The Economic Impact of Originator-To-Biosimilar Non-medical Switching in the Real-World Setting: A Systematic Literature Review

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Appendix 1. Search strategy

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	Embase 1974 to 2020 March 02, Database Field Guide All Ovid MEDLINE(R) 1946 to Present	
1	biosimilar$.tw.	9732
2	*Biosimilar Pharmaceuticals/	3432
3	originator$.ab,ti.	3740
4	**or/1-3**	**11924**
5	Epidemiologic Studies/	215252
6	exp Cohort Studies/	2516974
7	Cross-Sectional Studies/	529486
8	(epidemiologic adj (study or studies)).tw.	57231
9	(cohort adj (study or studies)).tw.	476236
10	cross sectional.ab,ti.	773178
11	cohort analy$.ab,ti.	19849
12	(follow up adj (study or studies)).ab,ti.	110205
13	longitudinal.ab,ti.	550776
14	prospective$.ab,ti.	1716761
15	(observ$ adj3 (study or studies)).ab,ti.	465107
16	(pragmatic clinical trial or pragmatic trial).mp.	3713
17	(real world or real*world).ab,ti.	102582
18	(real life or real*life).ab,ti.	48402
19	(observational adj (study or studies)).tw.	259236
20	*Retrospective Studies/	17291
21	phase IV.mp.	7416
22	*Pharmacovigilance/ or *Product Surveillance, Postmarketing/ or *Adverse Drug Reaction Reporting Systems/	23317
23	(adherence adj3 (study or studies)).tw.	10691
24	(persistence adj3 (study or studies)).tw.	3442
25	(compliance adj3 (study or studies)).tw.	7166
26	*drug surveillance programme/	12597
27	Longitudinal study/	267851
28	Prospective study/	1115090
29	**or/5-28**	**5654515**
30	*health care utilization/	45499
31	*Health Resources/	38508
32	*Health Care Costs/	52077
33	*"Length of Stay"/ or *Hospitalization/	93389

34	(health system utili*ation or "health system use" or medical system utili*ation or "medical system use" or Medical care expenditures or Medical expenditures or Health care expenditures or Healthcare expenditures or Health expenditures or resource$ utili*ation or "resource$ use" or "healthcare use" or "health care use" or "medical use").mp.	92091
35	Economics/	263787
36	exp "Costs and Cost Analysis"/	576184
37	Economics, Nursing/	34620
38	Economics, Medical/	40574
39	Economics, Pharmaceutical/	10154
40	exp Economics, Hospital/	854916
41	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	459156
42	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	669362
43	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	370201
44	*"cost"/ or *"health care cost"/ or *economic aspect/	91486
45	*Health Services/	66201
46	saving$.ab,ti.	159380
47	or/30-46	2130206
48	**29 or 47**	**7468699**
49	*drug substitution/	2007
50	Switch*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]	367594
51	substitut*.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]	889996
52	change.ab,ti.	2358332
53	launch*.ab,ti.	62413
54	alternative$.ab,ti.	1337096
55	management.ab,ti.	2538057
56	**or/49-55**	**7063944**
57	**4 and 48 and 56**	**2366**
58	remove duplicates from 57	1850
	Imported	**1845**
	Discard duplicates	**5**

Appendix 2. Conference websites included in search

American College of Rheumatology Annual Meeting (ACR/ARHP)
American College of Gastroenterology
Annual Scientific Meeting (ACG)
American Diabetes Association Scientific Sessions (ADA)
American Society of Hematology Annual Meeting (ASH)
American Thoracic Society International Conferences (ATS)
Annual Meeting of the European Association for the Study of Diabetes (EASD)
American Society of Clinical Oncology Annual Meeting (ASCO)
European League Against Rheumatism Annual Congress (EULAR)
European Congress of Endocrinology (ECE)
European Society of Cardiology Annual Congress (ESC)
European Crohn's and Colitis Organization Annual Congress (ECCO gastro)
International Society for Pharmacoeconomics and Outcomes Research Annual European Congress (ISPOR Europe)
International Society for Pharmacoeconomics and Outcomes Research Annual International Meeting (ISPOR International)
Scientific Sessions of American Heart Association (AHA)
European Cancer Congress (ECCO cancer)

