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Weighing harms, benefits, and alternatives for a young man with a recent flare of ulcerative colitis

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ABSTRACT A critical appraisal and clinical application of Sandborn WJ, Su C, Sands B, et al. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med.* 2017 May 4;376(18):1723-1736. doi: [10.1056/NEJMoa1606910](https://doi.org/10.1056/NEJMoa1606910)

Keywords: *ulcerative colitis, tofacitinib*

Clinical Context

Khalil Ahmed (pseudonym), a 23 year-old Arab-American male with ulcerative pancolitis, presented to the emergency department with rectal bleeding and left lower quadrant pain for three days. He reported that he had lost approximately two cups of blood per rectum during that time. Inflammatory markers were within normal limits with erythrocyte sedimentation rate 13 mm/hr and C-reactive protein 1.1 mg/L, but recent fecal calprotectin was elevated at 1,345 µg/g (N <50 µg/g). CBC, electrolytes, glucose, BUN, CO₂, and creatinine were within normal limits. He had been diagnosed with ulcerative pancolitis approximately eight months prior. Colonoscopy at his initial diagnosis showed an endoscopic subscore of stage 3 colitis on Mayo Score/Disease Activity Index for Ulcerative Colitis. This scoring tool rates the severity of disease from 0-12 with a maximum of 3 points in each category: stool frequency, rectal bleeding, appearance of the mucosa on endoscopy, and physician assessment of disease activity. At presentation to the emergency department, Mr. Ahmed had been receiving infliximab infusions every eight weeks and nightly mesalamine enemas. He was admitted to general medicine, and IV prednisolone therapy was initiated for treatment of ulcerative colitis flare. After four days of IV steroids and mesalamine enemas, sigmoidoscopy indicated endoscopic subscore of 3 on the Mayo Score from the anus to 40 cm proximal to the dentate line. He experienced continued improvement and was discharged after a total of seven days. Mr. Ahmed participated in his discharge plan and multiple options were discussed with the treatment team and the patient. One of the options included tofacitinib.

Clinical Question

Is tofacitinib an efficacious induction and maintenance therapy in achieving remission in moderate to severe ulcerative colitis?

Research Article

Sandborn WJ, Su C, Sands B, et al. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med.* 2017 May 4;376(18):1723-1736. doi: [10.1056/NEJMoa1606910](https://doi.org/10.1056/NEJMoa1606910)

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Related Literature

The literature review began by searching PubMed for the key terms “ulcerative colitis” and “tofacitinib” sorted by best match. This search yielded 86 results, including six relevant randomized controlled trials, one meta-analysis, and 41 review articles. The meta-analysis and 37 relevant review articles were perused for references and insights. An UpToDate search involving the key terms was performed, citing the three randomized control trials described in the article selected for appraisal.

The six randomized control trials were most heavily considered for appraisal given the solidity of their study designs. Three of these trials evaluated patients’ satisfaction with the drug.¹⁻³ Another article primarily studied fecal calprotectin as a biomarker for disease severity in patients on tofacitinib.⁴ The two remaining articles correlated disease severity with various tofacitinib doses, and were authored by the same principal investigator six years apart.^{5,6} The first article is a phase 2 clinical trial.⁵ The second article was selected for appraisal because it reports on three new phase 3 trials that stem from the aforementioned phase 2 trial, and it includes larger study sizes. These studies were multi-center randomized, double-blind, placebo-controlled studies spanning four years. They specify that patients had to have failed prior therapy and specifically focuses on moderate to severe ulcerative colitis, which applies to the previously described clinical scenario.⁶

Critical Appraisal

The selected article reports on three multi-center randomized, double-blind, placebo-controlled trials spanning from 2012-2016: OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain. According to the Strength of Recommendation Taxonomy (SORT), these studies have a strength recommendation of A and level 1 evidence.⁷

These trials were funded by Pfizer and were designed by Pfizer staff and the principal academic investigators. Data was collected by ICON, a contracted research organization and was analyzed by Pfizer personnel. Pfizer and the principal academic investigators interpreted the data. Pfizer has patented tofacitinib, which could be a source of funding bias in evaluating data. Notably, measures were taken to employ assistance and opinions of unbiased investigators, and all parties were sufficiently blinded. With this level of sponsorship involvement, physicians must be very skeptical when trying to use this evidence.

