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Review

Switching to biosimilar infliximab (CT-P13): Evidence of clinical safety, effectiveness and impact on public health

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ABSTRACT

CT-P13, the biosimilar of infliximab, has been recently approved in the EU, Australia, Canada, Japan and many other countries. Thus, it was the first biosimilar approved in the field of rheumatology, dermatology and gastroenterology. Since there has been debate about the issue of switching from RMP to the biosimilar and some national societies have expressed concerns, this review was written with the following objectives:

- Review the data evaluating the safety and effectiveness of switching to CT-P13 accumulated thus far from clinical studies and real-world experience.
- Assess the paradigm shift around the use of biosimilar products in terms of recent national decisions and stakeholder perspectives.

The review concludes that whilst prudent switching practices should be employed, growing safety experience accumulated thus far with CT-P13 and other biosimilars is favorable and does not raise any specific concerns.

1. Introduction

Biological agents have revolutionized therapy and transformed treatment paradigms due to improved short- and long-term clinical and public health outcomes, and general patient care of chronic and debilitating autoimmune disorders such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis (Ps) and psoriatic arthritis (PsA), ulcerative colitis (UC) and Crohn's Disease (CD) as well as for different forms of cancer and chronic kidney disease. However, with global spending on medicines approaching to reach $1.3 trillion by 2018 (IMS, 2014), colossal costs of biological treatments reaching $210 billion by 2016 (IMS, 2012) with relatively low numbers of patients being treated or assured access globally to these efficient treatments, long-term expenditure and costs has become unsustainable for payers and societies. Recent or impending expiry of patents for some key biologics has led to development of biosimilar products. With growing numbers of biosimilar products there are now more options for healthcare providers and patients not only to access biological products earlier but also to possibly switch from costly originator versions to biosimilar alternatives. The entry of biosimilar products into the market may well reduce the pressure on healthcare budgets, increase earlier access to biologic therapy, and may facilitate the efficient allocation of limited financial resources [1,2]. Biosimilars are expected to save 11.8–33.4 billion Euros between 2007 and 2020 in the EU and 44.2 billion US dollars over the 10 year period between 2014 and 2024 [3,4].

In accordance with regulatory frameworks laid out by the European Medicines Agency (EMA), the US Food & Drug Administration (FDA), the World Health Organization (WHO) and other authorities in highly regulated jurisdictions, development of biosimilars has to be accomplished by rigorous and comprehensive comparability exercises in order to assure similarity of the biosimilar with the reference medicinal product (RMP) in terms of quality characteristics, biological activity, safety, efficacy [5] including the absence of any clinically important differences from the RMP in terms of safety and effectiveness [6]. The EMA has pioneered the legal, regulatory and scientific framework for

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approval of biosimilars with 20 products approved between 2006 and 2015, while other assessments of biosimilar products are ongoing. The WHO enacted biosimilar guidelines in 2009 and its framework has been put forward into regional and national biosimilar legislation and allowed to strengthen global regulations of biosimilars [7].

The Biologics Price Competition and Innovation Act (BPCI Act) in the US has established an abbreviated approval pathway for biological products to demonstrate similar efficacy and safety with the RMP. The federal law has differentiated the approval of products into two stages: (1) the 'biosimilar' has to provide evidence of basic similarity to the RMP, and (2) an additional approval status called 'interchangeable biosimilar' is required to allow for unlimited transition from the RMP.

As indicated in Public Health Act subsection 351(k) (3), a biosimilar is considered to be interchangeable with the reference product if:

- the biological product is biosimilar to the reference product, and
- it can be expected to produce the same clinical result in any given patient.

In addition, for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biosimilar and the reference product is not greater than the risk of using the reference product without such switching or alternating.

Biosimilarity therefore does not imply interchangeability which is much more stringent. Interchangeability status allows substitution of RMP with biosimilar without healthcare provider involvement. In addition to interchangeability, there is a concept of switching between an RMP and its biosimilars. Switching can be carried out either under consent of healthcare provider or without such consent but following payer's policy or decision only (automatic substitution) [8].

