# Successful initial high-dose 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 UC patients do not recover with corticosteroids alone. Infliximab or cyclosporin is indicated to decrease the rates of colectomy of hospitalized ASUC patients. Although a previous study showed that moderate to severe UC had a rapid response to tofacitinib, few studies have reported the efficacy and safety of tofacitinib for ASUC.

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

## Case presentation

Patients diagnosed with ASUC at our institution between October 2018 and February 2020 were retrospectively evaluated. They were administered high dose of tofacitinib (20 mg) after they had no response to steroid therapy comprising a dose of 1 to 1.5 mg/kg/day. This study included a total of eight patients with ASUC. There were four (50%) men and four (50%) women with a median age of 47.1 years (range, 19–65 years). All patients had a median UC duration of 4 years (range, 0–20 years). Four patients had no previous history of UC.

A clinical response was observed in six of the eight 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 event, herpes zoster, which was treated with acyclovir without stopping tofacitinib.

## Conclusion

Clinical remission can be achieved with high probability and colectomy can be avoided by administering high-dose tofacitinib to steroid-resistant ASUC patients.

# Background

Acute severe ulcerative colitis (ASUC), which is determined 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 cyclosporin is indicated to decrease the rates of colectomy of 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 comprising the small-molecule Janus kinase (JAK) inhibitor (7,8,9). 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 pro-inflammatory cytokines (10,19) and is quickly consumed because of its short half-life of 3.2 hours; 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 a case series of successful first-line treatment comprising high-dose tofacitinib (20 mg/day) administered to ASUC patients with steroid resistance.

# Case Presentation

Patients diagnosed with ASUC at our institution between October 2018 and February 2020 were retrospectively evaluated. They were administered high-dose tofacitinib (20 mg) after they had no response to steroid therapy comprising a dose of 1 to 1.5 mg/kg/day. Screening was performed to confirm that these patients had no cardiovascular system or thrombotic system problems before tofacitinib treatment. All patients underwent a laboratory examination, stool testing for *Clostridium 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 patients required a dose reduction.

This study included a total of eight patients with ASUC. There were four (50%) men and four (50%) women with a median age of 47.1 years (range, 19-65 years). All patients had a median UC duration of 4 years (range, 0-20 years). Four patients had not experienced UC previously. All patients were bio-naïve before starting tofacitinib. Table 1 summarizes the baseline characteristics and laboratory data of the eight patients. Relevant clinical data were retrospectively surveyed by evaluating the electronic medical records of the patients. The Ulcerative Colitis Disease Activity Index (UCDAI) (12) and Mayo scoring system (13) were used to confirm the severity of the general condition of the patients. 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 determined as an improvement of 3 points or more in the UCDAI score and Mayo score. Clinical remission was determined as a UCDAI score and Mayo score of 2 points or less.

[insert Table 1 near here]

A clinical response was observed in six of the eight 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 event, herpes zoster, which could be 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) of 193 mg/dL, albumin (Alb) of 1.8 g/dL, and hemoglobin (Hb) of 8.4 g/dL. His UCDAI score and Mayo score were 12. He underwent colonoscopy (Figure 1a) and was administered tofacitinib after steroid resistance was observed. A clinical response was observed approximately 3 days after treatment administration. He was discharged from the hospital after clinical remission on March 3, 2020 (Figure 1b).

[insert Figure 1 near here]

Patient 2 was a 19-year-old woman admitted to the hospital on May 16, 2020. She had not been administered treatment previously and experienced her first onset of acute UC. The test results showed CRP of 71 mg/dL, Alb of 2.0 g/dL, and Hb of 4.7 g/dL. Her UCDAI score and Mayo score were 12. She was administered tofacitinib after steroid resistance was observed. Because there was no clinical response to tofacitinib, remission was achieved after switching from tofacitinib to infliximab (5mg/kg) at 5 days after its administration. She had a great response to infliximab and was discharged from the hospital after 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 of 7 mg/dL, Alb of 2.7 g/dL, and Hb of 8.6 g/dL. Her UCDAI score and Mayo score were 12. She underwent colonoscopy (Figure 2a) and was administered tofacitinib after steroid resistance was observed. A clinical response was observed approximately 2 days after treatment administration. She was discharged from the hospital after clinical remission on December 14, 2018 (Figure 2b).

