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

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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 patent for originator Remicade (infliximab) has expired in Europe, allowing pharmaceutical companies to develop biosimilar versions (2). A biosimilar form of originator Remicade (infliximab), initially called CT-P13, was approved for use in Europe in 2013 (3). The guidelines for evaluation of a biosimilar product are stringent (2, 3). 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 (4). 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, long-standing IA.

All patients receiving Inflectra (infliximab) via the Southampton Biological Therapies Review Service 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). The data for this study were analysed retrospectively from the database record. If treatment was discontinued, the reason for stopping was recorded. 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.

59 patients receiving Remicade (infliximab) were switched to Inflectra (infliximab) at the same dose. The patient demographics are listed in Table I. Since switching most individuals have received ≥3 infusions of Inflectra (infliximab) with 51 (86%) continuing at mean follow-up 362 days (12.1 months). 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 (AE). 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 II shows the rates of both inefficacy and AEs on Inflectra (infliximab) compared to the preceding 12 months of Remicade (infliximab) which are comparable.

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.

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); diz-

Table I. Characteristics of the 59 patients switched from Remicade (infliximab) to Inflectra (infliximab).

Characteristic	Patients switched to biosimilar (n=59)
Mean age, years (S.D.)	58.9 (13.1)
Gender: female, n (%)	30 (51)
On methotrexate (%)	33 (56)
On other DMARD (%)	10 (17)
Indications for therapy, n (%)	
Rheumatoid arthritis (RA)	29 (49)
Ankylosing spondylitis (AS)	14 (24)
Psoriatic arthritis (PsA)	14 (24)
Enteropathic arthritis (EnA)	2 (3)
Mean disease duration, years (SD)	19.0 (8.4)
Mean time on Remicade, years (SD)	5.7 (3.8)
Mean time from diagnosis to 1st biologic years (SD)	10.1 (7.6)

Table II. Comparison of rates of inefficacy and adverse events in Remicade (infliximab) *vs*. Inflectra (infliximab).

Reason for stopping	12 months prior to switching whilst using Remicade n= 67	12 months after switching whilst using Inflectra n= 59
Inefficacy	3	4
Adverse events	7 [a]	4

[a] Included 2 deaths: 1 out of hospital cardiac arrest (probable ischaemic event causing VF); 1 death due to malignancy, non-healing foot ulcers, low grade lymphoplasmacytic lymphoma, influenza requiring admission to ICU, infusion reaction, neuropathy.

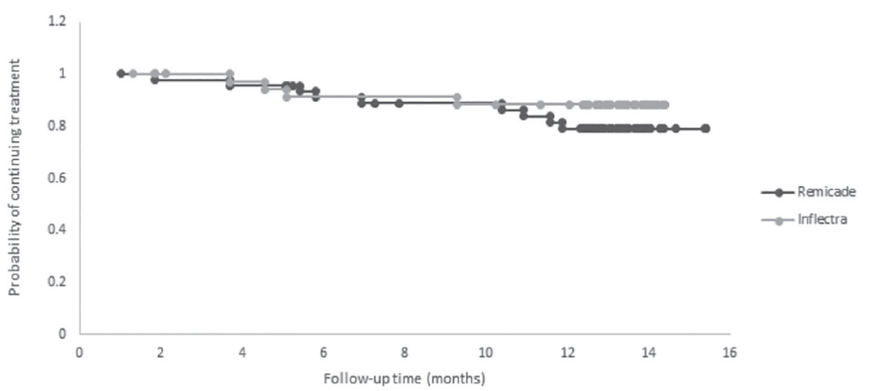

Fig. 1. Kaplan-Meier survival curve comparing probability of continuing treatment with Remicade (infliximab) *vs*. Inflectra (infliximab) over time.

ziness, 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 (Fig. 1).

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 (4, 5).

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.

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.

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Competing interests:
C. Holroyd has delivered educational talks and taken part in advisory boards for Abbvie, UCB, BMS, Janssen, Roche and Novartis;
C. Underhill has received honoraria from Pfizer;
C. Cooper has received consultancy fees and honoraria from Amgen, Eli Lilly, GSK, Medtronic, Merck, Nestle, Novartis, Pfizer, Roche, Servier, Shire, Takeda and UCB;
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