The role of biosimilars in the treatment of rheumatic diseases

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ABSTRACT

The first biological therapeutics in rheumatology are approaching patent expiration, encouraging development of ‘follow-on’ versions, known as ‘biosimilars’. Biological agents range from simple replacement hormones to complex monoclonal antibodies and soluble receptors: large, intricate proteins with unique tertiary and quaternary structures that are inherently difficult to replicate. Post-translational modifications, such as glycosylation, may occur from changes in cell lines and/or manufacturing processes, resulting in products that are highly similar, but not identical, to approved ‘reference’ agents, hence the term ‘biosimilar’, rather than ‘bioidentical’. Even minor modifications in manufacturing processes, which iteratively occur with reference products, may alter biological functions, such as efficacy and safety, and their impact on patient care.

INTRODUCTION

The introduction of biological therapeutics for treatment of rheumatic diseases has significantly improved patient outcomes.1 With some of these ‘reference (originator) products’ approaching patent expiration, manufacturers are developing follow-on versions.2 Biosimilars may improve access to expensive biological agents; however, concerns have been raised regarding their clinical use. In particular, due to the complexities of manufacturing ‘copies’ of biological therapeutics, physicians have questioned whether biosimilars will confer identical biological function, efficacy and toxicity to reference products, both in the short and long term.3 4 These concerns are not without substantiation, since even minor modifications in manufacturing processes, which iteratively occur with reference products, may alter biological functions and/or immunogenicity, potentially changing their safety and efficacy profile5 (table 1). Biological agents range from simple replacement hormones to complex monoclonal antibodies (mAbs) and soluble receptor constructs (Cepts)—large, intricate proteins with unique tertiary and quaternary structures that are inherently difficult to replicate. Post-translational modifications, such as glycosylation, may occur from changes in cell lines and/or manufacturing processes, resulting in products that are highly similar, but not identical to approved ‘reference’ agents, hence the term ‘biosimilar’, rather than ‘bioidentical’. The potential for protein modification to alter biological function is especially true for intricate therapeutic proteins, such as mAbs and Cepts.

With the expected introduction of biosimilar mAbs and Cepts, it is important that rheumatologists are familiar with biosimilars, so allowing informed treatment decisions. In order to facilitate this, a panel of international experts convened in Berlin in April 2012 for the roundtable on ‘the role of biosimilars in the treatment of rheumatic diseases’. The roundtable provided a forum to discuss the potential clinical utility of biosimilars in rheumatology, implications for product efficacy and safety, and their impact on patient care. This article reviews the topics discussed at this meeting, providing physicians with current information in this rapidly evolving field.

RATIONALE FOR THE DEVELOPMENT OF BIOSIMILARS

In 2012, worldwide sales of the top three selling TNFα inhibitors (TNFi) reached US$20 billion,13 with total annual sales for rheumatic disorders approaching US$30 billion per year. This amounts to a US$10 000–50 000 per patient per year financial burden to patients or third-party payers of healthcare. In addition, there is a humanistic burden due to restricted access caused by budget constraints in many countries around the world. Thus, there is significant interest in efficacious, lower-cost biosimilars.

DEFINING BIOSIMILAR

A biosimilar is ‘a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product’, with similarity defined as ‘the absence of a relevant difference in the parameter of interest’.14 Biosimilars should be developed strictly in accordance with comparative procedures used for reference products, as mandated by regulatory authorities, such as the European Medicines...
Agency (EMA) or US Food and Drug Administration (FDA). These stringent processes ensure that no clinically meaningful differences exist between the biosimilar and the reference product in terms of ‘safety, purity and potency’ (FDA), or ‘quality, safety and efficacy’ (EMA).\(^{15,16}\)

Currently, several products labelled as ‘biosimilars’ are approved for treatment of rheumatoid arthritis (RA) in a number of countries that, at the time of approval, did not have stringent regulatory processes in place to ensure comparability as defined by EMA and FDA (table 2).\(^{17}\) While these products apparently meet local regulatory requirements, they should not be considered biosimilars, but rather, ‘intended copies’. Physicians must be aware of the distinction between these and ‘true’ biosimilars that meet EMA/FDA standards, as well as the differences between biosimilars and other ‘biological copies’ (table 3).\(^{18}\)

Currently, there are no biosimilar mAbs or Cept.s approved by EMA or FDA for treatment of rheumatic diseases,\(^2\) although randomised controlled trials (RCTs) are complete or on-going (table 4).\(^{17}\) Earlier in 2012, the South Korean company, Celltrion, filed for EMA approval of a biosimilar infliximab product, CT-P13.\(^{20}\) Two large RCTs—one in 600 RA patients\(^{24}\) and another in 250 patients with ankylosing spondylitis (AS)\(^{25}\)—indicate that the efficacy, safety and immunogenicity of CT-P13 are highly similar to infliximab. This biosimilar has recently been approved by the Korean authorities for several indications, including RA and AS.\(^{19}\)