Supplementary Table 1. Data extracted

Subject of Data	Data Extracted
Publication information	• first author's name • year of publication • country
Drug information	• Drug name • Originator brand name • Biosimilar brand name
Study Design	• Study type • Patient data source • Study period • Patient follow-up • Outcomes • Implementation of switch programme
Study Population	• Disease area • Patient eligibility criteria • Sample size • Biologic-to-biosimilar switch rate • Biosimilar discontinuation rate • Reasons for discontinuation • Time to discontinuation • Biosimilar to alternative biologic switch rate • Biosimilar-to-biologic switch-back rate • Subsequent treatment list • Subsequent treatment rate • Treatment adherence and persistence
Cost and/or HCRU input	• Costing data source • Cost and/or HCRU inputs considered • Assumptions • Cost year • Currency
Efficacy outcomes	• Dose escalation or de-escalation • Events • PROs • Additional treatment
Cost outcomes	• Indirect costs/productivity loss • Cost differences between biosimilars and originators

Safety outcomes including HCRU	• Medical visits • Phone consultation • Hospitalization • Emergency room [ER] visits • Imaging • Laboratory tests (number and values) • Surgery • Adverse events [AEs]

HCRU: healthcare resource utilization; **PRO**: patient-reported outcome.

Supplementary Table 2. Reported characteristics associated with biosimilar discontinuation

Disease	Citation	Drug	Dose Escalation Rate	Discontinuation Rate	TTD	Reason for Discontinuation	Switch Back Rate	Switch to Alternative Biologic Rate	Subsequent Treatment
Gastroenterology									
CD	Ala 2016[50]	Infliximab	NR	4/20 (20%)	NR	Disease activity: 3 Remission: 1	NR	3/20 (15%)	Adalumimab: 2 Allopurinol/ Azathioprine: 1
CD	Plevris 2019[45]	Infliximab	5.5%	17/110 (15.5%)	NR	Pregnancy: 3 Patient choice: 2 Disease activity: 2 Surgery: 1 Remission: 1 Patient relocated: 1 AEs: 7	NR	1/110 (0.9%)	Vedolizumab: 1
CD, UC	Bergqvist 2018[51]	Infliximab	64/250 (25.6%) Dose reduction: 31/250 (12.4%)	48/313 (15.3%)	NR	Remission: 10 Disease activity: 23 AEs: 15	NR	NR	NR
CD, UC	Diaz Hernandez 2016[52]	Infliximab	NR	3/72 (4.2%)	NR	Primary non-response: 1 LOR: 2	NR	NR	NR
CD, UC	Fischer 2018[53]	Infliximab	NR	12/114 (10.5%)	NR	AEs: 6 LOR: 16	NR	NR	NR
CD, UC	Guerra Veloz 2019[54]	Infliximab	22/100 (22%)	CD: 16/64 (25%) UC: 12/36 (33.3%)	Median 15 months Range 8-24	*CD patients* LOR: 10 AEs: 2 Remission: 3 Switch to alternative drug: 1 *UC patients* LOR: 5 AEs: 2 Remission: 5	NR	1/100 (1%)	Adalimumab: 1
CD, UC	Hoivik 2018[55]	Infliximab	NR	12/143 (8.4%)	NR	LOR: 3 AEs: 4 Remission: 5	NR	4/143 (2.8%)	Vedolizumab
CD, UC	Rodriguez Glez 2017[56]	Infliximab	10/72 (13.9%)	7/72 (9.7%)	NR	LOR: 4	NR	NR	NR
CD, UC	Sieczkowska 2016[57]	Infliximab	NR	15/39 (38.5%)	NR	Remission: 3 LOR: 3 Infusion reaction: 1 AE: 3 Finances: 5	NR	2/39 (5.1%)	Adalimumab: 2
CD, UC	St Clair Jones 2017[39]	Infliximab	8/71 (11.3%) Dose reduction: 6/71 (8.5%)	17/71 (23.9%)	NR	Switch to alternative drug: 8 Antibodies: 7 LOR: 2	NR	8/71 (11.3%)	Adalimumab: 4 Golimumab: 3 Vedolizumab: 1
pediatric CD, UC	Kang 2017[58]	Infliximab	3/38 (7.9%)	1/38 (2.6%)	NR	Remission: 1	NR	NR	NR
CD, UC, IBDU	Huoponen 2020[35]	Infliximab	NR	3/54 (5.6%)	NR	Switch to alternative drug: 1 Remission: 1 Trough levels: 1	NR	1/54 (1.9%)	NR
CD, UC, IBDU	Smits 2017[59]	Infliximab	19% Dose reduction: 8%	15/83 (18.1%)	Median 16 weeks (Range 0 to 36 weeks)	Remission:1 AEs: 5 LOR:2 Antibodies:4 Arthralgia: 1	NR	NR	NR

