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Introduction of Biosimilar Rituximab: A Hospital Perspective

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Realizing the potential of biosimilars

Although transformative for the management of many hematological diseases, biologic medicines are expensive, causing pressure on healthcare budgets and potentially preventing access to patients who might benefit.[1] The introduction of biosimilars provides an opportunity to sustainably expand access to biologic therapies and reduce expenditure on medicines.

To realize the potential benefits of using biosimilars, there may be barriers to overcome, including resistance from prescribers, financial disincentives in the healthcare system, patient reluctance, and logistical or operational barriers.

Within 2 months of a biosimilar becoming available in the United Kingdom, it was prescribed for 100% of rituximab infusions administered in the hematology department at University College London Hospital, approximately 160 doses per month. At the time of launch, the biosimilar was 55% less expensive than the reference product and our rapid and complete adoption resulted in savings of more than £1.7m on rituximab acquisition costs for our hospital during the first 12 months. This was only made possible with advance planning, nimble decision-making, and a broad programme of healthcare professional education and engagement.

Rituximab biosimilars

The reference rituximab (MabThera; Roche) is a chimeric anti-CD20 monoclonal antibody approved by the European Medicines Agency (EMA)[2] to treat non–Hodgkin's lymphoma and chronic lymphocytic leukemia, and administered by intravenous infusion or as a subcutaneous bolus injection.

In April 2017, the first biosimilar rituximab CT-P10 (Truxima, Ritemvia, Blitzima; Celltrion) was approved by the EMA[3] for all indications of the reference biologic, followed shortly after by a second biosimilar, GP2013 (Rixathon, Riximyo; Sandoz).[4] With the addition of Ruxience (Pfizer), there are now 3 biosimilar rituximab products approved by the European Medicines Agency,[3-5] and more going through the approval process. All currently approved biosimilars are for intravenous use only.

Institutional considerations

The first step when introducing biosimilar rituximab into our hospital was to gain institutional approval. This allowed addition of the biosimilar to the hospital formulary ensuring that we could procure stock, and update those electronic systems involved in inventory management, prescribing, dispensing, and administration.

The hospital adoption process for biosimilar medicines differs to that for novel anticancer or supportive care medicines in that it is usually driven at the institutional level to support swift and comprehensive uptake, rather than by an individual or group of clinicians with a strong desire to prescribe the medicine. Similarly, the discussions around efficacy and safety are usually more limited for a biosimilar medicine as by definition these are not expected to differ from the reference product.

The decisions for each institution to make include which patient groups to prescribe biosimilar rituximab for, whether to switch patients already receiving treatment with the reference product or only prescribe to new patients, and, where there is a choice, which biosimilar to use.

At University College London Hospital, we favor a one-off, "big-bang" switch from reference product to biosimilar, starting all new patients and switching any existing patients from a prespecified date.

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The potential benefits of this approach are as follows: (1) reduced confusion for healthcare professionals when choosing which product to prescribe, dispense, or administer; (2) maximizing healthcare savings, and (3) to demonstrate confidence in biosimilars and encourage future market entrants. It might also be the easiest approach to take with some electronic prescribing, dispensing and inventory systems, remembering that pharmacovigilance requirements necessitate brand-name prescribing at all times.[6] To further support this approach, we also contacted all relevant clinical trial sponsors to gain agreement to use a biosimilar in place of the reference rituximab where necessary.

Choice of biosimilar

The biosimilar development paradigm is based on producing a molecule with no clinically meaningful differences to the reference product.[7,8] This means that, aside from price and time to market, differentiating between the available biosimilars can present a challenge.

Many product and manufacturer characteristics have been proposed as potential ways of comparing different biosimilars.[9] These include the availability of different vial sizes, minor changes in excipients, enhanced stability of prepared doses, the clinical trial population of the registration study, and manufacturer reputation and confidence in the supply chain. The choice may be also be directed by regional/national guidelines or tendering processes.

Novel biosimilar concepts for the hematology clinician

Although biosimilar growth factors (erythropoietin, filgrastim) have been available and prescribed to support hematology patients for more than a decade, the introduction of biosimilar monoclonal antibodies with therapeutic treatment intent may require an enhanced degree of confidence in prescribers.

