved adolescent or young adult males. Also, malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNFα-blocking agents including REMICADE®. Approximately half of these cases were lymphomas. The other cases represented a variety of malignancies including rare ones usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. Most of the patients were receiving concomitant immunosuppressants. The comparative studies of CT-P13 conducted in RA and AS do not appear to cover all relevant patient populations including pediatric patients and patients taking immunosuppressants other than MTX. Accordingly, extrapolation to patient populations and combination regimens for which safety studies have not been conducted should be considered with caution.

One may also question whether the limited safety database for CT-P13 at the time of approval will be representative of the benefit–risk profile of the product in the post marketing setting. In the pivotal RA study, the incidence of serious adverse events in patients receiving CT-P13 and infliximab up to week 54 was 14% and 10%, respectively [7,8]. The imbalance was attributed to cases of tuberculosis and pneumonia, which the sponsor linked to risk factors or pre-existing conditions in affected patients [7,8]. The risk of infection associated with CT-P13 versus infliximab remains unclear until future data can be generated. The sponsor committed to monitoring serious infections, including TB, as well as rare adverse reactions known to infliximab in the post marketing setting through registries [7,8].

Finally, even though REMICADE® (infliximab) is approved for use in RA, CD, and UC at dose levels up to 10 mg/kg (Table 2, which covers the terms of market authorization in Canada), patients with AS and RA treated with CT-P13 received dose levels of only 5 mg/kg and 3 mg/kg, respectively. Because CT-P13 and infliximab are manufactured through independent processes, they may have different product and process-related impurities [2–4]. Studies examining safety outcomes at higher dose levels may be warranted, and adverse events in the post marketing setting should be analyzed with attention to the associated dose levels. Notably, while EMA approved CT-P13 for use in RA at all dose levels and intervals approved for REMICADE®, Health Canada approved CT-P13 for use in RA only at a dose level of 3 mg/kg every 8 weeks, which was the dose level studied [9,10].

3.5. Pharmacokinetics

In a comparative PK study, patients with AS were randomized to receive infliximab or CT-P13 at a dose level of 5 mg/kg at weeks 0, 2, 6, and then every 8 weeks thereafter [19]. Primary endpoints were area-under-the-curve at steady-state (AUC_{SS}) and maximum steady-state serum concentration (C_{max}) between weeks 22 and 30. Similarity in these parameters was observed [7,8,19]; however, because single-dose PK, as recommended by Health Canada [3,44], has not been reported, the comparability of important parameters such as C_{max}, AUC_T, clearance and terminal $t_{1/2}$ in a sensitive population is unclear.

Monoclonal antibodies are cleared through several pathways (nonspecific catabolism, FcγR-mediated, target-mediated, and immunogenicity-related pathways), and most antibodies demonstrate nonlinear, dose-dependent pharmacokinetics [45,46]. Accordingly, single-dose PK comparability studies using low and high-dose levels would be appropriate for comparing elimination since the contribution of different elimination pathways differs at different dose levels [46].

Previous studies have identified that infliximab clearance varies in different patient populations. For example, clearance in CD is approximately 45% higher than in RA (Table 4). Clearance is also affected by concomitant medication (e.g., MTX, 6-MP, and azathioprine) [28,45] as well as ADAs [47]. As discussed above, patients with AS treated with infliximab are less prone to developing ADAs than patients with Pso treated with infliximab [13,47]. Given the multiple pathways through which mAbs are cleared from the body, the effects of concomitant drugs, differences in immunogenicity, and previous observations with infliximab discussed above, comparative PK data from the repeated-dose study in AS may not be reflective of PK in other indications.

3.6. Sites of action

Infliximab is active in various tissues and organ systems including joints, axial skeleton, gastrointestinal tract, and skin. However, the concentration of infliximab required for clinical effectiveness in each tissue is unknown. Infliximab is distributed primarily into the vascular compartment [13]; thus, drug levels measured in serum may not be an adequate surrogate for drug levels in target tissues [48]. Because all relevant target tissues have not been evaluated by the comparative studies in RA and AS, indication extrapolation for CT-P13 is problematic. The validity of such extrapolation relies on the assumption that CT-P13 and infliximab achieve similar distribution to all affected tissues.

3.7. Pathophysiology of disease

Health Canada identifies pathophysiological mechanisms of disease as a point to consider in support of indication extrapolation. RA, AS, PsA, CD, UC, and Pso are distinct conditions. Among these conditions, there appear to be both similarities and differences in the signaling pathways involved [22,49–54]. TNFα, a pro-inflammatory cytokine, is implicated in all of them, and treatment with TNFα antagonists has yielded positive outcomes. However, the contribution of TNFα to disease progression depends on

Table 4
Infliximab clearance rates in different patient populations.

