Intestinal stiffness in Crohn's disease treated by biologics: Comparison of ustekinumab and infliximab using ultrasound shear wave elastography

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Abstract

Background: Intestinal strictures represent an important serious complication of Crohn's disease (CD). Shear wave elastography (SWE) is one of the promising noninvasive ultrasound techniques for assessing tissue stiffness. This study was aimed to evaluate stiffness at the areas of intestinal stricture in CD patients using SWE, and the changes of stiffness after biologics.

Methods: Bowell wall thickness was examined by ultrasound sonography (US) and the stiffness of CD stricture lesions was evaluated using Shear wave speed (SWS) before and one year after anti-TNF-alpha antibody infliximab (IFX), anti-interleukin (IL) 12/23 antibody ustekinumab (UST), and bio-switch from IFX to UST.

Results: Bowell wall thickness was significantly improved after IFX, UST, and the bio-switch. However, SWS indices only in the UST group significantly decreased after treatment (p=0.028), but not in the other group.

Conclusion: UST may lead to suppression of obstruction in CD naïve patients with stricture lesions.

Background

Crohn's disease (CD) is a transluminal disease in which progressive inflammation leads to intestinal wall thickening and fibrous process. The positioning of biologics therapies in CD is increasing and challenging because of developing new therapies with different mechanisms of action. Tumor necrosis factor alpha (TNF-α) antagonists, such as infliximab (IFX), adalimumab (ADA) and certolizumab, have revolutionized the treatment of moderate to severe CD patients with an inadequate response to standard medication.[1, 2] Although IFX would be widely recognized as being effective in CD, it has been reported to cause strictures in some patients.[3] On the other hands, treatment options for CD have increased due to the development of new biologics such as ustekinumab (UST)(anti-p-40) and vedolizumab (anti-α4β7 integrin). [4, 5] Recently, comparative efficacy of IFX and UST in CD patients was reported indicating similar rates of week 6 clinical remission and response. [6] However, there would be the hypothesis that IFX and UST may have different effect on the healing, because UST may lead to suppression of fibrogenesis and stenotic formation.[7] UST suppresses the cytokine pathway of Th1 cells and Th17 cells by suppressing both IL-23 and IL-12 production. In addition, UST might affect decreased TGF-β production of Th1 cells via macrophages as well as decreased production of IL-22 and IL-17 from Th17 cells, leading to the suppression of myofibroblast proliferation (or transformation) and function.

Stricturing CD is a significant clinical problem developing obstruction, ileus. Intestinal strictures induced by CD are histologically characterized by the presence of mixture of inflammatory and mesenchymal cells with the deposition of excess of extracellular matrix (ECM), which results in different degrees of fibrosis. [8] According to population-based studies using the Montreal classification, the probability of progression to stricturing CD is about 15% at 10 years and 21.6% at 20 years. [9, 10,' 11] It is important to analyze types of intestinal stricture, the degree of stenosis and stiffness to select treatments against the intestinal stricture, such as anti-inflammatory drugs, endoscopic balloon dilation, and surgical resection.

Intestinal strictures are clinically evaluated by mainly cross-sectional images such as intestinal ultrasound (IUS), computed tomography (CT), and magnetic resonance imaging (MRI) examinations, because they allow sophisticated assessment of the entire intestinal wall. [12,' 13] Especially, IUS is a non-invasive, non-radiation, broadly available and accurate diagnostic tool not only to evaluate disease activity and complications, but also to monitor disease progression and assessment of therapeutic response in CD patients. [14, 15] Point-of-care bowel ultrasound (POCBUS) is reported to have a sensitivity of 80–90% and a specificity of 94–98% in properly discriminating inflammatory from non-inflammatory diseases in patients with abdominal symptoms, and lead the modification of treatment strategies in more than 60% of CD patients. [16, 17] Treat-to-target (T2T) strategy for IBD shifts the goal of treatment to long-term prevention of complications and propose close monitoring of disease activity. [18]