[insert Figure 2 near here]

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 of 241 mg/dL, Alb of 1.3 g/dL, and Hb of 6.3 g/dL. Her UCDAI score and Mayo score were 12. She underwent colonoscopy (Figure 3a) and was administered tofacitinib after steroid resistance was observed. A clinical response was observed approximately 4 days after treatment administration. She developed herpes zoster as she had never been vaccinated for it. However, she was cured with anti-viral drug combination, without stopping tofacitinib. She was discharged from the hospital after clinical remission on September 18, 2019 (Figure 3b).

[insert Figure 3 near here]

Patient 5 was 65-year-old man admitted to the hospital on August 1, 2019. He had not been administered treatment previously and experienced 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 of 3 mg/dL, Alb of 2.7

g/dL, and Hb of 9.3 g/dL. His UCDAI score and Mayo score were 12. He underwent colonoscopy (Figure 4a) and was administered tofacitinib after steroid resistance was observed. A clinical response was observed 3 days after treatment administration. He was discharged from the hospital after clinical remission on December 8, 2019 (Figure 4b).

[insert Figure 4 near here]

Patient 6 was a 20-year-old man admitted to the hospital on November 25, 2019. He had not been administered previous treatment because of intolerance to 5-ASA. The test results showed CRP of 241 mg/dL, Alb of 1.3 g/dL, and Hb of 6.3 g/dL. His UCDAI score and Mayo score were 12. He was administered tofacitinib after steroid resistance was observed. Because there was no clinical response to tofacitinib, remission was achieved after switching from tofacitinib to infliximab at 5 days after its administration. However, there was no clinical response to infliximab. Finally, he underwent total colectomy. He was discharged 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 been administered treatment previously and experienced 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 of 15.8 mg/dL, Alb of 1.4 g/dL, and Hb 8.7 of g/dL. His UCDAI score and Mayo score were 12. He was administered tofacitinib after steroid resistance was observed. A clinical response was observed approximately 3 days after treatment administration. 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 administered any previous treatment because of intolerance to 5-ASA. The test results showed CRP of 5.6 mg/dL, Alb of 1.4 g/dL, and Hb of 9.6 g/dL. His UCDAI score and Mayo score were 12. He underwent colonoscopy (Figure 5a) and was administered tofacitinib after steroid resistance was observed. A clinical response was observed approximately 5 days after treatment administration. He was discharged from the hospital after clinical remission on February 27, 2021 (Figure 5b).

# Discussion And Conclusions

There is no consensus regarding which biologic drugs, including anti-tumor necrosis factor (TNF)-α antibody and vedolizumab, should be first administered to treat ASUC. Retrospective studies of case reports have shown that tofacitinib is useful for hospitalized patients who have been administered previous treatment for ASUC (14-16). This study describes patients who were first administered tofacitinib for ASUC that was steroid-resistant. Tofacitinib is one of the possible treatments for ASUC. All but one of the patients in this case series was able to avoid total colectomy. Infliximab and cyclosporin 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 short half-life of 3.2 hours, it is possible to judge its efficacy more quickly compared to infliximab and cyclosporin. The short half-life of tofacitinib is beneficial because a response can be observed only 3 to 5 days after its administration.

During this case series, we could determine whether to continue tofacitinib or switch from tofacitinib to infliximab after only 3 to 5 days of observation.

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 have a complementary relationship because infliximab may be effective when tofacitinib achieves no response.

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 hours) for ASUC before attempting treatment with infliximab (half-life: 8.1 days) or cyclosporin (half-life: 7.4 hours).

