Drug-induced liver injury due to the infliximab biosimilar CT-P13 on switching from original infliximab in a patient with Crohn's disease

Mikihiro Fujiya (✉ fjym@asahikawa-med.ac.jp)

Asahikawa medical University <https://orcid.org/0000-0001-8309-4281>

Shin Kashima

Asahikawa medical university

Yu Kobayashi

Asahikawa medical university

Yuya Sugiyama

Asahikawa medical university

Yuki Murakami

Asahikawa medical university

Hiroki Sato

Asahikawa medical university

Takahiro Sasaki

Asahikawa medical university

Takehito Kunogi

Asahikawa medical university

Hidemi Hayashi

Asahikawa medical university

Keitaro Takahashi

Asahikawa medical university

Takumu Hasebe

Asahikawa medical university

Shunsuke Nakajima

Asahikawa medical university

Katsuyoshi Ando

Asahikawa medical university

Nobuhiro Ueno

Asahikawa medical university

Takuma Goto

Asahikawa medical university

Koji Sawada

Asahikawa medical university

Kentaro Moriichi

Asahikawa medical university

Hiroki Tanabe

Asahikawa medical university

Yusuke Mizukami

Asahikawa medical university

Toshikatsu Okumura

Asahikawa medical university

Case report

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Abstract

Background

IBD are chronic immune disorders of unclear etiology. TNF inhibitors are effective for IBD treatment but are much more expensive than traditional treatments. 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 originator to the biosimilar is recommended. 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.

Case presentations:

A 32-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 one month after switching from O-IFX to CT-P13. Serologic tests of auto-immune and hepatitis viruses were negative, and ultrasonography, computed tomography and magnetic resonance cholangiopancreatography revealed no abnormalities. A liver biopsy showed prominent pericentral canalicular 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.

Conclusions

This is the first report of DILI due to switching from O-IFX to CT-P13, and our case suggests the different immunogenicity between O-IFX and 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.

Background

Inflammatory bowel disease (IBD) is a chronic intestinal inflammation whose etiology has largely been unclear. TNF inhibitors are effective for IBD treatment but much more expensive than traditional treatments¹⁾. 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 has been recommended.

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 patients²⁾³⁾.

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 been diagnosed with Crohn's disease and treated with mesalazine and O-IFX. Nine years after the onset, she was in the remission phase, so O-IFX was switched to CT-P13. One month after switching, however, she developed severe jaundice.

Laboratory tests showed total bilirubin, 8.2 mg/dL; direct bilirubin, 5.9 mg/dL; alanine aminotransferase, 141 U/L; aspartate aminotransferase, 73 U/L; gamma glutamyl aminotransferase, 74 U/L; alkaline phosphatase, 514 U/L. Autoimmune antibodies (anti-mitochondrial antibody, antinuclear antibody, 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 A) 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) ⁴⁾ was seven points. So, we diagnosed as DILI associated with CT-P13. Because a TNF inhibitor was necessary to maintain remission for Crohn's disease, O-IFX was restarted 12 weeks after the discontinuation of CT-P13. 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 B).

Discussion And Conclusions

We encountered the first reported case of cholestasis-type DILI due to switching from O-IFX to CT-P13. Re-switching from CPT-13 to O-IFX did not re-induce DILI, illustrating the difference in immunogenicity between O-IFX and CT-P13.

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 perspective²⁾³⁾. 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)³⁾. 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 between these two drugs, possibly leading to the different immunogenicity. Appropriate monitoring and treatment are thus needed when switching from O-IFX to CT-P13.

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 outcome⁵⁾. However, in the present case, autoimmune antibodies, including anti-mitochondrial antibody, antinuclear antibody and anti-smooth-muscle antibody, were negative, suggesting that the direct toxicity 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 of CT-P13 in hepatocytes is dominant, as in our case, the discontinuation of CT-P13 is thought to be only effective treatment strategy. Because cases of DILI requiring liver transplantation have been reported⁵⁾, appropriate monitoring and immediate discontinuation of the responsible drug are quite important.

This is the first report of DILI due to switching from O-IFX to CT-P13, and our case suggests the different immunogenicity between O-IFX and CT-P13. Clinicians need to be alert for certain severe DILIs when switching from O-IFX to CT-P13 with careful monitoring and appropriate treatment.

Abbreviations

Inflammatory bowel disease (IBD), original infliximab (O-IFX), drug-induced liver injury (DILI), inflammatory bowel disease (IBD), tumor necrosis factor (TNF), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (T-Bil)

Declarations

Conflict of interests

Dr. Fujiya reports grants and personal fees from Nippon Kayaku Co., Ltd., and Mitsubishi Tanabe Pharma Corporation as well as grants from AYUMI Pharmaceutical Corporation.

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.

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None

Author contributions

Fujiya M and Kashima S were equally contributed to this work. Fujiya M and Kashima S wrote the manuscript and supervised all investigations. Kobayashi Y, Sugiyama Y and Murakami Y obtained the image of abdominal ultrasonography. Sato H, Sasaki T, Kunogi T and Takahashi K obtained the images of computed tomography. Ando K, Ueno N and Moriichi K obtained the images of magnetic resonance cholangiopancreatography. Hayashi H, Hasebe T and Nakajima S performed liver biopsy. Goto T, Sawada K and Tanabe H assessed the histological findings. Kashima S managed the enrolled patient and analyzed the data. Mizukami Y and Okumura T helped design works and prepare/review the manuscript.

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References

1. van der Valk ME, Mangen M-JJ, Leenders M, et al. Health care costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNF α therapy: results from the COIN study. *Gut* 2014;63:72–9.
2. Feagan BG, Lam G, Ma C, et al. Systematic review: efficacy and safety of switching patients between reference and biosimilar infliximab. *Aliment Pharmacol Ther.* 2019; 49: 31-40
3. Ye BD, Pesegova M, Alexeeva O, Osipenko M, Lahat A, Dorofeyev A, Fishman S, Levchenko O, Cheon JH, Scribano ML, Mateescu RB, Lee KM, Eun CS, Lee SJ, Lee SY, Kim H, Schreiber S, Fowler H, Cheung R, Kim YH. Efficacy and safety of biosimilar CT-P13 compared with originator infliximab in patients with active Crohn's disease: an

international, randomised, double-blind, phase 3 non-inferiority study. Lancet. 2019; 27;393(10182):1699-1707.

4 Bnichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs-II. An original model for validation of drug causality assessment methods: Case reports with positive rechallenge. J. Clin. Epidemiol. 1993; 46: 13311336.

5 French JB, Bonacini M, Ghabril M, et al. Hepatotoxicity Associated with the Use of Anti-TNF- Agents. Drug Saf. 2016;39:199-208.

Figures

Figure 1

A. Histological findings of the liver. The liver biopsy showed marked canalicular cholestasis, predominantly in a pericentral (zone 3) distribution. Numerous large intra canalicular bile thrombi were present throughout the hepatic parenchyma, associated with hepatocyte rosettes and patchy cytoplasmic condensation and eosinophilia. Lobular inflammation, as is the norm in cholestatic hepatitis, was minimal within the lobule. The portal tracts showed only minimal inflammation, without any evidence of bile duct injury or loss, and there was no interface hepatitis present (x 200).

Figure B

Figure 2

B. Changes in biochemical examination findings.