Digestive and Liver Disease 44 (2012) 649–654

Contents lists available at SciVerse ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

Nutritional therapy versus 6-mercaptopurine as maintenance therapy in patients with Crohn's disease

Hiroyuki Hanai[a,*], Takayuki Iida[a], Ken Takeuchi[a], Hajime Arai[a], Osamu Arai[a], Jinrou Abe[a], Tatsuo Tanaka[a], Yasuhiko Maruyama[a], Kentarou Ikeya[b], Ken Sugimoto[c], Toshio Nakamura[d], Kouichi Nakamura[d], Fumitoshi Watanabe[a]

[a] Centre for Gastroenterology and Inflammatory Bowel Disease Research, Hamamatsu South Hospital, Hamamatsu, Japan
[b] Fujieda Municipal Hospital, Japan
[c] First Department of Medicine, Hamamatsu University, Japan
[d] Second Department of Surgery, Hamamatsu University, Japan

ARTICLE INFO

Article history:
Received 8 November 2011
Accepted 4 March 2012
Available online 27 April 2012

Keywords:
Crohn's disease
Maintenance therapy
6-Mercaptopurine
Nutritional therapy

ABSTRACT

Background: 6-Mercaptopurine is often used as maintenance therapy in patients with Crohn's disease. However, toxicities like myelosuppression limit its clinical benefit.
Aims: To evaluate the efficacy of elemental diet versus 6-mercaptopurine as maintenance therapy in Crohn's disease.
Methods: Ninety-five eligible patients with Crohn's disease activity index ≤150 were randomly assigned to: 6-mercaptopurine (0.5–1.5 mg/kg/day, $n=30$); Elental as an elemental diet (≥900 kcal/day, $n=32$); none (control, $n=33$). In the three groups, patients were and remained on 5-aminosalicylic acid (2250–3000 mg/day). Patients were observed for 2 years and the rate of relapse (Crohn's disease activity index ≥200) was monitored.
Results: At 24 months, the fractions of patients who had maintained remission were 60%, 46.9% and 27.2% for 6-mercaptopurine, Elental and the control groups, respectively. Log-rank test showed better efficacy for 6-mercaptopurine ($P=0.0041$) and Elental ($P=0.0348$) versus control. No significant difference was found between 6-mercaptopurine and Elental. Further, in the 6-mercaptopurine group, 2 patients experienced liver injury and one developed alopecia.
Conclusions: This 24 months comparison study showed that Elental as maintenance therapy in Crohn's disease patients was as effective as 6-mercaptopurine. Elental should be useful for long-term maintenance therapy in Crohn's disease. This is the first comparison study evaluating nutritional therapy versus 6-mercaptopurine.

1. Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing-remitting immune pathology that one may refer to as an exuberant immune activity causing a dysregulated immune profile, primarily in the intestinal mucosa that may cause debilitating symptoms [1–4]. The major phenotypes of IBD are ulcerative colitis (UC) and Crohn's disease (CD). Whereas UC is confined primarily to the colon and the rectum, CD can affect any part of the gut from the mouth to the perianal region, and up to 65% of patients with CD have the disease affecting the lower part of the small intestine as well [1,2]. IBD afflicts millions of individuals throughout the world with symptoms, which impair ability to work and health related quality of life [1,3]. Currently, the principal treatment objectives are to induce and sustain remission and minimise treatment related adverse effects (AE), a strategy that depends on the medication having a low toxicity profile, but high efficacy. However, the complete eradication of IBD remains an ultimate challenge in the years to come. In the present report, we focus on maintenance therapy for CD.

The thiopurine drugs which include 6-mercaptopurine (6-MP) and its pro-drug, azathioprine (AZA) are frequently used in the treatment of patients with IBD, to induce remission, reduce steroid dosage, and sustain remission [1,5,6]. Although 5-ASA agents have been a mainstay in the treatment of both CD and UC, the data for their efficacy in patients with CD, particularly as maintenance therapy need thorough evaluation. Thiopurine based drugs

* Corresponding author at: Centre for Gastroenterology and Inflammatory Bowel Disease Research, Hamamatsu South Hospital, 26 Shirowacho, Hamamatsu 430-0846, Japan. Tel.: +81 534711013; fax: +81 534711013.
E-mail addresses: hanai@hamamatsu-minami.com, flw-1013@topaz.plala.or.jp (H. Hanai).

1590-8658/$36.00 © 2012 Editrice Gastroenterologica Italiana S.r.l. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.dld.2012.03.007

