Real Life Switching from Infliximab Innovator to Biosimilar in Rheumatic Diseases: A 6-Month Single-Centre Prospective Observational Study

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Abstract

Background: Although Inflectra, biosimilar infliximab, has been approved by the EMA since September 2013 for all licensed indications of Remicade (innovator infliximab) but there is a paucity of real-world data and guidelines regarding switching from innovator Remicade to Inflectra.

Objectives: To explore efficacy, safety, and retention rate of biosimilar Inflectra when switching from Remicade, in patients with rheumatic diseases.

Methods: Informed consent was sought from all patients attending our rheumatology unit to undertake a switching programme. Baseline demographics and clinical characteristics were obtained before switching to Inflectra. Disease activity and safety assessment were undertaken before and then every 12 weeks after switching. The retention rate of Inflectra switch patients was compared with a cohort of non-switch Inflectra naive (11 patients) and historic Remicade (31 patients) patients.

Results: Thirty out of thirty-one patients {median (IQR) age 50 (18), 20F} with various rheumatic diseases (9 with diagnosis of AS, 6 with RA, 6 with Behçet's disease, 3 with Enteropathic arthritis, 2 with psoriatic arthritis) agreed to the switch. There was no statistical difference noted between pre-switch and 6 months post-

switch mean values of PGA (p=0.37), BASDAI (p=0.60), ASDAS-CRP (p=0.90), DAS28CRP (p=0.85), DAS28ESR (p=0.45), CRP (p=0.09), Behçet's disease activity score (p=0.77) and HAQ-DI (p=0.18). The retention rate on Inflectra switch was 86.7% as compared to 90.9% in the Inflectra naive cohort and 100% for historic Remicade cohort.

Conclusion: These results demonstrate that in this cohort at 6 months Inflectra is comparable to Remicade in efficacy and there are no new safety signals.

Keywords: Biosimilars; Infliximab; Remicade; Inflectra; Rheumatic diseases; Real Life Switching; Disease activity; Retention rate; Nocebo effect

1. Introduction

Undoubtedly biological DMARDs (bDMARDs), including TNF-alpha inhibitors, have revolutionized the treatment of various rheumatic disorders such as AS, RA, and psoriatic arthritis [1-3] and these have become an integral component of treatment algorithms of these diseases [4, 5]. However huge costs associated with the use of bDMARDs have been a barrier to their widespread use and accessibility especially in the countries with the low gross domestic product [6, 7]. A European study has shown that bDMARDs cannot be reimbursed in some countries within Europe and bDMARDs treatment costs were more than the actual GDP in 26 countries [6]. It is anticipated that availability of biosimilar DMARDs (bsDMARDs) will reduce the economic burden and accessibility to biologics due to reduced cost and the addition of competition to the market [8]. Biosimilars are biological medicinal agents that contain a version of active substance of reference biological product, also called originator or reference biologics, are supposed to be administered at the similar dose to treat same disorders [9]. Due to large size and complex structure, an exact

copy of reference biologic is not possible. There is a rigorous process required to establish that a biosimilar product is similar to the reference product in terms of quality characteristics, biological activity, pharmacokinetics, safety, immunogenicity, and efficacy [10].

Inflectra (CT-P13), the biosimilar infliximab, has been approved by the European Medicine Agency since 2013 and for US Food and Drug Administration in 2016 for all licensed indications of Remicade (innovator infliximab) [11]. CT-P13 was authorized was on the basis on the basis of randomized controlled trials PLANETRA [12] and PLANETAS [13] comparing originator infliximab with CT-P13 in rheumatoid arthritis and ankylosing spondylitis respectively. Approval for other indications (psoriatic arthritis, plaque psoriasis, Crohn's disease and ulcerative colitis) was based on extrapolation of data from these trials, according to guidance for regulatory approval of biosimilars [14]. Although Inflectra has been found to offer significant cost, there is still a paucity of real-world data about its safety and efficacy, especially when switching from reference infliximab product [15]. The aim of our study was to investigate the real-life efficacy, safety and retention rate of switching from reference infliximab (INX) to biosimilar infliximab (CT-P13) in patients with various rheumatic diseases.

