Use of Ustekinumab in Pediatric Crohn's Disease – A Report of Three Cases

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Background

Treatment options for pediatric IBD patients are limited. Use of non-FDA approved agents to manage difficult patients may be considered. Ustekinumab (UST) is a humanized IgG1κ monoclonal antibody designed to block interleukin-12 and interleukin-23, suppressing cytokine activation and inflammatory response. UST is approved for the treatment of moderate-to-severe Crohn's disease (CD) in adults.[1] It is also approved for the treatment of adolescent patients 12 years or older with moderate-to-severe plaque psoriasis.

Presently, there are limited safety and efficacy data on UST use in pediatric CD patients.[2-6] We describe our experience with UST in three pediatric CD patients following anti-TNF therapy.

Case Descriptions

Patient 1 is currently a 15 y/o female, diagnosed with CD involving both small and large bowel in 2013. She was stable on adalimumab (ADA) alone until August 2018 when she presented with increased abdominal pain and hematochezia. ADA was discontinued, and UST initiated in September 2018 (390 mg IV, then 90 mg IV every 8 wks). Significant improvement was noted (CRP normal at 1.3 mg/L in December 2018 after 4 months on UST) with no reported adverse drug effects. Length of therapy to date is 14 months.

Patient 2 is currently a 20 y/o female, diagnosed with CD in 2015 following jejunal resection for small bowel obstruction. She was stable on infliximab (IFX) and methotrexate (MTX) but presented in November 2016 with worsening scalp psoriasis thought attributable to IFX. IFX was discontinued, and UST initiated in December 2016 (260 IV mg, then 90 mg every 8 wks). Concomitant MTX 15 mg weekly was continued. In February 2017, CD was quiescent and psoriasis improving. She presented in November 2017 with abdominal cramping and loose stools after running out of MTX. CRP was 8.8 mg/L on UST alone. Her psoriasis had resolved. MTX was restarted, and she continued to do well until early February 2019 when she had a CD flare associated with a delay in her UST dose due to change in insurance. She responded to a prednisone taper and restarted UST therapy. UST serum level in March 2019 was 2.5 mg/L, and the UST dose was increased to 90 mg every 4 weeks. The patient continues to do well. Length of therapy to date is over 2.5 years.

Patient 3 is currently an 18 y/o male, diagnosed with CD in 2017. He had intermittently unstable CD treated with various combinations of ADA, MTX, and prednisone in the past. ADA was discontinued due to poor symptom control in May 2018, and UST was initiated in August 2018 (390 IV mg, then 90 mg IV every 8 wks). MTX and prednisone were continued. His CD responded well to UST with a reduction in CRP from 18 to 1.6 mg/L. In late December 2018 he reported frequent bloody stools but was otherwise stable. Colonoscopy and upper GI endoscopy in early January 2019 were unremarkable; hematochezia resolved with the addition of mesalamine. Length of therapy to date is 14 months.

Summary of Patient Information and UST Therapy

	Patient 1	Patient 2	Patient 3
Date of diagnosis	September 2013	December 2008	October 2017
Age at diagnosis, years	9	16	16
Duration of disease, years	6	1	2
Prior biologic therapy	ADA	IFX	ADA
Date of UST initiation	September 2018	December 2016	August 2018
Age at UST initiation, years	14	18	17
Weight at UST initiation, kg	64.3	59.1	60.9
UST dosing regimen	390 mg initially, then 90 mg every 8 weeks	260 mg initially, then 90 mg every 8 weeks; every 4 weeks at 2 years	390 mg initially, then 90 mg every 8 weeks
UST therapy duration to date, months	13	34	14

Discussion

We report the successful treatment of CD with UST in three adolescents who were previously treated with anti-TNF agents. All patients had documented CD involvement of both small and large intestines. In each patient, improvement in clinical status was observed within 3 months of starting UST and has continued through the last reported clinic assessment. No patients experienced infusion-related adverse events or reported drug-associated side effects. All patients remain on UST therapy to date. Our experience is consistent with available published reports of UST use in pediatric CD patients, which are briefly summarized.

Literature on UST use in pediatric CD patients has expanded within the recent years, from case reports to larger cohort studies. Rinawi *et al* reported the first successful use of UST in a 7 y/o male with refractory Crohn's disease in early 2016.[2] Later that year Bishop *et al* described their use of UST for 4 adolescent CD patients.[3] Two showed clinical improvement with lower disease activity scores and continued UST therapy, while two patients discontinued UST due to lack of clinical response. Fusillo *et al* assessed differences between UST responders and non-responders in their cohort of 20 pediatric IBD patients receiving at least 2 doses of UST.[4] At 8 weeks, significantly more non-responders had disease limited to the colon and had previously failed at least two classes of biologic therapy. No patients in the non-responders group at 8 weeks achieved clinical response by 24 weeks.

Chavannes *et al* reported a retrospective cohort study of 44 pediatric patients with moderate-to-severe CD treated with UST.[5] All had previously failed at least one biologic agent prior to UST. UST significantly lowered the disease activity scores (aPCDAI) by ~16 points at 3 months and ~20 points at 12 months. At 12 months, 48% of patients demonstrated clinical response and 38% had achieved clinical remission. The probability of continuing UST therapy for 12 months was 77%. Serious adverse events were reported in two patients who received only one induction dose, though a clear association with UST was uncertain. Six patients experienced mild adverse events after the induction phase. No drug discontinuations due to adverse events occurred during the maintenance phase.

In the largest and most recent report to date, Dayan *et al* reported their experience with UST in 52 children and young adults with IBD (81% Crohn's disease, 8% ulcerative colitis, and 11% unspecified IBD) with a median age at induction of 16.8 years [IQR 14-18].[6] This was also the first study to describe UST use in bio-naïve pediatric patients. While 42 had failed more than one anti-TNF agent and 19 had failed both an anti-TNF agent and vedolizumab, 10 patients were bio-naïve. At 1 year of follow-up, 39 patients (75%) remained on UST treatment, and 30 patients (58%) were in steroid-free remission (9 bio-naïve and 21 bio-experienced). Infusion-related reactions were reported in two patients. Only one patient discontinued UST due to side effects, which included muscle and joint pains as well as fatigue. No serious adverse events or infections were observed.

These data are outlined below:

Author	Patients (n)	Diagnosis	Biologic-Exposed Patients (n)	Clinical Response (n; time)
Rinawi F[2]	1	CD	1 (100%)	1; 3 months
Bishop C[3]	4	CD	4 (100%)	1; 3-6 months
Fusillo SJ[4]	20	16 CD, 2 UC, 2 not specified	20 (100%)	13; 8 weeks 6; 4 weeks
Chavannes M[5]	44	CD	44 (100%)	21; 3 months
Dayan J[6]	52	42 CD, 4 UC, 6 not specified	42 (81%)	39; 12 months
Sarles	3	CD	3 (100%)	3; 3 months

Our case reports are limited due small number of patients and retrospective assessments of patient records.

Conclusion

Substantial clinical improvement in CD was observed in these young patients following conversion to UST therapy, with no significant safety concerns observed. Further studies are warranted to determine the place in therapy for UST in pediatric CD patients.

References

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