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Ustekinumab effectiveness in Crohn's disease with lesions in the intestines

Satoshi Tamura, MD, PhD[a], Yusuke Asai, MD[a], Natsuki Ishida, MD, PhD[a], Takahiro Miyazu, MD[a], Shinya Tani, MD, PhD[a], Mihoko Yamade, MD, PhD[a], Yasushi Hamaya, MD, PhD[a], Moriya Iwaizumi, MD, PhD[b], Satoshi Osawa, MD, PhD[c], Takahisa Furuta, MD, PhD[d], Ken Sugimoto, MD, PhD[a,*]

Abstract

Ustekinumab is prescribed for the treatment of patients with steroid-resistant moderate to severe Crohn's disease. We investigated its clinical outcome in patients with small and large intestinal lesions. Patients who were newly administered ustekinumab between March 2014 and December 2020 at Hamamatsu University Hospital were included in the study. The primary endpoint was Crohn's disease activity index score at baseline and weeks 8, 24, and 48 after the initiation of treatment, and secondary endpoints were albumin, hemoglobin, and C-reactive protein at these time points. Ustekinumab treatment retention was examined in both groups; the 2 groups were compared using the Friedman test, Mann–Whitney *U* test, or Fisher exact test. Overall, Crohn's disease activity index scores improved between baseline and 48 weeks, but the difference was not significant. However, there was a significant improvement between baseline and 48 weeks in patients with lesions in the small intestine only. Overall, patients showed significant improvement in albumin levels between baseline and 48 weeks but not in C-reactive protein or hemoglobin levels. When limited to patients with lesions in the small intestine, albumin and hemoglobin levels showed significant improvement. Both types showed high rates of treatment retention, although there was no significant difference. Ustekinumab appears to be a safe and effective treatment option that may be particularly effective in patients with lesions in the small intestine only.

Abbreviations: Alb = albumin, CD = Crohn's disease, CDAI = Crohn's disease activity index, CRP = C-reactive protein, Hb = hemoglobin, IBD = inflammatory bowel disease, IL = interleukin, Th1 = type 1 helper T, Th17 = type 17 helper T, TNFα = tumor necrosis factor alpha.

Keywords: albumin, Crohn's disease, Crohn's disease activity index, hemoglobin, large intestine, small intestine, ustekinumab

1. Introduction

Crohn's disease (CD) is an intractable chronic inflammatory disease characterized by discontinuous granulomatous inflammation and stenosis or fistulae that can occur anywhere in the gastrointestinal tract.[1] The pathogenesis of CD is still unknown, but it is thought that the complex effects of genetic predisposition, environmental factors, and dysbiosis of intestinal bacteria ultimately result in immune abnormalities, which are followed by excessive production of inflammatory cytokines, contributing to the onset and exacerbation of CD.[2] Therefore, suppressing such immune abnormalities, that is, excessive cytokine production, is a therapeutic strategy for CD.

The cytokines that exacerbate CD are thought to be type 1 helper T (Th1) cytokines and type 17 helper T (Th17) cytokines.[3] The predominance of Th1 and Th17 cytokines in CD is partly due to exosomes released by $CD14^+$ macrophages that express membrane tumor necrosis factor (TNF), which binds to TNFR2 expressed on Th1 and Th17 cells. This activates NF-κB, and the Th1 and Th17 cells acquire activation-induced cell death resistance, allowing them to evade apoptosis and proliferate.[4] Anti-TNFα antibody preparations, the earliest biological agents for CD, have been shown to circumvent the activation-induced cell death resistance mechanism.[4]

A certain percentage of patients with CD are resistant to anti-TNFα antibody preparations (nonresponders), and Th17 cytokine levels in mucosa and blood are predominantly

Written informed consent was obtained from all individual participants included in the study.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The study protocol was reviewed and approved by the Institutional Review Board of Hamamatsu University School of Medicine (20-086). The investigation was conducted in accordance with Good Clinical Practice principles in adherence to the Declaration of Helsinki.

