Tohoku J. Exp. Med., 2021, **255**, 57-60

Ustekinumab as the First Biological Agent for Crohn's Disease in a 10-Year-Old Girl

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Pediatric inflammatory bowel disease is associated with growth failure due to chronic inflammation, nutrient disorder, and the side effects of drugs, such as corticosteroids. Biological agents are therapeutic drugs that significantly improve the prognosis of patients with inflammatory bowel disease. The effectiveness of ustekinumab has been reported in the management of adult patients with inflammatory bowel disease. There are very few reports regarding the effectiveness and safety of ustekinumab in pediatric patients with inflammatory bowel disease, especially those who are biologically naive. A 10-year-old girl presented with chronic abdominal pain, diarrhea, and weight loss. Colonoscopy showed a longitudinal ulcer and cobblestone appearance in the ileum and discontinuous inflammation of the colon; therefore, she was diagnosed with Crohn's disease. She was prescribed a fat-restricted diet, elemental diet, 5-aminosalicylic acid, transient prednisolone, and ustekinumab. She achieved clinical and endoscopic remission based on the weighted Pediatric Crohn's Disease Activity Index, fecal calprotectin, and colonoscopy findings at week 75. This patient developed no adverse events, such as infusion reaction or susceptibility to infection over the 75 weeks. The use of ustekinumab as the first biological agent may be an effective and safe treatment for pediatric Crohn's disease.

Keywords: Crohn's disease; fecal calprotectin; inflammatory bowel disease; infliximab; ustekinumab
Tohoku J. Exp. Med., 2021 September, **255** (1), 57-60.

Introduction

Pediatric inflammatory bowel disease (IBD) is associated with growth failure due to chronic inflammation, nutrient disorder, and side effects of drugs, such as corticosteroids. Therefore, it is very important to control its activity. Biological agents are therapeutic drugs that significantly improve the prognosis of patients with IBD, and various biological agents have been developed in recent years. Although evidence of the efficacy of biological agents in adult patients is numerous, there have been few studies on their efficacy in pediatric patients. In Japan, only infliximab (IFX) has been approved (and covered by insurance companies) for the management of pediatric patients with IBD. The effectiveness of ustekinumab (UST) - a human monoclonal antibody that inhibits interleukin (IL)-12 and IL-23 functions by blocking the p40 subunit - has been reported in adult patients with IBD (Feagan et al. 2016). However, except for a report by Takeuchi et al. (2021) who describe the effectiveness and safety of UST in pediatric patients with IBD, there are very few reports regarding the effectiveness and safety of UST in pediatric patients with IBD, especially those who are biologically naive. Herein, we describe a pediatric case of Crohn's disease (CD) wherein UST was administered as the first biological agent. Informed consent to publish this case report was obtained from the patient's parents. We used UST in the management of our patient, considering its effectiveness and safety after the approval of the institutional ethics committee.

Case Presentation

A 10-year-old girl presented with chronic abdominal pain, diarrhea, and weight loss (35 kg to 32.6 kg for two months). The patient had no specific medical or family history. Laboratory examinations revealed 10,000 white blood cells/μL (neutrophils, 64.2%; lymphocytes, 23.7%) and