### Table 3 Definitions of therapeutic products

<table>
<thead>
<tr>
<th>Product</th>
<th>Alternative names</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic</td>
<td>–</td>
<td>Exact copy of a small-molecule drug, synthesised via chemical means, with structural and therapeutic identity to the reference product</td>
</tr>
<tr>
<td>Biosimilar</td>
<td>Follow-on biologic (USA); subsequent entry biologic (Canada); similar biotherapeutic product (WHO)</td>
<td>A biological product that is highly similar to a reference product in terms of quality, safety and efficacy and/or safety, purity and potency demonstrated by rigorous comparability exercises</td>
</tr>
<tr>
<td>Second-generation biological</td>
<td>Biobetter</td>
<td>A structurally/functionally altered biological product resulting in improved or different biological activity from the reference</td>
</tr>
<tr>
<td>Me-too biological</td>
<td>Non-innovator biological</td>
<td>A biological product developed with the same target antigen but without demonstrated comparability to the reference product</td>
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</tbody>
</table>

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**Table 1 Prior changes in manufacturing processes**

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturing change</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon α2A</td>
<td>Bifereonics bioplayers had only one cell but could not produce identical product.</td>
<td>No approval</td>
</tr>
<tr>
<td>Interferon β1A</td>
<td>Produced by biologen in new mammalian cell line.</td>
<td>Initial production stopped</td>
</tr>
<tr>
<td>rhHuEPO: Eprex</td>
<td>Ortho bohich switched protein stabiliser from human serum albumin to detergent polysorbate 80, with variations in storage and handling; 2003 introduced prefilled syringe w/rubber plug.</td>
<td>Aggregate formation led to formation of anti-EPO Abs and 175 cases of pure red cell aplasia 1998–2004</td>
</tr>
<tr>
<td>p55TNF-R:lg:</td>
<td>Manufacturing processes yielded product with differing glycosylation patterns, resulting in differences in pharmacokinetics and efficacy.</td>
<td>Development discontinued</td>
</tr>
<tr>
<td>Muromonab antithox:</td>
<td>Switch to manufacturing in dialysis tubing resulted in loss of efficacy.</td>
<td>Development discontinued</td>
</tr>
<tr>
<td>Primatised cCD4:</td>
<td>Working cell bank switched to facilitate manufacturing scale-up. Resulted in CD4 T cell depletion and loss of efficacy.</td>
<td>Development discontinued</td>
</tr>
<tr>
<td>p75TNF-R:lg: etanercept: Enbrel</td>
<td>Major differences in glycosylation pattern after 2009 suggest a manufacturing change.</td>
<td>Iterative manufacturing change</td>
</tr>
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</table>
there is no public regulatory determination of comparability similar to the European Public Assessment Report,26 so physicians and patients may never know a manufacturing change has occurred. Clinical testing is, however, mandated when sufficient changes to the reference product occur. Importantly, these alterations are made with a knowledge of the original manufacturing process, which differs from biosimilar development for altered biological activity and/or safety. Biosimilars manufactured under such conditions must be reproduced30: glycosylation patterns are not template set forth by EMA and FDA, neither an agreement nor a ‘superior’ product would qualify as a biosimilar,32 33 due to the potential for altered biological activity and/or safety. Biosimilars manufacturers must ensure sufficient analyses are performed to demonstrate a high degree of similarity between reference agents and biosimilars, prior to their entry into equivalence trials.

### Importance of conformational structure for biological effect

Affinity is a key determinant of the pharmacokinetic (PK) and pharmacodynamic (PD) profile of mAbs and Cepts, potentially impacting their dosing regimen.24 Thus, it is important to determine plasma levels and obtain accurate PK and PD data for biosimilars. Antibody binding to target antigen is determined by affinity, but even when affinity is high, concentrations must be adequate to maintain effective binding. The importance of affinity for determining dosing regimens is highlighted by two human TNFα mAbs, adalimumab and golimumab, with similar in vivo half-lives and sizes. Both recognise the same target, albeit different epitopes, yet one is administered every 2 weeks and the other monthly. Higher binding affinity for golimumab appears to be the predominant difference, allowing efficacy to be maintained at lower serum concentrations.24 These data highlight the importance of binding affinity for biological efficacy, reflecting the need for close reproduction of conformational structure for biosimilar mAbs and Cepts.
Immunogenicity

All biological agents are immunogenic because they are non-self; even humanised and ‘fully human’ mAbs and Cepts can result in measurable immune responses. Many factors can influence immunogenicity, such as changes in glycosylation patterns that may expose or hide antigenic components, alter solubility or influence protein degradation. Importantly, experience has demonstrated that presence of aggregates, impurities or contaminants can provoke unwanted immune responses. Thus, alterations in manufacturing processes/storage conditions may result in altered immunogenicity of biosimilars compared with reference products.

