**Switching to biosimilar infliximab: Real world data in patients with severe inflammatory arthritis**

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**Abstract**

**Objective.** To describe real world experience of switching from originator TNF inhibitor Remicade (infliximab), to the biosimilar Inflectra (infliximab) in severe inflammatory arthritis.

**Methods**. From May 2015 patients receiving Remicade (infliximab) were switched to Inflectra (infliximab). We compared discontinuation rates due to inefficacy and adverse events (AEs) after switching to Inflectra (infliximab) with discontinuation rates whilst receiving Remicade (infliximab) in the year prior to the switch.

**Results**. 59 patients agreed to switch, with 51 (86%) continuing after a mean follow-up 362 days (12.1 months.)

**Conclusion**. Safety and clinical efficacy of Inflectra (infliximab) appears similar to that of Remicade (infliximab).

**Key Words:** Infliximab, biosimilar, Inflectra, CT-P13

**Introduction**

The monoclonal antibody Remicade (infliximab), was licenced in Europe in 1999 for treatment of rheumatoid arthritis (RA). Its use is now widespread and has expanded to treatment of ankylosing spondylitis (AS) and psoriatic arthritis (PsA) [1]. The efficacy of biological disease modifying anti-rheumatic drugs (DMARD) in treatment of inflammatory arthritis is established [2], but drug acquisition costs are high [3].

The patent for originator Remicade (infliximab) has expired in Europe, allowing pharmaceutical companies to develop biosimilar versions [4]. A biosimilar form of originator Remicade (infliximab), initially called CT-P13, was approved for use in Europe in 2013 [1]. The guidelines for evaluation of a biosimilar product are stringent [5][4]. A randomised, international, phase III study has compared CT-P13 biosimilar infliximab with the originator product Remicade (infliximab), and demonstrated no difference in clinical efficacy or safety in patients with RA[6]. However, adoption of biosimilar infliximab in UK clinical practice remains limited.

The aim of this study was to provide real-world UK follow-up data comparing treatment of inflammatory arthritis (IA) with Remicade (infliximab) versus the biosimilar agent Inflectra (infliximab). Due to current UK rules governing the use of biological therapies all patients had severe, longstanding IA.

**Methods**

The Southampton Biological Therapies Review Service is provided by a dedicated consultant rheumatologist, specialist nurse and pharmacist. Patients receiving biological therapy for IA (RA, PsA & AS) are reviewed every 3 to 6 months in the outpatient clinic, and all data are recorded in a custom made database, created using Oracle Application Express (Oracle Corp. California, USA.

All patients receiving Inflectra (infliximab) were identified, and patients who commenced treatment without prior use of Remicade (infliximab) were excluded (n=6). All existing patients receiving Remicade (infliximab) were switched to biosimilar Inflectra (infliximab) from May 2015 onwards. A consultant rheumatologist discussed the potential switch with all patients in clinic in advance and a letter giving details of the switch, an Inflectra (infliximab) information sheet and a helpline number for further questions were sent to each patient. Patients were invited to discuss the switch in clinic, or at their next infusion unit attendance. Using this process all patients agreed to switch to the biosimilar Inflectra (infliximab).

All patients switched to Inflectra (infliximab) were continued on the same dose (3 or 5 mg/kg) that they used for Remicade (infliximab). The infusion rate was decreased to run over 2 hours from 1 hour for the first 2 attendances to allow monitoring for infusion related reactions. At each clinic appointment, disease activity was scored using DAS-28 for patients with RA and enteropathic arthritis, BASDAI for patients with AS, and PSARC response for patients with PsA. The data for this study were analysed retrospectively from the database record.

The following data were collected from each patient’s most recent clinic visit as entered into the database and recorded in a Microsoft Excel (Microsoft, Washington, USA) spreadsheet: age, gender, diagnosis, smoking status, date of diagnosis, duration of treatment with Remicade (infliximab), concurrent treatment with other DMARD, disease activity score prior to switching and at time of follow-up if available. If treatment was discontinued, the reason for stopping was recorded. If required, clinic letters were reviewed for additional information. Mean values and standard deviations were calculated using Microsoft Excel. Data were collated for all patients who stopped treatment in the preceding 12 months on Remicade (infliximab), prior to commencing the switching process, to allow direct comparison during the follow-up period.

Safety parameters were predetermined, following discussion with commissioning partners.

Patients were used as their own controls with statistical analysis using the efficacy and discontinuation rates from patients receiving inflectra in the 12 months after switching compared to the same rates whilst receiving originator Remicade in the 12 months prior to switching. Ethics approval was not required according to NHS Research Ethics Committee guidance.

**Results**

59 patients receiving Remicade (infliximab) were switched to Inflectra (infliximab) at the same dose. The patient demographics are listed in Table 1.

The mean disease duration was 19 (8.4) years, with mean time on Remicade (infliximab) of 5.7 (3.8) years. The mean time from diagnosis to first biologic therapy was 10.1 (7.6) years with methotrexate (MTX) used by 33 (56%) and another DMARD, (sulfasalazine or leflunomide) by 10 (17%). Since switching most individuals have received ≥3 infusions of Inflectra (infliximab) with 51 (86%) continuing at mean follow-up 362 days (12.1 months).

For RA the mean DAS-28 prior to switch was 3.4, and the latest DAS28 was 3.4 after switching (p-value 0.96). For AS the mean BASDAI prior to the switch was 3.7, and 3.6 after switching (p-value 0.61). During the 12.1 months of follow-up, 8 patients have discontinued treatment with Inflectra (infliximab); 4 patients due to clinical inefficacy and 4 following an adverse event. Of these, 4 patients have switched back to Remicade (infliximab), 2 have switched to ustekinumab, 1 to rituximab, and 1 patient remains off all biologic therapy.

