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Review

An Update on Anti-TNF Biosimilar Switching—Real-World Clinical Effectiveness and Safety

Susanna Meade[1], Elizabeth Squirell[1], Thomas Tam Hoang[1], James Chow[2], Gregory Rosenfeld[1,*]

[1]University of British Columbia, Vancouver, BC V6T 1Z4, Canada
[2]BioPro Biologics Pharmacy, 845 West Broadway, Vancouver, BC V5Z1J9, Canada
[*]Corresponding author: Gregory Rosenfeld, University of British Columbia, Vancouver, BC V6T 1Z4, Canada. Email: grosenfeld@ibdcentrebc.ca

Abstract

Background: Biological medications for inflammatory bowel disease (IBD) account for a significant burden on provincial budgets. In an effort to curb these rising costs, nationwide switching to biosimilars is expected to be complete in Canada before the end of 2023. Biosimilar products do not require the same rigor for licensing as the originator and therefore there has been appropriate scepticism as to how biosimilars will perform in real-world practice.

Methods: We have performed a systematic review including real-world observational studies of adult patients with IBD. The primary outcome was clinical effectiveness and/or safety in patients who had switched from originator to biosimilar anti-TNF. Secondary outcomes included loss of response (LOR), treatment persistence or cessation and immunogenicity.

Results: We included 43 studies (7,462 patients [70 percent Crohn's disease: 30 percent ulcerative colitis]; 32 infliximab studies, and 11 adalimumab studies). For infliximab, 75 percent patients were in clinical remission at the time of switch and 75 percent maintained clinical remission beyond 12 months, compared to 78 percent of patients who continued originator. For adalimumab, 86 percent patients were in remission at the time of switch with 82 percent maintaining remission at 6 months follow-up. Injection site pain was higher in patients who switched to a citrate containing adalimumab biosimilar, compared with those who continued originator. All other outcomes (LOR, treatment cessation or persistence and serious adverse events) were similar to patients who continued originator (in comparator cohorts or the available literature).

Conclusion: Whilst ongoing vigilance is required, these data are reassuring to both patients and clinicians and will significantly help to reduce health-care costs across Canada.

Introduction

Biological medications for inflammatory bowel disease (IBD) account for a significant burden of cost to healthcare systems around the world. Annual sales of biological medicines in Canada have increased from $3.3 billion to $10.0 billion over the last 10 years representing an annual growth rate of 13.2 percent. Pharmaceutical spending represents a significant burden on provincial budgets in Canada. To curb the rising costs of pharmaceuticals, most provinces have now adopted a mandatory biosimilar switch policy. British Columbia introduced the first such policy in May 2019 with several other provinces following suit (Alberta, New Brunswick and Quebec) and the remainder expected before the end of 2023. The initial switch focused on Remicade [Janssen, Belgium], with subsequent inclusion of Humira [AbbVie, US] in 2021. In BC, infliximab (IFX) biosimilars now account for 94 percent of the IFX market share. In the provinces that introduced the mandatory switch, estimated savings were $118.9 million in 2020 alone. This was projected to have been $452.2 million, had the mandatory switch been a national initiative.[1]

Biosimilar drugs are produced from replication within living cells and therefore, are dependent on the laboratory techniques and cell line being utilized. Hence, they are similar and not identical to the originator molecule. It is acknowledged that variations exist, not only amongst biosimilar but also within different batches of originator drug. Biosimilar products are eligible to be defined as such if they fulfil the following criteria: i) there is an appropriate reference biologic product with full pre- and post-marketing data from non-clinical and clinical trials (and therefore a reasonable body of evidence on safety and effectiveness), ii) both biosimilar and reference product can be easily characterized, and iii) therefore determined to be similar. Similarity is achieved if the knowledge of the two products is sufficient to predict that any product differences (largely structural, functional and pharmacokinetic) will not compromise safety or effectiveness and that accrued data from the originator remains relevant to the biosimilar. Despite these regulations, Health Canada states that authorization of a biosimilar is not a declaration of equivalence.[2,3] This has led to concern and scepticism as to how biosimilars will perform in the real-world for different indications.

As the Canadian health care system is a publicly funded system and most provinces are adopting a mandatory switch policy, we aimed to review the evidence of biosimilar switching for IBD. In this study, we have performed a systematic review to evaluate the real-world safety and effectiveness of IFX and ADA biosimilars ahead of the completion of nationwide switching in Canada.

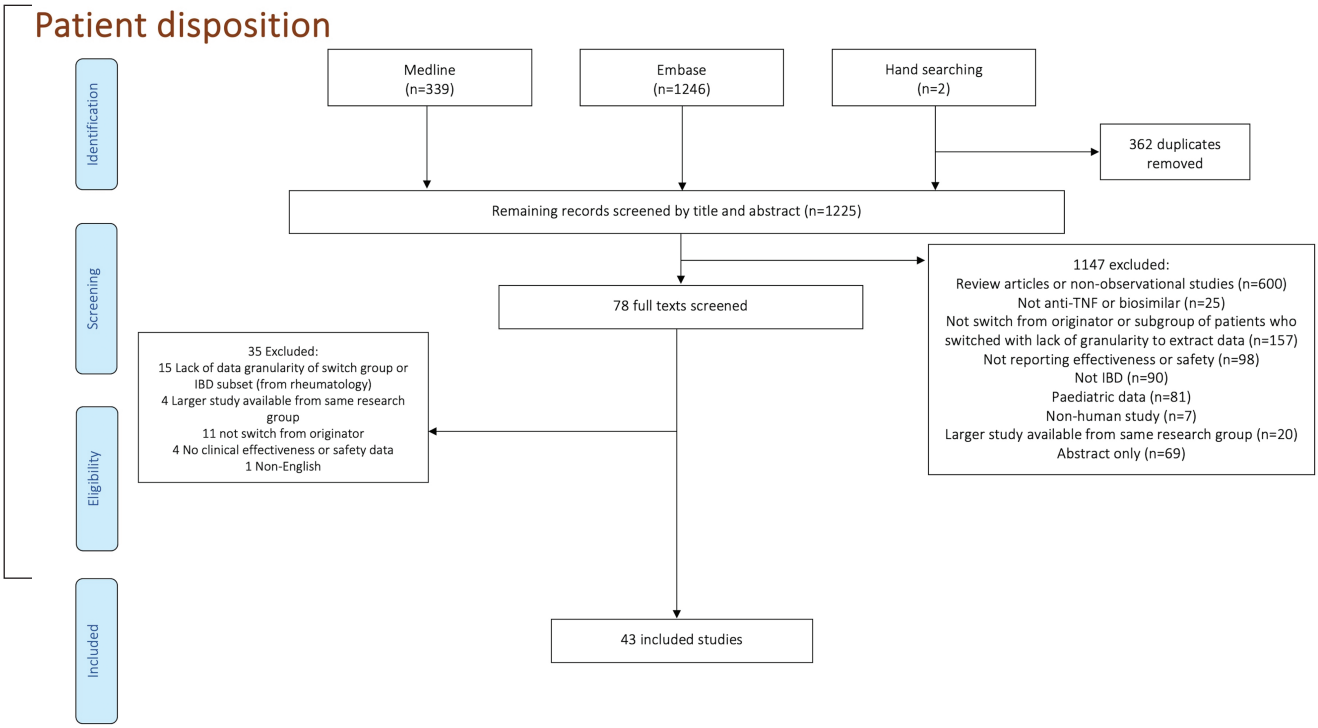

Figure 1. PRISMA flow diagram: patient disposition.

