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The effect of levamisole in the treatment of recalcitrant recurrent erythema multiforme major: An observational study

Ren-Feng Liu[a,b], Chun-Bing Chen[a,b,c], Rosaline C.Y. Hui[a,b], Yue-Zon Kuan[a,b], Wen-Hung Chung[a,b,*]

[a] Department of Dermatology, Drug Hypersensitivity Clinical and Research Center, Chang Gung Memorial Hospital, Keelung, Taipei, Linkou, Taiwan
[b] College of Medicine, Chang Gung University, Taoyuan, Taiwan
[c] Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, Taoyuan, Taiwan

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ABSTRACT

Background: Erythema multiforme major (EMM) is an immune-mediated mucocutaneous eruption mostly triggered by herpes simplex virus (HSV) infection. A vicious circle of recurrence may be developed due to HSV reactivation and prolonged use of systemic corticosteroids to control EMM. Levamisole is an immunomodulator and has been applied to prevent relapses of recurrent HSV infection.
Objective: To evaluate the clinical efficacy and safety of levamisole in patients with recalcitrant recurrent EMM.
Methods: We enrolled 23 patients with recurrent EMM treated with levamisole and 24 controls, and analyzed the demographics, treatments and outcomes.
Results: Patients with recurrent EMM for years (mean 3.99 ± 2.71) showed significantly reduced recurrences after various durations of levamisole treatment (recurrences after and before treatment: 3.98 ± 1.04 vs 6.75 ± 1.45 times per year, $p = 1.33 \times 10^{-8}$). The recurrences of EMM also significantly reduced after levamisole treatment comparing to that of patients without levamisole treatment ($p = 3.77 \times 10^{-9}$). No patient was reported to have severe side effects during or after levamisole treatment.
Conclusions: Levamisole was effective in reducing recurrences of recalcitrant recurrent EMM and can thus be considered an alternative or add-on therapy for this disorder.

1. Introduction

Erythema multiforme major (EMM) is an immune-mediated mucocutaneous eruption characterized by distinctive cutaneous target lesions with variable mucosal involvement. EMM is usually triggered by herpes simplex virus (HSV), *Mycoplasma pneumoniae* (*M. pneumoniae*), or other infections. Reactivation or reinfection of HSV accounts for more than 70% of cases of recurrent EMM. Although the majority of patients have a benign clinical course, more than 30% of patients suffer from frequent recurrences of EMM over years, leading to substantial morbidity [1,2]. Compared with acute EMM, recurrent EMM is more difficult to treat. Many treatment modalities have been used, including systemic corticosteroids, anti-HSV treatments, anti-*M. pneumoniae* antibiotics (macrolides and quinolones), and other immunosuppressants1 [3]. However, patients with recalcitrant disease may develop frequent recurrences of EMM once the medications are discontinued. Therefore, recurrent EMM remains a difficult problem for dermatologists to deal with.

Levamisole, an anthelmintic agent with a wide range of immunomodulatory actions, has been used successfully as a monotherapy, as an adjunct, or in combination therapies with other drugs in treating a variety of dermatologic diseases (e.g., inflammatory skin diseases including lichen planus and recalcitrant aphthous ulcers, as well as parasitic, viral, and bacterial infections including leprosy and recalcitrant warts), collagen vascular diseases (e.g., rheumatoid arthritis and systemic lupus erythematosus), and various cancers [4–11]. Although the reported severe side effects such as agranulocytosis (less than 20% neutrophils) and skin necrosis compromised its use, the combination therapy of levamisole and fluorouracil was used as an effective adjuvant therapy for locally advanced resected colon cancer in the 1990s [4,5,12]. Additionally, levamisole has played a very important role in treating relapsing steroid-sensitive nephrotic syndrome and maintaining its remission [13,14].

Abbreviations: BSA, body surface area; EMM, erythema multiforme major; HSV, herpes simplex virus; *M. pneumoniae*, *Mycoplasma pneumoniae*; SD, standard deviations.

* Corresponding author at: Director of Department of Dermatology, Drug Hypersensitivity Clinical and Research Center, Chang Gung Memorial Hospital, No. 5, Fusing St, Taoyuan, 333, Taiwan.
E-mail address: chung1@cgmh.org.tw (W.-H. Chung).

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There have been reports of the use of levamisole in the treatment of recurrent HSV infection, with these reports having found a variety of beneficial effects [6–8]. There have also been a few reports regarding the use of levamisole as an adjunct for the treatment of recurrent EMM, but these reports lacked detailed diagnostic criteria for EMM and statistical outcome measures (Supplementary Table S1) [9–11]. In the present study, we aimed to evaluate the clinical efficacy and safety of levamisole as an adjuvant therapy for the treatment of recalcitrant recurrent EMM.

2. Patients and methods

2.1. Data collection and assessment

Patients were diagnosed with recurrent EMM based on the presence of a symmetrically distributed, fixed eruption, including target lesions, with at least one mucosal involvement, occurring on at least three occasions according to the requirements published by Schofield et al. in 1993 [2]. The presence of newly active cutaneous and/or mucosal lesions after the total resolution of old lesions indicated recurrence. All the patients diagnosed with recurrent EMM by dermatologists at Chang Gung Memorial Hospital in Taiwan from January 2007 to March 2017 were reviewed for their clinical presentations, treatments, and outcomes. The photographs and medical records of each patient were obtained for review from our registration system, in which brief clinical data and photographs of the initial presentations, acute stages, and resolving stages of patients diagnosed with severe cutaneous adverse drug reactions (SCAR) or EMM since 2004 are collected. The patients characterized by an average > 5 recurrent episodes per year with or without levamisole therapy were selected for further analysis. Twenty-one patients were excluded from this study because of incomplete medical records, insufficient information for diagnosis, or being lost to follow-up during the treatment.