The follow-up period on Inflectra (infliximab) of mean 12.1 months has been directly compared with the preceding 12 months of treatment with Remicade (infliximab). Table 2 shows the rates of both inefficacy and adverse events on Inflectra (infliximab) compared to the preceding 12 months of Remicade (infliximab) which are comparable.

**Clinical Inefficacy**

Four patients have discontinued Inflectra (infliximab) due to inefficacy (1 RA: DAS-28 prior 1.89, post 5.31; 1 RA: DAS-28 prior 4.72, post 3.31; 1 AS: BASDAI prior 5.2; post 8.0, 1 PsA with grade 3 synovitis on ultrasound of the wrist). All 4 of these patients were switched back onto Remicade (infliximab) in the first instance, but one (RA) developed secondary failure after switching back to Remicade (infliximab) with a flare of disease requiring treatment with corticosteroids, and is now on rituximab therapy.

**Adverse Events**

Four AEs have occurred during the period of follow-up, 3 in patients with PsA and 1 in a patient with RA. One patient developed wide spread pain following 2 infusions, which resolved on switching back to Remicade (infliximab). One patient developed myalgia following 2 infusions, and was switched to ustekinumab. One patient reported multiple side-effects also present prior to switching to Inflectra (infliximab); dizziness, labile blood pressure, forgetfulness, poor concentration. Biologic treatment was discontinued for 4 months, in keeping with patient preference and at 4 month follow-up the patient had determined the side-effects were unrelated to biologic therapy, with a plan made to start treatment with ustekinumab. One patient had problems with an infected foot ulcer, which developed into osteomyelitis. The infection had been ongoing for several months prior to switching, and the patient had previously discontinued biologic therapy whilst receiving antibiotics. Inflectra (infliximab) was discontinued due to recurrent infection, and the patient remains off all biologic therapy whilst treatment continues.

A Kaplan Meier survival analysis of the 2 groups is shown in the survival curve (Figure 1).

**Discussion**

Over a mean 12.1 months of follow-up, 51 out of 59 patients receiving Inflectra (infliximab) for IA have continued with therapy (86%). Importantly, the incidence of discontinuation of therapy due to AEs and inefficacy appear similar to the preceding 12 months of Remicade (infliximab) therapy, which supports the findings of currently available trial data [6, 7].

When the decision was made to switch from Remicade (infliximab) to Inflectra (infliximab), the local cost price per vial of Remicade (infliximab) was significantly higher than for Inflectra (infliximab) providing a potential for cost saving that was reinvested in our clinical service via a gain-share agreement. Although cost pressures are an important reality of providing healthcare we wanted to approach the switch to a biosimilar infliximab in a measured way, providing clear information to patients. We think that this contributed to the high rate of patient acceptance of this change to treatment.

There are some limitations with this real life clinical study. The completeness of the database relies on the quality of the records of the clinical team (CH and SB)working in the biologics clinic, but has proven valuable in other studies [8]. If AEs or clinical inefficacy occurred in the patients newly started on Inflectra (infliximab) as their first infliximab they would have been missed within the remit of this study. As data were analysed retrospectively, there was no way to prove causality between the treatment and the AEs or instances of inefficacy that occurred. Detection of AEs relied heavily on patient reporting. As patient consent to switch was sought, this may have influenced patient interpretation of events.

In conclusion, from the data provided in this study, there does not appear to be any significant difference in the safety profile or efficacy of Inflectra (infliximab) versus Remicade (infliximab) in real world use. In addition, patients appear accepting of this change.

**Conflict of Interest Statement**

CJE has received research support, delivered educational talks and taken part in advisory boards for Abbvie, Pfizer, MSD, Biogen, Celltrion, Napp, Roche, Celgene, UCB, Samsung bioepis.

CH has delivered educational talks and taken part in advisory boards for Abbvie, UCB, BMS, Janssen, Roche and Novartis.

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**References**

1. European Medicines Agency Committee for Medicinal Products for Human Use. Remsima: EPAR- Public assessment report. EMA/CHMP/589317/2013. London: European Medicines Agency; 2013:13-97.

2. Nam JL, Ramiro S, Gaujoux-Viala C, Takase K, Leon-Garcia M, Emery P, et al. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2014 Mar; 73(3):516-28.

3. Yoo DH, The rise of biosimilars: potential benefits and drawbacks in rheumatoid arthritis. Expert Rev Clin Immunol 2014 Aug;10(8):981-983.

4. European Medicines Agency Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products. CHMP/437/04 Rev.1. London: European Medicines Agency; 2014:4-6.

5. World Health Organisation, Expert Committee on Biological Standardisation. Guidelines on evaluation of similar Biotherapeutic Products (SBPs), Annex 2, Technical Report Series No. 977. Geneva, Expert Committee on Biological Standardization; 2009:3-28.

6. Yoo DH, Racewicz A, Brzezicki J, Yatsyshyn R, Arteaga ET, Baranauskaite A, et al. A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study. Arthritis Res Ther 2016 Apr 2;18:82.

7. Park W, Yoo DH, Jaworski J, Brzezicki J, Gnylorybov A, Kadinov V, et al. Comparable long-term efficacy, as assessed by patient-reported outcomes, safety and pharmacokinetics, of CT-P13 and reference infliximab in patients with ankylosing spondylitis: 54-week results from the randomized, parallel-group PLANETAS study. Arthritis Res Ther 2016 Jan 20;18:25.

8. Marks JL, Holroyd CR, Dimitrov BD, Armstrong RD, Calogeras A, Cooper C, et al. Does combined clinical and ultrasound assessment allow selection of individuals with rheumatoid arthritis for sustained reduction of anti-tumor necrosis factor therapy? Arthritis Care Res (Hoboken) 2015 May;67(6):746-53.