[a] *First Department of Medicine, Hamamatsu University School of Medicine, Higashi-ku, Hamamatsu, Japan,* [b] *Department of Laboratory Medicine, Hamamatsu University School of Medicine, Higashi-ku, Hamamatsu, Japan,* [c] *Department of Endoscopic and Photodynamic Medicine, Hamamatsu University School of Medicine, Higashi-ku, Hamamatsu, Japan,* [d] *Center for Clinical Research, Hamamatsu University School of Medicine, Higashi-ku, Hamamatsu, Japan.*

* *Correspondence: Ken Sugimoto, First Department of Medicine, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu 431-3192, Japan (e-mail: sugimken@hama-med.ac.jp).*

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elevated in these patients compared with those in responders.[4–6] Ustekinumab is an antibody against the p40 subunit of both interleukin (IL)-12 and IL-23 and is capable of simultaneously inhibiting Th1-induced IL-12 and Th17-induced IL-23 production.[1] Remission-inducing and remission-maintaining effects of this antibody on CD have been demonstrated in large-scale clinical trials.[7]

Recently, the concept of mucosal healing, which is defined as deep remission, has been proposed as a therapeutic target for CD with such biologics, and endoscopic treatment monitoring has become increasingly important.[8] A recent report showed that the endoscopic mucosal healing rate of patients with CD treated with infliximab for 1 year was lower in patients with CD having small bowel lesions than in patients with CD having colorectal lesions.[6] In mice, Th17 cells targeted by ustekinumab are more abundant in the small intestine than in the large intestine,[9] suggesting that ustekinumab may be effective against small intestinal lesions. However, real-world data on the efficacy of ustekinumab in patients with lesions in the small intestine only versus those with lesions in both the small and large intestines are not yet available.

In this study, we retrospectively evaluated the clinical outcomes of ustekinumab in patients with CD up to 48 weeks after administration of ustekinumab in patients with small bowel disease (small bowel-type) and patients with small bowel and large bowel disease (small bowel-colorectal type).

2. Materials and methods

2.1. Patients

Thirty-five patients with CD treated at Hamamatsu University Hospital who were newly administered ustekinumab were included in the study. All patients provided informed consent before enrollment in the study. Patients whose consent was not obtained were excluded from the study. Patients with other inflammatory bowel diseases (IBDs), such as ulcerative colitis, Behcet disease, and indeterminate colitis, were excluded. Laboratory tests, including blood counts and blood biochemical analysis, and measurements of the Crohn`s Disease Activity Index (CDAI), were performed at baseline and 8, 24, and 48 weeks. All authors had access to the study data and reviewed and approved the final manuscript. The study protocol was reviewed and approved by the ethics committee of the Hamamatsu University School of Medicine (16–268). The investigation was conducted in accordance with Good Clinical Practice principles adhering to the Declaration of Helsinki.

2.2. Study design

This was a single-center, retrospective, observational study. Patients were divided into 2 groups, namely 15 patients with lesions in the small intestine only (small bowel type) and 19 patients with lesions in both the small and large intestines (small bowel-colorectal type), and the results of clinical examination (serum C-reactive protein [CRP], hemoglobin [Hb], and serum albumin [Alb] levels) and clinical activity (CDAI) were compared. Discontinuation of ustekinumab or switching to other biologic agents for worsening symptoms was left to the discretion of the attending physician.

2.3. Clinical assessment and trial endpoints

The primary endpoint was the CDAI score at 8, 24, and 48 weeks after the administration of ustekinumab and at initiation in patients with small bowel CD and small bowel-colorectal CD. Secondary endpoints were blood test data (CRP, Hb, and Alb levels) and ustekinumab retention rates at baseline and 8, 24, and 48 weeks after initiation of ustekinumab in patients with small bowel CD and small bowel-colorectal CD.

