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Case Report

Effective Treatment of Refractory Chronic Spontaneous Urticaria with Add-On Omalizumab and Ciclosporin: From Guideline to Real-Life Practice

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Abstract

Chronic spontaneous urticaria (CSU) is characterized by the presence of wheals and/or angioedema that occurs daily or almost daily at least two times per week for more than 6 weeks. More than 30% of patients with moderate to severe CSU are affected for longer than 5 years. Here, we report a patient with recalcitrant CSU whose symptoms were completely controlled with omalizumab and added-on ciclosporin. A 56-year-old Thai female presented at the Siriraj Urticaria Clinic with recurrent wheals and sporadic angioedema for 20 years. Her previous medication included desloratadine 20 mg/day, fexofenadine 720 mg/day, ranitidine 300 mg/day, and intermittent systemic corticosteroids, all of which failed to control her symptoms. We added ciclosporin 100 mg twice per day (3 mg/kg/day). One week later, our patient decided to discontinue ciclosporin by herself due to a worsening of her wheals, pruritus, and dyspnea. We then added omalizumab subcutaneous injection (150 mg at the beginning, 300 mg at 2 weeks, and 300 mg at 4 weeks) with no significant improvement. We decided to re-prescribe add-on ciclosporin 100 mg twice per day (3 mg/kg/day) together with subcutaneously injected omalizumab 300 mg every 2 weeks. After two months, this combination treatment led to complete symptom control, and prednisolone could be discontinued. Omalizumab in combination with ciclosporin for treatment of refractory CSU resulted in a markedly positive clinical response.

Keywords: Chronic spontaneous urticaria; Refractory; Omalizumab; Ciclosporin

Abbreviations: ASST - Autologous serum skin test; CsA - ciclosporin; CSU - chronic spontaneous urticaria; CU-Q_2oL - chronic urticaria quality of life questionnaire; EAACI - European Academy of Allergy and Clinical Immunology; GA^2LEN - Global Allergy and Asthma European Network; EDF - European Dermatology Forum; NFAT - nuclear factor of activated T cells; nsAHs - non-sedating H_1-antihistamines; IgE - immunoglobulin E; TNF-α - tumor necrosis factor-alpha; UAS7 - standard seven-day urticaria activity score; UCT - urticaria control test; WAO - World Allergy Organization

1. Introduction

Chronic spontaneous urticaria (CSU) is characterized by the presence of wheals and/or angioedema that occurs daily or almost daily at least two times per week for more than 6 weeks [1]. Based on the evidence from previous studies, the prevalence of pediatric CSU and adult CSU were unlikely to be greater than 0.3 % and 1.4 %, respectively [2, 3]. The pathogenesis of CSU is thought to be related to histamine, other mediators and cytokines that are released from activated mast cells, which leads to sensory nerve activation, vasodilatation, plasma extravasation, and cell recruitment to urticarial sites [4]. Appropriate diagnostic tests should be performed based on an indication by history and/or physical examination to exclude other urticaria subtypes and diagnose CSU. The European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA^2LEN)/European Dermatology Forum (EDF)/World Allergy Organization (WAO) guideline recommends starting treatment with non-sedating H_1-antihistamines (nsAHs) as first-line treatment. If inadequate control after 2-4 weeks or earlier, increasing nsAHs dose up to fourfold is recommended. For antihistamine-refractory patients, omalizumab should be added-on to nsAHs. Ciclosporin (CsA) is recommended for patients with severe disease who are unresponsive to nsAHs in combination with omalizumab [4].

CSU is a self-limited disorder, and its duration usually lasts from 1 to 5 years [5]. However, more than 30 % of patients with moderate to severe CSU are affected for longer than 5 years [6]. Here, we report a patient with recalcitrant CSU whose symptoms were completely controlled with omalizumab and added-on ciclosporin.

2. Case Presentation

A 56-year-old Thai female presented at the Siriraj Urticaria Clinic, Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand with recurrent wheals and sporadic angioedema. Patient's symptoms had started for at least the past 20 years with recurrent wheals and sporadic angioedema. Her previous medication included desloratadine 20 mg/day, fexofenadine 720 mg/day, ranitidine 300 mg/day, and intermittent systemic corticosteroids (prednisolone 5-20 mg/day or intravenous dexamethasone 5 mg) - all of which failed to control her symptoms.

She has been affected with diabetes mellitus for 8 months that is controlled with diet, and dyslipidemia that is treated with simvastatin 10 mg/day. She had previous history of thyrotoxicosis, but has been in complete remission without any treatment for 20 years.

