e - ISSN - 2349 - 8005

INTERNATIONAL JOURNAL OF ADVANCES IN CASE REPORTS

Journal homepage: www.mcmed.us/journal/ijacr

ACCELERATED INFLIXIMAB INDUCTION IN ACUTE SEVERE ULCERATIVE COLITIS

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Article Info
Received 15/12/2015
Revised 27/01/2016
Accepted 22/02/2016

Key words:
Ulcerative colitis, Infliximab, Accelerated induction.

ABSTRACT
The success of infliximab in steroid-refractory acute severe ulcerative colitis has been well documented. However, some patients remain unresponsive to treatment with the standard induction schedule of 0, 2, and 6 weeks. We present a case that describes a successful use of an accelerated induction of infliximab in a 41 year old female with a new diagnosis of ulcerative colitis and refractory nontoxic megacolon.

INTRODUCTION

Infliximab is a monoclonal antibody to the inflammatory cytokine Tumour Necrosis Factor (TNF)-α. It is often used in the treatment of Inflammatory Bowel Disease, particularly in those with acute severe ulcerative colitis (ASUC) who have failed intravenous (IV) steroids [1]. These patients also have a high risk of early colectomy and are typically started on infliximab in an attempt to postpone surgery [2]. However, the standard induction regimen for infliximab in ASUC is based on studies which excluded hospitalized patients with steroid-refractory disease [3]. Given the high risk of early colectomy in patients with severe disease [4], it has been proposed that an alternate accelerated induction of infliximab may provide some benefit as TNF-α may be more abundant in ASUC, and there is risk of gut leakage of the active drug due severity of ulcerations [5]. Until recently, only anecdotal evidence was available to support accelerated dosing of infliximab. Although a recently published paper demonstrated that accelerated induction significantly reduced the need for early colectomy in patients with ASUC [5], the results were limited by a small sample size. In support of these findings, we report a case of a newly diagnosed ASUC patient who responded well to an accelerated second dose of infliximab despite failing intravenous steroids.

COURSE IN HOSPITAL

An otherwise well 41-year-old female presented with a one month history of abdominal cramping, particularly over the left lower quadrant, and significant diarrhea including multiple bowel motions overnight. There was mucous and specks of blood in her stool and she complained of tenesmus. She did not report any fever, chills, cough, expectoration or chest pain. She had experienced a similar episode approximately two years prior and was treated at the time with antibiotics.

At the time of presentation, vital signs were stable and the patient was not in acute distress. There was left lower quadrant tenderness without any guarding or rigidity and no masses felt. She had a white blood cell count of 13,

$600x10^9$/L, hemoglobin of 141 g/L, albumin of 22 g/L with a normal lipase, and lactate. Her highest C-reactive protein (CRP), 4 days after admission, was 301.4 mg/L and erythrocyte sedimentation rate (ESR) was 76 mm/h. A digital rectal exam showed bloody mucous and a colonoscopy was performed after infectious causes were ruled out.

Colonoscopy revealed significant severe inflammation, deep ulceration and loss of vascularity from the sigmoid to the mid transverse colon. This was followed by moderate inflammation to the ascending colon. The terminal ileum and cecum were spared. Random biopsies showed varying degrees of active chronic colitis with cryptitis, crypt abscess and ulceration. No granulomas were identified leading to a diagnosis of severe ulcerative colitis. The patient was commenced on 3 days of IV methylprednisone with initial improvement of her clinical symptoms. However, when she was transitioned to oral steroids, her cramping and bloating returned and an abdominal X-ray revealed a dilated transverse colon measuring 10.6cm. Her symptoms persisted and the transverse colon remained dilated despite reinstating IV methylprednisone with a peak distension of 14.4cm on radiography. Her *C. difficile* toxin and stool cultures remained negative throughout her admission.

Twelve days after her admission, a 5mg/kg dose of infliximab was given intravenously. However, serial abdominal X-rays showed little improvement in the megacolon and the patient was still symptomatic. A second infliximab dose of 10mg/kg was given four days after the first dose. Five days after this accelerated induction dose, the patient's colon diameter had decreased to 6.1cm and her clinical symptoms had resolved. This dramatic improvement was seen despite an MRSA bacteremia which arose two days after the patient's second infliximab dose. Her bacteremia resolved with intravenous vancomycin and the patient remained clinically well despite her infection. She was discharged 26 days after admission on IV vancomycin with her final induction dose of infliximab scheduled to be administered upon completion of her antibiotics.

She remained well in clinical remission 3 weeks after discharge at her follow up visit. She will receive her 3rd dose 4 weeks after the second dose, and then resume the standard dosing of infliximab every 8 weeks.

