



Effect of elemental diet combined with infliximab dose escalation in patients with Crohn's disease with loss of response to infliximab: CERISIER trial

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The development and success of anti-tumor necrosis factor- α (anti-TNF- α) monoclonal antibodies (mAbs) have dramatically changed the therapeutic strategy of IBD and

contributed to improvements in patients' quality of life.¹ Many clinical observations have confirmed that anti-TNF- α mAbs are efficacious for the treatment of CD. Unfortunately, however, we are faced with a new complication: loss of response (LOR). In Japan at the time of this study, an infliximab (IFX) dose escalation regimen to 10 mg/kg was only allowed in patients who developed LOR during scheduled maintenance therapy with IFX (5 mg/kg every 8 weeks) according to the results of a preapproval clinical trial. However, we often encounter patients who cannot gain adequate control with increasing doses of 10 mg/kg of IFX in daily clinical practice. In this open-labeled prospective study (UMIN registration No. 000010058), patients with non-colonic CD who had developed LOR to scheduled administration of IFX (5 mg/kg every 8 weeks) were randomly assigned to IFX dose escalation (10 mg/kg every 8 weeks) with (combination group) or without (monotherapy group) an elemental diet (ED, 900–1200 kcal/day) for 56 weeks (Table 1, Supple-

Received October 23, 2017. **Revised** December 29, 2017.

Accepted January 9, 2018.

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Table 1. Baseline Characteristics

	IFX mono group (n=6)	ED+IFX group (n=14)	P-value
Demographics			
Sex (male/female)	5/1	11/3	1.0000
Age (yr)	35.20±10.11	34.80±8.81	0.9202
BMI (kg/m ²)	21.40±4.54	21.00±4.32	0.9044
CDAI score	210.70±17.47	211.00±60.78	0.1256
Disease duration	9.24±7.23	11.13±9.04	0.9680
Disease location			1.0000
Ileitis (L1)	1 (16.7)	3 (21.4)	
Ileocolitis (L2)	5 (83.3)	11 (78.6)	
Perianal lesion			1.0000
Yes	2 (33.3)	4 (28.6)	
No	4 (66.7)	10 (71.4)	
Previous surgical resections			1.0000
0	3 (50.0)	6 (42.9)	
≥1	3 (50.0)	8 (57.1)	
Current smoking	1 (16.7)	2 (14.3)	1.0000
Medication at entry			
Immunomodulator	2 (33.3)	4 (28.6)	1.0000
Steroid use	0	0	-
5-ASA	5 (83.3)	12 (85.7)	1.0000
Concomitant medication			
Immunomodulator	2 (33.3)	5 (35.7)	1.0000
Steroid use	1 (16.7)	0	0.3000
5-ASA	5 (83.3)	12 (85.7)	1.0000
CRP (mg/dL)	0.34±0.26	0.74±0.81	0.5466
Serum albumin (g/dL)	3.88±0.32	3.91±0.63	0.4268

For calculation of the *P*-value, Wilcoxon's exact test was used for continuous values and Fisher exact test was used for categorical values. Statistical analyses were performed at a significance level of 0.05 (two-sided).

IFX, infliximab; ED, elemental diet; 5-ASA, 5-aminosalicylic acid.

mentary Figs. 1 and 2). The study was approved by the Institutional Review Board of Keio University Hospital (IRB No. 20120438) and performed in accordance with the principles of the Declaration of Helsinki. The informed consent was written informed consents were obtained. The primary endpoint was the retention rate of IFX dose escalation therapy at week 56. Safety, the CDAI, and the serum albumin and CRP levels at each observation point were analyzed. Intermediate analysis was performed on 15 patients enrolled by 31 March 2015. At week 16, 8 of 11 patients in the combination

group and 0 of 4 patients in the monotherapy group showed a CDAI reduction from baseline (Δ CDAI) of ≥ 50 . The intermediate analysis showed the benefits of combination therapy and disadvantage of monotherapy, and the study was stopped. Subsequent analysis showed that the proportion of patients with Δ CDAI of ≥ 50 (Fig. 1A) and clinical remission (Fig. 1B) at each observation point tended to be higher in the combination group. Compared with the monotherapy group, the combination group showed a tendency toward a superior persistence rate of IFX (10 mg/kg every 8 weeks) at week 56 as the primary endpoint in both the per-protocol set analysis ($P=0.1066$) and full analysis set analysis ($P=0.1629$) (Fig. 2). No serious adverse events were observed in either group (Supplementary Table 1). This appears to be the first clinical trial to show the usefulness of combination therapy of enteral nutrition (EN) therapy with biologics for refractory CD.

