Is it time for biosimilars in autoimmune diseases?

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Abstract

The last two decades have witnessed a revolution in the treatment of autoimmune diseases due to the introduction of biological agents which, although now included as standard treatment in patients with autoimmune rheumatological, dermatological and gastrointestinal diseases. The use of biological agents is associated with greater costs compared with the mainly anti-inflammatory and immunosuppressant drugs used in the pre-biological era. Biosimilars are highly similar copies of biological drugs, but not identical to approved 'reference' agents. Biological agents are complex proteins involved in the immune response and their exact replicas are extremely difficult, if not impossible, to obtain. Three scenarios have converged to provide a specific opportunity for biosimilars in autoimmune diseases: growing demand for biologics due to successful clinical use; the nearing of patent expiry for the four top-selling biological brands; and the search to reduce health costs due to the financial crisis. We aimed to review the crucial topics of efficacy, safety and regulatory approach of upcoming biosimilars.

1. Introduction

The last two decades have witnessed a revolution in the treatment of autoimmune diseases due to the introduction of biological agents which, although now included as standard treatment in patients with autoimmune rheumatological, dermatological and gastrointestinal diseases, are associated with greater costs compared with the mainly anti-inflammatory and immunosuppressant drugs used in the pre-biological era. Biotechnological advances have resulted in the "generic" versions of biologicals, known as biosimilars. The term biosimilar was first used in Pubmed in 2004 [1]. Since then, 7 biosimilar products sold under 13 different names have been licensed in Europe: two human growth hormones (somatropin), three granulocyte-colony stimulating factors (filgrastim), and two erythropoietins that have received different international nonproprietary names, [epoetin-alfa (HX-575) and epoetin-zeta (SB-309)] [2].

Three scenarios have converged to provide a specific opportunity for biosimilars in autoimmune diseases: growing demand for biologics due to successful clinical use; the nearing of patent expiry for the four top-selling biological brands; and the search to reduce health costs due to the financial crisis.

The rapid expansion of the biosimilar market is attracting a swarm of pharmaceutical and biotechnology companies to a market estimated at US$2 billion in the USA alone in 2012 and a projected rise to nearly $20 billion by 2018 [3] and [4]. However, physicians may view this as something of a biotechnical bubble, far from the reality of clinical practice as, until now, there is no solid scientific evidence supporting the use of biosimilars in autoimmune diseases. The doubts expressed about the safe, efficacious use of biosimilars seem to augment rather than diminish. Biosimilars are copies of biological agents, which are complex proteins involved in the immune response [overwhelmingly monoclonal antibodies (mAbs)]. Biologicals are a complex collection of large protein isoforms with two crucial functional features: affinity and selectivity, which are highly dependent on post-translational events such as glycosylation[5] and [6]. All alterations result in significant functional variations and, therefore, exact replicas of mAbs are extremely difficult, if not impossible, to obtain [7]. Physiochemical and biological methods of characterizing mAbs are increasingly sophisticated, but comparison of biosimilars to the reference biologic remains difficult. Biosimilar development requires significant investment, technical capability and clinical trial expertise, with estimated average costs of $200–250 million [8].

Biosimilars are not generic drugs and their licensing requires a different regulatory approach. Europe was the first region to establish specific regulatory approval processes for biosimilars, based on scientific data and maintaining the stringent standards required for the original biologic. The Biosimilar Medicinal Products Working Party (BMWP) of the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) has launched various guidelines and rules for the use of biosimilars containing biotechnology-derived proteins (572643/2011 and 572828/2011), with an updated review discussing and accepting external amendments. The EMA guidelines on biosimilars based on mAbs (632613/2009 and 403543/2010) clearly differentiate between those with cytotoxic mechanisms of actions (mainly anti-cancer mAbs) and immunomodulatory mAbs (overwhelmingly used in autoimmune diseases). The main objective is to establish non-clinical and clinical requirements to guide applicants for standardized development programs. The USA lags somewhat behind Europe in this field, since the Food and Drug Administration (FDA) has not yet issued a specific regulatory pathway similar to the EMA proposal. The Biologics Price Competition and Innovation (BCPI) Act outlined shortened approval processes for “highly similar” biologic products, enabling evaluation of biosimilars against a single, already-licensed, reference biologic therapy [9]. In February 2012, the FDA issued draft industry guidance on implementation of the BPCI Act approval process.

The World Health Organization (WHO) also provided norms and standards for the evaluation of these products in 2009 [10]. Written standards established through the Expert Committee on Biological Standardization at the WHO (ECBS) may serve as a basis for setting national requirements for production, quality control and overall regulation of biological medicines. These norms require documentation of the manufacturing process, preclinical physiochemical studies, toxicity study in animals, clinical pharmokinetic studies comparing the biosimilar product to the original biological, phase III clinical efficacy studies, immunogenicity studies in humans, and an appropriated pharmacovigilance plan.

