ABOUT THE AUTHOR

Lauren Lam, MD, BScH, FRCPC

Dr. Lam is a Canadian board-certified dermatologist who completed her medical school training at the University of Calgary and her dermatology residency at the University of Alberta. Her particular passions in dermatology are acne & hidradenitis suppurativa deroofings. In addition to her regular practice, she volunteers on overseas medical trips. Her passion for providing care for under-served populations has taken her to Nunavut and rural Fiji.

Affiliations: Beacon Dermatology, Calgary, Alberta

Similarities and Differences in Biosimilars: A Literature Review and Summary

Lauren Lam, MD, BScH, FRCPC

Introduction

The use of biosimilars is becoming standard practice for Canadian dermatologists. However, most of these clinicians most likely graduated prior to their adoption of biosimilars and, as a result, are likely to have minimal to no experience with biosimilars. Considering this limited prior experience, it can be challenging to gain a full understanding of how one biosimilar differentiates from another. The objective of this paper is to educate clinicians so that they are well-informed on how to select the appropriate biosimilar for the patient at hand. This literature review and summary will review the current biosimilar landscape in Canada; review nuances between adalimumab biosimilars; and review available clinical experience data of adalimumab switch to biosimilar and vice versa for the treatment of hidradenitis suppurativa (HS). It also aims to highlight methodologies for improving biosimilar patient compliance when switching to alternative agents.

Literature Review

With the objective of providing additional context for the decision-making process in selecting an adalimumab biosimilar, a literature review was conducted with a focus on use in HS, as this is the most likely condition for which Canadian dermatologists would initiate a bio-naïve patient on a biosimilar. Biosimilars for ustekinumab are now on the market in Canada; however, for the purposes of this article the focus was limited to adalimumab.

Dermatologists may not be aware that in clinical trials it is only necessary to demonstrate non-inferiority and safety in one licensed indication of the originator product (most often rheumatoid arthritis). This is noteworthy, as the presumption that a biosimilar works with equal statistical significance in other disease states has not actually been substantiated with clinical trial evidence. No biosimilar molecules have randomized clinical trials for HS. Therefore, unfortunately, there is no clinical trial data to review, nor comparator studies between biosimilars. The data available for biosimilars in the treatment of HS in general is sparse, thus two relevant publications from Europe were reviewed in detail.