Methods

We performed a review of the medical literature from inception to January 20, 2023 using Medline and Embase, searched through the OVID platform. Search terms using subject headings and key words included, but were not limited to, the following: anti-TNF inhibitors, biosimilar pharmaceuticals, infliximab, adalimumab, inflammatory bowel disease, ulcerative colitis (UC), Crohn's disease (CD), clinical effectiveness, and safety. Full details of the search string are shown in Supplementary Materials. Hand searching of reference lists was also performed to obtain additional studies.

We included real-world observational studies investigating adult patients with IBD where clinical effectiveness and/or safety data were reported in patients who had switched from originator to biosimilar anti-TNF. We also included studies investigating patients with multiple switches and switches between biosimilars. We excluded abstracts, articles unavailable in English, non-IBD studies, paediatric studies, studies investigating biosimilar outcomes in patients who had not switched from originator or alternative biosimilar, and randomised controlled trials (RCTs). Study selection was performed independently by the primary author (SM) with resolution of any discrepancies by the senior author (GR).

The primary outcome was clinical effectiveness within the first year of therapy (<12 months) and during long term maintenance therapy (≥12 months). To avoid data duplication, where studies reported on multiple time points, the latest time point was reported. The secondary outcomes included loss of response (LOR), treatment cessation, adverse events (AEs), serious AEs, injection or infusion site reactions, and immunogenicity data.

Data were extracted from the selected manuscripts using a pre-defined data capture form (S2). A minority of studies included patients with IBD-U (IBD-undetermined), which are reported together with UC data. The combined data from three studies from the same group has been presented as one.[4–6] The Wilcoxon-signed rank test was used to compare samples at baseline and follow-up.

Results

The PRISMA flow diagram is shown in figure 1. The Medline, Embase, and hand searching of reference lists resulted in 1,225 unique references after removal of duplicates. Following screening and full text review 43 studies were included for analysis (Table 1 and Supplementary Table S1). This included a total of 7,462 patients (5,193 CD [70 percent] and 2269 UC/IBDU [30 percent]). IFX switching was investigated in 32 studies including 5,872 patients; switching to CT-P13,[4-27], SB2,[23,28-34] or both.[17] Seven studies included data on patients undergoing multiple switches.[17,23,29-31,34,35] ADA switching was investigated in 11 studies including 1,590 patients; switching to AB501,[35-38] SB5,[36,38-44] ABP501, MSB11022 or Hyrimoz®[45] and GP2017 or MSB11022.[38] Supplementary Table S2 outlines the biosimilar switches investigated for each outcome.

Demographics included: 40 percent female, 24 percent smokers, 32 percent receiving concomitant immunomodulator therapy (36 percent IFX, 13 percent ADA), median duration of originator was 45.0 (26.0–62.5) months for IFX, and 42.3 (25.5–66.3) months for ADA. Remission status was reported at baseline in 79 percent and 75 percent of patient receiving IFX and ADA, respectively.

Clinical effectiveness

Ten studies reported on rates of clinical remission within the first year of switch; 7 IFX[7,9,11,22,30,31,33] and 3 ADA studies[36,42,45] Patients receiving IFX with available short-term data

Table 1. Summary of included studies.

Author	Year	Study type	Primary outcome	*N*	Originator	Biosimilar	Duration originator (months)	CIM, *n* (percent)	Disease duration (years)	Remission at baseline *n* (percent)	FU	Clinical effectiveness *n* (percent)	Safety *n* (percent)		LOR *n* (percent)	Persistence *n* (percent)	Treatment cessation *n* (percent)			
													AEs	SAEs			Overall	LOR	Remission	AE
Armuzzi[7]	2019	Multicentre prospective	Evaluation of safety and SAEs	155; CD 87, UC 68	Remicade	CT-P13 (Inflectra/ Remisma)	17 infusions	48 (31)	7	NR	12	Clinical remission at 2 months: 151/155 (97)	NR	18 (12)	NR	24 months: 140/155 (90)	NR	NR	NR	10 (6)
Bergqvist[8]	2018	Multicentre prospective observational	Change in clinical disease activity at 2, 6, and 12 months	313; CD 195, UC 188	Remicade	CTP-13 (Remisma)	52.8	158 (50)	NR	173/252 (68)	12	Clinical remission at 12 months: 129/178 (72)	72 (23)	7 (2)	44 (14)	NR	NR	NR	NR	15 (5)
Bhat[9]	2020	Single centre retrospective cohort	(a)Describe a biosimilar adoption in patients on IFX for ≥ 6 months (b) cost savings I clinical outcomes	63; CD 41, UC 22	Remicade	Inflectra	31	34 (54)	11	NR	6	Clinical remission at 6 months: 37/42 (88)	NR	0	NR	NR	NR	NR	NR	NR
Binkhorst[10]	2018	Multicentre retrospective observational	Feasibility, efficacy and safety of switch	197; CD 145, UC 162	Remicade	CTP-13 (Inflectra /Remisma)	NR	NR	NR	NR	4	NR	12 (6)	NR	11 (6)	NR	20 (10)	NR	NR	4 (2)
Bronswijk[46]	2020	Prospective single centre	IFX discontinuation for any reason	361; CD 251, UC 110	Remicade	CTP-13	72	23 (6)	7	223 (61)	6	NR	8 (2)	2 (0.6)	48 (13)	346 (96)	15 (4)	8 (2)	NR	5 (1)
Buer[11]	2017	Prospective single centre	i) Drug persistence at 6 months ii) AEs @ 6 months	143; CD 99, UC 44	Remicade	CTP-13; Remsima	81	50 (35)	NR	124 (87)	6	Clinical remission at 6 months: 122/142 (86)	17 (12)	2 (1)	0	138/142 (97)	4/142 (3)	0	2 (1)	2 (1)
Chaparro[12]	2019	Retrospective multicentre	Clinical relapse	199; CD 142, UC 57	Remicade	CTP-13	45	106 (53)	NR	199 (100)	18	NR	12 (6)	NR	38 (19)	115 (58)	43 (22)	NR	NR	12 (6)
Cingolani[36]	2021	Prospective single centre	Maintenance of clinical and biochemical response after switch	80; CD 65, UC 15	Humira	ABP501 (55), SB5 (25), Amgen ABP501	40.8	10/55 (18)	NR	71/80 (89)	6	Clinical remission at 6 months: 63/80 (79)	2/55 (4)	NR	NR	NR	8/55 (15)	7 (13)	NR	1 (2)
Deprez[39]	2022	Multicentre phase IV interventional cohort study	Evaluate ADA trough levels at 12 months after switch	110; 84 CD, 26 UC	Humira	Imraldi (SB50	54	7 (6)	11.3	97 (88)	12	NR	16 (15)	15 (15)	NR	82 (75)	28 (25)	3 (3)	1 (1)	16 (15)

