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CASE REPORT

Six Cases of Antihistamine-Resistant Dermographic Urticaria Treated with Oral Ciclosporin

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ABSTRACT

Background: Dermographic urticaria (DU) is characterized by strong itch and wheals induced by mechanical scratching. H_1-receptor antagonists may reduce symptoms of DU to some extent, but other treatments being used for chronic spontaneous urticaria, such as H_2-receptor antagonists and corticosteroids, are not usually effective for DU.

Case Summary: We here report six cases of antihistamine-resistant DU treated with oral ciclosporin. Four cases suffering from severe itches that spontaneously occurred before the appearance of wheals in response to scratching were substantially improved by use of ciclosporin for 21, 16, 32, and 8 months, and one of them reached complete remission. Two cases did not obtain a benefit from the treatment, because of insufficient effects and/or side effects.

Discussion: Oral ciclosporin may be of value as a potential treatment of anti-histamine-resistant DU.

KEY WORDS

antihistamines, ciclosporin, dermographic urticaria, symptomatic dermographism, urticaria factitia

INTRODUCTION

Dermographic urticaria (DU), also known as 'urticaria factitia' or 'symptomatic dermographism', is a subtype of physical urticaria and commonly observed in daily clinical practices.[1] It is characterized by linear-shaped wheals that appear shortly after a scratch or any other mechanical stimuli on the skin, along with the area of stimuli. In most cases, patients also suffer from severe itching together with wheals and this thus markedly perturbs their quality of life (QOL). In certain cases, severe itching may occur on intact skin without apparent stimuli, followed by wheals which are subsequently induced by scratching. DU affects mainly young adults,[2,3] and mean duration is reported to be 6.5 years.[4]

A principle of the treatment for DU and other physical urticaria is the avoidance of responsible physical stimuli and medications based on H_1-receptor antagonists. However, it is impractical to completely avoid mechanical stimuli on the skin, and H_1-receptor antagonists may not be effective for many cases of DU, as those for acute and chronic spontaneous urticaria even at high doses. Several other therapies, including H_2-receptor antagonists[5] and phototherapy such as narrow-band UVB[6] have been reported, but do not usually bring further benefit over H_1-antagonists. Moreover, corticosteroids, which may suppress symptoms of many cases of chronic spontaneous urticaria and delayed pressure urticaria, are not effective for DU. Several guidelines for the treatment of urticaria indicate oral ciclosporin (CsA) as an option for the treatment of chronic spontaneous urticaria, when patients do not respond to updosing or changes of anti-histamines and the addition of a leukotriene antagonists.[7-9] So far, there is no study regarding the effectiveness of CsA on DU in the literatures. We here report six cases of severe and antihistamine-resistant DU who were treated with low doses of oral CsA.

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Table 1 Clinical characteristics of the 6 patients

Patient	Age, y/ Sex	Duration of DU, y	Starting dose of CsA, mg/kg/day	Duration of CsA, m	Previous medications	Outcome	Adverse effects
1	56/M	4	3.0	21	H_1-antagonists in 3-fold doses, corticosteroids (5 mg/day, 2 weeks)	Remission	None
2	67/F	5	3.4	16, continue	H_1-antagonists in 3-fold doses, leukotriene antagonists, corticosteroids (2.5-20 mg/day, 2 years)	Improvement	None
3	25/F	12	2.5	32, continue	H_1-antagonists in 3-fold doses, H_2-antagonists, leukotriene antagonists, corticosteroids (2.5-7.5 mg/day, 2 years)	Improvement	Epigastric distress
4	26/F	0.5	2.7	8, continue	H_1-antagonists in 3-fold doses, leukotriene antagonists, corticosteroids (10-30 mg/day, 2 weeks)	Improvement	None
5	65/F	15	2.0	0.5	H_1-antagonists in 4-fold doses, corticosteroids (5 mg/day, 2 weeks)	Inefficiency	None
6	43/M	5	0.8	0.25	H_1-antagonists in 3-fold doses, leukotriene antagonists	Inefficiency	Headache, nausea

Abbreviations: DU, dermographic urticaria; CsA, ciclosporin. Dose of corticosteroids, converted into predonizolone.

CLINICAL SUMMARY

We treated six adult patients (two men and four women, 25 to 67 years old) given a diagnosis of DU on the basis of medical history and provocation test. All patients developed wheal and flare in the inside of the forearm being rubbed by the strength of approximately 60 g/mm^2.[10] The other types of physical urticaria were excluded by the provocation test performed as necessary. In cases 1 to 4, patients had noted that severe itching with or without flare might have occurred spontaneously before they scratched, and developed wheals in that area. But wheals had never developed spontaneously without scratching or mechanical stimuli in all six cases. All patients had been treated with H_1-receptor antagonists, including their updosing and combinations with different H_1-antagonists (Table 1). However, their symptoms had not been sufficiently controlled, and their QOL had been markedly impaired. All patients did not show apparent blood abnormalities in complete blood counts and routine examinations of serum biochemistry. They thus took oral CsA (0.8 to 3.4 mg/kg per day) in addition to current treatments. Blood examinations including serum creatinine and serum level of CsA were performed every four weeks to monitor the occurrence of adverse effects. Ethic committee of the University Hospital approved about the administration of CsA for the patients with DU.

