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Safety and efficacy of transitioning inflammatory bowel disease patients from intravenous to subcutaneous infliximab: a single-center real-world experience

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Abstract

Background A new subcutaneous (SC) formulation exists for infliximab (CT-P13 SC). The aim of this study was to assess the durability of clinical and endoscopic responses after a switch from intravenous (IV) to SC infliximab.

Methods Patients were transitioned on maintenance infliximab, including those with dose-optimized therapy. The primary outcome was clinical, biochemical and overall remission at 6 months, as defined by a Harvey-Bradshaw Index <5 for Crohn's disease or a partial Mayo score <3 for ulcerative colitis, C-reactive protein less than 10 mg/L, and fecal calprotectin less than 100 μg/g.

Results Forty patients were switched from IV to SC infliximab. Twenty-seven (68%) had a diagnosis of Crohn's disease and 13 (33%) had ulcerative colitis. Twenty-three (58%) were on 5 mg/kg of IV infliximab every 8 weeks and 15 (38%) 5 mg/kg every 6 weeks. There were 2 patients (4%) on 10 mg/kg every 6 weeks. At the time of their switch, 37 (93%) patients were in clinical remission, 25 (76%) were in biochemical remission, and 25 (76%) were in both biochemical and clinical remission. At 6 months the proportion of patients in clinical remission decreased from 93% to 82%, with an overall relapse rate of 11%. Treatment persistence at 6 months was 77.5%.

Conclusion Switching patients from IV infliximab to 120 mg fortnightly SC injections is a safe and effective option for the treatment of inflammatory bowel disease, including for those patients on dose-escalated infliximab or with active disease at the time of switch.

Keywords Ulcerative colitis, Crohn's disease, biologics, subcutaneous, intravenous

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Introduction

Treatment of inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), has been rapidly changing over the past decade, with the current mainstay of treatment being biologic therapies [1]. The route of administration for biologics has historically been intravenous (IV); however, newer agents are increasingly given via other routes, including subcutaneous (SC) formulations. Although infliximab has traditionally been administered intravenously, new SC formulations have been developed more recently. In particular, the European Medicines Agency approved SC infliximab for the treatment of IBD in 2020.

There has been one large multicenter phase 1 trial that showed pharmacokinetic non-inferiority for SC infliximab compared to IV infliximab with comparable efficacy, safety, and immunogenicity profiles [2]. More recently there have been two real world observational trials that also showed similar efficacy for SC infliximab (dose of 120 mg fortnightly) in maintaining clinical remission compared to IV infliximab [3,4]. The follow up

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was variable between each of these trials (between 24 weeks and 12 months); however, the rate of remission was similar, between 88% and 92.3%, comparable to the baseline risk for secondary loss of response in infliximab, which ranges from 10-20% [5].

There are significant benefits to transitioning patients to SC infliximab. These can be grouped in terms of the medical considerations, including the efficacy of these agents, patient considerations, including a reduction in dependence on the medical system and increased autonomy, as well as financial considerations, including a reduction in costs for infusion lounge access and staff requirements [6]. This study focuses on the medical considerations for this transition, and our experience with the efficacy of SC infliximab in IBD patients who are switched to SC therapy. The aim of this study was to assess the clinical and biochemical response after a switch from IV to SC infliximab in patients with IBD who have been established on maintenance IV infliximab.

Patients and methods

Our study recruited all adult patients at Royal Perth Hospital in Australia (18 years and over) with IBD (CD and UC) transitioned from IV to SC infliximab between January 2022 and June 2022. Patients were transitioned at the discretion of the clinician managing care, with agreement from the patient. Patients who had quiescent disease, as measured by a Harvey-Bradshaw Index (HBI) less than 5 or a partial Mayo score less than 3, were recruited to be switched to SC. In addition, a number of patients were switched who did not meet these criteria, for reasons including remote location, ease of access and patient preference. All patients had been established on maintenance IV infliximab. Patients were excluded if they had not been on SC infliximab for at least 3 months and had not had a follow-up clinical review since starting treatment.

All patients were switched to 120 mg alternate weekly SC infliximab in the form of Remsima (CT-P13 SC). The dose of IV infliximab prior to the switch was variable, and there was no requirement to be on standard 5 mg/kg 8-weekly dosing. We collected data, including age, date of diagnosis, type of disease including Montreal classification (CD or UC), sex and smoking status. Details on treatments were also collected, including IV infliximab dose and frequency, use of immunomodulators, prior medication history, and previous IBD-related surgery.