UC patients with steroid-resistant idiopathic thrombocytopenic purpura can experience exacerbation of their condition. During our experience, one patient first administrated tofacitinib 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 anti-TNF-α antibody (19). This would indicate a complementary relationship between tofacitinib and anti-TNF-α antibody. However, more cases need to be investigated to prove this complementary relationship.

Regarding side effects, as patient 4’s case in the ASUC case series, there was no time to administer vaccine for herpes zoster. However, a similar possibility of exacerbating herpes zoster exists with infliximab as well. Additionally, patients with a risk of thrombophilia were treated with heparin anti-thrombotic therapy to protect from 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), four of the eight ASUC patients (50%) in this cases series experienced their first onset of acute UC and two of the eight patients (25%) were intolerant to 5-ASA. These results provide interesting evidence. Although the number of ASUC cases is small, further controlled, multi-center studies must be performed to confirm the safety and efficacy of tofacitinib for its treatment.

In conclusion, clinical remission could be achieved with high probability and colectomy could be avoided by first administering high-dose tofacitinib to steroid-resistant ASUC patients.

# Abbreviations

Acute severe ulcerative colitis (ASUC)

ulcerative colitis (UC)

Janus kinase (JAK)

Ulcerative Colitis Disease Activity Index (UCDAI)

Common Terminology Criteria for Adverse Events (CTCAE)

5-aminosalicylic acid (5-ASA)

C-reactive protein (CRP)

albumin (Alb)

hemoglobin (Hb)

anti-tumor necrosis factor (TNF)

# Declarations

### Ethical approval and consent to participate

The authors declare that the patients described in the case presentation have given their written consent for their personal or clinical details along with any identifying images to be published in this study. This study is registered under the committee's reference number 29-023.

### Consent for publication

Not applicable.

The datasets generated during and analyzed during the current study are available from the corresponding author.

### Competing interests

The authors declare that they have no competing interests.


### Funding

None.


### Authors' contributions

YK wrote the manuscript; MKono, HK, SM, RT, TN, SH, NN, MT, HH, SM, NT collected cases; MKudo, TG was responsible for the revision for the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.


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# Tables

Table 1 is available in the Supplementary Files section.