Table 1. Continued

Author	Year	Study type	Primary outcome	N	Originator	Biosimilar	Duration originator (months)	CIM, *n* (percent)	Disease duration (years)	Remission at baseline *n* (percent)	FU	Clinical effectiveness *n* (percent)	Safety *n* (percent)		LOR *n* (percent)	Persistence *n* (percent)	Treatment cessation *n* (percent)			
													AEs	SAEs			Overall	LOR	Remission	AE
Derikx[43]	2021	Single centre retrospective observational cohort	Drug persistence	256; CD 228, UC 28	Humira	SB5	32.5	56 (22)	10	123 (70)	12	NR	NR	NR	NR	213/252 (85)	90/256 (35)	37 (1)	37 (14)	46 (18)
Eberl[47]	2017	Prospective single centre	TLs, ADA, disease activity after switch	62; CD 32, UC 30	Remicade	CTP-13	NR	NR	NR	NR	6	NR	4 (6)	0	NR	NR	NR	NR	NR	NR
Fischer[48]	2021	Prospective single centre	Effectiveness (change in clinical disease activity)	144; CD 94, UC 50	Remicade	SB2	30.5	3 (2)	8	99 (69)	20	Clinical remission at 20 months 70/94 (74)	40 (28)	11 (7)	NR	112 (78)	42 (29)	20 (14)	1 (0.6)	9 (6)
Guerra Veloz[14]	2018	Multicentre prospective observational	Change in clinical remission at 12 months	167; CD116, UC 51	Remicade	CTP-13	NR	84 (50)	NR	146 (87)	12	Clinical remission at 12 months 116/167 (70)	12 (7)	3 (2)	30 (18)	152 (91)	15 (9)	NR	7 (4)	7 (4)
Guerra Veloz[13]	2019	Prospective single centre observational	LOR after switch	100; CD 64	Remicade	CTP-13	70	41 (64)	10.5	51 (80)	24	NR	14 (14)	NR	NR	NR	28 (28)	15 (15)	8 (8)	4 (4)
				UC 36					9.5	27 (75)										
Guiotto[15]	2019	Prospective single centre	Safety, effectiveness, pharmacokinetics comparing switch and non-switch	53; CD 29, UC 24	Remicade	CTP-13	48	7 (13)	16	41 (77)	NR	NR	4 (8)	NR	10 (19)	NR	14 (26)	8 (15)	NR	NR
Haifer[16]	2021	Prospective multicentre comparator cohort	Clinical disease worsening requiring steroids, escalation, switch or surgery.	204; CD 141, UC 64	Remicade	CTP-13 (Inflectra)	3.3	99 (57)	9.1	204 (100)	12	NR	8 (5)	NR	NR	NR	NR	NR	NR	8 (5)
Hanzel[17]	2021	Prospective multicentre cohort	Clinical remission at 12 months	176; CD 125, UC 51	Remicade	CTP-13	38.4	6 (22)	8	22 (93)	12	Clinical remission at 12 months: 20/26 (77)	9/176 (5)	NR	NR	19/27 (7)	14/27 (5)	4/27 (15)	6/27 (22)	4/27 (15)
					Remicade to CTP-13	SB2	82	45 (56)	5	55 (6)		40/52 (77)				59/69 (86)	14/69 (20)	6/69 (9)	6/69 (9)	2/69 (3)
					CTP 13	SB2	22.8	25 (36)	13	58 (84)		46/70 (66)				70/80 (88)	11/80 (14)	7/80 (9)	1/80 (1)	3/80 (4)
Hellstrom[18]	2022	Prospective single centre observational	All-cause treatment discontinuation	111; CD 63, UC 48	Remicade	CTP-13 (Inflectra, Remisma)	NR	97 (87)	5.9	NR	24	NR	6 (5)	NR	NR	37 (33)	74 (67)	NR	NR	6 (5)

