Induction with Infliximab and a Plant-Based Diet as First-Line (IPF) Therapy for Crohn Disease: A Single-Group Trial

Mitsuro Chiba, MD, PhD; Tsuyotoshi Tsuji, MD, PhD; Kunio Nakane, MD, PhD; Satoko Tsuda, MD; Hajime Ishii, MD, PhD; Hideo Ohno, MD; Kenta Watanabe, MD; Mai Ito, MD; Masafumi Komatsu, MD, PhD; Takeshi Sugawara, MD

Perm J 2017;21:17-009

E-pub: 10/06/2017

https://doi.org/10.7812/TPP/17-009

ABSTRACT

Background: Approximately 30% of patients with Crohn disease (CD) are unresponsive to biologics. No previous study has focused on a plant-based diet in an induction phase of CD treatment.

Objective: To investigate the remission rate of infliximab combined with a plant-based diet as first-line (IPF) therapy for CD.

Methods: This was a prospective single-group trial conducted at tertiary hospitals. Subjects included consecutive adults with a new diagnosis (n = 26), children with a new diagnosis (n = 11), and relapsing adults (n = 9) with CD who were naïve to treatment with biologics. Patients were admitted and administered a standard induction therapy with infliximab (5 mg/kg; 3 infusions at 0, 2, and 6 weeks). Additionally, they received a lacto-ovo-semivegetarian diet. The primary end point was remission, defined as the disappearance of active CD symptoms at week 6. Secondary end points were Crohn Disease Activity Index (CDAI) score, C-reactive protein (CRP) concentration, and mucosal healing.

Results: Two adults with a new diagnosis were withdrawn from the treatment protocol because of intestinal obstruction. The remission rates by the intention-to-treat and per-protocol analyses were 96% (44/46) and 100% (44/44), respectively. Mean CDAI score (314) on admission decreased to 63 at week 6 ($p < 0.0001$). Mean CRP level on admission (5.3 mg/dL) decreased to 0.2 ($p < 0.0001$). Mucosal healing was achieved in 46% (19/41) of cases.

Conclusion: IPF therapy can induce remission in most patients with CD who are naïve to biologics regardless of age or whether they have a new diagnosis or relapse.

(The study ID number is UMIN000019061, UMIN000020335: Registration at www.umin.ac.jp).

INTRODUCTION

The incidence and prevalence of inflammatory bowel disease (IBD) are increasing as the condition expands into new regions; consequently, IBD is now a global disease.[1]

Newly introduced biologics have revolutionized the treatment of various conditions, including malignant neoplasms, autoimmune diseases, and others.[2-4] Infliximab and adalimumab are monoclonal antitumor necrosis factor α antibodies that were introduced for IBD treatment and have effectively induced and maintained remission in Crohn disease (CD).[5-11] Therapy with biologics has popularized the concept of mucosal healing for IBD treatment.[12,13]

IBD is a polygenic disease triggered by environmental factors.[14] Despite the recognition that Westernization of lifestyle is a major IBD driver,[15,16] no countermeasures have been recommended against such lifestyle changes with the exception of nonsmoking for patients with CD.[17] Gut microflora may be the main environmental factor responsible for IBD[18]; further, diet influences gut microflora.[19,20]

IBD is prevalent in wealthy nations in which dietary Westernization has occurred.[21] Dietary Westernization is characterized by increased consumption of animal protein, animal fat, and sugar, with decreased consumption of grains. A consistent risk factor for IBD is the consumption of meat[22-26] and sweets,[24-26] whereas a preventive factor is the consumption of vegetables and fruits.[22,27] Consequently, we recognize from our clinical experience that IBD is highly associated with lifestyle and that it is mainly mediated by a Westernized diet. Additionally, diet-associated dysbiosis of the gut microflora seems to be the most relevant environmental factor in IBD.[18] Therefore, restoring and maintaining gut symbiosis with an adequate diet is fundamental for IBD treatment. We designed a semivegetarian diet (SVD), a type of plant-based diet (PBD), as therapy for IBD.[28] Since 2003, we have served the PBD to all inpatients with IBD at our center and found that PBD prevented CD relapse[28] and induced remission without medication in a subset of patients with mild ulcerative colitis.[29,30]

The Dietary Guidelines for Americans (US Department of Agriculture [USDA] Food Pattern) and dietary guidelines for chronic common diseases consistently recommend increased consumption of vegetables and fruits and decreased consumption of meats, processed meats

Mitsuro Chiba, MD, PhD, is the Chief of the Inflammatory Bowel Disease Section at Akita City Hospital in Japan. E-mail: mchiba@m2.gyao.ne.jp. **Tsuyotoshi Tsuji, MD, PhD,** is the Chief of the Gastrointestinal Endoscopy Section at Akita City Hospital in Japan. E-mail: ac070289@akita-city-hp.jp. **Kunio Nakane, MD, PhD,** is the Chief of the Gastroenterology Division at Akita City Hospital in Japan. E-mail: ac060950@akita-city-hp.jp. **Satoko Tsuda, MD,** is a Gastroenterologist at Akita City Hospital in Japan. E-mail: satokotsuda07@gmail.com. **Hajime Ishii, MD, PhD,** is a Gastroenterologist at Akita City Hospital in Japan. E-mail: acd00377@akita-city-hp.jp. **Hideo Ohno, MD,** is a Gastroenterologist at Akita City Hospital in Japan. E-mail: ac120502@akita-city-hp.jp. **Kenta Watanabe, MD,** is a Gastroenterologist at Akita City Hospital in Japan. E-mail: nabeken_9989@yahoo.co.jp. **Mai Ito, MD,** is a Gastroenterologist at Akita City Hospital in Japan. E-mail: pixmon1231@gmail.com. **Masafumi Komatsu, MD, PhD,** is a Gastroenterologist and the Director of Akita City Hospital, in Japan. E-mail: ac990892@akita-city-hp.jp. **Takeshi Sugawara, MD,** is a Gastroenterologist at Nakadori General Hospital in Japan. E-mail: nrp05157@nifty.com

and added sugars.[31,32] PBDs are listed as variations of USDA healthy eating patterns.[31] Epidemiologic studies provide convincing evidence that individuals who consume PBDs experience improved longevity and are less affected by common chronic diseases than those who eat omnivorous diets.[33,34]

Ideal treatment involves early commencement of therapy before irreversible damage occurs, namely during the window of opportunity.[35] This concept has been validated in rheumatoid arthritis treatment.[36-38] Current guidelines for CD limit the use of infliximab or adalimumab for patients who are unresponsive to conventional therapy.[17]

The natural history of CD usually is characterized by a disabling course; 10% to 15% of patients are relapse-free for the rest of their lives, however.[39-41] The current remission rate in CD with early use of infliximab is 64%.[8] This indicates that 30% to 40% of patients, even those treated early with infliximab, are likely to experience a disabling disease course after their first treatment. Reliable induction of remission is the first step toward improving the natural history of CD.

Our goal is a drastic enhancement of the relapse-free rate in CD—namely, induction of remission by incorporating three recently developed concepts in medicine (biologics, PBD, and window of opportunity), followed by maintenance of remission with a PBD rather than further use of biologics with or without immunosuppressants. We hypothesized that these modalities could enhance the relapse-free rate.

