Clinical Gastroenterology and Hepatology 2016;14:1685–1696

PERSPECTIVES IN CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Biosimilars in Inflammatory Bowel Disease: Facts and Fears of Extrapolation

Shomron Ben-Horin,[*] Niels Vande Casteele,[‡,§] Stefan Schreiber,[‖] and Peter Laszlo Lakatos[¶]

[*]Gastroenterology Department, Sheba Medical Center and Sackler School of Medicine, Tel-Aviv University, Tel Hashomer, Israel; [‡]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium; [§]Division of Gastroenterology, University of California San Diego, La Jolla, California; [‖]Klinik für Innere Medizin I, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Kiel, Germany; and [¶]First Department of Internal Medicine, Semmelweis University, Budapest, Hungary

Biologic drugs such as infliximab and other anti–tumor necrosis factor monoclonal antibodies have transformed the treatment of immune-mediated inflammatory conditions such as Crohn's disease and ulcerative colitis (collectively known as inflammatory bowel disease [IBD]). However, the complex manufacturing processes involved in producing these drugs mean their use in clinical practice is expensive. Recent or impending expiration of patents for several biologics has led to development of biosimilar versions of these drugs, with the aim of providing substantial cost savings and increased accessibility to treatment. Biosimilars undergo an expedited regulatory process. This involves proving structural, functional, and biological biosimilarity to the reference product (RP). It is also expected that clinical equivalency/comparability will be demonstrated in a clinical trial in one (or more) sensitive population. Once these requirements are fulfilled, extrapolation of biosimilar approval to other indications for which the RP is approved is permitted without the need for further clinical trials, as long as this is scientifically justifiable. However, such justification requires that the mechanism(s) of action of the RP in question should be similar across indications and also comparable between the RP and the biosimilar in the clinically tested population(s). Likewise, the pharmacokinetics, immunogenicity, and safety of the RP should be similar across indications and comparable between the RP and biosimilar in the clinically tested population(s). To date, most anti–tumor necrosis factor biosimilars have been tested in trials recruiting patients with rheumatoid arthritis. Concerns have been raised regarding extrapolation of clinical data obtained in rheumatologic populations to IBD indications. In this review, we discuss the issues surrounding indication extrapolation, with a focus on extrapolation to IBD.

Keywords: Biosimilar; Extrapolation; Inflammatory Bowel Disease; CT-P13; Infliximab; Infliximab-dyyb.

Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel disease (IBD), are chronic, relapsing immune-mediated inflammatory diseases of the gastrointestinal tract. The advent of biologic drugs, starting with the anti–tumor necrosis factor (TNF) monoclonal antibodies, has significantly improved outcomes for patients with IBD.

The relatively high cost of anti-TNF agents and their looming or actual patent expiration have triggered the development of highly similar versions of these drugs that are known as biosimilars. Compared with originator biologics, biosimilars follow an expedited process for regulatory approval. Most notably and provided that certain requirements are met, virtually all regulatory agencies allow, in principle, for extrapolation of indications. Extrapolation means that once biosimilarity has been established in 1 or more indications, a biosimilar may be approved for additional or all other indications for which the originator, or reference product (RP), has been approved without the need for clinical trials in the latter indications.[1,2] Nonetheless, there has been much debate on the validity of extrapolation of clinical data for biosimilars.[3–6] In this review, we consider the fears and facts regarding extrapolation of biosimilar data to IBD, starting with a brief introduction to some important biosimilar concepts.

Abbreviations used in this paper: **ADA, anti-drug antibody; ADCC, antibody-dependent cell cytotoxicity; AS, ankylosing spondylitis; CD, Crohn's disease; CRP, C-reactive protein; EMA, European Medicines Agency; FDA, Food and Drug Administration; IBD, inflammatory bowel disease; Ig, immunoglobulin; PK, pharmacokinetics; RA, rheumatoid arthritis; RCT, randomized controlled trial; RP, reference product; sTNF, soluble tumor necrosis factor; tmTNF, transmembrane tumor necrosis factor; TNF, tumor necrosis factor; UC, ulcerative colitis.**

Most current article

1542-3565
http://dx.doi.org/10.1016/j.cgh.2016.05.023

Biosimilars: Definitions and Regulations

The World Health Organization defines a biosimilar as a "biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product".[7] The primary amino acid sequences of a biosimilar and its RP are the same, although often subtle variations in their complex manufacturing processes mean the 2 products are not identical in every way. In fact, the inherent variability of the living bacteria-based systems used to make all biologic drugs means no 2 batches of a single biologic (either an RP or biosimilar) will ever be exactly alike.[8] For RPs, batch-to-batch microheterogeneity, or changes due to alterations in manufacturing processes, are acceptable if the product falls within defined tolerance boundaries.[9,10] This principle is similarly applied to the development of biosimilars; minor differences in clinically inactive components between the biosimilar and RP are considered acceptable as long as there are no clinically meaningful differences between the drugs in terms of safety, purity, and potency.[2]

Comprehensive comparability testing is required to prove biosimilarity and to show that any differences found are not clinically meaningful. Such testing begins with a detailed analytical comparison of a biosimilar and its RP in terms of structure and functional/biological activity, complemented with nonclinical in vivo studies. However, the expedited process for biosimilar development requires fewer clinical data than were needed for its RP. According to guidance provided by the U. S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), the clinical efficacy and side effects of a biosimilar are anticipated to be studied in one of the RP-approved indications.[1,2]

The Biosimilar Landscape in Inflammatory Bowel Disease

Four anti-TNF drugs (infliximab, adalimumab, certolizumab pegol, and golimumab) and 2 anti-integrin antibodies (natalizumab and vedolizumab) are presently approved in IBD indications in the United States. Expiration of patents protecting some anti-TNF drugs has heralded development of several biosimilars by different companies (Table 1).

The infliximab biosimilar CT-P13 (developed by CELLTRION, Inc, Incheon, South Korea and marketed under the trade name Remsima or Inflectra) was the first biosimilar licensed for use in IBD in Europe, receiving approval from the EMA in September 2013. In April 2016, CT-P13 was also approved in IBD by the U. S. FDA with the generic name infliximab-dyyb.[11] This

Table 1. Biosimilars Approved or Under Development for Possible Use in IBD[a]

