Efficacy and Safety of Thalidomide in Crohn’s Disease Patients with Perianal Fistula and Abscess

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Abstract

Background

Medical therapies of perianal Crohn's disease (CD) are limited. Thalidomide is an effective medical
therapy to alleviate disease activity of CD. However, the effects and safety of thalidomide in the treatment
of perianal fistula and abscess was not evaluated.

Methods

This retrospective cohort study was performed at a tertiary referral centre and recruited 73 patients with
perianal CD who received thalidomide (50–100 mg) daily for 1 year. Data collected included
demographics, medications, and disease behaviour. Clinical assessment of CD was conducted using the
Crohn's Disease Activity Index (CDAI), and perianal lesions were evaluated using the Fistula Drainage
Assessment index and Perianal Disease Activity Index (PDAI). At the same time, the occurrence of
adverse effects was recorded during treatment. Wilcoxon's signed-rank test and Student’s t-test were used
to analyse the data.

Results

The CDAI score and laboratory indices were significantly lower after thalidomide treatment than at
baseline (all \( P < 0.01 \)). The value of PDAI was significantly lower in patients with symptomatic perianal
abscess after thalidomide treatment than at baseline (10 [6.25, 10] versus 2.5 [1, 3.75]; \( P = 0.05 \)). PDAI
was also significantly reduced in all patients treated with thalidomide whether with or without perianal
abscess drainage (all \( P < 0.05 \)). The rates of responsive patients were similar between the thalidomide
group and thalidomide combined with azathioprine group (72.73% [8/11] and 84% [21/25], respectively; \( P
= 0.65 \)). In total, 31% (24/77) of patients experienced adverse events, and interventions were required in
15 patients to reduce or eliminate discomfort from adverse events. Four patients discontinued
thalidomide due to adverse effects. Side effects (rash, diarrhoea, peripheral neuropathy, somnolence,
constipation, and numbness) were mild and mostly transient.

Conclusions

Thalidomide is effective in inducing clinical remission and response in CD patients with perianal fistula
and abscess with or without abscess drainage. Thalidomide in combination with azathioprine is also
effective in these patients. Low-dose thalidomide is proven to be effective and safe in treating perianal
CD patients.

Introduction
Perianal Crohn's disease (PCD), which plays a major negative role in the quality of life of patients, is defined as inflammation at or near the anus, including tags, fissures, fistulae, abscesses, or stenosis. The reported incidence of PCD varies from 3–80%, depending on the location of the involvement of the gastrointestinal tract [1]. Over 50% of rectal and colonic Crohn's disease (CD) patients are associated with perianal complications [2]. Such complications are a marker of more severe disease activity, and are associated with multiple surgical interventions and frequent relapses. Treatment of perianal complications is very challenging and usually requires a combination of medical and surgical interventions.

With regard to medical management of PCD, the role of antibiotics, immunosuppressive drugs (e.g. thiopurines and oral tacrolimus), and biological agents in the management of PCD have been reported with variable success rates when used as single agents or in combination [2]. It was reported that there was no significant benefit of using aminosalicylates for the treatment of luminal CD [3], and there were no specific trials in PCD. Although corticosteroids are sometimes used in combination with other drugs to treat PCD, their contribution is limited [4, 5]. Several studies have reported that antibiotics may improve symptoms and contribute to the healing of fistulas [2]. Multiple studies and randomised controlled trials showed that anti-TNF alpha treatments, including infliximab and adalimumab, and other biologics such as vedolizumab, and certolizumab, are superior to placebo in induction and maintenance therapy for perianal fistulas in CD [2, 6–9]. However, the percentage of patients who do not achieve improvement or closure is high partly due to the development of antibodies against these agents that can result in a loss of clinical response. Besides, anti-TNF agents have been associated with opportunistic infections, serum sickness-like reactions, autoimmune disorders, and sepsis. The high cost of anti-TNF agents also limits their clinical application, especially in developing countries.

