Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

ScriptSwitch™ Rapid Update 3 – June 2017

Biosimilars: NOR-SWITCH study provides evidence to support switching from originator to biosimilar infliximab in stable patients

Whilst biosimilars are increasingly being adopted, with wider uptake offering substantial savings to the NHS, there has been some debate on the acceptability of switching patients who are stable on an originator product to a newer biosimilar. The NOR-SWITCH trial, which was funded by the Norwegian government, has addressed this important issue, investigating the switching of stable patients receiving Remicade (originator infliximab) for a variety of conditions to biosimilar infliximab CT-P13 (marketed as Remsima and Inflectra).

Switching to CT-P13 met the study's criterion for 'non-inferiority' for disease worsening versus continued treatment with Remicade. Adverse events were also similar between groups. These data add weight to the increasingly prevalent view that biosimilars should be used in the vast majority of patients for whom biologics are being considered, including switching those already on an originator product.

Reference: Jørgensen KK, Olsen IC, Goll GL *et al*. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. The Lancet. Published online 11 May 2017. DOI: http://dx.doi.org/10.1016/S0140-6736(17)30068-5

What do we know already?

- In 2015, biosimilar infliximab CT-P13 (Remsima; Inflectra) was approved by the European Medicines Agency. Since then, further biosimilar monoclonal antibody products have come to the UK market, including the first rituximab biosimilar Truxima, which was launched in April this year.
- A better understanding of biosimilars and their regulatory approval process has perhaps been important in the growing numbers of position papers from organisations in support of biosimilars, with many now also supporting switching for non-medical reasons. Organisations who have published position papers include:
  - The British Society of Gastroenterology - whilst the 2014 guideline recommended avoiding switching, the 2016 update on Inflectra and Remsima comments there is sufficient evidence to switch stable patients.
  - The British Association of Dermatologists – the latest position paper, which was updated ~2 months ago, no longer includes an earlier recommendation against switching stable patients.
  - The British Society for Rheumatology – the most recent position statement (January 2017) supports the inclusion of biosimilars as a therapy of choice for patients initiating biologic therapies. A decision to switch to a biosimilar should be on a case-by-case basis until there are further data to support safe switching. If patients are switched for non-clinical reasons, strong safeguards are required to ensure monitoring of efficacy and safety, and where efficacy is not maintained, a patient should have the option to revert to a reference product.
  - The British Oncology Pharmacy Association (BOPA) – whilst not relevant to infliximab, which does not have an oncology indication, the BOPA position is that biosimilars are therapeutically equivalent to originator molecules and can and should be used for all commissioned indications, provided safeguards are in place.
- All the above note the importance of prescribing by brand name, as is advised by the MHRA, and the key role of pharmacovigilance, e.g. reporting of adverse events and the inclusion of patients in treatment registries.
- NHS England's work on biosimilars includes the guide "What is a biosimilar medicine?" and data on biosimilar infliximab uptake are included in the Medicines Optimisation Dashboard. NICE's position on biosimilars is that they are considered in parallel with reference products, with existing guidance applying to biosimilars subsequently appearing on the market. See the NICE Key Therapeutic Topic on biosimilars for further discussion.
- Whilst the regulatory approval for biosimilars includes a robust analysis of bioequivalence to the originator, and may generally include trials in some but not all licensed indications, further studies are valuable to provide clinicians and patients with a greater understanding of the safety of switching to biosimilars.

What does this evidence add?

- This randomised, double-blind, 52-week study was carried out in 482 patients in Norway who had been stable for at least 6 months on treatment with originator infliximab for Crohn's disease, ulcerative colitis, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, or chronic plaque psoriasis. Patients were randomised to a single switch to biosimilar CT-P13 or continued treatment with originator infliximab.

- Disease worsening occurred 26% of patients in the infliximab originator group and 30% of patients in the CT-P13 group. The 95% Confidence Intervals (95% CI) of the adjusted treatment difference were within the pre-specified margin of 15%, thus the criterion for non-inferiority were met (treatment difference of −4·4%, 95% CI: −12·7 to 3·9).
- Questions not answered by the study include the effects of switching to a different infliximab biosimilar (*such as the more recently launched Flixabi*), the effects on the individual conditions (*the study was not powered for this outcome*) and the safety of multiple switches – a possible scenario as organisations may look to maximise cost savings through use of alternative lower-cost biosimilars. The authors also caution that the 15% margin might be too wide to exclude all clinically important outcomes.