RP	Biosimilar name	Company	Current development stage	Approval status
Infliximab	CT-P13 (Remsima®; Inflectra®)	CELLTRION	Phase III completed in RA and AS	Approved in Europe, USA, and elsewhere
	SB2 (Flixabi®)	Samsung Bioepis	Phase III completed in RA	Approved in Europe and Korea; under review by FDA
	BOW015 (Infimab™)	Epirus Biopharmaceuticals/Sun Pharma/Ranbaxy Laboratories	Phase III trial in RA currently recruiting	Approved in India only
	NI-071[21]	Nichi-Iko Pharmaceutical	Phase III completed in RA	Not approved or under review
	PF-06438179	Pfizer/Sandoz	Phase III ongoing in RA	Not approved or under review
Adalimumab	ABP 501	Amgen	Phase III completed in RA and PsO	Approved in USA; under review by EMA
	Exemptia	Zydus Cadila	Phase III completed in RA	Approved in India only
	SB5	Samsung Bioepis	Phase III completed in RA	Under review by EMA
	MSB11022[81]	Merck KGaA	Phase III ongoing in PsO	Not approved or under review
	GP2017	Sandoz	Phase III ongoing in PsO	Not approved or under review
	BI695501	Boehringer Ingelheim	Phase III ongoing in RA	Not approved or under review
	FKB327[82]	Fujifilm Kyowa Kirin Biologics	Phase III ongoing in RA	Not approved or under review
	PF-06410293	Pfizer	Phase III ongoing in RA	Not approved or under review
	CHS-1420	Coherus Biosciences	Phase III ongoing in PsO	Not approved or under review
	M923	Momenta Pharmaceuticals/Baxalta	Phase III ongoing in PsO	Not approved or under review
	LBAL[83]	LG Life Sciences/Mochida Pharmaceutical	Phase I completed in healthy volunteers	Not approved or under review
	ONS-3010	Oncobiologics/Viropro	Phase I completed in healthy volunteers	Not approved or under review
	BOW050	Epirus Biopharmaceuticals	Preclinical	Not approved or under review
Golimumab	BOW100	Epirus Biopharmaceuticals	Preclinical	Not approved or under review
Certolizumab pegol	PF688	Pfenex	Preclinical	Not approved or under review
	Xcimzane	Xbrane	Preclinical	Not approved or under review

PsO, plaque psoriasis.
[a]Information was obtained from company websites unless otherwise stated.

approval meant that CT-P13 became the first biosimilar monoclonal antibody to be licensed in the United States. Regulatory approval of CT-P13 was based on comprehensive structural, functional, biological, and other nonclinical comparisons with the infliximab RP. These analyses were supported by 2 randomized controlled trials (RCTs) that demonstrated pharmacokinetic (PK) and efficacy equivalence, as well as comparability of safety and immunogenicity, of CT-P13 and infliximab RP in patients with active rheumatoid arthritis (RA) or ankylosing spondylitis (AS).[12–15] Extension studies of these RCTs also demonstrated that treatment efficacy, safety, and immunogenicity were unaffected when patients were switched from RP to CT-P13 at week 54 of treatment and followed up to week 102.[16,17] On the basis of all available data, CT-P13 was approved in RA and AS plus extrapolated indications including CD and UC in regions/countries including Europe, Japan, Australia, the United States, and, most recently, Canada.[11,18]

Other infliximab biosimilars, namely SB2, BOW015, NI-071, and PF-06438179 (Table 1), have generally followed similar developmental routes involving comprehensive bioanalytical comparisons with the RP, and some have completed phase III clinical trials.[19–21] SB2 (developed by Samsung Bioepis, Incheon, South Korea) is the only other infliximab biosimilar to be approved in Europe.[22] None are yet approved in the United States.

Patents protecting adalimumab are due to expire in 2016 and 2018 in the United States and Europe, respectively. As a result, biosimilars for adalimumab are potentially nearing launch (Table 1). The first of these may be ABP 501 (Amgen, Thousand Oaks, CA), which has recently been approved by the US FDA, and is under review by the EMA. Findings supporting the approval of ABP 501 include PK equivalence versus adalimumab RP in a phase I study in healthy subjects[23] and equivalent efficacy and comparable safety and immunogenicity in RCTs in RA and psoriasis.[24,25] However, the United States Patent and Trademark Office has approved several patents that protect post-launch innovations regarding the RP, including formulation and dosing schemes. Potentially these new patents could effectively extend the life of the whole adalimumab patent for another decade or later. Thus, patent litigation will likely become an important factor influencing market entry for adalimumab biosimilars. Regarding other anti-TNF RPs, golimumab and certolizumab patents will expire around the end of this decade, and biosimilars of these drugs are also in development (Table 1).

For the majority of biosimilars tested in clinical trials, efficacy versus each RP has been assessed in patients with RA (Table 1). This choice was made and deemed appropriate by regulatory agencies because clinical experience with these drugs is greatest in RA, and because RA is considered a sufficiently sensitive model for establishing the equivalence of efficacy between an anti-TNF biosimilar and its RP.[26] Although most anti-TNF biosimilar developers chose RA as the population for efficacy testing, some have also performed an additional RCT in AS (as for CT-P13) or in psoriasis (as for ABP 501) (Table 1).

Extrapolation: Why Is It Allowed and When Is It Valid?

The guiding principle underpinning the development of biosimilars is the hope of healthcare providers and patients alike that these agents will reduce the financial costs of biologic therapy, thereby increasing access to these drugs and facilitating intensified treatment regimens when clinically required. For these benefits to be realized, extrapolation is necessary. This is because this process reduces the number of clinical trials required for biosimilar approval and thereby lowers development costs. Nonetheless, extrapolation has also created concerns regarding whether bioanalytical similarity coupled with proven clinical safety and efficacy in 1 or 2 indications can ensure safety and efficacy in other indications. However, although many unknowns exist during development of an RP biologic, biosimilars enjoy the conceptual advantage of having a known comparator drug with well-defined structure, biological function, and clinical safety and efficacy. On the other hand, each "current" batch of an RP enjoys the putative advantage of having been compared with the original batches used in RP clinical trials. Original batches of an RP are not usually available to the biosimilar manufacturers, raising the possibility of further "manufacturing drift" during the biosimilars' development.

For extrapolation to be considered valid by the FDA, the mechanism of action, PK (including biodistribution), immunogenicity, and safety of an RP all need to be similar in the extrapolated indication(s) and the clinically tested indication(s).[2] If one of these attributes is unique for an extrapolated indication, additional evidence is required to show why the biosimilar can be anticipated to behave similarly in that indication despite not being tested clinically. Furthermore, if minor differences in structure or function exist between the biosimilar and RP and have negligible impact in clinical trials in the tested indication, it should be shown why these differences would also have negligible clinical meaning in the extrapolated indication.

The validity of using extrapolation from clinical trials in rheumatologic diseases to approve a biosimilar in IBD can be tested by considering the following questions:

- Are the mechanisms of action, PK, pharmacodynamics, immunogenicity, and safety of the RP similar between IBD and the clinically tested population, and are they comparable between the RP and biosimilar in that population?

- After approval, does the evidence from post-marketing surveillance programs and other "real-life" data in IBD provide any reasons for concern?

In the following sections, we consider these questions by referring to information on biosimilars approved or in development for IBD.

Comparing Mechanisms of Action Across Indications

All indications for infliximab and other anti-TNF drugs are immune-mediated inflammatory diseases that share common underlying pathophysiological processes, with the proinflammatory cytokine TNF playing an especially pivotal role.[27] TNF can be expressed on the cell surface as transmembrane TNF (tmTNF) or cleaved and released as soluble TNF (sTNF). Binding of TNF to its receptor triggers numerous intracellular forward-signaling pathways, including induction of apoptosis in some cell lineages (eg, intestinal epithelial cells) or cellular activation and secretion of other proinflammatory cytokines in others (eg, effector T cells).[27]

Anti-TNF monoclonal antibodies have large complex structures comprising Fc and Fab regions, each mediating different immune functions via diverse mechanisms of actions. The binding and neutralization of TNF (both sTNF and tmTNF) is a mechanism common to all anti-TNF monoclonal antibodies (Figure 1). However, there are other possible mechanisms of action of these drugs that are also potentially instrumental in IBD.