Table 1. Continued

Author	Year	Study type	Primary outcome	*N*	Originator	Biosimilar	Duration originator (months)	CIM, *n* (percent)	Disease duration (years)	Remission at baseline *n* (percent)	FU	Clinical effectiveness *n* (percent)	Safety *n* (percent)		LOR *n* (percent)	Persistence *n* (percent)	Treatment cessation *n* (percent)			
													AEs	SAEs			Overall	LOR	Remission	AE
Ho[19]	2020	Retrospective multicentre cohort study	composite endpoint of disease worsening requiring acute f/u, defined by IBD-related ED visits, hospitalizations, surgeries	1409; CD 728, UC 681	Remicade	infliximab-dyyb (Inflectra)	39.6	403 (29)	8.1	NR	9	NR	NR	NR	347 (25)	NR	NR	NR	NR	NR
Hoivik[20]	2018	Prospective single centre	Drug persistence and immunogenicity at 18 months after switch	143; CD 99, UC 44	Remicade	CTP-13	81	50 (34)	NR	NR	18	NR	74 (52)	5 (3)	NR	130 (91)	12 (8)	3 (2)	5 (4)	4 (3)
Khan[29]	2021	Retrospective multicentre cohort study	Drug discontinuation/non-remission	271; CD 149, UC 122	Remicade	Renflexis, or double switch Inflectra to Renflexis	NR	65 (24)	13	NR	12	NR	NR	NR	24 (9)	NR	43 (16)	24 (9)	0	14 (5)
Kolar[21]	2017	Prospective single centre observational	Effectiveness and safety	74; CD 56, UC 18	Remicade	CTP-13	36	35 (47)	10.1	52 (72)	12	NR	35 (47)	NR	2 (3)	NR	NR	NR	NR	NR
Lontai[45]	2022	Prospective multicentre observational	Evaluation of clinical disease remission and drug persistence after switch	276; CD 205, UC 71	Humira	ABP501 (Amgevita)/ MSB11022 (Idacio) (174)	42	56/174 (32)	12.5	154/174 (89)	24	Clinical remission at 12 months 149/174 (86)	5/276 (2)	NR	NR	At 40 weeks: 159/174 (92)	29/276 (11)	20/276 (7)	NR	5/276 (2)
					Biosimilar	Hyrimoz (102)	6	32/102 (31)	8	80/102 (78)		74/102 (80)				89/102 (87)				
Lovero[30]	2020	Retrospective single centre	Explore safety and effectiveness of IFX SB2 after switching from CTP13	36; CD 14, UC 22	Multiple IFX, (single switch CTP-13 to SB2, Remicade > CTP13 > SB2)	SB2	27	NR	NR	NR	3	Clinical remission—21/36 (58) at 3 months	2 (6)	NR	11 (30)	NR	2 (6)	NR	2 (6)	NR
Luber[31]	2021	Prospective single centre	Clinical effectiveness	186; CD 151, UC 35	CTP13: 87 Remicade > CT-P13: 99	SB2	25 76	74 (85) 72 (73)	NR	169 (91)	4	Clinical remission—171/186 (92) at 4 months	NR	NR	28/178 (16)	162/178 (91) at 1y	NR	6/178 (3)	5/222 (2)	NR
Lukas[41]	2020	Retrospective single centre	Clinical effectiveness week 10	93; CD 80, UC 13	Humira	SB5	36	21 (23)	7	NR	16	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table 1. Continued

Author	Year	Study type	Primary outcome	*N*	Originator	Biosimilar	Duration originator (months)	CIM, *n* (percent)	Disease duration (years)	Remission at baseline *n* (percent)	FU	Clinical effectiveness *n* (percent)	Safety *n* (percent)		LOR *n* (percent)	Persistence *n* (percent)	Treatment cessation *n* (percent)			
													AEs	SAEs			Overall	LOR	Remission	AE
Lukas[40]	2022	Retrospective single centre	Clinical disease activity (HBI) at 52 weeks	54; CD 54	Humira	SB5	NR	14 (26)	13.9	NR	12	NR	NR	NR	NR	27 (50)	NR	2 (4)	NR	23 (43)
Macaluso[32]	2021	Prospective multicentre cohort	SAEs	340; CD 314, UC 26	Humira	ABP501	NR	9 (3)	10	NR	12	NR	NR	13 (4)	NR	317/323 (98) at 16 weeks, 281/295 (95) at 24 weeks, 112/124 (90) at 48 weeks	8/340 (2)	NR	NR	NR
Macaluso[35]	2021	Prospective multicentre cohort	SAEs	84; CD 43, UC 31	Remicade	SB2	NR	3/17 (18)	11	NR	6	NR	NR	18 (21)	NR	17/17 (100)at 12 weeks, 15/15 (100) at 24 weeks, 8/9 (89) at 48 weeks,	NR	NR	NR	8 (10)
					CTT-P13			4/43 (9)	8.08							40/41 (98) at 12 weeks, 29/32 (91) at 24 weeks, 5/7 (71) at 48 weeks				
					Multiple switch			3/24 (13)	11.9							22/23 (96) at 12 weeks, 17/20 (85) at 24 weeks, 1/2 (50) at 48 weeks				
Martin-Gutierrez[22]	2022	Prospective single centre observational	Prospective multicentre cohort	36; CD 29, UC 7	Remicade	CTP-13	NR	35 (97)	10	32 (89)	8	Clinical remission—33/36 (92) at 8 months	0	NR	NR	31 (86) at 2y	NR	2 (6)	0	0

Table 1. Continued

Author	Year	Study type	Primary outcome	*N*	Originator	Biosimilar	Duration originator (months)	CIM, *n* (percent)	Disease duration (years)	Remission at baseline *n* (percent)	FU	Clinical effectiveness *n* (percent)	Safety *n* (percent)		LOR *n* (percent)	Persistence *n* (percent)	Treatment cessation *n* (percent)			
													AEs	SAEs			Overall	LOR	Remission	AE
Massimi[33]	2021	Prospective multicentre cohort	Maintenance of clinical and biochemical response	85; CD 57, UC 28	Remicade	SB2	48	14 (16)	13	32 (89)	11.8	Clinical remission—59/76 (70) at 11.8 months	9 (11)	0	NR	NR	NR	8 (9)	2 (2)	5 (6)
Mazza[23]	2021	Retrospective multicentre centre	Evaluation of safety of double switch—frequency/rate over time Aes, treatment cessation due to AE after SB2	52; CD 39, UC 13	Remicade> CTP-13	SB2	53	2 (4)	13	NR	16	Clinical remission—46 (88)	4 (8)	0	3 (6)	51 (98) at 24 weeks, 47 (88) at 52 weeks	NR	5/118 (4) at 72 weeks	6/118 (5)	2/118 (2)
Plevris[49]	2018	Prospective single centre	Clinical effectiveness in patients with CD after switch	155; CD 155	Remicade	CTP-13	NR	41 (26)	9	142 (92)	12	NR	NR	NR	NR	93/110 (85) at 12 months	NR	NR	24/155 (15)	NR
Pugliese[24]	2021	Prospective single centre	Effectiveness (persistence, CSFR and CSF biochemical remission), safety, immunogenicity	119; CD 94, UC 25	Remicade	CTP-13	70	3 (2.5)	12.2	84 (71)	12	Clinical remission—77 (65)	24 (2)	NR	NR	110 (98) at 6 months, 92 (83) at 12 months	18 (15)	6 (5)	9 (8)	3 (3)
Ratnakumaran[25]	2018	Prospective single centre	Efficacy, safety, PK	191; CD 173, UC 18	Remicade	CTP13	55	117 (61)	42.7	NR	12	Clinical remission 111 (58) at 12 months	9 (5)	NR	47 (25)	NR	NR	NR	NR	9 (5)
Razanskaite[26]	2017	Prospective single centre	Drug persistence, costs, patient reported side effects, AEs, PROM, PK	143; CD 118, UC 25	Remicade	CTP13	NR	101 (71)	6	NR	12	NR	NR	NR	NR	104 (73) at 12 months	41 (29)	16 (11)	11 (8)	13 (9)
Ribaldone[37]	2020	Prospective single centre	Drug persistence, costs, patient reported side effects, AEs, PROM, PK	62; CD 62	Humira	ABP501	NR	NR	17.3	62 (100)	24	NR	22 (35)	NR	3 (5)	59 (95) at 24 months	NR	NR	NR	NR
Ribaldone[44]	2021	Prospective single centre	Success of switch to SB5, predictors of successful switch, AEs	68; CD 68	Humira > ABP501	SB5	27	NR	NR	NR	6	NR	7 (10)	7 (10)	NR	54/61 (89) at 6 months	7 (10)	5 (7)	NR	2 (3)
Schmitz[27]	2017	Prospective multicentre	Effectiveness and safety	133; CD 85, UC 48	Remicade	CTP-13 (Inflectra®)	NR	58 (44)	4.25	66/94 (70)	12	NR	NR	NR	NR	NR	35 (26)	12 (9)	5 (4)	13 (10)

