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VIEWPOINT

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.

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.[4–7] Others have generally supported extrapolation and advocated for careful post-authorization monitoring of the biosimilar.[8] 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.[9] A small difference in the amount of afucosylation was observed for CT-P13 that translated to a slightly lower binding affinity towards FcγRIIIa 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®.[3,10] 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 microheterogeneiety will affect PK behavior of the biosimilar.[11] Indeed, the PK properties of CT-P13 were comparable to Remicade® both in rodent in vivo models and in patients.[9]

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.[12] 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.[13] 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%).[14,15]

Table 1 Attributes of the comparability exercise of CT-P13.

Analytical	Primary structure, higher order structures, glycosylation, content, purity, charge variants
Binding studies	
Fab related	TNFα (monomeric, trimeric and transmembrane), TNF-β, different species TNFα, tissue cross reactivity
Fc receptor related	FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb and FcRn
Biological activity[a]	hTNFα neutralization assay, ADCC, CDC, C1q binding affinity, T-cell proliferation, apoptosis, cytokine secretion, reverse signaling, FcγRIIIa and FcγRIIIb binding of NK cells and neutrophils, macrophage function
Non-clinical	
PK	Single dose IV comparison in rats
Toxicity	3 repeat dose toxicity studies in rats
Clinical	
CT-P13 1.2 (pilot study)	PK study (n = 19) in RA patients receiving concomitant MTX (102 weeks)
CT-P13 1.1 (PLANET AS)	PK and long-term efficacy study (n = 250) in AS patients undergoing monotherapy (54 weeks)
CT-P13 3.1 (PLANET RA)	Long-term efficacy and safety study (n = 606) in RA patients receiving concomitant MTX (54 weeks)

ADCC = antibody-dependent cellular cytotoxicity, CDC = complement dependent cytotoxicity, MTX = methotrexate, PK = pharmacokinetic. From the European public assessment report.[3]

[a] Most assays were performed in cells derived from both healthy donors and Crohn's disease patients.

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.[3] 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.[10] 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