Received May 29, 2021; revised and accepted June 30, 2021. Published online September 28, 2021; doi: 10.1620/tjem.255.57.
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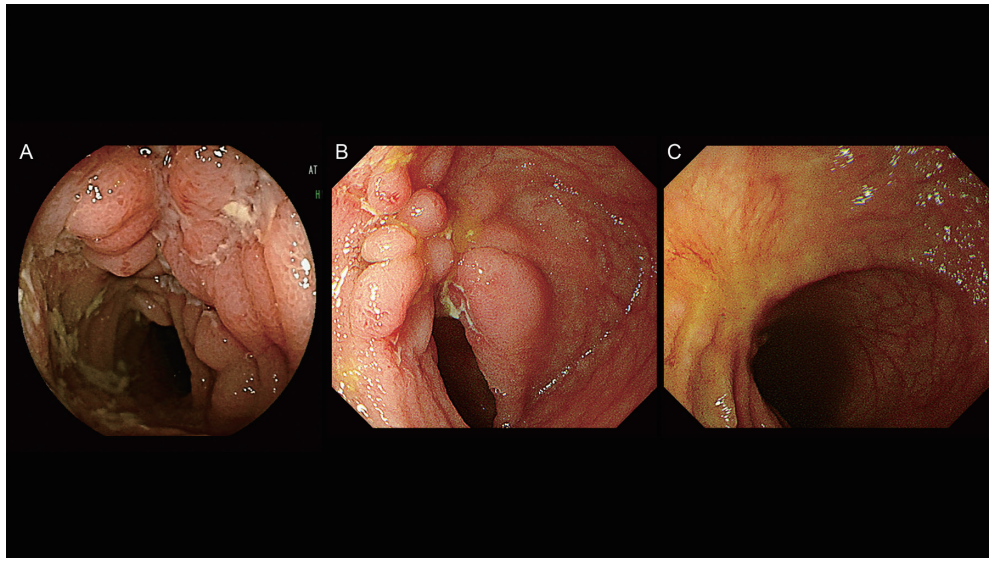
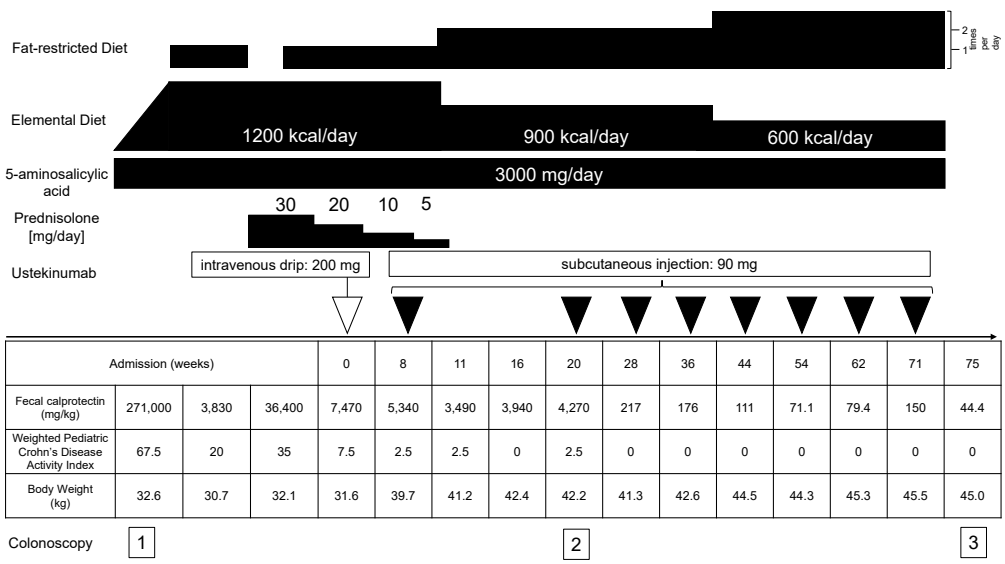


Fig. 1. Endoscopic findings of the ileum.
(A) At the time of diagnosis when the longitudinal ulcer and cobblestone appearance were visible. (B) At week 22 after initial ustekinumab administration when the ulcer had shrunk and was partially scarred, but active inflammation was still present. (C) At week 75 after initial ustekinumab administration, when the longitudinal ulcer scars were visible, and no active inflammation was observed.



Admission (weeks)				0	8	11	16	20	28	36	44	54	62	71	75
Fecal calprotectin (mg/kg)	271,000	3,830	36,400	7,470	5,340	3,490	3,940	4,270	217	176	111	71.1	79.4	150	44.4
Weighted Pediatric Crohn's Disease Activity Index	67.5	20	35	7.5	2.5	2.5	0	2.5	0	0	0	0	0	0	0
Body Weight (kg)	32.6	30.7	32.1	31.6	39.7	41.2	42.4	42.2	41.3	42.6	44.5	44.3	45.3	45.5	45.0

Fig. 2. Post-admission disease.
Since it is difficult to induce remission with nutrition therapy alone, and the small intestinal lesions were severe, prednisolone and ustekinumab were administered. Subsequently, the weighted Pediatric Crohn's Disease Activity Index (wPCDAI) improved promptly. Colonoscopy performed at week 22 showed that the discontinuous ulcers were shrunken and partially scarred; however, some were still active. The interval of ustekinumab administration was changed from every 12 to 8 weeks. Colonoscopy at week 75 showed that the longitudinal ulcer was scarred, and there was no active inflammation of the ileum and colon.

589,000 platelets/μL, with a hemoglobin concentration of 12.6 g/dL, serum albumin level of 2.7 g/dL, C-reactive protein of 1.33 mg/dL, erythrocyte sedimentation rate of 67 mm/h and serum immunoglobulin G of 2,353 mg/dL. The patient was negative for c- and p-antineutrophil cytoplasmic antibodies, cytomegalovirus antigenemia, and tuberculosis (T-SPOT assay). Her fecal calprotectin (FC) level was 271,000 mg/kg. Colonoscopy showed a longitudinal ulcer and cobblestone appearance in the ileum and discontinuous inflammation in the colon (Fig. 1A). Hence, she was diagnosed with CD. The patient's weighted Pediatric Crohn's Disease Activity Index (Turner et al. 2012) (wPCDAI) was 67.5. Mesalazine and an elemental diet led to improvement in her abdominal pain and laboratory findings; however, abdominal tenderness and diarrhea did not improve. Clinical symptoms and laboratory findings worsened after

the commencement of a fat-restricted diet.