Table 1. Continued

Author	Year	Study type	Primary outcome	*N*	Originator	Biosimilar	Duration originator (months)	CIM, *n* (percent)	Disease duration (years)	Remission at baseline *n* (percent)	FU	Clinical effectiveness *n* (percent)	Safety *n* (percent)		LOR *n* (percent)	Persistence *n* (percent)	Treatment cessation *n* (percent)			
													AEs	SAEs			Overall	LOR	Remission	AE
Smits (3 studies)[4-6]	2016	Prospective single centre	Change in disease activity at week 16	83; CD 57, UC 26	Remicade	CTP-13	25	55 (66)	NR	53 (64)	24	Clinical remission 61/83 (73) at 12 months	NR	3 (4)	NR	55 (66) at 24 months	25 (30)	10 (12)	7 (8)	8 (10)
Tapete[42]	2022	Prospective single centre comparator cohort	Effectiveness and safety	98; CD 78, UC 20	Humira	SB5	NR	3 (3)	9.8	NR	12	Clinical remission—74/98 (76) at 12 months	NR	NR	NR	NR	NR	15 (15)	2 (2)	1 (1)
Trystram[34]	2021	Prospective multicentre comparator cohort	Effectiveness, safety, PK	43; CD 26, UC 17	CTP13	SB2	1.6	23 (53)	6.9	158 (100)	12	Clinical remission—140/158 (89) at 12 months	63 (40)	NR	NR	146/158 (92) at 12 months	12/153 (8)	4/153 (3)	NR	4/153 (3)
				115; CD 84, UC 31	Remicade > CTP13		6.3	40 (35)	14.7											
Tursi[38]	2022	Retrospective multicentre	(1) comparison of the efficacy in maintaining clinical remission and safety among the different ADA biosimilars used after replacing the ADA originator for a non-medical reason (2) AEs	153; CD 127, UC 26	Humira	ABP501, SB5, GP2017	NR	3 (2)	8	153/153, (100)	12	Clinical remission—124 (81) at 12 months	12 (8)	1 (0.7)	29 (19) at 12 months	NR	NR	24 (16)	NR	NR

Abbreviations: ADA, adalimumab; CD, Crohn's disease; CIM, concomitant immunomodulation (with thiopurine or methotrexate); FU, follow-up; IFX, infliximab; LOR, loss of response; m, months; *n*, number; NR, not reported; PK, pharmacokinetics; PROM, patient reported outcomes; S/AE, serious/adverse event; time points: w, weeks; TL, trough levels; UC, ulcerative colitis; y, years.

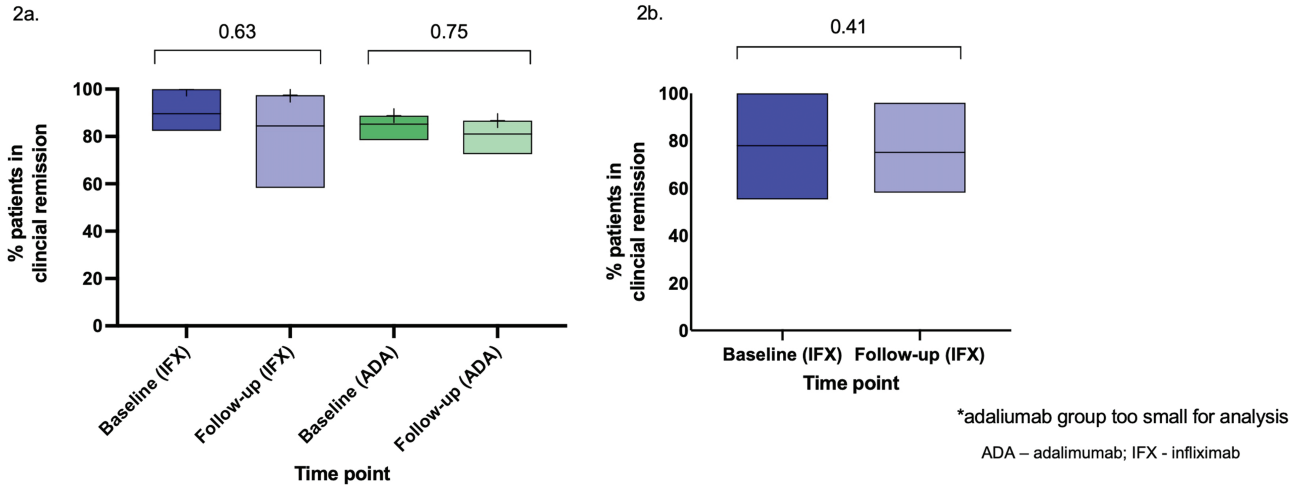

Figure 2. Proportion of patients in clinical remission at baseline and follow up. (a) Anti-TNF biosimilar switch at baseline and <12 months. (b) Infliximab* biosimilar switch at baseline and ≥12 months.

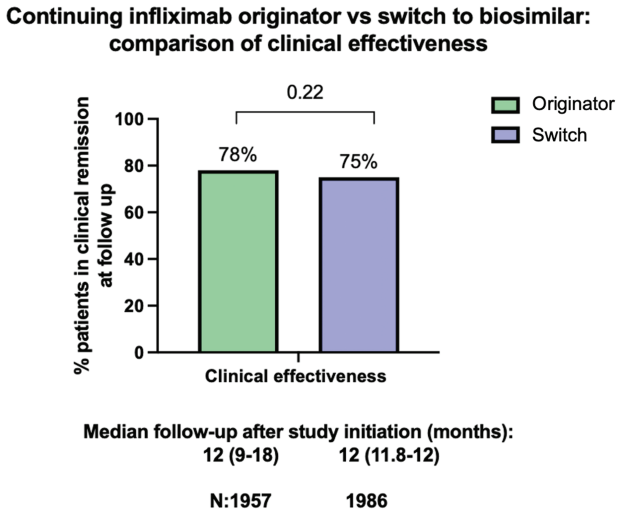

Figure 3. Continuing infliximab originator versus switch to biosimilar: comparison of clinical effectiveness.

