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Successful initial tofacitinib treatment for acute severe ulcerative colitis with steroid resistance: a case series

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Abstract

Background The standard therapy for acute severe ulcerative colitis (ASUC) is intravenous corticosteroids; however, 30% of ulcerative colitis (UC) patients do not recover with corticosteroids alone. Few studies have reported the efficacy and safety of tofacitinib for ASUC with steroid resistance. We report a case series of successful first-line treatment consisting of tofacitinib (20 mg/day) administered to ASUC patients with steroid resistance.

Methods Patients diagnosed with ASUC at our institution between October 2018 and February 2020 were retrospectively evaluated. They were administered a high dose of tofacitinib (20 mg) after showing no response to steroid therapy in a dose of 1-1.5 mg/kg/day.

Results Eight patients with ASUC, 4 (50%) men, median age 47.1 (range 19-65) years, were included. Four patients were newly diagnosed, and the median UC duration was 4 (range 0-20) years. Six of the 8 patients were able to avoid colectomy. One patient (patient 2) had no response; however, remission was achieved after switching from tofacitinib to infliximab. One patient (patient 6) with no response to tofacitinib underwent total colectomy. Only one patient (patient 4) experienced an adverse event, local herpes zoster, treated with acyclovir without tofacitinib discontinuation.

Conclusions Clinical remission without serious adverse events can be achieved with high probability and colectomy can be avoided by first administering high-dose tofacitinib to steroid-resistant ASUC patients. Tofacitinib may be one of the first-line treatment options for steroid-resistant ASUC.

Keywords Tofacitinib, JAK inhibitor, acute severe ulcerative colitis, steroid resistance, case series

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Introduction

Acute severe ulcerative colitis (ASUC), defined using the Trulove Witts criteria [1], is an emergent condition. A total of 25% of all ulcerative colitis (UC) patients are admitted to the hospital with ASUC [2]. The standard therapy for ASUC is intravenous corticosteroids; however, 30% of UC patients will not recover with corticosteroids alone [3]. Infliximab or a calcineurin inhibitor is also indicated to decrease the rates of colectomy among hospitalized ASUC patients [4,5]. Although a previous publication showed that moderate-to-severe UC had a rapid response to tofacitinib [6], few studies have reported the efficacy and safety of tofacitinib for ASUC.

Recently, tofacitinib has been administered for the maintenance of moderate-to-severe UC. A phase II randomized trial showed that tofacitinib is a quick-acting oral medicine containing the small-molecule Janus kinase (JAK) inhibitor [7-9]. JAK mediates signal transduction activity by multiple cytokines (interleukin [IL]-2, IL-4, IL-7, IL-9, IL-15, and IL-21). Tofacitinib directly inhibits signaling of an important subset of proinflammatory cytokines [10] and is quickly consumed because of its short half-life of 3.2 h; therefore, it provides the theoretical benefit of minimizing intraoperative and postoperative incidents because it would be cleared before colectomy, even in urgent cases [11]. We report

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Conflict of Interest: None

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a case series of successful first-line treatment comprising high-dose tofacitinib (20 mg/day) administered to ASUC patients with steroid resistance.

Patients and methods

Patients diagnosed with ASUC at our institution between October 2018 and February 2020 were retrospectively evaluated. They were administered tofacitinib (20 mg) after showing no response to steroid therapy in a dose of 1-1.5 mg/kg/day. The steroid dose for the patients in this case series was 40-50 mg/day. The case series also includes one thiopurine user (patient 1). The patients were screened for cardiovascular or thrombotic problems before tofacitinib treatment. All underwent a laboratory examination, stool testing for *Clostridioides difficile*, and endoscopic biopsies for cytomegalovirus. Tofacitinib has 70% hepatic metabolism and 30% renal metabolism; therefore, patients with hepatic dysfunction and renal dysfunction require a reduced dose. During this case series, no patient required a dose reduction.

The UC Disease Activity Index (UCDAI) [12] and Mayo scoring system [13] were used to determine the severity of the patients' general condition. Defecation frequency, rectal bleeding, mucosal appearance on colonoscopy, physician's rating of disease activity, gastrointestinal symptoms, adverse events, and drug changes were recorded. Adverse events were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. A clinical response was defined as an improvement of 3 points or more in the UCDAI and Mayo scores. Clinical remission was defined as a UCDAI score and Mayo score of 2 points or less.

The authors declare that the patients described in this case presentation have given their written consent for their personal or clinical details to be published in this study, along with any identifying images. This study was approved by the appropriate ethics committee (details blinded for peer review). This research was carried out in accordance with the Declaration of Helsinki.