Study details

Participants:

- This 52-week double-blind, randomised study was carried out at 40 Norwegian study centres and recruited 482 adult patients between Oct-14 and Jul-15 who had been treated in a hospital setting and who had been stable on the infliximab originator for at least 6 months. 39% were women, the mean age was 47.9 years and the mean duration of treatment with originator infliximab before randomisation was 6.8 years.
- Patients could be receiving infliximab treatment for any of the drug's licensed indications. The breakdown of participants who were included in the full-analysis set was as follows: 155 (32%) patients had Crohn's disease; 93 (19%) had ulcerative colitis; 91 (19%) had spondyloarthritis; 77 (16%) had rheumatoid arthritis; 30 (6%) had psoriatic arthritis; 35 (7%) had chronic plaque psoriasis.

Intervention and comparison:

- Patients were randomised in a 1:1 ratio to either continued treatments with the infliximab originator or a switch to CT-P13, with an unchanged dosing regimen. Patients, assessors and care providers were masked to treatment.

Outcomes:

- Disease worsening during the 52-week follow up was the primary outcome for this study. This was assessed according to disease-specific composite measures, or by consensus about disease worsening between an investigator and patient leading to a major change in treatment. The disease-specific composite measures were as follows:
  - Crohn's disease: change from baseline in Harvey-Bradshaw Index of ≥ 4 points and a score of ≥ 7 points
  - Ulcerative colitis: change from baseline in Partial Mayo Score of >3 and a score of ≥ 5
  - Spondyloarthritis: change from baseline in Ankylosing Spondylitis Disease Activity Score of ≥ 1.1, attaining a minimum score of 2·1
  - Rheumatoid arthritis and psoriatic arthritis: change from baseline in Disease Activity Score in 28 joints of ≥ 1.2, with a minimum score of 3.2
  - Chronic plaque psoriasis: change in Psoriasis Area and Severity Index of ≥3 and a score of ≥5.
- A non-inferiority margin of 15% was pre-specified. In other words, to demonstrate the non-inferiority of CT-P13 to originator infliximab, the 95% CI for the treatment difference had to be within 15%. This margin was agreed based on clinical discussions within the study group, the PLANETRA study (*a phase III study of CT-P13 vs. originator infliximab in patients with active rheumatoid arthritis*) and discussions with the Norwegian Medicines Agency.
- Secondary endpoints included time to disease worsening, study drug discontinuation, overall remission status based on the main composite measures, changes in investigator and patient global assessments *(e.g. various questionnaires, quality-of-life measures*), and the incidence of anti-drug antibodies.

Results:

- At 52 weeks, disease worsening occurred in 53 (26%) of patients in the infliximab originator group and 61 (30%) of patients in the CT-P13 group.
- In the per-protocol set (n = 206 for CT-P13; n = 202 for Remicade) the adjusted treatment difference was −4·4%, 95% CI: −12·7% to 3·9%, thus the study's criterion for non-inferiority was met. Robustness analyses adjusting for potential centre effect gave similar risk differences that were within the non-inferiority margin. The risk differences for disease worsening for the full analysis set were also within the 15% margin (*findings reported in the supplementary appendix*).
- Remission occurred in 61% of patients in both groups, with an adjusted rate difference in the per-protocol set of 0.6% (95% CI:-7.5 to 8.8%).
- Disease specific composite measures, patient reported outcomes, time to disease worsening and treatment discontinuations were similar between groups. Two endpoints (the Modified Health Assessment Questionnaire and SF-36 physical component summary score) were found to be statistically significant different between treatments, both in favour of the biosimilar.
- The frequency of adverse events was also similar between groups:
  - serious adverse events: there were 24 events (10%) in the infliximab originator group *vs.* 21 (9%) for CT-P13
  - overall adverse events: 168 events with originator (70%) *vs.* 164 (68%) for the biosimilar
  - adverse events leading to discontinuation: 9 events with the originator (4%) *vs.* 8 (3%) with the biosimilar
- The incidence of anti-drug antibodies detected during the study (excluding patients with detectable antibodies at baseline) was the same between groups (17 [7%] for infliximab originator and 19 [8%] for CT-P13).

Level of evidence: Level 1: good quality patient-oriented evidence according to the SORT criteria.
Study funding: Norwegian Ministry of Health and Care Services.