

# Effectiveness of an 'half elemental diet' as maintenance therapy for Crohn's disease: a randomized-controlled trial

S. TAKAGI\*, K. UTSUNOMIYA\*, S. KURIYAMA†, H. YOKOYAMA\*, S. TAKAHASHI\*, M. IWABUCHI‡, H. TAKAHASHI‡, S. TAKAHASHI\*, Y. KINOUCHI\*, N. HIWATASHI§, Y. FUNAYAMA¶, I. SASAKI¶, I. TSUJI† & T. SHIMOSEGAWA\*

\*Division of Gastroenterology, Department of Internal Medicine, Tohoku University Graduate School of Medicine, Sendai; †Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai; ‡Department of Gastroenterology, Sendai Medical Centre, Sendai; §Department of Gastroenterology, Iwaki Kyoritsu General Hospital, Iwaki; ¶Division of Biological Regulation and Oncology, Department of Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan

Correspondence to:  
Dr S. Takagi, Division of Gastroenterology, Department of Internal Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryō, Aoba, Sendai 980-8574, Japan.  
E-mail: stakagi@int3.med.tohoku.ac.jp

## Publication data

Submitted 18 June 2006  
First decision 27 June 2006  
Resubmitted 8 August 2006  
Accepted 8 August 2006

## SUMMARY

### Background

Although thiopurines have a proven role in maintenance therapy for Crohn's disease, an alternative therapy is needed for patients intolerant or resistant to thiopurines.

### Aim

To evaluate the effectiveness of home enteral nutrition as a maintenance therapy regimen in which half of the daily calorie requirement is provided by an elemental diet and the remaining half by a free diet. We refer to this home enteral nutrition therapy as 'half elemental diet'.

### Methods

Between 2002 and 2005, 51 patients in remission from two hospitals were randomly assigned to a half elemental diet group ( $n = 26$ ) or a free diet group ( $n = 25$ ). The primary outcome measure of this study was the occurrence of relapse over the 2-year period.

### Results

The relapse rate in the half elemental diet group was significantly lower [34.6% vs. 64.0%; multivariate hazard ratio 0.40 (95% CI: 0.16–0.98)] than that in the free diet group after a mean follow-up of 11.9 months. Compliance was similar in the two groups. No adverse event occurred in any of the patients throughout the study.

### Conclusion

This randomized-controlled trial shows the effectiveness of an half elemental diet, which is a promising maintenance therapy for Crohn's disease patients.

*Aliment Pharmacol Ther* 24, 1333–1340

## INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disorder, and no curative therapy for it has been established yet. Thus, the goal of treatment was to maintain the patients in remission for as long as possible after this has been induced. Although corticosteroids and sulfasalazine have long been used to induce remission, these drugs have little effect in preventing a relapse of CD.<sup>1-4</sup> In Western countries, the effectiveness of immunosuppressive agents, such as azathioprine or mercaptopurine (6-mercaptopurine) as maintenance therapy has been reported, but they may increase the risk of malignancy, severe opportunistic infection and bone marrow or liver toxicity.<sup>5-14</sup> There is a considerable number of patients intolerant or resistant to these drugs and for them an alternative effective maintenance therapy is needed.<sup>5-9</sup>

Dietary therapy has played an important role in the treatment of CD patients both to induce remission and to sustain it. Using an elemental diet (ED), home enteral nutrition (HEN) has become an effective maintenance therapy with long-term safety.<sup>15</sup> HEN therapy usually consists of nocturnal ED administration through a self-inserted feeding tube and daytime intake of low-residue and low-fat food.<sup>15</sup>

Matsueda *et al.*, in a study involving 410 patients with CD, reported that both the cumulative remission rate and non-hospitalization rate in the HEN group were significantly higher than those in the drug-treated group.<sup>15</sup> Another study involving 84 patients with CD by Hirakawa *et al.* showed that the cumulative continuous remission rate after 4 years was 63% in the group receiving HEN, 66% in the group receiving HEN and drugs, 0% in the group receiving drugs and 0% in the group receiving no maintenance therapy, demonstrating that HEN effectively contributed to the maintenance of remission in CD.<sup>16</sup> Verma *et al.* showed that oral supplementation of ED in addition to a normal diet was effective to maintain remission in 39 patients with CD.<sup>17</sup>

The main limitations of these previous studies were that: (i) none of them was a randomized-controlled trial and (ii), as they did not determine the amount of regular calories from ED and diet, there was considerable variation in calories intake among individual cases. The effectiveness of ED as maintenance therapy for CD patients should be evaluated by well-designed randomized-controlled trials.

