It Takes Two to Make It Right: Dual Biologic and Small Molecule Therapy for Treatment-Refractory Pediatric Inflammatory Bowel Disease

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The solution to any problem is to tackle the cause of the problem. The exact pathogenesis of inflammatory bowel disease (IBD) is not known nor are the molecular pathways involved in perpetuating the inflammation in IBD. Consequently, we clinicians are at a loss when choosing effective therapies. Although significant advances have been made with the availability of many effective FDA-approved biologic therapies, none offer "companion diagnostics" to guide and predict the ability for individual therapies to be efficacious in a given IBD patient. Current therapies are aimed at attenuating the immune system in IBD through the following mechanisms: neutralizing pro-inflammatory cytokines, preventing the homing of lymphocytes to the intestine, and impeding downstream cytokine receptor signaling.[1] Biologic therapies centered on inhibiting pro-inflammatory cytokines are monoclonal antibodies and encompass anti-tumor necrosis factor (TNF) medications that neutralize TNF-α and ustekinumab, which binds to the common p40 chain of interleukin (IL)-12 and IL-23. In contrast, vedolizumab is a monoclonal antibody that targets $\alpha_4\beta_7$, which is an integrin expressed on activated lymphocytes important for entry into gut tissue by binding to MAdCAM-1 on mucosal endothelial cells. Recently, tofacitinib, a small molecule inhibitor of Janus kinase (JAK) 1 and 3 involved in downstream cytokine receptor signaling, was approved by the FDA for treatment of moderate to severe adult UC.

Despite these additions to the clinician's armamentarium for the treatment of pediatric IBD, stifling the inflammatory response and achieving sustained disease remission continue to be an arduous task. Unfortunately, with the exception of anti-TNF medications (infliximab and adalimumab), no other biologic therapies are FDA-approved for children with IBD. Clinical disease remission is achieved in only 40%–60% of patients on anti-TNF medications,[2–4] and patients who fail to improve after induction with anti-TNF are 27% less likely to respond to second-line biologics such as ustekinumab.[5] Ustekinumab is FDA-approved for adult IBD, but limited pediatric data reveal that in patients who have failed at least 1 biologic therapy, 38.6%–58% achieve clinical remission by week 52.[6, 7] Vedolizumab is another FDA-approved biologic therapy for the treatment of adult IBD, but off-label application for pediatric IBD demonstrated steroid-free remission in 20% by week 22 in a single-center prospective observational cohort study.[8] Recently, the efficacy of tofacitinib was assessed in biologic-refractory pediatric IBD with Crohn's disease (CD, n = 5), ulcerative colitis (UC, n = 5), and IBD unclassified (IBD-U, n = 2) patients treated with 10 mg twice daily and observed over an average of 9.7 weeks.[9] Clinical response was noted in 8 of 12 patients, whereas clinical remission was achieved in 5 of 12 patients. Steroid-free clinical remission was obtained in 1 CD and 2 UC or IBD-U patients. Together, these data indicate that a significant proportion of pediatric patients with IBD fail to respond to any of the existing single biologic or small molecule therapies, highlighting the need for new medications or treatment regimens.

In this issue, Dolinger et al report the efficacy of utilizing a dual therapy regimen in a single-center cohort of 16 children with refractory IBD (n = 9 for UC/IBD-U and n = 7 for CD) who have failed at least 2 biologic therapies and have ongoing disease despite maximizing drug dosing. The 16 patients were divided accordingly: n = 9 for vedolizumab/tofacitinib, n = 4 for ustekinumab/vedolizumab, and n = 3 for ustekinumab/tofacitinib. Twelve (75%) patients (7 UC/IBD-U and 5 CD) reached the primary end point of steroid-free clinical remission at 6 months (weighted Pediatric Crohn's Disease Activity Index ≤12.5 or partial Mayo score [pMS] <2 and without steroid use for at least 4 weeks). Median time to steroid-free clinical remission was 88 days, and significant decreases in median C-reactive protein and erythrocyte sedimentation rate complemented an increase in the median albumin. A total of 3 patients discontinued therapy due to persistence of symptoms requiring surgery (n = 1) or transition to another treatment regimen (n = 2). Importantly, the only serious adverse event was a patient who developed septic arthritis 2 months into starting dual therapy with vedolizumab and tofacitinib (also

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prednisone) and subsequently developed a deep vein thrombosis after surgical debridement and immobility. These findings highlight both the efficacy and safety of implementing dual biologic therapy—especially as the first to combine a biologic therapy with tofacitinib in treatment-refractory pediatric IBD.

A caveat in the interpretation of these results is differentiating whether the therapeutic efficacy could be attributed to the synergistic effects of 2 medications or simply from the new medication added. The literature supports the former premise, drawing primarily from adult cohort studies and case reports.[10, 11] The only randomized-controlled trial for dual biologic therapy was in adults, which demonstrated improvements in mean CDAI with a natalizumab and infliximab regimen relative to infliximab alone.[12] However, postmarketing surveillance revealed natalizumab to be associated with progressive multifocal leukoencephalopathy, thus limiting its use for IBD treatment. A recent systemic review and pooled analysis of published case reports compiling a total of 18 adult patients treated with dual biologic therapies for refractory disease demonstrated clinical improvement in all patients, with 93% also showing endoscopic improvement.[10] Recently, a pediatric case series with refractory IBD treated with a dual therapy regimen was published.[13] Of the 8 children treated with infliximab and vedolizumab combination therapy, 2 had disease exacerbation with either medication alone, so the remaining 6 children already on infliximab maintenance therapy had vedolizumab added. Three of these 8 patients were able to achieve clinical and biochemical remission. Additionally, 5 children with CD who developed severe paradoxical psoriasis on infliximab monotherapy failed to have adequate intestinal disease control when switched to ustekinumab but achieved IBD and psoriasis remission on both infliximab and ustekinumab. No adverse events were reported.

In line with the adult literature, dual therapy seems to be an efficacious and well-tolerated option for pediatric IBD patients who are refractory to biologic or small molecule monotherapies. Given the phenotypic heterogeneity of pediatric IBD and the multiple inflammatory immune pathways implicated in its pathogenesis, the approach of biologic monotherapy—1 drug for all of IBD—may not be suitable for all patients. Instead, in the age of personalized medicine, patients may require specific combinations of biologic and/or small molecule therapies to quell multiple arms of their dysregulated immune response. Indeed, Dolinger et al identifies an alternative treatment option of combining a biologic therapy with tofacitinib to achieve steroid-free clinical remission in children with refractory IBD. Their findings support the growing literature on the use of dual therapies for IBD and highlight the need for larger, randomized-controlled trials to better understand the long-term efficacy and safety of these combined regimens—especially given concerns for immunosuppression, malignancy, and opportunistic infection.

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