(<12 months) received IFX for median 39.5 (28.0–72.8) months prior to switch. Where reported, 91.8 percent of cases (413/450) were in remission at the time of switch[11,22,31,33] compared with 88.1 percent of patients (594/673) in clinical remission at median 5 [2.8–6.5] months after switching (P = .63). Patients receiving ADA with available short-term data (all with 6-months follow-up) received ADA for median 40.8 [6.0–42.0] months prior to switch. Where reported, 86 percent (305/356) were in clinical remission at the time of switch[36,45] and 82 percent of patients (371/454) were in clinical remission at final follow-up (P = .75; Fig. 2a). One study[33] reported outcomes of patients with a median time of assessment at 11.8 (6.7–14.7) months post-switch. These data were included in the short-term data (<12 months) so as not to exaggerate longer-term outcomes.

Thirteen studies reported on rates of clinical remission ≥12 months after switch; 11 investigating IFX[4-6,8,13,14,17,23-25,31,34,48], and 2 investigating ADA.[38,42] Amongst the IFX studies, patients received IFX for median 52.8 (27.8–62.6) months prior to switch. Where reported 74.9 percent of cases (997/1331) were in remission at the time of switch and 75.0 percent (1091/1455) were in clinical remission at median 12 (12–15) months after switching (P = .41). For the ADA studies with clinical remission data ≥12 months, neither study reported on duration of originator prior to switch. One study reported rates of clinical remission at baseline (153/153, 100 percent).[38] Overall, 76.6 percent (197/251) patients were in clinical remission at 12 months after switch (Fig. 2b).

Median or mean change in clinical parameters (C-reactive protein, fecal calprotectin, or clinical disease scores [Harvey Bradshaw Index, Mayo score, Simple Crohn's, and colitis activity index]) were reported in several studies[4-6,8,10,11,13,14,16,17,20-22,25-27,31-34,36,40-49] none of which reported a statistical difference between baseline and final follow-up for either drug.

In five IFX studies[12,16,18,19,25] with a comparator originator cohort where data were extractable, overall clinical effectiveness was reported in 78 percent of patients (1533/1957) who continued originator at median 12 (9.0–18.0) months follow-up. Seventy two percent of this cohort is derived from a large propensity matched comparator study.[19] Figure 3 depicts the clinical effectiveness of switching to IFX biosimilar versus continuing on originator. The sample size was too small to compare available data in the ADA comparator studies. However, data from CHARM and ADHERE demonstrated that in the 145 patients who were in clinical remission at the end of the CHARM study, 62/74 (83.8 percent) were in remission at 4 years (non-responder imputation: 78/145, 53.8 percent; last observation carried forward 116/145, 80 percent).[50] These data are similar to our findings above, thus supporting the use of biosimilars in terms of clinical effectiveness.

Loss of response

LOR was reported in 13 studies investigating IFX switch.[8,10,12-14,16,19,21,23,25,29,31,46] After median duration of originator 45 (31.5–54.0) months, LOR occurred in 17.5 percent (666/3794) patients at median 28 (13.5–45.5) weeks.

Two studies reported on LOR after switch from Humira. After median 52 (24–52) weeks, LOR occurred in 14.9 percent (32/215) of cases.

Where reported, dose optimization occurred in 17.8 percent (308/1789) of patients receiving IFX at median 12.0 (6.0–14.0) months and 7.8 percent (53/679) of cases receiving ADA at median 12.0 (12.0–18.0) months follow-up.

These results are not dissimilar to data from originator studies. In ACCENT1, investigating IFX maintenance therapy for CD which included >6,000 patient-years of follow-up. The annual risk of LOR was 13 percent and, overall, about 40 percent of patients developed secondary LOR over time.[51] In a systematic review investigating LOR to Humira, including 39 studies (955 patients), the annual risk for LOR was 20.3 percent per patient-year.[52] LOR usually occurs within a year of induction. The cumulative rate of LOR becomes more gradual over time. This should be accounted for when evaluating LOR data from studies with short term follow-up.[53]

Drug persistence

Drug persistence at final follow-up was reported in 19 IFX studies.[4-7,11,12,17,18,20,22-24,26,29,31,34,35,48,46,49] Patients had received originator for median 53.0 (32.5–81.0) months and 29 percent were receiving concomitant immunomodulation. At median follow-up of 12.0 (12.0–18.0) months, 84.3 percent (2374/2815) of patients continued to receive IFX biosimilar. Drug persistence was reported in seven ADA studies.[35,37,39,40,43–45] Patients had received originator for median duration 32.5 (16.5–48.0) months prior to switch and 14.9 percent were receiving concomitant immunomodulation at baseline. After median 12.0 (6.0–12.0) months follow-up, 80.7 percent (745/923) of patients remained on therapy. Intuitively, the presence of anti-drug antibodies prior to switch was associated with shorter drug persistence after switch ($P < .01$) in one study.[43]

In four IFX studies with a comparator originator cohort where data were extractable, 328/527 (62 percent patients) who did not switch were still receiving originator at follow-up (median 20 [10.5–24.0] months).[12,18,25,26] This is significantly lower than the switch data and likely highlights underlying biases in these cohorts. 53 percent (n=277) of patients from this comparator cohort are from an unmatched study where more patients started IFX for prophylaxis in the originator group, whereas more patients in the switch group were induced for steroid refractory disease.[12] A total of 111 patients derive from another unmatched study where more stable disease was observed in the switch cohort.[18] For ADA, data were only available for two studies at 6 and 24 months follow up and 74/92 (80 percent) patients were still receiving originator at study end. In a retrospective study following 4,297 patients between 1999 and 2020 receiving anti-TNF, overall median treatment persistence was 2.3 years but this increased to 4.2 years after exclusion of patients who had received <6 months of therapy.[54] This latter figure is more relevant to our switch cohort who received drug for 3–4 years prior to switch. The study does not differentiate between originator and biosimilar and provides data on all anti-TNFs combined, but given the dates of inclusion, the majority of patients are likely to have received originator.[54]

