



BRIEF REPORT

Efficacy and safety of low-dose thalidomide combined with mesalazine in the treatment of refractory ulcerative colitis in adults

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Introduction

Inducing and maintaining clinical remission and mucosal healing is essential in the treatment of ulcerative colitis (UC), a non-specific chronic recurrent inflammatory disorder [1]. Mesalazine (5-ASA) is commonly prescribed as a first-line drug for UC. Despite the short-term efficacy of ciclosporin and infliximab, some patients may develop methylprednisolone resistance or dependence [2].

Thalidomide has been used to treat morning sickness, but was later withdrawn from the market due to its potential to cause congenital birth defects, like phocomelia or amelia. In recent years, thalidomide has been widely used to treat multiple myeloma, leprosy erythema nodosum, and rheumatoid arthritis, depending on its immunoregulatory, anti-angiogenic, anti-proliferative, or anti-apoptotic effects [3]. Thalidomide can resist the effects of TNF- α , NF- κ B, and IL-12, suggesting that it may be effective for UC. However, the clinical application of thalidomide is limited by its adverse effects, such as peripheral nerve inflammation, lethargy, and constipation, which may be related to dose accumulation. Our previous study also found

that thalidomide induced dose-related adverse drug reactions (ADRs), like lethargy and hand and foot numbness [4].

Patients and methods

We retrospectively selected adult patients with refractory UC treated with low-dose thalidomide combined with mesalazine in the Sixth Affiliated Hospital of Sun Yat-sen University from January 2018 to May 2020. The follow-up deadline was July 2020. The inclusion criteria were as follows: (i) the patient was diagnosed as UC based on the inflammatory bowel disease-classes criteria [5]; (ii) the patient with refractory UC was defined as having hormone inefficacy or hormone dependence; (iii) the patient was treated with low-dose thalidomide (25–50 mg/d) combined with oral administration of mesalazine (≥ 4 g/d) and retention enema (≥ 2 g/d); (iv) the patient provided informed consent to receive thalidomide. The exclusion criteria were as follows: (i) the patient failed to take medicine regularly during treatment; (ii) the patient was not followed up after treatment or missed some examinations during the follow-up. The

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research plan was approved by the Ethics Committee of the Hospital (2020ZSLYEC-241).

Severity was assessed as mild, moderate, or severe according to the modified Truelove and Witts severity index including defecation time, blood in the stool, temperature, pulse, hemoglobin, and erythrocyte sedimentation rate. The endoscopic severity assessment was carried out using the Mayo Endoscopic Score (MES) with an endoscopic score of 0–1 as mucosal healing. ADRs were assessed according to the symptoms and their durations during follow-up.

Results

A total of 14 patients (9 males and 5 females) with UC were included. The median age was 45 years (range, 26–67 years). The median clinical response time was 3.5 weeks. At 8 weeks, complete clinical remission was achieved in 78.6% (11 of 14) of patients. Of the 14 patients, 3 (21.4%) experienced primary treatment failure, including one receiving infliximab injection and two receiving surgery later. Remission maintained in 57.1% (8 of 14) of the patients for 52 weeks. UC relapsed in 9.1% (1 of 11) of the patients 1.2 years later and was treated with infliximab injection. Medication discontinued in 27.3% (3 of 11) of the patients during remission maintenance for complications. Nerve injury occurred in 21.4% (3 of 14) of the patients, characterized by numbness in the lower extremities. The ADRs are gradually resolved after drug withdrawal and nerve treatment (Fig. 1 and Table 1).

Discussion

Despite its good tolerance and few ADRs, 5-ASA does not induce a high remission rate in treating mild-to-moderate UC. Methylprednisolones and biological agents have limitations. Surgery is used for UC with strict indications, but also constrained by the risk of complications. Thalidomide can induce and maintain remission in the clinic [6]. In this study, low-dose thalidomide combined with mesalazine achieved a clinical remission rate of 78.6% (11 of 14) in UC patients, which is higher than those reported in the literature [7]. This suggests that this combination may have synergistic effects.

Lazzerini [8] reported that immunosuppressant therapy was effective in UC (1.5–2.5 mg/kg/d), with an 8-week remission induction rate of 78.3% (18 of 23). Considering its ADRs, we used low-dose thalidomide combined with mesalazine to treat adult patients with refractory UC, which achieved a 78.6% (11 of 14) clinical remission rate at 8 weeks. Previous reports suggested that the mucosal healing rate of thalidomide in refractory UC patients was 83.3% (10 of 12) at 52 weeks, suggesting the effectiveness of thalidomide in the long-term treatment of UC. Further research [9] found that the endoscopic mucosal healing rate of thalidomide for refractory inflammatory bowel disease (IBD) children was 41.4% (29 of 70) at 52 weeks. The long-term efficacy was comparable to that of infliximab and adalimumab. In this study, remission was maintained in 50% (7 of 14) of the patients during follow-up, with an average remission duration of 79 weeks.

