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## *Letter to the Editor*

# Call Me Anything but Thoughtless or Misguided in IBD Management

**Nicholas V. Costrini, MD, PhD, MBA***

*Gastroenterology Associates of Big Bend, Tallahassee, Florida, USA*

***Corresponding author***
**Nicholas V. Costrini, MD, PhD, MBA**
Gastroenterology Associates of Big Bend, Tallahassee, Florida, USA; E-mail: drcostn@gmail.com

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I read with interest the open access, original article, by S.K. Murthy, et al, *Introduction of anti-tumor necrosis factor (TNF) therapy has not yielded expected declines in hospitalization and intestinal resection rates in inflammatory bowel diseases: a population-based interrupted time series study* appearing in Gut 12 June 2019.[1] It must first be stated that the authors are to be congratulated for the magnificent demonstration of the benefits of the Canadian healthcare system in terms of collection of healthcare data. That said, I take issue with their explanation and hypothesis: "misguided use and failure to optimize use of infliximab, particularly among patients with Crohn's Disease (CD), as well as possible underuse of infliximab among patients with ulcerative colitis (CUC)…." In the follow-up press release, one summary recommendation was that "*doctors should be more thoughtful in managing inflammatory bowel disease (IBD).*" It is unfortunate, indeed, that the term "misguided use" would appear and then be translated into perhaps a deeper, and unwarranted, criticism that doctors managing IBD have been "less than thoughtful or misguided" in the use of biologics. I think the authors actually intended to report that the academic community has collected clinical trial data and offered practicing clinicians a plan for use of biologics only to find in retrospect that those recommendations were not likely to be effective given the general IBD patient population and the less than complete effectiveness of the biologics. Nonetheless, the message was certainly blurred.

Beyond the social implications of the article and its interpretations, there are numerous clinical areas of concern in this publication. The basic premise of the conclusions is that since the anti-TNF agent infliximab has been demonstrated to reduce hospitalizations and surgeries in controlled trials and observational studies, one should expect, for the price and deep intrusion into the marketplace, similar effectiveness to be demonstrable in population studies. Because such effectiveness was not demonstrated in this elegant study, the conclusion offered is that the fault must lay with the physicians. I believe the authors are quite mistaken and I offer more likely explanations for consideration.

The infliximab 2002 ACCENT I[2] and 2004 ACCENT II[3] trials reported clinical remission rates of twenty-two percent. The adalimumab 2007 CHARM trial[4] reported similarly less than spectacular remission rates. For the first decade after anti-TNF entry into the marketplace, practicing gastroenterologists were "guided" by the academic community to treat IBD patient with either "top-down or the bottom-up" programs based upon clinical parameters. The 2015 REACT trial[5] provided enough "real world" evidence to support treating patients with early introduction of combined immunomodulator plus biologic agent. While combined treatment (i.e. top-down) did not offer a statistically significant improved clinical remission rate compared to a conventional treatment program (i.e. bottom-up), early combined treatment was associated with a lower two-year aggregate rate of hospitalizations, surgeries, and serious infections. We can extrapolate from the clinical remission rates that the endoscopic remission rates would be in the twenty-five percent range. Hence, in clinical trials and in "real world" experience, the anti-TNF agents are rather weak in providing endoscopic remission and by extension a weak tool in altering the natural history of IBD. In fact, it was not until 2012, the year the study ended, that the EXTEND trial[6] was published. This was the first study to use endoscopic healing as the primary endpoint in a CD treatment trial. Mucosal healing was recorded in only twenty-four percent of patients treated with adalimumab for two years. In patients with a less than a two-year history of CD, endoscopic remission reached thirty-three percent at two years. I was very surprised by your explanation since it is agreed that while these agents provide gratifying clinical relief for an interval, anti-TNF agents have the power to alter the natural history of CD in only a small proportion of patient. That is why additional more tightly designed trials have been completed. In 2018, the CALM

trial[7] was completed. In this trial patients with CD of less than one-year duration and naïve to immunomodulators and biologics, were entered into programs in which the treatments were escalated on the basis of regularly measured biomarkers and endoscopy as well as clinical symptoms. In this highly selected, intensely investigated group of patients, endoscopic remission rates with adalimumab reached its zenith of forty-six percent, well above the remission rate of thirty percent in their patients managed conventionally. We have yet to learn if we have found a way to use anti-TNF agents in a manner that alters the natural history of the disease in the majority of patients and capable of deflecting adverse event curves. The population of CD patients exposed to anti-TNF agents between 2000 and 2012 were managed conventionally as directed by the controlled trials of the time. Hence, remission occurred in only a quarter of CD patients treated with infliximab (and for an unknown duration). It is not surprising that the population curves were not deflected. I offer that the fault lies not in "misguided" clinicians but in the fact that anti-TNF agents are only modestly effective in promoting endoscopic healing when used as they were in the years of the study. Comment is made that drug trough levels were not used regularly. It was not until well after the study was completed that the academic community embraced such testing as meritorious. The fact that we have spent a fortune on the drugs for IBD and have so little to show for it, as you so vividly demonstrate, is evidence enough of the frailty of this class of drugs in the mission of changing the natural history of the disease. This limited anti-TNF impact on CD natural history is justification for the aggressive search for new drugs and the design of studies such as CALM in order to find how to better select and manage patients and employ the drug. Regarding surgery for strictures in CD, anti-TNFs would not likely affect the rate of surgery as the expected remission rate in this study interval was simply too low to have a measurable population impact on CD natural history. Any contention that the failure of anti-TNFs is the fault of misguided physicians, is not supported by the literature or your data.