We designed the present trial to determine whether **i**nfliximab combined with a **P**BD as **f**irst-line (IPF) therapy could enhance the remission rate for patients with CD.

METHODS

Design and Settings

We designed a single-group, nonrandomized, open noncontrolled trial that was conducted at Nakadori General Hospital and Akita City Hospital, tertiary care facilities in northern Japan. The first author, MC, worked for the former facility between 2003 and 2012 and Akita City Hospital since 2013.

Patients

All patients with active symptom(s) regardless of their Crohn Disease Activity Index (CDAI) score[42] were advised to undergo hospitalization for potential IPF therapy. Between August 2003 and December 2015, 60 patients with active CD were admitted to the hospital (Figure 1). Subjects were tested for tuberculosis or hepatitis B infection[43]; no patient had a positive result. Patients previously treated with biologics or those taking prednisolone or azathioprine, which influence IPF efficacy, were excluded. Patients prescribed a partial elemental diet or 5-aminosalicylic acid were included.

Protocol: IPF Therapy

The protocol involved standard induction therapy with infliximab combined with an SVD.[28] Briefly, metronidazole 750 mg/d was administered after admission. Patients received a liquid infusion without meals during morphologic studies to assess clinical types and intestinal stenosis. Liquid infusion duration varied from 3 to 7 days depending on the extent of previous outpatient morphologic studies before admission. Infliximab (5 mg/kg) was infused at weeks 0, 2, and 6.[11] The PBD, which was initiated on the same day of the infusion, was a lacto-ovo-semivegetarian diet that included fish once a week and meat once every 2 weeks. Calories were gradually increased to a maximum of about 30 kcal per kg standard body weight. After about 1 month, metronidazole was switched to 5-aminosalicylic acids. After the third infusion of infliximab, patients were discharged. Patients who could not be admitted for the entire induction phase were discharged after the second infliximab infusion and readmitted for the third infusion.

IPF Therapy Efficacy

The primary end point was clinical remission at week 6 after the first infliximab infusion. Clinical remission was defined as the absence of active symptoms. Remission was assessed by the attending physician (MC). Secondary end points were normalization of C-reactive protein (CRP) concentration at week 6 and mucosal healing. CDAI also was evaluated. Patients were morphologically studied with colonoscopy and/or contrast barium enema before discharge. In this study, mucosal healing was defined as the absence of active findings of CD such as ulcer, aphthoid lesions, edema, redness, and bleeding. Symptoms and CDAI were

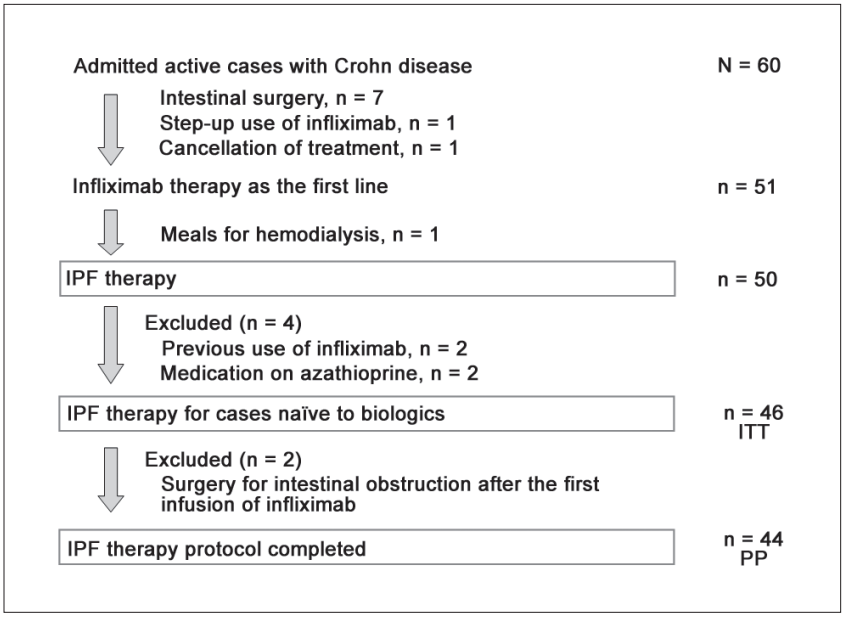

Figure 1. Enrollment of inpatients with active Crohn disease for IPF therapy.

IPF therapy = infliximab and plant-based diet as first-line therapy; ITT = intention to treat; PP = per protocol.

evaluated before and after infliximab therapy up to week 6.

Safety Evaluations

Vital signs, patient reports, findings during daily practitioner rounds, physical examinations, and weekly laboratory test findings were assessed to ensure safety.

Statistical Analysis

To evaluate differences of therapeutic effects among adults with a new diagnosis, children with a new diagnosis, and relapsed adults, the rates of remission, normalization of CRP concentration, and mucosal healing were assessed with a χ^2 test. CDAI score and CRP concentration were expressed as the mean plus or minus the standard deviation and median (interquartile range). To evaluate effects of treatment on CDAI and CRP, differences were first analyzed by repeated analysis of variance (ANOVA). If ANOVA results were statistically significant, data were analyzed using the post hoc Tukey-Kramer honestly significant difference test. A p value of 0.05 or lower indicated a statistically significant difference. Statistical analysis was performed using JMP 8 software (SAS Institute Inc, Cary, NC).

Ethical Considerations

For patients with strictures,[44] infliximab therapy poses risk for intestinal obstruction,[45-47] and the need for potential surgery was discussed. This protocol and the template informed consent forms were reviewed and approved by the Ethical Committee of Nakadori General Hospital and the Ethical Committee of Akita City Hospital (Protocol number 19-2003, 12-2013, 15-2015). The primary author/investigator (MC) obtained informed consent from all patients.

RESULTS

Patient Characteristics

Among 60 patients with active CD, 7 were indicated for intestinal surgery (Figure 1). Infliximab was used as a step-up approach for 1 patient. One patient cancelled medical treatment, and another patient on hemodialysis underwent standard first-line infliximab therapy; in that scenario, the patient required a diet for hemodialysis instead of a PBD. IPF therapy was administered to the remaining 50 patients. Two patients previously treated with infliximab and 2 patients receiving azathioprine were excluded. Forty-six patients who were naïve to biologics comprised the intention-to-treat subset and underwent IPF therapy. However, 2 patients with a new diagnosis (both men aged 21 years with stricture-type disease) developed intestinal obstruction after the first infusion of infliximab and underwent surgery. The 44 patients who completed the protocol (Figure 1) included 24 adults with a new diagnosis, 11 children ages 18 years and younger with a new diagnosis, and 9 relapsing

