Biosimilars: In support of extrapolation of indications
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Abstract
Biosimilars have the potential to lead to enormous cost savings in healthcare without reducing the level of care for patients. In Europe, biosimilars have to demonstrate comparability in an extensive biosimilarity exercise including analytical, preclinical and comparative clinical studies. By successfully completing the biosimilarity exercise, the biosimilar shows that all aspects that are considered relevant for the clinical activity of the product fall within the same range as observed for the innovator. It should be carefully considered whether the benefit of additional information from more comparative clinical studies weighs up to the additional barriers such studies create for biosimilars to enter clinical practice.

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1. Introduction
In September 2013 a biosimilar version of Infliximab (Remicade®) received marketing authorization in the European Union. The product is developed by Celltrion as CT-P13 and sold as Remsima® by Celltrion and Inflectra® by Hospira. In Europe, in order to obtain marketing authorization as a biosimilar, a stepwise approach should be followed. Generally this means starting with a comparison of physicochemical characteristics, followed by in vitro and (possibly) in vivo data, and finally comparative clinical studies that should be performed in the most ‘sensitive’ patient population. It should always be so that applicants provide sufficient data to support that a product is comparable to the reference product in all indications.1

Much debate has centered on which data is required to grant an approval for all indications of the reference product.2 European guidance states that — if adequately justified — biosimilars may receive all authorized indications of the reference product, even though comparative clinical data is only provided for a subset of authorized indications, so-called ‘extrapolation of indications’. In Europe, all indications belonging to Remicade® were granted to the biosimilar product based on comparative clinical studies in rheumatoid arthritis and ankylosing spondylitis only.3 Various learned societies have taken the position that extrapolation of

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indications should never be allowed and that clinical data should be required for all indications. Others have generally supported extrapolation and advocated for careful post-authorization monitoring of the biosimilar. Here some considerations are presented to support the extrapolation of data to allow marketing authorization based on a tailored clinical development program.

2. Preclinical

According to European guidance, products that do not have the identical primary structure as their reference product cannot follow the biosimilar pathway. The activity of tumor necrosis factor-α inhibitors (TNFis) can be assessed in various assays, although the exact contribution of the various functions to the clinical efficacy and safety is not fully elucidated. TNFα binding affinity is determined by the complementarity determining region of the antibody and the TNFα receptor-domain, in the case of etanercept. Effector functions are mainly mediated by the Fc-portions, whereas certolizumab lacks effector functions. For infliximab, glycosylation is limited to the Fc region and has been shown to influence Fc-mediated effector functions, including antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

For CT-P13 physicochemical characterization demonstrated that the product is highly similar to Remicade® (Table 1). The TNFα binding properties of CT-P13 were indistinguishable from Remicade® and consistent throughout various batches. A small difference in the amount of afucosylation was observed for CT-P13 that translated to a slightly lower binding affinity towards FcγRIIa receptor. However, this did not lead to differences in CDC or ADCC assays and was not considered to be clinically relevant by the EMA. All effector functions of CT-P13 fell within the range observed for Remicade®, CT-P13 demonstrated comparable dose-dependent suppression of cytokine secretion in various human cell lines including intestinal epithelial cells to support activity in inflammatory bowel disease.

Differences in glycosylation are not known to have a relevant impact on the pharmacokinetic (PK) behavior of monoclonal antibodies, so it is unlikely that microheterogeneity will affect PK behavior of the biosimilar. Indeed, the PK properties of CT-P13 were comparable to Remicade® both in rodent in vivo models and in patients.

3. Clinical comparability

If analytical and non-clinical studies demonstrate that a product is sufficiently similar to the reference product, comparative clinical studies are required to establish comparable safety and efficacy. These studies are not intended to demonstrate efficacy per se, but to confirm that the similarity observed in analytical, preclinical and PK studies translate into comparable clinical results. For CT-P13, rheumatoid arthritis patients were chosen (Table 1). Although RA patients are the largest patient population receiving TNFis, from a regulatory standpoint this is somewhat surprising as RA patients usually receive concomitant methotrexate therapy. Immunosuppressants such as methotrexate and azathioprine are known to reduce the incidence of anti-drug antibodies (ADAs) although the lower dose investigated in the PLANETRA study may make the assay to assess ADAs less susceptible to drug interference.

Furthermore, the efficacy of infliximab vs. placebo in rheumatoid arthritis as determined by its preferred endpoint (ACR20 response, 50% vs. 20%) is less pronounced than for example psoriasis (PASI75, 80% vs. 3%).

Nevertheless, the therapeutic efficacy was highly similar the proportion of patients achieving an ACR20 response were 60.9% and 58.6% for CT-P13 and Remicade® respectively for the intention to treat population. Also several pharmacodynamic markers related to the disease activity were measured, including erythrocyte sedimentation rate, C-reactive protein levels and rheumatoid factors, all of which showed a similar decrease for CT-P13 and Remicade®. The number of serious infections reported for CT-P13 was slightly higher than Remicade®, but the numbers were low and were considered to be a chance finding. The incidences of ADAs in both studies were comparable. At week 14, ADAs were detected in 25.4% of patients receiving CT-P13 and 25.8% of patients receiving Remicade®. At week 30 this was 48.4% and 48.2% for patients receiving CT-P13 and Remicade® respectively.

