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ORIGINAL ARTICLE

Thalidomide is a therapeutic agent that is effective in inducing and maintaining endoscopic remission in adult CD patients

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Summary

Background and aims: Previous studies have indicated that thalidomide may be effective in achieving clinical remission and response; however, there is a lack of studies on its effect in endoscopic remission. The aim of this study was to assess the efficacy and safety of thalidomide in inducing and maintaining endoscopic remission.

Methods: A retrospective study was conducted in adult Crohn's disease (CD) patients treated with thalidomide. Patients were assessed based on their medical records. Endoscopy was performed after 4–6 months of thalidomide administration, and the simple endoscopic score for CD (SES-CD) was obtained.

Results: Twenty of the 21 (95.2%) eligible patients were recruited. Endoscopic remission was achieved in 7 of the 14 (50%) endoscopy active patients who received thalidomide treatment, whereas 10 (71.4%) patients showed an endoscopy response. The other 6 patients in endoscopic remission still maintained remission after thalidomide treatment. The SES-CD in endoscopy active patients was significantly reduced after thalidomide treatment ($P < 0.05$). A total of 32 adverse events occurred in 17 of the 21 (81.0%) patients. Adverse events resolved spontaneously in 11 (64.7%) patients and resulted in treatment discontinuation and dose reduction in 4 (19.1%) and 2 (9.5%) patients, respectively.

Conclusions: Thalidomide therapy is effective in inducing and maintaining endoscopic remission in adult CD patients. However, side effects may limit its clinical use in CD treatment.

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Introduction

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal (GI) tract with intermittent clinical remissions and relapses, and its incidence is increasing globally [1—4]. The underlying etiology of CD remains unknown but is thought to result from an interaction between susceptibility genes, environmental factors, and the host immune response [5]. Inflammatory bowel disease (IBD) represents an important public health problem, as it affects mostly young people. Despite an increasing number of currently available treatment options, many CD patients still present a therapeutic challenge due to unsatisfactory drug response or serious side effects.

Tumor necrosis factor-α (TNF-α) is known to play an important role in the pathogenesis of CD [6,7]. Infliximab, a chimeric antibody against TNF-α, has been shown to be effective in CD, but it may increase the financial burden for patients in developing countries, such as China. Thalidomide is a small molecule with TNF suppressant properties and is an affordable drug in developing countries [8]. It was originally used as an antiemetic agent in pregnancy and was withdrawn from the market because of its teratogenic effects [9]. Although its bioactivities are not very clear, thalidomide had been re-introduced due to its efficacy in several immune-mediated diseases, such as Behçet disease, erythema nodosum leprosorum, and cutaneous lupus erythematosus [10—14]. Many CD-related clinical studies have also reported that thalidomide is effective in inducing and maintaining clinical remission in children and adults with refractory CD; however, to our knowledge, there have been few reports on the efficacy of thalidomide in endoscopic remission. Therefore, the aim of our retrospective study was to evaluate the efficacy of thalidomide in inducing and maintaining endoscopic remission in adult CD patients.

Patients and methods

Patients

This was a retrospective study of 21 adult CD patients treated with thalidomide from a population of 161 CD patients in the Department of Gastroenterology of the First Affiliated Hospital of Nanchang University between September 2013 and May 2016. The diagnosis of CD was established by prior clinical assessment, radiology, endoscopy, and histology. Disease location and behavior were categorized according to the Montreal classification scheme [15]. The study population included patients with steroid-dependent and/or azathioprine intolerance or azathioprine/infliximab treatment failure. Informed consent was obtained from all patients after an extensive questionnaire-based discussion about the potential side effects. Additionally, strict clinical monitoring was performed during follow-up.

Study design

Data collection

All medical records were independently reviewed by two investigators (ZZ and LM). Data were collected using a predetermined form. Each patient's demographic characteristics; CD history; past medical, drug, and surgical history; initial dose of thalidomide and dose modifications; duration of treatment; adverse events (AEs); reasons for withdrawal; Crohn's disease activity index (CDAI); and simple endoscopic score for Crohn's disease (SES-CD) were recorded.

Treatment

Thalidomide was administered at a starting dose of 25 mg per day and was increased stepwise by 25—50 mg per week to 2.5—3.0 mg/kg per day according to each patient's clinical response and thalidomide-related adverse events. The dose was tapered in patients with complaints of excessive sedation or other dose-related adverse effects during the treatment. To minimize the sedative effects of thalidomide, we recommended that patients take a single dose of the study drug in the evening. Any ongoing immunosuppressive drugs were discontinued, except steroids. Contraception was mandatory for female participants of childbearing age, and pregnancy testing was performed before the initiation of thalidomide and monthly thereafter. Male patients were advised to use condoms. Patients were evaluated at baseline, at weeks 2, 4, 8, and 12, and every three months thereafter for the measurement of several parameters, including physical examination, laboratory tests, and CDAI. Repeat endoscopy was performed 4—6 months after the administration of thalidomide, and the SES-CD was assessed. Any adverse events were closely monitored during follow-up.

Definition of endoscopic remission, response, and clinical remission

Endoscopic remission was defined as a SES-CD less than 2[16]. Endoscopy response was defined as a decrease in the SES-CD by 50% from baseline values. Clinical remission was defined as a CDAI less than 150 without steroids and after infliximab withdrawal for at least two months for patients taking infliximab at the time of thalidomide introduction.

Efficacy and adverse events

The primary outcomes were the efficacy of thalidomide in inducing and maintaining endoscopic remission based on the SES-CD. Secondary outcomes were clinical remission based on the CDAI and withdrawal of steroids. All adverse events during treatment were recorded. Because peripheral neuropathy is a possible adverse event related to thalidomide, a complete neurological examination, with special attention given to any signs and symptoms of peripheral and autonomic nervous system involvement, was performed.

Statistical analysis

All patients receiving at least one dose of thalidomide were eligible for analysis. Categorical variables are described as absolute numbers and percentages, and continuous variables are described as medians. Safety data are reported as the rate of adverse events. The median reduction in the CDAI and SES-CD from baseline to the study visit on thalidomide

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