Pharmacokinetics

It was not possible to collate data regarding immunogenicity due to the different assays used in each study. However, no studies reported higher than expected rates of immunogenicity. In the 23 studies[4–6,8,10,11,13,16,17,20–22,26,27,31,33,34,39–42,47–49] reporting on change in drug levels pre- and post-switch (18 IFX and 5 ADA), none demonstrated a significant reduction in median drug levels at final follow up. There was also no difference in therapeutic drug monitoring in patients who had undergone a first or second switch (n=186).[31]

Treatment cessation and adverse events

Rate of treatment cessation was reported in 17 IFX studies; 14 including switching to CT-P13[4-6,10-13,15,17,18,20,24,26,27,46,55] and 4 including switch to SB2.[17,26,34,48] At median follow-up 12.0 (12–18.0) months 17.8 percent (480/2696) of patients had ceased the biosimilar. Where reported, this was due to LOR (164/2447, 6.7 percent), remission (107/2238, 4.8 percent), or AE (148/3323, 4.5 percent). Rate of overall treatment cessation was reported in six ADA studies.[32,36,39,43–45] At median follow up 9.0 (6.0–12.0) months 170/1105 (15.4 percent) patients had ceased the biosimilar. Where reported, this was due to LOR (113/1070, 10.6 percent), remission 5/464 (1.1 percent), or AE (94/917, 10.3 percent). Treatment cessation for LOR is likely a reasonable indirect measure of true LOR despite dose escalation as judged by the treating clinician; particularly with the advent of an increasing number of alternative available therapeutic options.

SAEs were reported in 12 IFX studies[4-8,11,14,20,23,33,35,48,46,56] and occurred in 69/1793 (3.8 percent) cases at median 12.0 (6.0–19.5) months follow-up. Four ADA studies[32,38,39,44] reported SAEs in 36/671 (5.0 percent) at median 12.0 (7.5–12.0). Reporting of AEs was heterogeneous with variability in denominators. The most common AEs along with median frequency across all studies included: injection site pain (6 [1–35 percent]), infection (4 [1–10 percent]), articular (2 [1–5 percent]), infusion/injection site reaction (1 1–5 percent], and dermatological (2 (1–4 percent]). In the available comparator studies the frequency of injection site pain/reaction was higher in patients who switched to SB5 than those who continued on originator,[40-43] (37 percent versus 2 percent in one study).[40] Injection site pain/reaction was the most common reason for switch back to originator or to an alternative biosimilar after switch to SB5 (50/349, 14 percent) with successful second switch occurring in 34/35 cases in one study.[43] Hanzel et al. also demonstrated that five patients who were switched back to the index drug had resolution of the AE (eczema, headaches, and musculoskeletal pain) and maintenance of remission.[17] In total, 13 studies[10,19,25–27,34,38,39,41–43,45] reported frequency of switch back to originator (275/3185 [8.6 percent]) although reasons for, and success of, subsequent switching was seldom reported. Sixteen cancers (0.8 percent percent; chronic myeloid leukaemia, melanoma (2), melanocytic tumour of uncertain malignant potential, lymphoma, breast, prostate (2), NET, CLL, lung, rectal, four not reported), and three deaths were reported (1 ADA, 2 IFX). No deaths were deemed to be treatment-related. There were no reported cases of tuberculosis.

Overall, in the IFX studies, frequency of treatment cessation for AE (4.5 percent) was similar to data from the NOR-SWITCH study (3-4 percent).[57] Treatment cessation for AE was higher amongst ADA studies (10.3 percent), largely

relating to injection site reactions in the included SB5 studies; studies adjusting for this showed no difference in the rate of AE between switchers and those who continued originator.[42] Switching to an alternative biosimilar therefore appears to be worthwhile for certain AEs should the drug still be controlling disease activity. For IFX, infusion reactions were most commonly observed in patients with prior anti-TNF exposure rather than direct switch.[7]

Comparator studies

Nine studies compared switching biosimilar to the continuation of IFX[12,16,18,19,25,26] or ADA[36,40,41] originator with heterogeneous reporting of outcomes, some of which are mentioned above. The largest of these (comparing CT-P13 with originator; 1,409 matched patients in each group), met its non-inferiority composite primary outcome (disease worsening requiring emergency attendance, admission, or surgery; 10 percent switch versus 17 percent originator [non-inferiority margin set at 10 percent]). Notably, fewer events occurred in the patients that switched (admission: 1.4 percent versus 3.4 percent [$P < .001$], emergency attendance: 10 percent vs 15 percent [$P < .001$] and surgery: 1 percent vs 4 percent [$P < .001$]). Logistic regression demonstrated that switchers were 50 percent less likely to experience disease worsening requiring acute care. Predictors of this included: comorbidity, and use of acute care or steroids in the preceding 6 months. The secondary outcome was a composite endpoint of the primary outcome and the requirement for switch of therapy) which was similar in originator (26.6 percent) and switch (24.6 percent) groups. More patients ceased therapy in the switch group (15.7 vs 11.6 percent, $P < .01$), 77 percent of whom switched back to the originator whilst 100 percent of the originator switches were to an alternative drug class.[19]

Eleven studies compared originator switch to biosimilar induction in naïve patients[15,17,21,23,31,34,35,37,42,43,58,] which has its obvious limitations (comparison of patients likely already responding to drug versus those at risk of primary non-response). Active disease rather than cohort assignment, predicted future LOR in two studies.[15,34]

Seven of the included studies compared single and multiple switches[17,23,29,31,34,35,45] and found acceptable remission rates without significant differences in effectiveness or safety. Double-switch cohorts are small; only one study investigating multiple switches (n = 19/62) observed increased AEs in the double-switch cohort (6 versus 1) although these were all minor and did not require treatment cessation.[44] In a larger study (n = 340), AEs were more frequently observed in bio- or ADA-naive patients than those that switched from originator (17.4 versus 16.4 versus 4.8 per 100 PY respectively; $P < .001$).[32] The same was true when investigating IFX biosimilar SB2 with a similar study design. Again, multiple switches did not increase the risk of SAEs.[35]

Discussion

Several systematic reviews have been reported and the results of a Cochrane review are awaited.[59] These have focused on: infliximab[56,60-62] or adalimumab[63] biosimilars, RCTs,[64] biosimilar to biosimilar switching,[65] clinical effectiveness irrespective of switch status[58,66-69] and biosimilar outcomes in combined (non-IBD) cohorts.[70-72] Other groups have reviewed anti-TNF biosimilar switching in IBD[73,74]; but we present here a clinical update for both ADA and IFX, with a focus on real-world studies at a time when nationwide mandatory non-medical switching in Canada is due to be complete.