Reverse signaling. The binding of an anti-TNF antibody to tmTNF can trigger signaling pathways within the tmTNF-expressing cell. This process is referred to as reverse signaling, and its downstream effects include induction of apoptosis and suppression of proinflammatory cytokine expression, both of which are believed to be important mechanisms of action for anti-TNF agents in IBD.[28,29] This contention is supported by the fact that reverse signaling is induced by TNF inhibitors that are clinically effective in IBD, including infliximab and adalimumab, but not by etanercept (which primarily blocks sTNF and is ineffective in IBD).[30,31] As such, although the etanercept biosimilar SB4 was recently approved by the EMA, this drug (like its RP) is not licensed in IBD.[32] Both blockade of proinflammatory cytokines and induction of apoptosis via reverse signaling were shown to be highly comparable for CT-P13 and for ABP 501 versus their respective infliximab and adalimumab RPs (Table 2),[26,33,34] serving as part of the scientific justification for their extrapolation to IBD. Functional data on other anti-TNF biosimilars are not currently available.

Induction of regulatory macrophages. Regulatory (M2) macrophages can reduce T cell proliferation.[35] In an intestinal cell-line model, infliximab and adalimumab RPs were shown to induce regulatory macrophages in an Fc-dependent mechanism to mediate wound healing,[35,36] possibly explaining their mucosal healing capacity. In contrast, certolizumab (which lacks the Fc region) does not induce regulatory macrophages.[35] This fact may

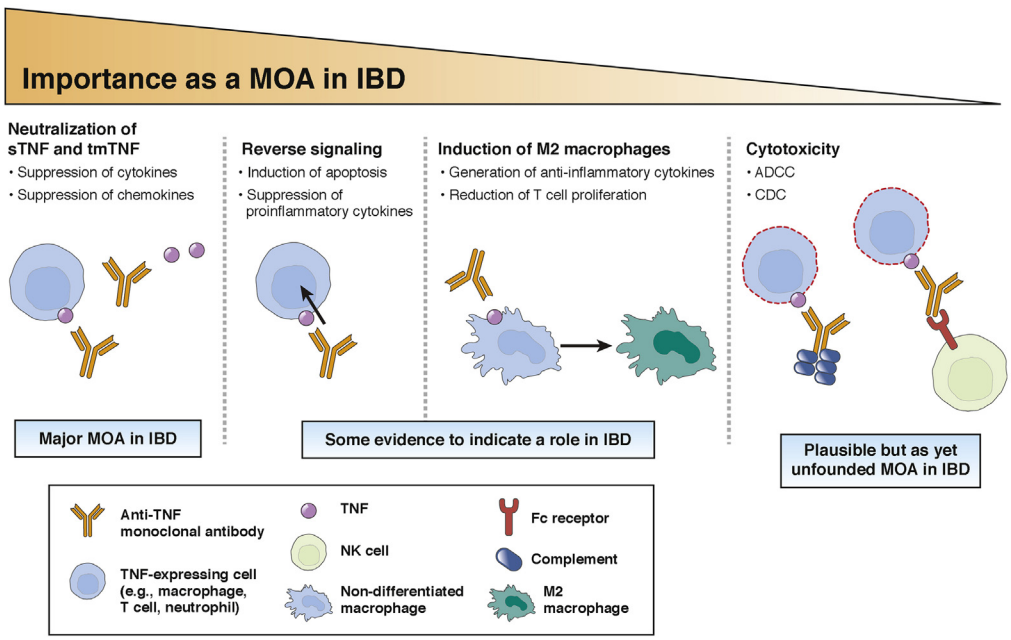

Figure 1. Established and possible mechanisms of action of infliximab and some other anti-TNF monoclonal antibodies in IBD. Binding to tmTNF and sTNF neutralizes the biological effects of TNF, preventing amplification of inflammation that can occur in IBD. Binding to tmTNF also causes reverse signaling and induction of apoptosis and regulatory M2 macrophages, which are thought to possibly play a role in the control of IBD. ADCC and CDC have been suggested but not shown to be a mechanism of action of anti-TNF antibodies. CDC, complement-dependent cytotoxicity; MOA, mechanism of action; NK, natural killer.

explain why, despite being approved for CD in the United States, certolizumab was associated with a low rate (4%) of complete mucosal healing in one clinical study.[37] It may also partly explain why an anti-TNF immunoglobulin (Ig) G1 construct with reduced Fc binding did not ameliorate murine colitis.[38] For biosimilars, data on this possible anti-TNF mechanism of action in IBD are relatively scant, although comparable induction of regulatory macrophages and wound healing in an intestinal cell model was observed for CT-P13 and infliximab RP (Table 2).

Antibody-dependent cell cytotoxicity. Antibody-dependent cell cytotoxicity (ADCC) is primarily mediated by antibodies that first coat a target cell. These antibodies then interact via their Fc region with the FcγRIIIa receptor on natural killer cells (and some macrophages) to induce lysis of the target cell.[39] There is still debate as to whether ADCC plays a role in mediating the effects of anti-TNF drugs in IBD. Supporting evidence includes the fact that etanercept is incapable of ADCC induction and is ineffective in IBD, although this could also be explained by the inability of etanercept to induce apoptosis via reverse

Table 2. Available Published Evidence on Comparable Functional/Biological Activity of CT-P13 and ABP 501 and Their Respective RPs

