Better Late than Never: Adding Thiopurines After Loss of Response to Infliximab Monotherapy

Emily M. Villareal¹ · Andres J. Yarur¹

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Since infliximab (IFX), a monoclonal antibody that specifically targets tumor necrosis factor (TNF), is efficacious and safe in the treatment for Crohn's disease (CD), IFX therapy has become a popular choice for the induction and maintenance of clinical remission [1]. Using biologic drugs in IBD therapy regimens comes with a set of unique challenges, such as avoiding loss of response (LOR), as well as reducing complications from adverse effects (AE), such as infections and malignancy [1, 2]. Furthermore, the development of antibodies to IFX (ATI) is a common cause of LOR and some AEs such as infusion reaction. Although LOR can exacerbate disease, ultimately leading to a switch in therapy [1, 2], CD therapy regimens that use IFX in combination with a thiopurine can reduce the risk of ATI development, improve IFX pharmacokinetics, and increase its efficacy [3], enabling patients with IBD to maintain IFX therapy for longer periods, in addition to reducing IFX infusion reactions.

Although the prospective randomized SONIC trial supports the early use of combination therapy, a potential drawback of this regimen is the risk for increased complications, including infections and malignancies such as hepatosplenic T cell lymphoma [4, 5]. Due to this, there is some debate as to whether a thiopurine should be started with IFX or potentially added only if the patient experiences nonresponse. Even though there is literature supporting the efficacy of early combination therapy, there is a lack of studies looking into outcomes after adding a thiopurine in patients already receiving IFX monotherapy who experience primary or secondary nonresponse. Nonetheless, some clinicians and patients may be hesitant to use combination therapy fearing a higher risk of AEs.

In this issue of *Digestive Disease and Sciences*, Zeze et al. [6] report the results of a single-institution retrospective study that compared patients starting combination therapy with IFX and a thiopurine (EC group) to a second cohort of patients receiving IFX monotherapy who commenced thiopurine therapy only after experiencing LOR (LC group). Of the total group of 176 patients with CD, 49 patients were identified as “EC” and 127 patients were identified as “LC” therapy users. Both groups had similar baseline characteristics including demographics and disease phenotype. Assignment was based on each physician's clinical decision. The primary outcomes of the study were rates of IFX discontinuation and AEs. Though the authors found that rates of IFX continuation were similar between groups, they also found higher rates of AEs in the EC group [6], which parallels results from previous studies [4, 5].

Though this study was retrospective, it suggests that adding a thiopurine “if needed” after developing LOR may be a valid strategy, especially in patients that have a higher risk of developing an AE with combination therapy. The findings could be explained by an improvement in the pharmacokinetic profile of IFX induced due to thiopurine, according to a post hoc analysis of the SONIC trial suggesting that the benefit of combination therapy may be due to an improved pharmacokinetic profile and not to the direct effect of the thiopurine on disease activity [7]. The effects of ATI can be overcome with the addition of an immunomodulator and/or by increasing the dose of IFX [2]. In this study, the LOR experienced by the LC group could have been explained by the development of ATI, where the addition of a thiopurine could have helped overcome that immunogenicity. It is possible that dose-escalating IFX in patients with LOR would have had the same effect. While briefly mentioned by Zeze et al. [4] systematic measurement of IFX levels and presence of ATI were not recorded in the patients included in this study. The contribution of therapeutic drug monitoring (TDM) to IBD treatment in these patients warrants further investigation.

✉ Andres J. Yarur
ayarur@mcw.edu

¹ Division of Gastroenterology and Hepatology, Department of Medicine, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA

Another important question is how thiopurine optimization could improve the rate of discontinuation in both study arms. Higher 6-thioguanine levels correlate with a lower rate of immunogenicity and higher infliximab trough levels [6]. Another limitation of this study is that the cause of drug discontinuation was unknown. Since the clinical reasoning behind the discontinuation of combination therapy is reliant on the individual clinical profile, it is difficult to know whether those patients experienced LOR despite concurrent thiopurine use or AEs severe enough to warrant a change in therapy. Though the difference in discontinuation rates was not significant, 81 out of 176 patients still required a change in therapy, regardless of the amount of time spent receiving combination therapy. Future studies should examine how many patients receiving combination or monotherapy that experience LOR can regain efficacy after drug optimization protocols that include the use of TDM.

The analysis provided by this article found that patients in the EC group experienced higher rates of AE than the LC group [4]. Other studies that evaluated combination therapies have supported these findings, suggesting that IFX–thiopurine combination poses a greater risk for serious infection, malignancy, and other complications [7, 8]. Whether this could be simply due to a higher degree of exposure to thiopurine therapy in the EC group or the occurrence of synergistic or additive AEs due to the combination is unclear.

A recent review of IFX use in CD reported that 50% of CD patients discontinue IFX, as well as thiopurine therapy due to serious AEs, which poses the question whether de-escalating therapy or adding a thiopurine on those patients with LOR may be a better strategy versus using combination therapy on all patients from the beginning [1]. Though some studies have reported an increased risk of AEs with combination therapy, others have not [9]. Nevertheless, many studies cannot control analyses based on IFX and thiopurine exposure alone, as many patients with CD receive concurrent corticosteroids or have had previous exposure to these drugs [9]. Specifically, while noted during data collection, this study did not take into account the effects of exposure or concomitant corticosteroid use in the evaluation of efficacy and safety [4], which is unfortunate given that corticosteroids can contribute to the clinical success and/or development of AE of either group.

In conclusion, the results outlined by Zeze et al.'s analysis of IFX–thiopurine combination therapy for CD show initial evidence that both early and late combinations of the drugs may have similar therapeutic efficacy. Comparisons between the groups have also shown that there is a potentially higher

risk for adverse drug effects in the EC group. While this is a hypothesis-generating study, the results suggest that early concomitant thiopurine may not be warranted until the patient develops LOR to IFX. Randomized controlled trials confirming these results are warranted.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest to disclose.

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