2.4. Statistical analysis

Statistical analysis of CDAI scores and blood test data was performed using the Friedman test. Comparisons between groups were made using the Mann–Whitney *U* test or Fisher exact test. Ustekinumab retention was also evaluated using the log-rank test. $P \leq .05$ was considered statistically significant. IBM SPSS statistics Ver. 25.0 (SPSS Inc., Chicago, IL) was used for all analyses.

3. Results

3.1. Background of enrolled patients

Thirty-five patients with CD were enrolled; the characteristics of the enrolled patients were as follows: mean age at ustekinumab initiation was 37.8 ± 12.2 years, 25 males, 10 females, mean disease duration was 14.6 ± 11.2 years, 4 current smokers, 20 nonsmokers, and 11 former smokers. Twenty-five had a history of bowel resection and 9 had anal lesions. According to the Montreal classification, the occupied sites were L1, L2, and L3 in 15, 1, and 19 patients, respectively.

Previous therapy included 1 anti-TNF agent in 31.4%, 2 anti-TNF agents in 31.4%, and vedolizumab in 5.7% of the patients; 28.6% of the patients were bio-naïve. Concomitant medications at study entry were budesonide in 11.4%, 5-aminosalicylic acid (5ASA) in 82.9%, and immunomodulators in 31.4% (Table 1).

3.2. Changes in CDAI in patients with small intestine CD and small and large intestine CD

Next, we divided the patients into 2 groups: 15 patients with lesions in the small intestine only (Montreal Classification L1) and 19 patients with lesions in the small and large intestines (Montreal Classification L3). There were no significant differences in age, duration of disease, smoking history, surgical history, presence or absence of anal lesions, pretreatment CDAI, prior therapy, or concomitant medications between the 2 groups (Table 2).

We first examined changes in CDAI (Fig. 1). In the small intestine type, the CDAI at the start of ustekinumab, 8, 24, and 48 weeks was 156.8, 134.5, 103.2, and 75.0, respectively, showing a significant decrease between the start and 48 weeks ($P \leq .01$). However, in the small and large intestine types, the CDAI was 146.6, 125.1, 132.7, and 142.6 at the start of ustekinumab, 8,

Table 1

Characteristics of patients.

	N = 35
Age (mean ± SD) (range)	37.8 ± 12.2
Sex (male/female)	25/10
Disease duration (years, mean ± SD) (range)	15.1 ± 10.9 (1–34)
Type (L1/L2/L3)	15/1/19
Smoking behavior (current/never/former)	4/20/11
Previous surgeries	25
Anal lesion	9
CDAI score at initiation	154.9 ± 103.1
Previous therapy	
1 anti-TNF agent	11
2 anti-TNF agents	11
Vedolizumab	2
Bio-naïve	10
Concomitant medications	
Budesonide	4
Mesalazine	29
Immunomodulator	11

CDAI = Crohn's Disease Activity Index, SD = standard deviation.

24, and 48 weeks, respectively, which were within the clinical remission range but not significantly different between the start and 48 weeks (P = .338).

3.3. Changes in blood laboratory data in patients with small intestine CD and small intestine-colon CD

We next examined the blood laboratory data. In patients with CD of the small intestine, Hb levels were 11.5, 11.8, 12.8, and 13.7 g/dL at the start of ustekinumab, 8, 24, and 48 weeks, respectively, showing a significant improvement between the start and 48 weeks ($P \leq .05$) (Fig. 2A). However, in patients with CD of the small and large intestine types, Hb levels were 12.8, 12.8, 12.9, and 13.5 g/dL at the start of ustekinumab, 8, 24, and 48 weeks, respectively, showing a trend toward improvement, but no significant difference was observed between the start and 48 hours (P = .883) (Fig. 2A). Serum Alb levels in patients with CD of the small intestine type were 3.61, 3.88, 3.98, and 4.23 g/dL at 8, 24, and 48 weeks after the start of ustekinumab, respectively, showing significant improvement between the start and 48 weeks ($P \leq .05$) (Fig. 2B). In patients with CD of the small and large intestine type, serum Alb levels were 3.93, 4.08, 4.22, and 4.24 at 8, 24, and 48 weeks after the start of ustekinumab, respectively, showing significant improvement between the start and 48 weeks ($P \leq .05$) (Fig. 2B). We also examined serum CRP levels and found no significant difference between the start and 48-week follow-up for either group (P = .833, P = .196) (Fig. 2C). The serum CRP levels of the small intestine and small colon types remained low after 8 weeks of treatment, both being <1.00 mg/dL (Fig. 3B).