The effects of antibiological antibodies include reduction in serum levels, adverse events and formation of neutralising antibodies. Anti-infliximab antibodies have been associated with infusion reactions in patients with Crohn’s disease, while antiadalimumab antibodies may heighten the risk of rare thromboembolic events in patients with RA and psoriatic arthritis. Postmarketing surveillance of TNfi mAbs has identified a potential link between antibiological antibodies and treatment-related vasculitis, albeit very rare events. It is therefore important to implement clinical trials of sufficient size and duration to determine the safety of biosimilars and postmarketing surveillance to identify rare adverse events. This is also important for reference products that undergo iterative manufacturing process alterations resulting in consequences if significant changes occur.

Most commonly, immunogenicity contributes to loss of clinical efficacy, that is, tachyphylaxis. Loss of clinical responses to TNfi occur over time, and have been associated with the presence of antibiological antibodies in some patients. This is more common in those with Crohn’s disease, where intermittent administration is more frequent and background medication less commonly utilised when compared with RA.

Route of administration and host-related factors also influence immunogenicity. Patients with autoimmune diseases more commonly develop antibiological antibodies, as well as naturally occurring anticytokine autoantibodies. Consideration of separate clinical trials for biosimilars in different therapeutic indications is therefore important.

Fc effector function

Activity of mAbs and Cepts depends not only upon interactions with target antigen, but also Fc receptor (FcR) function. Modifications of just one amino acid are sufficient to impair Fc interactions, thereby altering complement activation and/or antibody-dependent cytotoxicity, and reducing the efficacy of therapeutic mAbs. For example, two anti-CD20 mAbs, ofatumumab and rituximab, display different levels of B cell depletion, potentially due to altered fucosylation patterns. Due to constraints in confomational changes, etanercept exhibits reduced complement binding compared with infliximab and adalimumab. Efficacy of mAbs can also be affected by individual patient characteristics: in patients with RA and psoriatic arthritis, FcR polymorphisms result in different responses to TNfi. Biosimilars must, therefore, demonstrate highly similar efficacy and safety to the reference product in well-designed RCTs.

Properties of biosimilars: how similar is similar enough?

The key question for biosimilars is whether differences exist compared with the reference, but whether differences are clinically relevant. Microheterogeneity is a feature of batch-to-batch variability for any biological agent, and sometimes major changes occur with alterations to manufacturing processes; the degree of variability is assessed with quality control of each batch. As manufacturing processes for biologics become more efficient, batch sizes increase, and only one or two batches may account for the entire use of a reference product in the European Union (EU) or USA over a 1-year period. For biosimilars, it is necessary to establish ‘acceptable variation’ parameters for comparability with the reference product. If comparisons are to a single batch, then these parameters will be more narrow than the batch-to-batch variation of the reference product.

Given their inherent complexity, biosimilar mAbs and Cepts cannot be absolutely identical to the reference. However, certain fundamental features must be retained (table 5). Even sophisticated comparability testing, in vitro assays and animal studies cannot fully predict the biological and clinical activity of a therapeutic mAb; the only way to sufficiently assess the efficacy and safety of biosimilars is via RCTs in patients with the disease in question. Concerns surrounding the immunogenicity of biological products have previously been compounded by the limited clinical relevance of standardised assays for antibiological antibodies. However, the emergence of biosimilars has encouraged development of more robust assays that can detect antibodies in the presence of higher circulating levels of mAbs and Cepts, which can be used in clinical settings.

THE BIOSIMILAR APPROVAL PROCESS AND CLINICAL CONSIDERATIONS

EMA led the way in developing a pathway for the approval of biosimilar agents in the EU. Guidance for the approval of biosimilar agents containing mAbs was issued in May 2012. In February 2012, FDA released a three-part draft guidance document outlining the approval pathway for biosimilars in the USA based on the Biologics Price Competition and Innovation Act (BPCIA) passed on 25 March 2010.

