Examining maintenance care following infliximab salvage therapy for acute severe ulcerative colitis

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Author contribution: D. S. was involved in study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and statistical analysis. M. C. C. was involved in study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and statistical analysis. A. G. was involved in statistical analysis and interpretation of the data. W. R. C., M. P. S., D. V. L., G. H., and G. M. were involved in acquisition of data and critical revision of the manuscript. P. D. C. was involved in study concept and design, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and supervision of the study.

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Introduction

Patients with acute severe ulcerative colitis (ASUC), defined by Truelove and Witts’ criteria, experience significant morbidity and undergo colectomy within 3 years in up to 60% of cases.¹,²

The aim of treatment in the acute setting is induction of disease remission with intravenous corticosteroids and medical salvage therapies, such as infliximab (IFX) or cyclosporin. Clinical remission is achieved in 50% to 65% of patients at 1 year, following salvage therapy.³ Patients who fail to respond adequately to medical management require an early colectomy; however, even those who achieve clinical remission with salvage therapy continue to be at high risk of disease relapse and surgical intervention.

In this patient group, ongoing maintenance therapy and close monitoring in the outpatient setting are necessary to prevent further exacerbations. At present, an optimal maintenance strategy following ASUC is yet to be established and long-term colectomy rates in clinical trials remain high.³

Within the literature and current ECCO and ACG guidelines, there is minimal evidence to guide decision-making in this setting.

Methods:
Patients in six Australian tertiary centers treated with IFX for steroid-refractory ASUC between April 2014 and May 2015 were identified via hospital IBD and pharmacy databases. Patients were followed up for 1 year with clinical data over 12 months recorded. Analysis was limited to patient outcomes beyond 3 months.

Results: Forty one patients were identified. Five of the 41 (12%) patients underwent colectomy within 3 months, and one patient was lost to follow-up. Six of 35 (17%) of the remaining patients progressed to colectomy by 12 months. Maintenance therapy: Patients maintained on thiopurine monotherapy (14/35) versus IFX/thiopurine therapy (15/35) were followed up. Two of 15 (13%) patients who received combination maintenance therapy underwent a colectomy at 12 months, compared with 1/14 (7%) patients receiving thiopurine monotherapy (P = 0.610). Monitoring during maintenance: Post-discharge, thiopurine metabolites were monitored in 15/27 (56%); fecal calprotectin in 11/32 (34%); and serum IFX levels in 4/20 (20%). Twenty of 32 (63%) patients had an endoscopic evaluation after IFX salvage with median time to first endoscopy of 109 days (interquartile range 113–230).

Conclusion: Following IFX induction therapy for ASUC, the uptake of maintenance therapy in this cohort and strategies to monitor ongoing response were variable. These data suggest that the optimal maintenance and monitoring strategy post-IFX salvage therapy remains to be defined.

Abstract

Background and Aim: Data supporting the optimal maintenance drug therapy and strategy to monitor ongoing response following successful infliximab (IFX) induction, for acute severe ulcerative colitis (ASUC), are limited. We aimed to evaluate maintenance and monitoring strategies employed in patients post-IFX induction therapy.

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In this patient group, ongoing maintenance therapy and close monitoring in the outpatient setting are necessary to prevent further exacerbations. At present, an optimal maintenance strategy following ASUC is yet to be established and long-term colectomy rates in clinical trials remain high.³

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population in regards to: (i) individualized maintenance drug selection, (ii) monitoring strategy sensitivity in relation to clinical outcomes, and (iii) appropriate timing of outpatient surveillance. Maintenance therapies that are currently used in clinical practice include 5-aminosalicylate (5-ASA) derivatives, thiopurines, methotrexate (MTX), and biological agents—predominantly, IFX and more recently, vedolizumab.4–6 Combination therapy with IFX and a thiopurine has been proposed as a superior maintenance strategy, when compared with monotherapy with either agent7; however, this has not been investigated in a prospective setting.

We performed this study to evaluate the maintenance and monitoring strategies employed following successful induction of remission in our cohort. Clinical and biochemical markers of treatment response were also investigated to assess and compare the efficacy of each maintenance therapy and the effect of monitoring on long-term outcomes.

Methods

Study population. This study consisted of a 12-month retrospective review of adult UC patients, admitted consecutively to six Melbourne IBD referral centers. All patients were hospitalized with ASUC as defined by Truelove and Witts’ criteria.8 Patients who received IFX salvage therapy between April 2014 and May 2015 were eligible for inclusion. Patients who underwent urgent colectomy before salvage therapy initiation were excluded. Following successful induction of remission, maintenance, and monitoring strategies were determined individually by treating clinicians and clinical outcomes were recorded for 12 months. Patients who underwent a colectomy within 3 months of initial presentation were deemed to have had an unsuccessful induction of remission and were excluded from the maintenance analysis.

