Digestive Diseases and Sciences (2019) 64:614–615
https://doi.org/10.1007/s10620-018-5385-9

EDITORIAL

Real-World Success of Biologic Therapy in IBD: No More Reasons to Be Anti Antibody

Neil Gordon[1] · **Shaji Sebastian**[1,2]

Published online: 26 November 2018

Tumor necrosis factor-α antibodies (anti-TNFs), termed "biologics," have revolutionized the medical management of moderate–severe inflammatory bowel disease. Randomized control trials have reported the efficacy of these drugs in the induction and maintenance of remission in the inflammatory bowel diseases (IBD): Crohn's disease and ulcerative colitis. Published data regarding efficacy and safety of the drugs are usually generated from randomized control trials (RCTs). Nevertheless, results of RCTs may not always be replicated in routine clinical practice, given the stringent inclusion and exclusion criteria affecting patient selection combined with rigorous analytic methodology [1]. These exclusion criteria often relate to prior use of steroids and immunomodulators, the presence of TNF antibodies, past surgical history, coexisting medication use, and the presence of stricturing/penetrating Crohn's disease. The RCT-enrolled patient therefore may bear little resemblance to the patient in front of you in clinical practice; hence, good-quality "real-world" data are clearly useful to guide in IBD therapy in clinical practice [2].

Observational cohort studies have utilized a variety of outcome measures as markers of efficacy and tolerability in clinical practice, complicating the comparison of results among studies. In this issue of *Digestive Diseases and Sciences*, Sartini et al. [3] utilized three measures of IBD treatment success: persistence (defined as the probability of drug maintenance for each time point during follow-up), retention rate (the absolute proportion of patients who maintain therapy during follow-up), and adverse events as primary outcome measures in their observational, retrospective, single center study of Crohn's and ulcerative colitis (UC) patients treated with adalimumab from March 2008—March 2017. Though use of the terms "persistence" and "retention" are relatively new to the IBD literature, they are relevant concepts in real-world clinical practice.

In the study, 149 Crohn's and 32 UC patients completed 3 induction doses or more and maintained therapy for 12 months prior to withdrawal. Indications were steroid-dependent and steroid-refractory disease with patients predominantly infliximab naïve and not taking immunomodulators. Retention rates over the 9-years period of the study were 47% for Crohn's and 46.9% for UC. The reasons for withdrawal of treatment in order of frequency were: treatment failure (primary or secondary), remission—importantly assessed both clinically and endoscopically, and adverse events across both CD and UC [3]. The only statistically significant predictor of treatment withdrawal due to failure or adverse events was a disease duration of >6 years prior to starting adalimumab in Crohn's disease patients (HR 1.81, 95% CI 1.02—3.22, $p=0.04$). The low number of serious adverse events recorded over a long period of adalimumab therapy provides important safety data applicable to real-world practice.

The main strengths of this study include a good patient sample size and the use of objective clinical and endoscopic criteria for remission. A treat-to-target approach that includes mucosal healing as an endpoint reduces hospital length-of-stay and disease-related complications beyond the use of clinical indicators alone in IBD [4]. The retention rate of 50% in this real-world cohort is encouraging since it indicates that over nearly a decade, half of the patients studied continue to benefit from adalimumab therapy.

This study, as the authors readily acknowledge, has some limitations. Therapeutic drug monitoring (TDM), not used in this study, has become standard clinical practice in most IBD centers since the detection of anti-drug antibodies (immunogenicity) predicts the likelihood of primary or secondary

`**Tweet**` New concepts of retention and persistence rates evaluated in a long-term study in patients with IBD further adds to the literature on the efficacy and long-term safety of adalimumab.

