Real-world switching and discontinuation patterns of infliximab originator and biosimilars in patients with rheumatoid arthritis: a scoping review

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Background

- Rheumatoid arthritis (RA) is a debilitating autoimmune disease affecting 1.28-1.36 million adults in the United States.[1,2] It can lead to functional decline and adverse outcomes, including reduced QOL and premature mortality.[2]
- Infliximab (IFX) has proven effectiveness in improving symptom control and physical function and slowing joint changes.[3]
- Biosimilars have no clinically meaningful difference from their reference product with respect to safety, purity, and potency.[4] IFX biosimilars offer potential to reduce healthcare spending and improve patient access to biologic therapies.[4]
- Current literature body has limited large-scale comparative observational studies describing real-world treatment patterns of IFX for RA, with even fewer studies on IFX biosimilars.[5]

Figure 1. Chronic inflammation and joint deformity resulting in functional decline

Biosimilars of Remicade	Launch Date
Avsola (infliximab-axxq)	July 2020
Renflexis (infliximab-abda)	July 2017
Ixifi (infliximab-qbtx)	not launched
Inflectra (infliximab-dyyb)	Nov 2016

Table 1. Three IFX biosimilars in the United States

Objectives

To conduct a scoping review of observational studies investigating real-world evidence (RWE) on the switching and discontinuation patterns of IFX biosimilars in patients with RA. Findings will support the design of future comparative effectiveness and safety research studies and elucidate opportunities in IFX's treatment landscape.

Methods

- A comprehensive literature search was conducted in three databases (i.e. PubMed, Embase, and Web of Science). The most recent search was executed on February 18, 2021.
- Inclusion criteria: observational studies published between 2015-2020 examining switching and/or discontinuation outcomes of IFX biosimilar products in adult patients with RA.
- Exclusion criteria: non-English studies, RCTs, cost analyses (unless sub-analysis), biomarker studies, off-label indications, case series or reports
- Literature search, screening, review, and data charting were conducted by a primary reviewer. Quality assurance was performed by two additional reviewers.

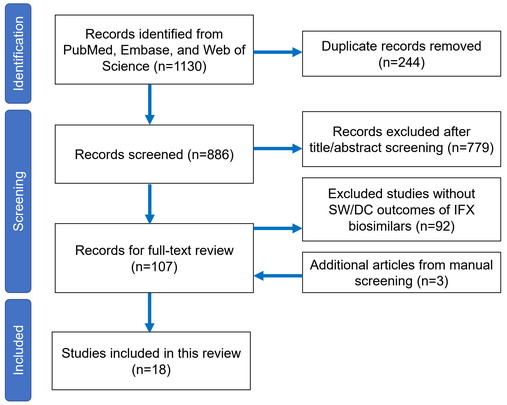

Figure 2. PRISMA flow diagram.