Thalidomide (a-N-phthalimidoglutarimide) was originally used over 40 years ago as a sedative and removed from the market because of its teratogenic effects. However, it has been used as an inexpensive anti-inflammatory immunosuppressant in many immune diseases more recently [10]. The efficacy of thalidomide in the treatment of patients with PCD has been reported. It acts by inhibiting TNF-a, interleukin-12, interferon-γ, and nuclear factor kappa B activation [11]. In a retrospective study, thalidomide was effective in CD patients with perianal fistula [9]. In an open-label study, it was confirmed that thalidomide plays an important role in the closure of the fistula and the reduction of drainage fistula in CD patients with perianal fistula [12].

Although a few small trials have been conducted to explore thalidomide for PCD, the safety and efficacy of thalidomide for PCD remain to be evaluated. Our retrospective study aimed to evaluate the efficacy and safety of thalidomide in the treatment of perianal fistulizing CD and CD with perianal abscess.

**Methods**

**Ethics statement**
The study protocol was approved by the Clinical Research Ethics Committee of The First Affiliated Hospital of Sun Yat-sen University (Application ID: [2015] 103).

**Study design and patients**

This was a retrospective observational cohort study of patients with an established diagnosis of CD at the Gastroenterology Department of the First Affiliated Hospital, Sun Yat-sen University (China). Patients with PCD treated with thalidomide who had complete clinical data between June 2008 and May 2018 were screened. CD diagnosis was based on a combination of clinical, radiologic, endoscopic, and histologic findings. The inclusion criteria were as follows. (1) After treatment with biologics, azathioprine, and/or methotrexate for more than 3 months, the perianal disease was still active. (2) The available perianal examination included an anal examination, perianal ultrasonography, perianal magnetic resonance imaging, and endoscopic ultrasonography. (3) The patient would provide informed consent in their case notes before treatment. The exclusion criteria were concomitant biologics during thalidomide treatment or within 3 months before a clinical assessment; birth plan; tumours; severe peripheral neuritis; human immunodeficiency virus; ongoing major infections; uncontrolled major diseases; transplanted organs; participation in other experimental studies; and patients with incomplete data. Informed consent obtained from all participants, and the informed consent of participants under 16 years old was obtained from the parent and/or legal guardian of the participant. All methods were carried out in accordance with relevant guidelines and regulations.

**Treatment**

Thalidomide (Changzhou Pharmaceutical Factory, China) was started at a dose of 50 mg per night orally, monthly evaluation of clinical response and laboratory assessments were performed, and for patients whose responded insufficiently without adverse events, the dose of thalidomide was increased to 100 mg per night. The dose of thalidomide was reduced gradually, discontinued, or withheld until the adverse effect was resolved according to the nature and severity of any adverse reactions. The medication could then be reintroduced at a lower dose at the discretion of the doctor, and azathioprine, 6-mercaptopurine, or methotrexate could be maintained during thalidomide treatment. The dose modifications during the treatment period, duration of treatment, and reasons for withdrawal were recorded in the case notes. Some patients received corticosteroids before thalidomide was started. The efficacy of thalidomide was defined as inefficient for patients with PCD if the patient’s symptoms occurred repeatedly during corticosteroid reduction, withdrawal, or increase. Antibiotics were used as appropriate when the perianal abscess was too small to allow incision drainage or inadequate drainage and when perianal fistula was complicated with infection.

**Clinical evaluation**

Patients underwent clinical and laboratory evaluations at baseline and every 4-6 weeks thereafter until 24 months, for the assessment of therapeutic effect and adverse events. Laboratory assessments included blood routine examination, platelet counts (PLT), albumin and C-reactive protein (CRP) levels, erythrocyte
sedimentation rate (ESR), total protein level, and electrolytes. Clinical activity was measured using the Crohn Disease Activity Index (CDAI). A CDAI score < 150 was defined as clinical remission, and clinical recurrence was further divided into mildly active (CDAI scores 150-220), moderately active (CDAI scores 221-450), and severely active (CDAI scores > 450). In addition, the Perianal Disease Activity Index (PDAI) and fistula drainage assessment were used to evaluate the clinical activity of perianal disease and its curative effect, and their reliability has been widely accepted and utilised as a means of quantifying perianal disease severity [13, 14]. PDAI ranged from 0 to 20, with higher scores indicating more severe disease [13]. In this study, clinical response (i.e. a reduction of 50% or more from baseline in the number of draining fistulas observed) and remission (i.e. the fistula was not drained despite gentle finger compression) were defined after two consecutive study visits [15]. In addition, the disappearance of the perianal abscess on imaging was considered to indicate treatment efficacy. Recurrence of the perianal abscess, i.e. the perianal abscess diffused or shrank without disappearing after treatment, indicated treatment inefficacy.

