Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

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Bioequivalence of biosimilar tumour necrosis factor (TNF)-alpha inhibitors compared with their reference biologics: A systematic review

A systematic review of published clinical studies that compared the pharmacokinetics, clinical efficacy, adverse events or immunogenicity of biosimilar TNF-alpha inhibitors with their reference biologics supports the biosimilarity and interchangeability of the products.

Reference: Chingcuanco F, Segal JB, Kim SC and Alexander GC. Bioequivalence of biosimilar tumor necrosis factor-alfa inhibitors compared with their reference biologics: A systematic review. Ann Intern Med. doi: 10.7326/M16-0428.

What do we know already?

- Biologics are medicinal products made by, or derived from, a living organism. Due to their large, complex structure and the variability inherent in the manufacturing process, it is impossible to create a precise replica, or "generic version" of a biologic. Instead, the term *biosimilar* is commonly used to refer to non-innovator biologics.
- The European Medicines Agency (EMA) defines a biosimilar as "a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product)". For marketing authorisation, manufacturers must show that the product is similar to the reference medical product in terms of physicochemical characteristics, adverse effects, and clinical efficacy.
- There is still a degree of uncertainty about the interchangeability of biosimilars and the originator products. The Royal College of Physicians recently published the results of the annual National Clinical Audit of Biological Therapies. Focusing on biological therapies for inflammatory bowel disease (IBD), the report endorses the use of biosimilar infliximab (*the first biosimilar to become available*), with a key recommendation that "clinicians should use infliximab biosimilars as the first line anti-TNF-alpha for appropriate patients with active IBD".
- Biologics can be expensive compared with conventional medicines and 11% of NHS hospitals medicine expenditure is on three TNF-alpha inhibitors: adalimumab, etanercept and infliximab. Due to their lower acquisition cost, use of biosimilars can result in significant savings.

What does this evidence add?

- Although there have been narrative reviews of biosimilar TNF-alpha inhibitors, this is the first systematic review of studies comparing biosimilars with their reference product in terms of pharmacokinetics, clinical efficacy, adverse events and immunogenicity.
- Of the 19 studies reviewed, eight were phase 1 randomised controlled trials, five were phase 3 randomised controlled trials and six were observational studies.
- The pharmacokinetic variables in the phase 1 trials supported the comparability of biosimilars and reference products.
- All the clinical efficacy endpoints in the phase 3 trials also supported comparability of the biosimilars to their reference products.
- The proportion of patients with treatment-emergent adverse events was similar between biosimilar and reference groups. No differences in the type of adverse event were noted.
- Four cohort studies provided limited quality evidence that **switching** of patients from reference to biosimilar products was associated with **similar efficacy and safety outcomes**. Available immunogenicity data appear to be reassuring.

Study details

Data Sources and Searches:
PubMed, EMBASE, Cochrane Central Register of Controlled Trials and LILACS were searched without language or publication type restrictions to identify eligible articles using relevant key words and subject headings. To help assess possible publication bias and identify ongoing trials, Clinical Trials.gov, WHO international trials registry platform, EU Clinical Trials Register, FDA and EMA websites were also searched.

Study Selection:
- Two reviewers independently reviewed the titles and abstracts of over 4,000 studies and came to consensus about eligibility. Only published studies were included.
- Studies were required to compare the adverse effects, immunogenicity, clinical efficacy or pharmacokinetic bioequivalence of a biosimilar TNF-alpha inhibitor and a reference biologic in humans. Biomimics, which are non-innovator biologics that were approved before the development of the biosimilars regulations, were excluded.
- Pharmacokinetic outcomes included area under the curve (AUC) and maximum (C_{max}) and minimum (C_{trough}) drug levels at different time intervals.
- Clinical efficacy was defined as the primary outcomes of the trials, which typically used standardised measures of disease activity (e.g. the American College of Rheumatology (ACR) remission criteria).
- Adverse events were defined as undesirable medical occurrences that may or may not have been causally related to the exposure in question. These were extracted as quantified in the included studies.
- Immunogenicity data on the proportion of patients exposed to a biosimilar or reference product who developed antibodies to the product were also extracted

Outcomes and results:
- **Pharmacokinetics**. Eight phase 1 trials, with sample sizes ranging from 23 to 250 persons, evaluated pharmacokinetic outcomes. All these trials specified a bioequivalence margin of 80-125% (*the accepted criterion for demonstrating bioequivalence*) and the means for each outcome were within this margin, indicating equivalence. Three phase 3 trials designed primarily to assess clinical efficacy also examined pharmacokinetic outcomes. Treatment groups in these trials had similar average C_{max} and C_{trough} values based on the 80-125% equivalence margin. However, in one phase 3 trial, the steady state AUC was higher for the biosimilar of etanercept than the reference product.
- **Clinical Outcomes**. All the phase 3 trials were parallel group trials in patients with rheumatoid arthritis (RA), with a sample size generally of between 250 and 606 patients, apart from one trial with only 120 patients. The primary clinical end point was the ACR20 outcome. All of these trials showed equivalence between the biosimilar and the reference product based on their pre-specified margins. A small phase 1 trial, which included patients with RA but which was not designed to establish equal clinical efficacy, reported a modestly higher clinical response in the biosimilar infliximab group for the ACR70 response rate at Week 54. The only other phase 1 trial reporting clinical outcomes was in patients with ankylosing spondylitis, which, although not powered to assess clinical efficacy, showed no statistical differences in disease activity outcomes between the biosimilar and reference product.
- **Adverse Events**. For most studies, the proportion of patients with treatment-emergent adverse events or serious adverse events was similar between biosimilar and reference products. However, in one study, one death due to renal failure was reported that may have been related to treatment with the reference etanercept product. No differences in the type of adverse event between biosimilars and reference product were noted.
- **Immunogenicity**. Ten of the thirteen randomised controlled trials assessed immunogenicity. Immunogenicity, examined in in all patients who received at least one dose of biosimilar or reference drug, was comparable in all studies, except one phase 3 trial and one phase 1 trial of etanercept and its biosimilar SB4. In the phase 3 trial, significantly fewer patients in the biosimilar group developed antibodies compared with the reference group (0.7% vs 13.1%; $p<0.001$). In the phase 1 trial, no patients in the biosimilar group developed antibodies compared with 15% and 20% of patients in the two reference product groups.
- **Observational Studies of Adverse Effects and Effectiveness**. All six observational studies involved infliximab in patients with rheumatoid disease or IBD. Two cross-sectional studies showed that sera that were positive for antibodies to the reference biologic were cross-reactive to the biosimilar. The four cohort studies provided some data on the effectiveness and safety of switching from reference product to biosimilar. All four studies reported that most patients who were in remission before switching remained in remission. The reviewers noted that the studies had small sample sizes, did not have comparator groups of patients who continued to receive the reference product and had significant heterogeneity in the times at which patients were switched.

Level of evidence: Level 1 (good quality patient-oriented evidence) according to the SORT criteria.

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