Results

This report included a total of 8 patients with ASUC, 4 (50%) men, with a median age of 47.1 (range 19-65) years. Four patients were newly diagnosed with UC, and the median UC duration was 4 (range 0-20) years. All patients were bio-naïve before starting tofacitinib. Table 1 summarizes the baseline characteristics and laboratory data of the 8 patients. Relevant clinical data were retrospectively evaluated from the patients' electronic medical records. A clinical response was observed in 6 of the 8 patients before they experienced remission. Six patients were able to avoid colectomy. One patient (patient 2) had no response; however, remission was achieved after switching from tofacitinib to infliximab. One patient (patient 6) with no response to tofacitinib underwent total colectomy. When we used tofacitinib during induction and the follow-up phase, only one patient (patient 4) experienced a major adverse

Table 1 Baseline characteristics of patients

Patient	Sex	Age, years	UC duration, years	Previous treatment	Disease type	Length of hospital stay, weeks	Tofacitinib effect	Stool frequency	UCDAI	Mayo score	MES	Complication
1	Male	60	7	5-ASA intolerance, AZA	Total colitis	4	Response	15	12	12	3	None
2	Female	19	First onset	None	Total colitis	5	No response	10	12	12	3	None
3	Female	53	20	5-ASA	Total colitis	7	Response	10	12	12	3	None
4	Female	52	2	5-ASA	Total colitis	6	Response	15	12	12	3	Herpes zoster
5	Male	65	First onset	None	Total colitis	4	Response	15	12	12	3	None
6	Male	20	3	5-ASA intolerance, none	Total colitis	4	No response	15	12	12	3	None
7	Male	57	First onset	None	Total colitis	5	Response	10	12	12	3	None
8	Female	51	First onset	None	Total colitis	4	Response	15	12	12	3	None

5-ASA, 5-aminosalicylic acid; AZA, azathioprine; Hb, hemoglobin; UCDAI, Ulcerative Colitis Disease Activity Index; MES, Mayo endoscopic subscore

event, herpes zoster, treated with acyclovir without stopping tofacitinib.

Patient 1 was a 60-year-old man admitted to the hospital on February 1, 2020. His previous treatment was azathioprine because of intolerance to 5-aminosalicylic acid (5-ASA). The test results showed C-reactive protein (CRP) 19.3 mg/dL, albumin (Alb) 1.8 g/dL, and hemoglobin (Hb) 8.4 g/dL. His UCDAI score and Mayo score were 12. He underwent colonoscopy (Fig. 1A) and was administered tofacitinib after steroid resistance was observed. A clinical response was observed after approximately 3 days of treatment. He was discharged from the hospital after clinical remission on March 3, 2020 (Fig. 1B).

Patient 2 was a 19-year-old woman admitted to the hospital on May 16, 2020. She had not been treated previously and was experiencing her first onset of acute UC. The test results showed CRP 7.1 mg/dL, Alb 2.0 g/dL, and Hb 4.7 g/dL. Her UCDAI score and Mayo score were 12. She was given tofacitinib after steroid resistance was observed. She showed no clinical response to tofacitinib, but after switching from tofacitinib to infliximab (5 mg/kg) remission was achieved in 5 days. She had an excellent response to infliximab and was discharged from the hospital in clinical remission on June 25, 2020.

Patient 3 was a 53-year-old woman admitted to the hospital on October 24, 2018. Her previous treatment was 5-ASA. The test results showed CRP 7 mg/dL, Alb 2.7 g/dL, and Hb 8.6 g/dL. Her UCDAI score and Mayo score were 12. She underwent colonoscopy (Fig. 2A) and was administered tofacitinib after steroid resistance was observed. A clinical response was observed after approximately 2 days of treatment. She was discharged from the hospital after clinical remission on December 14, 2018 (Fig. 2B).

Patient 4 was a 52-year-old woman admitted to the hospital on August 1, 2019. Her previous treatment was 5-ASA. The test results showed CRP 24.1 mg/dL, Alb 1.3 g/dL, and Hb 6.3 g/dL. Her UCDAI score and Mayo score were 12. She underwent colonoscopy (Fig. 3A) and was administered tofacitinib after steroid resistance was observed. A clinical response was observed after approximately 4 days of treatment. She developed local herpes zoster, against which she had never been vaccinated. However, she was cured with an antiviral drug combination, without stopping tofacitinib. She was discharged from the hospital after clinical remission on September 18, 2019 (Fig. 3B).