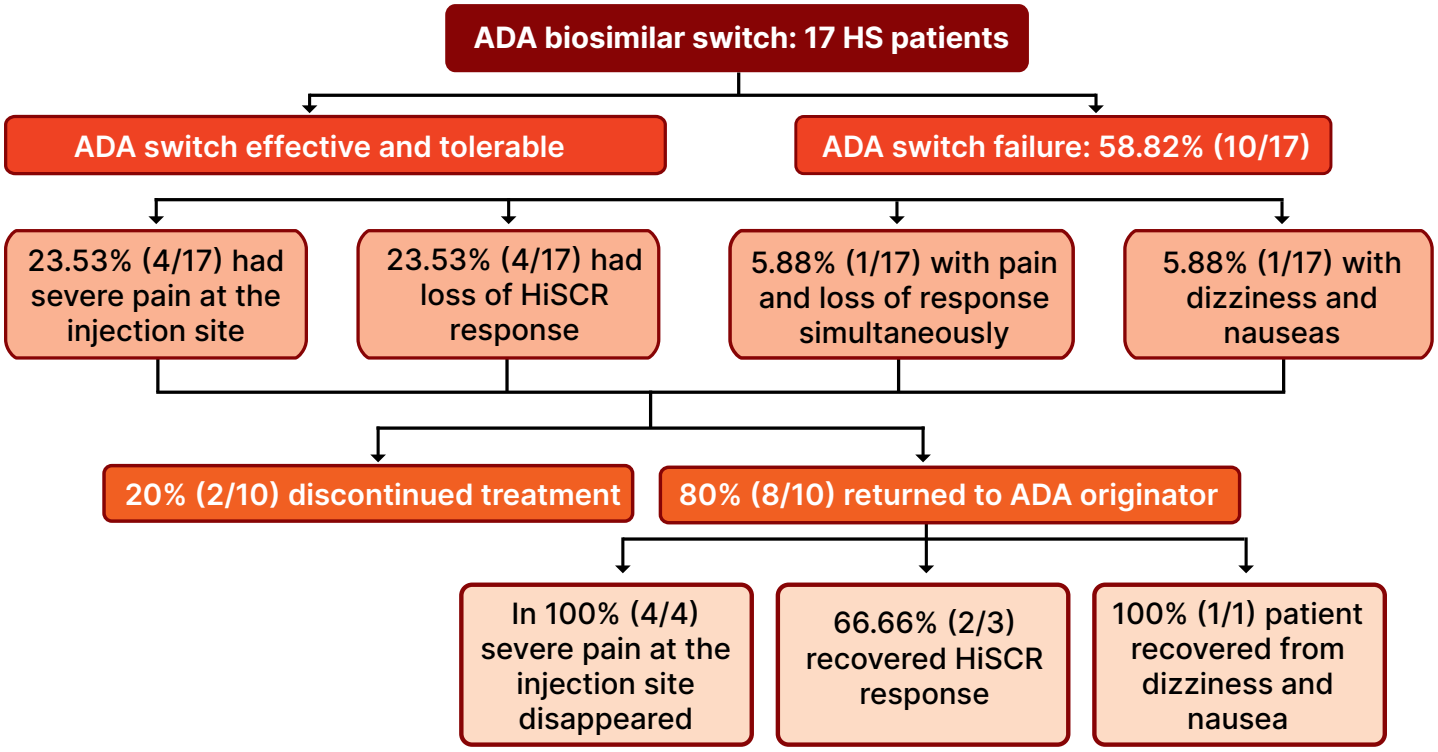

Figure 1. Patients switching flow chart; *adapted from Montero-Vilchez, T., et al, 2022.*

Abbreviations: ADA: Adalimumab, **HiSCR:** Hidradenitis Suppurativa Clinical Response, **HS:** Hidradenitis Suppurativa

Nuances in Biosimilars

Qualities of Biosimilars

It is important to highlight that biosimilars are similar to already licensed biotherapeutic products in quality, safety and efficacy. Heterogeneity of the production process and variations in manufacturing can potentially result in similar efficacy, non-inferiority, or even improved efficacy than that of the originator drug. By definition, biosimilars are required to perform similarly in quality, safety, and efficacy to an already licensed biotherapeutic product.

Biosimilars are Disease Specific

The literature contains clinical trial data substantiating the efficacy and tolerability of originator and biosimilar agents in the treatment of psoriasis. However, these results are not transferable between different biosimilars or diseases, therefore extrapolations regarding efficacy between biosimilar agents should be avoided. In addition, biosimilars may not perform equally in all diseases[1] and positive outcomes are not transferrable between disease states.

Scarcity of Switching data

Regulatory agencies typically do not require switching studies to approve a biosimilar; therefore, extensive clinical trial data on the effects of non-medical switching and switching between biosimilar agents is not available. However, two real-world studies examining biosimilar switches (**Figure 1**) provide some insight into clinical experiences, response rates and reasons for discontinuation. Clinical trial data shows that discontinuation rates post non-medical switching vary from 6.1% to 55.9%.

A large proportion of patients initiated on a biosimilar will likely be transitioned from the originator molecule for cost reasons (i.e., a non-medical switch).