2. Methods

2.1 Patients and study design

This was a single Centre observational prospective cohort study conducted by Department of Rheumatology, University Hospitals Limerick at rheumatology day ward (infusion center) in Croom Orthopedic Hospital. In August 2017, all the patients receiving reference infliximab (Remicade™, Janssen Biotech, Horsham, PA, USA) for various rheumatic diseases were proposed to switch to

biosimilar infliximab CT-P13 (Inflectra™, Lake Forest, IL, USA). Ethical approval was obtained from the local ethics committee to undertake this study. All these patients were physically interviewed by Rheumatology registrar to discuss switching and they were given information about biosimilar infliximab and data about its safety and efficacy. Informed consent was obtained from all the patients agreeing to participate. Patients were also informed about the option of switching back to reference infliximab in future if necessary. Any patient receiving reference infliximab was considered eligible for the study. The patients who agreed to switch were started on CT-P13 at the same treatment regimen (dose and frequency) after getting written consent. Associated treatments including csDMARDs and corticosteroids were not modified at inclusion.

For comparison of retention rate, two control cohorts from the same department were used:

1) A cohort of Inflectra-naïve (non-switch Inflectra patients). These were 11 patients who were started on Inflectra and they were never on Remicade.

2) A retrospective cohort of 31patients who were treated with Remicade during Ist half of the year 2017.

The primary outcome was to compare efficacy and safety indicators before the switch (on reference infliximab) and 6 months post-treatment with biosimilar infliximab. The secondary outcome was to compare retention rate of switch population of biosimilar infliximab with biosimilar infliximab naive population and the historic cohort of reference infliximab.

2.2 Assessments

Demographic, clinical and laboratory data were obtained pre-switch and then clinical and laboratory data were obtained at median 12 weeks follow up. This data included age, sex, rheumatologic diagnosis, duration of disease, comorbidities, vaccination status, seropositivity, current treatment, duration of infliximab therapy, concomitant immunosuppressive therapy, previous failed csDMARDs or bDMARDs, DAS28 CRP, DAS28 ESR, SDAI, tender joint count, swollen joint count, BADSAI, ASDAS CRP, Behçet's disease activity index (BD score), health assessment questionnaire disability index (HAQ-DI), patient global assessment (PGA) and side effects. Laboratory data included inflammatory markers, bone profile, Vit D, U and Es, LFTs and FBC.

2.3 Statistical analysis

The data were analysed using SPSS version 22. Descriptive statistics were used to report differences in patient demographics and disease characteristics between Inflectra switch population and Inflectra naive cohort. Normally distributed data were expressed as mean (Standard deviation) while nonnormally distributed data was shown as median (range or interquartile range, IQR). Pre-switch and 6 months post-switch disease activity measures were compared using paired sample t-test. p values below 0.05 were considered significant. Kaplan-Meier survival curves of retention rate were compared using a log-rank test.

3. Results

3.1 Population characteristics

Thirty out of thirty-one patients on Remicade agreed to switch to Inflectra. Patients's disease and treatment characteristics are elaborated in Table 1. Among switch population, 9 patients (30%) had ankylosing spondylitis (4 were HLA B27 Positive), 6 patients (20%) had RA (4 were seropositive for RF and Anti-CCP), 6 (20%) had Behçet's disease, 2 (6.7%) had psoriatic arthritis and 3 (10%) patients had Enteropathic arthritis. Their mean age was 50 (12.2) years and 20 (66.7%) were female. Mean duration of disease was 6.8 (2.9) years and median duration of being on Remicade prior to switch was 72 (24-192) months. More than half of the patients

(53.3%) were on csDMARDs and nearly one third (30%) were on corticosteroids along with Infliximab. Among 11 patients of non-switch Inflectra cohort, five patients (45.5%) had psoriatic arthritis, 3 (27.3%) had RA and one (9.1%) had AS. Their mean age was 47.2 (15.2) years and 6 (54.5%) were female. Mean duration of disease was 8 (5.2) years and median duration of being on Remicade prior to switch was 11 (2-26) months. More than half of the patients (53.3%) were on csDMARDs and nearly one third (30%) were on corticosteroids along with Infliximab. 6 (54.5%) patients were requiring concomitant csDMARDs and corticosteroids.