The effectiveness of EN therapy in patients with CD, especially for the maintenance of clinical remission, has been previously reported.²⁻⁴ Several recent reports have described combination therapy involving anti-TNF- α mAb therapy with EN therapy. Hirai et al.⁵ examined 102 patients with CD who were treated with IFX. The cumulative remission rate was significantly higher in the combination therapy group (IFX+EN) than in the non-EN group. Kamata et al.⁶ reported that concomitant ED therapy (≥ 900 kcal/day) with IFX scheduled maintenance therapy prevented LOR. Sazuka et al.⁷ also reported the benefit of concomitant use of EN therapy (≥ 600 kcal/day) with IFX scheduled maintenance therapy. Sugita et al.⁸ reported that ED therapy administered concomitantly with adalimumab reduced LOR to adalimumab in IFX-intolerant or IFX-refractory patients. Nguyen et al.⁹ performed a meta-analysis based on these reports and concluded that in patients with moderate to severe CD undergoing IFX therapy, combined EN therapy of ≥ 600 kcal/day affected the increase in the remission maintenance rate. In contrast, Yamamoto et al.¹⁰ reported the results of a prospective study showing that concomitant EN during IFX maintenance therapy did not show a beneficial effect in the maintenance rate of clinical remission in patients with CD. However, in the EN combination group, the CDAI tended to be lower at each observation time point than in the IFX alone group. In the study by Yamamoto et al.,¹⁰ the patients with CD had been newly introduced to IFX. These findings may suggest that IFX and EN combination therapy should be considered in only selected patients, including those with suspected LOR to IFX.