✉ Shaji Sebastian
shaji.sebastian@hey.nhs.uk

[1] IBD Unit, Department of Gastroenterology, Hull and East Yorkshire Hospitals NHS Trust, Hull, UK

[2] Hull York Medical School, Hull, UK

non-response. Furthermore, trough levels correlate with clinical and endoscopic parameters of efficacy, increasing the likelihood of dose escalation [4, 5]. Low trough levels, however, are associated with the development of anti-drug antibodies and increased serum concentrations of markers of systemic inflammation such as C-reactive protein, suggesting that a "treat-to-trough" strategy may evolve into more individualized patient-specific treatment regimens [6]. It is possible that dose optimization using TDM may have increased the retention rate and persistence in this study.

A second limitation is that only a few patients were prescribed immunomodulator combination therapy following adalimumab induction, despite the SONIC trial and other evidence suggesting that co-administration of azathioprine/6-mercaptopurine or methotrexate with anti-TNF therapy improves steroid-free remission and rates of mucosal healing versus monotherapy [7]. The authors, however, rightly highlight the ongoing debate regarding this, given that the CHARM study failed to demonstrate any benefit of combination therapy in the maintenance of remission and that the open-label RCT performed by Matsumoto et al. did not demonstrate a statistically significant difference in clinical remission rates for combination therapy versus adalimumab monotherapy in azathioprine-naïve patients [8, 9]. Finally, while there were stringent clinical end points, biomarkers such a fecal calprotectin were not used during follow-up in this cohort. The CALM study [10] has demonstrated that the use of biomarkers to monitor therapy improves outcomes, both clinical and endoscopic mucosal healing, likely due to earlier recognition of an inadequate therapeutic response with consequent dose escalation earlier than would occur in normal practice.

Overall this interesting study opens up the concepts of persistence and retention rate in anti-TNF therapy in a real-world setting, adding weight to the body of evidence regarding the safety and tolerability of adalimumab in patients treated outside of clinical trials. Further real-world studies conducted prospectively designed to evaluate the persistence and retention rates for biologics in patients with IBD will be needed to inform patients and their treating clinicians about optimal therapeutic strategies.

Compliance with ethical standards

Conflict of interest Professor Shaji Sebastian holds research grants from Takeda, AbbVie, Warner Chilcott, Ferring, MSD, serves on the advisory boards of Takeda, AbbVie, Merck, Ferring, Pharmacocosmos, Warner Chilcott, Janssen, Falk Pharma, Biohit, Tillots Pharma, and has received speaker fees from Abbvie, Jaansen, Merck, Warner Chilcott, and Falk Pharma. Neil Gordon has no conflicts to declare.

References

1. Ghosh S, Sandborn WJ, Colombel J-F, et al. Interpreting registrational clinical trials of biological therapies in adults with inflammatory bowel diseases. *Inflamm Bowel Dis*. 2016;22:2711–2723.
2. Ha C, Ullman TA, Siegel CA, Kornbluth A. Patients enrolled in randomized controlled trials do not represent the inflammatory bowel disease patient population. *Clin Gastroenterol Hepatol*. 2012;10:1002–1007.
3. Sartini A, Scaioli E, Liverani E, et al. Retention rate, persistence and safety of adalimumab in inflammatory bowel disease: a real life, nine-year, single center experience in Italy. *Dig Dis Sci*. (Epub ahead of print). https://doi.org/10.1007/s10620-018-5329-4.
4. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): Determining therapeutic goals for treat-to-target. *Am J Gastroenterol*. 2015;110:1324.
5. Karmiris K, Paintaud G, Noman M, et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in crohn's disease. *Gastroenterology*. 2009;137:1628–1640.
6. Adegbola S, Sahnan K, Warusavitarne J, Hart A, Tozer P. Anti-TNF Therapy in Crohn's Disease. *Int J Mol Sci*. 2018;19:2244.
7. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. 2010;362:1383–1395.
8. 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.
9. Matsumoto T, Motoya S, Watanabe K, et al. Adalimumab monotherapy and a combination with azathioprine for Crohn's disease: A prospective, randomized trial. *J Crohn's Colitis*. 2016;10:1259–1266.
10. Colombel J-F, Panaccione R, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. *Lancet*. 2017;390:2779–2789.