**Statistical analysis**

Statistical analysis was performed using the dedicated statistical software SPSS version 20.0 (IBM Corp.). Quantitative parameters are expressed as mean ± standard deviation, and paired comparisons before and after the treatment were tested by Wilcoxon's signed-rank test. Continuous data of normal distribution were analysed using Student's t-test. Categorical data were analysed using the chi-square test. All significance tests were two-sided, and $P < 0.05$ was considered statistically significant.

**Results**

**Demographic and clinical characteristics**

Ninety-three patients with PCD were evaluated between June 2008 and May 2018. Fifteen patients were lost to follow-up, and 4 patients had to be withdrawn because of the occurrence of serious adverse effects. Finally, 73 patients, including 39 patients with perianal fistula and 34 patients with perianal abscess, were followed up for one year (Fig. 1). The demographic and clinical characteristics of the patients are shown in Table 1. Among 39 patients with perianal fistula, 29 (74.36%) were combined with exudation when thalidomide treatment was started. Among 34 patients with perianal abscess before thalidomide treatment, 32 patients (94.12%) presented with symptoms of perianal local redness, swelling, and pain. The number of patients in clinical remission was greater than that before treatment (Table 2), CRP, PLT, ESR, and CDAI values were significantly lower after treatment than before treatment as well (all $P < 0.01$) (Table 3).
Table 1
Demographic and clinical characteristics of the patient.

|                                | Cases (n=73) |
|--------------------------------|--------------|
| Sex, No. (%)                   |              |
| Male                           | 51 (69.8)    |
| Female                         | 22 (30.1)    |
| Age (years), No. (%)           |              |
| ≤16                            | 6 (8.2)      |
| 16–40                          | 53 (72.6)    |
| >40                            | 14 (19.1)    |
| Disease location, No. (%)      |              |
| L1 (ileal)                     | 2 (2.7)      |
| L2 (colonic)                   | 6 (8.2)      |
| L3 (ileocolonic)               | 49 (67.1)    |
| L1+L4 (ileal+ upper GI disease)| 0            |
| L2+L4 (colonic+ upper GI disease)| 1 (1.3)    |
| L3+L4 (ileocolonic+ upper GI disease)| 15 (20.5) |
| Disease phenotype, No. (%)     |              |
| B1P (inflammatory with perianal disease) | 27 (36.9) |
| B2P (stenosis with perianal disease) | 24 (32.8) |
| B3p (penetrating with perianal disease) | 22 (30.1) |
| The type of perianal disease, No. (%) |      |
| Perianal fistula               | 39 (53.4)    |
| Perianal abscess               | 34 (46.6)    |
Table 2
Comparison of disease activity before and after thalidomide treatment.

| CDAI score | Before treatment (n=73) | After treatment (n=73) | P      |
|------------|-------------------------|------------------------|--------|
| < 150      | 22                      | 48                     | <0.01  |
| 150-220    | 21                      | 17                     | 0.45   |
| 221-450    | 28                      | 8                      | <0.01  |
| > 450      | 2                       | 0                      | 0.476  |

Table 3
CDAI and laboratory index comparisons between PCD patient's baseline and after treatment.

| Index       | Before treatment (n=73) | After treatment (n=73) | P      |
|-------------|-------------------------|------------------------|--------|
| CRP (mg/L)  | 21.33±25.18             | 8.75±13.40             | <0.01  |
| PLT (×10^9/L) | 342.96±107.82          | 305.04±100.52          | <0.01  |
| ESR (mm/h)  | 44.69±24.93             | 28.61±17.54            | <0.01  |
| CDAI        | 209.62±96.31            | 137.66±61.68           | <0.01  |