3.2 Efficacy

Pre-switch disease activity measures of Inflectra switch population were compared with 6 months post-switch disease activity measures of the same patients (Figure 1). Mean (standard deviation) PGA pre-switch was 33 (26.3) compared to 35.3 (24) following biosimilar switching without significant difference (p=0.37). Mean HAQ on reference infliximab also did not differ significantly following switching {0.42 (0.45) vs 0.45 (0.47) p=0.18}. Rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis patients didn't show any statistically significant worsening in disease activity measures following the switch as shown by mean values of BASDAI (3.12 (1.2) vs 2.98 (1.5) p=0.60}, ASDAS-CRP{1.7 (0.57) vs 1.7 (0.57) p=0.90}, SDAI {14.6 (16.5) vs 13.1 (10.4) p=0.65}, DAS28CRP {3.9 (1.6) vs 3.28 (1.0) p=0.85}, DAS28ESR {3.97 (2.04) vs 3.49 (1.20) p=0.45}, CRP {3.13 (4.2) vs 3.48 (4.8) p=0.09}.

Our cohort of Behçet's disease patients also maintained their efficacy following switch to biosimilar (mean Behçet's disease activity index 1.17 (1.3) vs 1.33 (2.16) p=0.77).

3.3 Retention rate and safety

At 6 months post-switch, 26 (86.7%) out of 30 patients are continuing Inflectra with good efficacy and without any serious safety concern. This retention rate is lower than that of the cohorts of historic Remicade (100%) and Inflectra (90.9%) Figure 2. All 4 patients who stopped Inflectra were successfully switched back to Remicade. Among these four drop-outs, one patient developed severe nausea, dizziness and abdominal pain after her first Inflectra infusion and another patient developed psoriasis flare 12 weeks after the switch (having had no active psoriasis for the years they were on Remicade). Two patients developed subjective worsening of pain without objective or serological worsening of disease activity (Figure 3). One patient among Inflectra naive group had to stop Inflectra because of recurrent chest infections. No patients on Inflectra developed serious infections requiring hospital admission. These 4 patients were successfully switched back to Remicade. Patient 1 with nausea and abdominal pain had no further symptoms. Patient 2 with flare of psoriasis had full clearing of psoriasis within 2 months of switching back and 2 patients with subjective flare of symptoms reported a return to pre-switching symptom levels. There was no malignancy and mortality during this study.

Characteristics at inclusion	Inflectra switch population (n=30)	Inflectra-naïve (non-switch) population (n=11)
Age, years, mean (S.D.)	50 (12.2)	47.2 (15.2)
Female Sex	20 (66.7%)	6 (54.5%)
Diagnosis: number (%) RA	6 (20%)	3 (27.3%)
AS	9 (30%)	1 (9.1%)
Behçet's disease	6 (20%)	1 (9.1%)
Psoriatic Arthritis	2 (6.7%)	5 (45.5%)
Enteropathic Arthritis	3 (10%)	0
JIA	1 (3.3%)	0
Undifferentiated inflammatory arthritis	1 (3.3%)	0
Juvenile Dermatomyositis	1 (3.3%)	0
GCA	0	1 (9.1%)
Graves Ophthalmopathy	1 (3.3%)	-
Disease duration mean years (S.D.)	6.8 (2.9)	8 (5.2)
Weight, Kgs, mean (S.D.)	72.4 (10.5)	94.2 (30.9)
Height, centimeters, mean (S.D.)	166.5 (9.1)	165.9 (8.4)
BMI, kg/m², mean (S.D.)	26.1 (3.5)	34.5 (11.8)
Infliximab dose, mg/kg, median (range)	5 (3-8)	5
Infliximab infusion frequency, median (range)	6 (4-12)	6 (6-8)
Duration of being on Infliximab before switch, months, median (range)	72 (24-192)	11 (2-26)
Concomitant csDMARDs, n (%)	16 (53.3%)	6 (54.5%)
Methotrexate, dose, mg, median (range)	15 (10-25)	15 (10-25)
Concomitant corticosteroids, n (%)	9 (30%)	6 (54.5%)
Previously been on other bDMARDS, n (%)	19 (63.3%)	11 (100%)

