Journal of Crohn's and Colitis (2014) 8, 200–207

Available online at www.sciencedirect.com

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Combined oral and rectal mesalazine for the treatment of mild-to-moderately active ulcerative colitis: Rapid symptom resolution and improvements in quality of life

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Received 25 March 2013; received in revised form 1 August 2013; accepted 12 August 2013

KEYWORDS
Mesalazine;
Oral;
Rectal suspension;
Ulcerative colitis;
Mucosal healing

Abstract

Background and aims: Mesalazine (5-aminosalicylic acid) is the standard first-line therapy for mild-to-moderate ulcerative colitis. In the PINCE study, remission rates were significantly greater with combined oral/enema vs. oral/placebo treatment at 8 weeks (64% vs. 43%, respectively; $p = 0.030$). In this analysis, we explored early response, mucosal healing rates, cessation of rectal bleeding, and quality of life in PINCE.
Methods: Patients with extensive mild-to-moderately active ulcerative colitis received 8 weeks of oral mesalazine 4 g/day, plus 4 weeks of daily active (1 g mesalazine) or placebo enema. Early response was assessed using the abbreviated ulcerative colitis disease activity index. Mucosal healing was assessed by disease activity index endoscopic mucosal appearance score. Cessation of bleeding (patient diaries), quality of life (EQ-5D), and patient acceptability (questionnaire) were also assessed.
Results: Combined mesalazine oral/enema treatment achieved a significantly higher rate of improvement in abbreviated ulcerative colitis disease activity index (score decrease ≥ 2) within 2 weeks, compared with oral-only treatment ($p = 0.032$). Bleeding ceased significantly more quickly with combination vs. oral therapy ($p = 0.003$). More patients showed mucosal healing (disease activity index endoscopic mucosal appearance score 0/1) with combination vs. oral

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http://dx.doi.org/10.1016/j.crohns.2013.08.007

therapy, which was significantly different between groups at week 4 ($p = 0.052$). Both groups showed quality of life improvements, with a significant benefit for combination vs. oral therapy at week 4 in multiple domains. Most patients reported finding the treatment acceptable.
Conclusions: Rapid cessation of symptoms was seen with combination therapy, which is particularly important to patients and may improve quality of life.
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1. Introduction

Mesalazine (5-aminosalicylic acid [5-ASA]) is recommended for the treatment of most forms of mild-to-moderately active ulcerative colitis (UC) in guidelines from the European Crohn's and Colitis Organisation,[1] reflecting the status of mesalazine as the current standard of care for both the induction and maintenance of remission in mild-to-moderate UC. Nevertheless, there is scope to further optimize drug delivery and dosing schedules, which may improve patient adherence.[2]

Mesalazine has been shown to be effective when used as either an oral therapy,[3–8] a rectal therapy administered as a suspension (enema), suppository, gel or foam,[9–18] or when oral and rectal formulations are used in combination.[15,19–23] A dose-related effect has been shown for oral mesalazine such that doses ≥2 g/day show superior efficacy compared with lower doses,[24] and 2.4–4.0 g daily oral therapy is generally used to induce remission.[22] Clinical response rates of 60–70% and clinical remission rates of 40–70% have been reported in various 6–8 week studies.[25] However, both the oral and the rectal routes of administration are limited in their sites of mesalazine delivery. Oral therapy alone may not be sufficient to achieve therapeutic response in the distal sites of the large bowel, while mesalazine suppositories and rectal suspensions do not have any effect above the rectosigmoid junction and splenic flexure, respectively.[22] Thus, combination therapy may show benefits over either route used in isolation.

The PINCE study was a European, multicenter, randomized trial, comparing therapy with combined mesalazine (PENTASA®; Ferring Pharmaceuticals, Denmark) oral (4 g/day) plus rectal suspension (1 g/day), and mesalazine (PENTASA) oral (4 g/day) plus placebo suspension in patients with extensive mild-to-moderately active UC. Remission rates, based on clinical and endoscopic criteria, were higher in the mesalazine combination therapy group than in the oral therapy group at weeks 4 and 8, significantly so at week 8 (combination, 64% vs. oral 43%, $p = 0.030$).[22]

UC treatment has several important goals in addition to remission.[25] Mucosal healing is an important outcome, and may prevent or reduce the risk of colorectal cancer.[26] Other important outcomes from the patient's perspective include the rapid cessation of distressing symptoms such as rectal bleeding, an important clinical endpoint in many trials of UC therapy. In the PINCE study, of those patients with rectal bleeding at baseline, 73% in the mesalazine combination therapy group, compared with 38% in the oral therapy group achieved cessation of rectal bleeding over the 8-week study.[22] Rectal bleeding, abdominal pain, and other symptoms of the condition can also have a significant impact on patient quality of life (QoL).[2] In the present secondary analysis of the PINCE study, we examined mucosal healing, early (week 2) clinical efficacy, time to cessation of rectal bleeding in patients with different types of bleeding at baseline (traces, frank, or mainly blood), and QoL in patients receiving combined or oral-only treatment.

2. Materials and methods

2.1. Patients

Patients were recruited between January 2002 and July 2003 in six European countries (France, UK, Spain, Germany, The Netherlands, and Sweden). The study was approved by local institutional review boards and ethics committees. Male and female patients >18 years of age were eligible to participate if they had previously established extensive UC with mild-to-moderate exacerbation, and a UC disease activity index (UCDAI) score of ≥3 and ≤8.[4] All patients gave written, informed consent prior to study entry. Exclusion criteria included: infectious colitis; oral maintenance treatment with total daily doses >3 g of sulfasalazine, mesalazine, or 4-ASA within 30 days prior to study entry; any immunosuppressive agents during the 30 days prior to study enrollment; chronic use of nonsteroidal anti-inflammatory drugs (oral and/or rectal routes) in the 7 days prior to inclusion (chronic use defined as drug intake for a minimum of 7 consecutive days); intake of corticosteroids (oral and/or rectal routes) within 7 days prior to enrollment; severe renal/hepatic impairment, malignant disease, allergy to salicylates, alcoholism, or drug addiction, or any other disease or condition that might interfere with study assessments, as judged by the investigator; participation in another clinical study in the previous 30 days; women of child bearing potential who were not using an effective method of contraception; or pregnancy and lactation.

2.2. Study design

This was a double-blind, multinational, randomized, parallel group, placebo-controlled, 8-week clinical study in outpatients with a previously established diagnosis of extensive mild-to-moderately active UC (macroscopic inflammation beyond the splenic flexure during a full colonoscopy).[22] Patients were randomized to receive either mesalazine (PENTASA) enema (1 g/day [OD] in 100 ml at bedtime) or placebo enema for a period of 4 weeks. Patients in both arms also received oral mesalazine (PENTASA; 2 g/twice daily [BD], granules swallowed with water or juice) for 8 weeks.

Patients, enrolled following a medical evaluation of the initial clinical and endoscopic severity of their UC, were

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