Patients recruited in OCTAVE Induction 1 and Induction 2 were adults with at least a four-month history of ulcerative colitis with moderate to severe disease (total Mayo Score of 6-12 with a rectal bleeding subscore of 1-3 and an endoscopic subscore of 2-3). Patients were required to have experienced failed prior therapy or adverse effects on glucocorticoids, azathioprine, mercaptopurine, infliximab, or adalimumab. Exclusion criteria included Crohn’s disease, ulcerative colitis localized to the distal 15 cm of the colon, toxic megacolon, signs of fulminant colitis, and indeterminate, microscopic, ischemic, or infectious colitis. Patients taking concomitant TNF-alpha antagonists, azathioprine, methotrexate, or mercaptopurine were excluded.⁶ These criteria would exclude the patient described in this case because of his current use of the TNF-alpha antagonist infliximab.

The goal of OCTAVE Induction 1 and Induction 2 was to investigate the efficacy of tofacitinib during the induction phase. The primary end point was remission, defined as total Mayo Score ≤ 2 with no subscore >1 and a rectal bleeding subscore of 0 after eight weeks. Doses were carefully selected based on data from the aforementioned phase 2 trial investigating tofacitinib in ulcerative colitis in 2012.⁵ There were 614 and 547 patients in Induction 1 and Induction 2 respectively. The patients in each trial were randomized to placebo, 10 mg twice daily, or 15 mg twice daily for eight weeks. The 15 mg arm was discontinued because of feedback on this dose in rheumatoid arthritis. Central telerandomization was used to assign patients to the tofacitinib or placebo arm in a 4:1 ratio. Data was stratified based on patients’ prior treatment with TNF-alpha antagonists, glucocorticoid use at study baseline, and geography.⁶

In OCTAVE Induction 1, remission was achieved in 8.2% of placebo and 18.5% in the 10 mg group (NNT = 10). In OCTAVE Induction 2, 3.6% of patients in the placebo group went into remission compared to 16.6% in the 10 mg group (NNT = 8).⁶

The goal of OCTAVE Sustain was to investigate maintenance therapy of ulcerative colitis using tofacitinib. Patients with a clinical response to the drug in OCTAVE Induction 1 or Induction 2 were eligible, thus 593 patients were randomized to placebo or 10 mg twice daily for 52 weeks (Figure 1). It is difficult to track patients from the initial induction trials to the OCTAVE Sustain trial because there is little transparency in what was considered to be “clinical response.” Doses were selected based off of clinical response to 10 mg in the induction trials, which was also halved to 5 mg to reflect results at a lower dose. Patients were randomized in a 1:1:1 ratio



using central telerandomization. Data was stratified according to whether patients were assigned to placebo or experimental group in the induction trial, as well as their current remission status. The final patient population of Octave Sustain included a well-rounded representation of patients with varying extent of disease, patients who were or were not using oral glucocorticoids at baseline, patients who had been previously treated with a TNF-alpha antagonist, and patients with previous treatment failure from either a TNF-alpha antagonist, a glucocorticoid, or non-biologic immunosuppressants such as azathioprine or mercaptopurine. Notably, there was a larger representation of male patients (58.6% in the placebo arm, 52.0% in the 5 mg arm, and 55.8% in the 10 mg arm).

