First line Anti-TNFs or other advanced therapy first followed by anti-TNFs?

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During the last decade inflammatory bowel disease (IBD) became a highly treatable disease. After two decades of anti-TNFs as the only treatment option finally new molecules were developed. These molecules were costly treatment. Finally, biosimilars dramatically changed access to biological treatment. Biosimilars of anti-TNFs reduced the cost, therefore most countries were able to pay for the new drugs for the patients who had contraindications or inappropriate response to anti-TNFs. Nowadays, there is an important clinical dilemma on the choice of first line treatment. Below we discuss two different approaches.

ARGUMENTS FOR FIRST LINE ANTI-TNFS

The development of anti-TNFs, followed by other advanced therapies, has revolutionized the management of inflammatory bowel disease. Despite the expanding therapeutic armamentarium, treatment goals are still not achieved in more than 50% of patients. In Crohn's disease, available evidence consistently demonstrates that favorable outcomes are more likely when effective therapy is introduced early after diagnosis, compared with the conventional "step-up" approach. To date, early intervention strategies have been evaluated exclusively with the combination of infliximab and azathioprine, showing superior rates of endoscopic remission and improved long-term outcomes (1,2). It is reasonable to assume that similar results could be achieved with other advanced therapies in the same patient population, but robust evidence is lacking. Moreover, all currently available advanced therapies are subject to secondary loss of response over time. With anti-TNFs, therapeutic drug monitoring (TDM) has become an established and widely accepted strategy, enabling optimization based on drug concentration and the presence of anti-drug antibodies. In contrast, with other therapies, loss of response is often managed empirically, which risks unnecessary delays at a time when achieving disease control is most critical. Safety concerns are often cited against the use of anti-TNFs, particularly the risk of infections and lymphoma. However, it is important to emphasize that active disease itself carries a significant risk of infections, which is effectively reduced through the use of appropriate therapy (3). Furthermore, the infection risk associated with treatment can be minimized to acceptable levels through adequate pre-treatment screening and careful monitoring during therapy. It should also be noted that the increase in safety risks is substantially higher when anti-TNFs are used in combination with immunomodulators. In this regard, the development of subcutaneous infliximab has shown comparable efficacy as monotherapy compared with parallel use of immunomodulators, with positive implications for treatment safety (4). In summary, initiating anti-TNF treatment first

offers the best evidence-based approach to maximize mucosal healing and achieve sustained remission with acceptable safety profile.

ARGUMENTS FOR OTHER ADVANCED THERAPY FIRST FOLLOWED BY ANTI-TNFS

Positioning of advanced therapies in inflammatory bowel disease should consider efficacy, safety and cost. A consistent finding across pivotal trials is the higher efficacy of non– anti-TNFs in bio-naïve patients compared with those previously exposed to anti-TNFs. For instance, the GEMINI vedolizumab program demonstrated that endpoints such as clinical remission and response were more frequently achieved in bio-naïve patients than in those who had failed anti-TNF therapy (5,6). Furthermore, the head-to-head VARSITY trial confirmed that vedolizumab was superior to adalimumab in achieving endoscopic improvement and mucosal healing in ulcerative colitis, with greater effect sizes in anti-TNF–naïve patients (7). From a safety perspective, newer agents such as vedolizumab and ustekinumab appear to be associated with lower risks of serious infections compared to anti-TNFs, as also supported by registry data from PSOLAR (8). The SEAVUE study reported similar efficacy of adalimumab and ustekinumab in Crohn's disease, confirming that both agents can induce and maintain remission (9). Another important consideration is immunogenicity: anti-TNFs often require concomitant use of thiopurines, which has been linked to increased risks of lymphoma and non-melanoma skin cancer (10,11). These long-term safety concerns, combined with the need for combination therapy, further support earlier use of newer biologics. Cost-effectiveness analyses in IBD remain limited, but future models should account not only for direct drug acquisition costs but also for indirect costs of disease complications and management of infections. Overall, available evidence supports consideration of vedolizumab, ustekinumab, or JAK inhibitors as appropriate first-line advanced therapies in IBD, reserving anti-TNFs for subsequent treatment lines.

References:

1. D'Haens G, Baert F, van Assche G, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet Lond Engl. 2008;371:660–7.
2. Noor NM, Lee JC, Bond S, et al. A biomarker-stratified comparison of top-down versus accelerated step-up treatment strategies for patients with newly diagnosed Crohn's disease (PROFILE): a multicentre, open-label randomised controlled trial. Lancet Gastroenterol Hepatol. 2024;9:415–27.
3. Holmgren J, Fröborg A, Visuri I, et al. The Risk of Serious Infections Before and After Anti-TNF Therapy in Inflammatory Bowel Disease: A Retrospective Cohort Study. Inflamm Bowel Dis. 2023;29:339–48.
4. D'Haens G, Reinisch W, Schreiber S, et al. Subcutaneous Infliximab Monotherapy Versus Combination Therapy with Immunosuppressants in Inflammatory Bowel Disease: A Post Hoc Analysis of a Randomised Clinical Trial. Clin Drug Investig. 2023;43:277–88.
5. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013;369:711–21.
6. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369:699–710.
7. Sands BE, Peyrin-Biroulet L, Loftus EV, et al. Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis. N Engl J Med. 2019;381:1215–26.
8. Kalb RE, Fiorentino DF, Lebwohl MG, et al. Risk of Serious Infection With Biologic and Systemic Treatment of Psoriasis: Results From the Psoriasis Longitudinal Assessment and Registry (PSOLAR). JAMA Dermatol. 2015;151:961–9.
9. Sands BE, Irving PM, Hoops T, et al. Ustekinumab versus adalimumab for induction and maintenance therapy in biologic-naive patients with moderately to severely active Crohn's disease: a multicentre, randomised, double-blind, parallel-group, phase 3b trial. Lancet Lond Engl. 2022;399:2200–11.
10. Deepak P, Sifuentes H, Sherid M, et al. T-cell non-Hodgkin's lymphomas reported to the FDA AERS with tumor necrosis factor-alpha (TNF-α) inhibitors: results of the REFURBISH study. Am J Gastroenterol. 2013;108:99–105.
11. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, et al. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. Gastroenterology. 2011;141:1621-1628.e1-5. doi: 10.1053/j.gastro.2011.06.05