There are several limitations in this study. First, we discon-

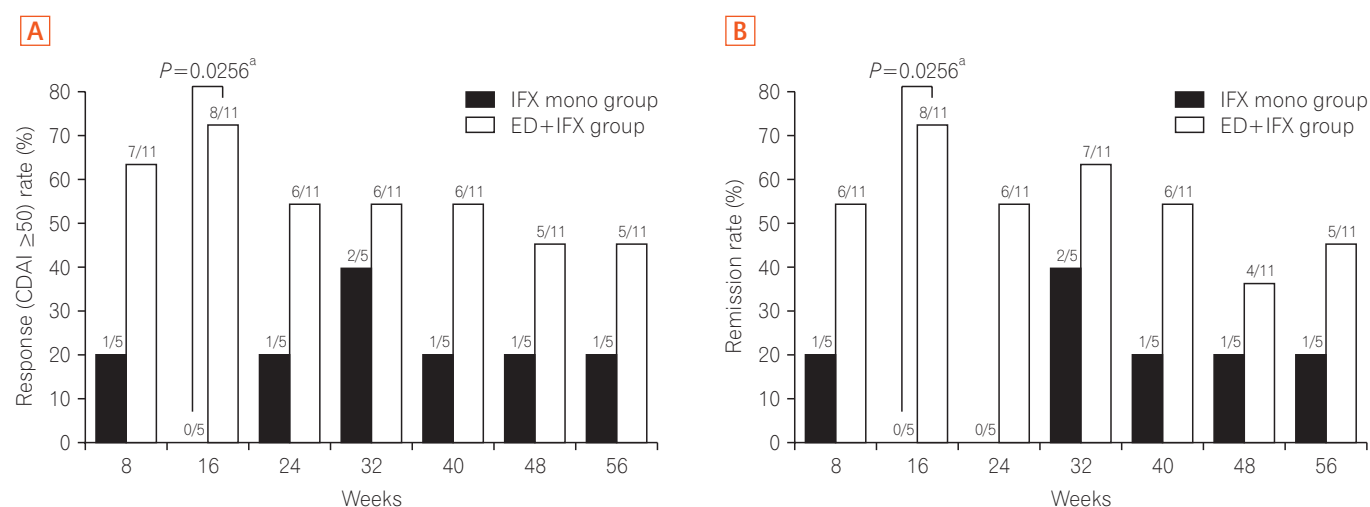


Fig. 1. Percentage of patients with a decrease in CDAI from weeks 8 to 56. (A) The percentage of patients who satisfied the Δ CDAI of ≥ 50 from weeks 8 to 56 of treatment is shown. Proportions of patients were compared between the groups by Fisher's exact test. Statistical analyses were performed at a two-sided significance level of 0.05. (B) The percentage of patients who achieved clinical remission, as indicated by a CDAI of < 150 , from weeks 8 to 56 of treatment is shown. Proportions of patients were compared between the groups by Fisher's exact test. Statistical analyses were performed at a two-sided significance level of 0.05. ^aSignificant difference. ED, elemental diet; IFX, infliximab.

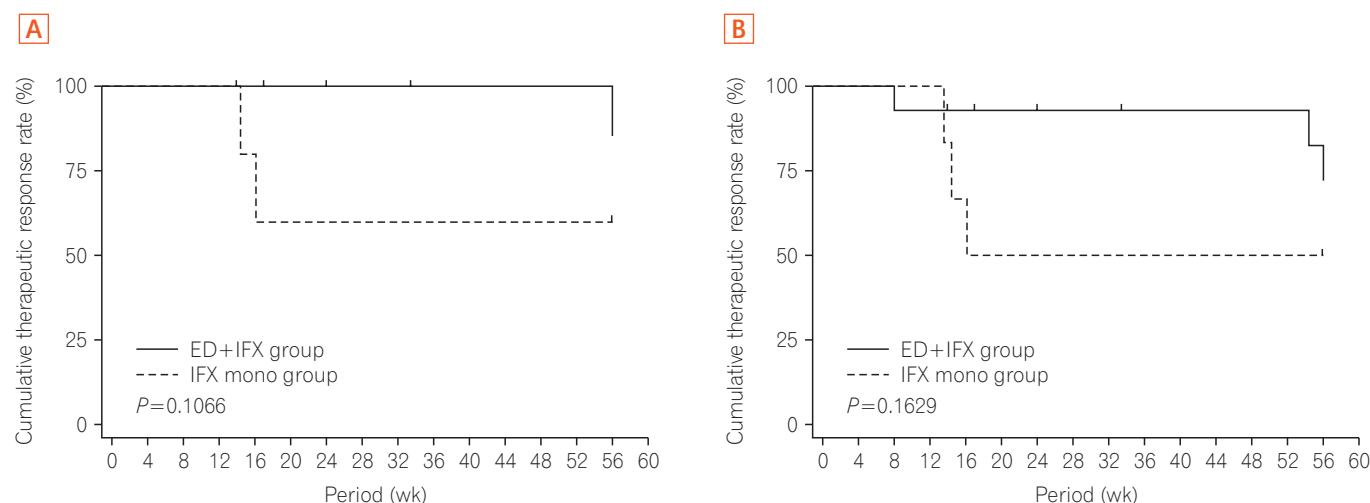


Fig. 2. Cumulative rate of successful completion of the scheduled maintenance treatment with IFX infusion at 10 mg/kg every 8 weeks until week 56. (A) The scheduled maintenance treatment continuation rate curve was estimated by the Kaplan-Meier method for each group, and the groups were compared by the generalized Wilcoxon test (per-protocol set). (B) The scheduled maintenance treatment continuation rate curve was estimated by the Kaplan-Meier method for each group, and the groups were compared by the generalized Wilcoxon test (full analysis set). IFX, infliximab; ED, elemental diet.

tinued this study after obtaining the results of the interim analysis, which actually resulted in statistical underpowering of this investigation. Second, the protocol of this study did not include evaluation of endoscopic activity. Third, maintenance of the relatively high acceptance rate of taking ED in the combination group was influenced by the enroll-

ment of only patients who had appropriate adherence to ED, as judged by the acceptability test before enrollment and the patients' history. Therefore, in daily clinical practice, adherence to oral ED administration is expected to be lower. Improvement of adherence to therapy is an important point when using ED to treat CD.

