Prescribing...

- Biosimilars are being increasingly adopted with wider uptake offering substantial savings.
- There has understandably been some debate on the safety of switching consenting stable patients.
- This bulletin summarises the results of the NOR-SWITCH study, funded by the Norwegian government, which found that switching was safe for the overwhelming majority of patients.

What do we know already?

As is well known, in 2015, biosimilar infliximab CT-P13 (Remsima; Inflectra) was approved by the European Medicines Agency. This has been in use for all patients in the Princess Elizabeth Hospital for some time and so far it has been problem free. However there were numerous problems with availability of stock and establishing the cold chain supply to Guernsey. This has resulted in a great deal of extra work for Community Pharmacies. We are most grateful for our pharmacists' patience and support, as well the engagement of doctors and patients.

The original advice from medical professional bodies was that a wholesale switch of patients stable on the reference product was inadvisable. More recently this has changed and now many are advocating switching.

Organisations who have published relevant 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.

NB : 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.

What does this latest evidence add?

This randomised, double-blind, 52-week study was carried out in 482 patients in Norway. They had all 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.

Patients:

NOR-SWITCH was carried out at 40 Norwegian study centres. It included 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 any licensed indication 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. Of the total 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. The primary outcome was disease progression and there were a number of secondary outcomes such as time to disease worsening, study drug discintinuation, overall remission status, changes in investigator and patient global assessments and incidence of anti-drug antobodies.

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.

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. 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 significantly different between treatments, both in favour of the biosimilar. The frequency of adverse events was also similar between groups. In terms of 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).

So what?

The results of this publically-funded trial in real patients and using patient-oriented outcomes is highly credible. There was no industry involvement, no issues with "enriched enrolment" or early termination. Its results , that there was no difference between outcomes in patients switched to the biosimilar, should provide further reassurance to patients and clinicians that switching to a biosimilar should have no effect on outcomes. This is already reflected in the advice of the UK professional bodies.

However the study did not address outcomes if/when patients were switched on more than one occasion. This is less of a probability in secondary care , but is highly relevant in patients in the community. Therefore this option cannot be recomended, so it remains very important that doctors in the community prescribe the **biosimilar by brand**.

A biosimilar version of Adalimumab may become available in 2018 and its use has the potential to retain significant sums in the Heath Fund which will be available to fund the ever-growing needs of the community. Be assured that lessons will be learned from the difficulties experienced with biosimilar etenercept, if/when bs adalimumab appears.

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