PGTM Clinical Intervention Model (CIM)

Comprehensive Evaluation of Biosimilars

State of Knowledge and Recommendations for Quebec's University Teaching Hospitals – 2017

Background

Biologics, drugs derived from living organisms, have been part of the therapeutic arsenal for the past few decades. They are represented in different pharmacological classes, such as insulins, growth hormones, vaccines, erythropoiesis-stimulating agents (ESAs), granulocyte colony stimulating factors (G-CSFs), and monoclonal antibodies. Their number has increased in recent years, especially in the case of monoclonal antibody biosimilars. This increase can be explained by technological and scientific advances in the biotechnology field and by the need to manage serious and debilitating diseases, such as cancer and autoimmune diseases. Biologics arise from a complex manufacturing method requiring elaborate resources for their production, which explains, in part, their generally high cost. Their cost can further be explained by the requirements for obtaining authorization to market them. The patent protection for many biologics will expire soon, which is spurring the development of "copies" of biologics, referred to as biosimilars. Because of their generally lower cost compared to that of the reference biologic drugs (RBDs), biosimilars can be seen as agents that improve access to biologics.

The first biosimilars made their appearance in the 2000s with the authorization of the biosimilar of somatotropin (Omnitrope®) in 2006 in Europe and the United States, and in 2009 in Canada. It is only more recently that monoclonal antibody biosimilars have been marketed. For instance, biosimilars of infliximab were approved in Europe, the United States and Canada in the past 3 years. The highest number of authorized biosimilars is in Europe. In 2011, the European market accounted for 80% of the world biosimilar market. As of December 2016, 22 biosimilars were being marketed in Europe and 6 were being marketed in the United States. Six biosimilars are marketed in Canada: Omnitrope® (somatotropin), Inflectra® (infliximab), Remsima® (infliximab), Grastofil® (filgrastim), Basaglar® (insulin glargine) and Brenzys® (etanercept). Only Inflectra® and Omnitrope® have been included on the Régie de l'assurance maladie du Québec's *List of Medications*.

The challenge for clinicians is to determine the role biosimilars can play in the pharmacological arsenal. One of the issues is to determine if substituting a RBD by a biosimilar (or vice versa) reduces the effectiveness of the treatment or increases the risk of adverse events, especially immunogenicity reactions. In the context of Quebec's university teaching hospitals (UTHs), the methods for evaluating biosimilars and guidance for the substitution, especially the automatic substitution, of a RBD for a biosimilar (or vice versa) are important issues as well.

Facts to consider

- Canadian regulatory agency and Canadian and Quebec assessment agencies have not adopted a position regarding the **substitution** or **interchangeability** of biosimilars and RBDs.

- Biosimilars constitute a heterogeneous group of drugs. A position on the **substitution** of all biosimilars and RBDs for all situations in the UTH context cannot be adopted at this time because of:

    - The differences in the properties of the different biosimilars (in particular, their immunogenic properties).
    - The differences in patient characteristics (e.g., age) and the stage of progression of the disease being treated (e.g., induction or maintenance, stable or in decompensation, patient treatment-naïve or treatment-experienced).
    - The differences in the diseases for which a given biosimilar can be used (in particular, their immunological profile, their chronicity and the role of biosimilars in their treatment, and the durations of use).
    - The qualitative and quantitative differences in the published data on the different biosimilars.

- A position on the **interchangeability** of all biosimilars and RBDs for all situations in the UTH context cannot be adopted at this time because of a lack of evidence for evaluating the effects of alternation.

- The indications for each biosimilar and the RBD may differ.

- The results of a number of observational studies of a single substitution of a RBD with its biosimilar seem to show a tendency toward globally comparable efficacies and safety profiles. Although few unexpected adverse effects are currently reported, a few differences have been observed in very rare instances.

- Predicting the actual effects of substitution is complicated by the relatively small number of patients evaluated and by the limited duration of observation in the existing published studies. The occurrence of unexpected effects, such as potentially low-incidence, long-term immunological effects, cannot be ruled out on the basis of the currently available observational data.

- The advent of biosimilars is an emerging phenomenon, with the result that some clinicians may not be well aware of the state of knowledge of these drugs. Furthermore, clinical experience is presently limited.

- Although most UTH patients are inpatients, a number of treatments are either already initiated prior to admission or continued in the community.

The PGTM's scientific recommendations

In light of the current state of knowledge of biosimilars, the PGTM's recommendations are as follows:

- The advisability of substitution, interchangeability and formulary listing should be assessed by the Pharmacy and Therapeutics Committee for each biosimilar individually.

- Substitution can be considered on the basis of the following criteria: treatment-naïve patient, biosimilar whose interchangeability is recognized by a regulatory agency, biosimilar with a low immunogenic profile, and biosimilar for which there is an objective efficacy measure.

- A plan for minimizing the risk of alternation should be put in place. The UTHs should assess the potential alternation situations when selecting listed products for inpatients and patients who visit outpatient clinics, as well as those who continue their treatment in the community.

- The UTHs should consider making joint decisions on the selecting of formulary-listed products and on their manner of use.

PGTM Clinical Intervention Model (CIM)

Comprehensive Evaluation of Biosimilars

State of Knowledge and Recommendations for Quebec's University Teaching Hospitals – 2017

Objective: To promote optimal biosimilar use in the UTHs.

