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TRUXIMA™ (rituximab for injection) is indicated for the treatment of patients with previously untreated Stage III/IV follicular, CD20 positive, B-cell non-Hodgkin’s lymphoma in combination with CVP (cyclophosphamide, vincristine and prednisolone) chemotherapy.

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TRUXIMA™ (rituximab for injection) is indicated for the treatment of patients with previously untreated or previously treated B-cell chronic lymphocytic leukemia (B-CLL), Binet Stage B or C, in combination with fludarabine and cyclophosphamide.

TRUXIMA™: A proud offering from Teva Canada Innovation.

TRUXIMA™ has been available in the EU since 2017.3**

For more information:
Please consult the Product Monograph at https://pdf.hres.ca/dpd_pm/00050545.PDF for important information relating to contraindications, warnings, precautions, adverse reactions, drug interactions, dosing, administration and conditions of clinical use, which have not been discussed in this piece. The Product Monograph is also available by calling Teva Canada Innovation at 1-833-662-5644.

Creative representation of a molecule.

* Comparative clinical significance is unknown.
† Please refer to the TRUXIMA™ Product Monograph to see the complete list of NHL indications.
‡ Indications have been granted on the basis of similarity between TRUXIMA™ and the reference biologic drug Rituxan®.

EU: European Union.


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Biosimilars in oncology in Canada and the role of nurses

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FOREWORD

The Editorial Board of the Canadian Oncology Nursing Journal is very pleased to have this supplement produced under the auspices of our journal. Not only does it mark the first such publication for us, but it reflects a very exciting time in cancer care.

The developments in science and technology have resulted in significant changes in cancer treatment over the past decade. We are seeing a growing cadre of cancer survivors who are living after their primary cancer treatment without clinical evidence of disease or with controlled disease. And the expectation is that this will continue and increase, as new disease screening and treatment techniques are introduced. For many individuals, cancer has become a chronic illness as they manage long-term treatments and cope with the late and long-term effects.

However, cancer is still seen as a dreaded disease. Many individuals will say life is never the same again following the diagnosis and hearing the words, “I’m sorry, but you have cancer”. Treatment is often characterized as dealing with a myriad of side effects and filled with uncertainty. More evidence is emerging about the financial impact of this disease and the burden of costs for patients and for the healthcare system.

The introduction of biosimilars into the cancer care arena heralds an exciting time where there could be more affordable and effective therapy for cancer patients. The financial savings for individuals, as well as the healthcare system are anticipated to be significant and, in turn, open the door to investment in future innovative therapies and biologics for a wider spectrum of patients.

As biosimilars appear within the clinical setting, oncology nurses will be on the frontline in terms of handling these medications and interacting with patients regarding them. Clearly, there will be administration procedures and policies that will have to be crafted and learned in every cancer care setting, but also there will be important roles in terms of educating patients and assessing, reporting, and managing any adverse effects. These roles demand that oncology nurses have the relevant knowledge base to engage in appropriate conversations with patients who are considering making a switch to a biosimilar, or as they begin taking a biosimilar and manage with it over time.

We hope this supplement will provide an in-depth understanding about how biosimilars are developed and the rigour with which they are approved. In turn, hopefully, this information will help nurses be confident about biosimilars during their conversations with patients and family members. Ultimately, we anticipate the information will facilitate patient education and caring for individuals who are receiving biosimilars.

Margaret I. Fitch, RN, PhD
Editor in Chief, CONJ
Biosimilars in oncology in Canada and the role of nurses

Sandeep Sehdev, MD, Karyn Perry, RN, BSN, MBA, CON(c), Kathy Gesy, BSP, MSc, FCAphO

ABSTRACT

Canadian nurses are familiar with biosimilars in general, but may have knowledge gaps in their specific understanding, resulting in a significant unmet need for education. To assist Canadian nurses in gaining a greater understanding of biosimilars within the oncology treatment landscape and to alleviate certain concerns regarding biosimilar agents, the objectives of this Supplement are to discuss:

- biologic drugs in general with an overview of their production
- biosimilarity and biosimilars relative to reference biologic drugs
- mechanisms of action: biosimilars versus reference biologic drugs
- steps to biosimilar development
- extrapolation of indications for biosimilars—“totality of evidence” for biosimilars
- interchangeability and substitution
- Health Canada’s approval process for biosimilars
- the role of nurses in introducing biosimilars and monitoring patients
INTRODUCTION