Disease	Citation	Drug	Dose Escalation Rate	Discontinuation Rate	TTD	Reason for Discontinuation	Switch Back Rate	Switch to Alternative Biologic Rate	Subsequent Treatment
						Lost to follow-up: 2			
CD, UC, IBDU	Razanskaite 2017[44]	Infliximab	NR	41/143 (28.7%)	NR	Elective withdrawal: 11 Primary non-response: 4 LOR: 12 Pregnancy: 1 AEs: 12 Patient's choice: 1	2/143 (1.4%)	NR	NR
CD, FCD, UC	Park 2015[60]	Infliximab	27/60 (45%)	3/60 (5.0%)		Infusion reaction: 1 AEs: 2	NR	NR	NR
LCD, FCD, UC, IBDU	Ratnakumaran 2018[61]	Infliximab	Switch vs Non-switch, increase in: Dose: 10.6% vs 25% Frequency: 19.1% vs 12.5% Both: 12.8% v 0%	36/191 (18.8%)		AEs: 9 Surgery: 5 Switched to alternative drug: 15 Other: 6 Patient's choice: 1	1/191 (0.5%)	15/191 (7.9%)	NR
NS	Gervais 2018[62]	Infliximab	16/33 (48.5%)	4/33 (12.1%)	Mean 6.5 months (3 to 9 months)	LOR: 1 Transitioned to adult services: 1 Remission: 2	NR	1/33 (3.0%)	Adalimumab: 1
Rheumatology									
RA	Dyball 2017[63]	Etanercept	NR	6/36 (16.7%)	NR	Infusion reaction: 1 AEs: 1 LOR: 4	5/36 (13.9%)	NR	NR
RA	Peral 2018[37]	Etanercept	NR	NR	NR	NR	NR	18.20%	Adalimumab : 1 Tocilizumab : 1 Abatacept : 1
RA	Shah 2018[43]	Etanercept	NR	NR	NR	AEs: 5 Difficulty with the autoinjector pen: 3 Disease activity: 2.	8/151 (5.3%)	NR	NR
RA	Tarallo 2019[32]	Etanercept	NR	332/1,259 (26.4%)	NR	NR	105/1,259 (8.3%)	179/1,259 (14.2%) to alternative biologic 48/1,259 (3.8%) to alternative etanercept biosimilar	Abatacept Adalimumab Tocilizumab SB4 or GP2015
RA	Nisar 2019[42]	Rituximab	NR	6/40 (15%)	NR	AEs : 6	4/40 (10%)	1/40 (2.5%)	Humira
RA, PsA, AS	Alkoky 2018[71]	Etanercept	NR	NR	NR	NR	14/158 (8.9%)	NR	NR
RA, PsA, AS	Chan 2019[41]	Etanercept	NR	NR	NR	Disease activity Intolerance	4/113 (3.5%)	3/113 (2.7%)	NR
RA, PsA, AS	Ma 2018[65]	Etanercept	NR	8/50 (16%)	NR	AEs: 4 Disease activity: 3 New contraindication: 1	NR	NR	NR

