

Biosimilars to treat inflammatory arthritis: the challenge of proving identity

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The introduction of targeted biological therapies has revolutionised the treatment of patients with inflammatory joint diseases. These medications are highly effective in reducing disease activity, improving physical function, and retarding or arresting the progression of structural damage. Their relative benefits and risks have been ascertained and contraindications to their use are well known. However, the high price of these drugs has limited their widespread application. The potential availability of biosimilar versions of these targeted therapeutics promises accessibility to biopharmaceuticals with similar efficacy and safety but at a lower cost.¹⁻² In this issue of *Annals of the Rheumatic Diseases*, the results of the first randomised, prospective clinical trials comparing a biosimilar to an original (or 'innovator') biopharmaceutical for a rheumatic disease indication, are published.³⁻⁴

A biosimilar is defined as a 'biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product', in which similarity is defined as the 'absence of a relevant difference in the parameter of interest'.⁵ In this context, it is important to note that there are complexities inherent in producing large proteins. A biosimilar must ensure similarity to the reference product with respect to many attributes, such as amino acid sequence, conformation, post-translational modifications, immunogenicity, affinity for its ligand or receptor, and function. However, it must be recognised that subtle process changes in the production of an innovator product inevitably occur

over time and have resulted in variations between commercial lots, such as changes in the glycosylation profile of rituximab that resulted in more potent antibody-dependent cellular cytotoxicity *in vitro*.⁶ Many of the commercially available innovator biopharmaceuticals that are used now to treat patients could thus be considered to be biosimilars of the originally produced lots of those products, all of which had undergone rigorous testing and are subject to ongoing quality assurance by their manufacturers.

To establish the biosimilarity of a biopharmaceutical to an innovator reference biopharmaceutical, *in-vitro* analytical studies and *in-vivo* animal studies are required to demonstrate that the two proteins are 'highly similar,... notwithstanding minor differences in clinically inactive components'.⁷ The US Food and Drug Administration (FDA) requires that clinical studies must then show 'that there are no clinically meaningful differences' between the biosimilar and the reference biopharmaceutical in 'the safety, purity, and potency of the product'.⁷ The European Medicines Agency (EMA) requires 'an appropriate comparability exercise... to demonstrate that the similar biological and reference medicinal products have similar profiles in terms of quality, safety and efficacy'.⁸ These studies must demonstrate that the pharmacokinetics and pharmacodynamics, efficacy, and safety of the biosimilar are essentially equivalent to those of the innovator biopharmaceutical at the same dose, and that the biosimilar is not more immunogenic than the reference product.⁷⁻⁹ Because the therapeutic doses of the innovator biopharmaceutical have already been established and the biosimilar must be administered at the same doses as the innovator biopharmaceutical, the development programme for a biosimilar need not include dose-ranging studies in patients. Instead, at least one 'non-inferiority' clinical trial comparing the biosimilar and the innovator reference biopharmaceutical is required to show that there are no significant differences in efficacy between the two drugs.⁹⁻¹¹

CT-P13 is a biosimilar infliximab that was compared to innovator infliximab in *in-vitro*

analytical studies, which demonstrated similar transmission of Fourier transform infrared spectrometry, relative tumour necrosis factor α (TNF α) neutralising potency, and comparative complement-dependent cytotoxicity.³ Subsequently, CT-P13 was studied in two randomised, double-blind, parallel-group, prospective clinical trials to assess its potential non-inferiority to the reference product with respect to efficacy and safety over 30 weeks. The PLANETAS trial was a phase 1 study that compared the pharmacokinetics, efficacy, and safety of CT-P13 to those of innovator infliximab, each as monotherapy in patients with ankylosing spondylitis.³ The PLANETRA trial was a phase 3 study that evaluated the efficacy and safety of CT-P13 compared to innovator infliximab, each in combination with methotrexate in patients with active rheumatoid arthritis.⁴

The PLANETAS trial achieved its primary endpoint, demonstrating that the steady state pharmacokinetic profiles of CT-P13 and innovator infliximab were equivalent between weeks 22 and 30. In addition, the secondary pharmacokinetic parameters were 'highly similar' between treatment groups for each of the six intravenous doses of CT-P13 and innovator infliximab that were infused over the 30-week study.³ In the PLANETRA trial, pharmacokinetic parameters were also 'highly similar' between treatment groups for each of the six doses of study drug.⁴ Some differences were observed in the change from baseline in levels of IgG rheumatoid factor at week 14 and anticyclic citrullinated peptide antibodies at week 30, which were measured as pharmacodynamic parameters. However, the relevance of changes in autoantibody levels to the pharmacological effects of a therapeutic anti-TNF monoclonal antibody in patients with rheumatoid arthritis is unclear.

