Real-World Clinical Experience with Oral Cyclosporine in Antihistamine Refractory Cases of Chronic Spontaneous Urticaria

Dear Editor,

Chronic spontaneous urticaria (CSU) presents with either transient wheals (hives) or angioedema, or both, without any definite triggers and reccurrence of signs and symptoms for more than six weeks. The degranulation of dermal mast cells (MCs) is believed to be the primary event in the development of skin changes such as sensory nerve stimulation, vasodilatation, and extravasation as well as the recruitment of pro-inflammatory cells.[1,2]

Patients with severe CSU are refractory to many of the available conventional treatments. In recent times, oral cyclosporine has emerged as a useful option in the treatment of CSU. In this brief clinical report, we have tried to assess the role of tapering doses of cyclosporine in severe CSU refractory to second-generation H1 anti-histamine therapy.

Patients with a Urticaria Activity Score summed over 7 days (UAS 7) score of ≥16 after one month of antihistamine therapy were considered poorly responsive/refractory, whereas UAS7 ≥28 was taken as the cut-off for labeling the disease activity as severe [Table 1].[3]

Patients with persistent symptoms of CSU (UAS ≥16) during the 15 days of the conventional dosing of second-generation H1 antihistamines followed by poor/no response to maximum permissible dosage for another 15 days were eventually administered oral cyclosporine (5mg/kg) for two weeks, and then tapered by 50 mg every 15th day until a dose of 50mg/day was reached. Reduction of dose by 50 mg was chosen due to the availability of cyclosporine in only a fixed formulation (capsule containing 50 mg cyclosporine) in our hospital. Tapering was done fortnightly to decrease the cumulative dose and minimize the risk of adverse effects. Clinical response to the tapering doses of cyclosporine was assessed by a decline in the mean of weekly urticaria activity score (UAS7).[2]

Cyclosporine therapy was stopped two weeks after reaching the dose of 50mg/day in each patient. Patients were followed for the next 4 weeks to look for the reappearance of any symptoms.

Inclusion criteria

1. Patients of CSU with UAS7 ≥16 after one month of antihistamine therapy were considered antihistamine refractory cases of CSU and were subsequently given oral cyclosporine.

Exclusion criteria

1. Clinical scenarios mimicking CSU such as acute urticaria, urticarial vasculitis, and physical urticaria were excluded from the study.
2. Patients with hypertension, deranged lipid, liver, renal biochemical profile, active infectious disease.
3. Pregnant women and lactating mothers.

The clinical and demographic profile of the patients is shown in Table 2. CSU was more common in females with a F/M ratio of 1.53:1. The mean age of the patients was 29.05 ± 10.19 years. The mean age for the onset of the CSU was 27.67 ± 9.27 years. The mean duration of disease at the time of presentation was 1.39 ± 0.98 years. Thirty-nine (90.70%) patients reported significant improvement (UAS7 of less than 16) in symptoms at the end of 2nd week which increased to improvement in 41 (95.35%) patients at the end of four weeks. The mean baseline UAS7 of the study group at the time of initiation of cyclosporine therapy was 31. The mean UAS7 for the study group decreased to 5.78 at the end of the first week, 3.56 and 0.90 at the end of the second week and fourth week, respectively (t value = 21.5, P = <0.001). The trend of decline in UAS7 is shown in Figure 1. Around one-third of the patients (32.56%) achieved UAS7 of zero at the end of the second week which increased to 76.74% and 93.02% at the end of the fourth week and sixth week, respectively. Two patients (4.65%) did not respond to the cyclosporine therapy during the first two weeks. However, symptoms

Table 1: UAS7 disease activity score bands

UAS7 score	Clinical rationale
0	Itch and hive free—indicative of no symptoms of CSU and considered a full treatment response
1–6	Well-controlled urticaria—indicates a good response to treatment
7–15	Mild urticaria—indicates also a lower response level
16–27	Moderate activity urticaria—entry criteria for clinical trials in CSU
28–42	Severe activity urticaria

Table 2: Clinico-epidemiological characteristics of patients

Clinico-demographic parameters	Results
Female	26
Male	17
F/M ratio	1.53:1
Mean age	29.05±10.19 years
Mean age at onset of the disease	27.67±9.27 years
Mean duration of the disease	1.39±0.98 years
UAS7 at the baseline	31
No. of patients with diurnal variation during active disease periods (evening/night flare-ups)	17 (39.53%)

significantly decreased in these two patients during the next two weeks (mean UAS7, at the baseline, = 27 to UAS7 = 1.5, at four weeks). Three patients (6.98%) reported isolated seven episodes of CSU (mean UAS7 = 8.58) while being on the dose range of 4–5mg/kg/day of cyclosporine during the first four weeks. The majority of the patients (41; 95.35%) did not develop any symptoms of CSU after four weeks of the therapy while being on the doses equivalent to 4–5mg/kg/day. Out of these 41 patients, 10 (24.39%) patients re-developed symptoms of CSU with decreased severity (mean UAS7 = 4.3), when doses were equivalent to 1–3mg/kg/day on subsequent tapering. In two other patients, cyclosporine was discontinued as no improvement was noted even after four weeks of therapy. During the post-therapy drug-free follow-up period of four weeks, 61.1% of patients developed relapse of CSU with a mean UAS7 of 28.3 which was close to the UAS7 at the baseline (31).