Additionally, ultrasound elastography is a promising, non-invasive technique, for assessing tissue stiffness.[19] There are two major types of elastography: shear wave elastography (SWE) and strain elastography (SE). In SWE method, an initial US push pulse, which induces a shear wave perpendicular to the US beam, is applied to the tissue.[20] SWE measures the scissoring speed of shear wave induced by an acoustic radiation force impulse (ARFI), while SE assessment is a derivative of comparison between targeted and surrounding tissues after external pressure induced by an operator presenting as a color-coded elastogram, Interpretation of SE is more subjective due to the diagnostic method itself, and the advantage of SWE is that the measurements are objective and do not depend on the surrounding tissues. Thus, SWE had proved to be more reliable and reproducible than SE.[21] SWE has also been shown to be useful for differentiating benign lesions from malignant lesions in breast, prostate, and thyroid.[22–24] Recently, there are some reports demonstrating that ultrasound elastography would be a useful examination to analyze bowel wall thickness and stricture in CD patients.[25, 26] Ding SS, et al [27] evaluated the diagnostic performance of both SE and SWE for intestinal stenosis in CD indicating the better performance of SWE for evaluating and differentiating intestinal stenosis in CD. However, there was no report to evaluate the impact of biologics on tissue stiffness in patients with CD stricture lesions using SWE.

This study aimed to evaluate and compare the change of stiffness of CD stricture lesions using SWE after anti-TNF-alpha antibody infliximab (IFX), anti-interleukin (IL) 12/23 antibody ustekinumab (UST), and bio-switch from IFX to UST.

Methods

Patients and Examination.

Outpatients and inpatients with stricturing CD who were paned to perform IUS were enrolled in this study from 2019 Dec to 2021 Jan. The patients who performed SWE before and one year after IFX, UST, bio-switch from IFX to UST were selected. Patients treated by other biologics were not included because of the small number of subjects. Patients lacking SWE images either before or after treatment were also excluded.

Intestinal ultrasound (IUS).

IUS was performed using US system Aplio i 900 (Cannon Medical system, Japan) with 7MHz linear transducer (3–11 MHz, PLI-705BX) in the most affected bowel segment, mainly ileocecal lesion in CD. All patients underwent IUS in supine position after at least 6h of fasting. These procedures were performed by one gastroenterologist (JH), with more than 35 years of IUS. Disease site was defined pathological wall thickness (on the basis of bowel wall thickening (BWT) > 3mm for ileum and > 4mm for colon, ileocecal area) were evaluated.[15, 28]

Intestinal stricture lesions.

In this study, the definition of intestinal stricture was both colonoscopy and/or small bowel x-ray, and IUS. The stricture lesion was defined un-passing lesion on the colonoscopy (scope dimer 13.2mm, CF-HQ290L, 290I, Olympus, JAPAN), or ileal luminal narrowing (< 3mm) with/without oral side expansion on small bowel x-ray examination. In patients with multiple small bowel stricture lesions of CD, the most bowel wall thickness lesion was evaluated.

Ultrasound Shear Wave Elastography (SWE).

The elasticity was quantified by SWE measuring the scissoring speed induced by ARFI using the same US system. [29] In the during SWS measurement, SWE was performed without unnecessary transducer compression to prevent technical error increasing SWS.[29] With respect to the full bowel wall elasticity in stenotic lesion, at least 5 regions of interest (ROI) of the stenotic bowel segment were measured. The ROI were placed at the position of full thickness of bowel wall without surrounding tissues and luminal content. SWS in each ROI was measured more than 5times and the mean value in each ROI was calculated excluding both maximum and minimum data. The data in inadequate ROI were also excluded. The adequate ROI was defined the below (Fig. 1): The rectangle surrounded with red line meaning that the standard deviation (S.D.) was less than 10% of the mean SWS value (A). Besides, in propagation map, the waveform of measurement point was not distorted (B).

Statistical analysis.

Values were presented as mean ± SD or median and interquartile range (IQR) [25–75% range] whichever was appropriate depending on whether the data were normally distributed or non-normally distributed. The category data were presented as counts with percentage and analyzed by chi-square test. Demographic characteristics of patients and values of ultrasound parameters were expressed as the median with range of measurements. The data were compared among three groups by Kruskal-Wallis analysis, Chi-square test or one-way ANOVA test and compared between before treatment and after treatment by paired t test, and Wilcoxon rank sum test in SPSS software (version 26). $P < 0.05$ was taken to indicate a significant difference.

Results

The patients consisted of the three groups, which were the IFX naïve (n=6) group, the UST naïve (n=8), and the bio-switch from IFX to UST (n=7) group. The duration of CD and biologics treatment were significantly longer and the operation history was significantly more frequent in the bio-switch group than in the other groups, while the duration of UST was not significantly different between the bio-switch group and the UST group (Table 1).