It is necessary that a biosimilar be non-inferior to the originally licensed biopharmaceutical. The goal of a comparative effectiveness trial that assesses a biosimilar in relation to the reference biopharmaceutical is to demonstrate that any difference in efficacy between the two drugs is less than a prespecified 'non-inferiority margin' or 'clinical equivalence margin'.¹² This margin becomes the upper bound for the 95% two-sided CI of the difference between the treatment effect of the biosimilar and that of the innovator reference biopharmaceutical. Ideally, the magnitude of this 'non-inferiority margin' is based on historical information obtained from placebo-controlled clinical trials about the treatment effect of the innovator

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biopharmaceutical, which is the difference in efficacy between the active drug and placebo. Among patients with active rheumatoid arthritis inadequately responsive to methotrexate, the weighted average for the treatment effect of the combination of infliximab with methotrexate was ‘nearly 30%’ for the American College of Rheumatology 20 (ACR20) response at 28–30 weeks, based on a meta-analysis of data from four placebo controlled trials (table 1).⁴ Subsequently, a smaller ‘non-inferiority margin’ is selected, based on clinical judgement, to specify the largest difference in efficacy that would be clinically acceptable. This ‘equivalence margin’ ensures an acceptable degree of similarity between a biosimilar and the innovator reference biopharmaceutical.

For the PLANETRA study, the equivalence margin was prespecified to be 15%, or 50% of the observed treatment effect derived from historical clinical trial data. In the actual clinical trial, the difference between CT-P13 and innovator reference infliximab in the primary efficacy endpoint of the ACR20 response at week 30, in the intent-to-treat population, was much less than the prespecified equivalence margin of 15%.⁴ Therefore, CT-P13 was considered to have ‘equivalent efficacy’ to reference infliximab at week 30 among patients with rheumatoid arthritis who were inadequately responsive to methotrexate. In addition, at weeks 14 and 30, the differences in the

secondary efficacy endpoints of ACR20, ACR50 and ACR70 responses and ACR/European League Against Rheumatism (EULAR) remission rates were ‘comparable’ for CT-P13 and reference infliximab, and the proportion of study subjects who achieved good or moderate EULAR responses was ‘highly similar’ between treatment groups. Likewise, in the PLANETAS study, the efficacy outcomes (assessment in ankylosing spondylitis (ASAS) 20 and ASAS40 responses at weeks 14 and 30) were ‘highly similar’ between the groups of subjects treated with CT-P13 and innovator reference infliximab.³ The ASAS20 and ASAS40 responses at week 30 were also comparable to those reported at week 24 in the placebo-controlled ASSERT trial of infliximab monotherapy in patients with ankylosing spondylitis (table 1).¹⁹

For a novel drug to treat rheumatoid arthritis, it is appropriate that efficacy be assessed in clinical trials of at least 3 months’ duration, if not longer. Studies of shorter length have been criticised as being inadequate to demonstrate clinically relevant therapeutic efficacy. Although effectiveness of the innovator biopharmaceutical has already been demonstrated in the relevant disease state, studies intended to demonstrate biosimilarity should be of at least the same duration as studies of novel drugs. However, it may also be informative to see data on the therapeutic efficacy of the biosimilar and the reference innovator biopharmaceutical for at least

one time point during the portion of the time response curve that is most sensitive to variation, which is usually the rapid rise phase that occurs early in the course of drug treatment.