Patient 5 was a 65-year-old man admitted to the hospital on August 1, 2019. He had not received previous treatment and was experiencing his first onset of acute UC. He was referred to the hospital by his former physician because of severe bloody stools. The test results showed CRP 3 mg/dL, Alb 2.7 g/dL, and Hb 9.3 g/dL. His UCDAI score and Mayo score were 12. He underwent colonoscopy (Fig. 4A) and was given tofacitinib after steroid resistance was observed. A clinical response was observed after 3 days of treatment. He was discharged from the hospital after clinical remission on December 8, 2019 (Fig. 4B).

Patient 6 was a 20-year-old man admitted to the hospital on November 25, 2019. He had not received previous treatment because of intolerance to 5-ASA. The test results showed CRP 24.1 mg/dL, Alb 1.3 g/dL, and Hb 6.3 g/dL. His UCDAI score and Mayo score were 12. He was given tofacitinib after steroid resistance was observed. He showed no clinical response to tofacitinib, but remission was not achieved after switching from tofacitinib to infliximab after 5 days. However, there was no clinical response to infliximab. Finally, he underwent total colectomy. He was discharged

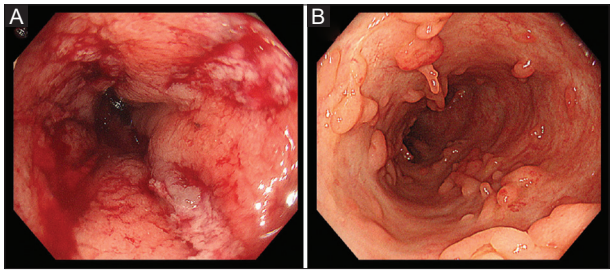

Figure 1 Comparison of 2 colonoscopies of patient 1. (A) February 1, 2020; (B) March 3, 2020

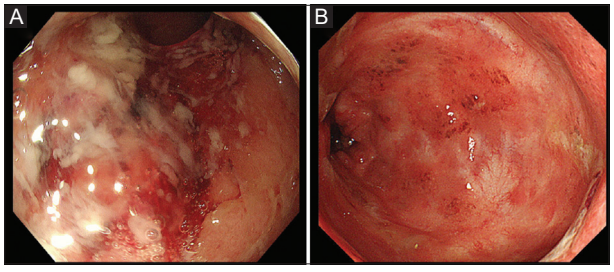

Figure 2 Comparison of 2 colonoscopies of patient 3. (A) October 24, 2018; (B) December 14, 2018

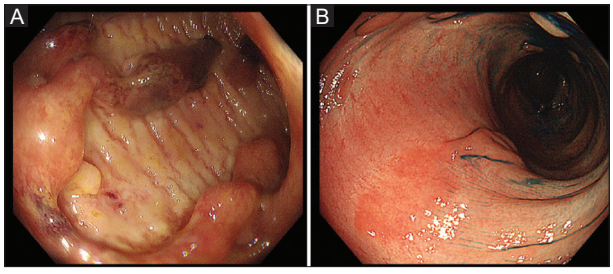

Figure 3 Comparison of 2 colonoscopies of patient 4. (A) August 1, 2019; (B) September 18, 2019

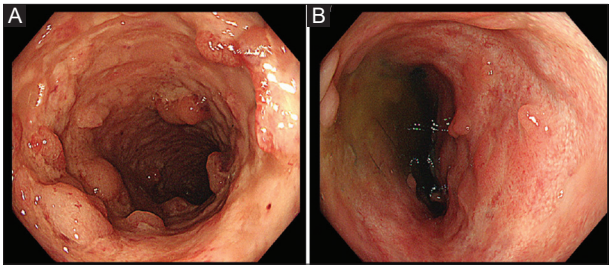

Figure 4 Comparison of 2 colonoscopies of patient 5. (A) August 1, 2019; (B) December 8, 2019

from the hospital after clinical remission on December 25, 2019.

Patient 7 was a 65-year-old man admitted to the hospital on November 18, 2020. He had not received treatment previously and was experiencing his first onset of acute UC. He was referred to the hospital by his former physician because of severe bloody stools The test results showed CRP 15.8 mg/dL, Alb 1.4 g/dL, and Hb 8.7 g/dL. His UCDAI score and Mayo score were 12. He was given tofacitinib after steroid resistance was observed. A clinical response was observed after approximately 3 days of treatment. He was discharged from the hospital after clinical remission on December 26, 2020.

Patient 8 was a 51-year-old man admitted to the hospital on January 30, 2021. He had not been given any previous treatment because of intolerance to 5-ASA. The test results showed CRP 5.6 mg/dL, Alb 1.4 g/dL, and Hb 9.6 g/dL. His UCDAI score and Mayo score were 12. He underwent colonoscopy (Fig. 5A) and was given tofacitinib after steroid resistance was observed. A clinical response was observed after approximately 5 days of treatment. He was discharged from the hospital after clinical remission on February 27, 2021 (Fig. 5B).