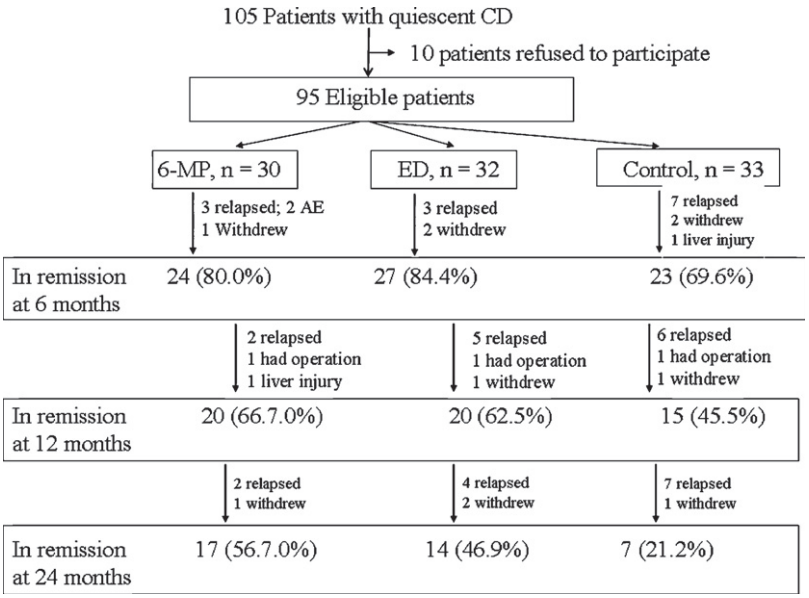

Fig. 1. Study design and the overall clinical outcomes in 95 eligible patients with quiescent Crohn's disease (CD) that were treated in three groups, 6-mercaptopurine (6-MP), Elental as an elemental diet (ED) and the control. All patients were on a salicylate; an 86 patients on 5-aminosalicylic acid (5-ASA) at 2250–3000 mg/day and 9 on sulphasalazine, at 3000 mg/day.

including 6-MP were introduced into clinical practice several decades ago [7,8]. In the past 10 years, 6-MP and AZA have become the mainstay of immunosuppressive therapy in patients with CD in spite of limited efficacy in acute flares of CD due to the long time lag between administration and the onset of clinical efficacy [7,9,10]. However, the main limitation of their clinical application is toxicity which can be diverse both in its severity and nature. Further, there is strong individual differences in the severity and the nature of toxicity, which include allergic reactions, pancreatitis, nausea, infection, hepatotoxicity and worse than all, myelosuppression among patients receiving a thiopurine like 6-MP [7,10–12].

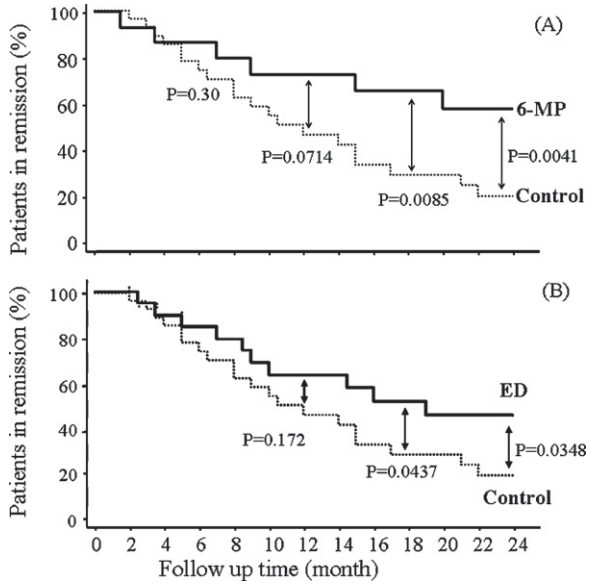

Fig. 2. (A), the Kaplan–Meier plots showing the percentage of patients remaining in remission in two groups of patients treated with 6-MP or control during the 24 months observation time of this trial. (B), the Kaplan–Meier plots showing the percentage of patients remaining in remission in two groups treated with ED or control during the 24 months observation time of this study. The *P* values are by the long-rank test (Mantel–Cox).

Although genetic background may be associated with the onset and certain dietary antigens are thought to have an important role in the aggravation of CD [13,14], it is true to say that factors which initiate and perpetuate CD are not well characterized at present. Diet, as a source of luminal antigens, potentially might have both provoking as well as inhibiting effects in the immunopathogenesis of CD, depending on the nature of its constituents [13–15]. Accordingly, antibodies against dietary antigens are suspected to be part of CD aetiology or significant factors in the initiation of intestinal inflammation [13]. This is like saying a relapse may be triggered by an inflammatory response to dietary antigens in the intestinal wall [13–15], and therefore, appropriate nutritional interventions should minimise the contribution of normal diet to disease activity and even induce remission in patients with active CD [16–22]. In line with these assertions, significant efficacy has been reported following a course of nutritional therapy [16,19,22–24]. In this trial, we were interested to evaluate the clinical efficacy of nutritional therapy with an elemental diet (ED) in the maintenance of remission in patients with quiescent CD. As 6-MP has shown efficacy as maintenance therapy in IBD [5,10–12,25], this thiopurine was used as a comparator.

This clinical study was to compare the efficacy and safety of Elental [22] with 6-MP in the maintenance of clinical remission in patients with CD. The composition of Elental was as described by Takagi et al. [24].

2. Patients and methods

2.1. Patients and study design

Ninety-five eligible patients, 19–48 years old with a diagnosis of CD and in clinical remission, with a CD activity index (CDAI) of ≤150 were randomly assigned to three groups: to receive 6-MP ($n = 30$); Elental as an ED (≥900 kcal/day, $n = 32$); without additional medication (control, $n = 33$). The dose of 6-MP was as established by Hanai et al. [25] described below. At entry, an 86 of the 95 eligible patients were (and remained) on 5-aminosalicylic acid (5-ASA, 2250–3000 mg/day), the other 9 patients were on sulphasalazine (3000 mg/day). These medication had been started at least 8 weeks prior to entry to this remission maintenance trial. Patients in the