Table 2

Characteristics of patients in the small bowel type and the small bowel and colon type groups.

	Small intestine type (n = 15)	Small and large intestine type (n = 19)	*P* value
Age (mean ± SD) (range)	38.5 ± 11.8	37.7 ± 13.1	N.S.
Sex (male/female)	10/5	14/5	N.S.
Disease duration (years, mean ± SD) (range)	17.6 ± 10.4 (0–34)	15.7 ± 12.1 (0–46)	N.S.
Smoking behavior (current/never/former)	4/20/11	1/13/5	N.S.
Previous surgeries	11	13	N.S.
Anal lesion	3	6	N.S.
Previous therapy			N.S.
1 anti-TNF agent	4	6	
2 anti-TNF agents	5	7	
Vedolizumab	1	0	
Bio-naïve	4	6	
Concomitant medications			
Budesonide	1	3	N.S.
Mesalazine	13	14	N.S.
Immunomodulator	4	8	N.S.

N.S. = not significant, SD = standard deviation.

3.4. Ustekinumab continuation rates in patients with small intestine CD and those with small intestine-colon CD

We next examined the ustekinumab continuation rate in patients with small bowel CD and those with small bowel-colon CD. The overall retention rate at 12 months was 91.4% (Fig. 3A). The overall continuation rate of ustekinumab in patients with and without concomitant immunomodulators was 84.6% at 12 months, with no statistically significant difference between the 2 groups (P = .211) (Fig. 3B). Finally, we examined the ustekinumab retention rates in patients with small bowel and small bowel-colon CD and found that at 24 months, the retention rates in patients with small bowel CD and those with small bowel-colon CD were 93.3% and 94.7%, respectively, with no statistically significant difference between the 2 groups overall (P = .724), but both groups had retention rates of at least 80%, indicating that the retention rate remained high (Fig. 3B). However, the treatment continuation rate in both groups was >80% (P = .724), indicating that a high continuation rate was maintained (Fig. 3C).

4. Discussion

This study is the first to involve real-world data to examine whether there is a difference in the outcome of ustekinumab treatment in patients with CD having lesions in the small intestine alone versus those with lesions in both the small and large intestines. The study showed that the use of ustekinumab reduced the clinical activity of patients with CD over 48 weeks, with significant improvements in clinical activity and Hb and Alb levels after 48 weeks, particularly in patients with CD showing small bowel involvement. There was no difference in ustekinumab treatment retention rates between patients with and without IM or between the small bowel and small bowel-colon types of CD, but both showed high rates of continued treatment.

