Tofacitinib in Checkpoint Colitis


Summary

Immune checkpoint inhibitors (ICIs) are a novel class of therapies that promote anti-tumor immunity by regulating the immune system. They are increasingly used and highly effective against metastatic melanoma. Unfortunately, ICI enterocolitis (ICI-C) is a common complication of therapy that may require cessation of otherwise successful ICI treatment. ICI-C is often treated with steroids while reserving infliximab (IFX) for refractory ICI-C. Vedolizumab and fecal microbiota transplantation may also be effective. Bishu et al report that tofacitinib is effective for ICI-C. Four patients who developed steroid-dependent, biologic-refractory ICI-C after receiving ICIs for metastatic melanoma (n = 3) or lung adenocarcinoma (n = 1) were treated with tofacitinib.

Patient 1 developed prednisone-dependent ICI-C with a partial response to IFX (5–15 mg/kg) with relapse verified by computed tomography and endoscopy. He achieved steroid-free remission (SFR) and endoscopic remission within 4 weeks of starting tofacitinib. The patient was ICI-C free at 60 weeks after receiving tofacitinib (10 mg BID) for a total of 9 weeks.

Patient 2 started tofacitinib after 28 weeks of steroid dependence and promptly achieved SFR within 4 weeks. His symptoms recurred with dose reduction but abated following an increase in tofacitinib, suggesting a dose response. Follow-up endoscopy demonstrated complete remission, and he was ICI-C free 37 weeks after a total of 25 weeks of tofacitinib (5–10 mg BID).

Patient 3 developed prednisone-dependent ICI-C with a partial response to IFX (5 mg/kg x 3, 10 mg/kg x 2) and fluctuating fecal calprotectin (FCP) (> 1000 – 413 µg/g). Active ICI-C was verified by computed tomography and endoscopy. Tofacitinib was started, and the patient achieved clinical remission and normal FCP (< 30 µg/g) within 6 weeks.

Patient 4 developed severe ICI-C refractory to steroids, IFX (5 mg/kg x 2), vedolizumab (300 mg x 1), and ustekinumab (390 mg IV), eventually requiring parenteral nutrition. Notably, he had pre-existing mild Crohn disease, which had been managed off therapy for years without disease progression. He improved dramatically with tofacitinib, but relapsed with de-escalation, and then recaptured SFR with a dose increase. His course was complicated with ongoing malignancy and tofacitinib dose-reductions and increases, exhibiting similar responses each time.

Three patients achieved cancer remission before starting tofacitinib, all of whom remained cancer-free after treatment with tofacitinib. Patient #4 had not achieved cancer remission when he received tofacitinib, and his cancer progressed through ICI-C therapy. Treatment for ICI-C is based on expert guidelines and diverges from that for inflammatory bowel disease despite their similarities. Bishu et al found that tofacitinib was effective for ICI-C and even led to SFR in 1 patient having ICI-C refractory to multiple biologies. The patients responded within days and achieved SFR within weeks. Given the nascency of this approach for ICI-C and the risk of reducing anti-tumor immunity, the authors advise caution when considering tofacitinib for ICI-C. In most of the study patients, the malignancies were resolved before they started tofacitinib. Overall, the data suggest that tofacitinib can be effective for refractory ICI-C, and works quickly.

Clinical Practice Take-Home Points

- Tofacitinib is effective in refractory immune checkpoint inhibitor enterocolitis.
- Doses are 5-10 mg twice a day with possible dose reduction after achieving an initial response (similar to ulcerative colitis).
- The optimal therapy duration is uncertain.
- Tofacitinib should be used cautiously because it is not known if it impairs anti-tumor immunity.
Figure 1. Clinical Course. The clinical course (left panels) and associated modified Mayo score and prednisone dose (right panels) of patients 1-4 A-G, respectively. A modified Mayo score could not be easily computed in patient 4 due to the complex disease course. Time is presented as weeks after starting immune-check point inhibitor (ICI) therapy. Serial endoscopies (E) and computed tomography (CT) scans are denoted by number and the presence or absence of colitis is indicated as positive (+) or negative (-), respectively. Fecal calprotectin (FCP; mcg/g) at select times is shown.
Figure 2. Endoscopic Response. 
A) The endoscopic appearance of patients 1–3 pre- (top panels) and post- (bottom panels) tofacitinib is presented. 
B) The endoscopic progression of patient 4.
Both corticosteroids and tumor necrosis factor (TNF) antagonists can induce remission in patients with Crohn’s disease (CD). Data from several studies, including the COMMIT study, indicated very high rates of remission in patients with Crohn’s disease who were treated with steroids during anti-TNF induction, which led to the hypothesis that corticosteroid co-induction could enhance rates of remission in Crohn’s disease. As corticosteroids also have well recognized adverse effect profiles, it is important clinically to determine whether there is additive benefit of corticosteroids during anti-TNF induction.

In the absence of prospective, randomized data to inform corticosteroid use during induction therapy, Faleck et al used existing clinical trial data to shed additional light on this question. They conducted a systematic review and pooled meta-analysis using both individual and aggregated data from pivotal trials of anti-TNF induction therapy for Crohn’s disease. In a systematic search conducted through January 20, 2016, the authors identified 14 clinical trials for analysis (5 of adalimumab, 5 of certolizumab, and 4 of infliximab). They acquired individual participant data for the infliximab and adalimumab studies, and aggregated data from the certolizumab studies.

The authors found that the clinical response and clinical remission rates were comparable between groups of patients receiving vs not receiving concomitant corticosteroids during anti-TNF induction therapy. The combination of corticosteroids and an anti-TNF agent induced clinical remission in 32.0% of patients and a clinical response in 42.7%, whereas anti-TNF monotherapy induced clinical remission in 35.5% of patients and a clinical response in 46.8% (odds ratio [OR], 0.93; 95% CI, 0.74–1.17 for remission and OR 0.84; 95% CI, 0.73–0.96 for response). Additionally, the authors found no difference in outcomes after adjusting for the baseline Crohn’s disease activity index or use of an immunomodulator, or between patients receiving low-dose vs high-dose steroids.

These data suggest that a synergistic benefit of corticosteroids plus anti-TNF therapy in patients already dependent on or failing steroids is unlikely. These findings along with the known risks of corticosteroid use, both alone and in combination, led the authors to suggest that clinicians consider early weaning of corticosteroids during induction with anti-TNF therapy.
Figure 1. Meta-analysis Results. Forest plot quantifying odds ratio of remission (A) or clinical response (B) of an anti-TNF agent with concomitant use of steroids.