Biologic drugs have revolutionized the treatment of cancer. Patents, as well as other periods of exclusivity, for a number of biologic drugs have expired or are nearing expiration. This has created the opportunity for the development and approval of products called biosimilars that are similar to approved biologic drugs (Declerck, Danesi, Petersel, & Jacobs, 2017). Biosimilars have the potential to reduce the cost of cancer care and to increase access to biologic therapies worldwide (Curigliano, O’Connor, Rosenberg, & Jacobs, 2016). Although Canadian oncology nurses may be familiar with biosimilars, there may be knowledge gaps in their understanding of the development of biosimilars and the potential role of biosimilars in the oncology treatment landscape. The purpose of this supplement is to discuss biologic drugs in general, biosimilarity and biosimilars relative to reference biologic drugs, mechanism of action of biosimilars versus mechanism of action of reference biologic drugs, steps to biosimilar development, extrapolation of indications for biosimilars based on the “totality of evidence”, interchangeability and substitution, Health Canada’s approval process for biosimilars, and the role of nurses in introducing biosimilars and monitoring patients.

A biosimilar is a biologic drug that is highly similar to an existing licensed biologic drug (the originator or reference biologic drug) with respect to its structure, function, efficacy, safety, and purity (Curigliano et al., 2016; Declerck et al., 2017). Biosimilars are not considered the same as generic drugs and are not bioequivalent to the originator or reference biologic drug (Table 1). Generic drugs are small molecules that are chemically synthesized and contain identical medicinal ingredients to their brand name reference drugs. In contrast, a biosimilar and its reference biologic drug can be shown to be highly similar with respect to chemical properties, but not identical. This is due to the size, complexity, and natural variability of biologic drugs, and because biologic drugs are made in living cells rather than chemically produced; therefore, they cannot be duplicated in the same way small-molecule drugs can (Health Canada, 2017b; Rugo, Rifkin, Declerck, Bair, & Morgan, 2019). Even different batches or lots of both reference biologic drugs and biosimilars are not identical, due to the production of these drugs in complex living systems. However, these variations are not clinically significant. Biosimilars are also not necessarily bioequivalent to the originator or reference biologic drug. Two drugs are said to be bioequivalent if there is no clinically significant difference in their bioavailability, assessed using two main pharmacokinetic variables: the area under the blood concentration versus time curve (AUC) and the maximum blood concentration (Cmax) (Canadian Agency for Drugs and Technologies in Health, 2012).

Biosimilars offer biologic activity comparable to reference biologic drugs with no clinically meaningful differences, often at a lower cost. Therefore, their use will provide cost savings to improve treatment accessibility for patients and provide alternative options for decision-makers, including prescribers, regulators, payors, policymakers, and drug developers. Recent, as well as impending patent expirations of biologics have opened up opportunities for the development of corresponding biosimilars that offer more affordable effective therapy for cancer patients (Chopra & Lopes, 2017). The financial savings to our healthcare systems can be significant, allowing for investment into new, innovative therapies for cancer treatment, as well as increased access to biologics for a wider spectrum of patients (Rugo et al., 2019). However, the Government of Canada’s Patented Medicines Pricing Review Board estimates that public drug plans across Canada could save from $332M to $1.81B in the third year following biosimilar entry across a portfolio of products. Actual savings will vary based on the listing status of biologic and biosimilar medicines, the speed and spread of uptake, the discount rate compared with that of the reference biologic drug, and the assertiveness of reimbursement policies (Patented Medicines Pricing Review Board, 2019).

Regulatory requirements for approving biosimilars are similar across health agencies worldwide, in that all require extensive evidence to show that a biosimilar is highly similar to a reference biologic drug in terms of critical biochemical attributes, efficacy, and safety. Approval for a biosimilar is granted based on comprehensive comparisons between the biosimilar and the reference biologic drug regarding structure, function, animal toxicity, human pharmacokinetics (PK), human pharmacodynamics (PD), and clinical immunogenicity. Finally, the safety and efficacy are confirmed in a clinical trial in a sensitive population previously agreed upon with regulators. Approval is, thus, based on the “totality of evidence” (Curigliano et al., 2016).