Assessment Of Perianal Lesions

Among the 39 patients with perianal fistula, 10 of 29 patients with quiescent fistula, 20 of 29 patients (68.97%) complicated with exudation achieved clinical response, and 6 patients (20.69%) achieved clinical remission. 3 of 29 (10.34%) patients were assessed as not responding to treatment, and 1 of 10 patients with quiescent fistula experienced relapse during follow-up. Thirty-two of 34 patients (94.12%) with perianal abscess presented with local symptoms; 53.13% (17/32) of patients had a fistula on imaging, while 15 patients (46.87%) did not. Of these patients, 19 (19/32, 59.38%) with perianal abscess underwent surgical intervention. To evaluate the efficacy of thalidomide, the PDAI was calculated before and after treatment. The value of PDAI was significantly lower in patients with perianal abscess combined with symptoms after thalidomide treatment than at baseline (10 [6.25, 10] versus 2.5 [1, 3.75]; P = 0.05). In total, 78.13% (25/32) of patients’ perianal abscesses had completely disappeared and did not relapse until the end of follow-up by magnetic resonance imaging. The results showed that PDAI was also significantly reduced in patients with perianal abscess after thalidomide treatment, regardless of whether the perianal abscess had been surgically intervened (all P < 0.05) (Table 4).
Table 4  
Comparison between the PDAI of baseline and after thalidomide treatment with or without interruption

| Interruption | Baseline (PDAI) | After treatment (PDAI) | Z   |  P   |
|--------------|-----------------|-----------------------|-----|------|
| With drainage| 10 (7.5, 10)    | 2 (1, 3)              | -3.643 | <0.001 |
| Without drainage | 10.5 (9, 10) | 8.5 (1, 7)          | -2.561 | 0.01  |

**Analysis Of Combined Medications**

Sixty-two patients (62/73, 84.93%) were treated effectively. Sixty-two of 73 patients (84.93%) were treated with thalidomide in combination with other medications, including mesalazine, methotrexate, azathioprine, corticosteroids, and antibiotics, as shown in Table 5. Furthermore, corticosteroids could be reduced to withdrawal in 6 patients (8.22%) who required additional corticosteroids.

Azathioprine was the most frequently used drug in combination with other medications to treat patients with perianal fistula and abscess in this study (Table 5). Twenty-five of 73 patients (34.24%) were treated with additional thalidomide when azathioprine monotherapy failed. The proportion of those who responded to treatment increased to 84.0% after treatment with only azathioprine combined with thalidomide ($P < 0.01$). We also compared the efficacy of thalidomide monotherapy and thalidomide combined with azathioprine in these patients. The rates of responsive patients were similar between the thalidomide monotherapy group and thalidomide combined with azathioprine group (72.73% [8/11] and 84% [21/25], respectively; $P = 0.65$).
Table 5
Thalidomide combined with other medicines to treat patients.

| Combination medication                  | Cases (n=73) |
|----------------------------------------|-------------|
| Non                                    | 11 (15.0)   |
| Mesalazine                             | 3 (4.1)     |
| Methotrexate                           | 4 (5.4)     |
| Azathioprine                           | 25 (34.2)   |
| Corticosteroids                        | 3 (4.1)     |
| Antibiotics                            | 9 (12.3)    |
| Mesalazine + Azathioprine              | 1 (1.3)     |
| Mesalazine + Azathioprine + Antibiotics| 2 (2.7)     |
| Mesalazine + Antibiotics               | 3 (4.1)     |
| Methotrexate + Antibiotics             | 1 (1.3)     |
| Azathioprine + Corticosteroid          | 2 (2.7)     |
| Azathioprine + Antibiotics             | 8 (10.9)    |
| Corticosteroids + Antibiotics          | 1 (1.3)     |

Adverse Events

The adverse events that occurred during the period of treatment are shown in Table 6. In total, 31% (24/77) of patients experienced adverse events, and interventions were required in 15 patients to prevent further adverse events. Only 4 patients (4/77, 5.19%) discontinued therapy because of an adverse event. In this study, the most common adverse events were somnolence, constipation, and peripheral neuropathy. Side effect events resolved: nine resolved spontaneously (sedation [two], rash [one], constipation [three], diarrhoea [one], and blurred vision [one] and two resolved with dose reduction (sedation [two]). The symptoms in all patients with adverse events were relieved after the intervention.
Table 6
List of adverse events of thalidomide