Discussion

There is no consensus regarding which biologic drugs, including anti-tumor necrosis factor (TNF)-α antibodies and calcineurin inhibitors, should be first administered to treat ASUC. Retrospective studies of case reports have shown that tofacitinib is useful for hospitalized patients who have received previous treatment for ASUC [14-16]. This study describes patients with steroid resistance who were first administered tofacitinib for ASUC. It is reported that tofacitinib is a good clinical response rate of 8 week was 57.6%/remission rate was 17.6% with a relatively severe UC background (Mayo score of 8±1.7) with an OCTAVE in an international joint phase 3 study with an induction 1 & 2 [7]. Therefore, tofacitinib is one of the possible treatments for ASUC. The results are not so different from those of anti-TNF. All but one of the patients in this case series were able to avoid total colectomy. Infliximab and calcineurin inhibitors have been reported as possible treatments for ASUC, but they have a long half-life and require more time before their efficacy can be judged [4,17]. Because tofacitinib has a very short half-life of 3.2 h, it is possible to judge its efficacy more quickly compared to infliximab and calcineurin inhibitors. The short half-life of tofacitinib is beneficial because a response can be observed only 3-5 days after its administration. During this case series, we could determine whether to continue tofacitinib or switch from tofacitinib to infliximab or a calcineurin inhibitor after only 3-5 days of observation (Fig. 6).

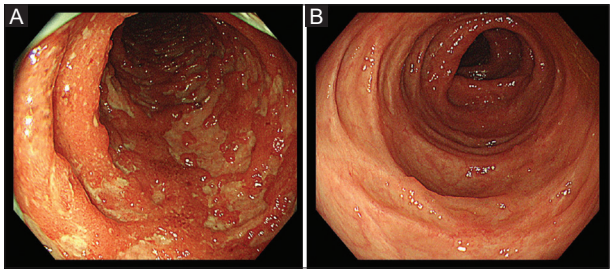

Figure 5 Comparison of 2 colonoscopies of patient 8. (A) January 30, 2021; (B) February 27, 2021

Infliximab, which mainly targets IL-6, may be effective when tofacitinib, which mainly targets IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21, has no effect [18]. Tofacitinib and infliximab may thus have a complementary relationship (Fig. 7).

The concomitant use of tofacitinib with other immunosuppressive therapeutic agents (thiopurine preparation, calcineurin inhibitor, anti-TNF-α antibody) is contraindicated. Therefore, we think it is reasonable to first consider tofacitinib (half-life 3.2 h) for ASUC before attempting treatment with infliximab (half-life 8.1 days) or a calcineurin inhibitor (half-life 34 h).

According to our previous experience, a UC patient with steroid-resistant idiopathic thrombocytopenic purpura can experience exacerbation of the condition. The first administration of tofacitinib to the patient achieved clinical remission and maintained remission of UC and idiopathic thrombocytopenic purpura for more than 1 year. Whole-transcriptomic sequencing was performed for this patient because of inflamed rectal mucosa indicated by biopsy results before and after JAK inhibitor administration. It was suggested that the distinct molecular signatures were JAK inhibitors and an anti-TNF-α antibody [19]. This would indicate a complementary relationship between JAK inhibitors and the anti-TNF-α antibody. As in Patient 2, although tofacitinib did not have any effect, infliximab was effective. However, more cases need to be investigated to prove this complementary relationship.

Regarding side effects, tofacitinib can induce severe lymphocytosis, anemia, herpes zoster infection, increased serum lipid level, or thrombosis. Although the patients in our case series did not have serious adverse events, patient 4 developed local herpes zoster because there was no time to administer a vaccine. However, infliximab and calcineurin inhibitors entail a similar possibility of exacerbating herpes zoster. Additionally, patients with a risk of thrombophilia were treated with heparin antithrombotic therapy to protect against a thrombotic event.

This study had some limitations. First, the sample size was small. Second, this was a single-center, retrospective case series. Although only 1% of UC cases are ASUC [20], 4 of the 8 ASUC patients in this case series (50%) were experiencing their first onset of acute UC and 2 (25%) were intolerant to 5-ASA. These results provide interesting patient background.

In addition, according to OECD health data, the length of hospital stay in Japan (34.7 days) tends to be longer compared to Europe (UK 8.7 days), and the United States (6.4 days). Since our ASUC patients included cases of the fulminant type, the average hospitalization period was 4 weeks or more. The longest hospital stay was 7 weeks.