In this study, we examined the effectiveness of 'half ED', in which the patients took half of their daily calories by ED and the remaining half by usual meals. The patients could choose the route of ED administration, i.e. through a feeding tube and/or oral intake at any time they preferred. This half ED could possibly enhance the quality of life of patients with CD and improve long-term compliance. The aim of this study was to investigate the effectiveness of half ED as maintenance therapy for CD patients.

## SUBJECTS AND METHODS

### Inclusion and exclusion

Crohn's disease patients were eligible for the study if they had just undergone induction of remission through one of the four methods described below. According to several previous reports, remission was defined as a Crohn's Disease Activity Index (CDAI) lower than 150.<sup>2, 18-21</sup>

### Patients

From December 2002 to June 2005, patients were recruited from two clinical centres in Sendai, Japan; Department of Gastroenterology of Tohoku University Hospital, and Sendai Medical Centre.

Patients had been diagnosed as having CD clinically, endoscopically, radiologically and/or histologically, i.e. they fulfilled the diagnostic criteria for CD as defined by the Ministry of Health, Labour and Welfare of Japan.<sup>22</sup> Remission had just been induced by one of the four commonly employed methods, plus surgical intervention when necessary: administration of total elemental enteral nutrition (1800-2100 kcal/day) through a feeding tube and/or oral intake for 6-8 weeks; total parenteral nutrition (1500-2100 kcal/day) for 6-8 weeks; oral or intravenous administration of prednisolone, starting with 40 mg/day, then tapered down and off every 2 weeks by 5-10 mg; or 5 mg/kg intravenous infusion of infliximab at weeks 0, 2 and 6.<sup>18</sup> Additionally, they had received proper guidance regarding eating by nutritionists or medical doctors at least once so as to calculate their daily calorie intake of diet composition using semi-weighed food diaries by themselves.

After total enteral or parenteral nutrition, the clinical course of the patients was monitored during 7 consecutive days from the start of oral intake of

normal diet and assessed using the CDAI.<sup>19</sup> In the case of patients treated with prednisolone or infliximab, the clinical course from the day when the dose had just been tapered down to 20 mg/day, or the day 14 after the third injection, was evaluated in the same way.

All participants were instructed to take mesalazine (2250–3000 mg/day/p.o.) after allocation to one of the groups since the guidelines of treatment for CD established by the Ministry of Health, Labour and Welfare of Japan recommend this medication as a primary treatment and most CD patients receive it continuously today. Some of them had taken azathioprine (50 mg/day/p.o.) before the study, and were permitted to continue taking the medication throughout the study. This dose of azathioprine is far below the one recommended in Western countries but has been reported to be effective and safe for the maintenance of remission in the Japanese population.<sup>23</sup> All other drugs associated with specific treatment for CD were prohibited from the time of the induction of remission until the end of the study.

### Randomization

Information on eligibility was sent to a randomization centre, Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, via facsimile. Then, the eligible patients were numbered and the registration numbers were returned to the doctors in charge.

Eligible patients were randomly assigned to either the half ED group or the free diet group. Randomized allocation was performed independently of the two clinical centres by the randomization centre. A block randomization (block size = 10) was made with a random number table, and it was stratified into three groups according to the frequency of relapse, i.e. that of the inductive therapy the patients had received: <0.5 time/year (low frequency), not <0.5 time/year (high frequency) from the onset until recruitment, or the first attack.

