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CASE SERIES

Successful and Risk-Minimizing Treatment of Ulcerative Colitis by Positive Switch from JAK Inhibitors to Ustekinumab

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Background: Janus kinase (JAK) inhibitors are highly effective at inducing remission in moderate-to-severe ulcerative colitis (UC). Because JAK inhibitors are small molecules, they can be administered orally, are rapidly absorbed, and have a rapid onset of action. However, potential adverse events, such as serious infections, opportunistic infections, herpes zoster infections, venous thrombosis, and cardiovascular events have been identified. To avoid the side effects associated with the long-term administration of JAK inhibitors, switching to biologics may be considered, even if remission is maintained with JAK inhibitors (positive switch).

Case Report: Case 1: A 53-year-old man with steroid-dependent UC achieved rapid symptomatic improvement and complete mucosal healing on upadacitinib. Due to recurrent common colds and concerns regarding long-term adverse events, he underwent a positive switch to ustekinumab. Clinical and endoscopic remission have been maintained for one year. Case 2: A 36-year-old woman with refractory UC achieved clinical remission and mucosal healing with filgotinib following inadequate response to vedolizumab and corticosteroids. Given her desire for pregnancy and the potential risks of long-term JAK inhibitor use, she was switched to ustekinumab, which is considered safe during pregnancy. Remission has been maintained for one year.

Conclusion: In two UC patients who achieved mucosal healing with a JAK inhibitor, remission was successfully maintained after switching to ustekinumab. These cases suggest that a positive switch may be a reasonable option for patients who respond to JAK inhibitors but have concerns about long-term safety. Additional cases are required to better define the clinical role of this strategy.

Keywords: ulcerative colitis, Janus kinase inhibitors, ustekinumab, adverse event, mucosal healing, positive switch

Introduction

Janus kinase (JAK) inhibitors are highly effective at inducing remission in moderate-to-severe ulcerative colitis (UC) and have a rapid onset of effect.[1] The OCTAVE trial confirmed the remission maintenance and mucosal healing effects of tofacitinib.[1,2] Because JAK inhibitors are low-molecular-weight compounds, they have the advantage of having a short half-life of several hours, allowing for rapid transition to the next drug.[3] However, potential adverse events, such as serious infections, thrombosis and the development of malignant tumors have been reported.[4] In particular, the risk of developing thrombosis as a side effect of tofacitinib is dose dependent.[4] To avoid the side effects associated with the long-term use of JAK inhibitors, it is considered beneficial to switch to biologics, which have a lower risk of these side effects, at least after achieving mucosal healing, even if remission is maintained with JAK inhibitors (positive switching).

Ustekinumab, an interleukin-12/23 inhibitor, has shown efficacy in UC and is characterized by a favorable safety profile, with rates of major adverse cardiovascular events, malignancies, and serious infections comparable to placebo. Its low immunogenicity and convenient dosing schedule also make it a suitable option for long-term maintenance therapy.[5] However, no studies have clarified the optimal timing of switching or provided real-world evidence to guide decision-making. To date, clinical reports describing elective switching after documented deep remission with JAK inhibitors remain lacking.

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We herein report two cases of UC in which mucosal healing was successfully induced with JAK inhibitors, followed by a proactive switch to ustekinumab, with remission maintained thereafter. These cases may provide insight into treatment sequencing strategies in UC management.

Case Report

Case 1

A 53-year-old Japanese man was diagnosed with total colitis-type UC at 51 years of age. He had no relevant medical history. He was treated with mesalazine at a local hospital. However, over the course of a month, his symptoms worsened, presenting with more than 20 bloody stools per day, a fever of 39°C, and lower abdominal pain. Colonoscopy revealed reddish and edematous mucosa with reduced vascular transparency throughout the colon (Figure 1a and b). He was referred to our hospital due to suspected 5-aminosalicylic acid (5-ASA) intolerance. The leucine-rich alpha2 glycoprotein (LRG) level was 46.6 μg/mL (reference value: <16 μg/mL). A drug-induced lymphocyte stimulation test was positive for all four 5-ASA drugs. Oral prednisolone (PSL; 40 mg/day) was administered, and his symptoms promptly improved within a week. Two months after the administration of PSL, azathioprine (50 mg/day) was started, and the PSL dose was tapered. His symptoms relapsed 2 months after the administration of azathioprine, presenting with more than 10 bowel movements per day but no blood in the stool (LRG 15.7 μg/mL). Therefore, azathioprine was switched to upadacitinib (45 mg/day and tapered to 15 mg/day after 8 weeks). His symptoms improved the day after the initiation of upadacitinib. Follow-up colonoscopy 8 months later demonstrated complete mucosal healing with an endoscopic Mayo score of 0 (Figure 1c and d). Nine months later, the LRG value was within the normal range (8.4 μg/mL). Because the patient experienced recurrent upper respiratory tract infections and was concerned about the potential long-term risks of JAK inhibitor therapy, a positive switch to ustekinumab was made. Standard intravenous induction with 390 mg was administered, followed by 90 mg subcutaneous injections every 8 weeks. To date, remission and mucosal healing have been maintained for one year.