The introduction of biosimilars in Canada has lagged behind other countries. Factors that contribute to this include the relatively small Canadian population compared to other world markets, which may lead to manufacturers submitting first to larger United States (US) or European Union (EU) markets. In addition, patent expiry dates for reference biologic drugs may differ between Canada and other countries. The EU has a much larger experience base regarding biosimilars. Thus, manufacturers of biosimilars can draw on EU precedents when submitting to Health Canada, and Canadian clinicians can benefit from the experience of European colleagues (Health Canada, 2017b).

<table>
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<tr>
<th>Reference Biologic Drug</th>
<th>Biosimilar</th>
<th>Generic Drug</th>
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<tr>
<td>Also referred to as the originator biologic drug</td>
<td>A biologic drug that is highly similar to an already existing licensed biologic drug (the originator or reference biologic drug) with respect to its structure, function, efficacy, safety, and purity</td>
<td>A small molecule that is chemically synthesized and contains the identical medicinal ingredient to its brand name reference drug</td>
</tr>
<tr>
<td>An approved product that is made in living cells rather than chemically produced</td>
<td>A biosimilar can be highly similar but not identical to its originator or reference biologic drug</td>
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In March 2019, the Pan-Canadian Oncology Biosimilars Initiative published an action plan to provide a high-level map for the implementation of biosimilars in oncology. The plan was developed through the joint efforts of patients, patient advocacy organizations, clinicians, healthcare administrators, and government officials from nine provinces. The goal of the plan is to provide guidance to support the implementation of oncology biosimilars across Canada that aligns with cost-saving goals (Pan-Canadian Oncology Biosimilars Initiative, 2019).

**BIOSIMILAR DEVELOPMENT**

The aim of the development program for a biosimilar is to show there are no clinically meaningful differences between the biosimilar and its reference biologic drug based on the totality of evidence. For the reference biologic drug, the approval process relies on conventional clinical trials to demonstrate efficacy, safety, and immunogenicity. In contrast, the approval process for a biosimilar relies on extensive analytical data, pre-clinical data, and abridged clinical data (Curigliano et al., 2016).

The development of a biosimilar differs from the process for a new molecular entity (Curigliano et al., 2016). To begin with, biologics are large, complex molecules, such as monoclonal antibodies that may exert their clinical effect through a variety of mechanisms of action, including ligand blockade, receptor blockade, receptor downregulation, cell depletion (via antibody-dependent cell mediated cytotoxicity, complement-dependent cytotoxicity, or apoptosis), and signaling induction (Scott, Klein, & Wang, 2015). Because the manufacturing process for the reference biologic drug is proprietary, the developer of a biosimilar must extensively analyze the reference biologic drug and use reverse engineering to develop the biosimilar agent (Camacho, Frost, Abella, Morrow, & Whittaker, 2014; Declerck et al., 2017; Kirchhoff et al., 2017).

Once the proposed biosimilar is created, biosimilarity with the reference biologic drug must be established using a stepwise approach (Figure 1). This starts with extensive structural and in vitro functional comparisons between the proposed biosimilar and the reference biologic drug followed by pre-clinical in vivo animal studies (Curigliano et al., 2016). This approach is utilized by Health Canada, as well as healthcare agencies around the world (European Medicines Agency, 2014; United States Food and Drug Administration, 2015; Health Canada, 2016; World Health Organization Expert Committee on Biological Standardization, 2019). Each step is designed with the aim of determining the level of biosimilarity of the proposed biosimilar and its reference biologic drug, and allows the developer to resolve any uncertainty around biosimilarity (Curigliano et al., 2016).

Health Canada recommends that when establishing the biosimilarity of a proposed biosimilar, the following should be evaluated: physicochemical and biological characterization data, results from analysis of relevant samples from the appropriate stages of the manufacturing process, stability data, and results from testing multiple batches or lots of the proposed biosimilar and its reference biologic drug (Health Canada, 2016). The physicochemical and biological characterization of the proposed biosimilar begins with analyses of primary (i.e., amino acid sequence), secondary, tertiary, and quaternary structures, including aggregation, post-translational modification (such as glycosylation, phosphorylation, and deamidation), intentional chemical modification (such as PEGylation), and biological activities (United States Food and Drug Administration, 2015; Health Canada, 2016). In addition, immunochemical properties, purity, impurity, and stability are assessed. These characterizations should be carried out side-by-side with the reference biologic drug to enable the direct comparison of the biosimilar and the reference biologic drug and evaluation of any differences (Health Canada, 2016).