The aim of the clinical development programme

Acceptance of biosimilars among rheumatologists requires an understanding of the regulatory processes governing their approval. For EMA and FDA, a biosimilar clinical development programme must demonstrate equivalence to a reference product already licensed (and manufactured) for use in Europe or the USA, respectively. The aim is distinct from a de novo approval pathway, where establishing safety and efficacy, respectively, is the ultimate goal. A demonstration of biosimilarity will establish patient benefit and safety.

Demonstrating biosimilarity

Demonstrating biosimilarity differs significantly from generic drug approval, where only PK equivalence must be shown. Extensive, non-clinical physiochemical and biological characterisation is required to address structural, functional and immunogenicity concerns, prior to efficacy and safety trials. Thus, the chemistry, manufacturing and controls portion of a biosimilar application is likely larger and more detailed than that of the reference product. The non-clinical portfolio must provide comparability data that are almost superimposable with the reference, through the use of ‘fingerprint’-like analyses to detect differences between highly complex mAbs.

Clinical data requirements differ in the EU and the USA (table 5). However, the same basic principle is followed: equivalence, as opposed to superior safety and efficacy must be demonstrated. Both EMA and FDA require RCTs to be of sufficient
size to establish clinical equivalence; however, rare adverse events and long-term efficacy and safety will be assessed through postmarketing surveillance. Thus, as for reference agents, stringent postapproval pharmacovigilance is paramount.

Extrapolation of clinical indications

Extrapolation of clinical data permits the approval of a biosimilar for a therapeutic indication in which it has not been clinically evaluated, but for which the reference agent is approved. Both EMA and FDA advocate extrapolation, and have outlined measures to address the concerns associated with it (table 6). The rationale is that if biosimilarity is confirmed using EMA/FDA criteria, it is scientifically reasonable to assume that the biosimilar will behave in a similar manner to the reference in all clinical scenarios. Indeed, Celltrion’s TNFi demonstrated equivalent efficacy to infliximab in RA and AS.24 25

However, extrapolation may be less appropriate when the two therapeutic indications involve distinctly different practices and disease biology,56 and will therefore be considered by EMA/FDA ‘case-by-case’ (table 6). While extrapolation criteria have been designed to mitigate many concerns, extrapolation should be clearly indicated in the product label.

Postapproval pharmacovigilance

Both EMA and FDA emphasise the need for postmarket surveillance for biosimilars. Adverse event reports should contain as much information as possible, identifying the specific agent, type of event and its occurrence.57 This will be particularly important for documenting events occurring as a result of switching between reference and biosimilar agents. The ability to differentiate between reference and biosimilar agents will also be paramount, raising issues regarding naming of biosimilars.

Automatic substitution and naming

Automatic substitution would enable pharmacists to dispense a biosimilar, instead of the reference agent, without prior consent of the prescribing physician. EMA does not have the authority to designate a biosimilar as automatically substitutable.2

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Table 5 Essential characteristics and clinical study requirements for the approval of biosimilar products in the EU and USA

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EMA requirements</th>
<th>FDA requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary amino acid sequence</td>
<td>One amino acid change respective to the innovator will deny biosimilarity</td>
<td>Must match the reference product</td>
</tr>
<tr>
<td>Potency</td>
<td>Must match the reference product</td>
<td></td>
</tr>
<tr>
<td>Route of administration</td>
<td>Must be the same as the reference product, although the administration device may be different</td>
<td></td>
</tr>
<tr>
<td>Higher-order structures, post-translational modifications and other potential variants</td>
<td>Must be as similar as possible to the reference product, with adequate analyses to demonstrate that any differences do not impact upon clinical efficacy, safety or immunogenicity</td>
<td></td>
</tr>
</tbody>
</table>

Clinical study parameter

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EMA</th>
<th>FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetic studies</td>
<td>Comparative human studies</td>
<td>Single dose, comparative human studies</td>
</tr>
<tr>
<td>Pharmacodynamic studies</td>
<td>Comparative human studies, where clinically relevant measures are available</td>
<td>Combine with PK studies where a clinically relevant PD endpoint is available. Otherwise non-clinical evaluation required</td>
</tr>
<tr>
<td>Efficacy</td>
<td>At least one, adequately powered equivalence trial</td>
<td>Highly sensitive, dose-comparative PD studies may be sufficient. Otherwise, at least one, adequately powered equivalence trial</td>
</tr>
<tr>
<td>Safety</td>
<td>At least one, adequately powered equivalence trial</td>
<td>At least one, adequately powered equivalence trial</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>At least two comparative trials, one pre- and one postmarketing</td>
<td>Must be assessed during the safety trial</td>
</tr>
</tbody>
</table>

*Differences in the specified parameters and the 95% CI fall within a predetermined equivalence margin, demonstrating that the biosimilar is both ‘non-inferior’ and ‘non-superior’ to the reference product.