Table 1. Patient demographics and clinical characteristics

Characteristic	Total	New diagnosis		Relapsed
		Adults	Children[a]	Adults
Number of patients	44	24	11	9
Male/female	29/15	15/9	9/2	5/4
Age (y)				
Range	13-77	19-61	13-18	21-77
Mean ± SD	27.2 ± 13.7	30.0 ± 11.9	15.9 ± 1.8	33.6 ± 18.8
Median (IQR)	22.0 (18.3-30.8)	27.5 (21.0-35.0)	16.0 (15.0-17.0)	24.0 (21.5-43.5)
Disease duration (mo)				
Range	1-240	1-39	1-60	22-240
Mean ± SD	26.9 ± 45.1	8.8 ± 10.6	12.7 ± 17.2	92.8 ± 64.1
Median (IQR)	8.0 (3.0-33.3)	4.5 (2.0-11.5)	6.0 (3.0-18.0)	72.0 (57.0-122.5)
Location of lesion				
L1 Ileal	1	1	0	0
L2 Colonic	13	8	2	3
L3 Ileocolonic	30	15	9	6
L4 Isolated upper lesions	0	0	0	0
Behavior				
B1 Nonstricturing, nonpenetrating	33	18	10	5
B2 Stricturing	11	6	1	4
B3 Penetrating	0	0	0	0
Perianal disease modifier	31	16	10	5
Anal fistula	24	11	9	4
Anal skin tag	13	8	3	2
Current smoker	5	4	0	1
Previous segmental resection	3	0	0	3
CDAI score				
Range	52-834	52-834	144-472	88-679
Mean ± SD	314 ± 188	348 ± 214	270 ± 97	279 ± 200
Median (IQR)	270 (177-357)	296 (195-547)	278 (157-322)	225 (130-404)
< 150	8	4	1	3
150-220 mild-moderate	7	4	2	1
220-450 moderate-severe	19	9	7	3
> 450 severe/fulminant	10	7	1	2
C-reactive protein concentration (mg/dL)				
Mean ± SD	5.4 ± 4.9	5.4 ± 5.9	5.2 ± 3.5	5.6 ± 3.9
Median (IQR)	4.0 (1.6-7.5)	2.8 (1.2-7.1)	4.4 (2.4-8.6)	5.9 (2.8-7.4)

[a] Children = 18 years of age or younger.
CDAI = Crohn Disease Activity Index; IQR = interquartile range; SD = standard deviation.

adults. The demographic characteristics of our 44 patients are presented in Table 1. The mean disease duration for relapsing adults (92.8 months) was longer than the mean for adults with a new diagnosis (8.8 months) or the mean for children (12.7 months). More than 50% of patients in all groups had 1 or more perianal fistula(s) that were draining pus and/or anal tag(s). Five of 33 (15%) adults were smokers who stopped smoking after their admission. Eight patients had a CDAI score lower than 150 (quiescent stage); 7 had a score of 150 to 220 (mild-moderate); 19 scored 220 to 450 (moderate-severe); and 10 patients had a score higher than 450 (severe/fulminant).[44] Three relapsing adults were on partial elemental diet: 600, 900, and 1200 kcal/d, respectively. The same elemental diet was maintained during the first half of hospitalizations and was decreased by 300 kcal during the latter half of hospitalizations, while the amount of PBD was increased. Five patients were discharged after the second infliximab infusion and were readmitted for the third infusion. Sixteen of 44 patients in the present protocol also were described in a 2010 paper.[28]

Efficacy

The primary end point was remission. Two patients were withdrawn from the protocol because of intestinal obstruction. All remaining patients reported considerable improvement 1 week after the first infliximab infusion. Most patients had no symptoms between weeks 1 and 3. A CDAI score lower than 150 indicates remission in many studies.[42] The rate of CDAI scores lower than 150 among patients with baseline CDAI scores higher than 150 was 50% (18/36), 69% (25/36), 86% (30/35), 94% (31/33), 94% (31/33), and 100% (36/36) at weeks 1, 2, 3, 4, 5, and 6, respectively. Among patients with draining perianal fistulas, 24 experienced fistula closure within weeks 1 and 3. All 44 patients who completed the protocol achieved remission at week 6. Remission rates by intention-to-treat and per-protocol analysis were 96% and 100%, respectively (Table 2).

Secondary End Points

The mean CDAI score was significantly decreased from 314 before IPF therapy to 163 after the first infliximab infusion ($p < 0.0001$). The scores were further decreased chronologically: 115, 98, 82, 74, and 63 at weeks 2, 3, 4, 5, and 6, respectively (Table 3, Figure 2). Chronologic CDAI score changes were similar among the 3 groups (Table 3).

The mean CRP concentration decreased from 5.3 mg/dL before IPF therapy to 0.9 mg/dL after the first infliximab infusion ($p < 0.0001$). The CRP concentration (reference range, ≤ 0.3 mg/dL) was within defined limits (0.2 mg/dL) at week 2 and thereafter (Table 3, Figure 2). The chronologic CRP concentration changes were similar among the 3 groups (Table 3). Among adults with a new diagnosis,

Table 2. Rates of remission and normalization of C-reactive protein concentration and mucosal healing at week 6 after infliximab and a plant-based diet as first-line therapy

Subjects	N	Remission	CRP concentration	Mucosal healing
Total	46	96% (44/46) ITT, 100% (44/44) PP	84% (37/44)	46% (19/41)
Adults, new diagnosis	24	92% (24/26)[a] ITT, 100% (24/24) PP	92% (22/24)[b]	38% (9/24)[c]
Children, new diagnosis	11	100% (11/11)[a] ITT	82% (9/11)[b]	60% (6/10)[c]
Relapsed adults	9	100% (9/9)[a] ITT	67% (6/9)[b]	57% (4/7)[c]

[a] p value for comparison among the three groups (χ^2 test) = 0.3085.

[b] p value for comparison among the three groups (χ^2 test) = 0.2344.

[c] p value for comparison among the three groups (χ^2 test) = 0.3980.

CRP = C-reactive protein; ITT = intention to treat; PP = per protocol.

Table 3. CDAI score and CRP concentration changes during induction phase after IPF therapy

Subjects	Number of patients	Weeks after IPF therapy (mean ± SD)							p value (ANOVA)
		0	1	2	3	4	5	6	
CDAI score									
Total	44	314 ±189	163 ± 116	115 ± 89	98 ± 70	82 ± 45	74 ± 45	63 ± 32	< 0.0001
Adults, new diagnosis[a]	24	348 ± 214	171 ± 141	121 ± 104	93 ± 73	76 ± 50	65 ± 44	57 ± 30	< 0.0001
Children, new diagnosis[a]	11	270 ± 97	145 ± 76	108 ± 78	112 ± 86	84 ± 37	89 ± 52	71 ± 35	< 0.0001
Relapsed adults[a]	9	279 ± 200	162 ± 87	109 ± 58	99 ± 40	93 ± 38	78 ± 38	69 ± 35	< 0.0001
CRP concentration (mg/dL) (normal ≤ 0.3)									
Total	44	5.3 ± 5.0	0.9 ± 1.7	0.2 ± 0.2	0.1 ± 0.1	0.1 ± 0.2	0.1 ± 0.2	0.2 ± 0.2	< 0.0001
Adults, new diagnosis[b]	24	5.7 ± 5.9	0.8 ± 1.4	0.1 ± 0.2	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.2	< 0.0001
Children, new diagnosis[b]	11	5.2 ± 3.5	1.1 ± 2.8	0.1 ± 0.3	0.1 ± 0.1	0 ± 0.1	0.2 ± 0.3	0.2 ± 0.2	< 0.0001
Relapsed adults[b]	9	5.6 ± 3.9	0.8 ± 0.7	0.3 ± 0.3	0.1 ± 0.2	0.2 ± 0.3	0.2 ± 0.2	0.2 ± 0.3	< 0.0001

[a] p value for comparison among three groups (ANOVA) = 0.7949.