After 52 weeks, remission occurred in 11.1% of patients in the placebo group, 34.3% the 5 mg group, and 40.6% of the 10 mg group (NNT = 4 for the 5 mg group and NNT = 3 for the 10 mg group). However, adverse events were reported in 72.2% of patients in the 5 mg group, 79.6% in the 10 mg group, and 75.3% in the placebo group in OCTAVE Sustain. Among all three groups of OCTAVE Sustain, the most frequently reported adverse events were worsening ulcerative colitis, nasopharyngitis, arthralgia, and headache. Other common adverse effects included infection, including two serious infections in the 5 mg group and two in the placebo group. There was also one cardiovascular event reported in both the 5 mg and 10 mg groups and three cases of non-melanoma skin cancer in the 10 mg group of OCTAVE Sustain. The adverse events reported for OCTAVE Induction 1 and 2 were comparable, however there was one reported case of intestinal perforation in the 10 mg group of Induction 1 and one case in the placebo group of Induction 2. A full summary of adverse events in each trial can be viewed in Table 4 of the article.⁶ Intestinal perforation is a serious adverse event, especially in patients with active inflammatory bowel disease. The risk of perforation must be considered along with all other risks and compared to the benefits of the drug on an individual basis, depending on the patient's past medical history, immune system strength, and treatment goals.

Clinical Application

These studies strongly support tofacitinib's efficacy in induction and maintenance therapy of ulcerative colitis.⁶ They do not compare their outcomes to the traditional standards of care in ulcerative colitis as the patients in the studies failed prior therapies. Therefore, this article should not be used to compare tofacitinib to standard drugs for ulcerative colitis in all patients.

Mr. Ahmed was a 23-year-old who had failed infliximab therapy and had experienced to adverse side effects of azathioprine. Failed prior therapy or adverse effects of these drugs were part of the inclusion criteria for the article described. He would not have met the full inclusion criteria because he was currently receiving infliximab infusions, but this article can still be useful in determining if patients like him could benefit from tofacitinib therapy.

During his hospital stay, the gastrointestinal medical and surgery teams were consulted to inform Mr. Ahmed of all of his options. He declined colectomy because of his young age and potential complications, including a permanent ostomy site. The primary team discussed his decision at length with him and his family, who also agreed that medical therapy was most appropriate. The primary team also spent significant time explaining to him how the drugs work because to his interest in learning about his care. Not only was the team able to support this patient emotionally and physically during this challenging time, we were able to support his decision with recent and trusted data.

Mr. Ahmed's discharge plan was ultimately tailored to his and his family's concerns and preferences. His medical plan included a two-week course of prednisone and continued nightly mesalamine enemas. Drugs that were discussed included the immunotherapeutic drugs infliximab and azathioprine, as well as the Janus kinase inhibitor tofacitinib. Because of failed treatment on infliximab and the inconvenience of infusions, as well as adverse events he had experienced from azathioprine, the patient and care team decided against these agents. However, tofacitinib had been recently investigated in various studies supporting its use in ulcerative colitis and had recently been FDA approved for this purpose. There are many adverse effects associated with tofacitinib, which must be considered when initiating therapy. Mr. Ahmed's disease was refractory and therefore the benefit of tofacitinib outweighed the risks of his disease worsening if he did not initiate a new drug. Adverse effects include increased risk for both common and opportunistic infections, active tuberculosis, cancer, worsening ulcerative colitis, arthralgias, headaches, and intestinal perforation.⁶ Mr. Ahmed was young and otherwise healthy without



significant risk factors, so he was therefore initiated on 10 mg oral tofacitinib twice daily and was scheduled for close follow-up with his gastrointestinal physician. This case serves as an example of the shared decision-making and using recent evidence to provide excellent care.

Learning points:

1. Tofacitinib is an efficacious drug in achieving and maintaining remission of ulcerative colitis, but physicians must compare the benefit of the drug with the risk of the patient experiencing an adverse outcome based off of the patient's past medical history and goals of treatment.⁶
2. Patient preference must be the primary consideration used in conjunction with shared decision-making.
3. Use of Janus kinase inhibitors, immunotherapy, and DMARDs in ulcerative colitis is currently an area of proliferative research, and clinicians must educate themselves on recently used and further appropriate therapies for their patients.

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