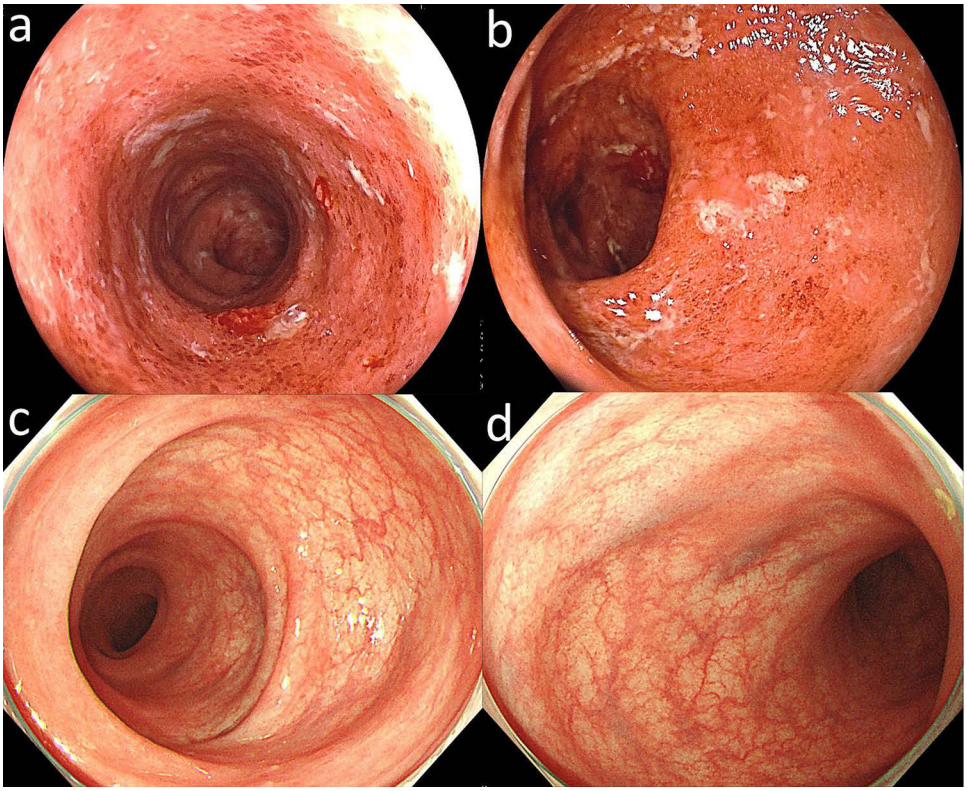

Figure 1 Colonoscopy images of Case 1. Initial colonoscopy revealed reddened and edematous mucosa with reduced vascular transparency ((**a**) transverse colon, (**b**) sigmoid colon). Eight months after the administration of upadacitinib, colonoscopy revealed mucosal healing ((**c**) transverse colon, (**d**) sigmoid colon).

