Published in final edited form as:

J Clin Gastroenterol. 2015 August ; 49(7): 539–540. doi:10.1097/MCG.0000000000000352.

Lower dose infliximab for ulcerative colitis: How low can we go and how much could be saved?

George P Christophi, MD, PhD and Matthew A Ciorba, MD*

Department of Gastroenterology, Washington University School of Medicine, St. Louis, MO

Keywords

Ulcerative Colitis; Remicade; infliximab; low-dose

In this issue of the *Journal of Clinical Gastroenterology* Jiang and colleagues report a randomized, placebo controlled, double-blind study evaluating the efficacy of low-dose (3.5 mg/kg) infliximab for induction and maintenance treatment in Chinese patients with active moderate-severe ulcerative colitis (UC).¹ The experimental design was modeled after the ACT 2 trial² but included both a 5 mg/kg (standard-dose) group and a 3.5 mg/kg (low-dose) group, as well as a placebo control arm. 123 UC patients were distributed equally among the cohorts. The authors report similar rates of clinical response at week 8 (73% vs 78%) and at week 30 (51% vs 53%) in both the low and standard infliximab dose treatment arms respectively. Placebo rates were 37% at week 8 and 27% at week 30 with response defined as a 3 point drop in the Mayo score. Differences in mucosal healing were also significantly greater in both infliximab groups. The study was not adequately powered to detect a difference between the low- and standard-dose groups, but the authors limit their conclusions to state that both doses are more effective than placebo.

The ACT 1 and 2 studies demonstrated a 61–64% clinical response at week 8 and 31–41% clinical remission at week 30 in UC patients receiving 5mg/kg of Infliximab. These studies did not identify a statistically significant clinical benefit to using 10 mg/kg over 5 mg/kg dosing as a starting dose, although 10 mg/kg over 5 mg/kg dosing resulted in higher serum infliximab levels.^{2, 3} A lowest-effective dose was not demonstrated in the ACT studies. Jiang et al used this as impetus in designing their study testing a dose lower than 5 mg/kg. A similar “low-dose” infliximab strategy was also recently evaluated and confirmed in psoriatic arthritis, where a recent observational cohort study of 462 patients showed that low dose infliximab (3 mg/kg) resulted in similar clinical response and drug levels following 12 months treatment.⁴

If the efficacy and long-term outcomes of this study’s findings are confirmed, this low-dose strategy could have important health care economic implications. While biosimilars may eventually change this, a 100 mg vial of infliximab costs ~\$900 in the United States.⁵ At this cost, an 80 kg person receiving 5mg/kg generates a drug cost of almost \$47,000 in the first

*Corresponding Author: Matthew Ciorba, MD, Assistant Professor of Medicine, Division of Gastroenterology, 660 S. Euclid Ave, Campus Box 8124, St. Louis, Missouri 63110, USA, Phone: (314) 747-IBD6 (4236), Fax: (314) 747-1277.

year of treatment. In contrast, that same individual receiving the low-dose (3.5mg/kg) infliximab strategy would require 280mg per infusion corresponding to less than \$33,000 for the first year. This is a \$14,000 per first year, per patient savings! The economic benefit is potentially staggering considering that tens of thousands of UC patients receive Infliximab for multiple years.

This low-dose is probably not for all UC patients. Jiang and colleagues enrolled patients with an average Mayo score of 6.0 compared to 8.4 used in ACT 1.^{1, 2} A Mayo score of 6 is at the border between mild and moderate ulcerative colitis. Patients with severe UC are often treated with higher doses of Infliximab. In severe colitis, infliximab may be lost through the leaky gut barrier,⁶ requiring higher infusion dose to maintain adequate serum levels. Additionally, infliximab systemic disposition is influenced by body weight, serum albumin levels (which are often decreased in severe UC), and formation of antibodies to Infliximab (ATI).⁷ Serum concentration of Infliximab is associated with efficacy in patients with moderate-to-severe ulcerative colitis.³ Unfortunately, Jiang et al did not measure or report drug levels. However, they did evaluate for ATIs and UC patients with 3.5mg/Kg vs 5 mg/Kg did not show any difference in formation of ATI (5 %) at 30 weeks and compared similarly to ACT 1 and 2 studies (6%).²