Population	Concomitant therapy	Mean infliximab clearance[a] (L/day)	Reference
RA	MTX	0.26	[58]
AS	(monotherapy)	0.27	[47]
UC	Corticosteroids ± AZA/6-MP (ACT1, ACT2) ± 5-aminosalicylates (ACT2)	0.41	[59]
CD	Corticosteroids ± 5-aminosalicylates, 6-MP/AZA, MTX	0.38	[45]

[a] Cross-study comparison may be confounded by dose levels, concomitant medications, and assay variability.

the receptor interactions and cooperating pathways in specific tissues. Also, TNFα is present in the body as a soluble form and a transmembrane form. These forms interact with the receptors TNFR1 and TNFR2, which themselves can be membrane-bound or soluble [32,55]. The involvement of specific forms of TNFα and their receptors in each disease is not fully understood.

RA, AS, PsA, CD, UC, and Pso exhibit variable responsiveness to different TNFα antagonists (Table 2), implying potential differences in disease pathophysiology, and/or differences in mechanisms of action and tissue penetration of the drugs (see above). This disease selectivity also applies to biologics directed against other targets. For example, abatacept (targets CD80 and CD86), tocilizumab (targets IL-6 receptor), and rituximab (targets CD20) have demonstrated efficacy in RA; however, they are not all universally active in other conditions including AS, PsA, CD, UC, and Pso. Collectively, these observations suggest that RA, AS, PsA, CD, UC, and Pso do not share a single, common pathophysiology, thus challenging the validity of indication extrapolation for agents that treat these conditions.

4. Conclusion

CT-P13 represents the first biosimilar mAb approved in South Korea, Europe, and Canada, and the first example of a biosimilar mAb granted indication extrapolation in these jurisdictions. Given the considerations reviewed above, broad extrapolation of comparative safety and efficacy data for infliximab to conditions that have not been studied remains a challenge. Questions remain as to whether PK, efficacy and safety data for CT-P13 in AS and RA can be extrapolated to, and provide adequate justification for use in PsA, CD, UC, and Pso, as well as pediatric patients with IBD. In this relatively unexplored area of biosimilars, a more conservative approach is warranted which would call for clinical trials in more sensitive indications, as well as studies encompassing all relevant mechanisms of action, sites of action, concomitant medications, and PK scenarios. It remains that EMA, following a totality-of-evidence approach, concluded that the benefit-risk balance for CT-P13 was positive in all studied and extrapolated indications [7,8]. Health Canada approved CT-P13 in some extrapolated indications (PsA, Pso) but not others (adult and pediatric CD and UC) [9,10,16,17]. As biosimilar mAbs move through development and regulatory review around the world, critical evaluation of the residual uncertainty in safety and efficacy in extrapolated indications will be key to ensuring that patients and healthcare providers can continue to benefit from all available treatment options.

Conflict of interest

In June 2013, the authors held a roundtable discussion on the topic of biosimilars to infliximab. BGF, DC, SG, DDG, VH, BM, GZ, and ASR received honoraria from Janssen for participation at this meeting. ZX, GS and DCFS are employees of Janssen.

BGF has received speaker honoraria from AbbVie, Janssen, Warner-Chilcott, and UCB; honoraria for consulting and/or advisory boards from AbbVie, Actogenix, Albireo Pharma, Amgen, Astra Zeneca, Avaxia Biologics, Axcan, Baxter, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, Celltrion, Elan/Biogen, EnGene, Ferring Pharma, Roche/Genentech, GiCare Pharma, Gilead, Given Imaging Inc, GlaxoSmithKline, Ironwood Pharma, Janssen, Kyowa Kakko Kirin, Lexicon, Lilly, Merck, Millennium, Nektar, Novonordisk, Prometheus Therapeutics and Diagnostics, Pfizer, Receptos, Salix Pharma, Serono, Shire, Sigmoid Pharma, Synergy Pharma, Takeda, Teva, Tillotts, UCB, Warner-Chilcott, Wyeth, Zealand, and Zyngenia; and research support from AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Janssen, Roche/Genentech, Millennium, Pfizer, Receptos, Santarus, Sanofi, Tillotts, and UCB.

DC has served as consultant or speaker for AbbVie, Amgen, Bristol-Myers Squibb, Janssen, Pfizer, Merck, Novartis, Takeda, Eli Lilly, Roche, and Celgene.

SG has received speaker honoraria from AbbVie, Merck, Janssen, and Ferring; research support from AbbVie; and honoraria for advisory boards from AbbVie, Merck, Janssen, Pfizer, Bristol-Myers Squibb, and Receptos.

DDG has received honoraria for lectures, consulting and/or advisory boards and has received research funds from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lily, Janssen, Pfizer, Novartis, and UCB.

VH has received speaker honoraria from Novartis and Janssen; research support from Amgen, Novartis, Merck, and Janssen; and honoraria for advisory boards from Amgen, AbbVie, Novartis, Janssen, and LEO Pharma.

BM has provided consultancy services to multiple entities in the pharmaceutical industry, including Janssen.

GZ declares no conflict of interest.

ASR has received honoraria for consulting and advisory boards from Janssen, Amgen, Bristol-Myers Squibb, Roche and Pfizer.

Author contributions

All authors provided intellectual contribution to the manuscript, and reviewed draft versions. In addition to these activities, DCS wrote the first draft and managed revisions. All authors approved the final article.

The article has not been published previously or is not under consideration for publication elsewhere.

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