RA: Rheumatoid Arthritis; AS: Ankylosing Spondylitis; JIA: Juvenile Idiopathic Arthritis; GCA: Giant Cell Arteritis; SD: Standard Deviation; BMI: Body Mass Index; csDMARDs; Conventional Synthetic Disease Modifying Anti-Rheumatic Drugs; bDMARDs: Disease Modifying Anti-Rheumatic Drugs.

Table 1: Baseline characteristics of Inflectra switch and Inflectra naïve (|non-switch) patients' groups.
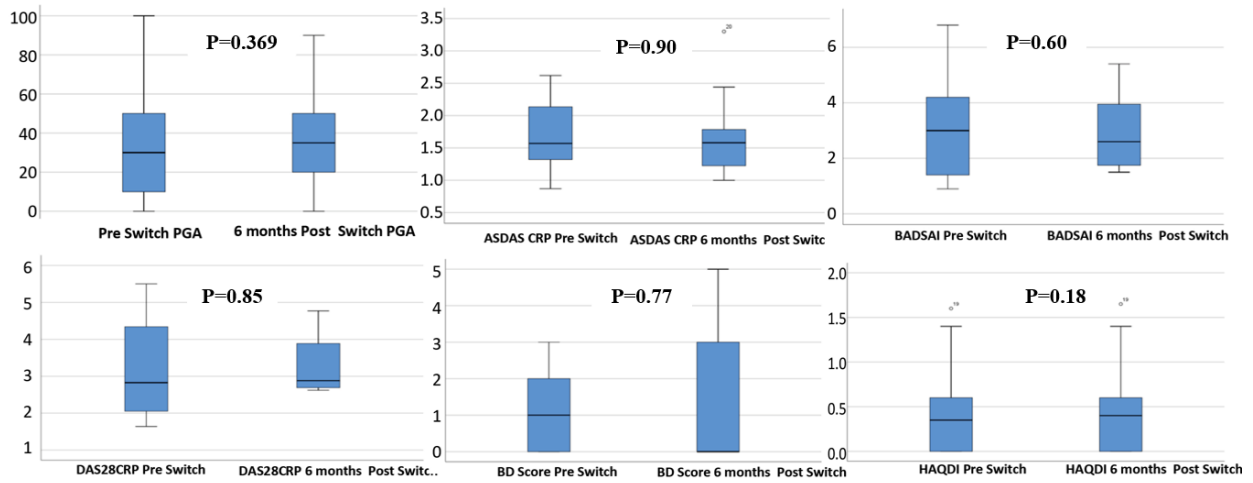
PGA: Patient global assessment score; BADSAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-C reactive protein; SDAI: Simplified Disease Activity Index; DAS28CRP: Disease Activity Score 28- C reactive protein; DAS28ESR: Disease Activity Score 28- Erythrocyte Sedimentation Rate; TJC: Tender joint count; SJC: Swollen Joint Count; BD score: Behcet disease activity index; HAQ-DI: health assessment questionnaire- disability index

