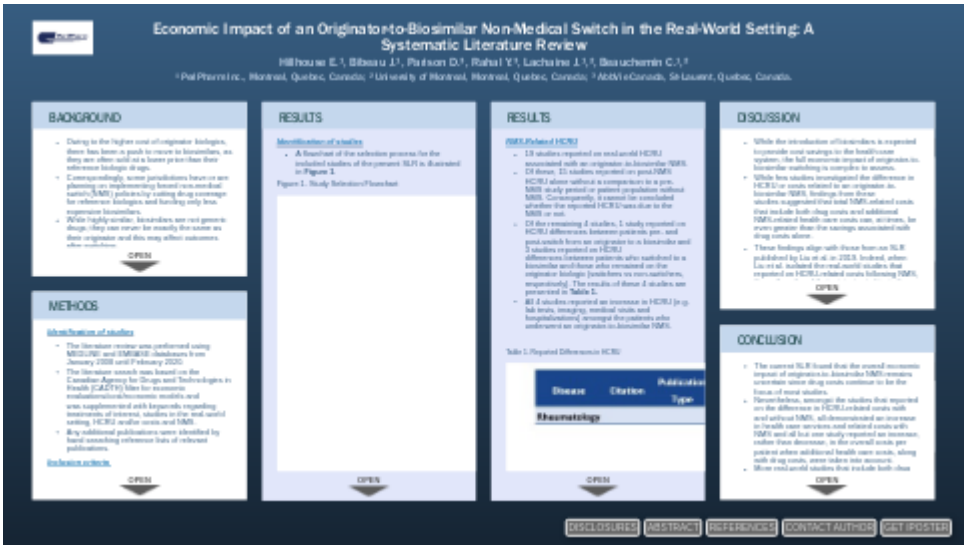
Economic Impact of an Originator-to-Biosimilar Non-Medical Switch in the Real-World Setting: A Systematic Literature Review



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BACKGROUND

- Owing to the higher cost of originator biologics, there has been a push to move to biosimilars, as they are often sold at a lower price than their reference biologic drugs.
- Correspondingly, some jurisdictions have or are planning on implementing forced non-medical switch (NMS) policies by cutting drug coverage for reference biologics and funding only less expensive biosimilars.
- While highly similar, biosimilars are not generic drugs; they can never be exactly the same as their originator and this may affect outcomes after switching.
- As a result, costs other than those associated with drug acquisition need to be taken into account when estimating the economic impact of originator-to-biosimilar NMS.
- The objective of this systematic literature review (SLR) is to identify studies evaluating health care resource utilization (HCRU) and costs associated with originator-to-biosimilar NMS in the real-world setting.

METHODS

Identification of studies

- The literature review was performed using MEDLINE and EMBASE databases from January 2008 until February 2020.
- The literature search was based on the Canadian Agency for Drugs and Technologies in Health (CADTH) filter for economic evaluations/cost/economic models and was supplemented with keywords regarding treatments of interest, studies in the real-world setting, HCRU and/or costs and NMS.
- Any additional publications were identified by hand searching reference lists of relevant publications.

Inclusion criteria

- The SLR was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Hutton, 2015).
- The review question was established using the **PICOS** framework:
  - **P**opulation: patients who underwent an originator-to-biosimilar switch for non-medical, or presumably non-medical, reasons, with no restrictions pertaining to patient age, gender, or disease area.
  - **I**nterventions: any biosimilar following treatment with the reference biologic.
  - **C**omparator: No restriction.
  - **O**utcomes of interest: HCRU and costs associated with originator-to-biosimilar NMS. Studies presenting post-switch discontinuation rate, as well as safety or efficacy outcomes were also included as they were assumed to support evidence of increased HCRU.
  - **S**tudy Design: interviews, surveys, cohort studies, database studies and patient-reported outcomes (PRO) studies in the real-world setting.

Study selection

- Two reviewers independently screened titles and abstracts for relevance.
- Any citation/abstract deemed relevant was obtained in full-text form.
- Full-text articles and conference abstracts were reviewed independently using a predefined eligibility form.
- Any publication failing to meet the eligibility criteria was excluded.
- Discrepancies in study selection were resolved by consensus or with the help of a third reviewer.