Functional/ biological activity	CT-P13 vs infliximab RP[34]	ABP 501 vs adalimumab RP[33]
Binding to TNF	• Comparable binding to hTNF as determined by ELISA • Comparable binding to monomeric and trimeric hTNF as determined by surface plasmon resonance • Comparable binding to tmTNF as determined by a cell-based ELISA	• Comparable binding affinity to sTNF as determined by surface plasmon resonance • Comparable binding to tmTNF as determined by competitive imaging cytometry-based assay
Neutralization	• Comparable and dose-dependent neutralization in a cell-based assay by using a TNF-sensitive cell line • Comparable and dose-dependent suppression of cytokine secretion by blocking sTNF in an IBD model (epithelial cells) • Comparable and dose-dependent suppression of apoptosis by blocking sTNF in an IBD model (epithelial cells)	• Comparable blocking of TNF-induced caspase activation • Comparable blocking of TNF-induced interleukin-8 secretion • Comparable blocking of TNF-induced cytotoxicity
Binding to Fcγ receptors	• Comparable relative binding affinities to FcγRI, FcγRIIa, FcγRIIb, and FcRn • Reduced relative binding affinities to FcγRIIIa and FcγRIIIb for CT-P13 • Reduced relative binding affinities to NK cells of healthy donors and CD patients for CT-P13 (difference was genotype-specific [V/V and V/F] and disappeared in presence of diluted CD patient serum) • Comparable binding affinities to neutrophils from healthy donors or CD patients	• Comparable binding to FcRn as determined in a competitive cell-based assay • Comparable binding to FcγRIIIa (158V) as determined by AlphaLISA™
Reverse signaling	• Comparable induction of apoptosis by reverse signaling through tmTNF by using a cell-based assay (PBMC from healthy donors and CD patients) • Comparable blockade of proinflammatory cytokine production by reverse signaling by using a cell-based assay (PBMC from healthy donors and CD patients)	• Not reported
Cytotoxicity	• Comparable C1q binding and CDC activity as determined by ELISA and other assays • Comparable ADCC activity by using tmTNF-expressing Jurkat cells as target cells and PBMC or NK cells from healthy donors as effector cells • Comparable ADCC activity by using tmTNF-expressing Jurkat cells as target cells and PBMC from CD patients as effector cells • Reduced ADCC activity for CT-P13 by using tmTNF-expressing Jurkat cells as target cells and NK from CD patients as effector cells (genotype-specific) • Comparable ADCC activity by using tmTNF-expressing Jurkat cells as target cells and whole blood from healthy donors or CD patients as effector cells • Comparable ADCC activity by using LPS-stimulated monocytes from healthy donors or CD patients as target cells and PBMC as effector cells	• Comparable dose-response profile for CDC by using cells expressing tmTNF • Comparable dose-response profile for ADCC by using cells expressing tmTNF • Comparable dose-response profile for ADCC by using NK92-M1 cells expressing FcγRIIIa (158V)

NOTE. Data on other biosimilars in development were not in the public domain at the time that this article was developed.
CDC, complement-dependent cytotoxicity; ELISA, enzyme-linked immunosorbent assay; hTNF, human TNF; LPS, lipopolysaccharide; NK, natural killer; PBMC, peripheral blood mononuclear cells.

signaling. Some studies have suggested that patients with an FF polymorphism variant of FcγRIIIa (which leads to reduced IgG binding and diminished ADCC) exhibit a diminished C-reactive protein (CRP) response to infliximab, thereby indirectly implicating ADCC in mediating infliximab efficacy.[40,41] However, none of these studies were able to show a correlation between FcγRIIIa and a clinical response to infliximab. Furthermore, a larger analysis based on the ACCENT I trial population did not find a statistically significant CRP-response correlation with specific polymorphisms.[42] Moreover, in 2 studies the VV genotype was associated with higher baseline CRP levels.[41,43] This suggests that FcγRIIIa polymorphisms may actually indicate a CD population with higher baseline inflammation, confounding any observations of an apparent reduction in CRP response. Indeed, the evidence against ADCC having a role in anti-TNF efficacy in IBD is also considerable and perhaps more compelling. First, experiments demonstrating ADCC by infliximab exclusively use target cells artificially engineered to overexpress tmTNF, whereas studies that use more physiological target cells (eg, lipopolysaccharide-triggered monocytes, activated T cells) show no ADCC with infliximab.[31,41] In addition, antibodies exerting ADCC in vivo, such as anti-CD20 rituximab or anti-CD3 visilizumab, are associated with cytokine release syndrome, an adverse event attributed in part to rapid ADCC-mediated cell death and consequent cytokine release.[44–46] In contrast, no such "cytokine storm" has been reported after infliximab administration in IBD. Interestingly, the entire debate about ADCC was stirred by the fact that because of a lower level of afucosylation, the binding affinity of CT-P13 to FcγRIIIa was reduced by around 10%–20% versus infliximab RP, resulting in lower ADCC activity toward cell lines engineered to express artificially high levels of tmTNF.[26,34,47] However, there was no difference in ADCC between CT-P13 and its RP when lipopolysaccharide-triggered monocytes or intestinal lamina propria cells were used as target cells, or when assays were performed in the presence of serum (ie, more physiologically relevant models for possible ADCC in IBD).[26] Overall, therefore, it seems that ADCC is unlikely to be a major mechanism of action of infliximab in IBD and that any differences in ADCC between CT-P13 and infliximab RP are not clinically relevant. These concepts were upheld by the EMA and the FDA when considering the approval of CT-P13 in IBD.

Pharmacokinetics Comparisons

PK equivalence of CT-P13 and infliximab RP has been demonstrated in 2 populations, AS and RA patients.[12,48] An additional PK trial in healthy individuals was thereafter conducted to bridge between the European Union–approved and US-approved formulations of infliximab RP and showed their comparable PK equivalence with CT-P13.[49] Equivalence of PK has also been shown for BOW015 and infliximab RP and for adalimumab RP and its biosimilars ABP 501 and BI695501, all in healthy subjects.[23,50,51]

Systemic clearance of infliximab seems to be somewhat higher in IBD than in rheumatologic indications.[52–54] Although direct comparisons are lacking, studies have indicated that albumin level is associated with clearance of infliximab in CD and UC but not in AS.[52,53] One mechanism that may cause reduced serum albumin as well as hastened anti-TNF clearance in IBD is fecal loss of drug. Fecal loss of infliximab has been documented in severe UC and is thought to be due to passive drug leakage to the gut lumen and the shedding of epithelial cells into the lumen, effects occurring as a consequence of severe diarrhea and protein-losing enteropathy.[55,56] The identical IgG backbone of an anti-TNF biologic and its biosimilar is likely to result in comparable fecal loss of these drugs via these passive mechanisms. A second mechanism of altered clearance in IBD relates to the high tissue concentration of TNF, which binds anti-TNF drugs and hastens clearance of the TNF–drug complexes in a process known as target-mediated drug disposition.[55–57] However, comparable TNF binding by an anti-TNF RP and its biosimilar, as shown for CT-P13 and other biosimilars, means the effects of high TNF-tissue burden will likely be similar.

Immunogenicity Comparisons

The immunogenicity of a biosimilar and its RP should be fully characterized before extrapolation to other indications because the generation of anti-drug antibodies (ADAs) can impact on efficacy and safety.[58] No difference in the proportion of ADA-positive patients was observed between CT-P13 and RP in RA and AS patients[12–15] or in such patients who switched to CT-P13 from RP.[16,17] Comparable immunogenicity between the biosimilar and its RP was also observed in phase III trials in RA involving the infliximab biosimilar BOW015[20] and the adalimumab biosimilar ABP 501.[25]

Questions have arisen as to whether it is appropriate to extrapolate immunogenicity data from RA and/or AS to IBD. Of note, RA patients mostly receive infliximab at doses of 3 mg/kg and are often co-administered the immunosuppressant methotrexate. In patients with IBD, however, thiopurines are more often used in combination with infliximab, and methotrexate is seldom used in this population. The comparability of immunogenicity suppression by methotrexate and thiopurines is unknown. Comparing immunogenicity between studies and patient populations is therefore hampered by the use of different concomitant immunomodulators but also by differences in drug doses, sampling time-points, and ADA analysis techniques.[59] However, in 2 studies (COMMIT in CD and ATTRACT in RA), overlapping doses of infliximab plus methotrexate and similar sampling time-points were used.[60,61] Although caution should be exercised in interpreting immunogenicity rates in the absence of head-to-head trials, comparable ADA development was demonstrated in CD and RA patients in these 2 trials