Indeed, both the PLANETAS and the PLANETRA studies not only met their primary endpoints at week 30, but also assessed comparative efficacy at week 14. Both trials demonstrated similar clinical responses to CT-P13 and innovator infliximab; however, despite the biological similarity of the two drugs, the similarity of their pharmacodynamic response curves over time can only be inferred from these publications, even though disease activity was assessed at only two time points. Although each of these time points correlated with the nadir of the drug concentration that occurred before the next infusion was due, each was on the plateau phase of the time response curve. Subsequent to these publications, additional data from both studies, demonstrating comparable efficacy at week 54, were presented at the EULAR Annual Scientific Meeting in Madrid, Spain, in June 2013.^{20 21}

Demonstration of equivalent clinical responses during the earlier, rapid rise phase of the time response curve would provide additional information on biosimilarity, because this earlier portion of the time response curve affords greater sensitivity to detect differences in efficacy between study drugs than does the plateau phase (figure 1). Assessment of response

Table 1 Treatment effect of infliximab in published clinical trials of rheumatoid arthritis and ankylosing spondylitis

| Study | Time of assessment | Drug regimen* | Subjects (n) | Responders | | |
|-------------------------------------|--------------------|------------------------------------|--------------|------------|------------|------------|
| | | | | ACR20 (%) | ACR50 (%) | ACR70 (%) |
| Rheumatoid arthritis | | | | | | |
| ATTRACT ¹³ | Week 30 | Infliximab (3 mg/kg)+MTX | 86 | 50 | 26.5 | 8.4 |
| | | Placebo+MTX | 88 | 20 | 5.0 | 0 |
| St Clair <i>et al</i> ¹⁴ | Week 54 | Infliximab (3 mg/kg)+MTX | 359 | 62.4 | 45.6 | 32.5 |
| | | Placebo+MTX | 282 | 53.6 | 32.1 | 21.2 |
| Zhang <i>et al</i> ¹⁵ | Week 18 | Infliximab (3 mg/kg)+MTX | 87 | 75.9 | 43.7 | 23.0 |
| | | Placebo+MTX | 86 | 48.8 | 25.6 | 14.0 |
| Abe <i>et al</i> ¹⁶ | Week 14 | Infliximab (3 mg/kg)+MTX | 49 | 61.2 | 30.6 | 10.2 |
| | | Placebo+MTX | 47 | 23.4 | 8.5 | 0 |
| ATTEST ¹⁷ | Week 28 | Infliximab (3 mg/kg)+MTX | 165 | 59.4 | 37.0 | 24.2 |
| | | Placebo+MTX | 110 | 41.8 | 20.0 | 9.1 |
| PLANETRA ⁴ | Week 30 | CT-P13 (3 mg/kg)+MTX | 302 | 60.9 | 35.1 | 16.6 |
| | | Innovator infliximab (3 mg/kg)+MTX | 304 | 58.6 | 34.2 | 15.5 |
| Ankylosing spondylitis | | | | | ASAS20 (%) | ASAS40 (%) |
| Braun <i>et al</i> ¹⁸ | Week 12 | Infliximab (5 mg/kg) | 34 | 52.9 | | ND† |
| | | Placebo | 35 | 8.6 | | ND† |
| ASSERT ¹⁹ | Week 24 | Infliximab (5 mg/kg) | 201 | 61.2 | | 47.0 |
| | | Placebo | 78 | 19.2 | | 12.0 |
| PLANETAS ³ | Week 30 | CT-P13 (5 mg/kg) | 125 | 70.5 | | 51.8 |
| | | Innovator infliximab (5 mg/kg) | 125 | 72.4 | | 47.4 |

*Infusions at weeks 0, 2, 6, and every 8 weeks thereafter.

†Not determined.

ACR, American College of Rheumatology; ASAS, assessment in ankylosing spondylitis; MTX, methotrexate.