[b] p value for comparison among three groups (ANOVA) = 0.9263.

ANOVA = analysis of variance; CDAI = Crohn Disease Activity Index; CRP = C-reactive protein; IPF therapy = infliximab and a plant-based diet as first-line therapy; SD = standard deviation.

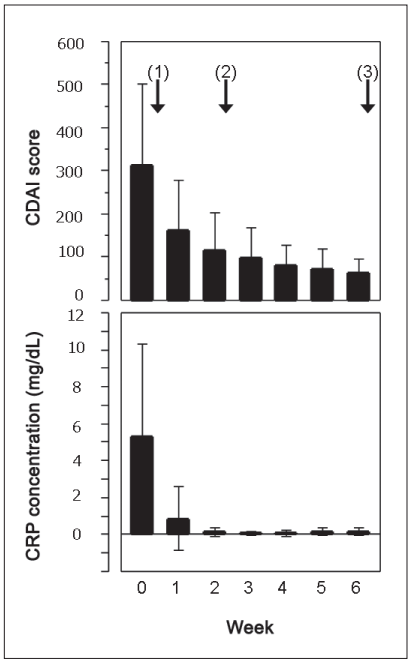

Figure 2. Change of CDAI score (upper panel) and CRP concentration (lower panel) before and after IPF therapy in 44 patients with CD. The solid bar denotes the mean and the thin line shows the standard deviation. Arrows with numbers in brackets indicate 3 infliximab infusions at weeks 0, 2, and 6. CDAI score and CRP concentration (mg/dL) (reference range ≤ 0.3) are presented in Table 3. All CDAI scores and CRP concentrations significantly decreased after IPF (analysis of variance $p < 0.0001$, Tukey-Kramer honestly significant difference test $p < 0.0001$).

CD = Crohn disease; CDAI = Crohn Disease Activity Index; CRP = C-reactive protein; IPF therapy = infliximab and a plant-based diet as first-line therapy.

CRP concentrations from weeks 2 to 6 remained stable (0.1 mg/dL). However, CRP concentration fluctuated within the reference range for the other 2 groups. The lowest concentration was 0 mg/dL at week 4 and 0.2 mg/dL at week 5 among children with a new diagnosis, and 0.1 mg/dL at week 3 and 0.2 mg/dL at week 4 among relapsing adults (Table 3). The rates of CRP normalization at week 6 were highest (92% [22/24]) among adults with a new diagnosis; intermediate (82% [9/11]) among children with a new diagnosis; and lowest (67% [6/9]) among relapsing adults, although the difference was nonsignificant ($p = 0.2344$) (Table 2). Normal CRP concentration was achieved by week 5 for 6 of 7 patients with abnormal CRP concentrations at week 6.

Three patients did not undergo morphologic assessment before discharge. Mucosal healing was achieved for 19 of 41 patients (46%) (Table 2).

Safety

Two patients were withdrawn from the protocol because of intestinal obstruction. Infusion reactions to infliximab were observed in two patients (eruptions with itching and vomiting). One child with a new diagnosis developed herpes zoster three weeks after completing IPF therapy. Metronidazole was withdrawn because of paresthesia (three patients) and leukocytopenia (one patient). 5-aminosalicylic acid was withdrawn because of mild pancreatitis (two patients), alanine aminotransferase elevation (one patient), and epigastralgia (one patient). All patients ate the PBD, and none experienced an adverse effect such as gaseous distress, abdominal discomfort, or diarrhea.

DISCUSSION

On the basis of the etiopathogenesis of IBD, we designed a PBD as a therapeutic diet for IBD.[28] To drastically improve the relapse-free rate associated with CD, the first step involves safe and reliable remission induction with initial treatment. Our study showed that IPF therapy can induce remission for most patients with CD regardless of age or new diagnosis or relapse status.

The CD population (Table 1) in this study reflects Japan's epidemiology. Male predominance is an Asian (including Japanese) characteristic related to CD.[48,49]

Clinical remission is far more important than clinical response in practice (the remission rate is lower than the response rate). In this study, the primary end point was induction of remission at week 6. Remission rates reported with infliximab or adalimumab are presented in Table 4.[5-10,50-52] In most of the studies reported, subjects had moderate to severe CD (CDAI 220-450),[42] but these studies did not include less severe (CDAI score < 220) or more severe (CDAI > 450) cases.[5-10,50,51] Our study, however, included cases involving all severity levels. Most patients with CD will experience a disabling course,[39-41] and even patients with mild CD experience relapse rates of 60% to 70% in a year.[53] Additionally, there is no way to predict which patients will have a disabling or relapse-free course.[39-41] If we attempt to improve the natural course of all patients with CD, we must study all patients with active CD regardless of severity. In this study, even if mild cases (CDAI score lower than 220 [n = 15]) were excluded, all 29 patients with CDAI scores higher than 220, including the 10 patients with severe/fulminant disease, achieved remission.

Patients who are naïve to biologics and those receiving infliximab combined with azathioprine achieved a higher remission rate with early use of biologics and had a better prognosis than those who began treatment at a later phase or those previously exposed to a biologic or infliximab alone.[8,50-52,54] One group of investigators evaluated remission rates under these conditions (early use of infliximab combined with azathioprine in biologics-naïve patients) by using a top-down approach; their patients achieved a remission rate of 64% at week 14.[8] So far, that is the highest remission rate reported for a large series (Table 4), demonstrating that 30% to 40% of patients with CD are nonresponders (primary nonresponders) to infliximab. As a result, many studies have been conducted to evaluate response predictors and primary nonresponders.[55-58] In our study, even though we included relapsed patients with a median disease duration of 6 years, all our patients achieved remission with IPF therapy. Therefore, disease duration of several years does not seem to be a critical factor for the induction of remission with IPF therapy. Our data show that most patients with CD who are naïve to biologics achieve remission with IPF therapy. Consequently, nonresponse to biologics seems to reflect the therapeutic modality chosen. Several factors may be involved in the successful induction of remission in our studies.

First, all patients in this study were admitted during IPF therapy. Although clinical remission could be obtained in a subset of patients after the first infusion of infliximab,[5] we considered that a certain period is needed for the recovery of morphologic changes in the intestine. Consequently, 3 inductive infusions of infliximab were given in 6 weeks[11] while

patients were hospitalized. However, mucosal healing was achieved only for 46% of patients (Table 2).

Patients' experience with a PBD, physician knowledge about IBD etiopathogenesis, and dietary guidance regarding PBD from a registered dietitian during hospitalization helped to ensure smooth PBD transitions from hospitals to homes after patient discharge. We confirmed a significantly higher PBD score (mean 25.0), indicating a higher adherence to a PBD[59] when compared with the mean base score of 6.4 in 24 patients with CD at approximately 6 years after discharge (p = 0.0131) (unpublished observation).