### Half ED group and free diet group

Participants allocated to the half ED group were required to take half the amount of their daily allowance of calories by ED and the remaining half by usual unrestricted meals. The dosage for the half ED group per day was 900–1200 kcal (240–320 g as powder, 900–1200 mL as solution in water, 3–4 sachets) of

Enteral (AJINOMOTO PHARMA Co., Tokyo, Japan) through a self-inserted tube and/or by oral intake whenever they liked. Details of the composition of Enteral are shown in Table 1. When part or all of the ED was administered through a feeding tube, this was given at a constant speed of <100 mL/h set using an electronic feeding pump. The participants allocated to the free diet group took all nutrients via their usual unrestricted meals. The daily calorie intake provided by usual meals was calculated using semi-weighed food diaries by the patients themselves in both groups. The energy requirements of individual patients were calculated as 35–40 kcal/kg ideal body weight/day.

### Outcome

The primary outcome measure of this study was the occurrence of relapse over the 2-year period. Relapse was defined as either a CDAI score of more than 200, or the need for therapy to induce remission.

### Follow-up

The patients were instructed to visit the clinics at least once in every 3 months. At these visits, data were collected from medical charts in which the parameters used to calculate the CDAI were entered by the patients themselves everyday. For example, the occurrence of liquid or very soft stools, daily abdominal pain, general well-being, episodes of fever, body weight, taking antidiarrhoeal drugs and any other symptoms, and the results of laboratory tests performed at each visit were recorded. To maintain the blinding of the principal investigators at each site, the results of the laboratory tests and the CDAI were reviewed by co-investigators who had no contact with the patients, and these results were reported in a separate case report form. Patients in the half ED group who could not continue taking more than 900 kcal/day for 2 days or those in the free diet group who took any amount of ED after the allocation were defined as having dropped out from the protocol, which was based on the reports by the patients themselves. They had been left uninformed about the definition for the blinding.

### Ethics

Written informed consent was obtained from all participants prior to their registration. The protocol of

Table 1. Composition of Elental

|                         | Per 100 g         |
|-------------------------|-------------------|
| Total                   | 100 g (375 kcal)  |
| Amino acids             | 17.6 g (66 kcal)  |
| Carbohydrate (dextrin)  | 79.3 g (304 kcal) |
| Lipid (soybean oil)     | 0.60 g (5 kcal)   |
| Vitamin A               | 810 IU            |
| Vitamin D               | 64.0 IU           |
| Vitamin B <sub>1</sub>  | 0.24 mg           |
| Vitamin B <sub>2</sub>  | 0.25 mg           |
| Vitamin B <sub>6</sub>  | 0.33 mg           |
| Niacin                  | 2.78 mg           |
| Pantotenic acid         | 1.38 mg           |
| Folic acid              | 55 µg             |
| Vitamin B <sub>12</sub> | 0.88 µg           |
| Vitamin C               | 9.75 mg           |
| Vitamin K               | 11.3 µg           |
| Vitamin E               | 4.13 IU           |
| Biotin                  | 48.8 µg           |
| Choline                 | 10.7 mg           |
| Na                      | 325 mg            |
| K                       | 272 mg            |
| Cl                      | 646 mg            |
| Mg                      | 50.0 mg           |
| Ca                      | 197 mg            |
| P                       | 152 mg            |
| Fe                      | 2.25 mg           |
| I                       | 19.0 µg           |
| Mn                      | 375 µg            |
| Cu                      | 250 µg            |
| Zn                      | 2.25 mg           |
| Amino acids (g)         |                   |
| L-Isoleucine            | 0.80              |
| L-Leucine               | 1.12              |
| L-Lysine                |                   |
| Hydrochloride           | 1.11              |
| L-Methionine            | 0.81              |
| L-Phenylalanine         | 1.09              |
| L-Threonine             | 0.65              |
| L-Tryptophan            | 0.19              |
| L-Valine                | 0.88              |
| L-Histidine             |                   |
| Monohydrochloride       |                   |
| Monohydrate             | 0.63              |
| L-Arginine              |                   |
| Hydrochloride           | 1.41              |
| L-Alanine               | 1.12              |
| Mg·K                    |                   |
| L-Aspartate             | 1.30              |
| Na·L-Aspartate          |                   |
| Monohydrate             | 1.08              |
| L-Glutamine             | 2.42              |
| Glycine                 | 0.63              |
| L-Proline               | 0.79              |
| L-Serine                | 1.45              |
| L-Tyrosine              | 0.14              |

this trial was approved by the ethics committee of Tohoku University Hospital and that of Sendai Medical Centre.