(4% versus 8.5%, respectively). This suggests a broadly similar immunogenicity profile in the 2 diseases when compared by using 2 similar methodology trials. Supporting this contention, a cross-reactivity study showed that ADAs against infliximab RP in IBD patients similarly recognize CT-P13, suggesting shared immune-dominant epitopes between these 2 molecules in IBD populations.[62]

Safety Comparisons and Risks Unique to Inflammatory Bowel Disease

Similar safety profiles for CT-P13 and infliximab RP were observed in AS and RA patients.[12–15] Comparable safety was also demonstrated for SB2 and infliximab in RA patients[19] and during a phase III RA trial of BOW015 versus infliximab RP.[20] In addition, ABP 501 is reported to have shown similar safety to adalimumab in both RA and psoriasis populations.[24,25]

In IBD, infliximab and other immunosuppressive agents have been associated with exacerbation of abdominal/perianal sepsis in fistulizing CD, although this risk can be negated if combined with appropriate surgical care.[63,64] In general, the risk of serious infection is increased with immunosuppression.[65] As such, all immunosuppressive agents are contraindicated in patients with active untreated infections.[65] Initial concerns regarding the development of intestinal stricture and bowel obstruction in CD patients treated with infliximab were not corroborated in a larger analysis of the ACCENT I trial and TREAT registry.[66] Similarly, no stricture progression was observed in an ultrasound study involving 15 CD patients who had strictures of the small intestine before starting infliximab.[67] Thus, stricture formation is unlikely to be a particular risk for CD patients treated with infliximab RP or its biosimilars.

Collecting Real-life Data After Approval

Once a drug is approved, observational "real-world" data can provide useful insights into its efficacy as well as important information regarding safety. These data should be collected in safety registries as part of formal post-marketing surveillance for RPs and biosimilars alike. Currently, CT-P13 is the only biosimilar for which real-world data in IBD are available. To date, most studies have found CT-P13 to be efficacious and well-tolerated in IBD (Table 3).[68–75]

A nationwide prospective and observational cohort study in Hungary examined the efficacy, safety, and immunogenicity of induction treatment with CT-P13 in 210 consecutively recruited patients with CD or UC.[69] At week 14, 81.4% and 77.6% of CD and UC patients, respectively, had a clinical response, and 53.6% and 58.6%, respectively, were in remission. Response and remission rates were maintained at week 30. Patients who had previously been exposed to infliximab RP had significantly higher baseline ADA positivity compared with infliximab-naïve patients and demonstrated lower early response and remission rates. Adverse events were reported in 17.1% of all patients. Infusion reactions occurred in 6.6% of patients and were significantly more common in those with previous infliximab exposure. Infectious adverse events were observed in 5.7% of patients, resulting in 1 death.[69] One study published as a congress abstract reported higher rates of surgery and other indicators of disease control in patients treated with CT-P13 compared with those treated with infliximab RP.[76] However, rates of response and remission were not reported, and there were some differences in baseline characteristics between the 2 cohorts.

The effects of switching to CT-P13 from infliximab RP were investigated in a Polish study of 32 children with CD and 7 with UC.[75] In the CD subgroup, 22 patients (69%) were in clinical remission before switching; the other 10 had active mild/moderate disease. At the time of the last assessment (mean follow-up after switch, 8 months; range, 2–11), 28 CD patients (87.5%) were in clinical remission, suggesting maintained clinical effects after switching. Remission was also observed in some UC patients, although this subgroup was too small for reliable efficacy comparisons. In general, adverse event incidence did not differ significantly before and after the switch from infliximab RP to CT-P13.

Biosimilars and Interchangeability

According to the US FDA, an interchangeable biological product refers to a biosimilar that "meets additional standards for interchangeability" and "may be substituted for the reference product by a pharmacist without the intervention of the health care provider".[77] Currently, no biosimilar manufacturers have applied for regulatory approval for interchangeable status. As such, interchangeability cannot be supported for any biosimilar at this stage. The issue of interchangeability should be distinguished from a physician's decision to switch between an RP and biosimilar, or vice versa, which is designated as transition. Single transitions from RP to biosimilar during maintenance therapy have been tested in clinical trials of CT-P13[16,17] and also reported in real-world cohorts.[75] No apparent new safety or immunogenicity signals or changes in efficacy seemed to arise after such single transitions. This is unlike multiple repeated transitions between an RP and its biosimilar/s, which should be discouraged because of absence of data on its safety and because of significant challenges to agent-specific surveillance when multiple transitions are performed.

Opportunities Offered by Reduced Cost of Biosimilars

The reduced price of biosimilars can lead to cost efficiencies and drive competition. In turn, this may benefit

Table 3. Summary of Real-world Efficacy and Safety of CT-P13 in IBDs

Study	Follow-up	IBD	N	TNF-naïve (n)	Efficacy		Safety	
					Clinical response (% of patients; [n/N])	Remission rate (% of patients; [n/N])	Adverse event (% of patients; [n/N])	IRR (% of patients; [n/N])
Farkas et al[68]	8 wk	CD	18	16	37.5[a] (6/16)	50.0[a] (8/16)	NR	NR
		UC	21	19	20.0[a] (3/15)	66.7[a] (10/15)	NR	NR
Gecse et al[69]	14 wk	CD	126	93	81.4 (79/97)	53.6 (52/97)	17.1[b] (36/210)	6.6[b] (14/210)
		UC	84	68	77.6 (45/58)	58.6 (34/58)		
Jahnsen et al[70]	14 wk	CD	46	33	NR	79.0 (34/43)	NR	2.2 (1/46)
		UC	32	27	NR	56.0 (18/32)	NR	3.1 (1/32)
Jung et al[71]	54 wk	CD	59	32	87.5[c] (7/8)	75.0[c] (6/8)	0.0 (0/59)	0.0
		UC	51	42	100.0[c] (12/12)	50.0[c] (6/12)	11.8 (6/51)	NR
Kang et al[72]	8 wk	CD	8	3	66.7[c] (2/3)	66.7[c] (2/3)	0.0	NR
		UC	9	5	100.0[c] (5/5)	100.0[c] (5/5)	0.0	NR
Keil et al[73]	14 wk	CD	30	30	100.0 (30/30)	50.0 (15/30)	NR	1.9 (1/52)
		UC	22	22	95.5 (21/22)	40.9 (9/22)		
Park et al[74]	30 wk	CD[d]	95	51	77.8[c] (35/45)	57.8[c] (26/45)	17.9 (17/95)	2.1 (2/95)
		UC	78	62	72.2[c] (39/54)	37.0[c] (20/54)	26.9 (21/78)	1.3 (1/78)
Sieczkowska et al[75]	8 mo (mean)	pCD	32[e]	26	NR	87.5 (28/32)	NR	3.1 (1/32)
	5 mo (mean)	pUC	7[e]	6	NR	57.1 (4/7)	NR	28.6 (2/7)