The patients' demographic information, clinical characteristics as of the initial EMM presentation, pathology reports regarding skin biopsies, predisposing factors including preceding HSV infection, disease duration, levamisole dosage and treatment duration, other systemic therapies, recurrence frequency and interval before and after levamisole treatment, and side effects of levamisole treatment were analyzed. The follow-up duration was defined as the duration from the initiation of levamisole treatment to July 2017. Complete remission of the disease was defined as a disease-free period of 2 years or more [1].

2.2. Statistical analysis

The data are shown as means, standard deviations (SD), ranges, and percentages, as appropriate. Data were entered into a spreadsheet (Excel, Microsoft, Redmond, WA) for analysis. Analyses of recurrence frequency/interval changes and dosage changes of systemic corticosteroids and anti-viral drugs before and after levamisole administration were compared with a paired-sample *t*-test or two-sample *t*-test using PASW Statistics software (version 20; SPSS, Chicago, IL). All of the *p* values were two-tailed, and $p < .05$ was considered statistically significant.

3. Results

3.1. Demographic information and clinical characteristics

Twenty-three patients (mean onset age: 35.30 ± 15.08 years; 11 males and 12 females) with recurrent EMM who received levamisole treatment and 24 patients (mean onset age: 31.25 ± 11.03 years; 16 males and 8 females) without levamisole were enrolled in this study (Table 1 and Supplementary Table S2). All the patients included in our study had acrally distributed or generalized cutaneous eruptions composed of typical target lesions with or without central blisters involving 3%–20% of body surface area (BSA), as well as at least one mucosal involvement manifested as erythema, erosions, bullae, and ulcerations on both non-keratinized and keratinized mucosal surfaces (Fig. 1). The patients who received skin biopsies had compatible histopathological findings of EMM, including the presence of epidermal necrosis, dyskeratotic cells, basal cell vacuolar degeneration, papillary edema, and perivascular lymphocytic infiltrates in dermis.

Approximately 80% of the patients were observed to have prodromal HSV infection presenting as grouped vesicular lesions and/or crusts around one week preceding each EMM episode. Most of the patients presented with prodromal HSV infection on the lips (65.2% in the levamisole group and 75.0% in the control group), while a smaller percentage presented with prodromal HSV infection on the buttock and genital area (13.0% in the levamisole-treated group and 8.3% in the control group). No patient was reported to have associated drug-induced EMM. All the enrolled patients were administered short-term use of systemic corticosteroids and/or anti-HSV medications during each recurrent episode (Table 1). In the levamisole-treated group, most of the patients received short-term treatment with systemic corticosteroids and/or anti-HSV medications (mean duration: 9.12 ± 2.72 and 3.13 ± 0.83 days, respectively) for the first several EMM episodes during the period of levamisole initiation (Fig. 2). Twenty-one patients (91.3%) were treated with systemic corticosteroids (mean number of treatments: 2.81 ± 1.44), and 8 patients (34.8%) were treated with systemic anti-HSV medications (mean number of treatments: 3.50 ± 2.07).

3.2. The dosage of systemic corticosteroids required for each recurrent EMM episode was significantly reduced after levamisole therapy

The dosage of systemic corticosteroids required for each recurrent EMM episode after levamisole treatment (mean dosage: 145.3 ± 60.8 mg, range: 60–224.3 mg) was significantly reduced compared with that before levamisole treatment (mean dosage: 215.6 ± 48.2 mg, range: 140–280 mg) ($p = 4.03 \times 10^{-5}$) (Table 2). The dosage of systemic anti-HSV medications after levamisole treatment compared with that before levamisole treatment was also decreased, although the difference was not significant ($p = 0.36$).

3.3. Levamisole significantly reduced the recurrence of recalcitrant recurrent EMM

Patients suffering from variable disease duration of recurrent EMM before levamisole administration (mean duration: 3.99 ± 2.71 years, range: 1.25 to 9.17 years) were treated with levamisole for 1.42 to 5.83 years (mean duration: 3.31 ± 1.13 years), with dosages ranging from 75 to 200 mg per week (mean dosage: 143.92 ± 29.30 mg; approximately 2.5 mg/kg/week). All of the patients were followed up for periods ranging from 1.42 to 7.25 years (mean duration: 3.59 ± 1.45 years).

Most of the patients were observed to have decreased numbers and sizes of the target lesions in terms of acral distribution, as well as shorter healing times and mild or no lip lesions, during the recurrent episodes after levamisole use was began (Fig. 1).

The patients exhibited variable outcomes, with decreased frequencies of EMM recurrence and increased intervals between recurrences after levamisole therapy was began. Six of the 23 patients (26.1%) experienced significant improvement, with > 50% reduction of recurrence frequency; 10 patients (43.5%) experienced a 25–50% reduction; and 5 patients (21.7%) experienced a <

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