Safety and Efficacy of Vedolizumab in a Patient With Crohn's Disease After Developing An Active Tuberculosis Infection Associated With Infliximab-Biosimilar: A Case Report

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Case report

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Abstract

Background: Screening of latent tuberculosis (TB) before the induction of anti-tumor necrosis factor (anti-TNF) agents is very important to prevent the reactivation of TB. However, active TB can still occur, and the ideal therapeutic strategy for IBD patients who develop active TB has not been established.

Case presentation: A 21-year-old Vietnamese man with active ileo-colonic Crohn's disease visited our hospital. While computed tomography (CT) revealed a nodular lesion at the right lung, a serological interferon gamma release assay (IGRA) and several culture tests were all negative. The intravenous administration of infliximab-biosimilar (IFX-BS) with an immunomodulator were initiated. After the induction therapy, he achieved clinical remission. However, he presented with a high fever 17 weeks after the initiation. CT revealed the expansion of the nodular lesion at the right lung, and serological IGRA was positive. He was diagnosed with reactivation of latent TB. He had not achieved mucosal healing when immunosuppressive therapy was discontinued. Thus, he was administered vedolizumab (VDZ), which was considered not to influence the TB status, as maintenance therapy. Consequently, he achieved mucosal healing without relapse of active TB.

Conclusions: This is the first report to describe the safe usage of VDZ as maintenance therapy without the induction of TB relapse in a CD patient. In Asian countries, clinicians must be alert for the reactivation of latent TB during the administration of anti-TNF agents. VDZ might be a safe option for maintenance therapy in CD patients, even in cases with active TB.

Background

Anti-tumor necrosis factor (anti-TNF) agents have a high therapeutic efficacy and safety profile for inflammatory bowel disease (IBD), but a small percentage of patients experience severe adverse effects, including infectious disease.¹ TNF-alpha plays an important role in the host defense against *Mycobacterium tuberculosis*, so anti-TNF agents are associated with an increased risk of active tuberculosis (TB).²

Most cases of active TB develop within several months after the initiation of anti-TNF agents, suggesting that they are caused by the reactivation of latent TB.³ Screening of latent TB before the induction of anti-TNF agents is important for preventing the reactivation of TB. Different scientific organizations from all over the world have published guidelines and recommendations concerning active and latent TB.^{4–6} However, active TB can still occur in IBD patients treated with anti-TNF agents despite compliance with recommended preventive measures.⁷ Furthermore, no therapeutic strategy for IBD patients who develop active TB associated with anti-TNF agents has yet been established.

Vedolizumab (VDZ), a gut-selective antibody to $\alpha 4\beta 7$ integrin for the treatment of IBD, has a favorable safety profile with low incidence rates of serious infections, infusion-related reactions and malignancies.⁸ However, its safety for patients who develop active TB associated with anti-TNF agents remains unclear.

We herein report the successful continuation of VDZ as maintenance therapy without the induction of TB relapse in a CD patient who developed active TB associated with infliximab-biosimilar (IFX-BS).

Case Presentation

A 21-year-old Vietnamese man presented to Asahikawa Medical University Hospital with hemorrhagic stool. He did not have any personal or family history of IBD or TB. A physical examination revealed the following: body height, 171.0 cm; body weight, 63.8 kg; body mass index, 21.8; body temperature, 36.7 °C; blood pressure, 115/58 mmHg; heart rate, 71 beats/min; and SpO₂, 99% on room air. A laboratory examination revealed high levels of inflammation markers, mild anemia and hypoalbuminemia: white blood cell (WBC) count, 11060/μl; hemoglobin, 12.9 g/dL; platelet count, 33.3×10⁴/μl; C-reactive protein (CRP), 4.43 mg/dL; and albumin, 3.7 g/dL. Serological tests for infection markers, including the interferon gamma release assay (IGRA), were all negative.