### Statistical analysis

Sixty-five subjects were estimated as required in each group for the study to provide at least 90% power to detect a 20% or greater difference in the relative risk of the primary outcome (at  $2P = 0.05$ ) between the two groups. This assumes a 25% or more annual relapse rate among participants assigned to the free diet group. This event rate is based on data from a retrospective follow-up study of patients with CD carried out at Tohoku University Hospital.

Baseline characteristics were compared between the two groups using the chi-squared test and Student's *t*-test as appropriate. Probabilities of relapse were compared by the Kaplan–Meier method and the Cox proportional hazards model was used to adjust for potential confounders for comparison between the two groups. The data were analysed according to an intention-to-treat basis including all patients randomly assigned to the two groups.

Interim analyses were scheduled once in a year by an independent data and safety monitoring board after the start of the enrolment. The interim analysis was based on a comparison of the relapse rate in the two groups. Stopping boundaries were designed to allow termination of the study for safety of the patients if a significant difference ( $P < 0.05$ ) in the relapse rate was found between them.

Analyses were performed using SAS statistical software version 9.1 (SAS Institute, Cary, NC, USA).

### RESULTS

The data and safety monitoring board recommended at the first interim analysis that interim analyses be conducted semiannually after that because a nearly significant difference in the relapse rate was found between the two groups. At the fourth analysis, after 51 patients had been assigned, the trial was stopped because the relapse rate in the half ED group was significantly lower than that in the free diet group. The analysis includes the seven non-relapsing patients who had been followed up for more than 24 months (25–28 months, mean 25.9). The follow-up of all the non-relapsing patients was discontinued when the trial was terminated, i.e. on 30 June 2005.

## Baseline characteristics of the study patients

Of the 82 patients enrolled, 26 were excluded because the CDAI did not decrease to <150 after the induction treatment. Five patients refused to participate, and 51 patients who matched the study criteria were randomized to either group: 26 patients to the half ED group, and 25 to the free diet group.

Forty-seven patients (92.2%) who had been induced by total enteral or parenteral nutrition prior to entry were in-patients and the other four were out-patients at the start of this trial. Five patients (one in the half ED group and four in the free diet group) in the two groups had undergone surgery as part of the induction of remission before entering the maintenance trial. Fourteen patients (five in the half ED group and nine in the free diet group) were malnourished, namely, had a body mass index lower than 18 at the start of the trial. Demographic and other baseline characteristics were similar in the two study groups (Table 2).

All patients could be followed up and continued to take mesalazine throughout the study. Six of them in the two groups had taken azathioprine before the study, and all of them could also continue taking the medication throughout the study. Five of the 26

patients (19.2%) in the half ED group chose to receive part or all of their ED via a self-inserted nasogastric tube and did so throughout the study. All of them could insert their tubes by themselves and there was no need of any invasive treatment, such as percutaneous endoscopic gastrostomy, for them.

The mean overall follow-up was 11.9 (1–28 months, s.d.: 7.7) months. Six patients in the half ED group discontinued ED (two patients at month 1 and one each at months 2, 4, 6 and 7), and five in the free diet group used some amount of ED (two patients at month 0 and one each at months 1, 3 and 5). The trial profile is illustrated in Figure 1.

## Primary outcome

Figure 2 shows the Kaplan–Meier estimates of the relapse rates for the two groups. The cumulative probability of relapse was significantly lower in the half ED group: nine patients (34.6%) in the half ED group, and 16 patients (64.0%) in the free diet group suffered relapses. Two of the six patients who had stopped the therapy halfway through the trial in the half ED group and three of the five patients who had discontinued the free diet suffered a relapse. The multivariate

