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IL12/23 blockade for refractory immune-mediated colitis: 2 center experience

Running title: Ustekinumab for refractory IMC

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Y.W., and D.F. who were the senior authors of this article, developed the concept, designed the study, interpreted the results, ensured the preservation of data accuracy and integrity at all stages, agreed to be accountable for all aspects of the study, was in charge of the overall direction and planning of the study, and contributed to the writing of the manuscript, with input from all authors. A.T., S.E.L. collected

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All data, analytic methods, and study material is available upon request by contacting the corresponding author.

Data availability statement

The data sets used and analyzed in this study are available from the corresponding author upon reasonable request.

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Abstract

Background and Aims: Immune checkpoint inhibitor mediated colitis (IMC) is commonly managed with steroids and biologics. We evaluated the efficacy of ustekinumab (UST) in treating IMC refractory to steroids plus infliximab and/or vedolizumab.

Results: Nineteen patients were treated with UST for IMC refractory to steroids plus infliximab (57.9%) and/or vedolizumab (94.7%). Most had grade ≥3 diarrhea (84.2%) and colitis with ulceration was present in 42.1%. Thirteen patients (68.4%) attained clinical remission with UST and mean fecal calprotectin levels dropped significantly after treatment (629±101.5 mcg/mg to 92.0±21.7 mcg/mg, p=0.0004).

Conclusions: UST is a promising therapy for treatment of refractory IMC.

Key words: Immune checkpoint inhibitor, cancer, toxicity, immune mediated colitis, refractory, ustekinumab

BACKGROUND

Immune checkpoint inhibitors (ICI) target regulators of the immune system and promote a highly efficacious anti-tumor response against several advanced cancers [1]. Immune-mediated colitis (IMC) is an ICI related toxicity that is highly reminiscent of IBD in its clinical and endoscopic presentation. Management of moderate to severe IMC (Grade 2 or higher according to the Common Terminology Criteria for Adverse Events (CTCAE v5) typically includes weight based systemic corticosteroids with the addition of biologics such as infliximab (IFX) or vedolizumab (VDZ) in severe or refractory case [2, 3]. Around 12-15% of patients have refractory disease despite the aforementioned treatments [4]. Fecal microbiota transplantation (FMT), tofacitinib and ustekinumab (UST) have been used to treat refractory IMC in select cases with encouraging preliminary efficacy in small case series [5-9]. UST is a human monoclonal antibody to the interleukin (IL) 12/23 p40 subunit that has proven efficacious in the management of severe inflammatory bowel disease (IBD) [10], but data on its utility in IMC is limited to two case reports [11, 12]. Therefore, we present the largest experience to date from two referral centers supporting the efficacy of UST for the management of refractory IMC.

METHODS

Study design and Methods

This retrospective, two-center study was conducted with approval from the Institutional Review Boards at The University of Texas MD Anderson Cancer Center and Memorial Sloan Kettering Cancer Center. Inclusion criteria accounted for patients who (1) developed IMC refractory to steroids and IFX and/or VDZ (2) received UST for IMC, and (3) had clinical or endoscopic follow-up. Demographic, oncologic, laboratory and endoscopic data were extracted from electronic medical records and endoscopy databases.

Diarrhea was graded using the CTCAE version 5. IMC was considered refractory when (1) symptoms incompletely improved after immunosuppression; (2) symptoms relapsed upon tapering or discontinuing immunosuppression. Endoscopic findings were classified as (1) ulcerative inflammation, (2) nonulcerative inflammation and (3) normal appearance. Clinical remission of symptoms was defined as sustained resolution of diarrhea to grade 1 or lower after UST. Endoscopic remission was defined as Mayo endoscopic sub-score of 0 or 1 after UST [13].

Statistical analysis

Categorical variables were summarized using frequencies and percentages. Continuous variables were summarized using means and standard deviations or medians and interquartile ranges except for values of fecal calprotectin which were presented as mean and standard error of the mean. Independent and paired-sample T-tests were used to compare the mean calprotectin levels between different groups after testing for normality. Logistic regression was used to test the association between different factors and response to ustekinumab. All tests were two-sided and p-values < 0.05 were considered significant.

RESULTS AND DISCUSSION

Details regarding the patient selection process from 2 tertiary cancer centers was shown in Figure 1. Table 1a highlights the demographic profile of our sample (n=19) wherein a majority were white women who received PD 1/L1 monotherapy for stage IV cancer. Sixteen patients (84.2%) had CTCAE grade 3-4 diarrhea and 14 patients (73.7%) required hospitalization for IMC. Eighteen (94.7%) patients were refractory to VDZ and 12 (63.1%) to IFX, with 11 (57.9%) patients failing both VDZ and IFX. Eight patients (42.1%) had high risk endoscopic features of ulcerative colonic inflammation, which bears a poor prognosis [14].