Data extraction and study quality assessment

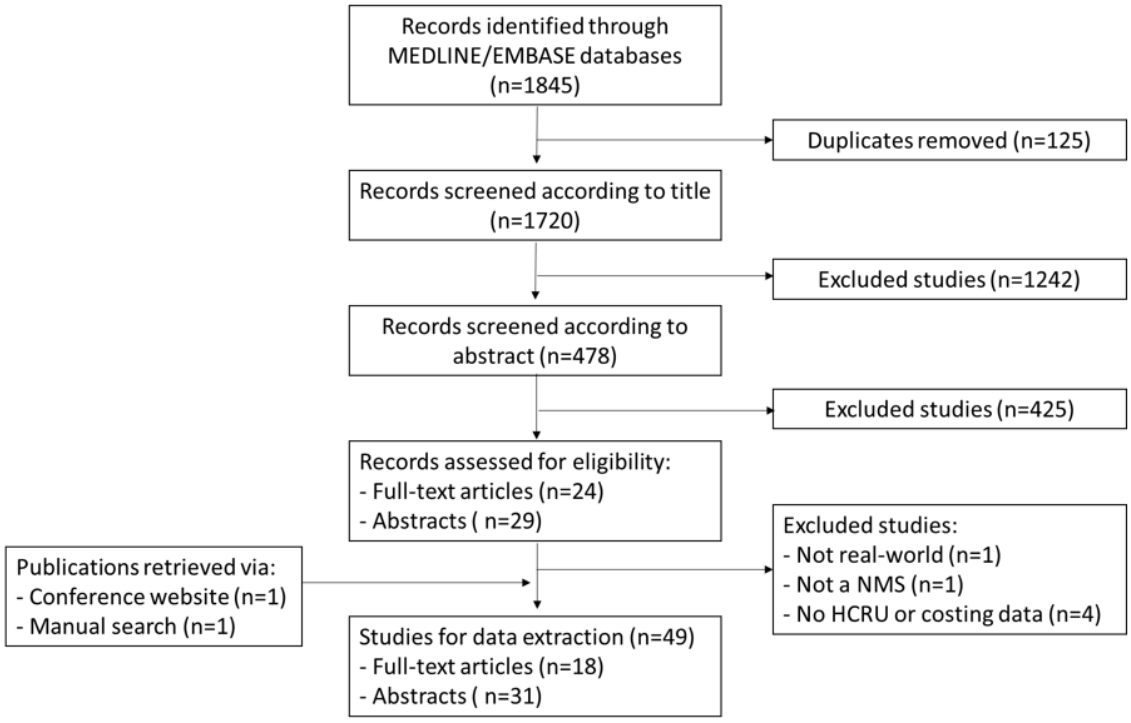
- Using a predefined extraction form, one reviewer extracted information from each eligible study, which was then validated by a second reviewer to ensure accuracy.
- The risk of bias of selected studies was assessed using the Cochrane Collaboration Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) (Sterne, 2016).

RESULTS

Identification of studies

- A flowchart of the selection process for the included studies of the present SLR is illustrated in **Figure 1**.

Figure 1. Study Selection Flowchart



Study Characteristics

- Of the 49 included studies, 18 were full-text articles while 31 were conference abstracts.
- The majority of studies were center-based cohort studies (n=41) and were conducted in Europe (n=43).
- The disease areas investigated were primarily in rheumatology (n=19) and gastroentorology (n=21), while 1 study each was performed in dermatology, growth development, hepatology and oncology. 5 studies focused on multiple disease areas or did not specify the disease area.
- Infliximab was the sole biosimilar drug investigated in gastroenterology, while studies in rheumatology included infliximab (n=5), rituximab (n=1) and etanercept (n=13).
- Additional biosimilar drugs included somatropin, erythropoiesis-stimulating agent and filgrastim.

Study Quality Assessment

- As both patients and physicians are not blinded to treatment allocation in a clinical setting, the risk of bias was evaluated as moderate for the domain pertaining to the measurement of outcomes for all except one study.
- As the overall risk of bias is judged to be moderate when the risk of bias is evaluated as moderate for at least one domain, the overall risk of bias for each of the 18 full-text publications was rated as moderate for 14 citations, serious for 3 citations, and non-applicable for 1 citation.

RESULTS

NMS-Related HCRU

- 19 studies reported on real-world HCRU associated with an originator-to-biosimilar NMS.
- Of these, 15 studies reported on post-NMS HCRU alone without a comparison to a pre-NMS study period or patient population without NMS. Consequently, it cannot be concluded whether the reported HCRU was due to the NMS or not.
- Of the remaining 4 studies, 1 study reported on HCRU differences between patients pre- and post-switch from an originator to a biosimilar and 3 studies reported on HCRU differences between patients who switched to a biosimilar and those who remained on the originator biologic (switchers vs non-switchers, respectively). The results of these 4 studies are presented in **Table 1.**
- All 4 studies reported an increase in HCRU (e.g. lab tests, imaging, medical visits and hospitalizations) amongst the patients who underwent an originator-to-biosimilar NMS.