Once structural and in vitro functional studies are complete, in vivo pre-clinical studies may be required. The extent and nature of in vivo animal studies will depend on the evidence obtained in the previous step (European Medicines Agency, 2014; United States Food and Drug Administration, 2015; Health Canada, 2016; World Health Organization Expert Committee on Biological Standardization, 2019). However, if biosimilarity is well established by structural and functional studies, and if extensive in vitro mechanistic studies show biosimilarity, in vivo pre-clinical studies may not be necessary. Specialized toxicological studies, including safety pharmacology, reproductive toxicology, and mutagenicity and carcinogenicity studies, are generally not required (Health Canada, 2016).

**BIOSIMILAR CLINICAL DEVELOPMENT**

Once extensive pre-clinical studies are completed, the next step in obtaining the data required to demonstrate biosimilarity involves clinical studies (Figure 1). While the approval process for the reference biologic drug relies heavily on clinical trials to demonstrate efficacy (noninferiority to the previous standard of care), safety, and immunogenicity, the approval process for biosimilars requires only abridged clinical data (Curigliano et al., 2016). Clinical trials for potential biosimilars are designed to compare the short-term efficacy and safety of the biosimilar to those of the reference biologic drug. They are not designed to re-establish efficacy and safety (Declerck et al., 2017; Kirchhoff et al., 2017).

The extent and nature of clinical studies required to establish biosimilarity depend on the evidence obtained with pre-clinical studies (European Medicines Agency, 2014; United States Food and Drug Administration, 2015; Health Canada, 2016; World Health Organization Expert Committee on Biological Standardization, 2019). Health Canada recommends the clinical trial program should begin with PK/PD studies (Health Canada, 2016). PK studies assess how the biosimilar is absorbed, distributed, metabolized, and excreted. PD studies assess the biological and physiological effects of the biosimilar on the body. In short, PK studies determine ‘what the body does to the drug’ while PD studies determine ‘what the drug does to the body’ (Meibohm & Derendorf, 1997). Health Canada recommends that comparative PK studies be conducted to rule out differences between the biosimilar and the

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Physicochemical and biological characterization
- Analyses of primary, secondary, tertiary, and quaternary structures
- Aggregation
- Post-translational modification
- Intentional chemical modification
- Biological activities
- Immunochemical properties
- Purity
- Impurity
- Stability

In vivo studies
- Extent and nature depend on evidence obtained from physiochemical and biological characterization

Pharmacokinetic (PK)/pharmacodynamic (PD) studies
- PK studies determine ‘what the body does to the drug’
- PD studies determine ‘what the drug does to the body’
- Extent and nature depend on evidence obtained from pre-clinical studies

Clinical Trial(s)
- Compare efficacy, safety, and immunogenicity with reference product
- Usually adequately powered, randomized, parallel group comparative clinical trials
- Preferably double-blind studies that use efficacy end points in either a non-inferiority or equivalence design

Figure 1. Pre-Clinical and Clinical Development Program of a Biosimilar, as per Health Canada Recommendations (Health Canada, 2016; Meibohm & Derendorf, 1997; Lai & La, 2016).
reference biologic drug. Health Canada also recommends that PK studies for the biosimilar should be carried out in healthy subjects because they are a homogenous and sensitive population. However, if the PK/PD is known to be altered in the patient population for which the biosimilar is being developed, Health Canada recommends carrying out PK studies in patients. PK studies should not be limited to determining absorption (i.e., maximum concentration, time to achieve maximum concentration), but should also determine elimination (i.e., clearance, terminal half-life). For PD studies, Health Canada recommends selecting PD markers that are relevant to the mechanism of action of the reference biologic. Whenever possible, PD studies should be combined with PK studies to enable characterization of the PK/PD relationship (Health Canada, 2016).

