Therapeutic efficacy of infliximab on active Crohn's disease under nutritional therapy

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ORIGINAL ARTICLE

Therapeutic efficacy of infliximab on active Crohn’s disease under nutritional therapy

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Abstract

Objective. The aim of this investigation was to elucidate retrospectively the therapeutic effect of infliximab in patients with active Crohn’s disease (CD) under nutritional therapy. Material and methods. Using a review of the clinical records in 24 nationwide institutions specializing in inflammatory bowel disease, the short-term effect of infliximab in 97 patients with active CD was retrospectively investigated. The Crohn’s disease activity index (CDAI) at baseline and after 2 weeks of a single infliximab administration (5 mg/kg) was compared among patients under total parenteral nutrition (TPN group, n = 30), those following an elemental or polymeric diet (EN group, n = 49) and those without TPN and EN (NN group, n = 12). A decrease in CDAI ≥70 or a CDAI value <150 at 2 weeks was regarded as effective. Results. There was no difference in CDAI at baseline among the three groups. In each group, CDAI decreased significantly (from 250 (195–290) [median (interquartiles)] to 152 (123–233) in the TPN group, p <0.001; from 259 (200–325) to 180 (130–238) in the EN group, p <0.001; from 278 (222–291) to 164 (132–196) in the NN group, p =0.003). Infliximab was effective in 63.9% of patients in the TPN group, in 55.1% of those in the EN group and in 75% of the NN group. There was no statistical difference in efficacy among the three groups (p =0.4). Multivariate logistic regression analysis revealed younger age to be a significant factor related to the efficacy of infliximab. Conclusions. Infliximab is effective in patients with CD under TPN or EN. Age at infliximab administration may be predictive of response to infliximab.

Key Words: Crohn’s disease, infliximab, nutritional therapy

Introduction

Infliximab, a chimeric antibody to tumor necrosis factor (TNF)-α, has become widely accepted as an effective agent for the treatment of active and refractory Crohn’s disease (CD) [1]. It has also been shown that infliximab prolongs remission in CD [2,3]. Based on an accumulation of a large number of clinical trials, guidelines for the clinical use of infliximab in patients with CD have been defined [4,5]. Recently, various clinical parameters and medications for the prediction of the efficacy have been identified for the use of infliximab [6–10].

In Japan, however, total parenteral nutrition (TPN) and enteral nutrition (EN) have been approved as primary therapies for the treatment of active CD [11]. These nutritional therapies have been shown to have a therapeutic effect equal to or less than that of steroids [12,13]. In addition, recent investigations confirmed that EN is effective in CD, regardless of nitrogen sources [14–16]. However, the effect of infliximab under nutritional therapy has not been examined previously.
On the basis of the results of a preliminary multicenter trial of infliximab in Japanese patients with CD [17], the agent has become available in Japan. In this study, we retrospectively investigated the effect of infliximab on Japanese patients with CD from a multicenter database in order to elucidate the short-term effect of infliximab under TPN or EN, and to identify the clinical characteristics predictive of response to infliximab in Japanese patients with CD.

**Material and methods**

**Subjects**

This study was performed retrospectively by reviewing the clinical records in 24 institutions specializing in the treatment of chronic inflammatory bowel diseases in Japan (see Appendix). Since the Japanese Ministry of Labor and Welfare approved infliximab as a therapeutic agent in June 2002, the practical use and the side effects of the drug have been monitored by Tanabe Seiyaku Corporation (Tokyo, Japan) during a period from November 2002 to March 2003. The purpose of monitoring was to specify the incidence of adverse events and infusion reaction of infliximab in Japanese patients with CD. The clinical data of 138 subjects, in whom infliximab was administered at a dose of 5 mg/kg, were obtained from the attending physicians (Figure 1). In 25 patients, the Crohn’s disease activity index (CDAI) values prior to treatment were less than 150. In 16 patients, TPN or EN was changed to the other nutritional treatment or was discontinued after infliximab administration. These 41 patients were excluded from the analysis. The remaining 97 patients were the subjects of the present investigation; 85 patients were continuously treated with TPN or EN during a period from at least 1 week prior to and 2 weeks after infliximab. The other 12 patients were not treated with either TPN or EN. We directly contacted each attending physician and the following clinical items were reviewed.