Upper gastrointestinal endoscopy showed multiple vertical small erosions in the duodenum. Small bowel capsule endoscopy (SBCE) showed multiple small ulcers in the jejunum and multiple longitudinal ulcers in the ileum. Colonoscopy showed multiple longitudinal ulcers and a cobblestone appearance in the terminal ileum and multiple small erosions and aphtha throughout the colon (Fig. 1A). An intestinal juice culture examination and polymerase chain reaction (PCR) for any bacteria, including acid-fast bacilli, showed negative findings. Contrast-enhanced computed tomography (CT) revealed a nodular lesion at the apex of the right lung and thickening of the wall with a contrast effect at the terminal ileum (Fig. 2A). A pathological examination did not demonstrate granuloma at the longitudinal ulcer in the terminal ileum.

He was diagnosed with ileo-colonic CD based on the endoscopic findings. The nodular lesion at the apex of the right lung was suspected of being latent TB. However, his serological IGRA and several culture tests (including sputum, urine and intestinal juice) were all negative. Thus, he did not receive a diagnosis of latent TB. His disease activity was a Crohn's disease activity index (CDAI) of 167, Lewis score of 1368 and simple endoscopic score for Crohn's disease (SES-CD) of 13. Because of his young age and the presence of high-activity inflammatory lesion throughout the small intestine and colon, the intravenous administration of IFX-BS with an immunomodulator was initiated as induction therapy. His CDAI and CRP levels immediately decreased after the induction of IFX-BS.

However, at 17 weeks after the initiation of IFX-BS, he visited our hospital with a high fever. A laboratory examination revealed high levels of inflammation markers: WBC count, 6560/μl; and CRP, 10.33 mg/dL. CT revealed the expansion of the nodular lesion at the apex of the right lung (Fig. 2B). Furthermore, his serological IGRA and acid-fast bacillus culture tests of gastric juice had all turned positive. He was diagnosed with reactivation of latent TB. IFX-BS with an immunomodulator was immediately discontinued, and anti-TB therapy with polypharmacy of rifampicin, isoniazid, ethambutol and pyrazinamide was initiated. At 10 weeks after the initiation of anti-TB therapy, his general condition and inflammation markers had recovered: WBC count, 4850/μl; CRP, < 0.10 mg/dL.

In July 2019, he had maintained clinical remission of CD without medication. However, colonoscopy still showed an active ulcer in the terminal ileum (Fig. 1B). Regarding his disease activity, he had a CDAI of 85 and SES-CD of 4. His endoscopic findings were improved compared with before induction therapy of IFX-BS, but he had not achieved mucosal healing. Thus, another intervention therapy for CD that would not induce a relapse of active TB was considered. VDZ has a favorable safety profile with low incidence rates of serious infections, so VDZ was selected for maintenance therapy.

In June 2020, all of his ulcerative lesions in the small intestine and colon had improved and changed to ulcer scars on SBCE and colonoscopy (Fig. 1C). Regarding his disease activity, he had a CDAI of 80, Lewis score of 0 and SES-CD of 0. CT revealed shrinkage of the nodular lesion at the apex of the right lung (Fig. 2C). Thus, he achieved both clinical remission and mucosal healing by maintenance therapy with VDZ without relapse of active TB.

Discussion And Conclusions

This is the first case report to describe how VDZ was able to be continued as maintenance therapy without relapse of TB in a CD patient who developed active TB associated with IFX-BS. VDZ might be a new therapeutic strategy for CD patients who develop active TB.

TNF-alpha plays a central role in the host immune defense against TB infection by inducing the formation and maintenance of granulomas, which prevent the dissemination of infection. Therefore, inhibiting TNF-alpha may increase susceptibility to TB infection and accelerate the reactivation of latent TB infection.² The prevalence of latent TB infection is much higher in Asian countries than in Western countries. The Asian Organization for Crohn's and Colitis (AOCC) recommends that IBD patients be screened for TB by chest radiography and a tuberculin skin test (TST) and/or IGRA before the initiation of anti-TNF agents.^{5,6}

In the present case, CT revealed a nodular lesion at the apex of the right lung. However, he did not have any symptoms, and his IGRA and several culture tests as well as a PCR examination were all negative. Therefore, he was not diagnosed with latent TB infection. Lu et al. reported that IGRA showed a superior capability to the TST for diagnosing TB because of its markedly greater sensitivity and specificity.⁹ However, Santos et al. reported that host factors, including inflammatory disease and pulmonary TB, are associated with false-negative IGRA results.¹⁰ Thus, the ideal way to diagnose latent TB has not yet been established. Even if IGRA is negative, as in our case, IBD patients with pulmonary lesions on CT should receive chemoprophylaxis before the initiation of anti-TNF agents.