| Adverse events                      | Patients (n=24) | Intervention                                                                 |
|-------------------------------------|-----------------|------------------------------------------------------------------------------|
| Sedation, No. (%)                   | 7(9.0)          | 2 patients withdrawal drug, dose reduction in 2 patients                     |
| Constipation, No. (%)               | 6(7.8)          | 1 patient withdrawal drug, 2 patients required lactulose                     |
| Peripheral neuropathy, No. (%)      | 7(9.0)          | 1 patient withdrawal drug, 6 patients required Vitamin B12 and B6            |
| Drug rash, No. (%)                  | 2(2.6)          | 1 patient withdrawal drug                                                    |
| Diarrhea, No. (%)                   | 1(1.2)          | no                                                                           |
| Blurred vision, No. (%)             | 1(1.2)          | no                                                                           |

**Discussion**

In this study, thalidomide was found to be beneficial in two-thirds of all patients with perianal fistula and abscess. CRP, PLT, ESR, and CDAI values of patients were significantly lower after treatment than before treatment. Thalidomide is an effective medical therapy to alleviate the disease activity of CD, and it could improve the clinical symptoms of patients with perianal lesions.

Although previous experience with thalidomide therapy was relatively limited in patients with PCD, the results in this study were generally consistent with the conclusions of previous studies. As early as 1999, two open-label pilot studies of thalidomide evaluated the use of thalidomide for treating fistulizing CD. The findings suggested that 83% (5/6) of patients with perianal fistula noted improvement after the first four weeks of thalidomide treatment, and three of four patients who completed 12 weeks of therapy showed improvement [16]. The results of another trial indicated that two patients with fistulas (13%) had complete closure of all fistulas after four weeks of treatment [10]. A total of 69% of the remaining patients with fistulas were responders, and 46% were in clinical remission at week 12 follow-up [10]. A case report described two patients (100%) with PCD who had fistulas that stopped draining after thalidomide treatment [17]. The findings of a subsequent study reported that 27% of patients had cessation of drainage, and perianal responses were found in 55% of patients, demonstrating that thalidomide was effective in inducing a clinical response and remission of fistulizing CD [18]. However, another study implied that thalidomide seemed to be less effective in patients with fistulas in light of a 50% (3/6) relapse rate [12]. Admittedly, fewer patients with PCD were included in these studies. A considerable number of cases would be needed to observe the efficacy of thalidomide in patients with PCD. We also considered whether the efficacy of thalidomide was affected by the abscess with drainage or without drainage. The results showed that the PDAI of patients with perianal abscess was significantly lower after thalidomide treatment, regardless of whether the perianal abscess had been surgically intervened. Thus, low-dose thalidomide could improve patients with perianal fistulas and abscesses. The
guidelines for the medical treatment of PCD also suggested that the efficacy of thalidomide for PCD was good [9].

Several open-label studies have confirmed that thalidomide is effective in inducing and maintaining clinical remission and mucosal healing in children, adolescents, and adults with refractory CD [19–25]. It was verified that thalidomide has anti-inflammatory, immunomodulatory, and angiogenesis inhibitory properties in animal studies [26]. Thalidomide can regulate macrophages and monocytes, resulting in reduced TNF-α production [27]. Thalidomide was effective for treating CD because it increased the degradation of messenger RNA encoding TNF-α, leading to inhibition of TNF-α production [28]. Bauditz et al. [29] indicated that thalidomide played a role in patients with CD by reducing the production of interleukin-12 and TNF-α. A study suggested that thalidomide may inhibit the effect of T cells and TNF-α, which could promote the clinical remission of intestinal symptoms in patients with IL10RA deficiency [30]. Besides, thalidomide may affect other immune cells and inflammatory cytokines to improve CD [12].

