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INVITED COMMENTARY

Invited commentary to immunotherapy withdrawal by step-down to mesalamine in pediatrics patients with ulcerative colitis

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The ideal treatment for pediatric ulcerative colitis (UC) should be efficacious, have an acceptable risk/benefit profile based on the severity of disease, and favorable route of administration. While the options for treatments are expanding, there are still limited Food and Drug Administration (FDA) approved pharmacological, surgical, and dietary options available for our patients. Treatment for UC is life-long, and the accumulated risk of treatment is a source of frequent clinical discussions. The only definitive treatment is colectomy, which has a significant impact on daily life and usually reserved for refractory acute severe disease or after medical management failure. Oral 5-aminosalicylate compounds, including mesalamine, are typically recommended as first line induction and maintenance therapy for mild to moderate disease.[1] Hyams et al showed in a multicenter pediatric UC induction trial that 38% of patients achieved 52-week remission on mesalamine alone.[2] Children who have mesalamine refractory disease or mesalamine intolerance typically will step up to an immunomodulator or antitumor necrosis factor (TNF) biologic or those with initial severe disease are started on anti-TNF as a first line treatment with or without steroid induction. Use of immunomodulators such as azathioprine or 6-mercaptopurine as monotherapy in pediatric UC has decreased over time due to the side effect profile and low efficacy. Infliximab (and biosimilars) and adalimumab are the only FDA approved biologics for moderate-to-severe pediatric UC. Once started on a biologic, there is little known about de-escalation strategies for pediatric UC patients.

Rzigeti and Kellermayer report in the current issue of *JPGN Reports* a single center case series of nine pediatric UC patients in remission who underwent step-down treatment from an immunomodulator or anti-TNF biologic to mesalamine.[3] Two patients were on 6-mercaptopurine, 6 on infliximab, and 1 on adalimumab. Patients were selected for step-down after at least 6 months of clinical remission and followed for an average of 3.49 years. All patients were initially changed to mesalamine at 60–75 mg/kg/day or maximal adult dosing. The main findings showed 5/9 (55.5%) had sustained remission, as defined by pediatric UC activity index (PUCAI) < 15, 5/8 (62.5%) had fecal calprotectin < 50 mcg/g, and 7/8 (87.5%) had fecal calprotectin < 250 mcg/g. In addition, 4/6 (66.6%) of those with poststep-down colonoscopy had mucosal healing as defined as Mayo endoscopic subscore of 0–1.

See referenced article, pages 97-100

The authors conclude stepping down to mesalamine could be a reasonable option for pediatric UC patients in sustained remission. This report highlights a gap in the published literature. Adult studies, including the HUYABUSA study in 2020 and meta-analysis of four studies by Zhang in 2020, indicate 25–45% of patients will experience a flare in disease activity the first year after the switch.[4,5] The current study noted 11.1% of patients had flares over 1 year, with 44.5% having a flare over an average follow-up of 3.49 years.

The authors note the inherent limitation of a single center case series and caution broad interpretation. There is also a lack of a control group that remained on immunotherapy as there is a risk of flare despite consistent treatment. A pre-step down baseline assessment with fecal calprotectin and colonoscopy would have aided the assessment of remission.

Patients, families, and clinicians are concerned about long term side effects of UC treatments, including cancer. A large prospective pediatric cohort study did show increased incidence of malignancy in thiopurine exposed infliximab patients, but not in non-thiopurine exposed infliximab exposed patients.[6] Immunotherapies increase risk of infection, but it is important to recognize the risk of infection in uncontrolled disease is often greater than risk of infection attributed to a medication.[7] The rate of serious infection in pediatric IBD patients treated with anti-TNF is low (352 per 10,000 person year follow-up [PYF]) and much lower than expected for steroids (730 per 10,000 PYF).[8] Although mesalamine medications do not suppress the immune system, they are still associated with side effects including worsening gastrointestinal symptoms, headache, arthralgias and, rarely, interstitial nephritis, pancreatitis and agranulocytosis.[9] The risk of restarting therapy after a drug holiday needs to be considered if there is mesalamine failure. A recent meta-analysis in adult IBD patients showed 85% pooled clinical remission rate and 9% risk of infusion reaction with infliximab retreatment.[10] Risk of infusion reaction can be mitigated using antibody measurement shortly after the first re-treatment dose as outlined by Baert and colleagues.[11]

As with any decision related to the addition or change of medications, it is of utmost importance to engage the family and patient in shared decision making, which ideally includes a thorough discussion of risks and benefits of each medication and patient specific factors, such as current pubertal growth state and ability to be adherent with specific therapies.

This case series offers provocative questions as well as early insight into strategies that may aid finding the right medication for some that maintains clinical remission with a favorable risk profile that is easy to administer and does not suppress the immune system. Further studies are required to better understand the role of de-escalation to mesalamine in pediatric patients with UC by use of pediatric specific real-world registries or prospective multicenter studies.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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