Characteristics of Biosimilars

Differences in formulation, packaging and excipients are the most tangible variances between biosimilar agents. In selecting a biosimilar, it is important to consider its formulation; packaging (latex vs latex-free), and excipients (citrate vs citrate-free) (**Table 1**). In particular, excipients associated with injection site reaction can contribute to higher levels of discontinuation in patients undergoing a non-medical switch. As excipients, citrates and phosphates are well-known causes of injection site reaction. Other aspects of formulations that can cause increased injection site pain include non-physiologic pH, higher viscosity, and higher volume.[2]

	Amgevita	Abrilada	Hulio	Hadlima	Hyrimoz	Idacio	Simlandi	Yuflyma
Citrate Free	X							
Latex & Citrate Free		X	X				X	X
Latex Free				X				
Contains Citrate					X	X		

Table 1. Current Canadian landscape for adalimumab biosimilar agents; *courtesy of Lauren Lam, MD, BScH, FRCPC.*

Literature Review

Switching from Adalimumab Originator to a Biosimilar: Clinical Experience in Patients with HS

Study #1

The first study reviewed was a single-centre, retrospective cohort study conducted in Spain in 2022.[1] The study focused on clinical experience switching from the adalimumab originator molecule to a biosimilar and, in some cases, switching back again to the originator molecule.

The study comprised 17 HS patients (age 18+) on originator adalimumab who were switched to a biosimilar for non-medical reasons. The patients had all achieved HiSCR after >12 weeks on the originator molecule. No repeat induction dose was administered upon switching to the biosimilar agent. The population was quite reflective of a typical HS practice, with younger patients (mean age 31) who had tried multiple treatments prior to adalimumab, and the majority of patients were Hurley Stage II (23%) or III (70%).

Study #1 Design

- Evaluated q12w post-switch
- Switch-back offered if efficacy or tolerability issues
- Continued evaluation q12w post-switch back
- Only 1 female patient received additional treatment:
  - Metformin 850 mg OD
  - Spironolactone 50 mg OD

Patients were offered the option of switching back to the originator molecule if issues with efficacy or tolerability arose. If a switchback was made, the patient continued to be monitored q12w after this second switch.

All but one patient was receiving adalimumab monotherapy. The single patient receiving combination therapy was also on metformin 850 mg QD, and spironolactone 50 mg QD.

Study #1 Results

- The majority of patients (10/17) experienced a switch failure.
- Of those 10 patients, an equal proportion of patients (4/10) experienced either severe pain at the injection site or loss of HS clinical response (HiSCR).
- One patient experienced both. Unfortunately, 2 of those who had a switch failure completely discontinued biologic treatment altogether.
- Of the remaining patients who returned to the originator molecule, injection site pain resolved in each case.
- Two of three patients recovered HiSCR response.

Study #2

Seven Years-Experience of Adalimumab Therapy for HS in a Real-life Dermatologic Setting

The second study was a single-centre, retrospective review conducted in Italy in 2020.[3] Its focus was clinical experience switching from the adalimumab originator to a biosimilar agent, in addition to initiating bio-naïve patients on a biosimilar agent.

The study comprised 10 patients. Of these, 4 patients were switched for non-medical reasons, while 6 bio-naïve patients were initiated on a biosimilar agent. Two of the four patients switched from the adalimumab originator to a biosimilar agent were switched back to the originator agent due to injection site reaction.

Variables	Total Sample (*n* = 17)	Switch Effective and Tolerable (*n* = 7)	Switch Failure (*n* = 10)	*P*
Age (years)	31 (19–51)	43 (17–50)	26.5 (19–53.5)	0.675
Sex				
Male	12 (70.59%)	5 (71.43%)	7 (70%)	1
Female	5 (29.41%)	2 (28.57%)	3 (30%)	
Smoking habit (yes)	8 (47.06%)	2 (28.57%)	6 (60%)	0.335
Age of onset (years)	15 (15–22.5)	16 (15–33)	15 (14.25–18)	0.085
Family history (yes)	8 (47.06%)	4 (57.14%)	4 (40%)	0.637
Hurley stage				
I	1 (5.88%)	1 (14.29%)	0	0.394
II	4 (23.53%)	1 (14.29%)	3 (30%)	
III	12 (70.59%)	5 (71.43%)	7 (70%)	
AN count	2 (0.5–6.5)	2 (0–9)	3 (0.75–5.75)	0.588
Draining tunnels count	3 (2–4.5)	3 (1–9)	2.5 (2–3.25)	0.129
Number of affected areas	4(3–4)	4(2–4)	4 (3.75–4.25)	0.473
Number of previous treatments	4 (2.5–4.5)	4(3–5)	4 (2–4.25)	0.429
Follow-up time before switching (weeks)	48 (28–80)	32 (20–80)	48 (43–87)	0.167

