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Brief Communication

Efficacy of Infliximab Dose Escalation in Patients with Refractory Immunotherapy-Related Colitis: A Case Series

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Abstract

Immune checkpoint inhibitor-related colitis is a common complication of immunotherapy use in patients with cancer. Current guidelines recommend treatment with standard dose infliximab (IFX) for corticosteroid-refractory colitis; however, this case series suggests IFX dose escalation may be a viable treatment option for refractory cases.

Immune checkpoint inhibitors (ICIs) have led to groundbreaking advances in cancer treatment, although they have been associated with multiple immune-related adverse events, including gastrointestinal, endocrine, pulmonary, and dermatological events. Immune checkpoint inhibitor-related colitis (irColitis) is one of the most frequent and severe complications of ICI use, with studies describing the incidence of all-grade colitis as 0.7%-1.6% in patients treated with anti-programmed cell death protein (PD)-(L)1 therapy, 5.7%-9.1% for patients treated with anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), and 13.6% in patients receiving combination therapy with anti-PD-(L)1/anti-CTLA-4 agents.[1] Severe irColitis, defined as grade 3 or grade 4 events of diarrhea and/or colitis by Common Terminology for Criteria for Adverse Events (CTCAE v5.0), occurs in 1% of patients on anti-PD-(L)1, but up to 9% of patients on combination anti-PD-(L)1/anti-CTLA-4 and involves an increase of ≥7 stools per day over baseline and/or severe abdominal pain which can have life-threatening consequences and often necessitates hospitalization.[2]

Guidelines for management of severe irColitis are based on clinical consensus in the absence of prospective trials to guide treatment, and generally recommend corticosteroids at doses of 1-2 mg/kg as initial therapy. Treatment algorithms for corticosteroid-refractory disease have been adapted from the treatment of inflammatory bowel disease, and recommend prompt initiation of infliximab (IFX), a tumor necrosis factor (TNF) antagonist, at a standard dose of 5 mg/kg or vedolizumab, an anti-integrin, in patients with severe irColitis that is not responsive to steroids within 48 to 72 hours.[3,4] The treatment of irColitis refractory to IFX treatment, however, is a challenging clinical scenario, as vedolizumab may be slower in onset and less effective after failure of a TNF antagonist, and there are limited data for other third line therapies including fecal microbiota transplantation.[5,6,7]

Infliximab dose escalation, generally defined as giving higher or more frequent dosing than the standard FDA-approved regimen of 5 mg/kg at 0, 2, and 6 weeks, is a common practice in the treatment of acute severe ulcerative colitis.[8] Infliximab pharmacokinetics appear to be altered in severe colitis due to fecal drug losses, TNF sink leading to increased drug clearance, and hypoalbuminemia.[9] As such, the use of IFX dose escalation to doses of IFX higher than 5 mg/kg is common for patients with acute severe ulcerative colitis, in particular among patients with high serum C-reactive protein and low serum albumin and those not responding to standard dose IFX.[10] The efficacy of dose escalating IFX in patients with irColitis not responding to standard dose IFX (5 mg/kg) has not been reported.

Patients escalated to high-dose IFX (ie, 10 mg/kg) after a failure of at least 1 standard dose IFX (5 mg/kg) for irColitis at Memorial Sloan Kettering Cancer Center in New York City from 2016 to 2020 were retrospectively evaluated by electronic chart review. Patient charts were manually reviewed to determine patient characteristics, onset and severity of symptoms, and response to treatment with high-dose IFX. Clinical response was defined as improvement in diarrhea to CTCAE grade ≤1, namely an increase of less than 4 stools per day over baseline. Incomplete response was defined as improvement in diarrhea by at least 1 grade but not achieving clinical response. Mann-Whitney *U* test was used to compare groups and a *P*-value of <.05 was considered statistically significant.

Ten patients were treated with high-dose IFX for refractory irColitis (Table 1). Of these patients, 3 patients were treated with immunotherapy for melanoma, 3 for genitourinary cancer, 3 for lung cancer, and 1 patient for gynecological

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Table 1. Patient demographics.