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Case 2

A 36-year-old Japanese woman who was diagnosed with total colitis-type UC at 27 years of age. She had no relevant medical history. She was treated with mesalazine, and her symptoms were unstable. She was referred to our hospital because of worsening symptoms, presenting with more than 10 bowel movements per day, a fever of 39°C, and lower abdominal pain (LRG 30.8 μg/mL) (reference value: < 16μg/mL). Colonoscopy revealed multiple ulcers with reddish and edematous mucosa throughout the colon (Figure 2a and b). She was administered oral PSL (30 mg/day), and her condition worsened during PSL tapering. Therefore, the PSL dose was increased to 40 mg/day, and vedolizumab was administered 2 weeks after PSL administration. Her symptoms subsided over time; however, after the PSL dose was tapered, within 6 months, the frequency of bowel movements increased to more than five times a day, and bloody stool appeared. Although she was advised to switch to other advanced therapies, she believed that the worsening of her symptoms was temporary due to work-related stress and did not agree. Her symptoms worsened with bloody stools more than 10 times a day and abdominal pain (LRG 45.3 μg/mL) and she was concerned about the choice of drug given her desire to have a baby. Pregnancy was planned after remission was achieved, and filgotinib (200 mg/day) was initiated. Her symptoms improved, with the blood in her stools disappearing and the number of bowel movements decreasing to less than five times a day within 2 weeks of starting treatment, and she subsequently achieved clinical remission (LRG 13.1 μg/mL). Eight months after the initiation of filgotinib, mucosal healing was confirmed by colonoscopy (endoscopic Mayo 0) (Figure 2c and d). Because ustekinumab has a favorable safety profile and can be used during pregnancy, she elected to switch from filgotinib to ustekinumab after achieving mucosal healing. Standard intravenous induction with 260 mg was administered, followed by 90 mg subcutaneous injections every 8 weeks. To date, remission and mucosal healing have been maintained for one year.

Discussion

Tofacitinib, the first JAK inhibitor, is a new orally administered small-molecule drug that was introduced in Japan in 2018. It has the ability to suppress multiple cytokine signaling pathways and regulate dysregulated immune responses associated with the

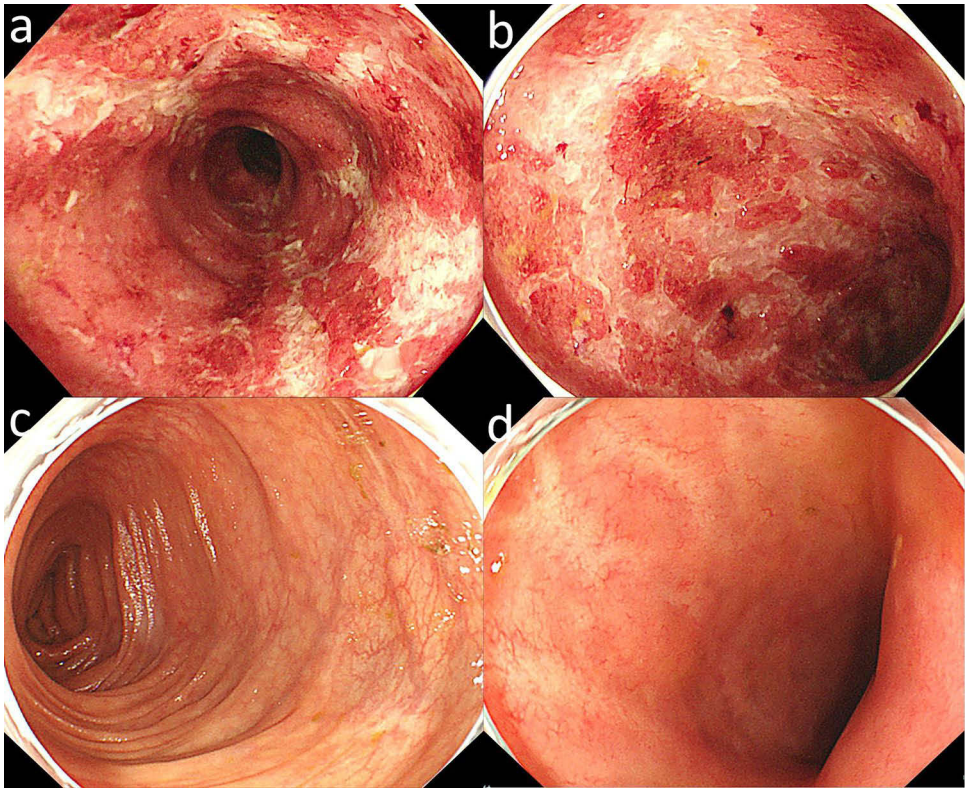

Figure 2 Colonoscopy images of Case 2. Initial colonoscopy revealed reddened and edematous mucosa with ulcers ((**a**) transverse colon, (**b**) sigmoid colon). Eight months after the administration of filgotinib, colonoscopy revealed mucosal healing ((**c**) transverse colon, (**d**) sigmoid colon).

