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EDITORIAL

Fast and Curious: An Algorithmic Approach to Infliximab Dosing in Acute Severe Ulcerative Colitis

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Steroid-refractory Acute Severe Ulcerative Colitis (ASUC), a medical emergency, affects roughly 25% of UC patients within 10 years of diagnosis. Infliximab rescue is given to this cohort of patients in order reduce the risk of emergency colectomy. Over the past 5 years, there has been an increased use of an 'accelerated dose (AD) induction', whereby the three induction doses are given during a shorter time than the 6 weeks traditionally used, based on the assumption that due to an increased burden of inflammation and a faster rate of clearance, there is a greater requirement for the drug early in the course of ASUC.

The original study of AD induction [1] showed a reduction in emergency colectomy, but many unanswered questions remain. Should patients receive an initial induction dose of 10 mg/kg rather than 5 mg/kg? Can biochemical parameters guide this decision? Does the use of AD induction just delay the need for colectomy and convert an emergency procedure into one that is semi-emergent? What maintenance dosing schedule should these patients receive? These and more questions have been addressed in multiple publications with variable success. Despite the unresolved issues, AD induction remains in widespread use, having been advocated by recent British Society Gastroenterology guidelines (BSG) [2].

In this issue of *Digestive Diseases and Sciences*, Govani et al. [3] describe their experience using a protocol to standardize infliximab use in patients with steroid-refractory ASUC. A retrospective review of cases published between 2013 and 2017 identified 70 patients who received infliximab, of whom 4 were excluded due to concurrent enteric infection, leaving 66 patients in their analysis. Dosing of infliximab was based on an algorithm, introduced from 2013 onwards. Initial infliximab dosing (either 10 mg/kg or 5 mg/kg) was based on the CRP/albumin ratio (CAR): a CAR > 1 prompted the 10 mg/kg dose, whereas patients with CAR ≤ 1 received 5 mg/kg. The next clinical decision was based on the change in CRP at day 3: if CRP was $> 80\%$ of CRP at day 0, the patients were referred for colectomy. If CRP was $\leq 80\%$, patients received another infliximab dose at the original dose. Subsequently at day 6, if CRP was $>$ 0.7 mg/dL, then patients were referred for colectomy and if ≤ 0.7 mg/dL, the 3rd IFX dose was scheduled at 2 weeks.

Accelerated dose induction was defined as a patient receiving a second infliximab dose prior to day 14, compared with standard dosing in which the second dose was given on day 14. The cohort was evenly split, with 33 patients receiving accelerated dosing and 33 receiving standard dosing. Patients were well matched, with the only significant difference being a higher CRP at induction in patients receiving accelerated induction ($p = 0.05$). Roughly two-thirds in each group received an initial dose of 10 mg/kg. The authors also compared postoperative complications between the 2 groups, but given the small numbers (7 vs. 9), it is unsurprising that there were no differences in outcomes.

Within 90 days of admission, there was no statistically significant difference in colectomy rates: 30.3% who received an accelerated induction versus 24.2% in those who received single-dose rescue ($p = 0.58$). An important biochemical predictor of 90-day colectomy was the serum albumin nadir. Although albumin was not included as a biochemical predictor in the original Oxford index [4], it does appear to be related to the pharmacokinetics of infliximab, with greater drug clearance observed with patients with hypoalbuminæmia [5].

What lessons can be learned from this study? Conducting a large retrospective series is commendable, with important results demonstrated such as the lack of difference in observed efficacy between the 10 mg/kg and 5 mg/kg infliximab doses. Furthermore, the use of biochemical

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parameters such as the CRP/albumin ratio helps to standardize an approach to the initial dose. Nevertheless, there are some concerns regarding this clinical approach: Firstly, we (the authors) believe that the majority of IBD physicians will be reluctant to protocolize their infliximab dosing since the condition of these patients is highly variable with substantial day-to-day changes requiring dynamic dosing schedules that can be rapidly changed according to patient condition. The decision to refer a patient for colectomy based solely on a CRP level (which can lag behind the clinical state) seems somewhat arbitrary; also, the patientsâ€™ contribution to the decision for surgery was not clarified. Furthermore, a problem with this type of analysis is that there will be an inherent bias toward an inferior outcome in the patients receiving accelerated dosing, as these patients have more severe disease. To combat this, a recently published paper from a UK group [6] used a propensity score matching system showing that in a subgroup analysis of 52 cases (from a total cohort of 131), outcomes were superior in the group receiving accelerated induction.

Along with the entire IBD community, we look forward to results of the only randomized controlled trial of IFX dosing in ASUC, PREDICT-UC. Yet, it is likely that even with these results, some unanswered questions will remain. Since no new medical therapies have become available for ASUC in the last decade that in turn restricts the available therapeutic options, it is paramount to further refine IFX dosing and the understanding of drug pharmacokinetics in this difficult-to-treat population. Perhaps with the addition of point-of-care testing using a minimal trough cutoff prior to next scheduled dose will help improve outcomes for our patients, although the desirable drug level in this cohort is unknown.

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