**Parenteral and enteral nutrition**

The TPN group comprised 36 subjects who were treated with intravenous hyperalimentation through catheterization in the superior vena cava at a dose of over 1500 kcal/day. Similarly, the EN group comprised 49 subjects in whom either an elemental or polymeric diet of over 1500 kcal/day was applied. The formula of EN included an elemental diet (Elental; Ajinomoto Farma Co., Tokyo, Japan) and polymeric diet (Ensure Liquid; Abot Japan Co., Racall; Otsuka Seiyaku Co., Tokyo, Japan). Twelve patients without TPN or EN treatment were classified as the NN group.

**Data collection**

Information collected included age, gender, duration and site of CD, prior surgery, intestinal complications (stricture and fistula), concomitant medications and smoking habits.

The location of the disease was divided into three types: small intestinal disease only, colonic disease only and both small and large intestinal disease. Intestinal stricture was defined as an obvious intestinal stricture demonstrated by radiography or endoscopy, regardless of abdominal symptoms. Fistulous disease was regarded to be positive when there was a fistulous tract between the intestine or between the intestine and the skin, or when there was a perianal fistula. Patients without any fistulous disease were categorized as having inflammatory disease. As for the prior surgery, intestinal resection and strictureplasty were counted as positive findings.

Treatments with corticosteroids and immnosuppressive drugs were analyzed separately. When any dose of prednisolone was administered during 2 weeks after infliximab treatment, the subject was regarded to be positive for steroid treatment. Similarly, the use of thiopurines (azathioprine or 6-mercaptopurine) was judged to be positive for immunosuppressive drugs. None of the subjects was treated with methotrexate.

**Disease activity and treatment efficacy**

Determination of response was based on the CDAI [18], which was calculated using a review of the clinical records of each patient. CDAI was determined prior to and 2 weeks after infliximab.
administration. A decrease in CDAI ≥70 was regarded as a response, and a CDAI value <150 after 2 weeks as clinical remission. The overall efficacy of infliximab was determined to be effective when a patient showed a response or achieved clinical remission. Otherwise, infliximab was regarded to be ineffective.

**Statistical analysis**

Non-parametric variables were expressed as frequencies and percentages, and the associations between them were tested among the groups by χ² test or Fisher’s exact probability test, when appropriate. Parametric variables were expressed as medians (interquartile ranges) and compared among groups using the Kruskal-Wallis test. When there was a significant difference among the groups, the value was compared between any two groups using the Mann-Whitney U-test. In each treatment group, CDAI was compared between prior to and after 2 weeks of infliximab using the Wilcoxon’s signed-rank test. A stepwise logistic regression analysis was applied to evaluate significant variables, which affected the efficacy of infliximab. All these statistics were calculated with the two-tailed test, using statistic software (SPSS version 10.0 for windows; SPSS Japan Inc., Tokyo, Japan). Probabilities of less than 0.05 were considered to be significant.

**Results**

**Demographic data**

The study included 97 patients, with a male predominance (21 F, 76 M, age range 17–53 years). Time interval from diagnosis of CD until infliximab administration ranged from 1 to 29 years. Eight patients had small intestinal disease only and 16 patients had large intestinal disease only, while the remaining 73 patients had both small and large intestinal involvement. Ninety-six patients were being treated with oral 5-ASA. In addition, 26 patients were being treated with prednisolone and 22 with thiopurines; 55 of 97 patients had a prior history of intestinal resection. None of the patients had been previously treated with infliximab.

A comparison of the demographic data of the TPN, EN and NN groups is presented in Table I. As indicated in the table, age, gender, time interval from onset, and site of involvement were no different between groups. However, there were differences in the frequency of fistulous disease and application of prednisolone. Fistulous disease was less frequent in the TPN group than in the other two groups, and prednisolone was more frequently applied in the NN group than in the other groups. Infusion reaction was recorded in three patients (one patient in the EN group and two patients in the TPN group). The infusion reaction, however, did not lead to discontinuance of infliximab. Thus, all 97 patients completed a course of infliximab.