The strictures of Bauhin's valve were detected in 17 patients (80.9% =17/21). The remaining patients were shown ileal strictures in small bowel x-ray examination. The ileal strictures were detected in 2 patients (33%) of the IFX group and the strictures of Bauhin's valve were detected in 4 patients (50%) in the UST group. Those percentages were tended to be lower than those in the other groups, however the frequency of strictures was not significantly different among the three groups (Table 1).

The median baseline data of CD activity indices (CDAI) and CRP were tended to be higher and the median baseline hemoglobin (Hb) and albumin (Alb) values were tended to be lower in the IFX group compared to the other groups, although the differences were not significant. Serum CRP levels after treatment were significantly higher and Alb levels after treatment were significantly lower in the bio-switch group than in the others. All values of the CDAI, the CRP, the Hb and the Alb were improved after IFX treatment, while the CRP and the Hb values in the UST group and the only CDAI in the bio-switch group were improved. (Table 1).

The median baseline BWT indices were not significantly different among the three groups. However, the median BWT after treatment were significantly different among the three groups, and was the highest in the bio-switch group (5.15mm) and decreases in the UST group (3.97mm) and the IFX group (2.89mm) (Table 2). The BWT indices significantly decreased one year after treatment in all three groups (IFX, r=0.028; UST, r=0.012; bio-switch r=0.018, Figure 2A).

On the other hands, the median SWS indices baseline and after treatment were significantly different among the three groups, and were higher in the switch group than those in the other groups. The median SWS indices subtraction in the UST group was significantly lower than those in the others (UST-1.58 vs IFX -0.22, p=0.029, UST-1.58 vs bio-switch -0.28 p=0.013) (Table 2). However, there was no significant difference between the IFX and the bio-switch groups. The SWS indices only in the UST group significantly decreased after treatment (2.81m/sec to 1.65 m/sec, p=0.028), but not in the other group (IFX 2.24 m/sec to 2.07 m/sec, p=0.715; bio-switch 3.5 m/sec to 3.62 m/sec, p=0.917) (Figure 2B).

Table 1

Clinical backgrounds of Crohn's disease patients with biologic treatments

		IFX n=6	UST n=8	IFX→UST n=7	*p value*
Age; mean ± SD		25.3±13.7	37.6±22.2	47.4±10.5	0.869 [c]
Gender (M/F)		4/2	4/4	5/2	NS [b]
BMI: median[IQR]		17.0[16.1-17.5]	19.8[17.5-21.3]	21.2[20.7-22.1]	0.281 [c]
Disease duration (yrs): median[IQR]		1.5[1.0-1.6]	1.7[1.0-2.0]	19.0[18.0-29.0]	0.003[c]
Bionaive case (%)		6 (100%)	8 (100%)	-	-
Duration of biologics (month): median [IQR]		17.0[12.0-28.5]	22.0[19.0-29.7]	228[204-336]	0.001 [a]
Duration of UST (month): median [IQR]		-	22.0[19.0-29.7]	21.0[20.0-29.0]	0.789 [a]
History of operations (%)		0	1(13%)	6(86%)	0.014 [b]
Obstruction/Ileus (%)		1(16%)	3(38%)	3(43%)	NS [b]
Endoscopic balloon dilatation (%)		1(16%)	1(13%)	3(43%)	NS [b]
Stricture location					
ileum		2(33%)	4(50%)	7(100%)	NS [b]
Bauhin's valve		6(100%)	4(50%)	7(100%)	
Endoscopically *impassable stricture*		6(100%)	4(50%)	7(100%)	NS [b]
Intestinal narrowing (<3mm) by x-ray exam		6(100%)	4(50%)	7(100%)	
Clinical Data					
Simple CDAI	Baseline; median[IQR]	5.5[2.0-11.0]	2.0[0.5-2.75]	1.0[1.0-3.0]	0.076 [a]
	1 yr after; median[IQR]	0[0-1.5]	0.5[0-2.5]	0[0-0]	0.347 [a]
	*p value**	0.027[e]	0.063 [e]	0.024 [e]	
CRP	Baseline; median[IQR]	4.26[2.22-13.7]	0.85[0.29-5.19]	0.65[0.6-1.65]	0.058 [a]
	1 yr after; median[IQR]	0.03[0.02-0.23]	0.07[0.03-0.19]	0.63[0.08-0.85]	0.046 [a]
	*p value**	0.028[e]	0.018 [e]	0.204 [e]	
Hemoglobin	Baseline; mean±S.D.	11.4±2.3	11.9±1.5	12.5±1.8	0.584 [c]
	1yr after; mean±S.D.	13.9±0.8	13.5±1.3	12.9±0.8	0.232 [c]
	*p value**	0.021 [d]	0.023 [d]	0.465 [d]	
Albumin	Baseline; mean±S.D.	2.9±0.5	3.7±0.6	3.7±0.7	0.053 [c]
	1yr after; mean±S.D.	4.2±0.2	4.1±0.4	3.8±0.2	0.030 [c]
	*p value**	0.001 [d]	0.092 [d]	0.73 [d]	