At the initial visited, physical examination revealed urticarial wheals on her trunk and extremities. Other aspects of that examination were unremarkable. Laboratory investigations included complete blood count, serum immunoglobulin E (IgE) level, thyroid function test, anti-thyroglobulin, anti-thyroid peroxidase, anti-nuclear antibodies, hepatitis B surface antigen, anti-hepatitis C virus antibodies, blood sugar, liver function test, and renal function test. All of those investigations were unremarkable, except that she had high cholesterol, high triglycerides, and high low-density lipoprotein levels. Autologous serum skin test (ASST) and skin prick test were not performed in this patient as she could not stop antihistamines, CsA, omalizumab prior to the test. Anti-FcεRI/IgE did not perform because this test is not routinely available yet in our hospital. Laboratory investigations were shown as Table 1. The final diagnosis of the presented case is refractory CSU.

A stepwise approach for urticaria treatment in combination with avoidance of diets containing histamine-releasing foods (cheese, raw and grilled sausages, ham, dried and grilled fish) were used in this patient [7]. Despite receiving desloratadine 20 mg/day, fexofenadine 720 mg/day, and prednisolone 5 mg/day, her standard seven-day urticaria activity score (UAS7) was 18, and her urticaria control test (UCT) score was 8. We added CsA 100 mg twice per day (3 mg/kg/day). One week later, our patient decided to discontinue CsA by herself due to a worsening of her wheals, pruritus, and dyspnea. We then added omalizumab subcutaneous injection (150 mg at the beginning, 300 mg at 2 weeks, and 300 mg at 4 weeks) with no significant improvement (UAS7 = 30, UCT = 8). We decided to re-prescribe add-on CsA 100 mg twice per day (3 mg/kg/day) together with subcutaneously injected omalizumab 300 mg every 2 weeks.

After two months, omalizumab in combination with CsA led to symptom improvement. Oral prednisolone could be discontinued with a follow-up time of 6 months. The results of assessment of disease activity were shown in Table 2. At the last follow-up, UAS7 was 2 and UCT was 10. For laboratory investigations, serum IgE level was not repeated after treatment because it was low at baseline. Complete blood count was repeated which revealed unremarkable finding. No adverse effects were observed or reported from the use of combination omalizumab and CsA.

Baseline laboratory	**Values**
Hematology	
White blood cell count (cell/mm^3)	8,850
Neutrophils (%)	66.0
Lymphocytes (%)	24.4
Eosinophils (%)	2.4
Basophils (%)	0.5
Total Immunoglobulin E (IgE) (U/ml)	< 4.34
Glucose	110
Hemoglobin A1c *(*Hb A1c)	6.0
Lipid profile	
Cholesterol	228
Triglyceride	135
High-density lipoproteins	41
Low-density lipoproteins	160
Blood urea nitrogen	13.2
Creatinine	0.72
Liver function test	
Albumin	4.1
Total protein	6.8
Globulin	2.7
Total bilirubin	0.41
Direct bilirubin	0.17
Aspartate aminotransferase	20
Alanine aminotransferase	28
Alkaline phosphatase	103

Thyroid function test	
Serum Triiodothyronine (T3)	107.0
Free Thyroxine (Free T4)	1.24
Thyroid stimulating hormone	1.04
Hepatitis profile	
Hepatitis B surface antigen (HBs Ag)	Negative
Hepatitis C virus antibody (Anti-HCV Ab)	Negative
Anti-nuclear antibodies	Positive (fine-speckled 1:100)
Anti-thyroglobulin antibodies	Negative
Anti-thyroid peroxidase antibodies	Negative
Specific allergy tests	
Autologous serum skin test (ASST)	Not done
Anti-FcεRI/IgE	Not done
Skin prick test	Not done

Table 1: Laboratory investigations.

	23/1/2019	**20/2/2019**	**27/3/2019**	**1/5/2019**	**15/5/2019**	**22/5/2019**	**29/5/2019**	**5/6/2019**	**26/6/2019**	**10/7/2019**	**24/7/2019**
UAS7	16	18	15	21	34	38	30	20	18	0	4
UCT	6	8	6	4	4	2	8	9	10	16	12
CU-Q_2oL	29 (31.52%)	-	-	-	-	-	-	-	13 (14.13%)	8 (8.7%)	-
	7/8/2019	**21/8/2019**	**4/9/2019**	**18/9/2019**	**9/10/2019**	**30/10/2019**	**29/11/2019**	**18/12/2019**	**15/1/2020**	**12/2/2020**	**11/3/2020**
UAS7	0	8	0	4	0	0	0	0	0	15	2
UCT	12	8	8	11	16	15	16	12	14	6	10
CU-Q_2oL	-	-	-	-	-	-	-	-	5 (5.43%)	-	-

Table 2: Assessment of disease activity at each follow-up visit. CU-Q_2oL - Chronic urticaria quality of life questionnaire; UAS7 - seven-day urticaria activity score; UCT - urticaria control test.

