An Accelerated Infliximab Induction Regimen Reduces the Need for Early Colectomy in Patients With Acute Severe Ulcerative Colitis

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BACKGROUND & AIMS: **Administration of infliximab to patients with acute severe ulcerative colitis (ASUC) (rescue therapy) can reduce the rate of early colectomy (within 12 months), but long-term rates of colectomy are the same as those of the pre-biologic era for these patients. The half-life of infliximab is shorter in patients with ASUC than in patients with non-severe UC, so more frequent dosing might be required to produce a therapeutic effect.**

METHODS: **We performed a retrospective analysis of 50 hospitalized patients who received infliximab for steroid-refractory ASUC at a single academic center from September 2005 through 2013. In 2011 an accelerated dosing strategy for infliximab was introduced; we compared outcomes of standard and accelerated dosing regimens. One group of patients (n = 35) were placed on a standard dosing regimen for infliximab and then given the drug at 0, 2, and 6 weeks and then every 8 weeks thereafter. A second group (n = 15) were placed on an accelerated regimen and received 3 induction doses of infliximab within a median period of 24 days. Rates of colectomy were compared between the groups during induction and follow-up periods.**

RESULTS: **There were no differences between groups in median baseline levels of C-reactive protein, albumin, or hemoglobin. The rate of colectomy during induction therapy was significantly lower with the accelerated regimen (6.7%, 1 of 15) than with the standard regimen (40%, 14 of 35) (Fisher exact test, $P = .039$). The standard regimen was associated with shorter time to colectomy (log-rank test, $P = .042$). Among patients who completed induction therapy, subsequent need for colectomy was similar between the groups during the follow-up period. Multivariate analysis showed that factors independently associated with successful induction therapy were level of albumin (g/L) when the treatment began ($P = .003$) and the accelerated dosing regimen ($P = .03$).**

CONCLUSIONS: **In patients with ASUC, an accelerated infliximab induction strategy reduces the need for early colectomy. An intensified infliximab dosing strategy in response to clinical or laboratory signs of breakthrough inflammation merits consideration in prospective studies.**

Keywords: Ulcerative Colitis; Infliximab; Accelerated Induction.

Acute severe ulcerative colitis (ASUC), as defined by the criteria of Truelove and Witts,[1] constitutes a medical emergency. Intravenous corticosteroids have been the mainstay of management during the past 40 years,[2] but approximately one-third of patients fail to respond adequately.[3] Cyclosporine has been used as a rescue medical therapy for nonresponders,[4] and more recently, infliximab (IFX) has provided an alternative treatment.[5] Both cyclosporine and IFX are effective and appear comparable in terms of initial response and reduced need for early colectomy.[6] However, IFX may emerge as the preferred rescue therapy because it can be used as maintenance therapy and has a superior adverse event profile.

Current IFX regimens for ASUC are based on the original ACT studies, which specifically excluded patients

Abbreviations used in this paper: AD, accelerated dosing; ASUC, acute severe ulcerative colitis; CRP, C-reactive protein; IBD, inflammatory bowel disease; IFX, infliximab; IQR, interquartile range; SD, standard dosing; TNF, tumor necrosis factor; UC, ulcerative colitis.

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hospitalized with steroid-refractory ASUC.[7] However, in studies of patients with ASUC treated with rescue IFX, significantly higher early colectomy rates have been observed than in milder forms of the disease. In a study by Sjoberg et al[8] of patients requiring colectomy during the first 12 months, 64% were carried out during the first 14 days. Similar patterns were seen in a United Kingdom study of 30 patients with refractory UC.[9]

ASUC is associated with higher circulating levels of tumor necrosis factor (TNF),[10] representing the increased inflammatory burden as well as more rapid drug clearance,[11] possibly also driven by shedding of drug in the stool.[12] This suggests that such patients may require either more frequent administration or higher dosing of IFX to maintain therapeutic drug levels. We have anecdotally observed an initial improvement in clinical features and inflammatory markers after IFX administration in ASUC, with a subsequent rebound in symptoms and inflammation within a few days of the initial IFX dose. We hypothesized that patients with ASUC might benefit from a more rapid induction than a standard 0, 2-, and 6-week schedule. We therefore adopted an accelerated IFX dosing strategy in ASUC to determine whether this would lead to a reduced colectomy rate both in the initial induction period and in the first 2 years after treatment.