Figure 1: Box plots to compare main study outcomes pre-switch and 6 months post-switch.
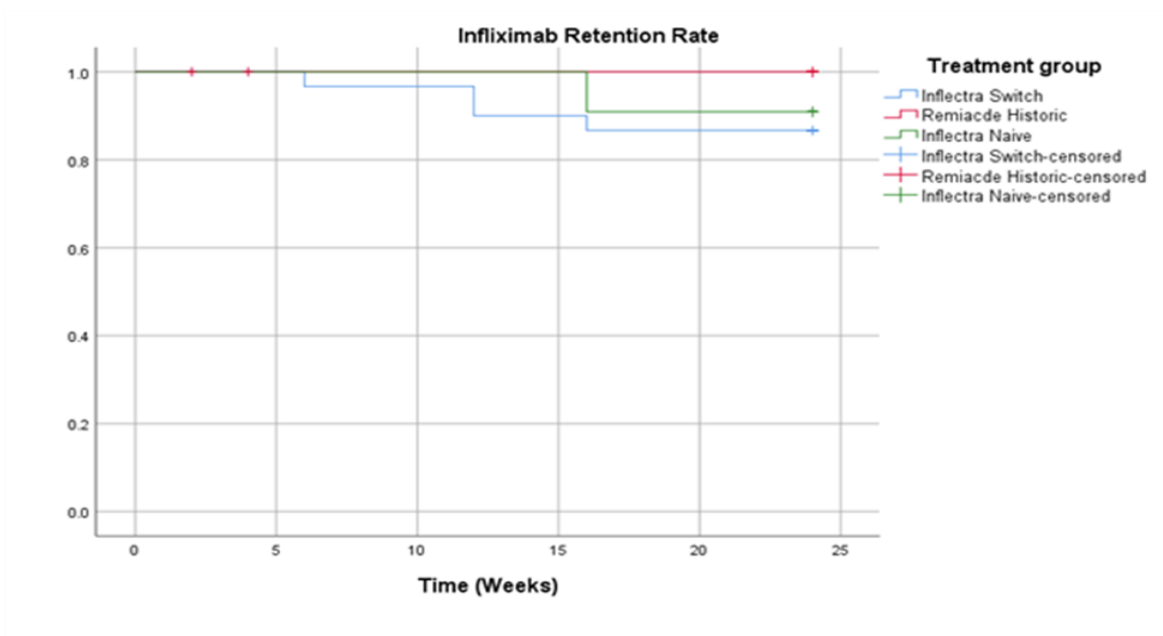

Figure 2: Comparison of 6 months retention rate among Inflectra switch, Inflectra Naïve (Inflectra non-switch) and Historic Remicade groups.
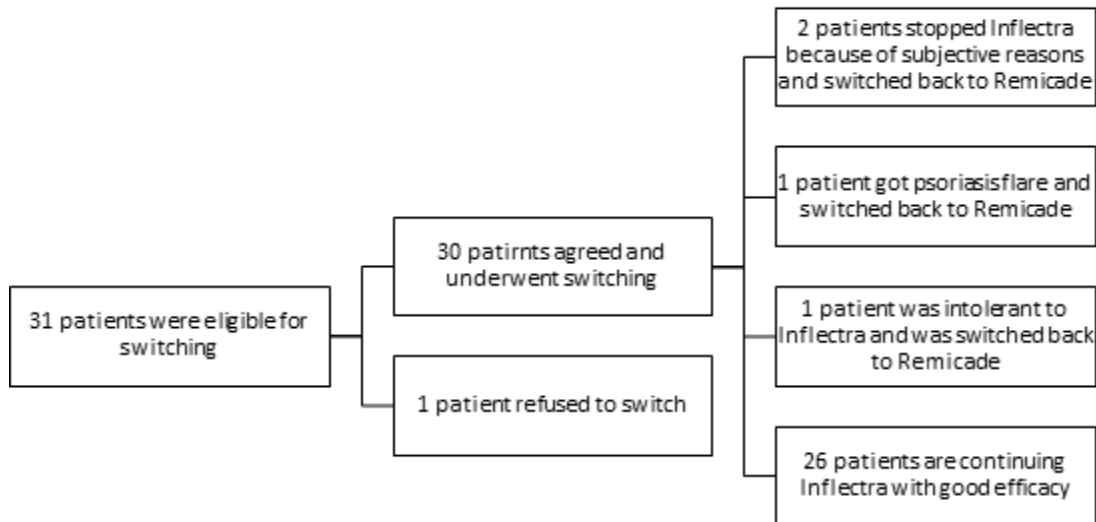
Figure 3: Flowsheet showing outcome of switch population at 6 months.