**Table 2.** Baseline characteristics of the study patients

| Characteristics                   | Half ED ( <i>n</i> = 26) | Free diet ( <i>n</i> = 25) | <i>P</i> -value |
|-----------------------------------|--------------------------|----------------------------|-----------------|
| Men                               | 20                       | 17                         | 0.48            |
| Mean age (s.d.; years)            | 30.8 (11.1)              | 28.9 (8.1)                 | 0.49            |
| Mean body mass index (s.d.)       | 20.1 (3.1)               | 20.0 (3.6)                 | 0.85            |
| Duration of disease (s.d.; years) | 4.1 (4.2)                | 5.6 (6.5)                  | 0.32            |
| Disease site                      |                          |                            |                 |
| Small bowel only                  | 8                        | 7                          | 0.50            |
| Colon only                        | 3                        | 6                          |                 |
| Both                              | 15                       | 12                         |                 |
| Perianal lesions                  | 12                       | 10                         | 0.66            |
| Previous gut operation            | 11                       | 11                         | 0.90            |
| Frequency of relapse              |                          |                            |                 |
| High (not <0.5/year)              | 10                       | 9                          | 0.98            |
| Low (<0.5/year)                   | 7                        | 7                          |                 |
| First attack                      | 9                        | 9                          |                 |
| Administration of azathioprine    | 2                        | 4                          | 0.42            |
| Inductive therapy (+surgery)      |                          |                            |                 |
| Total enteral nutrition           | 12 (0)                   | 10 (3)                     | 0.67            |
| Total parenteral nutrition        | 12 (1)                   | 13 (1)                     |                 |
| Administration of prednisolone    | 0 (0)                    | 1 (0)                      |                 |
| Administration of infliximab      | 2 (0)                    | 1 (0)                      |                 |
| Mean CDAI (s.d.)                  | 101.8 (34.1)             | 86.4 (31.3)                | 0.10            |

ED, elemental diet; CDAI, Crohn's Disease Activity Index.

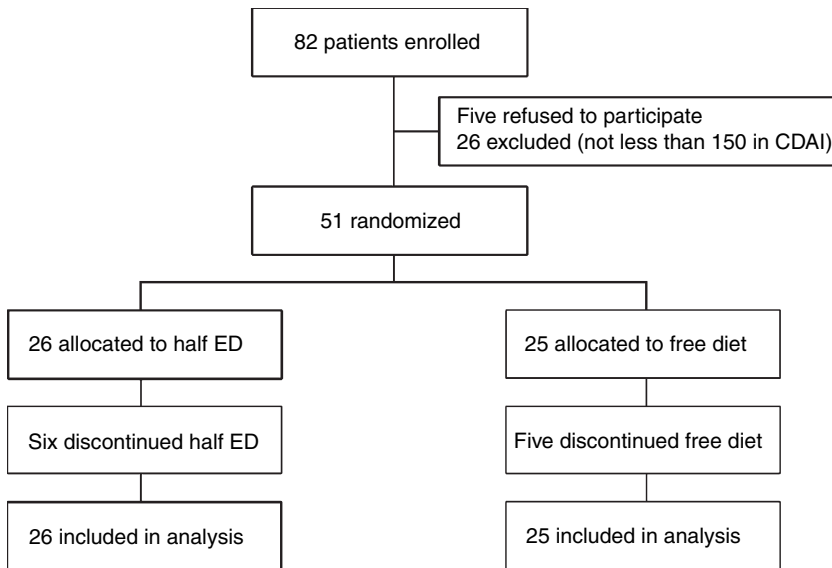


Figure 1. Trial profile.

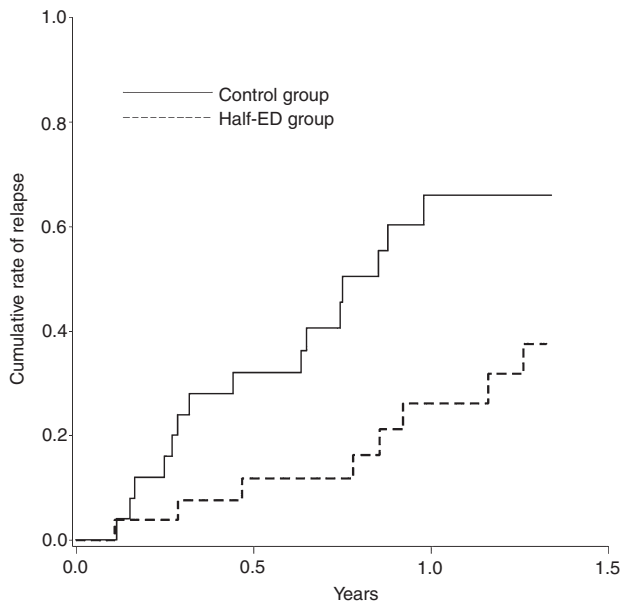


Figure 2. Relapse rate by group.