Disease	Citation	Drug	Dose Escalation Rate	Discontinuation Rate	TTD	Reason for Discontinuation	Switch Back Rate	Switch to Alternative Biologic Rate	Subsequent Treatment
RA, PsA, AS	Nascimento Junior 2018[66]	Infliximab	NR	5/78 (6.4%)	NR	LOR: 4 Loss to follow-up: 1	NR	NR	NR
RA, PsA, AS, JIA	Nisar 2019[42]	Etanercept	NR	6/82 (7.3%)	Range 3 to 10 months	AEs and disease worsening: 4 uncontrolled Disease activity: 2	4/82 (4.9%)	2/82 (2.4%)	NR
RA, PsA, SpA	Uke 2019[72]	Etanercept	NR	NR	NR	Personal reasons: 6 Disease activity: 11	17/157 (10.8%)	NR	NR
RA, PsA, SpA	Valido 2019[67]	Infliximab	NR	5/60 (8.3%)	NR	disease activity: 3 AE: 1	1/60 (1.7%)	3/60 (5.0%)	NR
NS	Ahmad 2019[68]	Etanercept	NR	11/104 (10.6%)	NR	Disease activity: 11	2/104 (1.9%)	9/104 (8.7%)	Adalidumab Certolizumab Tocilizumab Rituximab
NS	Sheppard 2016[73]	Infliximab	NR	NR	NR	AEs: 4	4/25 (16%)	NR	NR
Hepatology									
Chronic kidney disease	Minutolo 2017[8]	ESA	17.2% vs 3.7% (no switch) Dose increased by a mean of 39.6% Dose reduction: 21.5% vs 45.4% (no switch)	NR	NR	NR	NR	NR	NR
Growth Development									
GHD, TS, CRI, PWS children born small for gestational age	Flodmark 2013[7]	Somatropin	NR	NR	NR	NR	6/98 (6.1%)	NR	NR
Unspecified or Multiple Disease Areas									
IBD, RA, PsA, AS	Abdalla 2017[69]	Infliximab	NR	5/34 (14.7%)	NR	Pregnancy: 1 LOR: 2 AEs: 1 Disease activity: 1	1/34 (2.9%)	3/34 (8.8%)	NR
CD, UC, RA, AS	Ramos Rodriguez 2018[74]	Infliximab	1/48 (2.1%)	NR	NR	NR	NR	NR	NR
NS (areas include rheumatology, gastroentology, internal medicine)	Gutermann 2017[70]	Infliximab	NR	39/267 (14.6%)	NR	LOR: 30 AE: 1 Lost to follow-up: 2 Medical reason: 2 Switched to alternative drug: 4	31/267 (11.6%)	4/267 (1.5%)	NR

Disease	Citation	Drug	Dose Escalation Rate	Discontinuation Rate	TTD	Reason for Discontinuation	Switch Back Rate	Switch to Alternative Biologic Rate	Subsequent Treatment
NS (RA, AS most common)	Phillips 2017[36]	Infliximab	NR	*Switchers vs non-switchers* 13.2 vs 1.52 per 1000 person-years	NR	NR	79% of patients who discontinued	NR	NR

AEs: adverse events, **AS**: axial spondylarthritis, **CD**: Crohn's disease, **CRI**: chronic renal insufficiency, **ESA**: Erythropoiesis-stimulating agent; **FCD**: fistulizing Crohn's disease, **GHD**: growth hormone deficiency, **IBD**: inflammatory bowel disease, **IBDU**: inflammatory bowel disease unclassified, **JIA**: juvenile idiopathic arthritis, **LCD**: luminal Crohn's disease, **LOR**: loss of response, **NR**: not reported, **NS**: not specified, **PsA**: psoriatic arthritis, **PWS**: Prader–Willi Syndrome**, RA**: rheumatoid arthritis, **SpA**: spondylarthritis, **TS**: Turner Syndrome, **TTD**: time to discontinuation, **UC**: ulcerative collitis.