However, controversy is anticipated with interests supporting or opposing the biosimilar approval pathway [11].

Some government agencies in Asia (e.g. Japan, Malaysia, Singapore, South Korea, Sri Lanka and Taiwan) have established their own regulatory pathways for the evaluation and approval of biosimilar agents, which may differ from EMEA and FDA positions.

At present, China is developing regulations that specify requirements for the evaluation and approval of biosimilars based on the WHO guidance, although biosimilar agents to treat patients with rheumatic diseases are already commercialized [12].

Efforts are centered mainly on developing biosimilars for the four most-frequently used biological agents, whose patents expire in the next few years (Table 1).

2. Rituximab

The development of rituximab biosimilars is ongoing. Reditux®, a rituximab copy manufactured by India-based generic drug manufacturer, Dr Reddy's Laboratories, was the first intended copy of mAb launched, being introduced in India in April 2007 at 50% of the original price. Likewise, Kikuzubam® is manufactured by the Mexican firm, Probiomed, and is used in Mexico, Bolivia, Peru and Chile. Several companies are conducting phase I and II studies of rituximab biosimilars in rheumatoid arthritis (Table 1). The completion of Boehringer Ingelheim's phase III trial of its rituximab biosimilar (BI 695500) is expected in April 2015. However, recent communications have cast a shadow on the extremely-rapid, seemingly-promising development of biosimilars. In October 2012, Teva suspended plans for a phase III clinical trial of its rituximab biosimilar in rheumatoid arthritis, while Samsung Electronics has also temporarily ceased clinical development of its biosimilar [13]. Exact reasons were not given in either case, but it would be interesting to know whether economic and/or technical reasons were involved.

3. Infliximab and adalimumab

In February 2012, Celltrion announced the successful completion of a clinical program of its infliximab biosimilar, Remsima® (CT-P13) including 874 patients with active rheumatoid arthritis (257 patients in phase I; 617 patients in phase III) from 100 hospitals in 19 countries. The 30-week phase III trial measuring American College of Rheumatology 20% improvement criteria (ACR20) had response rates of 73% with Remsima® and 70% with original infliximab, and found no significant pharmacokinetic differences between the biosimilar and the original [14]. Infection-related adverse advents were reported in 46 (15%) and 51 (17%) patients in the CT-P13 and infliximab arms, respectively, and tuberculosis in 3 and 1 patients, respectively.

Preliminary positive results of a phase I randomized controlled trial in 250 ankylosing spondylitis patients were presented at the last EULAR meeting [15].

In late July 2012, the Korean Food and Drug Administration (KFDA) approved Remsima® for use in RA, Crohn's disease, ulcerative colitis, ankylosing spondylitis, and psoriatic arthritis. The price is 30% lower than the current original Infliximab price and it is already commercially available. According to the September 2012 EMA list of applications for new human medicines under CHMP evaluation, two applications for biosimilar versions of infliximab will be reviewed. Adalimumab will lose patent protection in the USA, Japan and European Union in 2016, 2017 and

2018, respectively, and companies are working to develop adalimumab-based biosimilars for the same indication of the original biological.

4. Etanercept

In October 2009, the Taiwan-based Mycenax announced its etanercept biosimilar, TuNEX®, had successfully completed phase I trials in 23 healthy Korean male volunteers[16]. A Taiwanese phase III study is underway and Mycenax is seeking partners for its introduction in other markets. Other etanercept intended copies are currently marketed in China (Yisaipu) and Colombia (Etanar), and the HD203 compound is under evaluation in Korean RA patients [17].

5. Immunogenecity

The number and diversity of reported autoimmune diseases triggered by biological agents has increased in parallel with their increasing use [18] and [19]. Biological agents have been related with the development of advert events including autoimmune process [20]and physicians should bear this in mind when biosimilars are postulated as therapies for autoimmune diseases. Impurities in biological products, structural modifications resulting from the manufacturing and/or suboptimal storage conditions can increase the risk of immunogenicity, leading to the possible production of antibodies against any biosimilar component [21]. Human anti-monoclonal antibodies (HAMAs) may bind to and attenuate or inactivate the biosimilar, resulting in hypersensitivity reactions such as allergy or serum sickness, or even unexpected autoimmune effects. This was reported in 2002, when some patients treated with a recombinant erythropoietin developed autoimmune-related pure red-cell anemia [22] and [23].

6. Current and future perspectives

Currently, there is a startling disconnect between the development of biosimilars and the scarcity of scientific information on their safety and efficacy in patients with autoimmune diseases. For example, at the 2012 European League Against Rheumatism (EULAR) and ACR meetings, only two abstracts on the use of biosimilars in autoimmune diseases were presented [14] and [15]. Physicians probably know the concept and potential cost-benefits but require further evidence before accepting that biosimilars are effective, safe, cheaper options to biologics. The outlook is further complicated by the fact that the regulatory rules for biosimilars are at very-different stages in the US, European and *pharmemerging*markets and even vary by country.