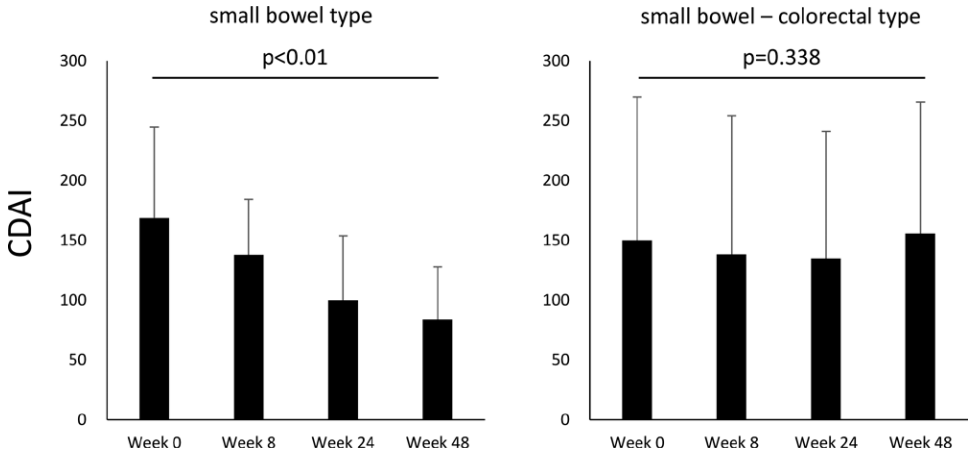

Figure 1. Comparison of CDAI scores in the small bowel type and small bowel and colon type groups.