**Changes in disease activity**

CDAI at baseline was 250 (195–290) in the TPN group, 259 (200–325) in the EN group, and 278 (222–291) in the NN group. There was no difference in CDAI at baseline among the groups (p=0.628).

Individual changes in CDAI between baseline and 2 weeks after infliximab are indicated in Figure 2. CDAI after 2 weeks was 152 (123–233) in the TPN group, 180 (130–238) in the EN group, and 164 (132–196) in the NN group. In each group, CDAI decreased significantly 2 weeks after treatment with infliximab (p<0.0001 in the TPN and EN groups, and p=0.003 in the NN group).

**Assessment of therapeutic efficacy**

Response rate, remission rate, and therapeutic efficacy are compared in Figure 3. Forty-six of 97 patients responded to infliximab. The response rate was 44.4% (16 of 36 patients) in the TPN group, 46.9% (23 of 49 patients) in the EN group, and 58.3% (7 of 12 patients) in the NN group. Although the value was the highest in the NN group, there was no statistical difference in response rate among the groups (p=0.7).

Thirty-six patients achieved remission 2 weeks after infliximab administration. The remission rate showed the highest value (17 of 36 patients, 47.2%) in the TPN group, followed by the NN group (4 of 12 patients, 33.3%) and the EN group (15 of 49 patients, 30.6%). As well as response rate, remission rate was not different among the three groups (p=0.28).

Overall, infliximab was effective in 59 of 97 patients (60.8%). There was no difference in efficacy of infliximab among the TPN group (23 of 36 patients, 63.9%), the EN group (27 of 49 patients, 55.1%) and the NN group (9 of 12 patients, 75%) (p=0.4).

Comparisons of the therapeutic efficacy of infliximab among the TPN, EN, and NN groups of inflammatory or fistulous disease are presented in Table II. No difference in response rate or remission rate was observed in either inflammatory disease or fistulous disease. In inflammatory disease, the efficacy rate was higher in the TPN group than in the other two groups (p=0.02), but this trend in efficacy rate was not found in fistulous disease.
Comparison of patients' characteristics according to the efficacy of infliximab

Comparison of the clinical features of CD classified by the efficacy of infliximab is presented in Table III. Patients in whom infliximab was effective were of younger age at time of administration than those in whom infliximab was ineffective. However, duration of CD until infliximab administration was not different between the two groups. There were trends towards more frequent application of thiopurines and less frequent intestinal stricture in patients who responded to infliximab than in those who did not. The application of TPN or EN was not different according to the efficacy of infliximab. As has been shown in the table, the age at the time of infliximab administration was the only variable that slightly but significantly affected the efficacy (odds ratio (OR); 1.09, 95% confidence interval (CI); 1.01–1.18; p = 0.028). Thiopurines (OR; 3.44, 95% CI; 0.92–12.82, p = 0.066) and stricture (OR; 0.039, 95% CI; 0.14–1.09, p = 0.073) were insignificant variables for the efficacy of infliximab. Neither TPN nor EN contributed to the efficacy of infliximab.

Discussion

Elemental or polymeric diet has been used as primary therapy in patients with active CD [13–16,19–21]. Whereas two meta-analyses showed steroids to be superior to enteral nutrition in inducing remission in patients with active CD [12,22], another recent meta-analysis in the field of pediatrics revealed no such difference in therapeutic efficacy [23]. More recent clinical trials have confirmed elemental diet and polymeric diet to be equally effective in the treatment of active CD [15,16]. Although treatment with infliximab is indicated for CD, which is refractory to steroids [4], the effect of infliximab on the disease under nutritional therapy has not been investigated to date. The aim in this investigation was to determine whether the short-term effect of infliximab is different according to simultaneous nutritional therapy. The results of the present investigation indicated that CDAI decreased significantly 2 weeks after a single dose of infliximab, that the effect was independent of simultaneous

![Figure 2](image_url)

Figure 2. Comparison of individual Crohn's disease activity index (CDAI) values between baseline and 2 weeks after infliximab administration. CDAI decreased from 250 (195–290) (median (interquartile range)) to 152 (123–233) in the total parenteral nutrition (TPN) group, from 259 (200–325) to 180 (130–238) in the enteral nutrition (EN) group, and from 278 (222–291) to 164 (132–196) in the no nutritional treatment (NN) group.
TPN or EN, and that the age at treatment was a significant predictor of the short-term effect of infliximab in Japanese patients with CD.