Hospitalization promotes smoking cessation, and smoking is prohibited in most hospitals in Japan. In our sample, 11% of patients (5/44) were smokers until admission, at which time they quit smoking; thus, all patients were considered nonsmokers. Smoking is a deteriorating factor in CD.[60,61] In other studies, the current smoking rate was as high as 43% (Table 4).[8-10] Hospitalization duration in our study was shorter than duration for a conventional

Table 4. Literature review: Induction of remission in Crohn disease

	Subjects							Outcomes	
Author	Inclusion criteria/ scores	Number of patients	CDAI score	CRP concentration (mg/dL)	Duration of disease	Current smoker, % (no.)	Regimen	Time of assessment	Remission rate (CDAI score < 150 unless otherwise specified), % (no.)
Targan et al, 1997[5]	CDAI 220-400	27	Mean 312	Mean 2.2	Mean 12.5 y	nd	IFX 5 mg/kg, single infusion	Wk 4	48.1 (13/27)
Mayer et al, 2001[6]	CDAI 220-400	385	Median 297	Median 0.8	Median 7.9 y	nd	IFX standard	Wk 6	38.4
Hyams et al, 2007[7]	Moderate to severe[a] Children, PCDAI > 30	112	Mean PCDAI 41	nd	Median 1.6 y	Unlikely	IFX standard and immunosuppressant	Wk 10	58.9 (66/112)
D'Haens et al, 2008[8]	CDAI > 200, age ≥ 16 New diagnosis	67	Mean 330	Median 1.9	Median 2.0 wk from diagnosis	43 (28/65)	IFX standard and AZA	Wk 14	64 (42/65)
Colombel et al, 2010[50]	Moderate to severe[a] (Naïve to anti-TNF, AZA)	169	Mean 290	Median 1.0	Median 2.2 y	nd	IFX standard	Wk 6	30 (50/169)
		169			Median 2.2 y		IFX standard and AZA		33 (55/169)
Hanauer et al, 2006[9]	Moderate to severe[a] Naïve to anti-TNF	76	Mean 295	Mean 1.4 Median 0.9	nd	42 (32/76)	Adalimumab standard	Wk 4	36 (27/76)
Sandborn et al, 2007[10]	Moderate to severe[a] Previous IFX	159	Mean 313	Mean 1.9 Median 0.9	nd	35 (55/159)	Adalimumab standard	Wk 4	21 (34/159)
Watanabe et al, 2012[51]	Moderate to severe,[a] Japanese	33	Mean 301	Mean 2.2	Mean 11.0 y	nd	Adalimumab standard	Wk 4	33 (11/33)
	Naïve to anti-TNF	14							43 (6/14)
	Previous anti-TNF	19							26 (5/19)
Miyoshi et al, 2014[52]	Active, Japanese	45	Median HBI 6.5	Median 1.3	Median 8.0 y	nd	Adalimumab standard	Wk 4	62 (28/45)[b]
		12			≤ 3 y				92 (11/12)
		33			> 3 y				52 (17/33)
Present study	Active, Japanese (Naïve to anti-TNF)	44	Mean 314 Median 270	Mean 5.4 Median 4.0	Mean 26.9 mo Median 8.0 mo	11 (5/44)	IPF therapy	Wk 6	Clinical remission 96 (44/46) ITT 100 (44/44) PP

[a] Moderate to severe, CDAI 220-450.
[b] Harvey-Bradshaw index ≤ 4.
Adalimumab standard = adalimumab 160/80 mg at weeks 0 and 2; AZA = azathioprine; CDAI = Crohn Disease Activity Index; CRP = C-reactive protein; HBI = Harvey-Bradshaw index; IFX = infliximab; IFX standard = infliximab 5 mg/kg at weeks 0/2/6; IPF therapy = infliximab and a plant-based diet as first-line therapy; ITT = intention to treat; nd = not described; PCDAI = pediatric Crohn Disease Activity Index; PP = per protocol; TNF = tumor necrotizing factor.

elemental diet therapy in Japan, for which more than 6 weeks is required.[62]

PBD was initiated on the same day as the infliximab infusion and was provided throughout hospitalization. We previously reported the efficacy of PBD in preventing relapse in CD.[28] In the current study, all patients who completed the protocol achieved remission. Altogether, these findings indicate that PBD is effective during the active and quiescent CD stages.

Preventive factors for IBD (eating vegetables and fruits)[22,27] are recommended, and risk factors (eating meat and sweets)[22-26] are moderated; indeed, a PBD includes these preventive recommendations and risk moderating factors. Considering that the most important environmental factor in IBD is diet-associated gut microflora,[18] we hypothesized that an adequate diet is the basis for IBD treatment during both active and quiescent stages. On the basis of our results, a PBD is recommended for patients with IBD. To date, most studies evaluating induction of remission or prognosis have not devoted resources to diet during treatment. Omnivorous and conventional low-residue diets might reduce the efficacy of biologics.

Metronidazole was used during the first half of hospitalization and is effective in CD with or without perianal fistulas.[63,64] An antibiotic is used during the active stage to eliminate potentially pathogenic bacteria in the intestine.[65]

Clinicians strive to provide the best therapy on the basis of their experience; as a result of our 30-plus years' experience in treating CD, IPF became routine therapy for CD in 2003 when infliximab was introduced in Japan. The therapeutic approach we propose is comprehensive, and we consider that all factors are necessary for induction of remission, although the contribution of each factor varies. This is the first study in which close attention was paid to diet during induction treatment of CD. In the absence of a control diet, the efficacy of PBD for induction of remission could not be demonstrated. It appears, however, that a PBD plus infliximab was a major contributor to our study's success.

The Ministry of Health, Labour, and Welfare of Japan designated ulcerative colitis and CD as intractable diseases. Patients with intractable diseases are provided with public medical aid on registration at the Public Health Office, so physicians in Japan are able to provide the best treatments for patients with IBD with less concern about medical expenses. Therefore, its immediate applicability in other countries may be limited.

IPF therapy, which can induce remission for most patients with CD, offers several advantages over the current induction therapy. No serious adverse events occurred with IPF therapy. The rapid efficacy of infliximab enabled patients to eat dinner on the same day of infliximab treatment. Mean CDAI scores at baseline and weeks 1, 2, and 4 in patients treated with adalimumab were 313, 264, 232, and 226, respectively.[9] In contrast, patients treated with IPF therapy had mean CDAI scores of 314, 163, 115, and 82, respectively (Table 3, Figure 2). With IPF therapy, the mean CDAI score was 115 as early as week 2, which is lower than the cutoff score of 150 that is recognized as denoting remission.[42]

The main disadvantage associated with IPF therapy is that hospitalization is required. However, most of our patients who were dealing with chronic symptoms recognized that they needed treatment and accepted hospitalization. There is risk for intestinal obstruction after infliximab treatment.[45-47] Infliximab is thought to be effective for inflammatory stenosis and ineffective for fibrotic stricture,[66] but it is difficult to distinguish between inflammatory and fibrotic stricture.[67] In the absence of signs of obstruction, stricture per se is no longer regarded as a contraindication for infliximab therapy; patients still are regarded as reasonable candidates.[66,68] In this study, intestinal obstruction developed within two weeks after the first infliximab infusion for two patients. There is scant literature about early obstruction after infliximab treatment.[45-47] We speculate that infliximab is so swiftly effective in ulcer healing[69] that the healing process further narrows the stenotic site, resulting in intestinal obstruction. If obstruction is a result of infliximab efficacy, an obstruction could also occur in CD with stricture. When obstruction occurs, it can be immediately diagnosed and surgically treated because patients are in a hospital. We fully inform patients with stricture about intestinal obstruction risk. Apart from two IPF study withdrawals attributable to intestinal obstruction, there were no other withdrawals.

