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ORIGINAL ARTICLE

Gastroenterology: Inflammatory Bowel Disease

# Immunotherapy withdrawal by step-down to mesalamine in pediatric patients with ulcerative colitis

**Reka Szigeti**[1] | **Richard Kellermayer**[2,3]

[1]Department of Pathology and Genomic Medicine, Houston Methodist Hospital, Houston, Texas, USA

[2]Section of Pediatric Gastroenterology, Hepatology and Nutrition, Texas Children's Hospital, Baylor College of Medicine, Houston, Texas, USA

[3]USDA/ARS Children's Nutrition Research Center, Houston, Texas, USA

**Correspondence**

Richard Kellermayer, Section of Pediatric Gastroenterology, Hepatology and Nutrition, Texas Children's Hospital, Baylor College of Medicine, 6621 Fannin St., CC1010.00, Houston, TX, USA.
Email: kellerma@bcm.edu

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## Abstract

**Objective:** Parents and pediatric patients with ulcerative colitis (UC) who progressed to systemic immunotherapy are concerned about lifelong risks from such treatments. There is limited knowledge about withdrawal of such agents and step-down (SD) to enteral 5-aminosalicylic acid (mesalamine) before transitioning to adult care.

**Methods:** We studied nine pediatric cases with moderate to severe UC who after a median of 2.18 years of clinical remission on systemic immunotherapy stepped down to oral mesalamine treatment.

**Results:** Average follow-up time from SD was 3.49 years. Five patients (55.5%) had sustained remission (without any flare noted) after SD during follow-up. Sustained clinical remission was 88.9% (8/9) at 1 year, 87.5% (7/8) at 2 years, and 66.7% (4/6) at 3 years after SD. Out of those tested (one patient was not tested), 62.5% (5/8) had fecal calprotectin <50 μg/g. Four out of six patients examined (66.6%) had mucosal healing on post-SD colonoscopy.

**Conclusion:** We propose that SD to mesalamine can be a reasonable therapeutic consideration for pediatric patients with UC before transitioning to adult gastroenterology care. Shared decision-making is important before such treatment changes.

**KEYWORDS**

anti-TNF, de-escalation, infliximab, thiopurines, treatment

## 1 | INTRODUCTION

Recent clinical trials and meta-analyses in adult patients with ulcerative colitis in remission on systemic immunotherapy have addressed the discontinuation or withdrawal of biologic agents, such as infliximab (i.e., therapeutic de-escalation).[1,2] Based on these studies, current data indicate that 25%–45% of patients with adult-onset UC may experience a disease flare within 2 years upon treatment de-escalation to mesalamine. Such data are lacking in pediatric patients. Pediatric patients with ulcerative colitis (PUC) more frequently need step-up to steroid-sparing immunotherapy beyond enteral 5-aminosalicylic acid (mesalamine),[3] have more rapid progression to colectomy,[4] and a higher risk for colon cancer[5] than adult-onset cases. While parents and patients are concerned about lifelong risks from systemic immunotherapy, there is limited knowledge about withdrawal of such agents and step-down (SD) to mesalamine before transitioning to adult care.[6]

See referenced article, pages 95-96

## 2 | CASE REPORTS

We studied all known pediatric patients with UC who stepped down from thiopurine or anti-tumor necrosis factor (TNF) immunotherapy to mesalamine (extended-release form) monotherapy at 60–75 mg/kg/day up to the maximum adult dosing after shared decision-making between 2015 and 2021, under the Baylor College of Medicine Institutional Review Board protocol H-33527 (Clinical outcomes in Pediatric Ulcerative Colitis).