CASE 1

A 56-year-old man had a four-year history of wheals and itching. Despite treatment with H_1-antagonists and corticosteroids, his symptoms had not improved. CsA was initiated at a dose of 3.0 mg/kg per day in addition to 10 mg olopatadine hydrochloride, 10 mg loratadine and 500 mg tranexamic acid. After 2 days of initiating treatment with CsA, he felt an apparent improvement in his itching. The frequency of wheals decreased gradually. One month later, the dose of CsA was reduced to 0.75 mg/kg per day, but no exacerbation was observed. We then tapered the dose to 0.38 mg/kg per day 11 months later. At this stage, he noted slight itching once for several days. We eventually discontinued CsA 21 months later, but his symptoms did not relapse. We sequentially stopped the other medications, and he became drug-free after 27 months of treatment. No apparent side effects were observed during the treatment. Thereafter, he has maintained full remission without any medication during 15 months of follow-up.

CASE 2

A 67-year-old woman had a five-year history of wheals and itching. She developed these symptoms even when exposed to water pressure from a shower. Despite treatment with H_1-antagonists, leukotriene antagonists and corticosteroids, her symptoms had not apparently improved. In addition to 20 mg cetirizine hydrochloride and 10 mg montelukast, CsA was undertaken at a dose of 3.4 mg/kg per day. After two weeks, she showed an apparent improvement in her itching. When we tapered the dose to 2.3 mg/kg per day after two months treatment with CsA, she felt her itching worsened. We then returned the dose to 3.4 mg/kg per day, and the itching decreased again. When the dose was decreased to 2.3 mg/kg per day after seven months treatment, her itching did not worsen. She continued to take this dose of CsA for 18 months without apparent side effects. At this stage, rubbing skin with 60 g/mm^2 pressure did not develop wheal, and the appearance of both flare and itching was substantially reduced as compared with that before the treatment with CsA.

CASE 3

A 25-year-old woman had a 12-year history of wheals and itching. Despite treatment with H_1 and H_2-antagonists, leukotriene antagonists and corticosteroids, her symptoms had not improved. In addition to 240 mg fexofenadine hydrochloride, 10 mg montelukast, 750 mg tranexamic acid and 0.75 mg betamethazone, CsA was undertaken at a dose of 2.5 mg/kg per day. After a week, she showed an apparent improvement in her itching, but, suffered from epigastric distress after taking CsA. We therefore tapered the dose to 0.9 mg/kg per day and the epigastric distress was improved, but her itching did not worsen. After the start of CsA, we tapered a dose of betamethazone and eventually discontinued 19 months later. When we tapered the dose of CsA to 0.5 mg/kg per day after nine months treatment, her itching worsened. We then returned the dose to 0.9 mg/kg per day and have continued this treatment for 32 months. At this stage, rubbing her skin with 60 g/mm^2 pressure did not develop wheal and itching, but flare in the area smaller than that before the treatment with CsA.

CASE 4

A 26-year-old woman had a six-month history of wheals and itching. Despite treatment with H_1-antagonists, leukotriene antagonists and corticosteroids her symptoms had not improved. She developed wheals even when she took a shower because of the water pressure. In addition to 10 mg bepotastine, 40 mg homochlorcyclizine, CsA was administered at a dose of 2.7 mg/kg per day. After two weeks, she felt a slight improvement in her itching. After one month, she recognized further improvement of the itching and a reduction of wheal frequency. She continued to take CsA for eight months without apparent side effects. In spite of clinical improvement, no apparent change was observed in skin reactions, exept for itching upon rubbing with 60 g/mm^2 pressure.

CASE 5

A 65-year-old woman had a 15-year history of wheals. Despite treatment with H_1-antagonists and corticosteroids, her symptoms had never improved. She took CsA at a dose of 2.0 mg/kg per day in addition to 40 mg homochlorcyclizine, 10 mg loratadine and 50 mg hydroxyzine pamonate. We discontinued it two weeks later, because her symptoms had not improved at all during this period and she did not hope to increase the dose of CsA. No apparent side effects were observed during the treatment with CsA.

CASE 6

A 43-year-old man had a five-year history of wheals. Despite treatment with H_1-antagonists and leukotriene antagonists, his symptoms had not improved. We administered CsA at a dose of 0.8 mg/kg per day in addition to 20 mg cetirizine hydrochloride, 10 mg montelukast and 1500 mg tranexamic acid. We discontinued CsA a week later because of a headache and nausea. His symptoms did not improve during this period.