In parallel with the formulary adoption process, it is important to identify and engage the full range of local healthcare professional stakeholders, including medical, nursing, and pharmacy staff, in addition to patients currently receiving the reference product.

The development and regulatory approval process for biosimilars differs from that for novel medicines. Clinical trials in patients are the final step of the process to confirm biosimilarity, and are not required in all of the approved indications of the reference medicine. This keeps cost and time of development down but may appear to leave gaps in the evidence base.

To explain this, it is necessary to understand one of the important and novel concepts with biosimilar medicines: extrapolation.

In the context of hematology, the registration studies for rituximab biosimilars have only included patients with follicular lymphoma[10-12] with approval being extrapolated to all of the licensed indications of the originator, without the requirement for additional clinical trials.

This extrapolation is justifiable as rituximab has the same receptor target and mode of action across B-cell malignancies with no expected differences in pharmacokinetics, immunogenicity or other safety risks. The choice of newly diagnosed follicular lymphoma allows a homogenous population, and a sensitive endpoint, overall response rate, that provides a direct measure of antitumor activity and that can be assessed within a short timeframe.

In addition, the registration trials are not intended to demonstrate a benefit of using the biosimilar in a particular condition but to confirm there is no clinically meaningful difference from the originator. In time, and with further improvements in the analytical and preclinical testing of biosimilars, it is possible to foresee a time when the confirmatory clinical trials are deemed unnecessary.

There may therefore be a local requirement for specific education to promote understanding of novel drug development concepts and subsequent acceptance of biosimilars.[13] To facilitate this, we undertook a collaborative project with colleagues at the Royal Marsden and Christie hospitals to develop educational support, project planning, and patient information resources that were subsequently made freely available via a dedicated website.[14]

Patient and service considerations

As the expected benefits and potential adverse effects of receiving a biosimilar are expected to be the same as the reference product, we took the decision that it would not be necessary to change the information provided as part of the consent process, nor to reconsent patients who were switching to the biosimilar mid-treatment. This decision was facilitated by our patients typically having been consented to receive "rituximab" or "R-chemotherapy" rather than a particular branded medicine.

Proactively communicating with patients about biosimilars should be encouraged to help counter any misinformation or address any doubts and we found that partnering with patient groups and charities to produce trusted patient information was a useful approach.[15] In addition, each patient who was in the middle of treatment and being switched to receive the biosimilar was written to in advance and given the opportunity to ask questions of an informed healthcare professional before their first infusion. Common questions were: "Will my treatment appointment take longer?," "Will I react to the infusion," and most commonly, "What does my doctor think?"

We found adopting a "one voice" approach to be beneficial, empowering all patient-facing staff with knowledge around biosimilars such that they could answer questions from patients using positive language.

Due to a high level of confidence in the similarity of the biosimilar to the reference product, we also decided to maintain our existing rapid infusion protocol rather than mandate retitration of the infusion rate for patients when switching them to the biosimilar. This was important to ensure that switching to the biosimilar had no adverse impact on chair-time, day unit capacity, or patient experience.

Gaining the acceptance of patients was crucial in achieving widespread adoption and since switching we have had no requests to use the reference product instead of the biosimilar rituximab, for any reason, from any patient or clinician.

Summary

Early adoption of biosimilars is desirable to maximize the financial benefits, expand patient access to biologic medicines, and encourage a competitive marketplace. There is a growing body of experience, from multiple European countries, demonstrating that this is achievable with biosimilar rituximab.[16] We have found horizon scanning to identify patent expiry of reference products and the expected availability of biosimilars is the key to local preparedness, allowing sufficient time for stakeholder engagement and project planning: introducing a biosimilar into a hospital is less straightforward than a generic medicine.

Broadly, there are 3 possible approaches when faced with continually rising healthcare costs. Matching the costs with increased expenditure is unsustainable, and rationing access to treatments is undesirable. The third approach is to increase efficiency by delivering the same healthcare benefits with less resource, and biosimilars are here to stay as a crucial part of achieving that ambition.

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