Baseline C-reactive protein (CRP), fecal calprotectin (FCP), infliximab level, and infliximab antibodies were recorded at the time of switch and at 6 months. Patients did not routinely have infliximab level and antibody testing done at 6 months, but this was included where it was available. We also recorded HBI and partial Mayo scores at the time of switch and at 6 months. These scores were collated from the Australian Pharmaceutical Benefits Scheme applications and clinic letters. All adverse drug reactions were collected and outcomes recorded. We defined clinical remission as a partial Mayo score of less than 3 for UC, and HBI less than 5 for CD. Biochemical remission was defined as a CRP level less than 10 mg/L, and FCP less than 100 μg/g, based on the recommendations in the most recent British Society of Gastroenterology consensus guidelines on the management of IBD in adults [7].

The primary outcome was clinical, biochemical and overall remission at 6 months, as defined above. We also measured the rate of treatment persistence at 6 months. The rates of clinical, biochemical and overall remission are reported on an "as observed" basis.

Statistical analysis

Statistical analysis was carried out using the SPSS statistics software package. Clinical remission rates over 6 months were compared using chi-squared analysis, with significance defined as a P-value <0.05. Kaplan-Meier survival analysis was used to determine the rate of durability over 6 months for SC infliximab. Univariate and multivariate analyses were performed using logistic regression to determine predictive factors for relapse over the 6-month period.

Our study was approved by the Quality Improvement (QI) Committee of the East Metropolitan Health Service and Royal Perth Hospital in Australia.

Results

At the time of the study there were a total of 221 patients on IV infliximab. Of these, 40 patients, 27 (68%) with CD and 13 (32%) with UC, were switched from IV to SC infliximab between January 2022 and June 2022. Nineteen (48%) patients were male, and the mean age was 42±17 years. Patient characteristics are summarized in Table 1.

The majority of patients were on 5 mg/kg IV infliximab every 8 weeks (23, 58%) or 5 mg/kg every 6 weeks (15, 38%) at the time of switch. There were 2 patients (4%) on 10 mg/kg every 6 weeks at the time of switch. The switch to SC was due to geographic location and poor access to services in 1 of these patients, and to patient preference in the other. All patients were switched to 120 mg of SC infliximab (Remsima) fortnightly, regardless of the IV dose they received previously.

Nine (23%) patients were using combination treatment with an immunomodulator (methotrexate or thiopurine) at the time of switch, while 18 (45%) had previously used an immunomodulator. Thirteen (33%) patients had never used an immunomodulator at the time of switch to SC. Only 4 patients had received a biologic therapy apart from IV infliximab at the time of switch: 3 patients (8%) had 1 other biologic and 1 patient (2%) 2 biologics. The majority of patients (36, 90%) had not been on any biologic besides infliximab at the time of switch to SC. No patients were using oral or IV steroids at the time of switch to SC.

The mean HBI score prior to the switch to SC for patients with CD was 1.6±3.0, while the mean baseline partial Mayo for

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Table 1 Patient characteristics at time of switch from intravenous to subcutaneous infliximab

Characteristics	Value
Total number of patients	40
Age at diagnosis (years, mean±SD)	42±17
Time without flare prior to switch (years, mean±SD)	3.9±3.0
Type of IBD (number, %)	
Ulcerative colitis	13 (32%)
Crohn's disease	27 (68%)
Male sex (number, %)	19 (48%)
Location (CD) (number, %)	
L1	4 (15%)
L2	9 (33%)
L3	12 (45%)
L4	2 (7%)
Behavior (CD) (number, %)	
B1	18 (67%)
B2	6 (22%)
B3	3 (11%)
Perianal disease (CD) (yes, %)	6 (22%)
Previous surgery (yes, %)	10 (25%)
Steroid use at time of treatment at switch (yes, %)	0 (0%)
Immunomodulator use at time of switch (number, %)	
Never used	13 (33%)
Previously used	18 (45%)
Currently using	9 (23%)
Previous biologic exposures (excluding IV infliximab) (number, %)	
0	36 (90%)
1	3 (8%)
2	1 (2%)
Infliximab dose (mg/kg) (number, %)	
5 mg/kg every 8 wk	23 (58%)
5 mg/kg every 6 wk	15 (38%)
10 mg/kg every 8 wk	0 (0%)
10 mg/kg every 6 wk	2 (4%)
Drug trough level at baseline (mean ± SD)	8.8±5.3
Baseline HBI (CD) (mean ± SD)	1.6±3.0
Baseline partial Mayo (UC) (mean ± SD)	0.4±0.6
Baseline FCP (mean ± SD)	74.9±59.3
Baseline CRP (mean ± SD)	3.2±3.3