The clinical application of thalidomide is restricted by its high incidence of ADRs (e.g. peripheral neuritis, lethargy, constipation) and high drug withdrawal rate. Lazzerini [8] reported that the cumulative rate of drug withdrawal due to ADRs, like peripheral neuritis and amenorrhea after remission induction, was 3.1/1,000 people/week; non-severe ADRs included neurological, cutaneous, and gastrointestinal reactions, with a cumulative incidence of 18.8 per 1,000 people per week. In our study, three patients developed nerve damage, which was resolved by the gradual reduction and eventual withdrawal of the drug. A low dose of thalidomide (50 mg/d) was used to reduce withdrawal due to ADRs and persist the treatment. Sehgal [10] reported an adverse reaction rate of 7.0% for mesalazine, which was mostly driven by dose-independent hypersensitivity. Our study found that after use of low-dose thalidomide combined with mesalazine, only nerve injury was observed, with an incidence of 21.4% (3 of 14) and an average drug maintenance of 1 year. However, this study is a single-center retrospective study with a small sample size and possible bias. The benefits of this combination should be validated with studies covering more centers.

In conclusion, low-dose thalidomide combined with mesalazine brings significant effect and limited ADRs in treating refractory UC, suggesting that thalidomide might be employed as a rescue therapy in severe UC cases refractory to conventional treatments.

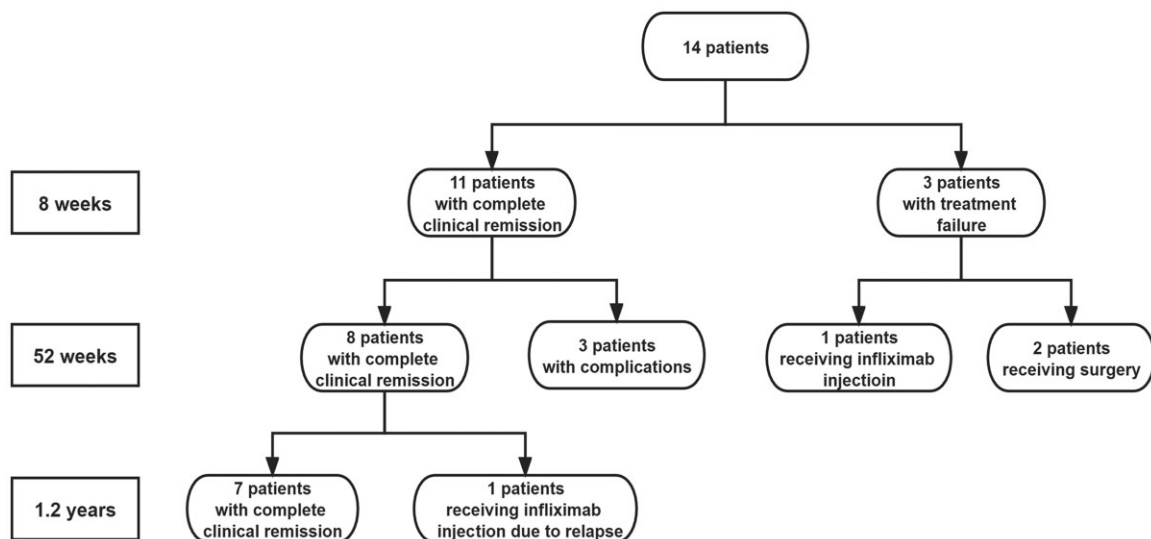


Fig. 1. The flowchart of low-dose thalidomide combined with mesalazine for adult patients with refractory ulcerative colitis

Table 1. Clinical data of 14 patients with refractory ulcerative colitis

No.	Gender	Age (years)	Course (years)	Thalidomide dose (mg)	Oral mesalazine dose (g)	Enema mesalazine dose (g)	Pretreatment MES	Severity	Duration (weeks)	Post-treatment MES	Ending
1	Male	26	9	50	6	4	3	Severe	69	–	Maintain remission
2	Male	55	10	50	4	2	2	Moderate	69	0	Maintain remission
3	Male	28	5	50	6	–	3	Severe	116	–	Maintain remission
4	Male	64	12	50	4	4	1	Severe	52	1	Maintain remission
5	Male	67	18	50	4	4	1	Severe	43	–	Maintain remission
6	Female	46	4	50	4	2	3	Severe	69	2	Maintain remission
7	Female	63	4	50	4	4	1	Severe	65	0	Maintain remission
8	Male	47	7	50	4	1	2	Severe	26	–	Nerve damage
9	Male	43	20	50	4	2	1	Moderate	82	1	Nerve damage
10	Male	45	5	25	3	4	2	Severe	43	0	Nerve damage
11	Female	61	2	50	3	Methylprednisolones	–	Severe	5	–	Operation
12	Female	61	2	50	4	–	–	Severe	8	–	Operation
13	Male	64	5	50	4	Methylprednisolones	2	Severe	6	2	Infliximab
14	Female	33	4	50	3	3	1	Severe	66	2	Infliximab

MES, Mayo Endoscopic Score.

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Conflict of Interest

None declared.

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