hazard ratio determined by the Cox proportional hazards model was 0.40 [95% confidence interval (CI): 0.16–0.98] after adjusting for age, sex, duration of the disease, disease site and mean CDAI at baseline (Table 3).

When the CDAI scores in all but three relapsing cases exceeded 200, they required inductive therapies. There were no significant differences in change of the calorie intake and weight of the patients between the two groups throughout the study.

Table 3. Hazard ratios and their 95% CIs of occurrence of relapse in each treatment group

|                                   | Treatment        |                 |
|-----------------------------------|------------------|-----------------|
|                                   | Half ED          | Free diet       |
| Number of cases                   | 9                | 16              |
| Age- and sex-adjusted HR (95% CI) | 0.36 (0.15–0.83) | 1.00 (referent) |
| Multivariate HR (95% CI)*         | 0.40 (0.16–0.98) | 1.00 (referent) |

HR, hazard ratio; CI, confidence interval; ED, elemental diet.  
\* Adjusted for age, sex, duration of disease, disease site and mean CDAI at baseline.

## Adverse events

Throughout the study, no adverse events, such as severe symptoms because of an excessive calorie intake, high osmotic pressure diarrhoea caused by ED, or instrumental trouble related to the feeding tube in the half ED group, occurred in any patient.

## DISCUSSION

In the present study, the frequency of relapse was significantly lower in the half ED group than in the free diet group. The effectiveness of HEN in lieu of food intake as a maintenance therapy for CD has been noted in several studies, and ED has also been reported to be effective as a primary therapy for active

CD.<sup>15–17, 24–26</sup> In most trials undertaken in Western countries, enteral nutrition showed in adult patients with active disease a response rate similar or slightly inferior to the response to corticosteroids obtained in adults with a lower compliance; and polymeric formulas were as effective as elemental formulas.<sup>26–29</sup> The response rates are better in children.<sup>30</sup> There is a high relapse rate, however, and maintenance therapy is greatly limited by adherence to therapy.<sup>30</sup> The present randomized-controlled trial has demonstrated the effectiveness of half ED as maintenance therapy for the first time. Some CD patients intolerant or resistant to thiopurines can benefit greatly from the results of this trial.

One of the characteristics of this trial was that patients in the half ED group were required to take half their daily allowance of calories by ED and the remaining half by usual unrestricted meals. The detailed mechanism by which half ED maintains patients with CD in remission remains unknown. One possible explanation is the response related to the low content of lipids in the diet. The fat profile of the feed was proposed to reduce proinflammatory eicosanoid synthesis and modify disease activity.<sup>31</sup> Because Elemental contains indeed only marginal amounts of lipids, the overall lipid intake could be less in the half ED group. Apart from this factor, reduced antigenic load, nutritional benefits, the supply of trophic amino acids, modification of the gut flora, intestinal permeability, faecal pH and bowel rest, among others, have been proposed as potential factors contributing to the maintenance of remission.<sup>31, 32</sup>

At the fourth interim data analysis, the trial was stopped for safety of the patients because a significant difference in the relapse rate was found between the two groups, in spite of the smaller number of study patients than we had assumed prior to the start of the trial. However, there seemed to be little possibility that a type I error had occurred in these analyses because the difference in the relapse rate between the two groups had kept on being larger each time, which was also shown by the Kaplan–Meier method.