According to Health Canada, the purpose of the clinical trial program for a biosimilar is to show there are no clinically meaningful differences between the biosimilar and the reference biologic drug in terms of efficacy, safety, and immunogenicity (Health Canada, 2016). Studies are usually adequately powered, randomized, parallel group comparative clinical trials – preferably double-blind – and use efficacy endpoints in either a non-inferiority or equivalence design (Lai & La, 2016). Endpoint selection is critical in designing a trial for biosimilars; endpoints should be chosen as to be clinically relevant to the oncologic disease state but also sensitive enough to detect any clinically relevant differences between the biosimilar and the reference biologic drug (Bui & Taylor, 2014; Gifoni, Fernandes, & Chammas, 2018). The primary endpoints of the clinical trials for the biosimilar may or may not be the same as those used in the pivotal clinical trials of the reference biologic drug (Declerck et al., 2017).

Comparative clinical studies should be conducted in an appropriate patient population. The most appropriate study population is selected based on evaluation of historical studies of the reference biologic drug, practical considerations, and input from clinicians in order to address advances in clinical practice and reflect the latest knowledge of the disease. The selected patient population may or may not be the same as in pivotal clinical trials with the reference biologic drug, but must be sensitive to detecting potential differences in efficacy, safety, or immunogenicity between the biosimilar and the reference biologic drug (Declerck et al., 2017; Melosky et al., 2018).

Health Canada recommends that the comparative clinical trials should be adequately sensitive to rule out clinically meaningful differences between the biosimilar and the reference biologic drug within predefined comparability margins. Sponsors are advised to consider the following when designing such a trial: the characteristics of the study population or populations, such as disease state and immune competence; the study design, such as duration, dosing regimen, route of administration, efficacy and safety outcomes, and time of assessment; risk and impact of immunogenicity; impact of concomitant treatments, if any; and appropriate comparability margins (Health Canada, 2016).

**BIOSIMILAR APPROVAL PROCESS IN CANADA**

In November 2016, Health Canada issued the revised guidance document *Information and Submission Requirements for Biosimilar Biologic Drugs*. The document provides guidance to sponsors to enable them to satisfy the information and regulatory requirements under the *Food and Drugs Act* and *Part C of the Food and Drug Regulations* for the authorization of biosimilars in Canada (Health Canada, 2016).

The guidance document highlights the need for extensive chemistry and manufacturing data to demonstrate similarity to the reference biologic drug, and it indicates that similarity should be primarily deduced from side-by-side quality studies. The guidance document notes that the final determination of biosimilarity can be based on a combination of analytical testing, biological assays, and non-clinical and clinical data. However, the weight of evidence should be provided by the analytical and biological characterization, and too much reliance on clinical data may preclude a product from being considered as a biosimilar. Once biosimilarity is established, the guidance document indicates that additional indications, for which the reference biologic drug is approved, may be granted on the basis of extrapolation (Health Canada, 2016). The regulatory process for the approval of biosimilars in Canada is similar to those of the US, the EU, and other countries (European Medicines Agency, 2014; United States Food and Drug Administration, 2015; World Health Organization Expert Committee on Biological Standardization, 2019).

**EVIDENCE EXTRAPOLATION**

Extrapolation is the appropriation of safety and efficacy data from clinical studies in one indication to support the authorization of other indications in which the biosimilar has not been studied, but for which the Canadian reference biologic drug is authorized and well-characterized. If the reference biologic drug is approved for multiple therapeutic indications, extrapolation of indications must be scientifically justified for the biosimilar to receive approval for use in an indication held by the reference biologic drug (Curigliano et al., 2016; Scott et al., 2015; Health Canada, 2016).

Clinical trials for biosimilars are, therefore, designed with the goal of establishing comparative efficacy and safety data that may be extrapolated to other indications. Two types of clinical trial designs that may be considered when evaluating biosimilars are equivalence trials and non-inferiority trials. Equivalence trials aim to demonstrate that the biosimilar and reference biologic drug are equivalent; that is, the biosimilar is neither better nor worse than the reference biologic drug. Therefore, the goal is to demonstrate that the difference between the biosimilar and reference biologic drug is not large. This requires a “minimally clinically important difference” (MCID), a predetermined margin that defines a magnitude of difference between the biosimilar and reference biologic drug that is considered clinically important. Typically, the smaller the MCID, the larger the study population required to establish equivalence. In contrast, non-inferiority trials aim...
to show that the biosimilar is not substantially less efficacious than the reference biologic drug. An advantage of this trial design is that a smaller study population may be needed than in an equivalence trial. Unlike equivalence trials that have two possible outcomes (the biosimilar is equivalent to the reference biologic drug or the biosimilar is not equivalent to the reference biologic drug), non-inferiority trials have six possible outcomes: the biosimilar is statistically and clinically superior to the reference biologic drug, the biosimilar is statistically superior to the reference biologic drug, the biosimilar is non-inferior but not superior to the reference biologic drug, the biosimilar is inferior to the reference biologic drug but still meets criteria for equivalence, the biosimilar failed to show equivalence based on the MCID, but results are inconclusive, or the biosimilar is inferior to the reference biologic drug (Bui et al., 2014).