IQR; interquartile range; IFX, infliximab; UST, ustekinumab; IFX→UST, bioswitch from IFX to UST; NS; not significant; p^a by Kuruskal-wallis test; p^b by Chi-square test; p^c by one-way ANOVA test; p^d paired t test; p^e Wilcoxon test; *p value**, Comparison before and after treatment

Table 2

Comparison of the change of bowel wall thickness (BWT) , Shear Wave Speed (SWS) analysed by US, Crohn's disease with biologic treatment; infliximab; IFX, ustekinumab; UST, bioswitch from IFX to UST; IFX→UST

IFX, infliximab; UST, ustekinumab; IFX→UST, bioswitch from IFX to UST IQR: interquartile range

Discussion

To our knowledge, this is the first study to evaluate the change of stricture stiffness of CD using SWE after biologics treatment. Interestingly, only the SWS indices in the UST naïve group were significantly decreased one year after the treatment, but not in the IFX naïve group and the bio-switch group. On the other hand, the BWT indices in each group were significantly decreased.

Intestinal stricture of CD is characterized by focal asymmetric, transmural, and granulomatous inflammation affecting any segment of the gastrointestinal tract [30], and could be subdivided into the 3 different types; predominantly fibrotic, inflammatory, and mixed type. [31, 32, 33] It is difficult to determine the type of stricture by clinical manifestations and using serological indicators. The strictures containing considerable fibrosis thought to be associated with intramural SWS indices, which may be higher in the fibrotic strictures compared to purely inflammatory strictures. On the basis of the bowel wall SWS, it may be possible to evaluate the presence of fibrosis at the time of initial diagnosis of stricture presentation. [34, 35] Fibrosis process results from the activation of mesenchymal cells by TNF-α, transforming growth factor-β (TGF-β), vascular growth factor, and insulin-like growth factor-1, matrix metalloproteinases, and other mediators released by leukocytes, epithelial and mesenchymal cells, and the gut microbiota. TGF-β induces myofibroblast transformation from fibroblast and epithelial cells, and myofibroblast produced collagen and fibronectin leading extracellular matrix and causing fibrotic strictures. Thus TGF-β is one of the important molecular targets against fibrotic strictures. The healing process could be different depending on the biologics, because of the different role of target molecules.

UST may suppress the activity of TGF-βactivated by IL-22 and IL-17, because UST blocks IL-23 and also decreases the expression of IL-17A downstream, which may lead to suppression of fibrogenesis and stenotic formation. [7, 36] UST downregulated TNF-α expression indirectly, which slows the healing of ulcerations as compared with anti-TNFαagents.[37] Thus, UST may lead to suppression of fibrogenesis and stenotic formation. Interestingly, Murate K, et al reported that UST could be an effective treatment for preventing re-stenosis of the small bowel after endoscopic balloon dilation (EBD) in two cases with small

	IFX(n=6)			UST(n=8)			IFX→UST(n=7)			p*
	Baseline	1yr after	subtraction:base from 1yr after	Baseline	1yr after	subtraction:baseline from 1yr after	Baseline	1yr after	subtraction:baseline from 1yr after	Baseline
Bowel wall thickness of stricuture (mm): median[IQR}	4.4 [3.85-7.5]	2.89 [2.19-3.69]	-1.51 [-4.61–1.07]	4.88 [4.15-6.48]	3.97 [3.78-4.17]	-1.03 [-2.66-0.39]	6.7 [6.02-7.48]	5.15 [4.02-6.17]	-1.2 [-2.0—0.53]	0.176
Shear Wave Speed (Vs:m/sec): median[IQR]	2.24 [1.99-2.63]	2.07 [1.88-2.39]	-0.22 [-0.12–0.99]	2.81 [2.20-4.48]	1.65 [1.53-1.76]	-1.58 [-3.28-0.67]	3.5 [2.95-4.04]	3.62 [2.77-4.39]	-0.28 [-1.74-0.89]	0.034

bowel lesions. [38, 39] On the other hands, anti-TNF-α antibodies induced small bowel stenoses in 8 of 15 (53.3%) patients after 6–22 maintenance infusion. [40] In another prospective study investigating the frequency of small bowel obstruction in CD stricture patients after IFX or adalimumab, 22.2% (2/9) had bowel obstruction requiring surgical resection. [41] However, the data about the development bowel obstruction after UST is lacking. The further prospective studies are required increasing the number of patients and extending observation period after the biologics therapy.