Intervention measures: Each institution is to determine which interventions apply to its situation and make one or more of them priorities.

Timetable: Institute applicable continuous measures at each UTH as soon as possible.

Intervention plan for the PGTM's biosimilar CIM:

1. The advisability of substitution, interchangeability and formulary listing should be assessed by the Pharmacy and Therapeutics Committee and ratified by its CPDP for each biosimilar used in the UTHs' patients. The assessment should consider or include the following:

    1.1. Health Canada's position (summary basis of decision) and that of the MSSS

    1.2. The recommendations of the assessment agencies CADTH (Common Drug Review program) and INESSS (notices to the Minister concerning entries on the *List of Medications*)

    1.3. The positions of foreign regulatory agencies regarding substitution and interchangeability

    1.4. The recognized indications and the differences

    1.5. An analysis of the available evidence concerning substitution, including data according to the different patient characteristics and the indications concerned. This includes clinical studies involving the recognized indications, and observational and postmarketing clinical studies.

    1.6. Pharmacovigilance reports

    1.7. Checking the applicability of the results to the UTHs' patients

    1.8. Any differences (e.g., administration details, stability data, available package sizes)

    1.9. The substitution plan for inpatients (treatment-naïve patients, patients already being treated)

1.10. The plan for patients who continue their treatment in the community

1.11. The monitoring plan contemplated

1.12. The prescriber and patient information plan

1.13. Opinions regarding expert positions so that prescribers' concerns can be taken into account

2. The elements to be considered in favour of substitution and interchangeability are as follows:

2.1. Treatment-naïve patients

2.2. A biosimilar whose interchangeability is recognized by a regulatory agency

2.3. Patients who are already being treated, provided the Pharmacy and Therapeutics Committee and the medical teams concerned deem the analysis of the evidence satisfactory. In particular:

2.3.1 The absence of data suggesting significant differences in terms of efficacy and safety
2.3.2 Available data applicable to the population
2.3.3 Data available supporting substitution
2.3.4 Biologic with a low immunogenic profile
2.3.5 Availability of an objective efficacy measure (e.g., blood glucose level, absolute neutrophil count)

3. Pending additional data or observations from clinical experience describing the impact of alternating or interchangeability, the UTHs should exercise caution and put in place a plan to minimize the risks associated with alternation or interchangeability. Some of the items that might be considered are as follows:

3.1 The minimization of these risks should be one of the arguments discussed during calls for tenders for the UTHs in a given region. To reduce the risks associated with the coexistence of several biosimilars and RBDs on the Quebec market, the UTHs might consider selecting only one product (or a very small number of products) that would be available to their patients. Concordance with the options available in the community should be considered as well.

3.2 The procedure for the exceptional use of a drug that a patient has with him/her could be put in place for cases such as:

3.2.1 A biosimilar for which the evaluation does not support alternation or interchangeability in patients who are already being treated

3.2.2 A patient in whom a substitution was made recently

3.3 In cases where the treatment is continued after the patient is discharged, to reduce the risks, a discharge prescription could indicate that the patient is to continue with the product used during his/her hospitalization. ("No substitutions").

4. Clinical monitoring after a substitution: A standardized procedure for all newly listed biosimilars. Objective efficacy and safety criteria.

5. Information for prescribers and patients:

5.1 Information tools intended for patients and prescribers could be used (e.g., a standardized memorandum, a newsletter)

6. Nomenclature: The UTHs should develop a nomenclature rule for distinguishing a given biosimilar from its RBD. Example: the generic name with the product's name in parentheses.

7. Traceability: The UTHs should ensure that the nomenclature rule is applied throughout the medication circuit

8. Follow-ups: Because of the rapid pace at which data on biosimilars is changing, the UTHs should keep abreast of:

8.1 The changes in the regulatory agencies' policies and positions

8.2 The recognition of the "interchangeability" of each biosimilar for which marketing authorization is granted, or observations drawn from clinical experience

8.3 The available clinical data

8.4 A centralized watch could be put in place

9. The UTHs' expectation for clearer positions on the part of Quebec regulatory and health technology assessment agencies. The UTHs should prepare a standardized communication for the OPQ, the CMQ and INESSS to inform them of their main concerns, in particular:

    9.1 For the OPQ and the CMQ: The need for a specific, comprehensive position on substitution with biosimilars that is separate from the current position developed vis-à-vis generic drugs. The aspects that would need to be clarified are the impact of a nomenclature rule adding a distinctive element to biosimilars and RBDs, and the methods that the UTHs can use to avoid alternation, such as the phrase "No substitutions".

    9.2 For INESSS: INESSS's expertise should be used to develop a more clinical position, among other things, with regard to the aspects to be taken into account when recognizing "interchangeability", and the minimum clinical data necessary for reasonably assuming interchangeability (the features of biosimilars, published clinical studies). Its expertise could also be used to develop patient advice tools, in particular, for non-naïve patients on an RBD who do not meet the criteria for an exception drug and who have to switch to a biosimilar for financial reasons. Furthermore, until additional and longer-term data are available, standardization between the hospitals and the community would reduce the risks associated with alternation.