Outcome measures. The primary outcome was colectomy rate at 12 months. Secondary outcomes included utilization of biochemical and endoscopic monitoring strategies. Biochemical monitoring consisted of therapeutic drug monitoring, where applicable—including thiopurine metabolites, serum IFX trough levels, and fecal calprotectin levels. Endoscopic monitoring was defined as a flexible sigmoidoscopy or colonoscopy following induction of remission.

Statistical analysis. Demographics, collected variables, and treatment outcomes at 12 months in the respective maintenance treatment groups were compared using chi-squared or Fisher’s exact tests. Continuous variables were analyzed using (parametric) t-tests and (non-parametric) Mann–Whitney U-tests for symmetrically and asymmetrically distributed data, respectively. Descriptive statistics included percentages and means and medians with interquartile ranges (IQR). Statistical analyses were performed using STATA Statistical Software (version 14, copyright © StataCorp 1985–2015). All P values were two-tailed, and statistical significance was defined as P ≤ 0.05.

Ethics. Ethics approval was obtained from the respective Human Research Ethics Committees of Austin Health, St Vincent’s Hospital Melbourne, Alfred Health, Eastern Health, Melbourne Health, and Monash Health.

Results

Patient population. The study population consisted of 41 patients. One patient was lost to follow-up, and five patients underwent a colectomy within 3 months of initial presentation. Following completion of IFX induction therapy, two of the remaining 35 patients (6%) received scheduled IFX maintenance only, 14/35 (40%) received thiopurine monotherapy, and 15/35 (43%) were maintained on both IFX and thiopurine treatment. One patient was given 5-aminosalicylate monotherapy (3%), two patients were maintained on IFX and MTX (6%), and one patient received IFX, MTX, and tacrolimus (3%). IFX maintenance infusions were initially administered at 5 mg/kg dosing. The distribution of maintenance therapies used is summarized in Figure 1.
Due to the significantly biased agent selection within this cohort, statistical analyses were limited to patients who received combination therapy with IFX and a thiopurine, and those who received thiopurine monotherapy.

Baseline demographics of the patients in these two groups are outlined in Table 1. Age, sex, and disease duration were similar in both populations. Patients who received combination maintenance therapy had higher rates of hospitalization for UC within the preceding 3 months (P = 0.242) and tended to be more likely to have had previous thiopurine exposure (P = 0.128); however, these differences did not reach statistical significance. Baseline C-reactive protein and albumin levels were comparable between the two groups, as was overall length of stay in hospital.

**Maintenance therapy.** Within our cohort, six patients, who had completed IFX induction therapy and remained colectomy-free at 3 months, progressed to colectomy by 12-month follow-up. Clinical outcomes following induction of remission are outlined in Table 2 and Figure 2. Thirteen percent (2/15) of patients who received combination maintenance therapy underwent a colectomy between 3 and 12 months. In comparison, 7% of those treated with thiopurine monotherapy (1/14) progressed to colectomy during the maintenance phase. One of the two patients managed with IFX and MTX had a colectomy; one of the two patients maintained on IFX monotherapy underwent colectomy also. The one patient who was maintained on 5-ASA monotherapy progressed to colectomy, while the one patient maintained on IFX, MTX, and tacrolimus remained colectomy-free.

Two patients who had originally been commenced on thiopurine maintenance therapy developed flares of disease activity and were subsequently commenced on combination maintenance therapy (IFX plus thiopurine). In addition, two patients experienced a further episode of ASUC while receiving IFX maintenance therapy and were subsequently switched to vedolizumab, with one progressing to colectomy by 12 months.

There was no statistically significant difference in 12-month colectomy rate following combination IFX and thiopurine maintenance and thiopurine monotherapy (P = 0.610). Median time to colectomy in the combination therapy group was 238 days (IQR 185–291) from last IFX induction infusion and 193.5 days (IQR 141–246) from 3-month post-admission. In the thiopurine monotherapy group, time to median colectomy was shorter, at 109 days from last IFX induction infusion and 26 days from 3-month post-admission (P = 0.949).