Our study had limitations. There was no control group, and the sample size was small. Nevertheless, we expect that large, controlled studies will be conducted to validate these results.

IPF therapy can induce remission for most patients with CD. Further study is required to determine how remission can be maintained in the long term. Normal CRP concentration is a good indicator of lasting remission, but CRP concentration outside of defined limits is a sign of forthcoming relapse.[59,70] Most adults in our study with a new diagnosis (92%) had a normal CRP concentration at week 6, as did children with a new diagnosis (82%) and relapsing adults (67%) (Table 2). About 50% of patients with newly diagnosed adult CD maintained long-term remission with a PBD without periodic maintenance infliximab therapy (the remission rate at 3 to 7 years was 58%, according to Kaplan-Meier analysis [unpublished observation]). Conversely, children and relapsing adults treated with PBD alone tended to relapse within 2 years. Out of 11 children and 9 relapsed adults, 9 and 4 patients experienced relapse, respectively (unpublished observation). IPF therapy should be provided to adults with a new CD diagnosis to help decrease relapse incidence.

CONCLUSION

IPF therapy can induce remission for most patients with CD regardless of age or new diagnosis or relapse status. ❖

Disclosure Statement

The authors have no conflicts of interest to disclose.

Acknowledgments

The authors thank Marcin J Schroeder, PhD, Professor of Mathematics at Akita International University, for the statistical review.

Brenda Moss Feinberg, ELS, provided editorial assistance.

How to Cite this Article

Chiba M, Tsuji T, Nakane K, et al. Induction with infliximab and a plant-based diet as first-line (IPF) therapy for Crohn disease: A single-group trial. Perm J 2017;21:17-009. DOI: https://doi.org/10.782/TPP/17-009.