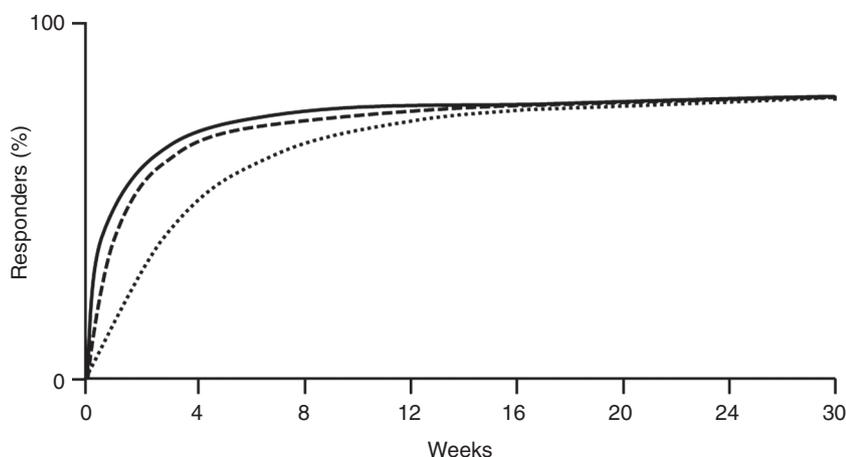


Figure 1 Patterns of pharmacodynamic response over time. At the primary endpoint of 30 weeks, each drug produces a similar clinical response and each had reached the plateau phase by 14 weeks. However, the kinetics of the clinical responses to the three drugs differ from one another. This difference is slight between the drugs represented by the solid and dashed lines, suggesting biosimilarity. However, during the initial 12 weeks of treatment, the difference in the proportion of responders between the solid and dotted lines is greater than that between the solid and dashed lines, although all three drugs both attain the same response rate during the plateau phase.

to therapy over the first 3 months of treatment allows comparison of the rapidity of onset, an attribute that is important for patients with rheumatoid arthritis. However, changes in drug therapy are not recommended before clinical improvement has been assessed after 3 months of treatment, as therapy should be changed if there is no improvement at 3 months and as it should be if the treatment target of remission or low disease activity has not been attained at 6 months.²² This strategic treatment approach ('treat-to-target') remains valid for synthetic and biological disease-modifying antirheumatic drugs alike, and thus also for biosimilar compounds. While in the PLANETRA study, a 'faster tendency of ACR20 response' was noted in the CT-P13 group compared to the innovator infliximab group, these differences were not statistically significant and were not observed with other endpoints; thus they may well have been due to natural variation in the measurement of composite clinical responder indices and might have been observed even had the same drug been administered at the same dose to subjects in two parallel arms of a study.

A clinical trial to assess biosimilarity can be likened to a musician's audition for a chair in a symphony orchestra. During that audition, the musician is asked to play difficult passages for his or her instrument from the symphonic repertoire. However, in the interest of time, the judges usually ask to hear only the specific challenging sections, rather than the instrumental part for the entire work. By doing so, the judges are able to assess

efficiently whether or not the musician is worthy of being chosen for a position in the orchestra. Similarly, the clinical trial that compares a biosimilar to the innovator biopharmaceutical should focus on the time interval that is most likely to demonstrate whether or not the two drugs are very similar and without clinically meaningful differences. Thus, clinical response should be assessed primarily at the endpoint of a trial, which would be the equivalent of the most difficult passage in a musical score. Performing assessments at additional time points is akin to having the musician play additional excerpts from the musical work so that the judges can gain a better sense of his or her musicianship; showing data from time points during the rapid rise phase of the time response curve when differences between the pharmacokinetics of the two drugs are most likely to be evident would correspond to the musician also playing an exposed passage from the beginning of the symphonic work. Indeed, just as the musician must prove his or her worthiness of membership in the ensemble by playing in entire works with the orchestra during a probationary period that follows the successful audition, subjects should be continued on treatment with study drug for a longer period of time during the plateau phase of the time response curve to validate biosimilarity and to demonstrate sustained efficacy and long-term safety and tolerability. This may be carried out during the post-marketing phase of clinical development and can use existing patient registries.

There is always concern that a biosimilar be as safe as the originally licensed innovator biopharmaceutical.²³ In both the PLANETAS and PLANETRA studies, the safety profile of CT-P13 was comparable to that of innovator infliximab and was similar to that observed for infliximab among patients with ankylosing spondylitis in the ASSERT trial¹⁹ and among patients with rheumatoid arthritis in the ATTRACT¹³ and ASPIRE¹⁴ trials. Both CT-P13 and innovator infliximab were immunogenic, and levels of anti-drug antibodies were similar for both biopharmaceuticals. Antibodies to infliximab were detected at week 24 in 27.4% and 22.5% of ankylosing spondylitis patients treated with CT-P13 or innovator infliximab as monotherapy, respectively, and at week 30 in nearly half of rheumatoid arthritis patients treated with either CT-P13 or innovator infliximab, each in combination with methotrexate. In both of these clinical trials, the proportion of clinical responders was lower among those with anti-drug antibodies than among those without.

