A case report of drug-induced liver injury due to the infliximab biosimilar CT-P13 on switching from original infliximab in a patient with Crohn’s disease

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Abstract: Inflammatory bowel diseases (IBDs) are chronic immune disorders of unclear etiology. Tumor necrosis factor (TNF) inhibitors are effective for IBD treatment and are cost-effective because they reduce hospital admissions and are associated with fewer surgery requirements and a better quality of life in IBD patients. A large number of clinical trials of infliximab biosimilar (CT-P13) have suggested that the administration of biosimilars provides high efficacy and safety similar to that of the originators, with a lower cost, so switching from the original to a biosimilar is considered an acceptable treatment. While several abnormalities of blood examination have been observed in patients with CT-P13 administration, no cases of drug-induced liver injury (DILI) caused by CT-P13 has been reported. A 23-year-old woman had been diagnosed with Crohn’s disease and was treated with original infliximab (O-IFX) for 9 years. She developed severe jaundice 1 month after switching from O-IFX to CT-P13. Serologic tests of autoimmune and hepatitis viruses were negative, and ultrasonography, computed tomography, and magnetic resonance cholangiopancreatography revealed no abnormalities. A liver biopsy showed prominent pericentral canicular cholestasis, without features of steatosis or sclerosing cholangitis, which was consistent with drug-induced cholestasis. The cholestasis improved 10 weeks after the discontinuation of CT-P13, and no DILI redeveloped even after re-switching from CT-P13 to O-IFX. This is the first report of DILI due to switching from O-IFX to CT-P13. While the efficacy and safety of CT-P13 are considered equal to those of O-IFX, clinicians need to be alert for certain severe DILIs when switching from O-IFX to CT-P13 with careful monitoring and appropriate treatment.

Plain Language Summary

A case report of drug-induced liver injury due to switching from original infliximab to infliximab biosimilar

Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the entire gastrointestinal tract, although its etiology has largely been unclear. Tumor necrosis factor (TNF) inhibitors are effective for IBD treatment and are cost-effective because they reduce hospital admissions and are associated with fewer surgery requirements and a better quality of life in IBD patients. A biological medicinal product that contains a version of the active substance of an already authorized biological medicinal product. Biosimilars of TNF inhibitors, such as CT-P13, are thought to possess equal efficacy and safety to the original with a lower cost, so switching from the original to a biosimilar considered an acceptable treatment. While several serious adverse reactions of TNF inhibitors have been reported, drug-induced liver injury (DILI) is uncommon, and liver dysfunction due to the administration of CT-P13 has not been reported in IBD patients. We herein report the first case of DILI due to CT-P13 after switching from original infliximab (O-IFX) in a patient with Crohn’s disease. While the efficacy and safety of CT-P13 are considered equal to those of O-IFX, clinicians need to be alert for certain severe DILIs when switching from O-IFX to CT-P13 with careful monitoring and appropriate treatment.
Background
Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the entire gastrointestinal tract, although its etiology has largely been unclear. Tumor necrosis factor (TNF) inhibitors are effective for IBD treatment and are cost-effective because they reduce hospital admissions and are associated with fewer surgery requirements and a better quality of life in IBD patients. Biosimilars of TNF inhibitors, such as CT-P13, are thought to possess equal efficacy and safety compared to the original and have dramatic cost benefits. Switching from the original to a biosimilar is thus considered an acceptable treatment.

While several serious adverse reactions of TNF inhibitors have been reported, drug-induced liver injury (DILI) is uncommon, and liver dysfunction due to the administration of CT-P13 has not been reported in IBD patients.

We herein report the first case of DILI due to CT-P13 after switching from original infliximab (O-IFX) in a patient with Crohn’s disease.

Case presentation
A 23-year-old woman had symptoms of a fever, abdominal pain, and frequent diarrhea. On total colonoscopy, she was found to have multiple longitudinal ulcers in the terminal ileum without structuring or penetration. She was diagnosed with Crohn’s disease. Her symptoms were severe, so we administered O-IFX first, not steroid therapy. Her symptoms gradually improved and led to clinical remission. Nine years after the onset, she was in the remission phase, so O-IFX was switched to CT-P13. Her physical condition was good, and no other changes to the treatment were made during or after the administration of CT-P13. One month after switching, however, she developed severe jaundice.

Laboratory tests showed total bilirubin, 8.2 mg/dL (0.2–1.2); direct bilirubin, 5.9 mg/dL (0–0.2); alanine aminotransferase, 141 U/L (6–40); aspartate aminotransferase, 73 U/L (6–37); gamma glutamyl aminotransferase, 74 U/L (4–32); and alkaline phosphatase, 514 U/L (96–284). Autoimmune antibodies (anti-mitochondrial antibody, antinuclear antibody, and anti-smooth-muscle antibody), hepatitis A, B, C, and E, and previous infections of the cytomegalovirus and Epstein–Barr virus were negative. Abdominal ultrasonography with doppler, computed tomography, and magnetic resonance cholangiopancreatography did not show any abnormalities, such as stones, strictures, beadings, or other features of primary sclerosing cholangitis. The drug-induced lymphocyte stimulation test for CT-P13 was negative. Histological findings of a liver biopsy (Figure 1) showed marked canalicular cholestasis (predominantly in a pericentral (Zone 3) distribution) associated with numerous large intracanalicular bile thrombi throughout the parenchyma. Only rare foci of lobular inflammation were present, and no significant portal tract expansion or edema and inflammation were identified. Bile duct injury was not present. Iron staining did not show any marked increase in iron.

