IL12/23 blockade for refractory immune-mediated colitis: A case series from two centers

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Background & Aims

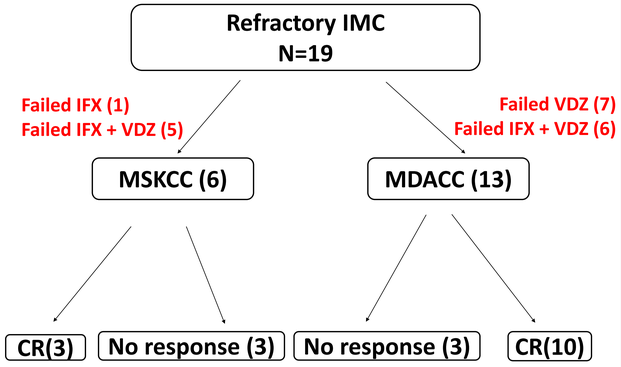
Immune checkpoint inhibitors (ICI) target regulators of the immune system, namely programmed cell death- 1 (PD-1), programmed cell death ligand 1(PD-L1), and cytotoxic T lymphocyte antigen -4 (CTLA-4) and thereby promote a highly efficacious anti-tumor response against several advanced cancers.

Immune mediated colitis (IMC) is highly reminiscent of Inflammatory bowel disease (IBD) in its clinical and endoscopic presentation. Current medical therapy is tailored to Common Terminology of Clinical Adverse Events (CTCAE) grading of severity of diarrhea and colitis and includes steroids, followed Infliximab (IFX) and/or Vedolizumab (VDZ). Fecal microbiota transplantation (FMT) is used for colitis refractory to medical therapy.

Ustekinumab(UST), a human monoclonal antibody to the interleukin (IL) 12/23 p40 subunit, is efficacious in the management of severe IBD. Data on the utility of IL12-23 blockade in the management of IMC is limited to anecdotal case reports.

We aim to present the largest case series to date on outcomes of patients with IMC treated with UST.

Patient Selection



Study Design and Methods

This is a descriptive, two-center study conducted after approval was obtained from IRB at The University of Texas MD Anderson Cancer Center (MDACC) and Memorial Sloan Kettering Cancer Center (MSKCC).

Patients included in our study (1) developed IMC refractory to steroids and IFX and/or VDZ (2) received UST for IMC

Demographic , clinic-oncologic, endoscopic, histologic and management variables were extracted from electronic patient health records and endoscopy databases.

Clinical remission (CR) of symptoms was defined as sustained resolution of diarrhea to grade 1 or lower after ustekinumab therapy.

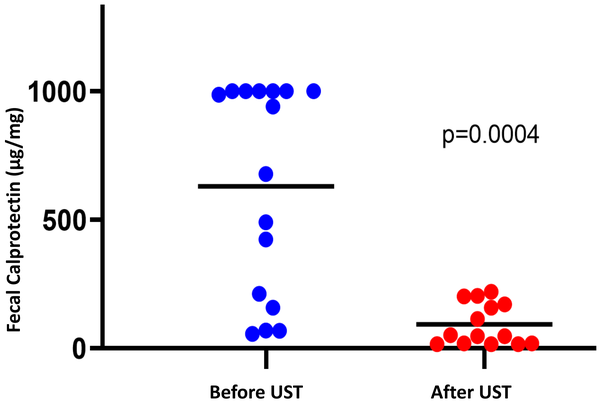
Clinico-Oncologic Characteristics	Cohort (N=19)
Median age at time of IMC – year (IQR)	63 (58-72.5)
Male sex – no. (%)	8 (42.1%)
White race – no. (%)	17 (89.5%)
Cancer type – no. (%)	
Melanoma	11 (57.9%)
GU	1 (5.3%)
Lung	2 (10.5%)
Breast	1 (5.3%)
Head and neck/Endocrine	3 (15.8%)
Hematological cancer	1 (5.3%)
Cancer Stage IV	11 (57.8%)
Checkpoint inhibitor type – no. (%)	
PD-1/L1	10 (52.6%)
Combination of CTLA-4 and PD-(L)1	9 (47.4%)
Median ICI doses before IMC (IQR)	6(2-9)
ICI stopped due to IMC– no. (%)	18 (94.7%)

Characteristics of IMC	Data (N=19)
Time from ICI to IMC, days, median (IQR)	98(37-180)
Highest grade of diarrhea (3-4) – no. (%)	16 (84.2)
Highest grade of colitis – no. (%)	
0-1	6 (31.6%)
2	11(57.8%)
3-4	2(10.5%)
Initial endoscopic findings—no (%)	
Ulcers	8 (42.1%)
Non-ulcer inflammation	5 (26.3%)
Normal	6 (31.6%)
Initial histology findings—no (%)	
Acute inflammation	7 (36.8%)
Chronic active inflammation	7 (36.8%)
Microscopic colitis	4 (26.4%)
Hospitalizations – no. (%)	14 (73.7%)
Other treatment of GI adverse event – no. (%)	
Steroid	19(100%)
Infliximab	11 (57.9%)
Vedolizumab	18(94.7%)
FMT	8 (42.1%)
Resumed ICI—no (%)	6 (31.6%)
Number of UST doses, median (IQR)	2(10.5%)
1 dose of UST	7 (36.8%)
>1 dose of UST	12 (63.2%)
Clinical remission with UST –no (%)	13 (68.4%)
Endoscopic remission at last follow up—n=7 (%)	5 (26.3%)

Results

1. The majority of our sample were Caucasians females with a median age of 63 years.
2. The most common cancer type was melanoma (52.7%) and nine patients had received combination CTLA-4/PD-1 regimens prior to onset of IMC.
3. Most (84.2%) patients had grade ≥3 diarrhea. 42.1% had ulcerative inflammation.
4. 13 (68.4%) improved following UST.
5. Eight patients in our cohort received FMT, 4 before and 4 after UST, six of whom improved after UST.

Calprotectin Levels Before and After UST



Conclusion

- IMC can be refractory to multiple lines of therapy including corticosteroids, IFX, VDZ, or FMT.
- IL12/23 inflammatory pathway may serve as a therapeutic target in managing refractory IMC.
- We observed that UST is safe and effective in achieving a high rate of clinical and endoscopic remission in patients with highly refractory IMC.
- The use of UST may be critical to avoid the sequelae of chronic steroid use namely, infection, metabolic dysfunction, and adrenal insufficiency.
- Larger, prospective studies are imperative to validate its use and determine appropriate positioning in the treatment of IMC .

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