Response to Infliximab After Loss of Response to Adalimumab in Crohn's Disease

Key Words: Crohn's disease, antitumor necrosis factor, adalimumab, infliximab, loss of response

To the Editors,

Over the past 2 decades, antitumor necrosis factor (anti-TNF) biologics have evolved as a mainstay of inflammatory bowel disease treatment. However, 10%–20% of patients have primary nonresponse to anti-TNF,[1] and 40% of patients have a secondary loss of response to anti-TNF treatment over time.[2] The emergence of therapeutic drug monitoring has helped to optimize IBD therapies and can be used to identify potential causes of loss of response. Recent guidelines have suggested that patients who have a lack of response to anti-TNF but continue to demonstrate therapeutic drug levels should be switched out of class due to mechanistic failure of the biologic.[3] However, anti-TNFs make up 3 of the 5 FDA-approved biologics for Crohn's disease, and a premature switch out of class may severely limit a patient's medical options in the future.

Casanova et al recently reported the efficacy of using a second and third anti-TNF agent in patients with intolerance or failure of a prior anti-TNF in a large Spanish patient cohort.[4] Remission was achieved with a second anti-TNF in 55% of patients. Combination therapy and switch due to a primary or secondary loss of response (as opposed to drug intolerance) were associated with decreased likelihood of remission on a second anti-TNF. However, no data on drug levels before switching were available.

We conducted a retrospective cohort study of 86 patients with Crohn's disease who received infliximab therapy after a loss of response to adalimumab. Clinical characteristics of the study population are described in Supplementary Table 1. Forty-eight patients (56%) were on weekly adalimumab dosing before discontinuation. Forty-four patients (52%) were on combination therapy before discontinuation of adalimumab. The median duration of treatment was 46 weeks (interquartile range [IQR], 20–74), with 29 patients (34%) treated with adalimumab for 12 weeks or less. Sixty-seven patients (78%) maintained response to infliximab at week 54. There was no significant difference in response to infliximab at 54 weeks when comparing patients treated with adalimumab for 12 weeks or less and those treated for more extensive time periods (72% vs 80%, $P = 0.381$). Of the 33 patients with available drug levels, the median adalimumab level before switch to infliximab was 4.0 (mcg/mL) (IQR, 1.7–5.4). Every other week, adalimumab dosing was associated with increased response to infliximab (odds ratio [OR], 4.30; 95% confidence interval [CI], 1.27–14.6) There was no difference in 54-week response to infliximab by adalimumab level before switch ($P = 0.643$, Supplementary Fig. 1).

This study confirms that a large portion of patients with a prior response to anti-TNF can respond to a second anti-TNF. Furthermore, drug levels of the first anti-TNF may not reliably predict nonresponse to a second anti-TNF.

SUPPLEMENTARY DATA

Supplementary data is available at *Inflammatory Bowel Diseases* online.

Supplementary Table 1. Demographics and clinical characteristics among patients switched within class to infliximab after secondary loss of response to adalimumab for Crohn's disease.

Supplementary Figure 1. Association of adalimumab serum levels at loss of response to adalimumab stratified by response to infliximab at week 54. Adalimumab levels were not significantly different in patients with week 54 response (n = 25) or no response (n = 8) to infliximab therapy ($P = 0.643$).

Christina M. Bauer, MD, MPH,[*,†] Adam Younis, MD,[‡] Hans Herfarth, MD, PhD,[*,†] and Edward L. Barnes, MD, MPH[*,†]

From the *Division of Gastroenterology and Hepatology, University of North Carolina–Chapel Hill, Chapel Hill, NC, USA; †Multidisciplinary Center for Inflammatory Bowel Disease, University of North Carolina–Chapel Hill, Chapel Hill, NC, USA; ‡Department of Internal Medicine, University of North Carolina–Chapel Hill, Chapel Hill, NC, USA

Conflicts of Interest: HH has received consulting fees from Alivio, AMAG, Finch, Gilead, Lycera, Merck, Otsuka, Pfizer, PureTech, and Seres and research support from Pfizer and Artizan Biosciences. ELB has received consulting fees from AbbVie, Inc. All other authors have no conflicts.

Address correspondence to: Edward L. Barnes, MD, MPH, Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill, 130 Mason Farm Road, Bioinformatics Building, CB #7080, Chapel Hill, NC, 27599-7080, USA. E-mail: edward_barnes@med.unc.edu.

REFERENCES

1. Ben-Horin S, Kopylov U, Chowers Y. Optimizing anti-TNF treatments in inflammatory bowel disease. *Autoimmun Rev.* 2014;13:24–30.
2. Papamichael K, Gils A, Rutgeerts P, et al. Role for therapeutic drug monitoring during induction therapy with TNF antagonists in IBD: evolution in the definition and management of primary nonresponse. *Inflamm Bowel Dis.* 2015;21:182–197.
3. Vande Casteele N, Herfarth H, Katz J, et al. American Gastroenterological Association Institute technical review on the role of therapeutic drug monitoring in the management of inflammatory bowel diseases. *Gastroenterology.* 2017;153:835–857.e6.
4. Casanova MJ, Chaparro M, Minguez M, et al. Effectiveness and safety of the sequential use of a second and third anti-TNF agent in patients with inflammatory bowel disease: results from the Eneida Registry. *Inflamm Bowel Dis.* 2019. doi: 10.1093/ibd/izz192.

doi: 10.1093/ibd/izz286
Published online 21 November 2019