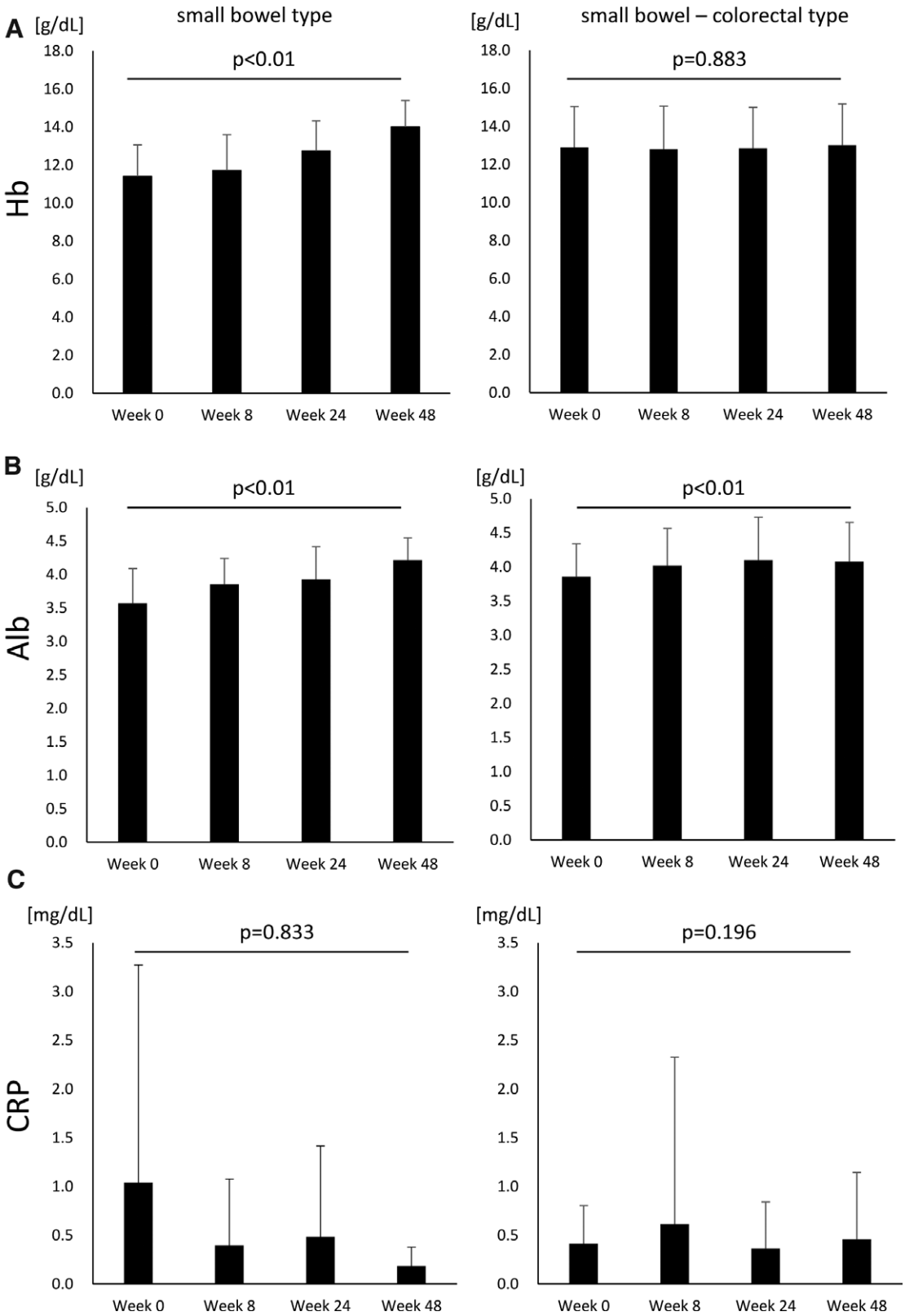

Figure 2. Comparison of levels of (A) Hb, (B) Alb, and (C) CRP in the small bowel type and the small bowel and colon type groups. Alb = albumin; CRP = C-reactive protein; Hb = hemoglobin.

Long-term data on ustekinumab for CD are presented as long-term extension results from the IM-UNITY trial over 5 years,[10] and in an intention to treat analysis, 34.4% of patients in the group that received ustekinumab every 8 weeks and 28.7% of patients in the group that received ustekinumab every 12 weeks achieved clinical remission at 252 weeks, and there were no significant differences in adverse events between the placebo and ustekinumab groups, indicating long-term efficacy and safety.[10] In our case series, no adverse events were observed with ustekinumab, and it is considered to be a safe