The total score according to the diagnosis criteria proposed the Roussel Uclaf Causality Assessment Method (RUCAM) was seven points. So, we diagnosed as DILI associated with CT-P13. Because biologic therapies were considered suitable for maintaining remission in this case, we explained to the patient the risk of relapse of DILI when restarting O-IFX and recommended other new biologic therapies, including adalimumab. However, she wished to restart O-IFX, so O-IFX was restarted 12 weeks after the discontinuation of CT-P13 with careful monitoring. The cholestasis improved 10 weeks after the discontinuation of CT-P13, and no DILI redeveloped, even after re-switching from CT-P13 to O-IFX (Figure 2). We reported this case to the Japanese National Pharmacovigilance Authority.

Discussion and conclusion
We encountered the first reported case of cholestasis-type DILI due to switching from O-IFX.
to CT-P13. Although various factors can cause DILI, we determined that CT-P13 had caused the DILI in this case based on the RUCAM score. While we considered potential batch problems, there have been no similar reports thus far. In addition, to eliminate the possibility of an administration error, we inspected the administration procedures and confirmed that there were no issues. Thus, the DILI in this case was deemed likely to have been caused not by the batch used but by the patient’s idiosyncratic drug metabolism enzymes. Re-switching from CT-P13 to O-IFX did not re-induce DILI, illustrating the difference between O-IFX and CT-P13 in this case. She was able to maintain remission of her Crohn’s disease without any relapse of DILI after restarting O-IFX, which had previously caused hepatic toxicity.

Many clinical studies have revealed that CT-P13 possessed a sufficient efficacy and safety equal to O-IFX, thus supporting switching from O-IFX to CT-P13 from a cost-effective perspective. A recent international, randomized, double-blind study revealed no marked differences in the efficacy and safety among four switching groups (who received CT-P13 or infliximab without switching, or CT-P13 and then infliximab or infliximab and then CT-P13, with switching occurring at week 30). Although such large-scale studies have shown that the incidences of adverse events were not significantly different among the drugs, the immunogenicity of CT-P13 was not proven to be the same as that of O-IFX. While the amino acid sequences of CT-P13 are the same as those of O-IFX, the sugar chain sequences are known to differ very slightly between these two drugs, which may have led to the DILI in this case. Appropriate monitoring and treatment are thus needed when switching from O-IFX to CT-P13.

Drug hepatic toxicity associated with TNF inhibitors could be more frequently observed.
primarily as higher level of transaminases and cholestasis pattern occurs less commonly. The enzyme pattern of this case was compatible with cholestatic hepatitis. DILI associated with TNF inhibitors is commonly characterized by autoimmune antibodies and it responds well to glucocorticoid treatment and tends to show a relatively good outcome. However, in this case, autoimmune antibodies, including anti-mitochondrial antibody, antinuclear antibody, and anti-smooth-muscle antibody, were negative, suggesting that the direct toxicity or idiosyncratic hepatotoxicity of CT-P13 in hepatocytes was dominant against autoimmune toxicity. If DILI develops based on an autoimmune mechanism, the administration of glucocorticoids is an option for the treatment. However, when the direct toxicity or idiosyncratic hepatotoxicity of CT-P13 in hepatocytes is dominant, as in our case, the discontinuation of CT-P13 is thought to be the only effective treatment strategy. Generally, direct hepatotoxicity is thought to be caused in a dose-dependent manner. Although many patients with Crohn’s disease have been administered CT-P13, our case was the first case of DILI caused by CT-P13, suggesting that idiosyncratic hepatotoxicity was also a conceivable type of DILI in this patient. Because cases of DILI requiring liver transplantation have been reported, appropriate monitoring, immediate discontinuation of the responsible drug and prompt treatment are quite important.

This is the first report describing DILI due to switching from O-IFX to CT-P13. Clinicians need to be alert for certain severe DILIs when switching between different brands of infliximab and conduct careful monitoring and appropriate treatment.

Ethics approval and consent to participate
This is a case report, and we did not receive any approval from the ethics review board. We obtained the patient’s written informed consent to publish the material.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Author contribution(s)
Shin Kashima: Conceptualization; Data curation; Writing – original draft; Writing – review & editing.
Koji Sawada: Investigation.
Kentaro Moriichi: Formal analysis; Visualization.
Mikihiro Fujiya: Writing – original draft; Writing – review & editing.

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Availability of data and materials
Data and materials are available from the corresponding author upon reasonable request.

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