4. Discussion

Our study is one of only a few studies done in real-life setting examining efficacy and safety of switching from reference infliximab (Remicade) to biosimilar infliximab, CT-P13 (Inflectra). It clearly shows that the clinical efficacy and tolerability of Inflectra is equivalent to Remicade even after switching in a real-life setting; supporting data from previous randomised controlled trials and observation single and multicentre studies. PLANETAS [12], a phase I RCT, confirmed pharmacokinetic equivalence of CT-P13 and reference infliximab without any significant difference in disease activity and safety measures at week 30. Bio clinical equivalence was demonstrated by PLANETRA [13], a phase III RCT, which showed comparable ACR20 responses at week 30: 60.9% for CT-P13, 58.6% for reference infliximab (95% CI, −6% to 10%). 54 weeks results of these trials demonstrated persistent disease activity without any safety concerns [16, 17]. In the extension phase of PLANETRA [18] and PLANETAS [19], patients who received reference infliximab were switched to CT-P13 at week 52 and compared to

the group receiving CT-P13 from the beginning. After an additional year of follow-up, there was no difference in terms of efficacy and tolerance as shown by comparable ACR 20, ACR 40, ACR 70, ASAS 20 and ASAS 40 responses. The NOR-SWITCH, a Norwegian study, was 52-week randomized double-blind, non-inferiority, phase IV trial [20]. In this trial, 482 patients of inflammatory bowel disease and various rheumatic disease were randomised in a 1:1 ratio to either continued infliximab originator or to switch to CT-P13 treatment. At 52 weeks, CT-P13 was found to be non-inferior to reference infliximab with the predefined non-inferiority margin of 15%.

The Danish DABINO registry published results of 802 patients with RA (403), SpA (279), PsA (120) who underwent a non-medical switch to CT-P13 from reference Infliximab [21]. These results showed similar disease activity and flares 3 months before and 3 months after the switch for the three diseases. The retention rate at 1 year was 84% for CT-P13 and 86% for reference infliximab. A single Centre observational

real-life French study examined the weight of patient acceptance and retention rate of CT-P13 for patients with various rheumatic diseases [22]. After a median follow-up of 33 weeks, the retention rate was significantly lower in CT-P13 switch cohort (72%) as compared to the prospective CT-P13 naive cohort (88%) and retrospective historic reference infliximab cohorts (90%). Data from a local, single Centre observational study showed the CT-P13 retention rate of 85.3% at 6 months [23]. It is important to note that 2 0f 30 patients (13%) did have an objective adverse outcome from switching. One patient developed nausea and abdominal pain and the second a flare of long quiescent psoriasis. All four patients switched back to Remicade did so successfully which is reassuring, but the cases noted remind us that Biosimilars medications are not Generic and there are significant and relevant differences between biosimilar and bio-originator products.

Among all observational switch studies, our trial showed the best retention rate 86.7% at 6 months. Subjective reasons were the most important reason (50%) of dropouts. This can be due to nocebo effects of non-medical infliximab switch. A nocebo effect occurs when patient's negative perception of treatment causes an unexplained worsening of disease outcome. Significant price difference between bio-originators and biosimilars can also be a leading factor resulting in negative perception and nocebo effect. Our strategy of patient empowerment could be one of the factors contributing towards high retention rate of CT-P13. The nocebo effect associated with non-medical infliximab switch was studied in a recently published Dutch study [24]. Our cohort of Behçet's disease patients [25] maintained good disease control after switching to CT-P13. This is first real-time study showing efficacy of CT-P13 in Behçet's disease patients. The main strengths of our study were that it was conducted in

real-life clinical setting on a wide variety rheumatology patient and we used two other cohorts to compare retention rate of switch population. The small number of patients, being observational rather than randomised and short follow-up were main limitations of our study.

5. Conclusion

Based on the results of our real-life clinical study, we are satisfied that CT-P13 is a safe and efficacious option to treat a variety of rheumatology patients and it is reassuring that switching to CT-P13 can lead to substantial savings essential for the sustainability of the healthcare system. Switching back to Remicade where necessary was effective and safe. Randomised controlled trials are required to prove long-term safety and efficacy of CT-P13 with higher patient number and longer-term follow-up.

Data availability

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Disclosure Statement

The authors declare no conflict of interest.

- Mrs. Breda McCarthy

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