Methods

Study Population

This was a retrospective review of 50 consecutive patients (median age, 36 years; 27 men) admitted to a single university teaching hospital between September 2005 and September 2013. Hospitalized patients requiring rescue therapy with IFX for ASUC were identified from a prospectively maintained database of patients with inflammatory bowel disease (IBD) (n = 3214). Patients who received rescue cyclosporine were excluded. All patients carried a diagnosis of ulcerative colitis (UC) by using standard clinical, endoscopic, radiographic, and histologic criteria.[13] All underwent lower gastrointestinal endoscopy with biopsy on admission, and laboratory parameters were measured on the basis of clinical need. Before 2011, all patients requiring rescue IFX received a standard dosing schedule of 5 mg/kg at weeks 0, 2, and 6. Responders continued to receive maintenance dosing every 8 weeks. In 2011, an accelerated dosing induction strategy was adopted, whereby patients received their 3 induction doses (5 mg/kg), with the timing of each infusion guided by clinical need (worsening symptoms or inflammatory markers), permitting induction dosing during a much shorter period. After initial improvement in symptoms or C-reactive protein (CRP), any rebound in inflammation during the induction period triggered a repeat infusion. This was then followed by a standard 8-weekly maintenance regimen. The study was approved by the St Vincent's University Hospital Ethics and Medical Research Committee.

Statistical Analyses

Continuous data are presented as medians and interquartile ranges (IQRs). For presentation purposes, continuous data were categorized around the median value, and differences between groups were assessed by using the Mann–Whitney *U* test. Categorical variables were analyzed by Fisher exact test or the χ^2 test as appropriate. Time-to-event statistics were generated by using Kaplan–Meier analysis with log-rank statistics. Multivariate survival analyses were performed by using Cox proportional hazards model with backward regression to eliminate variables not independently associated with time to colectomy. Original raw continuous and categorical variables were used in all multivariate analyses. Calculations were performed by using the Statistical Package for the Social Sciences (SPSS 20.0; SPSS, Chicago, IL). *P* values less than .05 were considered statistically significant.

Results

Fifty patients with ASUC received rescue IFX during the study period; 35 received a standard dosing (SD) regimen and 15 an accelerated dosing (AD) regimen. The patient demographics are shown in Table 1. Clinical and laboratory parameters were similar in both groups. All patients had severe inflammation with endoscopic Mayo scores of either 2 or 3 and median CRP levels of 32 mg/dL in the SD group and 67 mg/dL in the AD group. Patients also had significant hypoalbuminemia, with a median albumin of 23 g/L in the SD group and 22 g/L in the AD group. Intravenous corticosteroids (hydrocortisone 100 mg 4 times each day) were administered to all patients on admission. The median duration of intravenous corticosteroids before IFX therapy was 7 days (IQR, 6–8) in both groups. By definition, the median duration of IFX induction was significantly shorter in the AD group than in the SD group (median total AD induction, 24.5 days [IQR, 21–29] vs median total SD induction, 43 days [IQR, 41–44]; $P < .0001$). Both the first induction interval, between first and second dose (median AD first interval, 7 days [IQR, 5–8]; median SD first interval, 15 days [IQR, 14–16]; $P < .0001$), and second induction interval, between second and third dose (median AD second interval, 17.5 days [IQR, 14–23]; median SD second interval, 28 days [IQR, 27–30]; $P < .0001$) were significantly shorter with AD induction.

Twenty-two of 35 patients (63%) who received SD completed induction compared with 14 of 15 patients (93%) in the AD group ($P = .04$). Figure 1 shows median daily CRP levels for patients in the SD and AD groups during induction. AD induction was associated with greater suppression of CRP, as evidenced by a lower area under the curve (SD, 254; AD, 715; $P < .0001$).