Clinical remission was achieved in 13 patients (68.4%) after treatment with UST, with 63.2% receiving more than 1 dose. We observed a striking improvement in fecal calprotectin post-UST therapy (Figure

2). Of the 11 patients who underwent endoscopic follow-up, 64% had mucosal healing, similar to rates of healing seen in the UNIFI trial in ulcerative colitis (Table 1b) [15].

We found no significant differences in terms of clinical/endoscopic presentation of IMC or prior exposure to immunosuppression among UST responders versus non responders (Table 1c). Numerically more non-responders had cancer progression compared to responders (83% vs 31%, p=0.057). We note a numeric difference in prior biologic exposure between the groups, with UST response rates of 87.5% after a single prior biologic, versus 54.5% after two prior biologics (Table 1c) (p=0.18). This mirrors poorer IBD response rates in patients with prior exposure to anti-TNFs [16], and highlight an important need for additional data to guide biologic sequencing in IMC.

One patient developed severe side effects of sinus congestion/infection attributed to UST, which resolved after discontinuing the medication and treatment with antibiotics. While larger studies are necessary to determine safety profile of IL-12/23 blockade in an immunocompromised cancer population, our findings suggest preliminary safety of UST in this group. That being said, the implications of opposing roles of IL-12 and IL-23 in maintaining dormancy and outgrowth of tumors in a cancer patient population is yet to be determined [17]. In fact, pre-clinical mouse models have demonstrated that titrating this balance in combination with ICIs can promote tumor suppression [18,19].

Lastly, 2 patients responded to FMT post UST. FMT for refractory IMC represents a novel approach wherein the gut microbial composition is targeted to confer a therapeutic benefit. While little is known about the effect of IL-12/23 blockade on the gut microbiome, the question of a synergistic effect of such blockade with prior SIT needs to be considered.

Our study is limited by its retrospective nature, small sample size and lack of a control arm to appropriately measure the impact of UST on IMC and cancer.

Conclusions

Blockade of IL-12/23 with Ustekinumab is a promising therapy for management of refractory IMC. Larger studies are needed to guide sequencing of biologics in IMC and explore their potential impact on cancer outcomes.

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Tables and Figures

Table 1a. Patients' characteristics	
Characteristic	Cohort (N=19)
Median age at time of IMC – yr (IQR)	63 (58-72.5)
Male sex – n. (%)	8 (42.1%)
White race – n. (%)	17 (89.5%)
Cancer type – n. (%)	
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%)
Immune checkpoint inhibitor type – n. (%)	
PD-1/L1	10 (52.6%)
Combination of CTLA-4 and PD-(L)1	9 (47.4%)
Median number of ICI infusions before IMC, (IQR)	6 (2-9)
Immunotherapy was stopped due to IMC– n. (%)	18 (94.7%)
Table 1b. Characteristics of gastrointestinal adverse events	
Time from ICI to immune related adverse events, days, median (IQR)	98 (37-180)
Peak fecal calprotectin prior to UST, mean ± SEM	629.8±101.5
Highest grade of diarrhea (3-4) – n (%)	16 (84.2)
Highest grade of colitis – n (%)	
1-2	17 (89.5%)
3-4	2 (10.5%)
Initial endoscopic findings—n (%)	
Ulcers	8 (42.1%)
Non-ulcer inflammation	6 (31.6%)
Normal	5 (26.3%)
Hospitalizations – n (%)	14 (73.7%)
Other treatment of GI adverse event – n (%)	
Steroid	19 (100%)
Infliximab	12 (63.2%)
Vedolizumab	18 (94.7%)
FMT**	8 (42.1%)
Resumed cancer treatment after Rx—n (%)	8 (42.1%)
Resumed ICI—n (%)***	6 (31.6%)
>1 dose of ustekinumab	12 (63.2%)
Clinical remission following ustekinumab treatment**** –n (%)	13 (68.4%)
Endoscopic remission at last follow up—n=7 (%)	5 (26.3%)
Fecal calprotectin after UST, mean ± SEM	92.0±21.7
Cancer status at the last follow up –n (%)	
Remission	5(26.4%)
Stable disease	6(31.6%)