DISCUSSION

Two placebo-controlled studies showed that infliximab rescue therapy leads to a significantly higher proportion of colectomy-free survival at 3 and 12 months [2,4]. The ACT studies established the current infliximab regimen in ulcerative colitis which consists of both the induction doses (0, 2 and 6 weeks) with maintenance doses every 8 weeks thereafter. Interestingly, these studies did not find a significant difference in efficacy when infliximab doses were increased to 10mg/kg [3].

The use of monoclonal anti TNF-α antibodies as a treatment for inflammatory bowel disease arose from evidence that disease severity correlated with the degree of circulating TNF [8]. Subsequent studies found that remission rates were inversely correlated with pre-treatment expression of TNF-α in colorectal mucosa [9]. There is also evidence to suggest that patients with higher circulating levels of tumor necrosis factor (TNF) have more rapid drug clearance by shedding of the drug through the leaky mucosa and into the stool [10,11]. In addition, infliximab clearance is accelerated in inflammatory states with high CRP [12]. Therefore, it would be reasonable to suggest that for patients with more severe presentation, accelerated dosing, either through shorter dosing intervals or increased drug dosages, might be needed to elicit a response if standard dosing does not produce a response.

The idea of using accelerated infliximab dosing in patients who are initially slow to respond to induction has only been anecdotally supported. However, a recent retrospective analysis of 50 hospitalized patients found that those who underwent an accelerated induction schedule were less likely to need early colectomy. In the 15 patients receiving a modified induction regimen, the median duration of dosing was 24 days [5]. The patients in the accelerated dosing group were also more likely to complete their induction [5], suggesting that compliance may be improved with a more rapid induction. There may also be some medium-term benefits to accelerated induction, however the sample size of this study is too small to draw any firm conclusions. It is therefore imperative that cases of successful accelerated induction are documented and additional studies completed to further validate the observational data.

ACKNOWLEDGEMENT: None

CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

STATEMENT OF HUMAN AND ANIMAL RIGHTS

All procedures performed in human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

REFERENCES

1. Järnerot G. (2006). Infliximab or cyclosporine for severe ulcerative colitis. *Gastroenterology*, 130 (286; author response 287).
2. Järnerot G, Hertervig E, Friis-Liby I, et al. (2005). Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. *Gastroenterology*, 128, 1805-1811.

3. Rutgeerts P, Sandbom WJ, Feagan BG et al. (2005). Infliximab for induction and maintenance therapy for ulcerative colitis. *New England Journal of Medicine*, 353, 2462-2476.
4. Sjoberg M, Magnuson A, Bjork J, et al. (2013). Infliximab as rescue therapy in hospitalized patients with steroid-refractory acute ulcerative colitis: a long-term follow-up of 211 Swedish patients. *Alimentary Pharmacology and Therapeutic*, 33, 77-387.
5. Gibson DJ, Heetun ZS, Redmond CE, et al. (2015). An accelerated infliximab induction regimen reduces the need for early colectomy in patients with acute severe ulcerative colitis. *Clinical Gastroenterology and Hepatology*, 13, 330-335.
6. Sands BE, Tremaine WJ, Sandborn WJ, et al. (2001) Infliximab in the treatment of severe, steroid-refractory ulcerative colitis: a pilot study. *Inflammatory Bowel Disease*, 7, 83-88.
7. Probert CS, Hearing SD, Schreiber S, et al. (2003). Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomized control trial. *Gut*, 52, 998-1002.
8. Gardiner KR, Halliday MI, Barclay GR, et al. (1995). Significance of systemic endotoxaemia in inflammatory bowel disease. *Gut*, 36, 897-901.
9. Olsen T, Goll R, Cui G, et al. (2009). TNF-alpha gene expression in colorectal mucosa as a predictor of remission after induction therapy with infliximab in ulcerative colitis. *Cytokine*, 46, 222-227.
10. Kevans D, Murthy S, Iacono A, et al. (2012). Accelerated clearance of infliximab during induction therapy for acute ulcerative colitis is associated with treatment failure. *Gastroenterology*, 142, S-384-S-385.
11. Brandse JF, Wildenberg ME, de Bruyn JR, et al. (2013) Fecal loss of infliximab as a cause of lack of response in severe inflammatory bowel disease. Vienna, Austria: Poster presentation, ECCO.
12. Wolbink GJ, Voskuyl AE, Lems WF, et al. (2005). Relationship between serum trough infliximab levels, pretreatment C reactive protein levels, and clinical response to infliximab treatment with patients with rheumatoid arthritis. *Annals of the Rheumatic Diseases*, 64, 704-707.