Among other features, in 17 (39.53%) cases, symptoms of CSU showed diurnal variation. In these patients, symptoms either developed/aggravated more during evening/night time. CSU was associated with angioedema in four (9.30%) patients. In seven (16.28%) patients, there was a history of atopic diathesis. CSU was noted to occur more frequently during the rainy season. Twenty-one (48.84%) patients reported either onset or recurrence of CSU during the monsoon season. Five patients (11.6%) developed at least one side effect [Table 3]. Cyclosporine was permanently discontinued in one patient, also a non-responder to the therapy during the first four weeks who acquired varicella during the treatment with cyclosporine.

CSU presents with a diverse range of symptoms, including occasional localized or widespread wheals and/or angioedema.[1,2,4] Average duration of CSU is estimated to be 1–5 years, with lesions appearing unpredictably on most days and virtually affecting any part of the body.[2] Determining the cause of CSU is often difficult, rendering cause-specific management challenging for physicians and frustrating for patients.[2,5,6] The burden of the disease goes beyond the skin, as it may also cause pain, sleep disturbances, sexual dysfunction, and substantial psychological impact (anxiety, depression). The duration of CSU and its impact on patients are difficult to predict, highlighting the need for better treatment options.

The current international guidelines (EAACI/GAL^{2}EN/EuroGuiDerm/APAAACI) for CSU are shown in Figure 2. Real-world clinical practice often deviates from these guidelines with a significant discrepancy between recommendations and actual treatment received by patients.[7] AWARE study (Germany) pointed out that among the patients with uncontrolled CSU and who were eligible for treatment escalation, only 3% received up-dosing of H1 antihistamines.[8] Regardless of the current guidelines, corticosteroids are still being used in the treatment of CSU. In a study conducted by Ledford *et al*.[9] involving 12,647 patients of CSU, it was found that 55.4% of the patients had a history of oral corticosteroid use.

Several theories exist for the pathogenesis of CSU but none have been definitively established. Increased recruitment of mast cells (MC) and the release of pro-inflammatory

Table 3: Adverse effects observed with cyclosporine

Adverse effects	Number of patients	Percentage (*n*=43)
Burning sensation over the face	3	7%
Increased sensation of generalized body temperature	2	4.6%
Facial hypertrichosis	2	4.6%
Gastric discomfort (nausea, vomiting)	3	7%
New onset hypertension during the study period	1	2.3%
Infections (Varicella)	1	2.3%