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onset of UC. Subsequently, two JAK inhibitors (filgotinib and upadacitinib) were added to treat UC. Thus, three JAK inhibitors are currently available for the treatment of UC. JAK inhibitors are a treatment option for moderate-to-severe UC and are particularly useful when existing treatments are ineffective or intolerable. However, the use of JAK inhibitors is limited in patients who do not receive advanced therapy. The FDA label recommends the use of JAK inhibitors in patients with previous failure or intolerance to tumor necrosis factor (TNF) antagonists. In Europe, the European Medicines Agency recommends using JAK inhibitors with caution in patients at risk for cancer and adverse cardiovascular outcomes, such as those ≥ 65 years of age, current or former long-term smokers, and those with a history of cardiovascular disease (eg, heart attack or stroke), particularly when no appropriate alternative therapies are available.[6] Because JAK inhibitors are small molecules, they can be administered orally, are rapidly absorbed, have a rapid onset of effect, and are superior to antibody preparations in that they have a short half-life and are non-immunogenic.[4]

Adverse events associated with JAK inhibitors include serious infections, opportunistic infections, herpes zoster infections, and gastrointestinal perforation,[4] as well as an increased risk of venous thrombosis and death. In general, the incidence of these adverse events is dose dependent. Relative to adalimumab and etanercept, the incidence of cardiovascular events, including death, is higher (eg, venous thromboembolism and pulmonary embolism [hazard ratio, 1.33; 95% confidence interval, 0.91–1.94]).[7] Although the difference was not statistically significant, the incidence of pulmonary thrombosis in patients receiving tofacitinib (5 mg, b.i.d.) was three times higher than that in patients receiving TNF inhibitors. However, the incidence was reported to be eight times higher when administered at a dose of 10 mg b.i.d. Therefore, the recommended dose of tofacitinib for induction therapy of UC is 10 mg twice a day for up to 16 weeks, preferably for less than 8 weeks. The long-term safety of tofacitinib for UC was demonstrated, similarly to a previous analysis, except for cases involving herpes zoster or serious infections.[8] However, considering the risk of adverse events, we believe that switching from JAK inhibitors to biologics may be an effective strategy.

In our cases, ustekinumab was selected as the antibody preparation for switching from a JAK inhibitor. Ustekinumab is a monoclonal antibody targeting the p40 subunit of interleukin-12 and interleukin-23, approved for the treatment of psoriasis, psoriatic arthritis, Crohn's disease, and UC.[5] Safety profiles of ustekinumab have been well established, with rates of key adverse events, including major adverse cardiovascular events (MACE), malignancies, infections, and serious infections, generally similar to those observed with placebo and not higher in patients treated with ustekinumab.[9] Whether or not IL-12/23 inhibitors that signal through JAK2 would be equally effective in patients who have achieved mucosal healing with upadacitinib or filgotinib, agents traditionally described as JAK1-selective, is unclear. Although upadacitinib was developed as a JAK1-preferential inhibitor, recent studies suggest that its selectivity is relative rather than absolute, and that some degree of JAK2 inhibition may occur in vivo.[10] Mucosal healing is believed to play a crucial role in preventing subsequent clinical relapse.[11] If switching is not effective, our strategy is to re-administer the JAK inhibitor because the re-administration of JAK inhibitors is relatively effective.[12] We prioritized convenience for patients and selected ustekinumab because it allows patients to only visit the hospital 8 weeks after induction therapy and patients are not required to learn self-injection skills.

Because this report is based on two individual cases, the observations cannot be generalized. However, these cases may offer early clinical insight into the potential role of a positive switch to ustekinumab for patients achieving mucosal healing with JAK inhibitors.

Conclusion

This report describes two cases of ulcerative colitis in which mucosal healing was achieved with a JAK inhibitor, and remission was successfully maintained after a positive switch to ustekinumab. These observations suggest that, for patients who respond well to JAK inhibitors but have concerns regarding long-term safety, switching to ustekinumab can be considered a viable maintenance strategy. Although further clinical experience is needed, our cases provide initial insight into the potential role of this treatment approach.

Abbreviations

JAK, Janus kinase; UC, ulcerative colitis; 5-ASA, 5-aminosalicylic acid; LRG, leucine-rich alpha2 glycoprotein; PSL, prednisolone; TNF, tumor necrosis factor.

Ethics Approval and Informed Consent

The Ethics Committee (Jichi Medical University Bioethics Committee for Clinical Research, Saitama Medical Center) exempted this study because it was not covered by the "Ethical Guidelines for Life Science and Medical Research Involving Human Subjects."

The patients have provided written informed consent for the publication of the case details and accompanying images.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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