The approval for interchangeability is rigorous to achieve and FDA demands to establish safety data clearly showing that no additional risk is incurred when patients are switched to the biosimilar as compared to the continuous use of the RMP [9]. Interchangeability refers to achievement of same clinical result in any given patient in terms of quality, safety and efficacy when a biosimilar is switched or substituted with its respective innovator biological product, when compared to the use of the reference product alone. In principle, once the biosimilar product gains 'interchangeable' status, it can be automatically substituted for the prescribed biological product by the pharmacist without consent of the prescribing physician [9]. However, this provision is subject to U.S. state laws enforcing substitution legislation. The BPCI Act gives FDA the authority to designate a biosimilar as interchangeable with its reference product. This means that the biosimilar may be substituted for the originator product by the pharmacist without reference to the prescribing physician. FDA unveiled biosimilar guidelines in 2012 and in January 2015 approved first US-approved biosimilar, Sandoz's Zarxio™ (filgrastim-sndz) [10]. However, as of 2015 there are no interchangeable biosimilars approved in the USA. Despite that the concept of interchangeability has been laid in BPCIA, the requirements and the data required to accomplish interchangeable status have not been clearly defined. After long-term debates no defined path, guidance and clear requirements were issued in the USA. FDA has yet to clarify the requirements for interchangeability, although the agency has stated that it highly recommends that sponsors use a two-step process for obtaining the interchangeable biologic designation, first gaining approval as a biosimilar and then submitting a supplement with new data to support interchangeability.

Recommendations around interchangeability and substitution between biosimilar and its RMP are not within the remit of EMA but reside with EU member national authorities [11,12]. Recently some national agencies in the EU experts issued their position statements welcoming switching to biosimilar products and raising concerns over the scientific purpose, feasibility, utility and usefulness of over-complex and often unsurmountable interchangeability requirements and how these fit with economically sustainable placement of these products onto the market [13–19].

Following approval of biosimilars, it is important to decide whether it is possible to alternate or switch from the originator product to the biosimilar or vice versa in clinical practice or also to switch between different biosimilars. However, concepts of interchangeability and switcheability have been insufficiently studied - not only in context of biosimilars but also with originator biologics in general. Switching from one therapy to another one has been an integral part of medical practice. Indeed, switching can possibly occur between small molecule drugs, branded and generic synthetic medicines, between synthetic agents in biological agents and also from one type of biological originator agent (e.g. anti-tumor necrosis factor (TNF) agent) to a biological product from a different class (e.g. rituximab). However, switching studies have never been routinely conducted and sequencing of agents or their positioning in treatment paradigm was largely based on empirical evidence or limited clinical trial data. Strategy studies such as TICORA and BEST have provided some evidence that earlier initiation and more intensive treatment and whenever appropriate switching to other more potent synthetic disease-modifying antirheumatic drugs (DMARD) resulted in better control of disease activity in RA patients and improved clinical outcomes at no additional cost for healthcare [20,21].

Therefore, it is important to recognize that switching may become necessary for numerous reasons which can be broadly categorized into the following groups:

- Loss of response of effectiveness of the primary agent;
- Safety concerns including adverse events or immunogenicity;
- Adherence and compliance related factors (e.g. more convenient route, frequency of administration, palatable oral formulation etc.);
- Healthcare provider induced switching that can take place in form of automatic substitution under budgetary or cost-effectiveness considerations.
- Other considerations that could be prompted by both pharmacists and patients, e.g. longer product half-life and stability, lesser cold-chain requirements, etc.

CT-P13, the biosimilar of infliximab, has been recently approved in the EU, Australia, Canada, Japan and many other countries. Thus, it was the first biosimilar approved in the field of rheumatology, dermatology and gastroenterology. Since there has been debate about the issue of switching from RMP to the biosimilar and some national societies have expressed concerns, we decided to write this paper with the objectives to review switching experience between RMPs and their biosimilar versions and principles around switching to biosimilar products could assure both safe and economically sustainable use of these products.

2. Original experience with switches between different biological products

Sequencing of patients with autoimmune diseases through different lines of immunomodulatory therapies is a cornerstone approach of clinical practice and is outlined in recommendations of EULAR, ECCO and other bodies [22–24]. The typical approach is to

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