BIOSIMILAR NAMING CONVENTION

In February 2019, Health Canada adopted a naming convention for biosimilars so as to distinguish them from their reference biologic drugs and reduce confusion: biologic drugs, including biosimilars, will be identified by their unique brand name and non-proprietary (common) name, without the addition of a product-specific suffix (a naming convention currently used in the US). In addition, Health Canada recommends that both the brand name and non-proprietary name be used throughout the medication use process; use of the brand name allows distinction between biosimilars and reference biologic drugs that share the same non-proprietary name (e.g., TRUXIMA™ is the biosimilar for the reference biologic drug RITUXAN®; the non-propriety name for both is rituximab). Health Canada highlights that all biologics, including biosimilars and reference biologic drugs, will continue to have a unique Drug Identification Number (DIN). The DIN can, thus, be used to distinguish key characteristics of a drug product, including the brand name, manufacturer name, medicinal ingredient(s), strength(s), dosage form, and route of administration (Health Canada, 2019).

INTERCHANGEABILITY AND SWITCHING

Although interchangeability and switching both result in a patient changing from treatment with a reference biologic drug to treatment with a biosimilar, the actual processes differ somewhat. Switching refers to the one-time change from one drug to another (Health Canada, 2017b). Health Canada considers well-controlled switches from a reference biologic drug to a biosimilar in an approved indication to be acceptable (Health Canada, 2017a). Health Canada recommends that switching be guided by the treating physician in consultation with the patient. The treating physician should take into consideration all available clinical evidence and any relevant healthcare policies in the jurisdiction.

In contrast, interchangeability refers to the ability to change the patient’s treatment from one drug to another with the guidance of a pharmacist, without the intervention of the prescribing physician. In Canada, each province and territory has its own authority to declare two products interchangeable, according to that province’s own rules and regulations (Health Canada, 2017b; Scott et al., 2015).

Although healthcare providers generally hold a positive attitude towards biosimilars, they have less confidence in switching patients from the reference biologic drug to its biosimilar. Providing clinicians with guidance on how to explain biosimilars to patients and written patient material may help overcome some of the barriers to the use of biosimilars (Cook et al., 2019; Hemmington et al., 2017; Ismailov & Khasanova, 2018; Meldstedt, Niederwieser, & Ludwig, 2008). Extensive European experience with switching will be helpful to guide Canadian policy in the future, as will data pending from prospective trials of switch strategies.