Table 2. Sociodemographic and clinical characteristics of the patients; *adapted from Odirici, G. et al, 2023.*

Abbreviations: AN: total abscess and inflammatory nodule count

Data are expressed as relative (absolute) frequencies and median (interquartile range). Student's *t*-test for independent samples or the Wilcoxon test were used to compare continuous variables, depending on the normality of the variable. The chi-square test or Fisher's exact test, as appropriate, were applied to compare categorical data. A two-tailed $p < 0.05$ was considered statistically significant for all tests.

Study #2 Design

- Single-centre, retrospective review in Italy in 2020
- Clinical experience switching from adalimumab originator to biosimilar and initiating bionaive patients on biosimilar

Study #2 Results

- 4 patients switched from the adalimumab originator to a biosimilar agent for non-medical reasons
- 6 patients were initiated on a biosimilar
- 2 patients who switched to a biosimilar switched back to originator product due to *injection site reaction*

No patient characteristics were statistically significant to predict the likelihood of biosimilar failure or success (**Table 2**).

Study Summaries

Both studies highlight two important considerations when switching patients to a biosimilar. First, injection site pain is the most likely cause of discontinuation of biosimilar treatment, sometimes leading to discontinuation of all biologic treatment as a result. This would ultimately be to the patient's detriment, as without systemic treatment, further progression of the disease will occur. Therefore, choosing an agent with the fewest excipients that may cause pain could potentially help avoid this.

Second, ensuring that injection site pain protocols have been adhered to is critical in reducing the likelihood of intolerable injection site pain reaction (**Box 1**).

Conclusion

Biosimilars are exactly that – similar, but not equivalent to the originator, and not equivalent to one another. Biosimilar agents have safety and non-inferiority data, but not necessarily for every disease, unlike their originator molecule.

Two key considerations when comparing biosimilar agents are their excipients and packaging. As the most common cause for discontinuation of biosimilar agents is injection site pain, consider a biosimilar agent's excipients and, where possible, select the agent with the lowest excipient load to help reduce the likelihood of injection site pain.

Unfortunately, to date there are no clinical studies demonstrating statistically significant patient characteristics that help predict a higher likelihood of achieving HiSCR with biosimilars.

As Canadian practitioners continue to gain experience with biosimilar agents, perhaps further studies could explore these important clinical concerns.

- Apply a topical anesthetic or ice 30 minutes prior to injection
- Apply a topical steroid 2–3 days to anticipated site prior to injection
- Inject at 45 or 90 degrees
- Inject slowly
- Use an auto-injector, which can reduce patient-related injection techniques that are inadvertently causing increased pain
- Allow medication to warm up to room temperature for 30–45 minutes prior to injection
- Inject abdomen rather than thigh
- Alternate injection sites
- Advise patients to take antihistamine or NSAID/acetaminophen 1 hour prior to injection

Box 1. Injection Protocols and Patient Counselling; *courtesy of Lauren Lam, Md, BScH, FRCPC.*

Key Clinical Pearls
Biosimilar but not equivalent
• Biosimilars have safety and non-inferiority data, but *not necessarily for every disease indication* as with the originator
Not all biosimilars are the same
• Each biosimilar contains its own unique excipients and packaging. *Consider this during switching, if injection site pain becomes a concern*
Pain equates to reduced patient compliance
• Pain is the primary cause for patients discontinuing a biosimilar
Lack of predictability
• No particular factors have been established to predict achieving HiSCR with biosimilar use

Correspondence

Lauren Lam, MD, BScH, FRCPC
Email: drlaurenlam@gmail.com

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