The AOCC suggests that anti-TNF agents be withheld when active TB is diagnosed during the administration of anti-TNF agents.⁶ However, the British guideline contrarily recommend that anti-TNF agents be continued if clinically indicated.⁴ Thus, there is little consensus on the impact of immunosuppressive therapy, including anti-TNF agents, on the risk of active TB. In the present case, active lesion in the small intestine remained when the anti-TNF agent with an immunomodulator was

discontinued. Achieving mucosal healing in CD patients is associated with improved rates of long-term clinical remission; accordingly, such healing is considered to be a crucial therapeutic target.¹¹

VDZ is a humanized monoclonal antibody that selectively binds to the $\alpha_4\beta_7$ integrin. VDZ inhibits the adhesion of lymphocytes to mucosal addressin cell adhesion molecule-1 (MAdCAM-1) and subsequent migration. Several clinical trials have demonstrated that VDZ has long-term safety and efficacy.^{8,12} According to the results of the post-marketing surveillance of VDZ, only 3 out of approximately 30,000 patients had reactivation of latent TB.¹³ Furthermore, in a retrospective study of IBD patients who received biologic therapy with latent TB infection, there were no cases of reactivation of TB in any of the 10 patients who were treated with VDZ.¹⁴ Thus, we suspect that VDZ might have a safe profile as maintenance therapy even in patients who develop active TB based on these previous reports describing the extremely low risk of reactivation of latent TB. The present patient has now achieved and maintained complete mucosal healing without relapse of active TB.

In conclusion, this is the first case report describing a patient in whom VDZ was able to be continued as maintenance therapy without inducing relapse of TB in a CD patient who developed active TB associated with IFX-BS. In Asian countries, clinicians must be alert for the reactivation of latent TB during the administration of anti-TNF agents. VDZ might be a safe option for induction and maintenance therapy in CD patients, even in cases with active TB. A new therapeutic strategy using VDZ for CD patients with TB is expected to be established following the accumulation of similar cases.

Abbreviations

TB: tuberculosis, anti-TNF: anti-tumor necrosis factor, CT: computed tomography, IGRA: interferon gamma release assay, IFX-BS: infliximab-biosimilar, VDZ: vedolizumab, IBD: inflammatory bowel disease, WBC: white blood cell, CRP: C-reactive protein,

SBCE: small bowel capsule endoscopy, PCR: polymerase chain reaction, CDAI: Crohn's disease activity index, SES-CD: simple endoscopic score for Crohn's disease, AOCC: Asian Organization for Crohn's and Colitis, TST: tuberculin skin test, MAdCAM-1: mucosal addressin cell adhesion molecule-1

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing Interests

Y. Sugiyama, S. Tachibana, N. Ueno, Y. Kobayashi, Y. Murakami, T. Sasaki, T. Kunogi, K. Takah

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Authors' contributions

NU designed entire treatment. YS, ST, YK, YM and KA were in charge of the management of patient's hospitalization. TK, TS, KT, SK and HT performed the endoscopic procedure and cross-section imaging. KM, NU and MF were in charge of the pathological diagnosis. All authors discussed the patient's clinical diagnosis and treatment plan. YS and NU wrote the manuscript. TO and MF reviewed the manuscript. All authors approved the final version of this manuscript.

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Figures

Figure 1

Endoscopic findings. A: Multiple longitudinal ulcers in the terminal ileum at the initial diagnosis. B: Persistent active ulcer in the terminal ileum after the administration of anti-tuberculosis therapy. C: Mucosal healing in the terminal ileum one year after the administration of VDZ.

Figure 2

Chest computed tomography findings. A: A nodular lesion at the apex of the right lung before the administration of IFX-BS. B: A worsening nodular lesion 17 weeks after the initiation of IFX-BS. C: A shrunk nodular lesion one year after the administration of VDZ.