**Monitoring in the maintenance phase.** The uptake of biochemical and endoscopic monitoring strategies in our cohort are outlined in Table 3. A total of 29 patients received thiopurine maintenance, either alone or in combination with other maintenance agents. Follow-up of thiopurine testing utilization was not available for two patients. Fifty-six percent (15/27) were monitored with thiopurine metabolite testing as an outpatient. Fecal calprotectin monitoring was utilized in 11/32 patients (34%). The rate of therapeutic drug monitoring among patients who received IFX maintenance therapy was lower in comparison, with only 4/20 (20%) undergoing serum IFX trough level testing.

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<td>Prior hospitalization for UC flare, n (%)</td>
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CRP, C-reactive protein; IFX, infliximab; IQR, interquartile ranges; UC, ulcerative colitis; 5-ASA, 5-aminosalicylate.
Endoscopy was performed in 20/32 patients (63%) following induction of remission, with the median time to endoscopy being 119 days following initial presentation (IQR 113–230).

Numerically lower rates of colectomy were observed in patients who underwent thiopurine drug monitoring compared with those who did not (10% vs 13%, respectively, \( P = 1.000 \)). None of the patients who underwent serum IFX monitoring progressed to colectomy at 12 months (\( P = 0.538 \))—this result, while not reaching statistical significance, is a clinically relevant finding. Of note, patients who underwent endoscopy progressed to colectomy at a numerically higher rate than those who were unmonitored (\( P = 0.066 \)).

A total of five IFX trough levels were measured between four patients in our sample, with a median value of 3 ug/mL. IFX dose escalation (increased from 5 to 10 mg/kg) was undertaken in one patient (5%) and occurred in the context of ongoing disease activity with a subtherapeutic drug level (i.e., < 0.1 ug/mL). The same patient underwent subsequent dose de-escalation and infusion interval lengthening once clinical remission had been achieved. Two patients received only one IFX infusion before experiencing symptom relapse that necessitated re-induction therapy. The majority of the remaining patients received eight weekly maintenance IFX (12/18 (67%)). IFX infusions were administered according to a number of different schedules, including—six weekly (1/18 (6%)) and two weekly (1/18 (6%)). Three patients received maintenance IFX at irregular intervals, ranging from 2 to 10 weekly, during the study period. No truncation of scheduled infusion intervals was observed.

**Adverse drug reactions.** Following IFX induction therapy, one patient developed acute cholecystitis, which has previously been described in association with IFX use\(^9–11\); however, it was not clear as to whether IFX was the cause in the patient in our study. Another patient developed an axillary rash while receiving eight weekly maintenance IFX, which settled with topical therapy. There were no other major side effects reported in this study.

**Discussion**

This real-life cohort study is the first in the literature to focus on the use of maintenance therapy and monitoring strategies following successful IFX salvage for ASUC. Despite the known high risk of colectomy with ASUC, we found that the use of maintenance therapy following IFX was highly variable and monitoring practices were ad hoc. This variability in practice highlights the fact...
that the optimal maintenance therapy and monitoring strategy following successful induction therapy for ASUC is yet to be defined.

The maintenance strategies employed in our cohort varied to such an extent that only a limited analysis could be undertaken despite multicenter involvement in this study. We observed a bias toward the use of thiopurine maintenance, either in combination with IFX or as monotherapy, in those who were thiopurine naïve compared with the use of IFX in those who were thiopurine experienced, despite limited data to support either approach. The heterogeneity of these results most likely reflects the current lack of evidence-based data to inform clinical decision-making regarding the optimal maintenance strategy.

Previous studies evaluating salvage therapy in ASUC have focused on induction therapy, whereas the optimal maintenance strategy following induction remains unclear. Although a recent retrospective study indicated a significant improvement in colectomy rates out to 1 month between those receiving accelerated versus standard induction therapy with IFX, there was no significant difference between the two groups at 2 years, suggesting a failure of maintenance therapy. Maintenance of remission with IFX has demonstrated efficacy in chronic active colitis, and concomitant therapy with IFX and a thiopurine has been associated with a lower colectomy rate. However, to our knowledge, few studies have specifically explored the role of maintenance therapy following ASUC. Two large multicenter prospective trials—CySIF and the more recent CONSTRUCT, evaluated clinical outcomes at 3 months and 3 years following ASUC, respectively. Patients in the CySIF study, who demonstrated clinical response at 1 week following salvage therapy, received azathioprine maintenance therapy; maintenance care in the CONSTRUCT study was unregulated beyond 3 months, receiving a combination of thiopurines and/or MTX in the maintenance phase. Five-year follow-up of patients from the CySIF trial identified disease relapse in 35% of patients (9/26) who had primary response to IFX salvage therapy (defined by symptom recurrence beyond 3 months) and 38% of patients (9/24) of those who had primary response to cyclosporin. A variety of regimens ranging from topical therapies to oral 5-ASA, thiopurines, and monoclonal antibodies have been used as maintenance therapies in published studies with limited data to support their efficacy.