Table 1. Reported Differences in HCRU

Disease	Citation	Publication Type	Drug	Cohort Size	Data Source	Reported HCRU
Rheumatology						
RA	Tarallo 2019	Journal Article	Etanercept	1,259	Survey	**In comparison to non-switchers, 0-3 and 4-6 months post-switch** Blood tests: +0.38; +0.40 X-rays: +0.18; +0.22 Ultrasounds: +0.26; +0.29 ER visits: +0.46; +0.54 Hospitalization: +0.47; +0.52 *Visit with*: Rheumatologist: +0.65; +0.70 Rheumatology nurse: +0.64; +0.51 Physiotherapist: +0.53; +0.57 Occupational therapist: +0.33; +0.37 Podiatrist: +0.18; +0.33
RA, PsA, AS	Gibofsky 2019	Abstract	Infliximab	119	Medical records	**Non-switchers vs switchers** Frequency of outpatient visit: 76.4% vs 89.1% Number of outpatient visits: 1.8 vs 2.0
RA, PsA, AS	Glintborg 2018	Journal Article	Infliximab	769	Registry	**6 months pre- vs 6 months post-switch** *Mean days with services per patient* 5.4 vs 5.8 (p<0.01) *Mean rate of service per patient* Ultrasound: shoulder, elbow, hand: 0.09;0.07 hip, knee, foot: 0.08;0.10 Phone consultation: 1.03;1.17 (p=0.03) Medical visit: 3.86; 3.95. Outpatient visit: 1.44; 1.45 Nurse activity: 0.61; 0.58 Treatment consultation: 0.09; 0.07 Patient guidance: 0.35; 0.49 (p<0.01) Clinical investigations: 0.31; 0.47 (p<0.01) Clinical control: 2.08; 2.26 (p<0.01) Observation: 0.17; 0.22 (p<0.01) BP measurement: 0.61; 0.60
Oncology						
Solid tumors, hematological malignancy	Al Rabayah 2018	Abstract	Filgrastim	37	NR	**Switchers vs non-switchers** Frequency of hospitalization: 15.6% vs 12.6% Hospital duration: 7 days vs 6.4 days

AS: axial spondylarthritis, **BP**: blood pressure, **ER**: emergency room, **HCRU**: health care resource utilization, **NR**: not reported, **PsA**: psoriatic arthritis, **RA**: rheumatoid arthritis.

NMS-Related Costs

- 33 studies reported on HCRU- and drug-related costs associated with NMS.
- Out of 16 studies reporting on the drug-related costs associated with NMS, 15 studies (94%) reported significant savings following NMS based on drug costs alone.
- However, 4 studies reported specifically on the difference in costs between patients pre- and post-switch or between switchers and non-switchers. The results of these 4 studies are presented in **Table 2**.
- These studies found that, when both HCRU-related costs and drug costs are considered, the overall savings associated with originator-to-biosimilar NMS were reduced and, at times, resulted in an increase, rather than decrease, in annual costs per patient.

Table 2. Reported Differences in Cost

Disease	Citation	Publication Type	Drug	Cohort Size	Data Source	Drug-Related Costs and Savings (2020 $C)	Overall Costs and Savings (2020 $C)
Gastroenterology							
CD, UC, IBDU	Huoponen 2020	Journal Article	Infliximab	54	Hospital data	**Pre- vs post-switch annual drug costs** CD: €11,784 vs €4,163 (18,691$C vs 6,603$C) UC/IBDU: €8,978 vs €3,568 (14,240$ vs (5,659$C)	**Pre- vs post-switch Total annual secondary health care costs** CD: €3,202 vs €3,898 (5,079$C vs 6,183 $C) UC/IBDU: €2,648 vs €2,763 (4,200$C vs 4,382$C)
Rheumatology							
RA	Peral 2018	Abstract	Etanercept	NR	Survey and Registry	NR	**Switcher vs non-switcher annual costs** €11,478.90 (17,801$C) vs €10,251.14 (15,897$C)
RA	Tarallo 2019	Journal Article	Etanercept	1,259	Survey	Annual drug costs per patient: SB4: £8,528 (14,836$C) GP2015: £8,365 (14,552$C) Originator: £9,295 (16,170$C)	**Switcher vs non-switcher annual HCRU costs per patient**: Originator to GP2015: +£1,120 (1,948$C) Originator to SB4: +£1,283 (2,232$C)
NS (RA, AS most common)	Phillips 2017	Abstract	Infliximab	136	National database	Pharmacy costs: TL 1,473 vs TL 1,329 (590$C vs 533$C)	**Switchers vs non-switchers** Outpatient costs: TL 269 vs TL 181 (108 $C vs 73 $C) Inpatient costs: TL 64 vs TL 29 (26$C vs 12 $C) Total health care costs: TL 2,009 vs TL 1,640 (805$C vs 657$C)