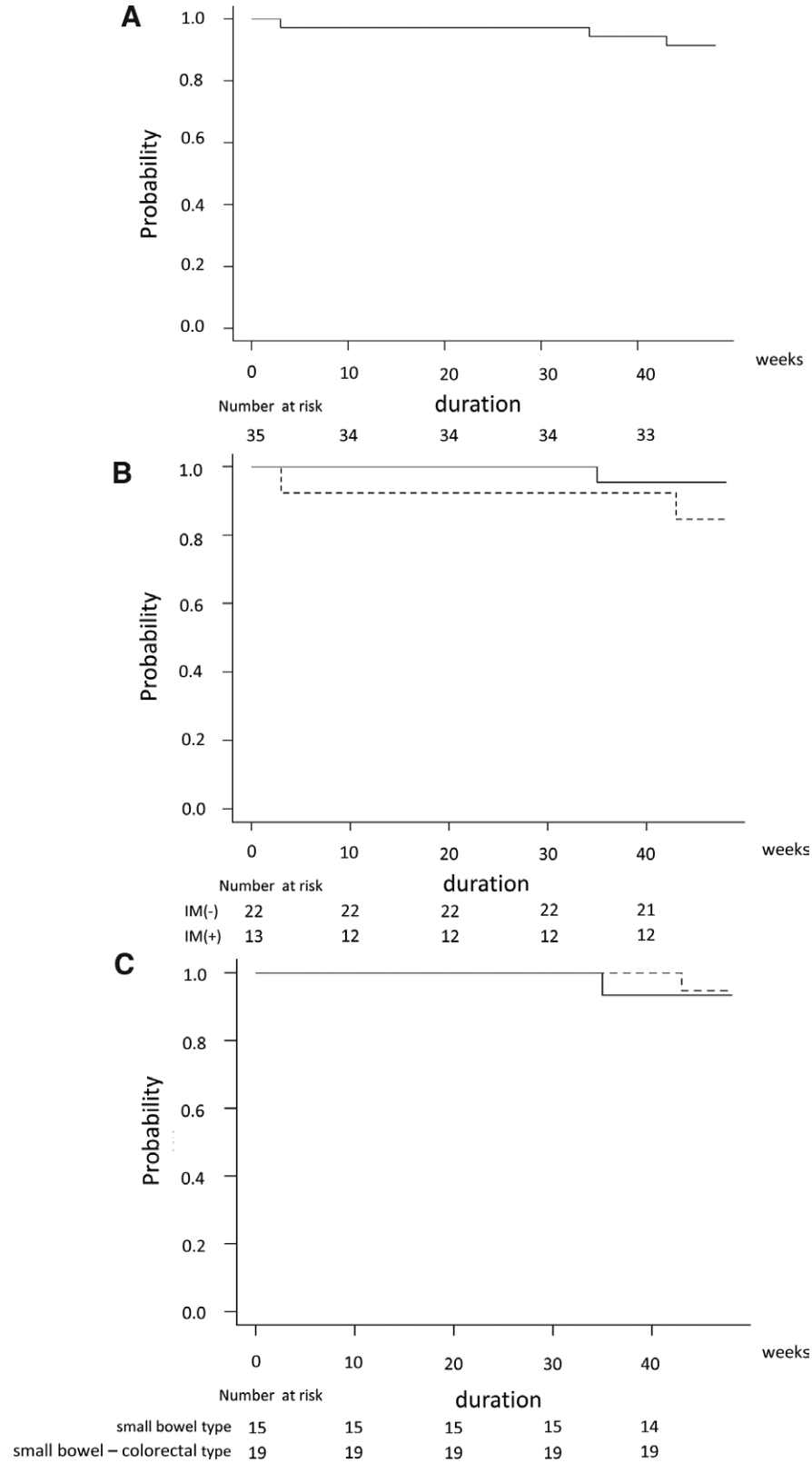

Figure 3. Survival curves up to 48 weeks, with Kaplan–Meier representation. (A) Overall, (B) comparison between immunomodulator- and non-immunomodulator-using groups. Solid lines indicate the immunomodulatory–non-immunomodulator group; dashed lines indicate the immunomodulatory–immunomodulator group. (C) Comparison between the small intestine group and the small and large intestine groups. The solid line shows the small intestine group, and the dashed line shows the small and large intestine groups.

drug. Although there is concern that the administration of the drug may reduce the immune status and weaken the efficacy of vaccines, especially in the context of a COVID-19 pandemic, previous reports suggest that ustekinumab can be used relatively safely in patients with IBD even in the context of the COVID-19 pandemic.[11,12]

In this study, we focused specifically on patients with CD that had lesions in the small intestine only. Interestingly, Takenaka et al[13] reported that the endoscopic cure rate of patients with CD treated with anti-TNF inhibitors depended on small bowel involvement. The mucosal healing rate for patients with CD having lesions in the large intestine only was 79%, compared to 36% for patients with lesions in the small intestine only and 35% for patients with lesions in the small and large intestines, suggesting that patients with lesions in the small intestine are less likely to respond to anti-TNF inhibitors. Rivière et al[14] conducted a randomized controlled trial of biologic-naïve active CD with endoscopic ulcer lesions treated with combination therapy, including IFX, and evaluated patients using ileocolonoscopy at 0, 12, and 54 weeks. The endoscopic mucosal healing rates at 12 and 54 weeks were 45% and 59%, respectively, for patients with CD having small bowel disease, compared with 72% and 82% for patients with the colon-only disease, indicating that patients with small bowel disease are also less likely to respond to biologic agents, including anti-TNF inhibitors.

Because few studies on ustekinumab have focused on the location of the lesions, we investigated the effect of ustekinumab on clinical severity and hematologic parameters in patients with small bowel and small bowel-colorectal CD with lesions in the small bowel. In our study, CDAI showed significant improvement after 48 weeks of ustekinumab treatment in patients with the small intestine type and, while there was a trend toward improvement in patients with the small and large intestine types, no significant differences were observed. One reason why ustekinumab is more effective in the small intestinal form of CD is related to the distribution of Th17 and Th1 cells, which are targeted by ustekinumab. In the mouse intestinal tract, Th1 cells are evenly distributed in the small and large intestines, whereas Th17 cells are more abundant in the small intestine than in the large intestine.[9] Because Th17 cells are probably more abundant in the small intestine in humans, ustekinumab may exert its anti-inflammatory effect more effectively when lesions are located only in the small intestine.