<table>
<thead>
<tr>
<th>Table 2. Roles of Oncology Nurses in the Use of Biosimilars (Rak Tkaczuk &amp; Jacobs, 2014; Sugay, 2018; Vizgirda &amp; Jacobs, 2017; Wolff-Holz et al., 2018; Zack, 2018).</th>
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<tr>
<td><strong>Education</strong></td>
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<tr>
<td>• Educating other healthcare providers (other nurses, physicians, pharmacists), patients, and patients’ families on the use of the biosimilar to treat cancer</td>
</tr>
<tr>
<td>• Educating patients and their families on the biosimilar development process, and how the efficacy and safety of the biosimilar are established</td>
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<tr>
<td>• Answering questions on the differences between the biosimilar and its reference biologic drug regarding administration, handling, and storage</td>
</tr>
<tr>
<td>• Educating patients on the monitoring for and reporting of adverse events</td>
</tr>
<tr>
<td>• Collaborating with pharmacists to educate patients on biosimilar delivery and administration</td>
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<tr>
<th><strong>Integrating biosimilars into clinical practice</strong></th>
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<tbody>
<tr>
<td>• Evaluating new cancer treatments, including biosimilars</td>
</tr>
<tr>
<td>• Identifying, reporting, and managing adverse events</td>
</tr>
<tr>
<td>• Monitoring patient compliance</td>
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<tr>
<td>• Maintaining and improving patient adherence</td>
</tr>
<tr>
<td>• Educating other healthcare providers on the rigorous regulatory process involved in the approval of the biosimilar to promote acceptance of the biosimilar</td>
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<th><strong>Transitioning patients from the reference biologic drug to the biosimilar</strong></th>
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<tr>
<td>• Assessing patient readiness for education about biosimilars</td>
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<tr>
<td>• Educating patients about the biosimilar to promote patient acceptance of the biosimilar</td>
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<th><strong>Ensuring the safety of the biosimilar</strong></th>
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<tr>
<td>• Collaborating with physicians conducting clinical trials</td>
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<tr>
<td>• Assessing, monitoring, and reporting adverse events associated with a biosimilar during clinical trials</td>
</tr>
<tr>
<td>• Tracing, monitoring, and reporting of adverse events associated with a specific biosimilar following approval (pharmacovigilance)</td>
</tr>
<tr>
<td>• Evaluating and monitoring patients, and recognizing and recording adverse events, particularly delayed adverse events</td>
</tr>
<tr>
<td>• Educating patients on the importance of self-monitoring and reporting of biosimilar-related adverse events</td>
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Oncology nurses play an important role in education (Table 2). As biosimilars are approved and their use becomes more widespread in Canada, oncology nurses are in a unique position to educate not only themselves, but other healthcare providers, patients, and patients’ families about biosimilars to ensure accurate understanding, optimal use, and safe implementation of biosimilars. In particular, oncology nurses play an important role in educating patients about how biosimilars are developed, and how their efficacy and safety are established and ensured. The specialized oncology nurse is responsible for integrating and applying knowledge of cancer treatment modalities. Increasing patients’ understanding of biosimilars is vital to patients’ acceptance of their use (Vizgirda & Jacobs, 2017; Canadian Association of Nurses in Oncology, 2006).

Oncology nurses also play an important role in answering patients’ questions, not only about differences between biosimilars and generic drugs, but also about differences between biosimilars and their reference biologic drugs. Any potential differences in administration, handling, and storage would need to be explained to ensure optimal and safe patient care with biosimilars. In terms of ensuring patient safety, oncology nurses are well-positioned to collaborate with pharmacists, who are an additional resource for information about biosimilar delivery and administration (Vizgirda & Jacobs, 2017; Canadian Association of Nurses in Oncology, 2006).

Oncology nurses play an important role in integrating biosimilars into clinical practice and transitioning patients from reference biologic drugs to biosimilars (Table 2). Oncology nurses are responsible for implementing and evaluating new cancer treatments, including biosimilars. They identify, report, and manage adverse events, they monitor patient compliance, and they assist with maintaining and improving patient adherence (Wolff-Holz et al., 2018). The successful integration of biosimilars into clinical practice relies heavily on ensuring not only patient safety, but that patients continue treatment. Successful integration also depends on nurses educating other healthcare providers on biosimilars and the regulatory processes involved in the approval of a biosimilar (Rak Tkaczuk & Jacobs, 2014). Understanding the rigorous evaluation of biosimilarity that leads to the approval of a biosimilar increases acceptance of the biosimilar into clinical practice.

Oncology nurses are vital in fostering the transition from a previously-patented, branded, and typically more expensive reference biologic drug to a biosimilar that achieves the same efficacy at a reduced cost (Zack, 2018). Oncology nurses are well-positioned to assess patient readiness for education about biosimilars. They are also well-positioned to implement and integrate the relevant provincial or jurisdictional policies on biosimilars. The specialized oncology nurse is responsible for educating and counselling individuals with cancer and their families in all aspects of cancer care (Canadian Association of Nurses in Oncology, 2006). Patient education leads to increased patient confidence in biosimilars which, in turn, leads to patient acceptance.