There were two reports evaluating SE against intestinal lesions of CD treated with anti-TNF therapy. Orlando et al. [42] evaluated as a method of monitoring outcomes of anti-TNF therapy, no statistically significant difference in strain ratio values at baseline and at 14 and 52 weeks after therapy.[42] Our results also indicated no statistically significant difference in SWE indices in the IFX group and the bio-switch group. Only the SWS indices in the UST naïve group were significantly decreased one year after the treatment. The reason of no improvement in the bio-switch group might be due to the fibrotic strictures, which have formed during the longer duration of CD. Our results suggested that early induction of UST could be related with suppression of fibrosis, however immunochemical histologic analysis of stenosis lesion treated UST are required to confirm in the further study.

BWT would be useful to monitor biologics-induced bowel activity improvement in CD.[15, 28, 43] There is an increase in echogenicity of the third layer of the intestinal wall (submucosal layer) that is currently thought to be an expression of submucosal fibrosis, whereas hypoechogenicity of the intestinal layers is related to hyperemia and edema. [44, 45] Increased BWT are important components of inflammation,[46] and improvement lesions are generally defined as those with improvement (> 1mm) or normalization of BWT. [28] In this study, the BWT in each group including the bio-switch group decreased significantly after biologics treatments, and both biologics improved simple CDAI regardless bio-naïve status. Therefore, BWT may be a beneficial tool to evaluate activity reflecting mainly inflammation, while SWS might be a better tool to evaluate fibrotic stricture reflecting tissue stiffness.

This study has several limitations. At first, there was no reference standard, such as histological fibrosis analysis using surgical resection organs. Secondary, the number of patients is small and the study is retrospective. The baseline of clinical data among the three groups were not matched and selection bias should be considered. Especially, the baseline CDAI were different between the IFX group and the UST groups. Almost our CD patients with perianal and perirectal lesions were treated by IFX, because IFX is reported to be more effective against perianal lesion compared to UST. [47] The further prospective study evaluating the development of obstruction after biologics treatment are required to confirm the difference in SWS. The multicenter large-scale study adjusting the clinical data between the UST group and the IFX group is required to conform the results.

In conclusion, only the SWS indices in the UST naïve group were significantly decreased one year after the treatment, but not in the IFX naïve group and the group with switching from IFX to UST. Early induction of UST in patients with CD might lead to suppression of stenotic formation.

Abbreviations

CD: Crohn's disease, SWE: Shear wave elastography, US: ultrasound sonography, TNF-α:Tumor necrosis factor alpha, IFX: infliximab, ADA: adalimumab, UST: ustekinumab, IUS: intestinal ultrasound, CT: computed tomography, MRI: magnetic resonance imaging, POCBUS: Point-of-care bowel ultrasound, T2T; Treat-to-target, SE; strain elastography, ARFI: acoustic radiation force impulse, IL; interleukin, EBD: endoscopic balloon dilation, ROI: regions of interest, BWT: bowel wall thickening, S.D.: standard deviation, TGF-β: transforming growth factor-β, EBD: endoscopic balloon dilation,

Declarations

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Author's contribution

H.M. and J.H. designed the study. H.M. wrote the original draft of the manuscript. H.M. and J.H. and A.S wrote the main manuscript text. J.H and H.I prepared figure 1. S.Y., M.S., H.M., M.O., T.M., O.H., E.U., are obtaining patient consent and data. All authors read and approved the final manuscript.

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Availability of data and materials

All data analysed during this study are included in this published article.

Ethics approval and consent to participate

All methods were performed in accordance with the Declaration of Helsinki and complied with relevant guidelines and regulations. Ethical approval was obtained from Kawasaki Medical School Ethic and Medical Research Committee (no.3749). Written informed consent was achieved from each research subject before enrollment. All patients were enrolled at the Division of Gastroenterology of Kawasaki Medical School Hospital. The study was registered at the University Hospital Medical Information Network Center (UMIN 000037596).