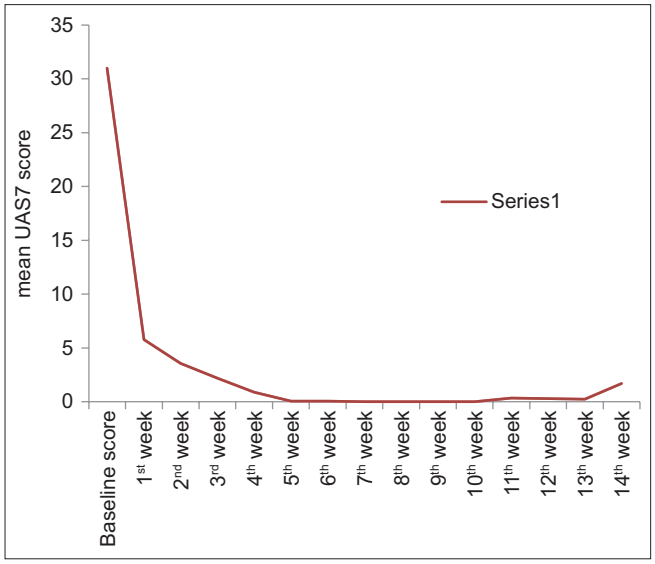

Figure 1: Trend of decline in mean UAS7 score with cyclosporine therapy

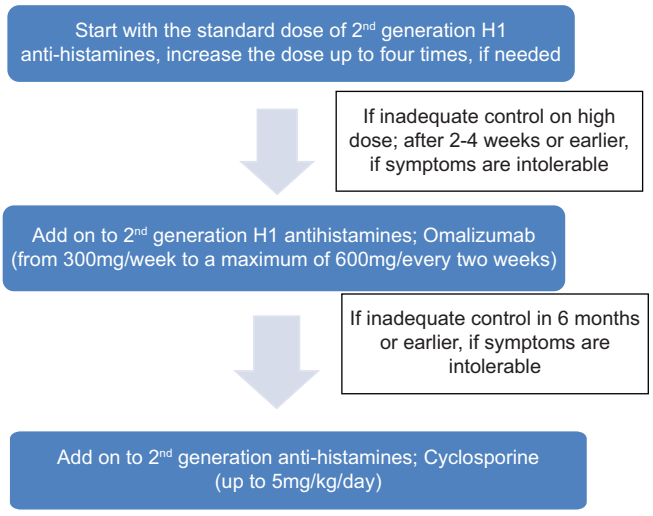

Figure 2: The current international guidelines (EAACI/GAL2EN/EuroGuiDerm/APAAACI) for the management of CSU

mediators, such as histamine, prostaglandins, and cytokines play a central role in the pathogenesis of CSU by causing increased vascular permeability and nerve stimulation.[10-12] The activated coagulation system may also contribute to MC activation.[13] Basophils, which carry IgE receptors and release histamine upon activation, show enhanced recruitment to lesional skin in CSU.[14,15] Cyclosporine is known to inhibit histamine release from both MC and basophils.[16] Recent studies have identified autoreactive Tcells to the IgE receptors.[17] In the presence of an autoimmune association, activation of MC by autoreactive IgE antibodies and self-antigens is a known phenomenon.[18] Cyclosporine exhibits antipruritic activity through neuromodulation, suppressing pruritogenic cytokines, and directly acting on cutaneous nerve endings. It leads to decreased levels of neuropeptide substance-P, nerve growth factors, and neurotrophin-3. Cyclosporine also inhibits pruritus via interleukin-31 inhibition and decreased expression of TRPV1 and NKR1 genes. Additionally, cyclosporine's vasospastic effects also contribute to alleviating CSU symptoms.[19]

Cyclosporine is being used in CSU for years now. However, the optimum dosage and duration of cyclosporine in CSU are still not well-established. A meta-analysis/systematic review suggested a dose range of 1–5mg/kg/day, with 3mg/kg/day as a mean starting dose for most patients.[20] However, in our study, higher doses of cyclosporine (4–5mg/kg/day) demonstrated better efficacy in controlling symptoms. Majority of the patients did not experience any symptoms at the higher doses (4–5mg/kg/day) while approximately one-quarter of patients (23.26%) experienced symptom reappearance at lower doses (1–3mg/kg/day) albeit with reduced severity and frequency. This indicates that, perhaps, lower doses of cyclosporine may not be sufficient for complete disease control. Biomarkers such as a positive autologous serum skin test (ASST), positive basophil histamine release assay (BHRA), basophil activation test (BAT), elevated d-dimer and CRP levels, lower serum IgE levels, and higher levels of certain cytokines (IL-2, IL-5, TNF-a) can help predict patient response to the various therapies. However, we did not evaluate the role of the prognostic markers in our study.

We also observed that cyclosporine provided no significant residual protection against chronic spontaneous urticaria (CSU). Within four weeks of discontinuing the therapy twenty-nine patients (67.44%) experienced a recurrence of symptoms with a similar level of severity. However, it is important to note that our study had a relatively short duration, and therefore, we cannot draw definitive conclusions regarding the outcomes of prolonged treatment durations.

Interestingly, we noted a peculiar observation in three patients (6.98%) who continued to develop urticarial wheals without experiencing any itching. The exact mechanism behind this phenomenon is unknown. It is possible that cyclosporine's action on either nerve endings or pruritogenic cytokines may be responsible for the occurrence of wheals without the accompanying itch. Further research is needed to gain a better understanding of the underlying mechanisms involved in this phenomenon.

In this study, cyclosporine (4–5mg/kg/day) has shown significant effectiveness in controlling disease activity in CSU within a short period (3–5 days). We believe that initiating treatment with higher doses of cyclosporine can be safely employed as a short-term therapy for patients with refractory CSU, particularly those with a prolonged history of the condition or those who may experience triggering events (such as stress-induced cases during major life events or cases with seasonal patterns). Subsequently, the dosage of cyclosporine can be tapered to a lower range (1–3mg/kg/day), which has a well-demonstrated favorable safety profile, making it more suitable for long-term management.

A smaller sample size, lack of a control group, short follow-up period, lack of blinding, and complete reliability on subjective patient-reported outcomes are the major limitations of our study.

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Conflicts of interest

There are no conflicts of interest.

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