NOTE. Data are from studies published in full form and listed on PubMed.
IRR, infusion-related reaction; NR, not reported; p, pediatric.
[a]Of patients who completed induction treatment.
[b]At week 30.
[c]In TNF-naïve patients only.
[d]Including fistulizing active CD (n = 12).
[e]Patients had switched from infliximab to CT-P13.

healthcare systems and improve patient care by increasing access to biologic therapy and to intensified dosing when indicated. In addition, increased affordability and competition may allow more clinical trials in certain clinical scenarios that are presently missing. For example, some patients treated with infliximab eliminate the drug faster than others. Further research and application of therapeutic drug monitoring for both RPs and biosimilars could address such issues and facilitate personalized dosing, with expected improved outcomes and additional cost savings.[78]

Conclusions

There is continued scientific debate on extrapolation to IBD of anti-TNF biosimilars that are clinically tested in RA populations, with concerns voiced by some experts as well as some national professional societies.[3–6] In agreement with regulatory agencies around the world, it appears that extrapolation can be a valid, evidence-based approach for the expedited development of these new, more accessible drugs. However, for this approach to be valid, comprehensive analyses and well-thought justifications should be provided, and extrapolation should be considered on a case-by-case basis. This requires in-depth understanding of a drug's mechanisms of actions in IBD and careful evaluation of differences in PK, immunogenicity, and safety in IBD versus other indications. For IgG monoclonal anti-TNF agents, it seems that the major determinants of these attributes are highly similar between IBD and other immune-mediated inflammatory diseases, thereby justifying extrapolation under the conditions outlined above. For CT-P13, the only anti-TNF biosimilar currently approved in IBD, real-world efficacy and safety data appear to support extrapolation to CD and UC indications, but more data are pertinent, including those from ongoing phase III RCTs in IBD.[79,80]

References

1. European Medicines Agency. Guideline on similar biological medicinal products. October 23, 2014. CHMP/437/04 Rev 1. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf. Accessed February 28, 2016.
2. U. S. Food and Drug Administration. Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry. April 2015. Available at: http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed February 28, 2016.
3. Annese V, Vecchi M. Use of biosimilars in inflammatory bowel disease: statements of the Italian Group for Inflammatory Bowel Disease. Dig Liver Dis 2014;46:963–968.
4. Devlin SM, Bressler B, Bernstein CN, et al. Overview of subsequent entry biologics for the management of inflammatory bowel disease and Canadian Association of Gastroenterology position statement on subsequent entry biologics. Can J Gastroenterol 2013;27:567–571.
5. Feagan BG, Choquette D, Ghosh S, et al. The challenge of indication extrapolation for infliximab biosimilars. Biologicals 2014;42:177–183.
6. Danese S, Fiorino G, Michetti P. Viewpoint: knowledge and viewpoints on biosimilar monoclonal antibodies among members of the European Crohn's and Colitis Organization. J Crohns Colitis 2014;8:1548–1550.
7. World Health Organization. Expert Committee on Biological Standardization: guidelines on evaluation of similar biotherapeutic products. 2009. Available at: http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf. Accessed February 28, 2016.
8. Al-Sabbagh A, Olech E, McClellan JE, et al. Development of biosimilars. Semin Arthritis Rheum 2016;45(Suppl 5):S11–S18.
9. U. S. Food and Drug Administration. Demonstration of comparability of human biological products, including therapeutic biotechnology-derived products. Available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122879.htm. Accessed April 4, 2016.
10. International Conference on Harmonisation. Q5E Comparability of biotechnological/biological products subject to changes in their manufacturing process. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf. Accessed April 4, 2016.
11. INFLECTRA prescribing information. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125544s000lbl.pdf. Accessed April 11, 2016.
12. Park W, Hrycaj P, Jeka S, et al. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Ann Rheum Dis 2013;72:1605–1612.
13. Park W, Yoo DH, Jaworski J, et al. Comparable long-term efficacy, as assessed by patient-reported outcomes, safety and pharmacokinetics, of CT-P13 and reference infliximab in patients with ankylosing spondylitis: 54-week results from the randomized, parallel-group PLANETAS study. Arthritis Res Ther 2016;18:25.
14. Yoo DH, Hrycaj P, Miranda P, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. Ann Rheum Dis 2013;72:1613–1620.
15. Yoo DH, Racewicz A, Brzezicki J, et al. A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study. Arthritis Res Ther 2016;18:82.
16. Park W, Yoo DH, Miranda P, et al. Efficacy and safety of switching from reference infliximab to CT-P13 compared to maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. Ann Rheum Dis 2016; http://dx.doi.org/10.1136/annrheumdis-2015-208783.
17. Yoo DH, Prodanovic N, Jaworski, J, et al. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. Ann Rheum Dis 2016; http://dx.doi.org/10.1136/annrheumdis-2015-208786.
18. Health Canada. Regulatory decision summary for REMSIMA (Control number 184568). August 5, 2016. Available at: http://

www.hc-sc.gc.ca/dhp-mps/prodpharma/rds-sdr/drug-med/rds-sdr-remsima-184568-eng.php. Accessed October 7, 2016.