# Figures

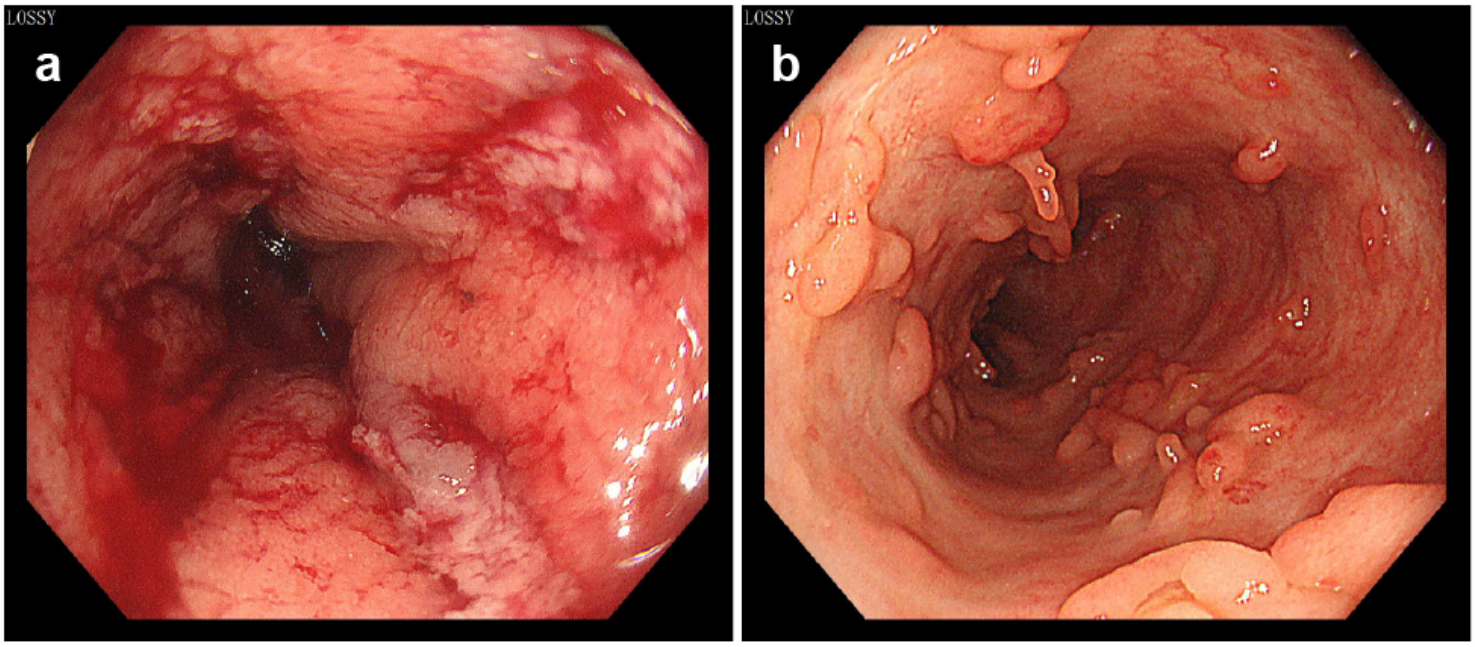


**Figure 1**

Comparison of two colonoscopies of patient 1. **a** February 1, 2020. **b** March 3, 2020