CD, Crohn's disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; SD, standard deviation; HBI, Harvey-Bradshaw index; wk, weeks; FCP, fecal calprotectin; CRP, C-reactive protein; IV, intravenous

UC was 0.4±0.6. Baseline FCP was 74.9±59.3 μg/g, and CRP was 3.2±3.3 mg/L. As shown in Table 2, at the time of switch to SC (baseline), 37 (93%) patients were in clinical remission, 25 (76%) were in biochemical remission and 25 (76%) were in both biochemical and clinical remission. Of these patients, 100% of those with UC were in both clinical and biochemical impression at baseline.

Fig. 1 shows the rates of remission between baseline and 6 months. Overall, for UC and CD the proportion of patients in clinical remission decreased from 93% to 82% with a relapse rate of 18% at 6 months. For biochemical remission this was 76% and 65%, respectively. However, there was no statistically significant difference between these 2 groups (P=0.335). For patients with CD, the proportion of patients in clinical remission decreased from 89% to 83%, with a relapse rate of 17%, and for biochemical remission there was a similar reduction from 70% to 60% (P=0.662). For UC, the proportion of patients in clinical remission decreased from 100% to 82%, with an associated relapse rate of 18%. For biochemical remission the decrease was from 100% to 75%. There was a statistically significant difference between these groups, with a P-value of 0.026. It should be noted, however, that only a small proportion of patients had biochemical data available for analysis at the 6-month mark, as noted in Table 2. Of the 2 patients who were on 10 mg/kg 6-weekly infliximab, 1 remained in clinical and biochemical remission at 6 months, while the other relapsed at 6 months.

None of the baseline variables described in Table 1 were found to be predictive of relapse in univariate analysis. Similarly, multivariate analysis of baseline infliximab level, FCP, IV infliximab regimen and age was not found to be significant in predicting relapse.

Treatment persistence was also assessed, with 9 patients (22.5%) ceasing SC infliximab over the 6-month period as shown in Fig. 2. The reason for treatment discontinuation was worsening of disease activity in 5 (56%) patients, adverse drug reactions in 2 (22%), development of melanoma in 1 (11%), and disease quiescence and commencement of a drug holiday in 1 (11%). Adverse drug reactions were noted in 3 patients (7.5%). Two of these patients had their treatment discontinued as described above, for drug-induced lupus and a severe injection site reaction respectively. The 1 remaining patient developed a mild injection site reaction and has remained on therapy.

Discussion

This study presents real-world data relating to the transition of patients from IV to SC infliximab, in a cohort where almost half the patients were on dose-escalated infliximab at the time of transition, and that also included those with evidence of active disease. Despite this, we have demonstrated that patients can be effectively and safely considered for transition to SC infliximab. The baseline rate of immunogenicity and secondary loss of response of IV infliximab is quite variable amongst studies, with an estimated risk of around 10 to 20% per patient-year for infliximab [5,8-10]. This is comparable to our rate of relapse at 6 months of 18%. We have also shown a high rate of treatment persistence over this time.

We found that IV infliximab dose, baseline FCP, CRP, HBI, and partial Mayo score were not predictive of the rate of remission at 6 months, but we note that the event rate was small in our cohort because of the sample size. We have also demonstrated a good safety profile for SC infliximab, with no major adverse side effects over 6 months.

Table 2 Baseline and 6-month outcomes for patients switching from intravenous to subcutaneous infliximab