Following induction therapy, 20/35 patients (57%) were commenced on maintenance IFX, either alone or in combination with other maintenance agents. The remaining 15/35 patients (43%) discontinued IFX and instead received ongoing treatment with a thiopurine or 5-ASA.

Factors influencing choice of maintenance therapy in our study included: (i) the discretion of the treating gastroenterologist at each respective center; (ii) the availability of scheduled maintenance IFX therapy via the Pharmaceutical Benefits Scheme of Australia whereby scheduled maintenance therapy was only available for patients with chronic active UC, which has been refractory to thiopurines, aminosalicylates, and steroids for > 3 months; and (iii) the provision of maintenance IFX via a pharmaceutical compassionate access program for a small subset of patients at the discretion of the treating physician.

Previous thiopurine experience has been proposed as an indication for maintenance IFX; however, this did not appear to influence maintenance selection in this study. Half of the patients who received maintenance IFX were thiopurine-naïve (10/20); notably, one of the two patients who received concomitant IFX and MTX was thiopurine-naïve. Combination IFX, MTX, and tacrolimus was used in a patient who had previous thiopurine experience. In our study, there was no significant difference in outcome between those on thiopurine maintenance therapy and those on combination IFX and thiopurine; however, we acknowledge that larger studies are required to investigate the optimal maintenance strategy.

Utilization of biochemical and endoscopic monitoring following induction of remission was variable in our cohort, despite evidence suggesting that these methods of surveillance are useful in evaluating loss of therapeutic response. Although undertaken in patients with chronic active UC, a post-hoc analysis of the ACT1/2 trials found that higher median IFX concentrations measured at weeks 8, 30, and 54 following IFX induction were associated with higher rates of clinical response, remission, and mucosal healing. IFX drug monitoring was not routinely undertaken in our cohort. Nonetheless, recent evidence indicates that patients with UC are more likely to require dose adjustment compared with patients with Crohn’s disease with a median time to dose optimization of 7 months (95% confidence interval [CI] 4.8–9.2) in UC and 27 months (95% CI 7.3–46.7) in CD, \( P = 0.00003 \). On this basis, it is likely that therapeutic drug monitoring is of benefit in the maintenance phase, following successful induction of remission in ASUC; however, the value of therapeutic drug monitoring during maintenance care requires prospective evaluation.

Higher rates of colectomy were observed in patients who underwent endoscopy compared with those who did not, suggesting that objective monitoring in these cases was performed reactively in response to clinical deterioration rather than monitoring being proactively applied to all patients as part of routine clinical assessment. A similar trend was observed in a dual-center audit of thiopurine metabolite monitoring in IBD, in which 79% of thiopurine testing was performed in response to active disease. Overall, our study identifies a lack of standardization in clinical practice, beyond the acute hospital setting of severe UC and emphasizes the need to find the optimal monitoring strategy.

Limitations of this study include its retrospective design and relatively small sample size. The heterogeneity of maintenance therapy administered in our cohort, restricted statistical analysis, and findings are largely descriptive in nature as a result. Moreover, analysis of the efficacy of each maintenance drug regimen, with respect to colectomy rate, was not possible due to the small number of subgroup subjects. Disease activity was not recorded uniformly across all centers—as such, disease activity and remission rates during the study period were not analyzed.

The recent STRIDE guidelines recommend the use of standardized treat-to-target strategies in UC, with clinical assessment that is corroborated with objective measures of disease activity such as surveillance endoscopy 3–6 months after treatment initiation and adjunct monitoring of biomarkers such as C-reactive protein and fecal calprotectin. Such an approach is particularly pertinent following successful induction for acute severe ulcerative colitis, given that recurrence of acute severe colitis may occur in up to 36% of patients following their first episode. The detection of subclinical disease may afford the opportunity to step-up therapy to avoid disease progression to the point of symptom relapse.
Conclusion

Although the focus of management of ASUC has been on induction of remission with salvage therapy, our data suggest that attention must also be given to the maintenance of remission in order to improve disease outcomes. The optimal maintenance strategy needs to be defined based on treatment experience and clinical markers of disease course until predictive biomarkers are available to guide therapeutic selection. Well-designed prospective studies evaluating different maintenance strategies are now required in order to find the optimal maintenance strategy and approach to monitoring following successful induction for ASUC.

References