DISCUSSION

We treated six patients with antihistamine-resistant DU with oral CsA. Both wheals and itching in four patients were improved by 2.5-3.4 mg/kg/day CsA added to other preceding medications without severe adverse effects. One of them developed epigastric distress at a dose of 2.5 mg/kg/day, but it disappeared at a dose of 0.9 mg/kg/day. Other common side effects of CsA, such as renal dysfunction and hypertension, were not observed in all cases in this report. The common clinical feature in the four effective cases was severe itching that appeared before apparent wheal development. The time from the commencement of CsA treatment to the first recognition of improvement was two days, two weeks, one week and two weeks, respectively. Hyper-sensitivities of skin for mechanical stimuli were not completely abolished by the treatment except for Case 1. However, the degrees and frequencies of wheal development were satisfactorily improved together with incidence of scratching for eight months or longer. Moreover, corticosteroids used in Case 3 was successfully discontinued during the treatment with CsA.

Two patients, Cases 5 and 6, did not show an apparent improvement of clinical symptoms. The patient in Case 5 received only 2.0 mg/kg/day CsA for two weeks, and the other one in Case 6 received as low as 0.8 mg/kg/day CsA for one week and stopped it because of headache and nausea. In general, a dose of 2.5 to 5.0 mg/kg/day CsA is used for other skin diseases, such as psoriasis, atopic dermatitis, and chronic spontaneous urticaria. Therefore, ineffectiveness in these two cases may be due to a shortage of CsA administration in either dose and/or period.

General treatment for DU is an avoidance of mechanical stimuli and administration of safe and effective medications. However, in cases with severely high sensitivity against stimuli, any conventional medication is not effective and patients may develop symptoms by essential daily life activities, such as clothing, face washing and even by touching their own hair. Moreover, patients may suffer from itching even without apparent scratching, probably because of the extremely reduced threshold for skin reactions.

H_1-receptor antagonists are a mainstay in the treatment for DU.[11,12] But they usually do not abolish symptoms as they do for many cases of chronic spontaneous urticaria. The effect of several other treatments, including H_2-receptor antagonist,[5] narrowband UVB,[6] calcium antagonist,[13] and anti-immunoglobulin E[14] have been reported. The combination of

H_1 and H_2-antagonist may increase the threshold to induce wheals, but could not inhibit spontaneous itching.[5] Although narrow-band UVB showed high efficacy and few adverse effects,[6] it is not practical for many patients who are young adults, because of the necessity for frequent hospital visits. No significant difference was found between a calcium antagonist and placebo in double-blind cross-over trials.[13] Anti-immunoglobulin E appears to have great potential for the treatment of various types of urticaria, but only one case report with DU has been published very recently.[14] In general, remission rates for urticaria become lower, the longer they persist for, especially when this is beyond a year from the onset. However, three patients in this report showed an improvement in two weeks, after the treatment course, of 4, 5 and 12 years respectively. Moreover, all symptoms of the patient with a four years history had completely disappeared after the treatment with CsA for 21 months (Case 1).

The mechanism of CsA, which inhibits functions of T-cells, to improve DU is a matter of discussion. CsA, but not corticosteroid, inhibits the release of histamine from human mast cells[15] and basophils[16] in vitro. On the other hand, Grattan *et al*. have reported that treatment of chronic idiopathic urticaria with CsA did not change the degrees of skin reactions against preserved autologous serum, in spite of clinical improvement, suggesting that CsA had no effect on the releasability of skin mast cells.[17] Moreover, no additional effect on wheal and flare formation, induced by mechanical stimuli under the treatment with anti-histamines, was observed in Case 4 by the treatment of CsA in spite of the remission of itching. Alternatively, CsA may either inhibit production of certain IgE, which could be passively transferred from sera of patients with DU[18] or vaso-neurological activities of the skin via a mechanism that has not yet been recognized by us.

Regarding the period of treatment, many patients with chronic spontaneous urticaria treated with CsA for one to three months relapsed after stopping it. Recently, Kessel and Toubi have reported that prolonged treatment with CsA may reduce the risk of relapse in chronic urticaria.[19] In our cases, two of three patients who took tapering of CsA had relapsed after two- and nine-months treatments (Case 2 and 3). However, in Case 2, the second trial of tapering after seven months treatment from the first trial did not cause a recurrence. Therefore, sufficient treatment with CsA in both amount and period may be important for prolonged control and possibly for the cure of DU.

In conclusion, CsA may be worth trying for antihistamine-resistant DU, especially in those patient cases characterized by severe itching. Further studies on a larger scale are expected to be conducted in order to generate stronger levels of clinical evidence.

CONFLICT OF INTEREST

No potential conflict of interest was disclosed.

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