Turning to the impact of anti-TNF agents in the course of CUC, it is difficult to make much of the fact that adverse event incidences were not changed over time for the entire group since only 2.1% of the CUC group was exposed to anti-TNF agents. The authors suggest that doctors did not use the biologics often enough. It was surely effective, however, as hospitalization rates were reversed and declined "markedly" with an Odds Ratio of 0.515, 95% CI 0.342 to 0.777. I would offer the explanation that CUC has many more options for maintenance of remission (i.e. mesalamine and immunomodulators), has very commonly a limited disease profile (i.e.proctosigmoiditis); and as a hemorrhagic mucosal disease, is less likely to progress silently to dangerous fistulae or strictures. Thoughtful clinicians are aware of all this. The two-fold increase in drug costs was highly effective in CUC management. That surgery rates were unaffected in the anti-TNF subgroup is expected as the drug will not reduce cancer and resistant-to-treatment rates until we have drugs that produces high proportions of long-lasting endoscopic remissions. Is it possible that many more CUC patients should have been treated with anti-TNF drugs? That is difficult to say. If many more were treated, the cost for any incremental benefit would have been higher. Additionally, fifty to eighty percent of patients would have failed to benefit at all given the defined rate of remission with the conventional care practiced during 1995-2012 interval.

In closing, I offer my personal experience. I studied two hundred CD patients in my private practice as a very early adopter of anti-TNF treatment. The incidences of surgery and steroid use in the interval of 2000 to 2010 with and without exposure to anti-TNF agents were identical to those parameters in the decade of 1990 to 2000. I was disappointed by the results to be sure. The patient demographics in my study group and in this publication were identical. The explanation for the elegant study results and for my small office results rests in the fact that as far as anti-TNFs are concerned, IBD patient groups with long-standing disease (five years or more), prior exposure to other agents (biologics and immunomodulator), and managed principally by clinical measures cannot be expected to generate a substantial proportion of patients with long-term endoscopic remissions. Without long-term endoscopic remissions with mucosal healing, we cannot expect to change the natural history of IBD. As we consider new drugs in the pipeline and aggressive management programs now being promoted, we can hope for better directions and more appealing curves along the road leading to a cure for IBD. I thoughtfully offer my explanations for this data. The explanations, sir, resides in the potion and not in the physician.

## REFERENCES

1. Murthy SK, Begum J, Bechamel EL, et al. Introduction of anti-TNF therapy has not yielded expected declines in hospitalization and intestinal resection rates in inflammatory bowel disease: A population-based interrupted time series study. *Gut.* 2019; 1-9. doi: 10.1136/gutjnl-2019-318440

2. Hanauer SB, Feagan BG, Lichtnestein GR, et al. Maintenance infliximab for Crohn's Disease: The ACCENT I randomized trial. *Lancet.* 2002; 4: 1541-1549. doi: 10.1016/S0140-6736(02)08512-4

3. Sands, BE, Anderson FH, Bernstein CN, et al. Infliximab Maintenance Therapy for Fistulizing Crohn's Disease. *N Engl J Med.* 2004; 350: 876-885. doi: 10.1056/NEJMoa030815

4. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's Disease: The CHARM trial. *Gastroenterology.* 2007; 132: 52-65. doi: 10.1053/j.gastro.2006.11.041

5. Khanna R, Bressler B, Levesque BG, et al. Early combined immunosuppression for the management of Crohn's Disease (REACT): A cluster randomized controlled trial. *Lancet.* 2015; 386: 1825-1834. doi: 10.1016/S0140-6736(15)00068-9

6. Rutgeerts P, VanAssche G, Sandorn WJ, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's

disease: Data from the EXTEND trial. *Gastroenterology*. 2012; 142: 1102-1111. doi: 10.1053/j.gastro.2012.01.035

7. Colombel JF Panaccione r, Bossuyt P, et al. Effect of tight control management on Crohn's Disease (CALM): A multicenter, randomized, controlled phase 3 trial. *Lancet*. 2018; 390: 2779-2789. doi: 10.1016/S0140-6736(17)32641-7