Since the introduction of infliximab as a therapeutic strategy for CD [24], there has been an accumulation of clinical data regarding the effect of the agent. A randomized, controlled study has shown the clinical response rate (decrease in CDAI ≥70) to be 77% and remission rate (CDAI <150) to be 39% at 2 weeks after 5 mg/kg infliximab [1]. Retrospective institutional analyses by means of various clinical parameters have also shown that 65 to 81% of patients with active CD responded to a single infliximab administration within 4 weeks [8,25–27]. In our Japanese patients, the response rate (47.7%) was lower than, and the remission rate (37.7%) was equivalent to those values reported previously. The difference in response rate between our analysis and those prior reports could be explained by the difference in CDAI value at baseline. In fact, the mean CDAI value of our patients at baseline was lower than in the study by Targan et al. [1] by approximately 50 points. Because patients with severe disease are more likely to respond to infliximab [28], a clinical response rate of our analysis as defined by the absolute decrease in CDAI seems to have been calculated as a low value.

The possible contribution of TPN or EN to the effect of infliximab on CD has not previously been examined. Our analysis failed to demonstrate any synergistic effect of TPN or EN and infliximab. This result may have partly been derived from the retrospective nature of the present investigation. Because fistulous disease was the least frequent in the TPN group and prednisolone was the treatment most frequently applied to the NN group, we may have underestimated the contribution of EN. However, these factors are unlikely to explain the lack of synergistic effect, since both univariate and multivariate analyses failed to show these items to have affected the therapeutic efficacy of infliximab. These observations suggest that nutritional therapy of any type does not enhance the short-term effect of infliximab in CD.

Previous investigations have shown that the therapeutic effect of TPN and EN becomes evident within 4 weeks in CD [13–16,19–21]. Because CDAI at baseline was similar among the TPN, EN, and NN groups, and since TPN and EN preceded the administration of infliximab in our subjects, it is possible that patients in the TPN and EN groups were in fact refractory to nutritional therapy. It thus seems likely that active CD, which is refractory not only to steroids but also to nutritional therapy, is a candidate for infliximab. This may be especially the case for inflammatory CD, because there was a significant difference in efficacy rate in this type of CD. A randomized clinical trial seems to be necessary to examine the therapeutic effect of nutritional therapy coupled with infliximab.

Recently, various clinical features have been shown to be predictive of the effect of infliximab. A retrospective analysis of 100 patients with CD by Parsi et al. [6] showed non-smoking and concurrent use of immunosuppressives to be associated with a better short-term effect of infliximab. Arnott et al.
[29] subsequently reported the same observation after a retrospective analysis of 74 patients treated with infliximab. In another multicenter retrospective analysis, prior abdominal surgery was inversely correlated with response, and isolated colitis as well as the use of immunosuppressives correlated positively with response, whereas smoking habit did not contribute to the efficacy [30]. In our subjects, immunosuppressives showed marginal significance on the efficacy of infliximab. The insignificant contribution of immunosuppressives to the efficacy presumably seems to be due to less presence of autoantibody to infliximab [10], because our subjects had not been treated with infliximab previously. Our results were in concert with the analysis by Vermeire et al. [30], who showed age at infliximab administration to be an independent predictor of efficacy. Because shorter disease duration has been shown to be related to better response in pediatric and adolescent CD [31], the better outcome in younger patients could be explained by the shorter duration of CD. However, our analysis, as well as that of Vermeire et al. [30], failed to prove disease duration as a predictive factor for the short-term effect of infliximab. It thus seems possible that changes in immunity according to the increase in age (so-called immune senescence) are related to the practical therapeutic effect of biologic strategy, such as infliximab.

In conclusion, an analysis of the short-term effect of infliximab in Japanese patients with CD confirmed that the drug was effective for CD under treatment with conventional nutritional therapy. While age at treatment was a significant predictor of the efficacy of infliximab, use of immunosuppressives made a marginal and insignificant contribution to the efficacy. Furthermore, neither application nor type of nutritional therapy was related to the efficacy. These observations suggest that CD, which is

Table II. Efficacy of infliximab according to type of Crohn’s disease.