Outcomes	Baseline		6 months		P-value
	Value	Number	Value	Number	
All					
CRP (mean±SD)	3.2±3.3	33	5.8±10.7	23	
FCP (mean±SD)	74.9±59.3	16	262.5±396.6	6	
Infliximab level (mean±SD)	8.8±5.3	15	16.5	1	
Remission					
Clinical remission (number, %)	37 (93%)	40	28 (82%)	34	0.335
Biochemical remission (number, %)	25 (76%)	33	15 (65%)	23	
Clinical and biochemical remission (number, %)	25 (76%)	33	15 (65%)	23	
UC					
CRP (mean±SD)	2.1±2.4	10	2.8±2.7	8	
FCP (mean±SD)	23.8±13.9	6	22.0±11.5	3	
Infliximab level (mean±SD)	9.5±6.3	5	-	0	
Remission					
Clinical remission (number, %)	13 (100%)	13	9 (82%)	11	0.026
Biochemical remission (number, %)	10 (100%)	10	6 (75%)	8	
Clinical and biochemical remission (number, %)	10 (100%)	10	6 (75%)	8	
CD					
CRP (mean±SD)	3.7±3.5	23	7.5±10.2	15	
FCP (mean±SD)	105.5±61.1	10	503.0±217.0	3	
Infliximab level (mean±SD)	8.4±4.8	10	16.5	1	
Remission					
Clinical remission (number, %)	24 (89%)	27	19 (83%)	23	0.662
Biochemical remission (number, %)	16 (70%)	23	9 (60%)	15	
Clinical and biochemical remission (number, %)	16 (70%)	23	9 (60%)	15	

CD, Crohn's disease; UC, ulcerative colitis; SD, standard deviation; FCP, fecal calprotectin; CRP, C-reactive protein

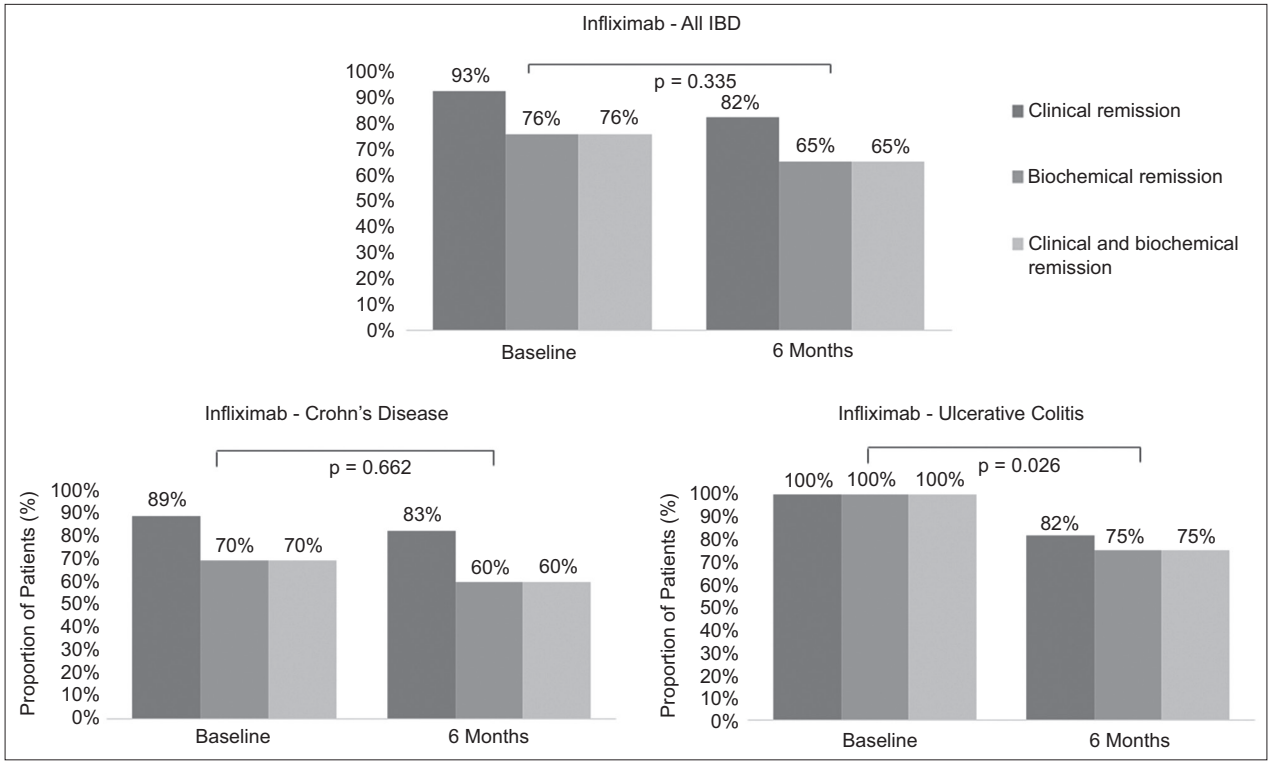

Figure 1 Clinical and biochemical remission rates at baseline and 6 months for patients switching from intravenous to subcutaneous infliximab
IBD, inflammatory bowel disease