References

1. Molodecky NA, Soon IS, Rabi DM, et al. Increased incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012 Jan;142(1):46-54.e42. DOI: https://doi.org/10.1053/j.gastro.2011.10.001.
2. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 2008 Oct 23;359(17):1757-65. DOI: https://doi.org/10.1056/NEJMoa0804385.
3. Bijlsma JW, Welsing PM, Woodworth TG, et al. Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): A multicentre, randomised, double-blind, double-dummy, strategy trial. Lancet 2016 Jul 23;388(10042):343-55. DOI: https://doi.org/10.1016/s0140-6736(16)30363-4.
4. Cummings SR, San Martin J, McClung MR, et al; FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009 Aug 20;361(8):756-65. DOI: https://doi.org/10.1056/NEJMoa0809493. Erratum in: N Engl J Med2009 Nov 5;361(19):1914. DOI: https://doi.org/10.1056/nejmx090058.
5. Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's disease cA2 Study Group. N Engl J Med 1997 Oct 9;337(15):1029-35. DOI: https://doi.org/10.1056/nejm199710093371502.
6. Mayer L, Han C, Bala M, Keenan G, Olson A, Hanauer SB. Three dose induction regimen of infliximab (Remicade) is superior to a single dose in patients with Crohns disease (CD). Am J Gastroenterol 2001 Sep;96(9 Suppl 1):S303. DOI: https://doi.org/10.1016/s0002-9270(01)03740-6.
7. Hyams J, Crandall W, Kugathasan S, et al; REACH Study Group. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology 2007 Mar;132(3):863-73. DOI: https://doi.org/10.1053/j.gastro.2006.12.003.
8. D'Haens G, Baert F, van Assche G, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: An open randomized trial. Lancet 2008 Feb 23;371(9613):660-7. DOI: https://doi.org/10.1016/s0140-6736(08)60304-9.
9. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: The CLASSIC-I trial. Gastroenterology 2006 Feb;130(2):323-33. DOI: https://doi.org/10.1053/j.gastro.2005.11.030.
10. Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: A randomized trial. Ann Intern Med 2007 Jun 19;146(12):829-38. DOI: https://doi.org/10.7326/0003-4819-146-12-200706190-00159.
11. Sandborn WJ, Hanauer SB. Infliximab in the treatment of Crohn's disease: A user's guide for clinicians. Am J Gastroenterol 2002 Dec;97(12):2962-72. DOI: https://doi.org/10.1016/s0002-9270(02)05510-7.
12. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel disease: A systematic review. Gut 2012 Nov;61(11):1619-35. DOI: https://doi.org/10.1136/gutjnl-2012-302830.
13. Frøslie KF, Jahnsen J, Moum BA, Vatn MH; IBSEN Group. Mucosal healing in inflammatory bowel disease: Results from a Norwegian population-based cohort. Gastroenterology 2007 Aug;133(2):412-22. DOI: https://doi.org/10.1053/j.gastro.2007.05.051.
14. Lees CW, Barrett JC, Parkes M, Satsangi J. New IBD genetics: Common pathways with other diseases. Gut 2011 Dec;60(12):1739-53. DOI: https://doi.org/10.1136/gut.2009.199679.
15. Bernstein CN, Shanahan F. Disorders of a modern lifestyle: Reconciling the epidemiology of inflammatory bowel diseases. Gut 2008 Sep;57(9):1185-91. DOI: https://doi.org/10.1136/gut.2007.122143.
16. Hold GL. Western lifestyle: A 'master' manipulator of the intestinal microbiota? Gut 2014 Jan;63(1):5-6. DOI: https://doi.org/10.1136/gutjnl-2013-304969.
17. Mowat C, Cole A, Windsor A, et al; IBD Section of the British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. Gut 2011 May;60(5):571-607. DOI: https://doi.org/10.1136/gut.2010.224154.
18. Chiba M, Tsuda H, Abe T, Sugawara T, Morikawa Y. Missing environmental factor in inflammatory bowel disease: Diet-associated gut microflora. Inflamm Bowel Dis 2011 Aug;17(8):E82-3. DOI: https://doi.org/10.1002/ibd.21745.
19. De Filippo C, Cavalieri D, Di Paola M, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proc Natl Acad Sci U S A 2010 Aug 17;107(33):14691-6. DOI: https://doi.org/10.1073/pnas.1005963107.
20. Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbial enterotypes. Science 2011 Oct 7;334(6052):105-8. DOI: https://doi.org/10.1126/science.1208344.
21. National Institutes of Health (US) National Heart, Lung, and Blood Institute. Arteriosclerosis, 1981: Report of the Working Group on Arteriosclerosis of the National Heart, Lung, and Blood Institute. Vol 2. Bethesda, MD: National Institutes of Health; 1981.
22. Hou JK, Abraham B, El-Serag H. Dietary intake and risk of developing inflammatory bowel disease: A systematic review of the literature. Am J Gastroenterol 2011 Apr;106(4):563-73. DOI: https://doi.org/10.1038/ajg.2011.44.
23. Ge J, Han TJ, Liu J, et al. Meat intake and risk of inflammatory bowel disease: A meta-analysis. Turk J Gastroenterol 2015 Nov;26(6):492-7. DOI: https://doi.org/10.5152/tjg.2015.0106.
24. Morita N, Minoda T, Munekiyo M, et al. Case-control study of ulcerative colitis in Japan [Abstract in English]. In: Ohno Y, editor. Annual report of Research Committee on Epidemiology of Intractable Diseases, the Ministry of Health and Welfare of Japan. Nagoya, Japan: The Department of Preventive Medicine, School of Medicine, Nagoya University; 1996. p 153-8.
25. Morita N, Ohnaka O, Ando S, et al. Case-control study of Crohn's disease in Japan [Abstract in English]. In: Ohno Y, editor. Annual report of Research Committee on Epidemiology of Intractable Diseases, the Ministry of Health and Welfare of Japan. Nagoya, Japan: The Department of Preventive Medicine, School of Medicine, Nagoya University; 1997. p 58-64.
26. Sakamoto N, Kono S, Wakai K, et al; Epidemiology Group of the Research Committee on Inflammatory Bowel Disease in Japan. Dietary risk factors for inflammatory bowel disease: A multicenter case-control study in Japan. Inflamm Bowel Dis 2005 Feb;11(2):154-63. DOI: https://doi.org/10.1097/00054725-200502000-00009.
27. Amre DK, D'Souza S, Morgan K, et al. Imbalances in dietary consumption of fatty acids, vegetables, and fruits are associated with risk for Crohn's disease in children. Am J Gastroenterol 2007 Sep;102(9):2016-25. DOI: https://doi.org/10.1111/j.1572-0241.2007.01411.x. Erratum in: Am J Gastroenterol 2007 Nov;102(11):2614. DOI: https://doi.org/10.1111/j.1572-0241.2007.01627.x.
28. Chiba M, Abe T, Tsuda H, et al. Lifestyle-related disease in Crohn's disease: Relapse prevention by a semi-vegetarian diet. World J Gastroenterol 2010 May 28;16(20):2484-95. DOI: https://doi.org/10.3748/wjg.v16.i20.2484.
29. Chiba M, Tsuda S, Komatsu M, Tozawa H, Takayama Y. Onset of ulcerative colitis during low-carbohydrate weight-loss diet and its treatment with plant-based diet: A case report. Perm J 2016 Winter;20(1):80-4. DOI: https://doi.org/10.7812/TPP/15-038.
30. Chiba M, Tsuji T, Takahashi K, Komatsu M, Sugawara T, Ono I. Onset of ulcerative colitis after Helicobacter pylori eradication therapy: A case report. Perm J 2016 Spring;20(2):e115-8. DOI: https://doi.org/10.7812/TPP/15-085.
31. 2015-2020 Dietary Guidelines for Americans. 8th ed [Internet]. Washington, DC: US Department of Health and Human Services; 2015 [cited 2017 Jul 13]. Available from: https://health.gov/dietaryguidelines/2015/guidelines/.
32. World Cancer Research Fund; American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: A global perspective [Internet]. Washington, DC: American Institute for Cancer Research; 2007 [cited 2017 Jul 13]. Available from: www.wcrf.org/sites/default/files/Second-Expert-Report.pdf.
33. Tuso PJ, Ismail MH, Ha BP, Bartlotto C. Nutritional update for physicians: Plant-based diets. Perm J 2013 Spring;17(2):61-6. DOI: https://doi.org/10.7812/TPP/12-085.
34. Orlich MJ, Singh PN, Sabaté J, et al. Vegetarian dietary patterns and mortality in Adventist Health Study 2. JAMA Intern Med 2013 Jul 8;173(13):1230-8. DOI: https://doi.org/10.1001/jamainternmed.2013.6473.
35. O'Dell JR. Treating rheumatoid arthritis early: A window of opportunity? Arthritis Rheum 2002 Feb;46(2):283-5. DOI: https://doi.org/10.1002/art.10092.
36. Kiely PD, Brown AK, Edwards CJ, et al. Contemporary treatment principles for early rheumatoid arthritis: A consensus statement. Rheumatology (Oxford) 2009 Jul;48(7):765-72. DOI: https://doi.org/10.1093/rheumatology/kep073.
37. Smolen JS, Emery P, Fleischmann R, et al. Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: The randomised controlled OPTIMA trial. Lancet 2014 Jan 25;383(9914):321-32. DOI: https://doi.org/10.1016/s0140-6736(13)61751-1.
38. Heimans L, Akdemir G, Boer KV, et al. Two-year results of disease activity score (DAS)-remission-steered treatment strategies aiming at drug-free remission in early arthritis patients (the IMPROVED-study). Arthritis Res Ther 2016 Jan 21;18:23. DOI: https://doi.org/10.1186/s13075-015-0912-y.
39. Munkholm P, Langholz E, Davidsen M, Binder V. Disease activity courses in a regional cohort of Crohn's disease patients. Scand J Gastroenterol 1995 Jul;30(7):699-706. DOI: https://doi.org/10.3109/00365529509096316.
40. Loftus EV Jr, Schoenfeld P, Sandborn WJ. The epidemiology and natural history of Crohn's disease in population-based patient cohorts from North America: A systematic review. Aliment Pharmacol Ther 2002 Jan;16(1):51-60. DOI: https://doi.org/10.1046/j.1365-2036.2002.01140.x.