Prednisolone 30 mg/day (1 mg/kg/day) and UST 200 mg (6 mg/kg based on UNITI study) were administered orally and intravenously, respectively (week 0) (Feagan et al. 2016) (Fig. 2). Immunomodulators, such as azathioprine, were not administered. The patient was discharged that same week as her condition did not worsen, and she continued receiving a fat-restricted diet once per day and an elemental diet of 1,200 kcal/day. PSL administration was gradually decreased and stopped after eight weeks; UST 90 mg [in reference to the regimen approved for the phase 1 clinical trial of UST in children with CD (NCT02968108)] was subcutaneously administered at eight and 20 weeks (bodyweight was > 40 kg at the time of subcutaneous UST administration). Colonoscopy performed at week 22 showed that the discontinuous ulcers were shrunken and partially scarred; however, some were still active. However, there were no active ulcers in the colon (Fig. 1B). The interval of UST administration was changed from every 12 to 8 weeks. Clinical remission was maintained, FC level decreased, and the fat-restricted diet was gradually increased to three times per day while the elemental diet was gradually decreased to 600 kcal/day (Fig. 2). At week 75, the longitudinal ulcer was scarred, and there was no active inflammation of the ileum and colon (Fig. 1C).

Discussion

Although only a few reports have assessed the effectiveness of UST as the first biological agent in both the induction and maintenance phases in the management of pediatric CD, the efficacy of UST for pediatric CD refractory to anti-tumor necrosis factor (TNF) therapy has been reported (Chavannes et al. 2019; Dayan et al. 2019; Takeuchi et al. 2021). In our case, although PSL was administered along with UST in the induction phase, clinical and endoscopic remission was maintained after the discontinuation of PSL; hence, the patient's diet was increased. We assessed the wPCDAI, FC, and CS over time; slightly active findings were noted in the ileum at week 20, after which the interval of UST administration was shortened, and no findings were observed at week 75 when dietary restrictions were relaxed. Our patient achieved clinical remission (wPCDAI 0) at week 16 and remains in steroid-free clinical remission, which is the primary outcome in the report by Takeuchi et al. (2021), even at week 75. Although Takeuchi et al. (2021) did not evaluate FC in their study, the FC level in our patient was assessed. FC level decreased after UST administration at week 20 and subsequently remained low. An FC of < 250 mg/kg is considered indicative of endoscopic and histological mucosal healing (Zittan et al. 2016). FC is recommended as a marker of treatment response in patients with luminal CD following induction therapy (van Rheenen et al. 2020). FC may be useful as a non-invasive biomarker when evaluating endoscopic activity in pediatric patients with CD. In our case, the wPCDAI, FC, and endoscopic findings were satisfactory, and UST was considered effective.

It is unclear which group of patients with CD benefit from the use of UST as the first biological agent. CD leads to the destruction of the microvilli of the small intestine, which are involved in nutrient absorption; however, this has been reported to be ameliorated by UST (Van Dussen et al. 2018), indicating that UST may be suitable for the management of patients with widespread and severe small intestinal lesions with failure to thrive. Although the microvilli were not assessed in our case, weight gain improved after discharge despite unchanged dietary requirements (Fig. 2), indicating that the destruction of microvilli in the small intestine was reduced by UST.

The safety of UST has been reported in terms of adverse events, such as susceptibility to infection (Papp et al. 2015) or infusion reaction, compared to IFX. No significant adverse events were observed in the studies demonstrating the effectiveness of UST (Chavannes et al. 2019; Dayan et al. 2019; Takeuchi et al. 2021). In this study, our patient experienced no adverse events over the 75 weeks of treatment. Immunomodulators, such as azathioprine, have been recommended to be administered with IFX to prevent the appearance of anti-biological antibodies (Gormollon et al. 2017). However, azathioprine was reported to induce various adverse events during short-term use, such as gastrointestinal symptoms, and during long-term use, such as lymphoproliferative disorders, especially in combination with an anti-TNF biological agent (Biancone et al. 2015; Tominaga et al. 2021). Although adalimumab, an anti-TNF-α biological agent, does not require the combination with thiopurine (Matsumoto et al. 2016), it also causes susceptibility to infection. Similarly, there is no difference in the effectiveness of UST with or without immunomodulators (Feagan et al. 2016); this perhaps offers an advantage for children who require long-term treatment.

Compared with IFX in terms of efficacy and adverse events, as described above, UST was considered suitable for the patient; hence, we selected UST for the management of this patient. In summary, we consider that the use of UST as the first biological agent may be an effective and safe treatment for pediatric patients with CD.

Acknowledgments

We would like to thank Editage (https://www.editage.com) for English language editing.

Conflict of Interest

The authors declare no conflict of interest.

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