In ankylosing spondylitis patients ADAs were detected in 9.1% (n = 11) and 11.0% (n = 13) of patients for CT-P13 and Remicade® at week 14 and 27.4% (n = 32) and 22.5% (n = 25) of patients for CT-P13

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Attributes of the comparability exercise of CT-P13.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analytical</strong></td>
<td><strong>Primary structure, higher order structures, glycosylation, content, purity, charge variants</strong></td>
</tr>
<tr>
<td>Binding studies</td>
<td>TNFα (monomeric, trimeric and transmembrane), TNF-α, different species TNFα, tissue cross reactivity</td>
</tr>
<tr>
<td>Fab related</td>
<td>FcγRI, FcγRIIA, FcγRIIB, FcγRIlla, FcγRIllB and FcRn</td>
</tr>
<tr>
<td>Fc receptor related</td>
<td>Biological activity</td>
</tr>
<tr>
<td>Non-clinical</td>
<td>PK</td>
</tr>
<tr>
<td>Toxicity</td>
<td>3 repeat dose toxicity studies in rats</td>
</tr>
<tr>
<td>Clinical</td>
<td>CT-P13 1.2 (pilot study)</td>
</tr>
<tr>
<td>PK</td>
<td>CT-P13 1.1 (PLANET AS)</td>
</tr>
<tr>
<td>CT-P13 3.1 (PLANET RA)</td>
<td>Long-term efficacy and safety study (n = 606) in RA patients receiving concomitant MTX (54 weeks)</td>
</tr>
</tbody>
</table>

ADCC = antibody-dependent cellular cytotoxicity, CDC = complement dependent cytotoxicity, MTX = methotrexate, PK = pharmacokinetic. From the European public assessment report. Most assays were performed in cells derived from both healthy donors and Crohn’s disease patients.
and Remicade®, respectively, at week 30. Despite that the patient population chosen may not have been the most sensitive, the incidence of ADA was sufficiently high in both CT-P13 and Remicade® to conclude that it is similar for the two products. The company also provided preliminary clinical data from an observational study in 23 inflammatory bowel disease patients that showed comparable efficacy to historical Remicade® data.

4. Post authorization

To obtain marketing authorization a risk management plan should be submitted for every biosimilar MAB. The following data were considered to be ‘missing information’ for CT-P13: long-term safety in not studied indications (including pediatric indications), use during lactation, lack of efficacy and hypersensitivity reactions (HSRs). The labels of biosimilars contain a black triangle to make prescribers aware that the product is subject to additional post authorization monitoring by the EMA, which should encourage them to report adverse drug reactions. In addition to ‘routine pharmacovigilance’ activities, like collecting adverse event reports, the risk management plan for CT-P13 includes various long term extensions of pre-authorization studies, two additional randomized controlled trials in Japan and Russia and additional post-authorization observational studies to assess the incidence of serious infections (including tuberculosis) with a total targeted enrollment of 6200 patients (Supplementary info Table 1). The companies will also contribute to various existing European registries, like the Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) and British society for rheumatology biologics register.

European regulators granted all indications, including CD and UC, based on literature data, in vitro data and preliminary observational data in a limited number of patients, stating that this evidence is convincing and sufficient to support extrapolation. It is therefore somewhat contradictory that a randomized controlled trial is included to study the efficacy and safety of CT-P13 in Crohn’s disease. The question arises