41. Beaugerie L, Seksik P, Nion-Larmurier I, Gendre¸JP, Cosnes J. Predictors of Crohn's disease. Gastroenterology 2006 Mar;130(3):650-6. DOI: https://doi.org/10.1053/j.gastro.2005.12.019.
42. Hanauer SB, Sandborn W; Practice Parameters Committee of the American College of Gastroenterology. Management of Crohn's disease in adults. Am J Gastroenterol 2001 Mar;96(3): 635-43. DOI: https://doi.org/10.1016/s0002-9270(01)02234-1.
43. van der Have M, Oldenburg B, Fidder HH, Belderbos TD, Siersema PD, van Oijen MG. Optimizing screening for tuberculosis and hepatitis B prior to starting tumor necrosis factor-α inhibitors in Crohn's disease. Dig Dis Sci 2014 Mar;59(3):554-63. DOI: https://doi.org/10.1007/s10620-013-2820-9.
44. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: Controversies, consensus, and implications. Gut 2006 Jun;55(6):749-53. DOI: https://doi.org/10.1136/gut.2005.082909.
45. D'haens G, Van Deventer S, Van Hogezand R, et al. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: A European multicenter trial. Gastroenterology 1999 May;116(5):1029-34. DOI: https://doi.org/10.1016/s0016-5085(99)70005-3.
46. Toy LS, Scherl EJ, Kornbluth A, et al. Complete bowel obstruction following initial response to infliximab therapy for Crohn's disease: A series of newly described complication. Gastroenterology 2000 Apr;118(4 Pt 1):A569. DOI: https://doi.org/10.1016/s0016-5085(00)84412-1.
47. Vasilopoulos S, Kugathasan S, Saeian K, et al. Intestinal strictures complicating initially successful infliximab treatment for luminal Crohn's disease. Am J Gastroenterol 2000 Sep;95(9):2503. DOI: https://doi.org/10.1111/j.1572-0241.2000.02675.x.
48. Yao T, Matsui T, Hiwatashi N. Crohn's disease in Japan: Diagnostic criteria and epidemiology. Dis Colon Rectum 2000 Oct;43 (10 Suppl):S85-93. DOI: https://doi.org/10.1007/bf02237231.
49. Ahuja V, Tandon RK. Inflammatory bowel disease in the Asia-Pacific area: A comparison with developed countries and regional differences. J Dig Dis 2010 Jun;11(3):134-47. DOI: https://doi.org/10.1111/j.1751-2980.2010.00429.x.
50. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010 Apr 15;362(15):1383-95. DOI: https://doi.org/10.1056/NEJMoa0904492.
51. Watanabe M, Hibi T, Lomax KG, et al; Study Investigators. Adalimumab for the induction and maintenance of clinical remission in Japanese patients with Crohn's disease. J Crohns Colitis 2012 Mar;6(2):160-73. DOI: https://doi.org/10.1016/j.crohns.2011.07.013.
52. Miyoshi J, Hisamatsu T, Matsuoka K, et al. Early intervention with adalimumab may contribute to favorable clinical efficacy in patients with Crohn's disease. Digestion 2014;90(2):130-6. DOI: https://doi.org/10.1159/000365783.
53. Sandborn WJ, Löfberg R, Feagan BG, Hanauer¸SB, Campieri M, Greenberg GR. Budesonide for maintenance of remission in patients with Crohn's disease in medically induced remission: A predetermined pooled analysis of four randomized, double-blind, placebo-controlled trials. Am J Gastroenterol 2005 Aug;100(8):1780-7. DOI: https://doi.org/10.1111/j.1572-0241.2005.41992.x.
54. Schreiber S, Reinisch W, Colombel JF, et al. Subgroup analysis of the placebo-controlled CHARM trial: Increased remission rates through 3 years for adalimumab-treated patients with early Crohn's disease. J Crohns Colitis 2013 Apr;7(3):213-21. DOI: https://doi.org/10.1016/j.crohns.2012.05.015.
55. Parsi MA, Achkar JP, Richardson S, et al. Predictors of response to infliximab in patients with Crohn's disease. Gastroenterology 2002 Sep;123(3):707-13. DOI: https://doi.org/10.1053/gast.2002.35390.
56. Leal RF, Planell N, Kajekar R, et al. Identification of inflammatory mediators in patients with Crohn's disease unresponsive to anti-TNFα therapy. Gut 2015 Feb 1;64(2):233-42. DOI: https://doi.org/10.1136/gutjnl-2013-306518.
57. Billiet T, Paramichael K, de Bruyn M, et al. A matrix-base model predicts primary response to infliximab in Crohn's disease. J Crohns Colitis 2015 Dec;9(12):1120-6. DOI: https://doi.org/10.1093/ecco-jcc/jjv156.
58. Biancheri P, Brezski RJ, Di Sabatino A, et al. Proteolytic cleavage and loss of function of biologic agents that neutralize tumor necrosis factor in the mucosa of patients with inflammatory bowel disease. Gastroenterology 2015 Nov;149(6):1564-74. DOI: https://doi.org/10.1053/j.gastro.2015.07.002.
59. Chiba M, Nakane K, Takayama Y, et al. Development and application of a plant-based diet scoring system for Japanese patients with inflammatory bowel disease. Perm J 2016 Fall;20(4):62-8. DOI: https://doi.org/10.7812/TPP/16-019.
60. Cosnes J, Beaugerie L, Carbonnel F, Gendre JP. Smoking cessation and the course of Crohn's disease: An intervention study. Gastroenterology 2001 Apr;120(5):1093-9. DOI: https://doi.org/10.1053/gast.2001.23231.
61. Nunes T, Etchevers MJ, García-Sánchez V, et al. Impact of smoking cessation on the clinical course of Crohn's disease under current therapeutic algorithms: A multicenter prospective study. Am J Gastroenterol 2016 Mar;111(3):411-9. DOI: https://doi.org/10.1038/ajg.2015.401.
62. Okada M, Yao T, Yamamoto T, et al. Controlled trial comparing an elemental diet with prednisolone in the treatment of active Crohn's disease. Hepatogastroenterology 1990 Feb;37(1):72-80.
63. Brandt LJ, Bernstein LH, Boley SJ, Frank MS. Metronidazole therapy for perineal Crohn's disease: A follow-up study. Gastroenterology 1982 Aug; 83(2):383-7.
64. Prantera C, Zannoni F, Scribano ML, et al. An antibiotic regimen for the treatment of active Crohn's disease: A randomized, controlled clinical trial of metronidazole and ciprofloxacin. Am J Gastroenterol 1996 Feb;91(2):328-32.
65. Sartor RB. Therapeutic manipulation of the enteric microflora in inflammatory bowel diseases: Antibiotics, probiotics, and prebiotics. Gastroenterology 2004 May;126(6):1620-33. DOI: https://doi.org/10.1053/j.gastro.2004.03.024.
66. Sorrentino D. Role of biologics and other therapies in stricturing Crohn's disease: What have we learnt so far? Digestion 2008;77(1):38-47. DOI: https://doi.org/10.1159/000117306.
67. Miehsler W, Novacek G, Wenzl H, et al; Austrian Society of Gastroenterology and Hepatology. A decade of infliximab: The Austrian evidence based consensus on the safe use of infliximab in inflammatory bowel disease. J Crohn Colitis 2010 Sep;4(3):221-56. DOI: https://doi.org/10.1016/j.crohns.2009.12.001.
68. Pelletier AL, Kalisazan B, Wienckiewicz J, Bouarioua N, Soulé JC. Infliximab treatment for symptomatic Crohn's disease strictures. Aliment Pharmacol Ther 2009 Feb 1;29(3):279-85. DOI: https://doi.org/10.1111/j.1365-2036.2008.03887.x.
69. Chiba M, Sugawara T, Tsuda H, Abe T, Tokairin T, Kashima Y. Esophageal ulcer of Crohn's disease: Disappearance in 1 week with infliximab. Inflamm Bowel Dis 2009 Aug;15(8):1121-2. DOI: https://doi.org/10.1002/ibd.20769.
70. Boirivant M, Leoni M, Tariciotti D, Fais S, Squarcia O, Pallone F. The clinical significance of serum C reactive protein levels in Crohn's disease. Results of a prospective longitudinal study. J Clin Gastroenterol 1988 Aug;10(4):401-5. DOI: https://doi.org/10.1097/00004836-198808000-00011.

Food

Everything in food works together to create health or disease.

— T Colin Campbell, MD, b 1934, American biochemist, author of *The China Study*