Bioequivalence between biosimilar and reference tumour necrosis factor–alpha inhibitors

Biosimilar medicines have the potential to offer the NHS considerable savings at a time when the NHS is facing financial challenges, as well as potentially widening access to innovative medicines. This systematic review of randomised controlled trials (RCTs) and observational studies assessed the evidence about the comparability of clinical efficacy, adverse effects, immunogenicity and pharmacokinetics of biosimilar tumour necrosis factor (TNF)–alpha inhibitors and their reference biological medicine. It provides further assurance about the safety, effectiveness and comparable immunogenicity of biosimilar medicines. This should help to promote their use within the NHS, in line with NICE’s position statement on evaluating biosimilar medicines and NHS England’s programme of work on the appropriate use of biosimilar medicines.

Overview and current advice

The NHS England publication, What is a biosimilar medicine? states that a biosimilar medicine is a biological medicine which is highly similar to another biological medicine already licensed for use. It is a biological medicine which has been shown not to have any clinically meaningful differences from the reference biological medicine in terms of quality, safety and efficacy. The continuing development of biological medicines, including biosimilar medicines, creates increased choice for patients and clinicians, increased commercial competition and enhanced value propositions for individual medicines. Biosimilar medicines have the potential to offer the NHS considerable cost savings and widen the access to innovative medicines.

In the development of a biosimilar medicine, there is no requirement to demonstrate clinical benefit to patients per se, as this has been shown for the reference biological medicine. Instead, biosimilars undergo a comprehensive regulatory process which demands extensive comparability studies that demonstrate similarity to the reference biological medicine. Biosimilar medicines introduced into the UK market are authorised by the European Medicines Agency (EMA). The EMA has produced a document covering a series of questions and answers on biosimilar medicines. NICE’s position statement on evaluating biosimilar medicines was published in January 2015.

In the UK, the MHRA recommends that all biological medicines, including biosimilar medicines, are prescribed by brand name so that products cannot be automatically substituted at the point of dispensing. The choice of whether a patient receives a biosimilar or reference biological medicine rests with the responsible clinician in consultation with the patient.
A NICE key therapeutics topic on **biosimilar medicines** summarises the evidence-base for biosimilar medicines. NICE has also published an adoption resource **Introducing biosimilar versions of infliximab: Inflectra and Remsima** to help manage the introduction of biosimilar medicines into care pathways safely and effectively. See also the NHS England publication, **What is a biosimilar medicine?** and the NHS publication **Answers to commonly asked questions about biosimilar versions of infliximab** for more information.

**New evidence**

This systematic review of 13 **randomised controlled trials** (RCTs) and 6 **observational studies** assessed the evidence about the comparability of clinical efficacy, adverse effects, immunogenicity and pharmacokinetics of biosimilar tumour necrosis factor (TNF)–alpha inhibitors and their reference biologic medicine (Chingcuanco et al. 2016)\(^1\). Of the 13 RCTs, 8 were phase 1 studies that were mainly conducted in healthy volunteers, and 5 RCTs were phase 3 studies (all in people with rheumatoid arthritis [RA]). All 6 observational studies assessed biosimilar infliximab (4 studies in people with inflammatory bowel disease and 2 studies in people with rheumatoid diseases). Overall, of the 13 RCTs, 8 assessed infliximab, 4 assessed etanercept and 1 assessed adalimumab. Study duration ranged from 3 to 54 weeks.

Seven of the 13 RCTs assessed clinical response to treatment. All of the phase 3 studies (n=5) found no **statistically significant** differences in ACR20\(^a\) or ACR70\(^b\) between the biosimilar and reference biological medicine, based on prespecified margins. These trials were of longer duration (48 to 54 weeks) and the patient sample size generally ranged from about 250 to 600. The 2 phase 1 studies were not powered for clinical efficacy; 1 study found no significant differences in ASAS\(^c\) outcomes while the other study reported a numerically higher clinical response in ACR20 and ACR70 in the biosimilar group at 54 weeks, compared with the reference biological medicine. In addition, 4 observational **cohort studies** of people switched from reference to biosimilar products indicated similar efficacy at maintaining disease remission\(^1\).

Ten of the 13 RCTs also assessed immunogenicity and this was found to be comparable between biosimilar and reference groups in all studies, with the exception of 2 trials of an etanercept biosimilar (SB4)\(^1\).

Adverse events were assessed in all 13 RCTs and, in most studies, the proportion of patients with adverse events and serious adverse events were similar between the biosimilar and reference groups. In addition, no consistent differences in the type of adverse events were noted. All 8 phase 1 RCTs showed that pharmacokinetic parameters of the biosimilar and respective reference biologic medicines were within the prespecified equivalence margin of 80% to 125%. This was also the case in 2 out of the 3 phase 3 RCTs, but these studies were not designed to measure pharmacokinetics.

Most of the RCTs were assessed as having moderate risk of bias and the observational studies had moderate to high risk of bias (assessed by the **Cochrane risk of bias tool**). The phase 3 studies only assessed clinical efficacy in RA, so it is unclear whether the results can be extrapolated to other conditions. However, some biosimilars have been approved for inflammatory bowel disease, having only been studied in RA and ankylosing spondylitis. The magnitude of possible publication bias is unclear and there are a lack of published studies for some biosimilars\(^1\).

\(^a\) 20% or greater improvement in American College of Rheumatology response criteria  
\(^b\) 70% or greater improvement in American College of Rheumatology response criteria  
\(^c\) Assessment of Spondyloarthritis International Society response criteria
Biosimilar medicines have the potential to offer the NHS considerable savings at a time when the NHS is facing financial challenges, as well as potentially widening access to innovative medicines. However, the uptake of biosimilars throughout the UK is variable and generally slow in comparison to Scandinavian countries. Part of the reason for this remains a lack of awareness of what a biosimilar medicine is, the clinical data available, and the regulatory procedures supporting their use.

This systematic review by Chingcuanco et al. (2016) compares the evidence for TNF–alpha biosimilars against the relevant reference biologic medicines in relation to pharmacokinetics, clinical efficacy, adverse events and immunogenicity. A range of databases and clinical trial registries were searched, together with the EMA and US Food and Drug Administration (FDA) websites.

The study does not necessarily provide any new evidence; however it is a very good systematic review showing the extent of studies related to biosimilars. The results table showing ACR response outcomes between biosimilars and their reference biological medicines shows non-inferiority between both products in each of the phase 3 studies.

The study supports current advice suggesting that biosimilars and reference biological medicines are generally very similar, and that the minor differences in structure do not make any difference to clinical effectiveness. Unfortunately, Chingcuanco et al. (2016) only briefly mentioned the 6 observational studies which include studies where patients were switched between the reference and biosimilar products. Most clinicians will be very interested in the detailed data for these ‘switch’ studies to inform decision-making around switching from reference biological medicines to biosimilars. In addition, the paper does not consider the extrapolation of evidence between indications. However, this was mentioned in the discussion as one of the remaining uncertainties around biosimilar medicines and is a possible limitation to their use.

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References
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