Perianal fistula and abscess are common complications of CD, which lead to poor quality of life in patients. The risk of perianal fistula seems to depend on the location and activity of the disease. The active disease was located in the rectum, while the risk of developing a perianal fistula was high [31]. Combination regimens for treating perianal fistulas in CD are often adopted by clinicians for better improvement and maintenance of disease remission. In this study, patients with combination regimens were not excluded, and patients with thalidomide in combination with other drugs accounted for 89% of the total (Table 6). Compared with other combination regimens, 25 of 73 patients (34.25%) accepted thalidomide combined with azathioprine, and this was the most common treatment in the study. However, thalidomide was added when azathioprine was no longer effective. Although the response rate of patients with PCD to azathioprine was low, azathioprine may have a beneficial role in combination treatment [9]. Few studies have explored the use of azathioprine in combination with other drugs for PCD. Thus, we compared the efficacy of thalidomide alone and thalidomide combined with azathioprine in the treatment of PCD patients with perianal fistula and abscess. The rates of responsive patients were similar between the thalidomide group and thalidomide combined with azathioprine group, indicating that both thalidomide and a combination of thalidomide and azathioprine were effective for treating PCD. It has been reported that patients with PCD can obtain more improvement when patients accept azathioprine in combination with antibiotics or infliximab [2]. To date, there have been no specific and comparatively large studies designed to investigate the efficacy of thalidomide monotherapy or combination regimens for PCD. Therefore, more studies are needed to confirm the efficacy of thalidomide monotherapy or combination regimens.

Although thalidomide is useful for treating PCD, its toxicity and side effects are the major problems that clinicians have focused on. There are quite a few side effects of thalidomide, including neuropathy, rash, and sedation. A previous study showed that 34% of patients discontinued thalidomide because of side effects at one year and 46% at two years [20]. The percentage for withdrawal due to adverse events was 35.5% of patients in a recent study [22]. In He et al.'s study [19], the percentage of thalidomide withdrawal due to severe adverse reactions was 10.6% at three months. It was demonstrated that 29% of all patients
discontinued thalidomide because of neuropathy [32]. In our study, 31% of patients experienced adverse events, and 15 patients needed surgical intervention. A total of 5.19% of patients discontinued treatment because of the adverse event. The incidence of adverse events was congruent with that reported in previous studies. Discontinuation rates were relatively low, probably because a lower dose (100 mg/day) of thalidomide was used in our study compared with that in some of the previous studies and all adverse events were relieved after the intervention.

This study is probably the original, specialised, and largest retrospective study to evaluate the effect of thalidomide and thalidomide combined with azathioprine for PCD patients with perianal fistula and abscess. However, it has certain limitations. First, the benefit of thalidomide over placebo could not be contrasted without a non-controlled study. Second, the efficacy of thalidomide in combination with other drugs, except for azathioprine, was not been studied. The effects of some factors, such as treatment course, lesion regions, sex, and smoking status, were not considered when the efficacy of thalidomide was investigated. Lastly, some inevitable problems including recall bias and data loss occurred because of the lengthy duration of data collection.

**Conclusions**

This retrospective study’s results demonstrated that thalidomide is effective in inducing clinical remission and response in CD patients with perianal fistula and abscess. Thalidomide in combination with azathioprine was also effective in these patients which warrants further evaluation. Thalidomide played a role in patients with PCD, and its toxicity and side effects needed to be assessed frequently during treatment follow-up. Thalidomide may be efficacious in patients with paratal CD which and needs further evaluation in dedicated prospective clinical studies.

**Abbreviations**

CD: Crohn’s disease; CDAI: Crohn’s Disease Activity Index; PDAI: Perianal Disease Activity Index; PCD: Perianal Crohn’s disease; PLT: platelet counts; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

**Declarations**

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None.

**Authors’ contributions**

ZT and LN performed the study, analyzed the results, and drafted the manuscript. RF and SZ designed the study, and edited the manuscript. SX, YQ, RM and BC performed sample collection. RZ, YH and MC contributed to strategic development decisions. All authors have read and approved this version of the
article. Neither the entire paper nor any part of its content has been published or has been accepted elsewhere.

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Availability of data and materials

All data and materials are not available in this study, and are available from the corresponding author on reasonable requests.

Ethics approval and consent to participate

The study protocol was approved by the Clinical Research Ethics Committee of The First Affiliated Hospital of Sun Yat-sen University. Informed consent obtained from all participants, and the Informed consent of participants under 16 years old was obtained from the parent and/or legal guardian of the participant. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

There are no conflicts of interest to declare.

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Figures
Figure 1

The flow chart of selecting the CD patients with perianal fistula and abscess.