Progression			8(42.1%)
Table 1c. Characteristics of UST responders and non-responders			
	N (%)		
Characteristics	Responders N=13	Non-responders N=6	p-value
History of autoimmune disease, n=13	3(30%)	2(66.7%)	0.252
Cancer status prior to IMC, n=13			0.079
Stable disease	6(60%)	0	
Progression	4(40%)	3(100%)	
Median days from IMC to UST, (IQR)	389(287-583)	345.5(161.25-757.75)	0.898
Peak calprotectin prior to UST	627.8±119	635.8±223.6	0.976
Drop in calprotectin after treatment, mean ± SEM	563±140.4	635±161.3	0.758
Colitis grade≥2	8(61.5)	5(83.3)	0.605
Diarrhea grade≥2	10(76.9)	6(100)	0.517
Endoscopic Findings			1.000
Normal	3(23.2)	2(33.3)	
Non-ulcerative	5(38.4)	1(16.7)	
Ulcerative	5(38.4)	3(50)	
Histologic Findings			1.000
Acute inflammation	5(38.4)	2(33.3)	
Chronic inflammation	5(38.4)	3(50)	
Microscopic colitis	3(23.2)	1(16.7)	
Steroid duration, days, median (IQR)	34(20-57.5)	48.5(33-62.5)	0.412
Previous biologic treatment			0.177
Single biologic agent	7(53.8)	1(16.7)	
Two biologic agents	6(46.2)	5(83.3)	
Doses of SIT, median (IQR)	6(2.5-9.5)	6.5(4.5-10)	0.701
Median days from last biologic to UST, (IQR)	52(26-153)	68.5(21-129.25)	0.831

Table 1d. Multivariate logistic regression of factors related to ustekinumab treatment response		
Characteristic	Odds ratio (CI)	p-value
Ustekinumab doses	0.4 (0.2-1.2)	0.122
Failure of single or dual SIT agents	0.05 (0.01-2.69)	0.143
Total doses of SIT	0.9 (0.6-1.3)	0.576
Male gender	0.22 (0.01-3.42)	0.277

IMC: immune-mediated colitis; GU: genitourinary; PD-(L)1: Programmed cell death protein (ligand) 1; CTLA-4: Cytotoxic T lymphocyte Associate protein-4; IQR: interquartile range

Footnote:

**8 patients received FMT: 4 prior to ustekinumab, 4 after ustekinumab. Of the 4 after ustekinumab, 2 did not respond to ustekinumab. 2 discontinued the drug due to allergic reactions, and loss of insurance coverage.

*** 4 of these patients (66.7%) were ustekinumab responders, 2 were non-responders.

****1 patient had a good response to ustekinumab after one dose initially but then developed severe side effects that led to its discontinuation. Another patient also had a good initial response to

ustekinumab but discontinued the drug due to loss of insurance coverage. Finally, one patient received 1 dose of ustekinumab with persistent symptoms initially, then lost insurance coverage and responded to FMT afterwards.

Figure legends:

Figure 1: Patient selection flowchart

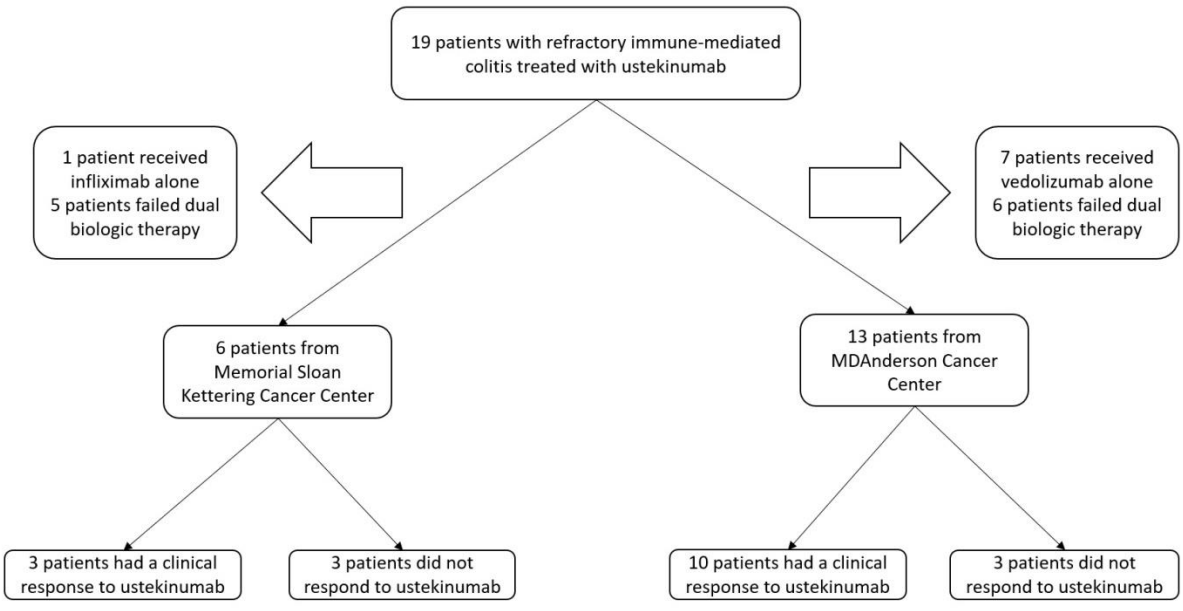

Figure 2: Change in calprotectin levels before and after treatment with ustekinumab, with the black bar representing mean values