Nine (two female) patients fulfilled the inclusion criteria (see Table 1). All advanced to immunotherapy with thiopurine (2/9, 22.2%) or anti-TNF biologic agents (7/9, 77.8%) due to steroid-dependent or refractory disease, and reached sustained clinical remission for at least 6 months. Only two patients (patients 6 and 9) were trialed on mesalamine during the induction phase of their disease (i.e., only two "stepped up" from mesalamine to systemic immunotherapy for steroid sparing). Whether the patients were on thiopurine immunomodulator or anti-TNF biologic agent at the time of SD did not influence the outcomes. The average time of clinical remission was over 2 years (2.18 years) before withdrawal of immunotherapy, and SD to mesalamine treatment. The average follow-up time from SD was 3.49 years. All patients remained in clinical remission (defined by the pediatric ulcerative colitis activity index [PUCAI] as less than 15[7]) for an average of 3.13 years, and a minimum of 11 months. One patient (11.1%) experienced a clinical flare by 1 year after SD. Six patients (66.6%) were in clinical remission at follow-up. Five patients (55.5%) had sustained remission (without any flare noted) after SD. Overall, sustained clinical remission was 88.9% (8/9) at 1 year, 87.5% (7/8) at 2 years, and 66.7% (4/6) at 3 years after SD (Figure 1). Out of those tested, 87.5% (7/8) reached or sustained a fecal calprotectin (FC) level <250 µg/g (normal <120 µg/g) and 62.5% (5/8) had FC <50 µg/g. Four out of six patients examined (66.6%) had mucosal healing on post-SD colonoscopy defined as mucosa that had a normal appearance, slight or erythema, or granularity, comparable to Mayo endoscopic subscore 0–1 (as in Sandborn et al.[8]). Two patients had treatment change from extended-release mesalamine to balsalazide therapy due to worsening FC, and they responded favorably to this switch by >75% decline in FC. One of these patients (patient 6) had idiosyncratic exacerbation to mesalamine at diagnosis but still tolerated the drug well at SD. This patient had subsequent elevation of FCs up to 504 µg/g in spite of adding oral curcumin[9] to his augmented dosing (from 3 g daily to 4.5 g daily). Nevertheless, 3 weeks after his high calprotectin test, he had endoscopic and histologic healing at colonoscopy. The other patient switched to balsalazide (patient 7) was experiencing a clinical flare at his most recent follow-up, 2.3 years after SD.

**What is Known**

- In our small pediatric UC cohort, sustained clinical remission was 88.9% (8/9) at 1 year, 87.5% (7/8) at 2 years, and 66.7% (4/6) at 3 years after de-escalation to mesalamine.
- Treatment de-escalation to mesalamine could be a reasonable therapeutic option for pediatric patients with UC before transitioning to adult gastroenterology care.

**What is New**

- Patients with ulcerative colitis (UC) and caregivers are concerned about long-term side effects from lifelong systemic immunotherapy.
- 25%–45% of patients with adult-onset UC may experience a disease flare within 2 years upon treatment de-escalation to mesalamine.

## 3 | DISCUSSION

SD to mesalamine could be a reasonable therapeutic option for pediatric patients with UC in sustained remission before transitioning to adult gastroenterology care. We propose that similar to adult-onset disease (over 2/3 of cases in adults),[10] pediatric patients commonly experience a milder disease course after initial high activity. Consequently, a lower potency maintenance medication such as mesalamine could sustain remission in many, after the resolution of their high acuity disease at presentation. In our case series, we found SD to be successful in 55.5% of patients to maintain clinical remission, but the true efficacy requires further study. Our cohort had lower 1-year relapse rate (11.1%) than that reported in adult studies (25%–45%).[1,2] Inherent limitations from the retrospective and small cohort nature of our observations, however, limit the reliability of such comparison. A recent study found that adherence to mesalamine declines with age in young people with UC,[11] which may be one explanation for the lower relapse rates in our pediatric patients compared to adults.