AS: axial spondylarthritis, **CD**: Crohn's disease, **HCRU**: health care resource utilization; **IBD**: inflammatory bowel disease, **IBDU**: inflammatory bowel disease unclassified, **NR**: not reported, **NS**: not specified, **RA**: rheumatoid arthritis, **TL**: Turkish lira, **UC**: ulcerative colitis; **$C**: 2020 Canadian dollars.

DISCUSSION

- While the introduction of biosimilars is expected to provide cost savings to the health care system, the full economic impact of originator-to-biosimilar switching is complex to assess.
- While few studies investigated the difference in HCRU or costs related to an originator-to-biosimilar NMS, findings from these studies suggested that total NMS-related costs that include both drug costs and additional NMS-related health care costs can, at times, be even greater than the savings associated with drug costs alone.
- These findings align with those from an SLR published by Liu et al. in 2019. Indeed, when Liu et al. isolated the real-world studies that reported on HCRU-related costs following NMS, the authors found that originator-to-biosimilar NMS was associated with increased HCRU and associated costs.
- Additional factors not assessed here but that can have an impact on the total cost associated with originator-to-biosimilar NMS include the costs associated with: NMS programs; treatment discontinuation and consequential switch back to the originator or to another molecule; as well as the difference in the costs associated with adverse events pre- vs. post-switch.
- More real-world studies that include both drug costs and additional NMS-related health care costs are needed to better evaluate the true economic impact of NMS.

CONCLUSION

- The current SLR found that the overall economic impact of originator-to-biosimilar NMS remains uncertain since drug costs continue to be the focus of most studies.
- Nevertheless, amongst the studies that reported on the difference in HCRU-related costs with and without NMS, all demonstrated an increase in health care services and related costs with NMS and all but one study reported an increase, rather than decrease, in the overall costs per patient when additional health care costs, along with drug costs, were taken into account.
- More real-world studies that include both drug costs and additional NMS-related health care costs are needed to better evaluate the full economic impact of an originator-to-biosimilar NMS.

DISCLOSURES

AbbVie Disclosure

This study was funded by AbbVie, Corp. AbbVie sponsored the study, contributed to the design and to the review, and approval of the final version. No honoraria or payments were made for authorship.

Author Disclosure

Jean Lachaine and Catherine Beauchemin are partners at PeriPharm, a company that has served as a consultant to AbbVie and has received funding from AbbVie. Jean Lachaine, Catherine Beauchemin, Erin Hillhouse, and Joëlle Bibeau, are employees of PeriPharm. Yasmine Rahal and Diana Parison are AbbVie employees and have stock/stock options.

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ABSTRACT

OBJECTIVES: To save costs to the health care system, forced non-medical switch (NMS) policies that cut drug coverage for originator biologics and fund only less expensive biosimilars are being implemented. However, costs related to the impact of NMS on health care resource utilization (HCRU) must also be considered. This study aims to summarize the evidence on the true economic impact of an originator-to-biosimilar NMS.

METHODS: A systematic literature review (SLR) was conducted. Publications reporting on HCRU or costs associated with originator-to-biosimilar NMS in the real-world setting were searched in MEDLINE and EMBASE from January 2008 to February 2020. In addition to hand searching the reference lists of relevant publications and SLRs, key conference websites, PubMed and various government sites were also searched for the two years preceding the search (2018-2020).

RESULTS: A total of 1,845 citations were identified, of which 49 were retained for data extraction. Most studies reporting on the HCRU associated with NMS reported on post-NMS HCRU alone without a comparison pre-NMS. However, all 4 studies that described a difference in HCRU reported an increase in resources, including laboratory testing, imaging, medical visits, and hospitalizations, amongst patients who underwent an originator-to-biosimilar NMS. Most studies reporting on the costs associated with NMS reported a significant savings following NMS based on drug costs alone. However, all 4 studies specifically reporting on the difference of costs found that, when both HCRU-related costs and drug costs are considered, the overall savings associated with originator-to-biosimilar NMS were greatly reduced and, at times, resulted in an increase, rather than decrease, in annual costs per patient.

CONCLUSION: Amongst the studies that reported on the difference in HCRU, all showed an increase in HCRU and related costs associated with NMS. Nevertheless, more real-world studies that include NMS-related healthcare costs in addition to drug costs are needed.

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