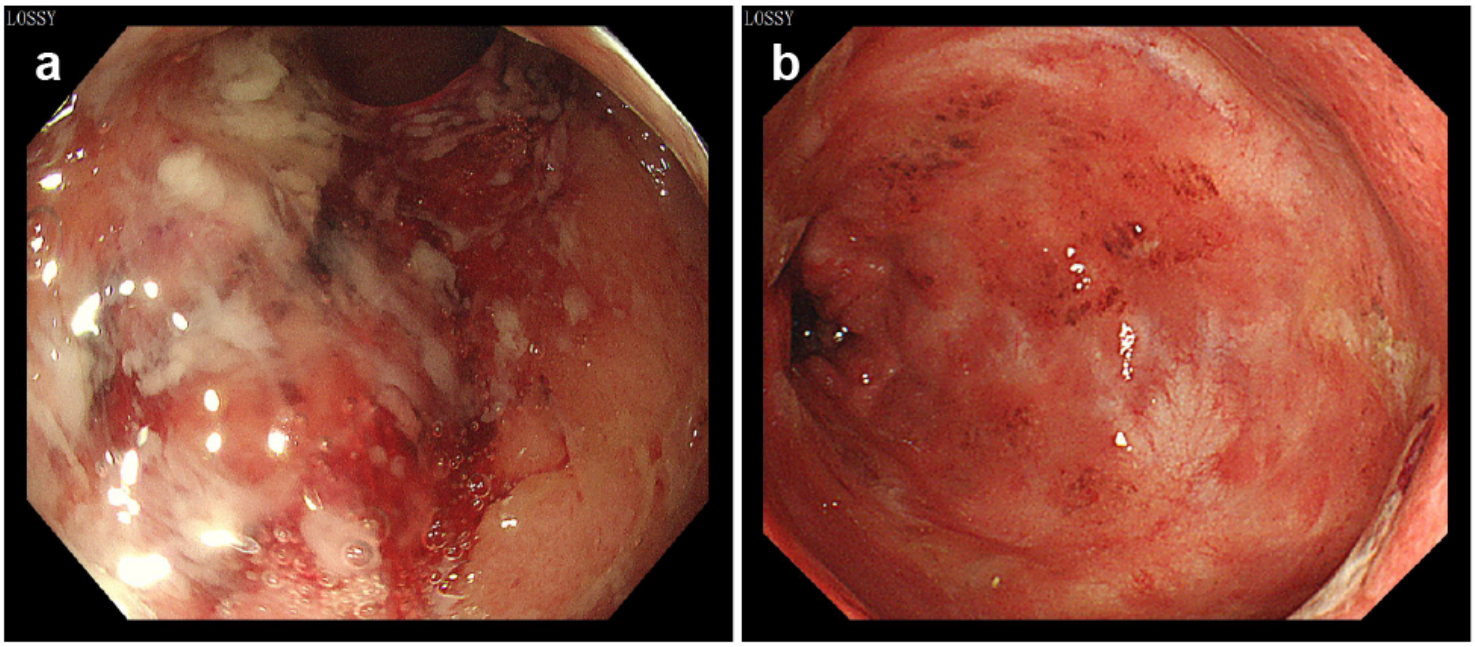


**Figure 2**

Comparison of two colonoscopies of patient 3. **a** October 24, 2018. **b** December 14, 2018


**Figure 3**

Comparison of two colonoscopies of patient 4. **a** August 1, 2019. **b** September 18, 2019

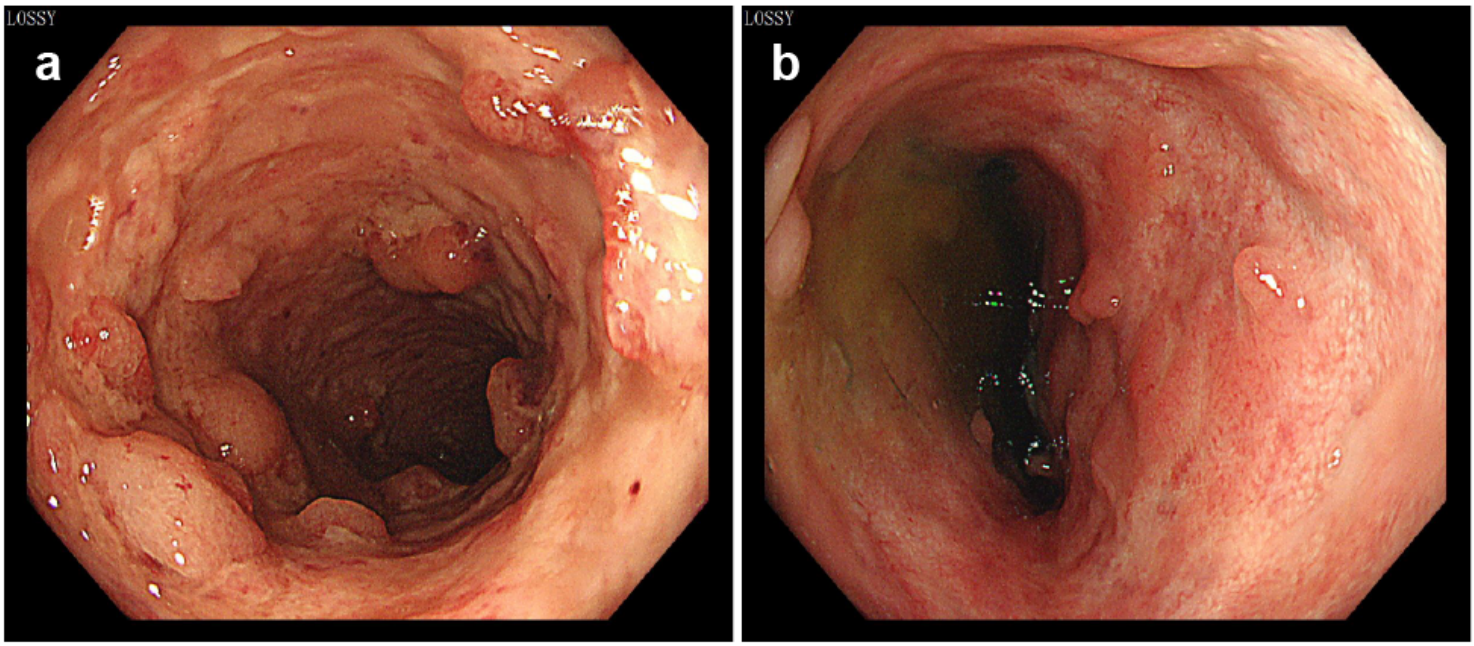


**Figure 4**

Comparison of two colonoscopies of patient 5. **a** August 1, 2019. **b** December 8, 2019