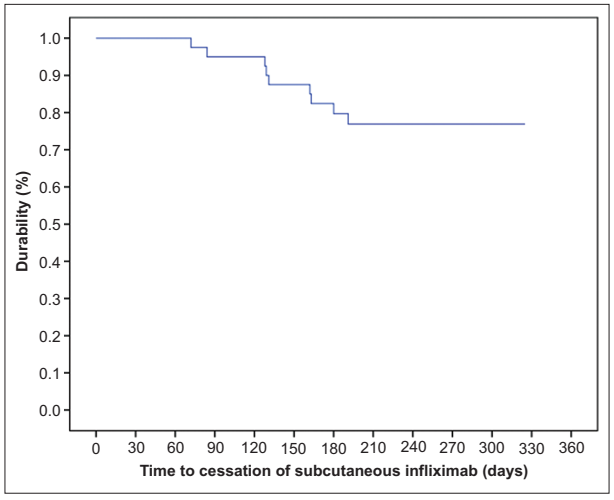

Figure 2 Kaplan-Meier curve of subcutaneous infliximab durability over 6 months after switching from intravenous infliximab

Two other real-world studies have looked at the transition from IV to SC infliximab. A recent multicenter observational study in France included 133 patients who were in steroid-free clinical remission and made the switch from IV to 120 mg fortnightly SC infliximab [11]. At 16-24 weeks post switch, the relapse rate was 10.2% (for patients who transitioned from IV dose 5 mg/kg 8-weekly), 7.3% (from 10 mg/kg 4-weekly), 16.7% (from 10 mg/kg 6-weekly) and 66.7% (from 10 mg/kg 4-weekly) (P<0.001). The risk of relapse for SC infliximab of 10.2% (for those transitioning from non-intensified IV infliximab of 5 mg/kg 8-weekly) was similar to the baseline risk for secondary loss of response. This trial also suggests that standard 120 mg fortnightly SC infliximab may not be suitable for patients receiving dose-intensified IV infliximab 10 mg/kg 4-weekly.

Another multicenter cohort study in the United Kingdom studied 181 patients who switched from IV to SC infliximab over 1 year [4]. The majority of these patients were in clinical remission at the time of switching (CD: 92.2%, UC: 76.7%, IBD-unclassified: 83.3%). The study found no significant difference between baseline and repeat HBI, Simple Clinical Colitis Activity Index, CRP or FCP. They also found an overall treatment persistence rate of 92.3% over 1 year. It should be noted that patients who were on increased dosing of IV infliximab at the time of switch were started on weekly SC infliximab rather than fortnightly.

Follow up for the former study was 24 weeks, which may not be long enough to accurately predict remission rate. In the latter study, the primary outcome of treatment persistence did not necessarily correlate with the overall rate or response or remission at 6 months, as it may have included other factors resulting in withdrawal of therapy. One strength of our study was its 6 months follow up, while we also captured more standardized outcome measures of clinical and biochemical remission. We also had access to regular review and clinical scores of these patients, based on a government mandated follow-up period that allows for more accurate comparison between patients.

The main limitations of our study are the small cohort size, which resulted in low event numbers for subgroup analysis, and the lack of endoscopic reassessment. In addition, we did not have regular blood monitoring of FCP, CRP, infliximab level, or antibodies at 6 months.

It should be noted that SC biologics are not suitable for all patients, the main issue being that of treatment compliance and reduced face-to-face follow up[6]. We believe that the decision to switch to an SC formulation should be made on a case-by-case basis, weighing the positives and negatives of doing so.

In conclusion, switching patients from IV infliximab to 120 mg fortnightly SC injections should be considered for the treatment of IBD. Our study found that this was a safe and effective option, including for those patients on dose-escalated infliximab or with active disease at the time of switch. We did not find any specific baseline characteristics that were predictive of future relapse on SC infliximab. Similarly, there was high treatment persistence over 6 months after switching to SC infliximab.

Summary Box

What is already known:

- The route of administration for biologics in inflammatory bowel disease (IBD) has historically been intravenous (IV)
- Infliximab has traditionally been administered IV
- A new subcutaneous (SC) formulation exists for infliximab (CT-P13 SC)

What the new findings are:

- Switching patients from IV infliximab to 120 mg fortnightly SC injections should be considered for the treatment of IBD
- Our study found that this was a safe and effective option, including for those patients on dose-escalated infliximab or with active disease at the time of switch
- We found a high rate of treatment persistence over 6 months after switching to SC infliximab

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