Oncology nurses play an important role in ensuring the safety of biosimilars (Table 2). This begins early on during the clinical development of a biosimilar with the collaboration between nurses and physicians conducting clinical trials of the biosimilar. Nurses are involved in the assessment, monitoring, and reporting of adverse drug reactions associated with a biosimilar during clinical trials (Sugay, 2018; Wolff-Holz et al., 2018). The specialized oncology nurse is responsible for anticipating treatment adverse events and symptoms, and for planning and implementing strategies to manage side effects on an ongoing basis (Canadian Association of Nurses in Oncology, 2006).

Oncology nurses also play a vital role in pharmacovigilance for biologics and for biosimilars (Table 2) once they are approved, particularly in tracing, monitoring, and accurate reporting of adverse events associated with a specific biosimilar (Sugay, 2018). Biosimilars are not identical to the licensed reference biologic drugs. Therefore, unexpected side effects of biologics, including biosimilars, up to and post-approval need to be monitored closely through post-marketing pharmacovigilance procedures (Abraham, 2013). Biologic drugs (biosimilars and their reference biologic drugs) have the potential to induce hypersensitivity reactions, as well as other adverse events. Nurses are ideally positioned to evaluate and monitor patients, and to recognize and record adverse events (Canadian Association of Nurses in Oncology, 2006). In particular, oncology nurses are positioned to identify a delayed adverse event and intervene if a patient reports such an event. Finally, oncology nurses are key patient advocates who educate patients about the importance of self-monitoring and reporting of biosimilar-related adverse events (Vizgirda & Jacobs, 2017; Canadian Association of Nurses in Oncology, 2006). Ongoing pharmacovigilance efforts instill confidence that the biosimilar continues to be safe and efficacious (Canadian Association of Nurses in Oncology, 2006).

Biosimilars, reference biologic drugs, as well as all other drugs, undergo rigorous post-marketing surveillance in Canada. Health Canada not only conducts market surveillance, but also monitors adverse drug reaction reports, investigates complaints and problem reports, and takes action as appropriate. Health Canada requires all drug manufacturers to set up a system to monitor reported side-effects, report any new information about serious side-effects to Health Canada, notify Health Canada about any new safety information from clinical studies, and request authorization for any major changes to the manufacturing process, dosing regimen, or recommended uses of the drug (Health Canada, 2016; Health Canada, 2017b).

The role of the oncology nurse will continue to expand with respect to the introduction of biosimilar agents and their necessary acceptance by patients that can only occur with thoughtful education.
CASE STUDY

As similar treatment prescribed by their respective physicians continues for Ms. Jones and Ms. Yee, they have formed a peer support relationship and discover that Ms. Yee, who is receiving Mvasi (a bevacizumab biosimilar), has hypertension (HTN) while Ms. Jones, who is taking Avastin (bevacizumab originator drug), has not. Ms Yee questions if she should be on Avastin.

You explain to Ms. Yee that baseline clinical risk factors for VEGF inhibitor-induced HTN have yet to be established, but pre-existing HTN has been consistently shown to correlate directly with the development of treatment-related HTN.

Ms. Yee states she has had mild HTN for the last several years, but she was told there was no need for medical intervention. You explain that because of her baseline HTN she may find her HTN worsens with bevacizumab therapy (a VEGF inhibitor), but her risk of increased blood pressure would be expected to be the same with either Avastin or Mvasi.

Soon Ms. Yee’s (bevacizumab biosimilar) cancer progresses and while visiting the clinic for her treatment review, she asks if she should have been receiving the “real drug”, and requests it instead of changing to a second line treatment regimen.

You counsel her that the biosimilar she received was a real drug and has no clinically meaningful differences in safety, potency or effectiveness as compared to Avastin. As well, continuous monitoring by Health Canada occurs for both the originator drug and the biosimilar following the same process to ensure both drugs maintain their safety, quality and effectiveness.

CONFLICT OF INTEREST DECLARATIONS

Dr. Sehdev reports personal fees from MYLAN, SANDOZ, AMGEN, APOBIOLOGIX, and TEVA.

Karyn Parry reports personal fees from TEVA, personal fees from ROCHE, outside the submitted work; and Contributor to the pan Canadian Oncology Biosimilars Education Working Group and Oncology Biosimilars Operations Working group.

Kathy Gesy reports personal fees from AMGEN, personal fees from TEVA, personal fees from APOBIOLOGIX, outside the submitted work.
REFERENCES