3. Discussion

The previous 2013 revision and update of the EAACI/GA^{2}LEN/EDF/WAO guideline recommends modern nsAHs as first-line treatment for CSU. Up to four-fold increased dosage of nsAHs is suggested as a second-line approach if symptoms persist after 2 weeks. Omalizumab, CsA, or montelukast is suggested as a third-line add-on treatment if symptoms persist after 1-4 additional weeks [8]. A short course of systemic corticosteroids may be considered during exacerbation of symptoms [9]. Later on, the current 2018 EAACI/GA^{2}LEN/EDF/WAO guideline recommends omalizumab as a third-line treatment option in CSU patients who are unresponsive to the maximum fourfold increase in the licensed daily dose of nsAHs. The next step is add-on CsA if omalizumab is not effective within 6 months or earlier [4]. The risk/benefit profiles of both treatments favor the use of omalizumab [10].

However, CsA is often prescribed prior to omalizumab in routine clinical practice in many countries due to its affordable price [11]. Similarly, our patient was prescribed with CsA 100 mg twice per day prior to omalizumab. After one week of CsA initiation, she discontinued CsA by herself due to a worsening of her wheals, pruritus, and dyspnea which were not related to CsA side effects. CsA, which is an immunosuppressive agent, acts by targeting the calcineurin complex. Generally, following T-cell receptor activation, calcineurin complex is activated and leads to a dephosphorylation of cytoplasmic nuclear factor of activated T cells (NFAT). CsA binds to cyclophilin thereby, inhibiting calcineurin migrates into the nucleus. Calcineurin inhibition prevents the dephosphorylation of NFAT and subsequent downregulates interleukin-2 production [12]. Moreover, CsA reduces IgG, IgE and FcεRI and prevents a release of histamine by inhibition of mast cell degranulation [13]. CsA has also shown to inhibit tumor necrosis factor-alpha (TNF-α) that is one of the mediators releasing from activated mast cells. There are some evidences suggest that TNF-α inhibitors may play a role in the management of CSU [14].

CsA is available in modified and nonmodified formulations. Modified CsA is more generally used as it exhibits increased bioavailability and less unpredictable absorption. Most patients will get improvement within 3 months but there are some patients respond within 1-2 weeks. The optimal dose of CsA for CSU has not been well-studied or determined. A previous meta-analysis and systematic review suggests the appropriate dosage of CsA ranging from 1 to 5 mg/kg/day [15]. A dosage of 3 mg/kg/day is an appropriate starting dose for CSU patients [16]. Adverse events such as nephrotoxicity, hypertension, gastrointestinal symptoms, hirsutism, paresthesia are associated with higher doses and longer duration of CsA treatment [16].

Due to unwanted use of CsA in this patient, omalizumab was started which failed to control her symptoms after 6 weeks of treatment. There may be two possible reasons why our patient did not respond well to omalizumab. Firstly, our patient had low serum IgE (≤ 4.34 IU/ml) at baseline. A multicenter retrospective study demonstrated that patients with low serum IgE (≤ 15.2 IU/ml) had significantly lower omalizumab treatment response [17]. Secondly, it might be too early to evaluate the treatment response to omalizumab. Based on the experience published by

Gericke et al. [18], the dose of omalizumab should be increased in patients who showed a partial response to omalizumab after 3-month of treatment. Thus, some author suggests that evaluation of omalizumab treatment should be considered every 3 months [19]. The studies by Sanchez J et al. [20] and Turk M et al. [10] suggested periodic evaluation of omalizumab treatment every 4 months and 6 months, respectively. The current international guideline recommends an add-on CsA if omalizumab is not effective within 6 months or earlier [4].

Interestingly, our review yielded two studies that reported the use of concomitant omalizumab and CsA for CSU. Mawhirt et al. reported four patients with omalizumab-resistant CSU. All of them received 300 mg of omalizumab every 4 weeks with a range of 3-7 omalizumab injection. After adding CsA to omalizumab, all patients achieved complete response [21]. Recently, Sanchez et al. reported 21 patients who did not achieve clinical control with the use of each one of CsA or omalizumab for at least 4 months [20]. Sixteen out of 21 patients (76.2 %) reached a UAS7 of less than 6 points after 4 months of receiving both drugs. The authors did not observe a significant increase in adverse events of this combination. Due to uncontrolled symptoms of our patient, re-prescribed CsA concomitant with omalizumab was discussed with her. She agreed to use this combination which revealed successful outcome.

4. Conclusion

In patients who did not achieve clinical control with the use of each one of the CsA and omalizumab. These two therapies together may be an alternative option. The time to evaluate an efficacy of each treatment should be 6 months after initiation or earlier, if the there is no financial constrain. This case report supports current international guidelines, which recommend the use of omalizumab in combination with ciclosporin for treatment of refractory CSU.

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Conflict of Interest

Kulthanan K, Tuchinda P and Chularojanamontri L involve in clinical trial of Novartis. The other authors declare no personal or professional conflicts of interest relating to any aspect of this study.

Author Contributions

Trakanwittayarak S, Kiratiwongwan R and Kulthanan K reviewed the literature and contributed to manuscript drafting; Tuchinda P and Chularojanamontri L reviewed the manuscript critically; all authors issued final approval for the version to be submitted.

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