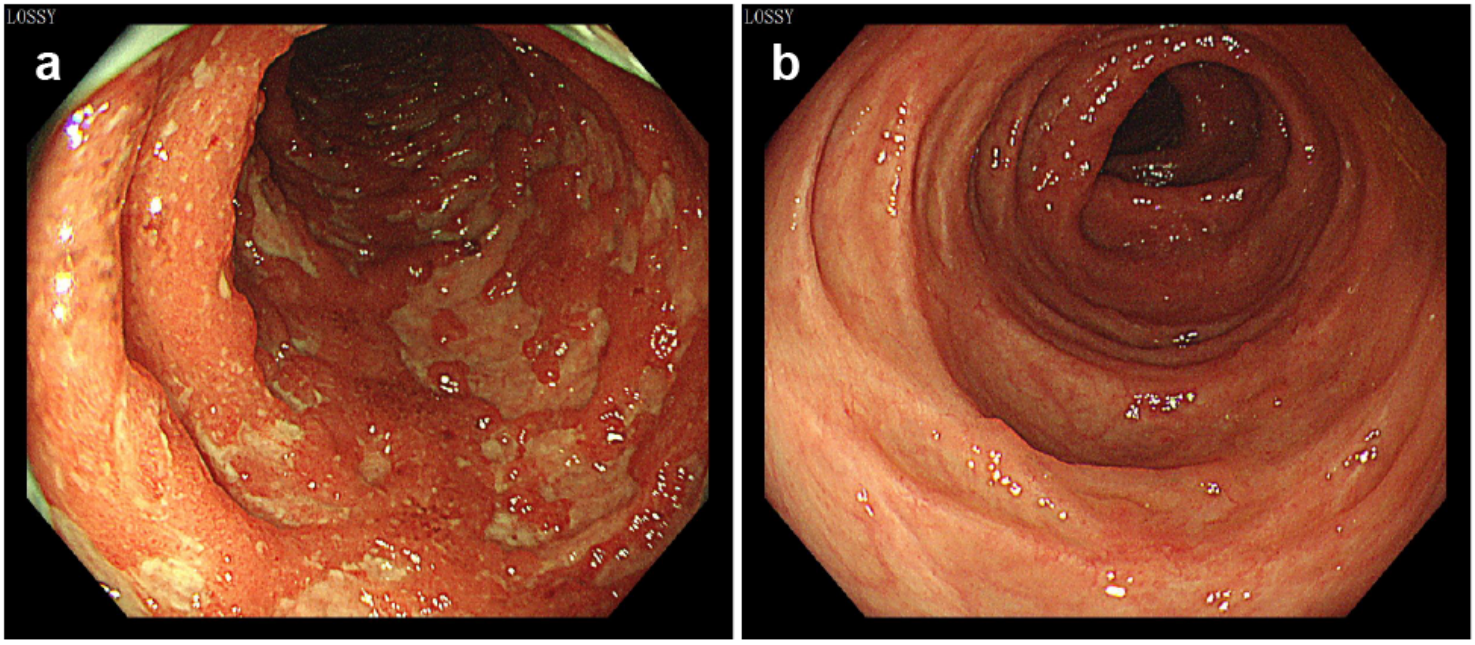


**Figure 5**

Comparison of two colonoscopies of patient 8. **a** January 30, 2021. **b** February 27, 2021

## Supplementary Files

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- Table1.xls