How might this study influence our current practice? Based on this single center study, we are probably not yet ready to implement this low-dose strategy, at least in the US. However, we do propose that the results of this study support consideration of a few practical management tips for use of infliximab in UC patients. First, infliximab does not need to be “maxed-out” or given at high dose in all patients, especially in those with moderate disease severity or limited extent. Second, these results further validate an approach where patients initially receive standard dose Infliximab that is escalated as needed based on clinical and endoscopic response.^{8, 9} Third, for patients maintained on Infliximab who are in long-term “deep” remission, consideration should be given to reducing or spacing out their dose, especially if they are on a concomitant immunomodulator.

In conclusion, these results suggest that a low-dose infliximab induction strategy may be both an effective and cost-advantageous option in patients with moderately active ulcerative colitis. Confirmative studies are warranted in this same population before management is likely to change. Larger, confirmative studies are needed and should also include data on long-term outcomes. Given the potential cost savings, perhaps governmental medical payers (CMS) or commercial health insurers would be interested in sponsoring such a trial.

References

1. Xue-Liang, JH-F, Cui; Jing, Gao; Hua, Fan. Low-dose infliximab for induction and maintenance treatment in Chinese patients with moderate-to-severe active ulcerative colitis. *Journal of Clinical Gastroenterology*. 2015
2. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005; 353:2462–2476. [PubMed: 16339095]
3. Adedokun OJ, Sandborn WJ, Feagan BG, Rutgeerts P, Xu Z, Marano CW, Johanns J, Zhou H, Davis HM, Cornillie F, Reinisch W. Association between serum concentration of infliximab and

efficacy in adult patients with ulcerative colitis. *Gastroenterology*. 2014; 147:1296–1307. e5. [PubMed: 25173754]

4. Glintborg B, Gudbjornsson B, Krogh NS, Omerovic E, Manilo N, Holland-Fischer M, Lindegaard HM, Loft AG, Nordin H, Johnsen L, Oeftiger SF, Hansen A, Rasmussen C, Grondal G, Geirsson AJ, Hetland ML. Impact of different infliximab dose regimens on treatment response and drug survival in 462 patients with psoriatic arthritis: results from the nationwide registries DANBIO and ICEBIO. *Rheumatology (Oxford)*. 2014; 53:2100–2109. [PubMed: 24939677]
5. Ung V, Thanh NX, Wong K, Kroeker KI, Lee T, Wang H, Ohinmaa A, Jacobs P, Fedorak RN. Real-life treatment paradigms show infliximab is cost-effective for management of ulcerative colitis. *Clin Gastroenterol Hepatol*. 2014; 12:1871–1878. e8. [PubMed: 24674943]
6. Clayburgh DR, Shen L, Turner JR. A porous defense: the leaky epithelial barrier in intestinal disease. *Lab Invest*. 2004; 84:282–291. [PubMed: 14767487]
7. Fasanmade AA, Adedokun OJ, Ford J, Hernandez D, Johanns J, Hu C, Davis HM, Zhou H. Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis. *Eur J Clin Pharmacol*. 2009; 65:1211–1228. [PubMed: 19756557]
8. Seow CH, Newman A, Irwin SP, Steinhart AH, Silverberg MS, Greenberg GR. Trough serum infliximab: a predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis. *Gut*. 2010; 59:49–54. [PubMed: 19651627]
9. Cesarini M, Katsanos K, Papamichael K, Ellul P, Lakatos PL, Caprioli F, Kopylov U, Tsianos E, Mantzaris GJ, Ben-Horin S, Danese S, Fiorino G. Dose optimization is effective in ulcerative colitis patients losing response to infliximab: a collaborative multicentre retrospective study. *Dig Liver Dis*. 2013; 46:135–139. [PubMed: 24246151]