Transparency regarding the results of ongoing trials (especially with respect to emerging safety issues) and involvement in the planning and conduct of future trials and regulatory rules is required. Feedback on the EMA draft guidelines mainly comes from representatives of regulatory agencies, pharmaceutical companies and patient organizations, but not from any national or European medical associations. As stated by Ebbers et al. [24], “when regulators fail to involve doctors in their activities, this will impede the acceptance of the cost-effective and innovative medicinal products of the future.” Greater engagement between regulatory authorities, pharmaceutical companies and the medical community would be welcome to be sure that the full process, from synthesis to manufacturing meets the highest standard to guarantee efficacy and safety. The potential save in cost related to biosimilar use should not have an impact in the outcome of our patients.

Take-home messages

• Biological agents represent a revolution in the treatment of autoimmune diseases.

• Biosimilars are not “generic” of biological agents as biological cannot be copied.

• Biosimilars' license requires a different regulatory approach from generic ones.

• Biosimilar may represent a potential save in cost.

• The highest standards in manufacturing are required to guarantee efficacy and safety.

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Table 1.

Pipeline for development of biosimilars in autoimmune diseases.

Drug	Correspondent biological	Manufacturer (location)	Primary outcome measures
Preclinical trails			
Avent™[a]	Etanercept	Avesthagen (India)	Efficacy and toxicity
PRX-106[b]	Etanercept	Protalix Biotherapeutics (Israel)[a]	Efficacy and toxicity
Clinical trials (phase/state[c])			
BI695501 (I/completed)[c]	Adalimumab	Boehringer Ingelheim Pharmaceuticals (Germany)	– Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity [Time Frame: 72 days] – Maximum measured concentration of the analyte in plasma [Time Frame: 72 days]
LBEC0101 (I/completed)[c]	Etanercept	LG Life Sciences Ltd. (South Korea)	Etanercept levels in blood [time frame: 22 day]
CT-P10 (I in AR/recruiting)[c]	Rituximab	Celltrion (South Korea)	Compare pharmacokinetics in terms of C_{max} [time frame: up to week 24]
PF-05280586 (I and II in AR/recruiting)[c]	Rituximab	Pfizer (US)	Pharmacokinetic parameter C_{max} [time frame: week 25] Pharmacokinetic parameter AUC 0-∞ [Time Frame: Week 25]
GP2013 (I and II in AR/recruiting)[c]	Rituximab	Sandoz Biopharmaceuticals (Switzerland)	Compare pharmacokinetics of GP2013 and rituximab following IV infusion in patients with RA [time frame: 24 weeks]
TL011 (I and II in AR/completed)[c]	Rituximab	Teva Pharmaceutical Industries (Israel)	Compare pharmacokinetics of rituximab following IV infusions of TL011 and MabThera® in subjects with RA
HD203 (I and III in AR/completed; Active, not recruiting)[c]	Etanercept	Hanwha Chemical (South Korea)	Etanercept levels in blood [time frame: 21 days] – To prove the equivalence between two groups by comparing the ACR20 of W24 with the baseline after injecting HD203 and Enbrel® into rheumatoid arthritis patients for 24 weeks
TuNEX (III)[c]	Etanercept	Mycenax Biotech (Taiwan)	The primary efficacy endpoint is defined as ACR20 responder at last treatment visit (Week 24).

Drug	Correspondent biological	Manufacturer (location)	Primary outcome measures
CT-P13 (I in AS and III in AR/active, not recruiting)[c]	Infliximab	Celltrion (South Korea)	Long term efficacy evaluated by American College of Rheumatology (ACR) criteria and Long term safety evaluated by immunogenicity and clinical laboratory test [time frame: up to week 40]
Marketed (location)			
Yisaipu (China)	Etanercept	Shanghai CP Goujian Pharmaceutical Co. (China)	
Etanar® (Colombia)	Etanercept	Shanghai CP Goujian Pharmaceutical Co. (China)	
Reditux® (Bolivia, Chile, India and Peru)	Rituximab	Dr Reddy's Laboratories (India)	
Kikuzubam® (Bolivia, Chile, Mexico, and Peru)	Rituximab	Probiomed (Mexico)	
Development or pipeline			
Development	Adalimumab, rituximab	BioXpress Therapeutics S. A. (Switzerland)	
Pipeline	Abatacept, Etanercept, Golimumab, Infliximab, Tocilizumab	BioXpress Therapeutics S. A. (Switzerland)	

AS: ankylosing spondylitis; AR: rheumatoid arthritis.

a http://www.avesthagen.com/docs/020910pr.pdf

b http://www.protalix.com/index.asp.

c Data from clinicaltrails.gov at February 2013.