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A randomized clinical trial of mesalazine suppository: The usefulness and problems of central review of evaluations of colonic mucosal findings☆

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Abstract

Background: The methods of evaluating endoscopic mucosal findings and the definition of mucosal healing in inflammatory bowel disease have not been standardized.
Aim: To examine a third-party central review of colonic mucosal evaluations.
Methods: A double-blind, placebo-controlled, parallel-group trial was performed for 4 weeks, which involved continuous administration of a 1-g mesalazine suppository to 129 patients with mild to moderate ulcerative colitis and active rectal inflammatory findings. Mucosal findings were evaluated by using a 4-grade score (0, 1, 2, 3). Reviews by attending physicians were considered the primary evaluations. Concurrently, a central review committee of 7 gastroenterologists served as the third party.

Abbreviations: ICC, intra-class correlation coefficients.
☆ The clinical trial registration: JapicCTI-111421.
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Results: The endoscopic remission induction rate from the attending physicians' evaluations was 82.8% in the mesalazine suppository group and 31.1% in the placebo suppository group, whereas the respective rates from the central review committee were 90.6% and 59.0%. However, there was a difference of 27.9 percentage points between the remission induction rates of the placebo group found by the two groups of raters. Differences in the evaluations of mucosal finding scores were also found among the third-party reviewers.
Conclusions: The evaluations of the attending physicians were consistent with those of the central review committee in showing the effectiveness of mesalazine suppository through the index of mucosal healing. However, differences were observed among the raters in their evaluations of mucosal finding scores. Therefore, standardizing evaluation criteria and improving review methods for mucosal findings would enable the more effective use of third-party central reviews in clinical drug trials.

1. Introduction

Ulcerative colitis is an inflammatory bowel disease with primary symptoms that include frequent diarrhea, hemafecia, and abdominal pain. The disease involves repeated stages of active subjective symptoms and stages of remission of these symptoms. Patients are rarely cured completely, and the disease tends to be chronic.[1–3] The cause of ulcerative colitis remains unclear; however, it involves erosion and ulceration of the colonic mucosa.[4] Therefore, a definitive diagnosis requires not only the presence of clinical symptoms such as persistent or recurrent diarrhea or stool with mucous and blood, but also an evaluation of mucosal findings through colonoscopy or confirmation with histopathological findings. Recent advancements in colonoscopy equipment have enabled a more precise evaluation of mucosal findings in ulcerative colitis.

Traditionally, the aim of ulcerative colitis treatment is to ameliorate clinical symptoms such as frequent bowel movements and hemafecia. However, mucosal healing is becoming a therapeutic target with the use of long-term, high-dose mesalazine, anti-tumor necrosis-α antibody drugs, and immunomodulators such as azathioprine.[5–7] Moreover, there have been reports on methods for evaluating ulcerative colitis activity, such as qualitatively categorizing clinical symptoms and physical and mucosal findings, as well as quantitatively scoring activity indices.[8–12] However, as methods of evaluating mucosal findings or defining mucosal healing have yet to be standardized, evaluations are left to the discretion of individual physicians. Therefore, naturally, large physician-dependent differences in the evaluations of mucosal findings have been reported.[13–15]

In everyday medical care, treatment based on the attending physicians' evaluation of mucosal findings is not considered problematic. However, there are concerns that in clinical trials, differences between the assessments of individual physicians could affect the evaluation of drug effectiveness. Therefore, our objective was to confirm the reliability of the attending physicians' evaluations for the performance of uniform evaluations of mucosal findings in clinical trials. To achieve this goal, we recruited third parties not involved in the clinical trial (a central review committee) to also perform evaluations.[11,16–20] However, considering the evaluations by a central review committee as the results of a clinical trial would require many stipulations over the mucosal images presented to the committee, such as concerning the capabilities of the imaging device and the photographic methods used. The central review committee would also have to perform its evaluations quickly. The more members the committee has, the more difficult it would be to perform speedy evaluations. Therefore, when a central review committee is formed to perform evaluations, it is important to find an evaluation method that can be executed both quickly and precisely under a limited number of conditions.

In this double-blind, parallel-group mesalazine suppository trial[21] of patients with mild to moderate ulcerative colitis and active inflammatory findings in the rectal area, the endoscopic remission induction rate from the mucosal finding scores given by attending physicians were considered as the primary evaluations. To confirm the reliability of those results, a central review committee was formed consisting of 7 gastroenterologists who did not participate in the trial. For each case, the committee evaluated mucosal findings only from the end of the trial (or at drop-out). These evaluations were used to examine the reliability of the results of the attending physicians' evaluations, as well as to check for differences between the evaluations of the attending physicians and those of the central review committee, and among the 7 members of the committee. This was expected to clarify the issues related to uniformity in evaluating mucosal findings and help with proposing countermeasures.

2. Materials and methods

2.1. Outline of the clinical trial

This phase III, randomized, placebo-controlled, double-blind, multi-institutional, parallel-group trial[21] was performed across 45 institutions in Japan after enrolling 129 patients with mild to moderate active ulcerative colitis and active inflammatory rectal findings. The subjects were men and women aged $\geq$15 years and $\leq$74 years who had ulcerative colitis and met the following criteria: (i) a score of 4–8 on the ulcerative colitis disease activity index[22,23] and a score of $\geq$2 considering the mucosal findings in the rectum; and (ii) initial episode-type patient or flare-up and remission-type patient. Patients who met any of the following criteria were excluded: (i) having a score of $\geq$2 considering the colonic mucosal findings in areas other than the rectum at the start of the trial; (ii) receiving any of the following treatments within 4 weeks after initiating the

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