The majority of included studies investigate switching from originator to biosimilar. We also included biosimilar to biosimilar switches since the principle is the same; switching biosimilar (rather than initiating in naïve patients) poses the most anxiety to clinicians and patients[75] and other jurisdictions have experienced several mandatory switches based on drug availability at their institution.[31,34,76] Whilst scepticism was warranted, the available data support the use of biosimilars since no significant differences have been demonstrated with regard to clinical effectiveness or serious safety concerns. The majority of patients remain on biosimilars at final follow-up and no significant changes in therapeutic drug monitoring were observed. The available data mainly include switch to CT-P13, SB2, SB5, or ABP501 with minimal or no data for other biosimilars. Additionally, outcomes are reported up to 24 months and only up to 12 months for ADA studies. The available data for adalimumab are clearly less robust than for infliximab with significantly fewer patients, a fewer number of biosimilars investigated and a shorter duration of follow-up. Other biosimilars would be presumed to have similar outcomes if they have reached the threshold required for Health Canada approval, although this will require ongoing monitoring in real-world studies. Previous concerns included increased rates of admission or surgery that would negate the benefit of drug cost savings but this has not been observed in large matched cohorts.[19,77] Rates of LOR are not dissimilar to the expected rate of LOR observed with anti-TNF therapy prior to the biosimilar era.[54] In line with this, the European Crohn's and Colitis Organisation considers it acceptable to switch to a biosimilar.[78] The only significant difference with regard to AEs was the frequency of injection site pain/reaction in patients receiving SB5. Biosimilar excipients that may be associated with this are outlined in Supplementary Table S3.

Our results are different from those published in this journal in 2019. The Canadian Association of Gastroenterology and Crohn's and Colitis Canada provided a joint position statement suggesting IFX biosimilar induction should be recommended in naïve patients only. It was acknowledged that this recommendation was weak and based on low quality evidence.[79] A meta-analysis of the very limited randomized controlled trial (RCT) data available at this time was performed (including just two studies)[58,80] demonstrating that a similar number of patients were not in remission at 1 year, but a higher frequency of patients experienced disease worsening in the switch group. A similar trend was seen in the observational data (also only two studies)[16,81] but was non-significant. Notably, one of the included RCT abstracts provided no information on randomization or blinding.[80] In the NOR-SWITCH study included in this review, patients receiving originator IFX for IBD, rheumatological or dermatological indications, were randomized to continue originator or switch to biosimilar CT-P13. Results after the switch were non-inferior in terms of clinical effectiveness, safety, and immunogenicity at week 52.[57] Since then, the results have been replicated in the long-term extension study through to week 78 including 248 patients with CD and 173 patients with UC. Although these studies were not powered to provide outcome data for the specific diseases, disease worsening in patients with CD fell just within the pre-set non-inferiority margin of 15 percent.[82] A specific RCT addressing the efficacy

and safety of CT-P13 in CD comparing 4 switching groups (CTP-13:CTP13, CTP13-Remicade, Remicade-Remicade, Remicade-CTP-13) demonstrated non-inferior outcomes at 30-weeks but it was underpowered to detect differences after the switch at 30-weeks.[83] Several anti-TNF biosimilar agents are now available (Supplementary Tables S3 and S4). Much of the initial biosimilar data were extrapolated from rheumatological cohorts and have since been corroborated in dedicated trials in IBD cohorts with scrutiny of their use in real-world clinical practice.[77,82-87] Real-world data largely originates from European cohorts where biosimilar use was initiated as early as 2013 for naïve patients and 2015 for patients already receiving originator.[79] We have synthesized the data from several studies published since this time, including comparator studies, which likely account for the differences in our results. The largest included >1,000 matched patients where biosimilar switch was demonstrated to be non-inferior, including for the outcome of disease worsening.[19]

Earlier this year Crohn's and Colitis Canada recommended a decision matrix with the suggestion that it may be prudent to either defer or exempt, certain patients from switching therapy.[88] Anecdotally, loss of response has been observed in patients following switch but this is not demonstrated in large data sets and the presented algorithm is seemingly based on no evidence. It does, however, serve to highlight the importance of joint clinical decision making, particularly in patients deemed to have high-risk disease. Whilst requests for deferring switch could be considered, once provinces adopt mandatory switching the choice of deferring or averting switch will be a financial one and likely only available to those with private health care coverage. We hope our article will allay concerns with regard to switching therapy and reassure patients and physicians that care is not likely to be compromised.

There are several limitations to our study. The included studies are heterogeneous in design, with significant variations in how outcomes were defined (Supplementary Table S1). We have presented the data as described by the authors in the individual studies. It is accepted that clinical remission correlates poorly with objective measures of disease activity[89] and several studies did not include the latter in their definition of response to therapy, nor report on corticosteroid use during study follow-up. In addition, several studies did not objectively report rates of remission at baseline. When objectively assessed, patients with active disease at baseline were more likely to lose response at the final follow-up.[15,34] This needs to be considered when counselling patients prior to mandatory switch. The data is also open to biases inherent to the included observational studies. For example, in the observational comparator studies where the originator cohort was contemporary, patients selected to continue on the originator may have been a more refractory group. Treatment cessation in earlier studies may be confounded by patient or clinician concerns with regards to AEs. The available data did not allow for the evaluation of outcomes for UC versus CD nor for patients with a higher risk phenotype (perianal disease, previous surgery) where apprehension about switching therapy may be higher. In addition, since the efficacy of ADA is likely more favourable in CD than UC,[90,91] the proportion of cases within each study may affect the results.

We also did not include data on switching from biosimilar to originator which was reported in a few patients in several studies with limited information on outcomes on response after switching back. This has been investigated elsewhere with no significant difference in clinical or biochemical disease scores[92] or new anti-drug antibodies.[93] Improvement in perceived side effects was reported in 74 percent of patients (GI symptoms, dermatological, neurological, rheumatological, fatigue), although objective assessment of these is key as it remains unclear as to whether improvement was true, or relates to the nocebo effect.[93,94]

We present here a summary of the available real-world data on the clinical effectiveness and safety of anti-TNF biosimilar switching in IBD. We have additionally reported on LOR, drug persistence, treatment cessation, and pharmacokinetics. No significant differences in clinical effectiveness or serious AEs have been reported, which should be reassuring to patients and clinicians. This does not negate the need for appropriate counselling, objective assessment of disease activity and potential side effects prior to switching and careful follow-up post-switch. This approach will help to ensure optimal patient care while helping to achieve the financial benefits of a mandated switch policy.

Supplementary material

Supplementary data are available at *Journal of the Canadian Association of Gastroenterology* online.

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Conflicts of interest

None of the authors have any conflicts of interest to declare.

Data availability

Data will be made available upon reasonable request to the authors.

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