A brief overview of biosimilars and factors limiting their uptake

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OVER THE LAST FEW DECADES, AN INNOVATIVE class of medications known as biologics has made its way onto the Canadian market and revolutionized the treatment of many diseases, including inflammatory conditions and certain types of cancer. Unlike small-molecule medications that are chemically synthesized compounds, biologics are large, complex proteins that are grown from cells and living organisms.¹ While effective, biologic medications are significantly more expensive than their small-molecule counterparts. As a result, Canadian government spending on biologics has steadily increased from 14.8% of total drug spending in 2011 to 22.1% in 2016, despite relatively low use in the population.²

In an effort to lower government spending on biologics and free up resources for other innovative treatments, several countries have created an alternate approval pathway for biologic drugs that are highly similar to biologics already on the market.^{1,3-5} These highly similar drugs are known as biosimilars.

In Canada, the biosimilar approval process requires companies to demonstrate that their product has similar efficacy, safety and immunogenicity when compared to the innovator biologic (the “bio-originator”) through head-to-head clinical trials.⁴ Most of these studies are performed as equivalency trials that use well-established surrogate markers as endpoints. These trials aim to prove that there is no clinically significant difference between the 2 drugs, thus showing “clinical equivalency.”⁶

To expedite biosimilar approval, Health Canada may approve a biosimilar for some or all of the reference biologic indications while only requiring trials for one of the requested indications.⁴ This process is termed *extrapolation of indication*. With this process, clinical equivalency data are paired with data showing

highly similar physicochemical properties, pharmacokinetics, pharmacodynamics and quality between the biosimilar and bio-originator. If the evidence sufficiently supports no significant difference in how the biosimilar acts in the human body compared to the bio-originator, the biosimilar can become indicated for conditions it was not studied in. The extrapolated indications must have similar pathology and use the same mechanism of action of the reference biologic as the studied indication.⁴

These reduced approval requirements allow biosimilars to enter the market at a lower price than their respective bio-originator, with most Canadian biosimilars offering a 12% to 23% discount.^{7,8} While only a few biosimilars have been approved in Canada to date, several more are expected to hit the market over the next few years as patents on bio-originators expire.⁷ Unsurprisingly, this has prompted insurers to reevaluate their biosimilar policies. In May 2019, the government of British Columbia was the first to announce that they would be terminating their coverage of select bio-originators in favour of their biosimilar alternatives.^{9,10} Whether other insurers will emulate this decision has yet to be determined.

Despite the economic benefit biosimilars offer, patient uptake and acceptance of these medications have been lower than expected. As several studies have identified, the perception and knowledge that health care providers have about biosimilars can influence biosimilar uptake.^{5,11-13} In 1 Belgian survey conducted in 2016, about 60% of rheumatologists stated that they believe there are differences in quality,

efficacy and safety between biosimilars and bio-origimators and that they would only prescribe a biosimilar in a biologic-naïve patient. Many of these concerns originate from a lack of confidence in the approval process of biosimilars.⁵ Another survey showed that about two-thirds of pharmacists in France felt that they did not know enough about biosimilars to properly counsel a patient.¹² Advice from health care providers can have a direct effect on patient uptake, both because physicians must be willing to prescribe biosimilars and because health care provider perceptions affect patient perceptions.⁵ While these studies were not conducted in Canada, it is reasonable to assume they are applicable here.

Additionally, the uncertainty felt by health care professionals can be transferred to patients when making recommendations or during counselling, putting patients at risk of the nocebo effect.^{14,15} The nocebo effect is when a patient takes a medication and gets a negative outcome or side effect that is otherwise unexplained. It is often caused by negative connotations or expectations about the medication.¹⁶ An example of the nocebo effect was observed during open-label studies of biosimilar infliximab CT-P13. The biosimilar arm had a statistically significant increase in discontinuation rates for any reason, for adverse drug events and for a lack of efficacy, even though previous double-blind studies investigating the switch between Remicade (the bio-origimator) and this biosimilar showed no difference in these outcomes.¹⁷⁻¹⁹

In order to improve the uptake of biosimilars, these factors need to be addressed by providing education for both health care professionals and patients. Preliminary data suggest that the nocebo effect can be prevented by having confident health care professionals thoroughly educate patients on what a biosimilar is and on the requirements for biosimilar approval.^{14,15,20,21} Thus, health care provider education should target pharmacists as well as specialists who

prescribe biologics and should cover the biosimilar approval process in detail, along with communication strategies to effectively educate patients on biosimilars. Continuing education courses would be a good way to reach these populations and would help assure specialists that there are no clinical differences between biosimilars and their bio-origimators. These topics should also be covered in medical and pharmacy schools to ensure that new professionals are able to educate patients on biosimilars.

Another way to educate patients is to provide patient advocacy groups with reliable information and handouts about biosimilars that they can share with the public. Doing so will not only ensure that the information provided by these groups is consistent with the information provided by health care professionals but might also empower patients to initiate conversations about biosimilars with their physicians.

To summarize, biologics are innovative medications that have revolutionized the way we treat many disease states. However, they exert a significant amount of stress on the insurers' drug costs. To reduce biologic spending, Health Canada has allowed biosimilars to enter the market, creating a more affordable alternative. As a result, British Columbia has stopped covering select bio-origimators in favour of their biosimilar counterparts. Other insurers may decide to do the same. Despite biosimilars being clinically equivalent to innovator biologics, their uptake is being impeded by the perceptions and inadequate knowledge of health care providers. To overcome these barriers, health care providers must be thoroughly educated on the requirements for biosimilar approval and how to communicate that information to patients. By doing so, the uptake of biosimilars can be increased, leading to a reduction in health care costs and improved health care accessibility for patients requiring biologic therapy. ■

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