19. Choe JY, Prodanovic N, Niebrzydowski J, et al. A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. Ann Rheum Dis 2015; http://dx.doi.org/10.1136/annrheumdis-2015-207764.
20. Kay J, Wyand M, Chandrashekara S, et al. BOW015, a biosimilar infliximab, in patients with active rheumatoid arthritis on stable methotrexate doses: 54-week results of a randomized, double-blind, active comparator study. Arthritis Rheumatol 2014;66:3538 (L20).
21. Nichi-Iko Pharmaceuticals. Phase III testing for NI-071 results (preliminary report). June 22, 2015. Available at: http://www.nichiiko.co.jp/finance/gif/4541_20150622_01.pdf. Accessed February 28, 2016.
22. Biogen press release. FLIXABI®, Biogen's infliximab biosimilar referencing Remicade®, approved in the European Union. May 30, 2016. Available at: http://media.biogen.com/press-release/biosimilars/flixabi-biogens-infliximab-biosimilar-referencing-remicade-approved-europe. Accessed October 7, 2016.
23. Kaur P, Chow V, Zhang N, et al. A randomized, single-blind, single-dose, three-arm, parallel group study in healthy subjects to demonstrate pharmacokinetic equivalence of ABP-501 and adalimumab: results of comparison with adalimumab (EU). Ann Rheum Dis 2014;73:479 [FRI0264].
24. Amgen press release. Amgen announces positive top-line results from phase 3 study evaluating the efficacy and safety of biosimilar candidate ABP 501 compared with adalimumab in patients with moderate-to-severe plaque psoriasis. October 8, 2014. Available at: http://investors.amgen.com/phoenix.zhtml?c=61656&p=irol-newsArticle&ID=1975377. Accessed February 28, 2016.
25. Cohen SB, Genovese MC, Choy EH, et al. Randomized, double-blind, phase 3 study of efficacy and safety of ABP 501 compared with adalimumab in subjects with moderate to severe rheumatoid arthritis. Arthritis Rheum 2015;67(Suppl 10):A2054.
26. European Medicines Agency. Remsima assessment report. June 27, 2013. EMA/CHMP/589317/2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002576/WC500151486.pdf. Accessed February 28, 2016.
27. Blandizzi C, Gionchetti P, Armuzzi A, et al. The role of tumour necrosis factor in the pathogenesis of immune-mediated diseases. Int J Immunopathol Pharmacol 2014;27:1–10.
28. Sedger LM, McDermott MF. TNF and TNF-receptors: from mediators of cell death and inflammation to therapeutic giants—past, present and future. Cytokine Growth Factor Rev 2014;25:453–472.
29. Van den Brande JMH, Koehler TC, Zelinkova Z, et al. Prediction of antitumour necrosis factor clinical efficacy by real-time visualisation of apoptosis in patients with Crohn's disease. Gut 2007;56:509–517.
30. Shen C, Assche GV, Colpaert S, et al. Adalimumab induces apoptosis of human monocytes: a comparative study with infliximab and etanercept. Aliment Pharmacol Ther 2005;21:251–258.
31. Van den Brande JM, Braat H, van den Brink GR, et al. Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn's disease. Gastroenterology 2003;124:1774–1785.
32. European Medicines Agency. Benepali assessment report. November 19, 2015. EMA/CHMP/819219/2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004007/WC500200380.pdf. Accessed April 4, 2016.
33. Born T, Velayudhan J, Chen Y, et al. Demonstration of functional similarity comparing adalimumab to biosimilar candidate ABP 501. Arthritis Rheum 2014;10(Suppl):S661 [A1503].
34. U. S. Food and Drug Administration. FDA briefing document. Arthritis Advisory Committee Meeting. BLA 125544. February 9, 2016. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM484859.pdf. Accessed February 28, 2016.
35. Vos AC, Wildenberg ME, Duijvestein M, et al. Anti–tumor necrosis factor-α antibodies induce regulatory macrophages in an Fc region-dependent manner. Gastroenterology 2011;140:221–230 e3.
36. Vos AC, Wildenberg ME, Arijs I, et al. Regulatory macrophages induced by infliximab are involved in healing in vivo and in vitro. Inflamm Bowel Dis 2012;18:401–408.
37. Hebuterne X, Lemann M, Bouhnik Y, et al. Endoscopic improvement of mucosal lesions in patients with moderate to severe ileocolonic Crohn's disease following treatment with certolizumab pegol. Gut 2013;62:201–208.
38. McRae BL, Levin AD, Wildenberg ME, et al. Fc receptor-mediated effector function contributes to the therapeutic response of anti-TNF monoclonal antibodies in a mouse model of inflammatory bowel disease. J Crohns Colitis 2016;10:69–76.
39. Long EO, Kim HS, Liu D, et al. Controlling NK cell responses: integration of signals for activation and inhibition. Annu Rev Immunol 2013;31:227–258.
40. Louis E, El Ghoul Z, Vermeire S, et al. Association between polymorphism in IgG Fc receptor IIIa coding gene and biological response to infliximab in Crohn's disease. Aliment Pharmacol Ther 2004;19:511–519.
41. Moroi R, Endo K, Kinouchi Y, et al. FCGR3A-158 polymorphism influences the biological response to infliximab in Crohn's disease through affecting the ADCC activity. Immunogenetics 2013;65:265–271.
42. Louis EJ, Watier HE, Schreiber S, et al. Polymorphism in IgG Fc receptor gene FCGR3A and response to infliximab in Crohn's disease: a subanalysis of the ACCENT I study. Pharmacogenet Genomics 2006;16:911–914.
43. Ternant D, Berkane Z, Picon L, et al. Assessment of the influence of inflammation and FCGR3A genotype on infliximab pharmacokinetics and time to relapse in patients with Crohn's disease. Clin Pharmacokinet 2015;54:551–562.
44. Baumgart DC, Lowder JN, Targan SR, et al. Transient cytokine-induced liver injury following administration of the humanized anti-CD3 antibody visilizumab (HuM291) in Crohn's disease. Am J Gastroenterol 2009;104:868–876.
45. Brennan FR, Morton LD, Spindeldreher S, et al. Safety and immunotoxicity assessment of immunomodulatory monoclonal antibodies. MAbs 2010;2:233–255.
46. Winkler U, Jensen M, Manzke O, et al. Cytokine-release syndrome in patients with B-cell chronic lymphocytic leukemia and high lymphocyte counts after treatment with an anti-CD20 monoclonal antibody (Rituximab, IDEC-C2B8). Blood 1999;94:2217–2224.
47. Reinisch W, Louis E, Danese S. The scientific and regulatory rationale for indication extrapolation: a case study based on the infliximab biosimilar CT-P13. Expert Rev Gastroenterol Hepatol 2015;9(Suppl 1):17–26.