In the present study, relapse of CD was defined as a CDAI of more than 200, or the need for therapy to

induce remission, based on the data from a retrospective follow-up study of patients carried out at Tohoku University Hospital. This definition indeed seemed to be clinically practical as the CDAI in most of the cases who required inductive therapies exceeded 200 in this study. In a previous report, relapse was defined as a CDAI of more than 250, a CDAI between 150 and 250 during 3 consecutive weeks with an increase of at least 75 points above the baseline value, and/or the need of surgery for CD.<sup>33</sup> The definition of relapse in the present study included even transient increases of the CDAI that resulted from causes other than 'real' relapse, such as intestinal infection. However, given the actual clinical course, such a definition was certainly appropriate. The results of the current study showed that patients with CD administered half ED were clinically stable with a CDAI under 200 and were unlikely to have flare-ups.

In the present study, the compliance demonstrated in the half ED group was similar to that of the free diet group and there was no adverse event in the half ED group, which itself was noteworthy as a maintenance therapy for CD.

The purpose of this study was to evaluate the effectiveness of half ED itself as maintenance therapy for CD patients, not to assess the nutritional status of the patients. Thus, this was not examined in detail, for example, vitamins, trace elements, which was a limitation of this study. In the present study, only four patients of the 51 (7.8%) had achieved remission by drug therapy prior to entering the maintenance trial although the CDAI was lower than 150 in all the 51 patients at the start of the trial. This was also a limitation of this study.

In conclusion, this trial has shown the effectiveness of half ED, which can be a promising maintenance therapy for CD, especially in some patients intolerant or resistant to immunosuppressive agents.

## ACKNOWLEDGEMENT

No external funding was received for this study.