Patient	Age at colitis onset	Sex	Cancer type	Cancer stage	Immunotherapy type (PD-1, PD-L1, combination anti-CTLA-4+ anti-PD-(L)1)	Time to colitis onset (days)	Time from colitis onset to IFX start (days)	Number of 5 mg/kg doses prior to 10 mg/kg dose(s)	Number of 10 mg/kg doses	10 mg/kg dose effective (0 = no, 1 = yes)
1	39	M	Lung	4	PD-1	190	90	2	1	Yes
2	47	M	Melanoma	4	Combination	13	8	2	1	No
3	76	F	Lung	4	Combination	119	2	4	1	Yes
4	56	F	Genitourinary	4	Combination	44	16	3	9[a]	Yes
5	42	M	Genitourinary	3	Combination	6	20	2	3[b]	Yes
6	66	M	Melanoma	4	Combination	78	19	2	1	No
7	79	F	Genitourinary	4	Combination	71	10	1	1	No
8	78	F	Melanoma	4	Combination	56	30	2	1	Yes
9	59	F	Lung	3	PD-L1	71	20	2	1	No
10	65	F	Endometrial	4	PD-1	252	9	1	2[c]	No

[a]High-dose IFX (10 mg/kg) was given as maintenance therapy concomitantly with resumption of ICI (single agent nivolumab).
[b]Clinical response achieved after first dose; 2 additional doses given for persistent G1 symptoms and endoscopic colitis.
[c]Tried 2 doses of high-dose IFX (10 mg/kg) before initiating therapy with vedolizumab.

cancer. The patients had been treated with immunotherapy for a median of 66 days (interquartile range [IQR] 21-147) and developed colitis at a median of 71 days after the first immune checkpoint inhibitor (ICI) dose (IQR 44-149). The median age of the patients was 62 years old (IQR 47-76) and the cohort included 6 males (60%) and 4 females (40%). Seven of the 10 patients were treated with combination CTLA-4/PD-1 treatment and 3 of the 10 patients were treated with anti-PD(L)-1 monotherapy.

High-dose IFX was started after a median of 2 (IQR 2-2) doses of IFX 5 mg/kg for patients with non-response (n = 2) or incomplete response (n = 8). Five (50%) patients had a clinical response to an initial high dose of IFX 10 mg/kg after a median of 4 (IQR 3-6) days. Five (50%) patients were refractory to one or more high doses of IFX and were treated with vedolizumab. Three of these 5 patients responded to vedolizumab and 2 did not respond and subsequently underwent fecal microbiota transplantation for persistent symptoms with good response. There were no significant differences between non-responders and responders to high-dose IFX in median body mass index (BMI; 23.7 vs 24.2, P = .53), albumin level (3.6 vs 3.7 g/dL, P = .6), or C-reactive protein (0.29 vs 0.79 mg/dL, P = .23) at the time of high-dose IFX. The patients were followed for a median of 457 (IQR 325-567) days from initiation of ICI therapy. No adverse events attributed to IFX were observed in any of the patients.

In summary, in this series of patients with irColitis refractory to standard dose IFX, high-dose IFX was successful in achieving clinical response of irColitis in 50% of patients. Dose escalation of IFX may therefore represent a viable therapeutic option for irColitis unresponsive to standard dose IFX. We observed that the median time to response after initiation of high-dose IFX was only 4 days, suggesting that response to treatment can be determined with little delay. There were no observed adverse events attributed to IFX for the duration of follow-up in these patients. Prospective studies are needed to further elucidate the role and optimal dosing of IFX in irColitis.

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Conflict of Interest

Michael A. Postow: BMS, Merck, Array BioPharma, Novartis, Incyte, NewLink Genetics, Aduro, Eisai, Pfizer (C/A), BMS, Merck (H), RGenix, Infinity, BMS, Merck, Array BioPharma, Novartis, AstraZeneca (RF [institutional]); **David M. Faleck:** Kaleido Biosciences,AzurRx Biopharma (C/A). Jessica P. Harris indicated no financial relationships.

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Author Contributions

Conception/Design: D.F. Collection and/or assembly of data: J.H. Data analysis and interpretation: J.H., M.P., D.F.

Manuscript writing: J.H., D.F. Final approval of manuscript: All authors.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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