48. Takeuchi T, Yamanaka H, Tanaka Y, et al. Evaluation of the pharmacokinetic equivalence and 54-week efficacy and safety of CT-P13 and innovator infliximab in Japanese patients with rheumatoid arthritis. Mod Rheumatol 2015; 25:817–824.
49. Park W, Lee SJ, Yun J, et al. Comparison of the pharmacokinetics and safety of three formulations of infliximab (CT-P13, EU-approved reference infliximab and the US-licensed reference infliximab) in healthy subjects: a randomized, double-blind, three-arm, parallel-group, single-dose, Phase I study. Expert Rev Clin Immunol 2015;11(Suppl 1):S25–S31.
50. Lambert J, Wyand M, Lassen C, et al. Pharmacokinetic results from a phase 1, single-centre, double-blind, randomised, single-dose, parallel group study comparing 5 mg/kg IV infusion of BOW015 and reference infliximab in healthy male volunteers. Ann Rheum Dis 2015;74(Suppl 2):462 (FRI0116).
51. Wynne C, Petkova M, Rombout F, et al. BI 695501, a proposed biosimilar for adalimumab, shows bioequivalence to adalimumab reference products in a randomized, double-blind phase I trial in healthy subjects. Arthritis Rheumatol 2015;67(Suppl 10):A2727.
52. Fasanmade AA, Adedokun OJ, Blank M, et al. Pharmacokinetic properties of infliximab in children and adults with Crohn's disease: a retrospective analysis of data from 2 phase III clinical trials. Clin Ther 2011;33:946–964.
53. Fasanmade AA, Adedokun OJ, Ford J, et al. Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis. Eur J Clin Pharmacol 2009;65:1211–1228.
54. Xu Z, Seitz K, Fasanmade A, et al. Population pharmacokinetics of infliximab in patients with ankylosing spondylitis. J Clin Pharmacol 2008;48:681–695.
55. Brandse JF, van den Brink GR, Wildenberg ME, et al. Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis. Gastroenterology 2015;149:350–355 e2.
56. Vande Casteele N, Gils A. Pharmacokinetics of anti-TNF monoclonal antibodies in inflammatory bowel disease: adding value to current practice. J Clin Pharmacol 2015;55(Suppl 3):S39–S50.
57. Yarur AJ, Jain A, Sussman DA, et al. The association of tissue anti-TNF drug levels with serological and endoscopic disease activity in inflammatory bowel disease: the ATLAS study. Gut 2015;65:249–255.
58. Lee H. Is extrapolation of the safety and efficacy data in one indication to another appropriate for biosimilars? AAPS J 2014; 16:22–26.
59. Ben-Horin S, Heap GA, Ahmad T, et al. The immunogenicity of biosimilar infliximab: can we extrapolate the data across indications? Expert Rev Gastroenterol Hepatol 2015;9(Suppl 1):27–34.
60. Feagan BG, McDonald JW, Panaccione R, et al. Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease. Gastroenterology 2014; 146:681–688 e1.
61. St Clair EW, Wagner CL, Fasanmade AA, et al. The relationship of serum infliximab concentrations to clinical improvement in rheumatoid arthritis: results from ATTRACT, a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002;46:1451–1459.
62. Ben-Horin S, Yavzori M, Benhar I, et al. Cross-immunogenicity: antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima. Gut 2015; 65:1132–1138.
63. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999;340:1398–1405.
64. Hyder SA, Travis SP, Jewell DP, et al. Fistulating anal Crohn's disease: results of combined surgical and infliximab treatment. Dis Colon Rectum 2006;49:1837–1841.
65. Van Assche G, Lewis JD, Lichtenstein GR, et al. The London position statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organisation: safety. Am J Gastroenterol 2011; 106:1594–1602.
66. Lichtenstein GR, Olson A, Travers S, et al. Factors associated with the development of intestinal strictures or obstructions in patients with Crohn's disease. Am J Gastroenterol 2006; 101:1030–1038.
67. Pallotta N, Barberani F, Hassan NA, et al. Effect of infliximab on small bowel stenoses in patients with Crohn's disease. World J Gastroenterol 2008;14:1885–1890.
68. Farkas K, Rutka M, Balint A, et al. Efficacy of the new infliximab biosimilar CT-P13 induction therapy in Crohn's disease and ulcerative colitis: experiences from a single center. Expert Opin Biol Ther 2015;15:1257–1262.
69. Gecse KB, Lovasz BD, Farkas K, et al. Efficacy and safety of the biosimilar infliximab CT-P13 treatment in inflammatory bowel diseases: a prospective, multicentre, nationwide cohort. J Crohns Colitis 2015;10:133–140.
70. Jahnsen J, Detlie TE, Vatn S, et al. Biosimilar infliximab (CT-P13) in the treatment of inflammatory bowel disease: a Norwegian observational study. Expert Rev Gastroenterol Hepatol 2015; 9(Suppl 1):45–52.
71. Jung YS, Park DI, Kim YH, et al. Efficacy and safety of CT-P13, a biosimilar of infliximab, in patients with inflammatory bowel disease: a retrospective multicenter study. J Gastroenterol Hepatol 2015;30:1705–1712.
72. Kang YS, Moon HH, Lee SE, et al. Clinical experience of the use of CT-P13, a biosimilar to infliximab in patients with inflammatory bowel disease: a case series. Dig Dis Sci 2015; 60:951–956.
73. Keil R, Wasserbaeur M, Zádorvá Z, et al. Clinical monitoring: infliximab biosimilar CT-P13 in the treatment of Crohn's disease and ulcerative colitis. Scand J Gastroenterol 2016; 51:1062–1068.
74. Park SH, Kim YH, Lee JH, et al. Post-marketing study of biosimilar infliximab (CT-P13) to evaluate its safety and efficacy in Korea. Expert Rev Gastroenterol Hepatol 2015;9(Suppl 1):35–44.
75. Sieczkowska J, Jarzebicka D, Banaszkiewicz A, et al. Switching between infliximab originator and biosimilar in pediatric patients with inflammatory bowel disease: preliminary observations. J Crohns Colitis 2016;10:127–132.
76. Murphy C, Sugrue K, Mohamad J, et al. Biosimilar but not the same. J Crohns Colitis 2015;9(Suppl 1):S331–S332 (P505).
77. U. S. Food and Drug Administration. Information on biosimilars. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.htm. Accessed March 25, 2016.
78. Vande Casteele N, Gils A. Preemptive dose optimization using therapeutic drug monitoring for biologic therapy of Crohn's

disease: avoiding failure while lowering costs? Dig Dis Sci 2015; 60:2571–2573.

79. ClinicalTrials.gov. Demonstrate noninferiority in efficacy and to assess safety of CT-P13 in patients with active Crohn's disease. Available at: https://clinicaltrials.gov/ct2/show/NCT02096861. Accessed February 28, 2016.
80. ClinicalTrials.gov. The NOR-SWITCH Study. Available at: https://clinicaltrials.gov/ct2/show/NCT02148640. Accessed February 28, 2016.
81. Generics and Biosimilars Initiative. Merck Group starts phase III trial for adalimumab biosimilar. March 18, 2016. Available at: http://www.gabionline.net/Biosimilars/News/Merck-Group-starts-phase-III-trial-for-adalimumab-biosimilar. Accessed April 5, 2016.
82. ClinicalTrials.gov. A study to compare FKB327 efficacy and safety with Humira® in rheumatoid arthritis patients (ARABESC). Available at: https://clinicaltrials.gov/ct2/show/NCT02260791. Accessed April 5, 2016.
83. ClinicalTrials.gov. Pharmacokinetics and safety study of LBAL in healthy subjects. Available at: https://clinicaltrials.gov/ct2/show/NCT02206867. Accessed April 5, 2016.

Reprint requests
Address requests for reprints to: Shomron Ben-Horin, MD, Gastroenterology Department, Sheba Medical Center, Tel Hashomer, Ramat-Gan 52621, Israel. e-mail: shomron.benhorin@gmail.com; fax: +972-3-5303160.

Conflicts of interest
The authors disclose the following: Shomron Ben-Horin has received consultancy and/or advisory board fees from Schering-Plough, AbbVie, CELLTRION, Janssen, and Takeda and has received research support from CELLTRION and AbbVie. Niels Vande Casteele is a Postdoctoral Fellow of the Research Foundation - Flanders (FWO), Belgium (grant number 1260714N) and has received consultancy fees from MSD, Janssen Biologics BV, UCB, Pfizer, and Takeda and lecture fees from AbbVie. Stefan Schreiber has served on advisory boards for AbbVie, Biogen, CELLTRION, Hospira, Merck, Mundipharma, Takeda, and UCB and has given paid lectures for AbbVie, Hospira, Merck, Mundipharma, and Takeda. Peter Laszlo Lakatos has served as a speaker and/or advisory board member for AbbVie, CELLTRION, EGIS, Falk Pharma GmbH, Ferring, Genentech, Kyowa Hakko Kirin Pharma, Mitsubishi Tanabe Pharma Corporation, MSD, Otsuka, Pharmacosmos, Pfizer, Roche, and Takeda and has received unrestricted research grants from AbbVie, MSD, and Pfizer/Hospira.

Funding
Medical writing assistance was provided by Alice Wareham, PhD at Aspire Scientific Limited (Bollington, United Kingdom) and was funded by CELLTRION Healthcare Co, Ltd (Incheon, Republic of Korea).