FINANCIAL SUPPORT

This work was funded by EA Pharma Co., Ltd. and undertaken by the Japanese Society for Inflammatory Bowel Disease.

CONFLICT OF INTEREST

This work was funded by EA Pharma Co., Ltd.

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ACKNOWLEDGEMENTS

The authors would like to thank all CERISIER Trial collaborators, investigators, and patients for their participation and contribution to this study. The authors also thank Dr. Fumiaki Ueno, PhD from the Center for Gastroenterology and Inflammatory Bowel Disease, Ofuna Chuo Hospital, Kamakura, Kanagawa, Japan and Prof. Kitaro Futami, PhD from the Department of Surgery, Fukuoka University Chikushi Hospital, Chikushino City, Fukuoka, Japan for their clinical review of the efficacy and adverse events of this trial as the Data and Safety Monitoring Board. The authors thank the

Japanese Society for Inflammatory Bowel Disease and EA Pharma Co., Ltd. for supporting the implementation system of this study. The authors thank Angela Morben, DVM, ELS, from Edanz Group (www.edanzediting.com/ac), for editing a draft of this manuscript.

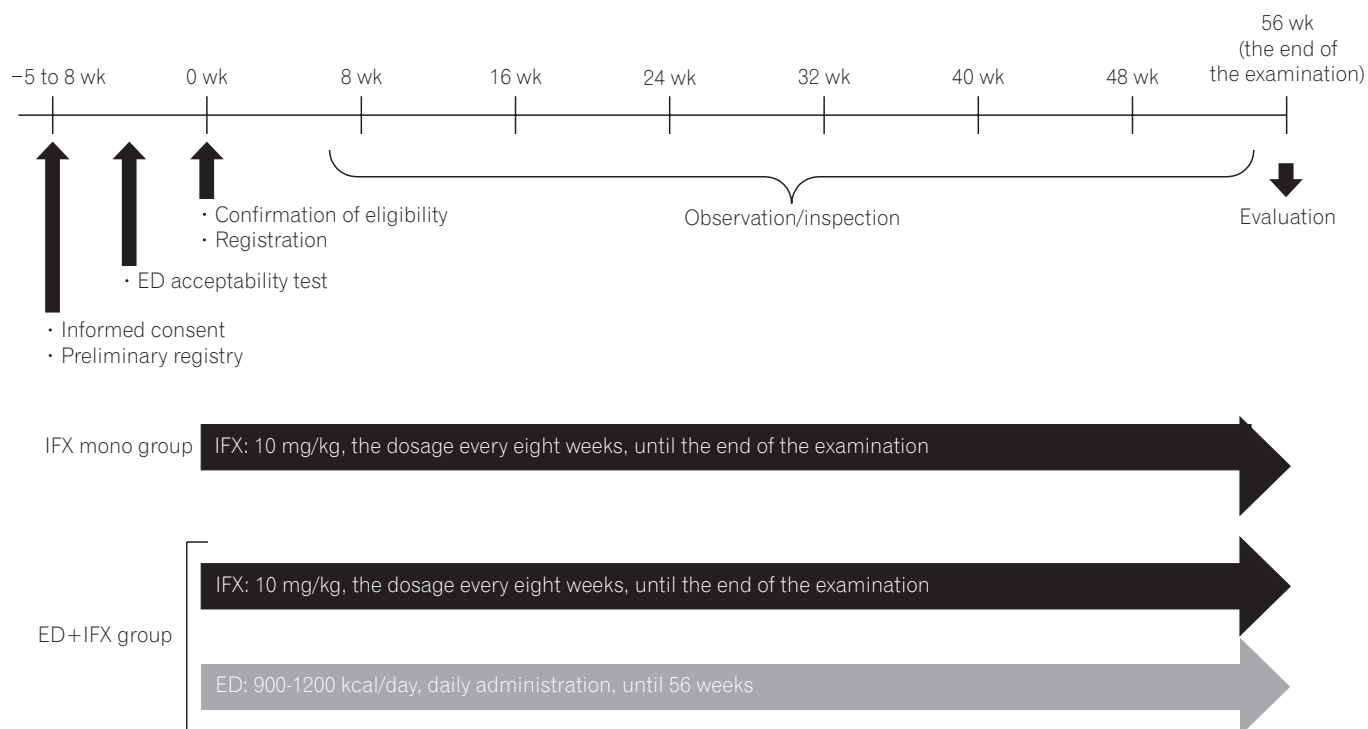
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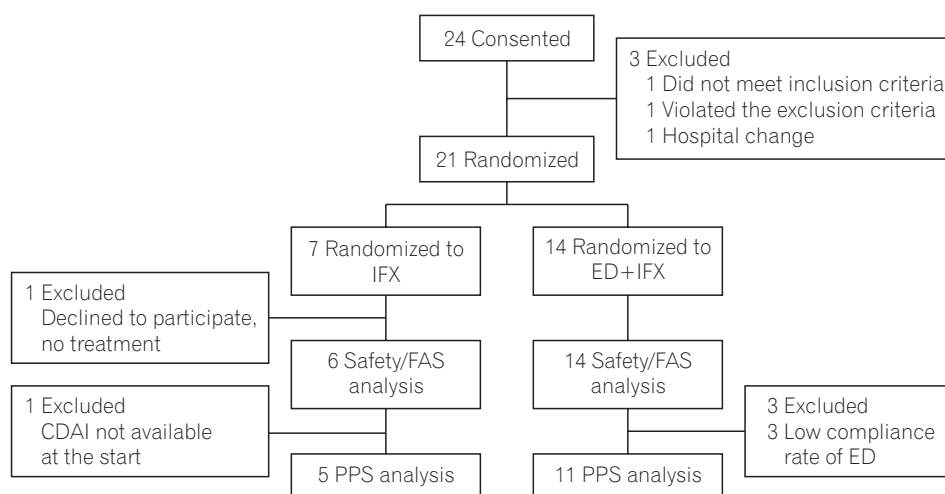
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Supplementary Fig. 1. Protocol design. IFX (10 mg/kg) was infused intravenously every 8 weeks until week 56 or the end of the study (discontinuation). The dosage of ED (900–1200 kcal/day), determined by the examining physician at the time of main registration, was administered daily until week 56. After obtaining informed consent from the patient, the preliminary registration was carried out. At 5 to 8 weeks after the last IFX administration, and after confirming eligibility, the patients were enrolled and observed until week 56. IFX, infliximab; ED, elemental diet.