Our opinion is that SD should only be considered after the completion of pubertal development to limit adverse effects on growth from potential disease flares. Our case 7 is an exception to this recommendation (his SD at 12 years of age was due to disseminated Histoplasmosis), and he was experiencing a significant clinical flare at age 14 at the time of this manuscript write-up. Shared decision-making,[12] biochemical and preferably mucosal disease assessment to ensure deep remission, is important before such treatment changes. This SD strategy could be considered even in those with prior severe, steroid-dependent or refractory

**TABLE 1** Patient characteristics.

| Patient | Age at Dx (years) | Gender | UC (PC) | Remission before SD (years) | Age at SD (years) | Biologic/ immunomodulator at SD | Colonoscopy after SD (time in months) | Last FC (μg/g) after SD (time from SD; months) | Clinical remission length (years) | FU (years) | Disease activity FU |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 8 | M | E2,S1 | 3 | 18 | Vnfliximab | NA | NA | 2.17 | 2.17 | Remission |
| 2 | 14 | F | E4,S1 | 2 | 20 | Infliximab | NA | 32 (7) | 0.92 | 2.58 | Flare |
| 3 | 14 | F | E2,S0 | 1 | 16 | 6-Mercaptopurine | Focal Mayo 1 (25) | <15.6 (20) | 2.08 | 2.08 | Remission |
| 4 | 12 | M | E4,S1 | 2 | 16 | (Infliximab refractory) 6-Mercaptopurine | Focal Mayo 1 (44) | <15.6 (38) | 7 | 7 | Flare |
| 5 | 16 | M | E4,S0 | 3 | 20 | Infliximab | MH (36) | 7 (19) | 3.83 | 3.83 | Remission |
| 6 | 13 | M | E4,S1 | 3 | 17 | Infliximab | MH (11) | 362 (3)[a]; then 40 (5); then 154 (9),[b] then 504 (10) – colonoscopy recommended | 1.16 | 1.16 | Remission |
| 7 | 11 | M | E4,S0 | 0.5 | 12 | Adalimumab (stopped due to disseminated histoplasmosis) | Patchy Mayo 2 (17) | 1020 (18)[a]; then 232 (22); then 1950 (26); then 408 (27) | 2.25 | 2.33 | Flare |
| 8 | 14 | M | E4,S0 | 0.5 | 15 | Infliximab | Mayo 1–2 (7) | 396 (13), NC | 6 | 7.5 | Remission |
| 9 | 15 | M | E3,S0 | 4.6 | 20 | Infliximab | NA | 66 (4) | 3 | 3 | Remission |
| Average | 13 | | | 2.18 | 17.1 | | | | 3.13 | 3.49 | |

*Note*: UC type is based on the widely used Paris classification (PC: E2: left-sided colitis; E4: pancolitis; S0: never severe, S1: at least one episode of severe activity). Colonoscopy endoscopic severity was based on the widely accepted Mayo endoscopic severity scale (0: normal to E3: severe endoscopic disease).

Abbreviations: Dx, diagnosis; FC, fecal calprotectin (μg/g; normal range <120 μg/g); FU, follow-up; MH, microscopic healing; NA, not applicable; NC, not collected; remission, pediatric UC activity index <15; UC, ulcerative colitis.

[a]Switch from extended-release mesalamine (daily dosing) to twice daily balsalazide (5-aminosalicylic acid [mesalamine] linked to 4-aminobenzoyl-β-alanine via an azo bond).

[b]Increase from 1.5 g balsalazide twice daily to 2.75 g twice daily with curcumin 1.5 g twice daily.


**FIGURE 1** Sustained clinical remission was 88.9% (8/9) at 1 year, 87.5% (7/8) at 2 years, and 66.7% (4/6) at 3 years after step-down to mesalamine.

disease, even if they did not tolerate mesalamine during the induction phase of treatment. Balsalazide may be an option for patients who do not respond optimally to the extended-release form of mesalamine, as seen in case 6. Of note, case 6 also indicates that FC-based interpretation of mucosal disease activity should be exercised with caution. When clinical and biochemical disease activity markers of UC are incongruent, endoscopic evaluation should be considered before significant treatment changes are made.

The long-term outcomes from therapeutic de-escalation or SD to mesalamine compared to long-standing/lifelong systemic immunotherapy (biologic agents, small molecules, or traditional thiopurines) in patients with UC are unknown and should be studied in clinical trials.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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