BSG Guidance on the Use of Biosimilar Infliximab CT-P13 in Inflammatory Bowel Disease

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Introduction

Biological medicines are complex products that are made or derived from a biological source, and as a result have inherent structural variability. Biosimilar medicines are drugs which are highly similar to other biological medicines already licensed, and that do not have any clinically meaningful difference to the originator drug in structure, pharmacokinetics, quality, safety or efficacy(1). Biosimilars are not considered to be generic equivalents as they are not identical to the original drug(2). The European Medicines Agency (EMA) grants marketing authorisations for biological medicine products in the European Union, including biosimilar drugs(3). Assessment of biosimilar applications is carried out according to guidelines of the Committee for Human Medicinal Products (CHMP) of the EMA. This rigorous process has granted marketing authorisation to 21 biosimilar drugs since 1998. None of these biosimilars have been withdrawn from the market because of safety concerns. Once authorised, individual member states develop processes for the prescription, delivery, and use of these drugs. Assessment of substitution and interchangeability are not part of the scientific evaluation that leads to marketing authorisation. Biosimilar infliximab, CT-P13, received marketing authorisation in June 2013(4). The comparability studies showed a small difference in the amount of afucosylated infliximab, resulting in lower binding affinity towards specific Fc receptors (FcgRIIIa - V and F allotypes), and lower antibody-dependent cellular cytotoxicity (ADCC) activity, but only in the most sensitive assays. This difference was not considered clinically meaningful, as there were no significant behaviour differences in experiments conducted in more physiological conditions. The evidence considered also included clinical trials in rheumatoid arthritis(5) and ankylosing spondylitis(6), the latter including a pharmacokinetic comparison between Remicade and Remsima showing close similarity in all parameters.

Evidence for clinical benefit in inflammatory bowel disease

Controlled trials of CT-P13 were not undertaken in Crohn's disease (CD) or ulcerative colitis (UC). Once licensed however, the drug has been used in clinical practice. An observational cohort of 210 consecutive patients from Hungary (126 Crohn's disease and 84 ulcerative colitis)(7) has reported

induction data for CT-P13. 22.3% of the patients had previously received infliximab. At week 14, 81.4% of CD and 77.6% of UC patients were in clinical response, and 53.6% and 58.6% respectively were in clinical remission. Remission rates were higher in those who had not received infliximab, compared to those with previous exposure. With follow-up to week 30, adverse events were experienced in 17.1%, infusion reactions in 6.6% and infectious adverse events in 5.7% of patients. Infliximab trough levels, and anti-drug antibodies (ADA) were measured using LISA TRACKER (Theradiag, France). Trough levels were slightly lower in patients with previous infliximab exposure, and associated with significantly higher baseline ADA positivity. A single centre Norwegian study(8) also reports induction therapy with CT-P13 in 46 CD and 32 UC patients, with 79% and 56% respectively in remission at week 14. Six patients (7.7%) had previously received infliximab. A Korean report(9) details 173 patients (CD 95, UC 78), with week 30 responses of 79.5% and 72.2%, and week 30 remission of 59% and 37% respectively. Another study from six Korean hospitals reported 59 CD (27 switching from infliximab) and 51 UC patients (9 switching from infliximab)(10). Overall, there were similarly high response and remission rates, with follow-up up to one year in a small number of patients. Of the 27 CD patients switching from infliximab, 25 (92.6%) maintained similar response, whilst two stopped due to lack of efficacy. Of 9 UC patients switching from infliximab, 6 maintained response (66.7%), and three stopped (one due to lack of efficacy, one chose to switch back to infliximab, and one had an adverse event). There is more extensive switching data in ankylosing spondylitis from an open-label switching extension of the PLANETAS study(11), for 86 patients switching from Infliximab to CT-P13. There is similar comparability in 128 patients completing one year follow-up after switching from infliximab to CT-P13 for rheumatoid arthritis(12).

In an in vitro study, Ben-Horin et al studied the cross-reactivity of antibodies to Remicade to Remsima (CT-P13) (13). Sera from 125 patients and controls were tested. Sixty-nine were positive for anti-Remicade antibodies, and all cross-reacted to Remsima. Titres strongly correlated against the two drugs, and the antibodies from ten IBD patients exerted similar functional inhibition of TNFα binding capacity of both Remicade and Remsima.

Summary

There is sufficient data from observational studies to show that safety and clinical efficacy of CT-P13 are comparable to the originator drug, with similar immunogenicity, and that switching from Remicade to CT-P13 is also safe and effective.

Recommendations

1 Infliximab must be prescribed by brand name (ie Remicade, Remsima or Inflectra) and not by International Non-proprietary Name (INN).

2 For patients starting infliximab: Remicade, Remsima or Inflectra can be prescribed, taking into account the evidence showing similar clinical effectiveness. There is evidence that monitoring of patients, including measurement of drug and anti-drug antibody levels, is no different for the biosimilar drugs compared to Remicade. The choice of preparation should take into account the cost of the drug and its administration.

3 There is sufficient evidence to recommend that patients who are in a stable clinical response or remission on Remicade therapy can be switched to Remsima or Inflectra at

the same dose and dose interval. This should be done after discussion with individual patients, with explanation of the reason for switching (which is usually on the grounds of benefit to the overall service by reduction in costs of the drug and its administration).

4 Automatic substitution, (dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber), is not appropriate.

5 Pharmacovigilance is essential for any new biological medicine, and patients prescribed Remsima or Inflectra should be followed for safety, in a registry such as the UK National IBD Registry.

References

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