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Figures

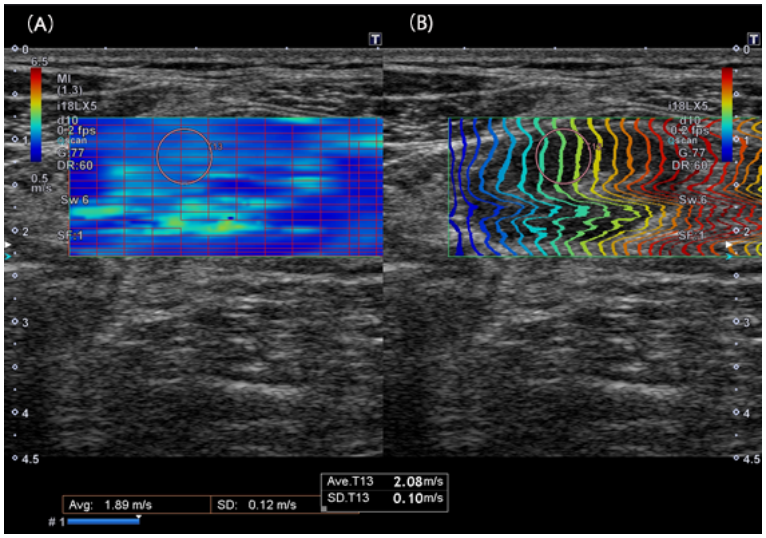

Figure 1

Shear Wave Elastography (SWE) image (A) The rectangle had small 96 rectangle surrounded with/without red line. The rectangle surrounded with red line means that the standard deviation (S.D.) was less than 10% of measure mean shear wave speed (SWS) value, thus ROI in the rectangle were reliable to measure. On the other hands, the rectangle surrounded without red line means that S.D. was more than 10% of measure mean SWS value, thus ROI in the rectangle without red line were unreliable to measure.

(B) Propagation map; the waveform of measurement point was not distorted. Measure ROI (Ave T13) showed 2.08 m/s and S.D. T13 was 0.10m/s in the middle in the below table. S.D. T13 was lower than Ave T13(2.08)/10 =0.208. Thus, this ROI is unsatisfied area to be measured. Beside you also could confirm this ROI area was in rectangle without red line in Fig 1(A), the waveform of ROI was not distorted in Fig1(B).

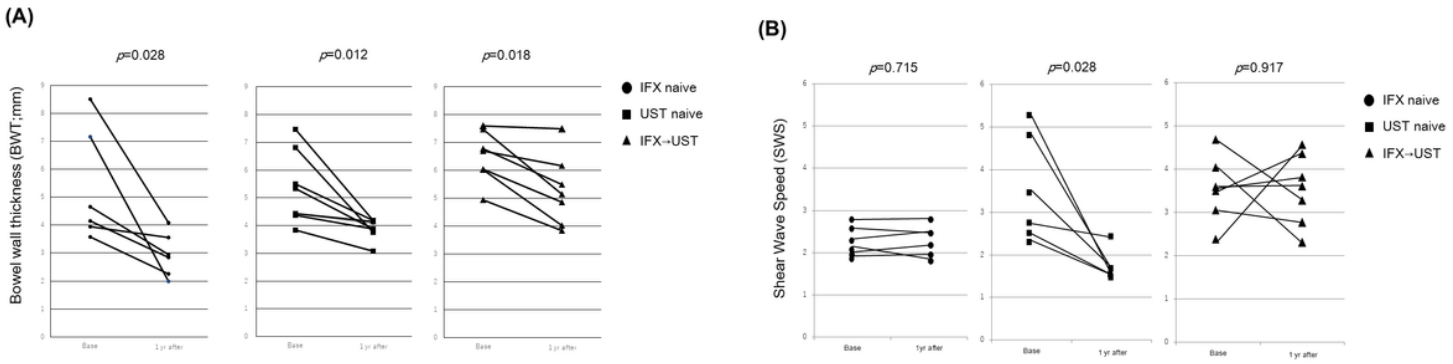

Figure 2

the change of BWT and SWS of each case in three treatment groups, IFX, UST, bio-switch from IFX to UST(IFX→UST). The data were compared between the two groups by Wilcoxon rank sum test. (A) BWT (B) SWS