### Table 2  Characteristics of currently authorized tumor necrosis factor-α inhibitors.

Adapted from Tracey et al.19

<table>
<thead>
<tr>
<th></th>
<th>Infliximab</th>
<th>Etanercept</th>
<th>Adalimumab</th>
<th>Certolizumab-PEGol</th>
<th>Golimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class</strong></td>
<td>MAB</td>
<td>Fc-fusion protein</td>
<td>MAB</td>
<td>PEGylated Fab fragment</td>
<td>MAB</td>
</tr>
<tr>
<td><strong>Structure</strong></td>
<td>Chimeric IgG1 κ</td>
<td>TNFR2-Fc fusion protein</td>
<td>Human IgG1 κ</td>
<td>PEGylated Fab fragment human IgG1</td>
<td>Human IgG1 κ</td>
</tr>
<tr>
<td><strong>Production cell line</strong></td>
<td>Sp2/0 CHO</td>
<td>150 CHO</td>
<td>CHO</td>
<td>E. coli Sp2/0</td>
<td>150</td>
</tr>
<tr>
<td><strong>Molecular weight (kDa)</strong></td>
<td>TNF</td>
<td>TNF/LT</td>
<td>TNF</td>
<td>TFN</td>
<td>TFN</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>IV SC</td>
<td>RA, PsA, AS, CD, UC, Pso</td>
<td>RA, PsA, AS, JIA, Pso</td>
<td>RA, PsA, AS, CD, Pso, UC</td>
<td>RA, CD a</td>
</tr>
<tr>
<td><strong>Administration route</strong></td>
<td>3–5 mg/kg wk 0, 2, 6 Q8W</td>
<td>25 mg TIW or 50 mg QW</td>
<td>80 mg, 40 mg EOW (except UC, 160 mg wk0, 80 mg wk 1, 40 mg EOW)</td>
<td>400 mg at wk 0, 2, 4 and 200 mg EOW</td>
<td>50 mg/month (except UC: 200 mg wk 0, 100 mg wk 2, 50 mg/4 wk</td>
</tr>
<tr>
<td><strong>Half-life (t1/2)</strong></td>
<td>8–9.5 days</td>
<td>-3 days</td>
<td>-14 days</td>
<td>14 days</td>
<td>-12 days</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>++</td>
<td>- c</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Neutralization potency</strong></td>
<td>Soluble TNF</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Trans membrane TNF neutralization</strong></td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Reverse signaling (apoptosis)</strong></td>
<td>+++</td>
<td>+/-</td>
<td>+++</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Reverse signaling (cytokine suppression)</strong></td>
<td>+++</td>
<td>+/-</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>FcγR function</strong></td>
<td>CDC</td>
<td>+++</td>
<td>+++</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td><strong>ADCC</strong></td>
<td>+++</td>
<td>+/-</td>
<td>+++</td>
<td>–</td>
<td>+++</td>
</tr>
</tbody>
</table>

MAB = monoclonal antibody, PEG = poly-ethylene glycol, CHO = Chinese hamster ovary cell line, Sp2/0 = mouse myeloma cell line, TNF = tumor necrosis factor α, LT = lymphotoxin, IV = intravenous, SC = subcutaneous, RA = rheumatoid arthritis, PsA = psoriatic arthritis, AS = ankylosing spondylitis, CD = Crohn’s disease, Pso = psoriasis, EOW = every other week, TIW = twice a week, QW = per week, CDC = complement dependent cytotoxicity, ADCC = antibody dependent cellular cytotoxicity, wk = week, –, not; +/-, very weak; +, weak; ++, moderate; ++++, strong.

a Authorized in the US only.
b Has not been studied in CD.
c Isolated cases of non-neutralizing antibodies against etanercept have been reported, but without loss of clinical response.
5. Residual risk of immunogenicity

If the potency of the product is similar both in the lab and in the clinic and the incidence of ADAs can be reliably assessed pre-authorization and is highly similar, there is no reason to assume that the long-term safety differs from the innovator product. The residual uncertainty is largely limited to a potential increase in hypersensitivity reactions (HSRs). HSRs to the product substance are contraindications in all authorized TNFIs and non-serious reactions occur commonly in all currently authorized TNFIs. In Study CT-P13 3.1, 23 (8%) patients in the CT-P13 arm and 31 (10%) patients in the Remicade® arm experienced HSRs and infusion-related reactions. Serious HSRs such as anaphylaxis are included as safety warnings in all TNFIs with a labeled frequency of uncommon (<100 and >1000) or rare (<1000→10,000). Although it has been reported that murine glycosylation sequences may elicit immune responses, most serious HSRs to infliximab are the result of IgG and/or IgM antibodies against the murine part Fab portion of the antibody and thus its incidence is unlikely to differ significantly from Remicade®.16-18

6. How do biosimilars compare to currently available TNFIs?

One argument against the extrapolation of clinical data for TNFIs is that, even though they all target TNFα, different products vary in their efficacy in different indications. For example, etanercept and certolizumab are not authorized for treating inflammatory bowel disease in the EU, while the full length antibodies are. This has been used as an argument supporting the need for comparative clinical data in all indications before a biosimilar can be granted marketing authorization. Currently authorized TNFIs have widely differing characteristics, in terms of structure, binding affinity, elimination half-life and frequency of administration, which clearly differentiates them from biosimilars.20 (Table 2). Even so, taking only the full length MABs into account, despite considerable differences in characteristics, such as TNFα binding affinity and half-life they all show efficacy in those rheumatology, gastroenterology and dermatology indications that they have been studied in. While differences in efficacy of TNFIs may support the view that product attributes contribute differently to the efficacy in different indications, this cannot be applied to disqualifying biosimilars, which are designed to be highly similar to a product which has demonstrated efficacy in a given indication.

7. Conclusion

Currently authorized TNFIs differ in many aspects that all may affect their efficacy across different indications and differentiate them from biosimilars. Biosimilars are designed to be used exactly the same way as their reference products. Before a biosimilar is authorized in the EU all aspects that are considered relevant for its biological activity are thoroughly assessed and fall within the variation observed for the originator. Furthermore, comparable clinical efficacy, safety and immunogenicity are established in a sensitive patient population. For such products, extrapolating the clinical safety and efficacy to all authorized indications of the reference product based on the overall evidence of comparability provided from the comparability exercise is justified.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.crohns.2014.02.007.

Conflict of interest

No competing interests to declare.

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