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Supplementary Fig. 2. Patient flow diagram. IFX, infliximab; ED, elemental diet; FAS, full analysis set; PPS, per-protocol set.

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Supplementary Table 1. Adverse Events

	IFX mono group (n=6)	ED+IFX group (n=14)
Summary of adverse events		
Study drug-related adverse events		
Death	0	0
Serious adverse events	0	0
Adverse events leading to treatment discontinuation	1 (16.7)	0
Common adverse events		
Infections and infestations		
Influenza	-	1 (7.1)
Upper respiratory tract infection	2 (33.3)	-
Pharyngitis	1 (16.7)	-
Common cold	1 (16.7)	6 (42.9)
Herpes labialis	-	1 (7.1)
General disorders and administration site conditions		
Chills	-	1 (7.1)
Pyrexia	-	3 (21.4)
Malaise	2 (33.3)	-
Nervous system disorders		
Headache	1 (16.7)	-
Gastrointestinal disorders		
Abdominal pain	2 (33.3)	-
Cheilitis	1 (16.7)	-
Diarrhoea	2 (33.3)	-
Condition aggravated	-	1 (7.1)
Eye disorders		
Eyelid oedema	1 (16.7)	-
Conjunctivitis	1 (16.7)	-
Respiratory, thoracic and mediastinal disorders		
Epistaxis	-	1 (7.1)
Reproductive system and breast disorders		
Genital haemorrhage	-	1 (7.1)
Musculoskeletal and connective tissue disorders		
Ligament sprain	-	1 (7.1)

Values are presented as number (%). IFX, infliximab; ED, elemental diet.