<table>
<thead>
<tr>
<th>Type of CD</th>
<th>Response rate</th>
<th>Remission rate</th>
<th>Efficacy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TPN</td>
<td>EN</td>
<td>NN</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>77% (10/13)³</td>
<td>33% (4/12)³</td>
<td>75% (3/4)³</td>
</tr>
<tr>
<td>Fistulous</td>
<td>26% (6/23)⁴</td>
<td>51% (19/37)⁴</td>
<td>50% (4/8)⁴</td>
</tr>
</tbody>
</table>

Abbreviations: TPN = total parenteral nutrition; EN = enteral nutrition; NN = without TPN or EN; CD = Crohn’s disease.

³p = 0.07; ⁴p = 0.31; ²p = 0.02; ³p = 0.14; ⁴p = 0.55; ⁵p = 0.37.

Table III. Comparison of clinical characteristics between infliximab-effective and -ineffective patients.

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>Effective (n = 59)</th>
<th>Ineffective (n = 38)</th>
<th>p-value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>32 (27–36)</td>
<td>36 (31–44)</td>
<td>0.028</td>
<td>1.09 (1.01–1.18)</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>16/43</td>
<td>5/33</td>
<td>0.257</td>
<td>0.43 (0.10–1.86)</td>
</tr>
<tr>
<td>Duration of disease (years)*</td>
<td>7 (4–13)</td>
<td>11 (7–14)</td>
<td>0.146</td>
<td>1.08 (0.96–1.18)</td>
</tr>
<tr>
<td>Smoking habit (+/−)</td>
<td>16/43</td>
<td>9/29</td>
<td>0.685</td>
<td>1.27 (0.40–4.05)</td>
</tr>
<tr>
<td>Site of involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small intestine only</td>
<td>2 (3%)</td>
<td>6 (16%)</td>
<td>0.816</td>
<td></td>
</tr>
<tr>
<td>Small and large intestine</td>
<td>46 (78%)</td>
<td>27 (71%)</td>
<td>0.524</td>
<td>2.18 (0.20–23.76)</td>
</tr>
<tr>
<td>Large intestine only</td>
<td>11 (19%)</td>
<td>5 (13%)</td>
<td>0.759</td>
<td>1.26 (0.29–5.47)</td>
</tr>
<tr>
<td>Intestinal complication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stricture</td>
<td>25 (42%)</td>
<td>23 (61%)</td>
<td>0.073</td>
<td>0.39 (0.14–1.09)</td>
</tr>
<tr>
<td>Fistulous disease</td>
<td>39 (66%)</td>
<td>29 (76%)</td>
<td>0.642</td>
<td>0.78 (0.27–2.27)</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>16 (27%)</td>
<td>10 (26%)</td>
<td>0.812</td>
<td>0.86 (0.24–3.04)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>16 (27%)</td>
<td>6 (16%)</td>
<td>0.066</td>
<td>3.44 (0.92–12.82)</td>
</tr>
<tr>
<td>Prior intestinal resection</td>
<td>28 (47%)</td>
<td>27 (71%)</td>
<td>0.554</td>
<td>0.72 (0.24–2.16)</td>
</tr>
<tr>
<td>Nutritional therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPN</td>
<td>23 (39%)</td>
<td>13 (34%)</td>
<td>0.173</td>
<td>2.14 (0.72–6.40)</td>
</tr>
<tr>
<td>EN</td>
<td>27 (46%)</td>
<td>22 (58%)</td>
<td>0.928</td>
<td>0.92 (0.16–5.20)</td>
</tr>
<tr>
<td>None</td>
<td>9 (15%)</td>
<td>3 (8%)</td>
<td>0.28</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: OR = odds ratio; CI = confidence interval; TPN = total parenteral nutrition; EN = enteral nutrition.

*Data are expressed as median (interquartile values).

Probabilities and OR are calculated by logistic regression analysis.
refractory to nutritional therapy, is a rational candidate for infliximab.

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References

Appendix

This study was undertaken with the cooperation of the following doctors from nationwide Japanese institutions:

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