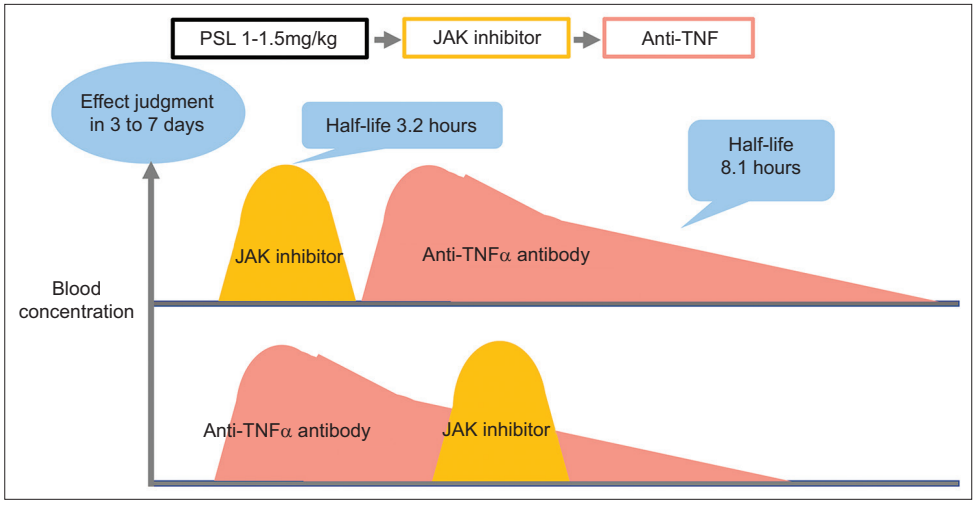

Figure 6 Treatment recommendation for acute severe ulcerative colitis with steroid resistance
PSL, XXX; TNF, tumor necrosis factor

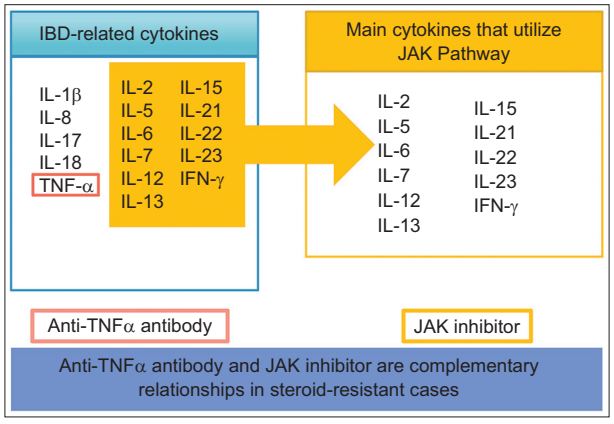

Figure 7 Cytokines involved in the pathology of inflammatory bowel disease [18]
IBD, inflammatory bowel disease; IL, interleukin; IFN, interferon; TNF, tumor necrosis factor IBD, inflammatory bowel disease; IL, interleukin; IFN, interferon; TNF, tumor necrosis factor

Although the number of ASUC cases is very small, further multicenter studies must be performed to confirm the safety and efficacy of tofacitinib for its treatment. Initial administration of tofacitinib to steroid-resistant patients with ASUC was able to avoid total colectomy in 6 of 8 patients in this case series. If tofacitinib is started first, the effect can be judged within a short period of time (3-5 days), and anti-TNF can be safely administered without overlap. It should be noted that, if anti-TNF is administered in advance, it takes time to wash out and start tofacitinib.

In conclusion, a high rate of clinical remission can be achieved and colectomy can be avoided by first administering tofacitinib to steroid-resistant ASUC patients. Evaluation of tofacitinib for steroid-resistant ASUC and the efficacy associated with sequential drug transition needs to be demonstrated in multicenter studies in the near future.

Summary Box

What is already known:

- Only 1% of ulcerative colitis (UC) cases are acute severe UC (ASUC)
- The standard therapy for ASUC is intravenous corticosteroids; however, 30% of UC patients will not recover with corticosteroids alone
- Infliximab and calcineurin inhibitors have been reported as possible treatments for ASUC, but they have a long half-life and require more time before their efficacy can be judged
- Tofacitinib directly inhibits signaling of an important subset of proinflammatory cytokines

What the new findings are:

- Tofacitinib is one of the possible first-line treatments for ASUC with steroid resistance
- All but one of our patients was able to avoid total colectomy in this case series
- The very short half-life of tofacitinib is beneficial, because a response can be observed only 3-5 days after its administration in a real clinical case series
- A high rate of clinical remission can be achieved without severe adverse events, and colectomy can be avoided, by initial administration of high-dose tofacitinib

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