In the development programme for CT-P13, each of the two clinical trials was carried out in a different rheumatic disease for which the use of innovator infliximab is licensed: the phase 1 PLANETAS study in patients with active ankylosing spondylitis and the phase 3 PLANETRA study in patients with active rheumatoid arthritis. Because infliximab is licensed for use as monotherapy to treat patients with ankylosing spondylitis, whereas its licence to treat patients with rheumatoid arthritis requires combination with methotrexate, comparison of the pharmacokinetics of CT-P13 with those of the innovator infliximab was most appropriately assessed with each administered as monotherapy in the PLANETAS study in subjects with ankylosing spondylitis.²⁴ The efficacy, safety and immunogenicity of these biopharmaceuticals was also compared in this study. Data regarding comparative efficacy and safety, as well as immunogenicity, pharmacokinetics and pharmacodynamics, when each drug was administered in combination with methotrexate were acquired in subjects with rheumatoid arthritis in the PLANETRA study.⁴ The demonstration that each of these parameters is comparable, both with and without methotrexate co-therapy and in two different rheumatic diseases, strengthens the assertion that CT-P13 and the innovator infliximab are biosimilar.

Both the EMA and FDA allow for the possibility that clinical efficacy and safety data might be extrapolated to other disease

states for which the innovator biopharmaceutical is licensed, but in which comparability of the biosimilar has not been studied.^{9–11} Both agencies recommend studying the biosimilar in that disease state and patient population which is ‘most sensitive’ to detect ‘clinically meaningful differences in safety (including immunogenicity) and effectiveness’ between the two biopharmaceuticals. If the biosimilar and the innovator biopharmaceutical share the same mechanisms of action in the various disease states and the requirements for licensure as a biosimilar have been met, the biosimilar might be licensed for use in some or all of the other indications for which the innovator biopharmaceutical is licensed. Because the innovator infliximab is also licensed for the treatment of psoriasis, psoriatic arthritis, Crohn’s disease and ulcerative colitis, data from the PLANETAS and PLANETRA studies are useful to support approval of CT-P13 for these additional indications. However, careful postmarketing pharmacovigilance is necessary to ensure that the biosimilar is both safe and effective in treating each of the conditions for which it has been approved.

The PLANETAS and PLANETRA studies are the first clinical trials to demonstrate unequivocal efficacy of a biosimilar for the treatment of rheumatic disease indications. Based on the results of these studies, the Korean Ministry of Food and Drug Safety approved CT-P13 in South Korea on 23 July 2012, for the treatment of rheumatoid arthritis, ankylosing spondylitis, ulcerative colitis, Crohn’s disease and psoriasis.²⁵ On 28 June 2013, the Committee for Medicinal Products for Human Use (CHMP) of the EMA recommended that CT-P13 be granted marketing authorisation for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn’s disease, and ulcerative colitis in both children and adults.²⁶ As such, PLANETAS and PLANETRA are landmark studies that will serve as the foundation for future clinical trials of biosimilars in patients with rheumatic diseases.

In the USA, the patent for innovator infliximab does not expire until 4 September 2018, and thus biosimilar infliximab will not become available in the USA until after that date.²⁷ Because the patent for innovator infliximab in the European Union does not expire until 13 August 2014, CT-P13 will not be marketed in European Union countries until after that date.²⁷ However, its launch in other eastern and central European countries, where patents are not in effect, is

expected in 2013.²⁸ One financial analyst has estimated that, by 2018, biosimilars will occupy a 40% share of the European market for therapeutic monoclonal antibodies.²⁸ This will probably result in a reduction of the high cost of targeted biological therapies and should extend the availability of these effective therapeutic agents to a larger number of patients.

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