Results

Author, Year	Country	TNFi comparators	Data Source	Sample	DC Causes	DC or Retention rate	SW rate
Glintborg, B 2017	Denmark	IFX RP, CT-P13	registries, other (records from 2 hospitals)	RP n=602 CT-P13 n=403	CT-P13 (n=132): inefficacy 53.8%, AE 28%, remission 3.8%, cancer 3.8%, death 1.5%, several reasons 2.3%, other reasons, 6.1%, unknown 0.8%	• DC: CT-P13 (18.9%) • 1-yr CT-P13 retention 81%; similar for pt w/out DAS28 remission at baseline: 83% vs 74%, p=0.08 • 1-yr retention: RP (86.2%); CT-P13 (84.1%); p=0.22. CT-P13 w/ prior RP ≤5 yr had poorer retention (78 vs 87%, p=0.001)	
Grøn, KL 2019	Denmark	1: CTZ 70% 2: CTZ 9%, CT-P13 2% 3: CTZ 16%, CT-P13 59%	registries	CT-P13: 1; 0/474, 2: 7/329 3: 225/379	inefficacy 36-60%, AEs 15-42%, other <10%	• 1-yr crude retention: CT-P13 (69%); CT-P13 had higher 1-yr retention than CTZ	
Valido, A 2019	Portugal	CT-P13	registry (clinical data)	n=16	CT-P13 (n=5): disease progression 60%, AE 20%, lost to follow-up 20% Following DC: 1 pt reinitiated RP, 3 switch to different MOA	• DC: CT-P13 (8.3%)	
Sung, YK 2017	South Korea	IFX RP, CT-P13	registry, medical records	total n=100: IFX RP 45, CT-P13 55	AE: RP 38%; CT-P13 19% DC due to effectiveness only reported for RP	• DC (any reason): IFX RP (46.7%); CT-P13 (43.6%) • <6-mos DC: overall (29%); RP (35.6%); CT-P13 (23.6%) • >2yr retention: RP (36.9%); CT-P13 (52.6%); p=0.98	
Codreanu, C 2018	Bulgaria, Czech Republic, Romania	CT-P13	clinical data	n=81	CT-P13 (n=20): AE 35%, therapeutic failure 25%, noncompliance 10%, pt request 10%, sponsor request 5%, lost to follow-up 15%	• DC: CT-P13 (13%)	
Boone, NW 2018	Netherlands	CT-P13	medical records, other	total n=9; nocebo n=1			• 1 pt with nocebo response (after SW to CT-P13) reinitiated RP
Nikiphorou, E 2015	Finland	CT-P13	clinical data, PRO	n=15	total n=4: AE (antidrug Ab prior to CT-P13 infusion) 75%, subjective reasons 25%	• DC: CT-P13 (26.7%)	• SW (20%): 1 restarted RP, 2 switched to other biologics
Avouac, J 2018	France	CT-P13	medical records	n=31	inefficacy 80%, AEs 8%, lost to follow-up 10%, pregnancy 2%	• DC at last visit: CT-P13 (23%)	• Restart RP (80%), TNFi switch (8%); Switch to new MOA (3%); Biologic-free (8%)
Fisher, A 2020	Canada	IFX RP, ETN RP	claims	IFX cohorts: (2016) 3190, (2017) 3341, (2018) 3360, (2019) 3212			• RP to biosim (20.5%); • RP to another biologic (<5%)
Kim, TH 2020	South Korea	CT-P13	medical records	n=154 (87.7% naïve, 12.3% switched)	inefficacy 52%, AEs 12%, loss to follow-up 9%, pregnancy 4%, remission 0%, drug holiday 16%, other 9%	• DC: overall (66.9%); naïve (68.1%); switch (57.9%) • 5-yr survival: overall (43.3%); naïve (41.2%); switch (52.9%); p=0.61	
Bansback, N 2020	US	IFX-dyyb, IFX RP	registry	IFX-dyyb 536/2728, RP 2192/2728		• 20-mos crude persistence: IFX-dyyb (80%); RP (75%); p=0.02	
Layegh, Z 2019	Netherlands	Remsima transitioned from RP	medical records, other	n=41	Remsima n=1 AE (lung malignancy)	• DC: Remsima (13%) • 2-yr persistence (87%)	• 2-yr SW: Remsima to other TNFi 4%
Yazici, Y 2018	Turkey	IFX RP, CT-P13	claims	n=697 (92 switchers, 605 continuers)		• DC: Continuer (33.9%); switcher (87.5%); P<0.001	• Switchers (81.5%)
Yazici, Y 2018	Turkey	IFX RP, CT-P13	claims	IFX n=575, CT-P13 n=204		• DC: IFX (42.1%); CT-P13 (62.8%); p<0.001; sensitivity analysis confirmed DC rate: IFX (43.2%) vs CT-P13 (72.1%), p<0.001	• SW: RP (23.5%) vs CT-P13 (35.8%), p<0.001
Tweehuysen, L 2018	Netherlands	CT-P13 transitioned from RP	medical records, clinical data	n=75	CT-P13: inefficacy 55%, AE 23%, combination 21%	• 6-mos DC: CT-P13 (24%); p=0.78 between diseases	• DC CT-P13 n=47: 79% restarted RP, 15% SW to another biologic, 6% biologic-free
Nikiphorou, E 2019	Finland	IFX RP, CT-P13 (new initiation; switched from RP)	clinical data	n=123: RP 105, CT-P13 18	new users (RP vs CT-P13): inefficacy (18 vs 5%), AE (9.1 vs 5%), Ab (2 vs 5%), policy (24 vs 10%), other (8.8 vs 5%); RP to CT-P13 switchers): inefficacy (3.2%), AE (5.4%), Ab (2.1%), SW 6.5%, unknown 4.3%, other (2.2%)	• 2-yr DC: RP (62%); CT-P13 (30%) • CT-P13 new initiators had better 2-yr survival vs RP; RP to CT-P13 Switch had better survival than CT-P13 new initiators	• 2-yr SW: RP (24%); CT-P13 (10%)
Vergara-Dangond, C 2017	Spain	IFX RP, CT-P13	clinical data	n=13: 7 switchers, 6 continuers	DC due to AE: CT-P13 (14.3%); RP n=0		
Kim, SC 2016	South Korea	IFX RP, IFX biosim	medical claims	total n=7274: biosim n= 983		• IFX biosim uptake increased to 19% (11/2012-03/2014)	• biosim users: 41% switched from RP

Abbreviations: Ab: antibody, AE: adverse effect, biosim: biosimilar, CTZ: certolizumab, CT-P13: IFX biosimilar, DAS28: disease activity score, DC: discontinuation, ETN: etanercept, MOA: mechanism of action, pt: patient, RP: IFX reference product, SW: switching

Table 2. Switching and discontinuation study outcomes of IFX biosimilar

Discussion

- Outcomes of switching and discontinuation are reflective of factors associated with IFX persistence and are conducive to the assessment of long-term IFX utilization.
- Many outcomes reported were pooled for a combination of inflammatory diseases, such as RA and psoriatic arthritis. About 1/3 of the studies had a biosimilars sample size less than 50.
- A total of 12 studies reported discontinuation reasons. The most common causes of discontinuation were lack of effectiveness and adverse effects.
- The discontinuation rates of IFX biosimilars varied significantly ranging from 8.3 to 87.5%; similarly, the switching rates reported were between 4 to 81.5%.
- Among clinical outcomes, DAS28 was the most frequently reported measure of treatment response. Among authors that reported study design, 5 stated using a prospective analysis and 6 used a retrospective method.

Strengths and Limitations

Strengths
- Provides a scope of coverage of literature on the SW/DC outcomes of IFX and examines how research was conducted around this topic.
- Serves as a precursor to large-scale comparative studies by identifying relevant SW/DC outcomes, drug comparators, and study methods.
- Observational studies are noninterventional and provide RWE on use patterns.

Limitations
- Studies with a smaller sample may not represent the overall patient population.
- Scoping reviews do not critically appraise included studies and do not assess the risk of bias.
- Findings do not reflect the clinical impact of the 2021 American College of Rheumatology Clinical Practice Guideline.

Future Direction

- New biosimilar therapies are continually introduced to the market. It is important to assess the RWE on the longitudinal utilization patterns of biologics, including IFX, as they are integrated into clinical practice.
- Trends and study methods observed in this review will be used to inform the design of a retrospective, descriptive observational study using administrative claims from the distributed research network of BBCIC.

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