EMAs, European Medicines Agency; FDA, Food and Drug Administration; PD, pharmacodynamic; PK, pharmacokinetic.

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Table 6 EMA and FDA response to concerns regarding extrapolation of clinical data

<table>
<thead>
<tr>
<th>Concern</th>
<th>EMA</th>
<th>FDA</th>
<th>Points to consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA may be distinct in each therapeutic indication</td>
<td>Extrapolation will be considered on a case-by-case basis. Where the MOA differs between indications or are not fully understood, separate clinical trials are likely to be necessary</td>
<td>For instance, separate trials are likely to be necessary for rheumatology versus oncology.</td>
<td></td>
</tr>
<tr>
<td>For a given MOA, several mechanisms may exist</td>
<td>Almost superimposable biological data must be provided, covering all functional aspects of the agent, even if not considered clinically relevant. Where MOA are not fully understood, separate clinical trials are likely to be necessary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of undertreating patients/varied safety profiles in different patient groups</td>
<td>Data should be produced using a patient population and clinical endpoint most sensitive to detect clinically meaningful differences in efficacy and safety</td>
<td>Disease activity at baseline represents an important variable related to outcome measures in RA—likely to have limited impact on a direct comparison between biosimilar and reference products when sensitive measures are used, but needs consideration when efficacy is compared with reference product trials.</td>
<td></td>
</tr>
<tr>
<td>Individual patient characteristics may influence the response</td>
<td>Homogeneous population should be used—differences in response can then be attributed to the biosimilar.</td>
<td>Careful consideration must be given to comorbidities/comorbid medications and intersubject variability.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EMA approach—it will be difficult to identify a homogeneous population for a heterogeneous condition such as RA</td>
</tr>
</tbody>
</table>

EMA, European Medicines Agency; FDA, Food and Drug Administration; MOA, mechanism of action; RA, rheumatoid arthritis.
although each country will follow its own national guidelines. In the USA, two approval pathways are expected, one for biosimilar
which are ‘highly similar’ to the reference, and another, more rigorous pathway for ‘interchangeable’ products that are
eligible for automatic substitution.54 BPCIA states: ‘to meet the
higher standard of ‘interchangeability’, an applicant must
provide sufficient information to demonstrate biosimilarity, and
also to demonstrate that the biological product can be expected
to produce the same clinical result as the reference product in
every patient and, if the biological product is administered
more than once to an individual, the risk in terms of safety or diminished
efficacy of alternating or switching between the use of
the biological product and the reference product is not
greater than the risk of using the reference product without
such alternation or switch.55 The exact criteria allowing
designation of a product as ‘interchangeable’ are still under consider-

Substitution may complicate effective pharmacovigilance, as
repetitive switching of agents may subvert the ability to attri-
bute adverse events to the appropriate agent, and could force
withdrawal of treatment. Therefore, it will be important that a
name or feature can distinguish those biosimilars with au-

mation of a product as

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dequate information to demonstrate biosimilarity, and
also to demonstrate that the biological product can be expected
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efficacy of alternating or switching between the use of
the biological product and the reference product is not
greater than the risk of using the reference product without
such alternation or switch.55 The exact criteria allowing
designation of a product as ‘interchangeable’ are still under consider-
by FDA.

WILL BIOSIMILARS BE SUCCESSFUL?
The role of biosimilars in rheumatic diseases will be determined
by the confidence placed in them by rheumatologists; stringent
regulatory approval processes are designed to provide this. To
date, the uptake of biosimilars in European and US markets has been
limited,2 56 which may be explained by the relatively
modest cost savings of 15–50% compared with ~80–90% afforded by generic drugs.57 58 It is currently difficult to predict
cost savings for biosimilar mAbs and Cepts in highly regulated
markets. In other regions, economic pressures and significant
cost savings have forced the use of ‘intended copies’ despite the
concern that their safety and efficacy have not been adequately characterised.17 Regarding ‘true’ mAbs and Cepts, several ‘refer-
ence product’ manufacturers are currently engaged in biosimilar
development and production,21 22 60–62 indicating that this field is
of significant interest.

SUMMARY AND CONCLUSIONS
It is important that rheumatologists distinguish between bio-
logical ‘intended copies’ and biosimilars. To attain biosimilar
status, an agent must undergo the required comparability qual-
ification in accordance with scientific principles endorsed by
authorities, such as EMA or FDA. Despite these stringent
approval processes, significant savings in costs are expected.
Once available, physicians prescribing them must be aware of
any developments concerning biosimilars, and be vigilant in
their use.

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