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Monoclonal Antibody Biosimilars in Oncology: Critical Appraisal of Available Data on Switching

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ABSTRACT

Purpose: With the introduction of biosimilars of anticancer monoclonal antibodies (mAbs) in oncology, physicians are potentially confronted with the question whether it is clinically adequate to switch patients who are clinically stable on treatment with the reference product to a newly available biosimilar (or vice versa/from 1 biosimilar to another). For a proper impact assessment of switching, robust, product-specific, and clinically relevant evidence should be required, ideally including data from appropriately designed switching studies. In this article, we assess the current body of switching data available for approved or proposed biosimilars of anticancer mAbs.

Methods: PubMed was systematically searched and ClinicalTrials.gov and abstract databases of selected congresses were hand-searched to identify all switching studies including biosimilars of anticancer mAbs.

Findings: We identified 8 switching studies with biosimilars of rituximab (CT-P10, GP2013, PF-05280586, and BCD-020) and trastuzumab (ABP 980). Two were performed in oncology indications and the other 6 in rheumatoid arthritis (RA). Key elements of a well-designed switching study, such as randomization and blinding, were contained in several of the studies, but significant limitations were also present. The most frequent limitations were low statistical power because of small patient numbers, lack of an appropriate control arm, short follow-up, chosen outcome measures, and (for studies performed in RA) the concern whether switching data can be extrapolated to oncology indications. Accordingly, the data from these studies need to be interpreted with caution. Of note, all identified studies included a single switch only, whereas multiple switches may occur in the real-world setting. The scientific need to evaluate the impact of repeated switching has been recognized by the US Food and Drug Administration, who incorporated such a requirement in its draft guidance on interchangeability.

Implications: From the scarce data available, the consequences of switching between reference product mAbs and their biosimilar(s) in the oncology setting are as yet unknown. Additional clinical evidence from well-designed switching studies is needed to guide switching decisions. (*Clin Ther*. 2018;▮:▮▮▮–▮▮▮)

Key words: biosimilarity, biosimilars, monoclonal antibodies, oncology, switching.

INTRODUCTION

In oncology, biological drugs (biologics) are widely used for the treatment of cancers and for the management of treatment-related side effects. As originator products approach the end of their exclusivity period, development of biosimilars, that is, biologics that are similar to an already approved (reference) biologic, has grown.[1,2] Although biosimilars of hematopoietic

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growth factors (epoetin and filgrastim) have been in use for some time in oncology as supportive treatments, biosimilars of monoclonal antibodies (mAbs) have only just started to become available. Most mAbs are significantly more complex from a structural and functional perspective than, for example, epoetin and filgrastim.[3] In addition, their complex functional properties are highly sensitive to particular structural features (eg, Fc-mediated properties versus glycosylation). The first biosimilar of an anticancer mAb, the rituximab biosimilar CT-P10 (Truxima*), was approved in Europe in February 2017.[4] In the same year, a second rituximab biosimilar, GP2013 (Rixathon†),[5] was approved as well as the trastuzumab biosimilar SB3 (Ontruzant‡). In the United States, the bevacizumab biosimilar ABP 215 (Mvasi§) was recently approved. More biosimilars of rituximab, trastuzumab, and bevacizumab are expected to become available in the near future.

After an initial induction treatment, anticancer mAbs are often used as maintenance treatment until disease progression. After the approval of a biosimilar, physicians are potentially confronted with the question whether it is clinically adequate to switch a patient who is clinically stable on treatment with the reference product to this newly available biosimilar (or vice versa). The motivation for such a switch may be a nonmedical one, for example, related to cost-driven procurement policies. Because biosimilars are not identical to their reference product, residual uncertainty is associated with switching between products, including potential concerns related to immunogenicity. Immunogenicity is not only a tolerability concern but also an efficacy concern, because neutralizing antibodies can block the effectiveness of a therapeutic agent.

In the context of switching, it is important to differentiate terminologies, for example, interchangeability (a product property/regulatory designation), physician-mediated switching, and automatic substitution at pharmacy level (Table I).[6–8] The US Food and Drug Administration (FDA) and the European Medicines Agency differ in their regulatory approach to switching. The FDA acknowledges that approval of a biosimilar does not automatically imply interchangeability (as it typically would for a small-molecule generic) and distinguishes between noninterchangeable and interchangeable biosimilars.[9] An interchangeability designation constitutes an additional standard, and appropriate evidence is required to indicate that an interchangeable biosimilar "can be expected to produce the same clinical result as the reference product in any given patient." Switching studies need to indicate that "the risk in terms of safety or diminished efficacy of alternating or switching between use of the proposed interchangeable product and the reference product is not greater than the risk of using the reference product without such alternation or switch."[7] Only interchangeable biosimilars may be (automatically) substituted by a pharmacist for the reference product without the intervention of the prescribing health care professional, subject to individual state law.

In Europe, there is no additional classification of biosimilars. The European Union (EU) regulatory designation of biosimilarity does not include recommendations on whether the biosimilar is interchangeable with the reference product and, thus, whether the reference product can be switched or substituted with the biosimilar.[6] Switching and substitution policies are within the remit of the individual EU member states.

The different regulatory positions and residual uncertainty associated with switching raise the question of the weight (eg, quality and quantity) of evidence required for sound clinical decision making. Clinical data to support the approval of a biosimilar are generally derived from studies in treatment-naive patients. However, studies that assess the biosimilarity of products are not reflective of a switch situation. For a proper impact assessment of switching between a reference product and its biosimilar, robust, product-specific, clinically relevant evidence is required, ideally including data from appropriately designed switching studies. In this article, we identify and critically appraise the current body of switching data available for biosimilars of mAbs used in oncology indications.

METHODS OF LITERATURE SEARCH

The present literature search was restricted to therapeutic antibodies used in oncology indications. Trials were selected for inclusion if they contained at least 1

*Truxima™, Celltrion Healthcare Hungary Kft, Budapest, Hungary.

†Rixathon®, Sandoz GmbH, Kundl, Austria.

‡Ontruzant®, Samsung Bioepis UK Limited, Brentford, United Kingdom.

§Mvasi®, Amgen Inc., Thousand Oaks, CA, USA.