We next examined the effect of ustekinumab on blood test data. Serum Alb levels showed significant improvement after 48 weeks of ustekinumab treatment in both small intestine and small colorectal types. This suggests that ustekinumab not only improves the clinical severity of the disease but also improves the nutritional status of the patients. Interestingly, the microvilli in the small intestinal epithelium of patients with CD are shorter and more irregular in morphology than those in non-IBD patients.[15] In addition, microvilli length correlates with the expression of genes that regulate microvilli structure and function, such as F-actin bundling, membrane-cytoskeleton cross-linking, and intermicrovillar adhesion. The expression of these genes is downregulated in CD compared with that in non-IBD.[15] In addition, a subanalysis of the UNITI-2 trial showed that ustekinumab significantly restored microvilli length after 8 weeks of treatment compared with the placebo.[15] Thus, ustekinumab may have the ability to improve the microstructure of the small intestinal microvilli, which would improve the ability of the small intestine to absorb nutrients, thereby improving the nutritional status of patients with CD and increasing serum Alb levels. Hb levels also improved in patients with the small intestinal form after 48 weeks of ustekinumab treatment. This may be due to the increased absorption of hematopoietic substances, such as iron, folic acid, and vitamin B12, resulting from the normalization of the microstructure of the small intestine. Serum CRP levels were low but not significantly improved after 48 weeks of treatment with ustekinumab in both the small and large intestine types. This may be because CRP levels were low at the time of ustekinumab administration. In this study, the small bowel type exhibited better blood test results than the small and large bowel type, but there was no significant difference in the treatment retention rate. This suggests that ustekinumab may be highly effective even in patients with colorectal disease.

Limitations of this study include the single-center, retrospective design, small sample size, lack of endoscopic improvement, and lack of evaluation of biomarkers, such as calprotectin and LRG.

5. Conclusion

The results indicate that ustekinumab may be more effective in patients with small bowel CD than in those with small bowel colorectal CD. In addition, our results suggest that continued treatment with ustekinumab not only improves clinical severity and inflammatory response but also contributes to improved nutritional status.

Author contributions

Conceptualization: Satoshi Tamura, Natsuki Ishida, Takahiro Miyazu, Shinya Tani, Mihoko Yamade, Yasushi Hamaya, Moriya Iwaizumi, Satoshi Osawa, Ken Sugimoto.
Data curation: Satoshi Tamura, Yusuke Asai, Natsuki Ishida, Takahiro Miyazu, Shinya Tani, Mihoko Yamade, Yasushi Hamaya, Moriya Iwaizumi, Satoshi Osawa, Takahisa Furuta, Ken Sugimoto.
Formal analysis: Natsuki Ishida, Takahiro Miyazu, Shinya Tani, Mihoko Yamade, Moriya Iwaizumi, Takahisa Furuta, Ken Sugimoto.
Funding acquisition: Ken Sugimoto.
Investigation: Satoshi Tamura, Yusuke Asai, Natsuki Ishida, Takahiro Miyazu, Shinya Tani, Mihoko Yamade, Yasushi Hamaya, Moriya Iwaizumi, Satoshi Osawa, Takahisa Furuta, Ken Sugimoto.
Methodology: Ken Sugimoto.
Project administration: Yasushi Hamaya, Ken Sugimoto.
Resources: Satoshi Tamura, Takahiro Miyazu, Ken Sugimoto.
Software: Satoshi Tamura, Takahiro Miyazu, Takahisa Furuta.
Supervision: Satoshi Osawa, Ken Sugimoto.
Validation: Yasushi Hamaya, Takahisa Furuta, Ken Sugimoto.
Visualization: Yusuke Asai, Yasushi Hamaya, Satoshi Osawa, Ken Sugimoto.
Writing – original draft: Satoshi Tamura, Ken Sugimoto.
Writing – review & editing: Satoshi Osawa, Ken Sugimoto.

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