## REFERENCES

- 1 Summers RW, Switz DM, Sessions JT, *et al.* National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology* 1979; **77**: 847–69.
- 2 Malchow H, Ewe K, Brandes JW, *et al.* European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. *Gastroenterology* 1984; **86**: 249–66.
- 3 Jones JH, Lennard-Jones JE. Corticosteroids and corticotrophin in the treatment of Crohn's disease. *Gut* 1966; **7**: 181–7.
- 4 Anthonisen P, Barany F, Folkenborg O, *et al.* The clinical effect of salazosulphapyridine in Crohn's disease: a controlled double-blind study. *Scand J Gastroenterol* 1974; **9**: 549–54.
- 5 O'Donoghue DP, Dawson AM, Powel-Tuck K, Bown RL. Double-blind withdrawal of azathioprine as maintenance treatment for Crohn's disease. *Lancet* 1978; **2**: 944–6.
- 6 Candy S, Wright JP, Gerber M, Adams G, Gerig M, Goodman R. A double-blind controlled study of azathioprine in the treatment and maintenance of remission in Crohn's disease. *Gut* 1995; **37**: 674–8.
- 7 Present DH, Korelitz BI, Wisch N, Glass JL, Sachar DB, Pasternack BS. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. *N Engl J Med* 1980; **302**: 981–7.
- 8 Bouhnik Y, Lemann M, Mary JY, *et al.* Long-term follow-up of patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. *Lancet* 1996; **347**: 215–9.
- 9 Fraser AG, Orchard TR, Jewell DP. The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. *Gut* 2002; **50**: 485–9.
- 10 Korelitz BI, Mirsky FJ, Fleisher MR, Warman JI, Wisch N, Gleim GW. Malignant neoplasms subsequent to treatment of inflammatory bowel disease with 6-mercaptopurine. *Am J Gastroenterol* 1999; **94**: 3248–53.
- 11 Kumar S, Fend F, Quintanilla-Martinez L, *et al.* Epstein-Barr virus-positive primary gastrointestinal Hodgkin's disease: association with inflammatory bowel disease and immunosuppression. *Am J Surg Pathol* 2000; **24**: 66–73.
- 12 Posthuma EFM, Westendorp RGJ, van der Sluys Veer A, Kluin-Nelemans JC, Kluin PM, Lamer CBHW. Fatal infectious mononucleosis: a severe complication in the treatment of Crohn's disease with azathioprine. *Gut* 1995; **36**: 311–3.
- 13 Khatchatourian M, Seaton TL. An unusual complication of immunosuppressive therapy in inflammatory bowel disease. *Am J Gastroenterol* 1997; **92**: 1558–60.
- 14 Connell WR, Kamm MA, Ritchie JK, Lennard-Jones JE. Bone marrow toxicity caused by azathioprine in inflammatory bowel disease: 27 years of experience. *Gut* 1993; **34**: 1081–5.
- 15 Matsueda K, Shoda R, Takazoe M, *et al.* Therapeutic efficacy of cyclic home elemental enteral alimentation in Crohn's disease: Japanese Cooperative Crohn's Disease Study. *J Gastroenterol* 1995; **30** (Suppl. 8): 91–4.
- 16 Hirakawa H, Fukuda Y, Tanida N, Hosomi M, Shimoyama T. Home elemental enteral hyperalimentation (HEEH) for maintenance of remission in patients with Crohn's disease. *Gastroenterol Jpn* 1993; **28**: 379–84.
- 17 Verma S, Kirkwood B, Brown S, Giaffer MH. Oral nutritional supplementation is effective in the maintenance of remission in Crohn's disease. *Dig Liver Dis* 2000; **32**: 769–74.
- 18 Hanauer SB, Feagan BG, Lichtenstein GR, *et al.* Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial. *Lancet* 2002; **359**: 1541–9.
- 19 Best WR, Beckett JM, Singleton JW, Kern F. Development of a Crohn's Disease Activity Index. National Cooperative Crohn's Disease Study. *Gastroenterology* 1976; **70**: 439–44.
- 20 Best WR, Beckett JM, Singleton JW. Rederived values of the eight coefficients of the Crohn's Disease Activity Index (CDAI). *Gastroenterology* 1979; **77**: 843–6.
- 21 Mekhjian HS, Switz DM, Melnyk CS, Rankin GB, Brooks RK. Clinical features and natural history of Crohn's disease. *Gastroenterology* 1979; **77**: 898–906.
- 22 Yao T. Criteria for diagnosis of Crohn's disease (preliminary proposal). In: Muto T, ed. *Annual Report of the Research Committee of Inflammatory Bowel Disease*. Tokyo: The Ministry of Health and Welfare of Japan, 1996: 63–6.
- 23 Hibi T, Naganuma M, Kitahora T, Kinjyo F, Shimoyama T. Low-dose azathioprine is effective and safe for maintenance of remission in patients with ulcerative colitis. *J Gastroenterol* 2003; **38**: 740–6.
- 24 Fukuda Y, Kosaka T, Okui M, Hirakawa H, Shimoyama T. Efficacy of nutritional therapy for active Crohn's disease. *J Gastroenterol* 1995; **30** (Suppl. ): 83–7.
- 25 Zoli G, Care M, Parazza M, *et al.* A randomized controlled study comparing elemental diet and steroid treatment in Crohn's disease. *Aliment Pharmacol Ther* 1997; **11**: 735–40.
- 26 Fernández-Banares F, Cabre E, González-Huix F, Gassull MA. Enteral nutrition as primary therapy in Crohn's disease. *Gut* 1994; **35**: S55–9.
- 27 Fernández-Banares F, Cabre E, Esteve-Comas M, Gassull MA. How effective is enteral nutrition in inducing clinical remission in active Crohn's disease? A meta-analysis of the randomized clinical trials. *J Parenter Enteral Nutr* 1995; **19**: 356–64.
- 28 Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for inducing remission of Crohn's disease. *Cochrane Database Syst Rev* 2001; **3**: CD000542.
- 29 Griffiths AM, Ohlsson A, Sherman PM, Sutherland LR. Meta-analysis of enteral nutrition as a primary treatment of active Crohn's disease. *Gastroenterology* 1995; **108**: 1056–67.
- 30 Knight C, El-Matary W, Spray C, Sandhu BK. Long-term outcome of nutritional therapy in paediatric Crohn's disease. *Clin Nutr* 2005; **24**: 775–9.
- 31 O'Sullivan MA, O'Morain CA. Nutritional therapy in Crohn's disease. *Inflamm Bowel Dis* 1998; **4**: 45–53.
- 32 Moran A. Bowel rest and elemental diet in Crohn's disease. *Gastroenterology* 1993; **104**: 1238–9.
- 33 Lemann M, Mary JY, Colombel JF, *et al.* A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. *Gastroenterology* 2005; **128**: 1812–8.