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Autologous Whole Blood Injection for the Treatment of Antihistamine-Resistant Chronic Spontaneous Urticaria

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Dear Editor:

Recently, the term chronic spontaneous urticaria (CSU) is used to indicate spontaneous and persistent wheals, independent of external physical stimuli[1]. CSU is classified into two groups according to the presence of autoantibodies: chronic autoimmune urticaria (CAU) and chronic idiopathic urticaria (CIU)[2]. Several treatment methods are available for patients with CSU. However, CSU can be resistant to conventional treatment, including high-dose antihistamines (up to 4-fold dose of H1 antihistamines). Autologous whole blood (AWB) injection, a prevalent method to treat allergic rhinitis, atopic dermatitis, and viral disease, is scientifically unproven[3,4]. Few reports have documented the clinical improvement of CSU after injection of AWB[5,6]. Although its mechanism of action remains widely unknown, we believe that AWB injection may desensitize the patient against triggering factors including autoantibodies.

The aim of this study was to evaluate the efficacy of AWB injection in treating CSU, and to compare its efficacy on CAU and CIU. The study was approved by the hospital ethics committee (E-2013096), and all patients gave their informed consent. We treated 22 patients with CSU, who had uncontrolled urticaria most days of the week despite antihistamine therapy for >6 weeks, by administering AWB injections for 8 consecutive weeks. Patients who had developed urticarial due to foods, drugs, or physical and environmental factors, female patients who were

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Table 1. Efficacy of AWB injection after 8 week of treatment

Variable	CSU (n=22)	CAU* (n=7)	CIU* (n=15)
Responder†	8 (36.4)	2 (28.6)	6 (40.0)
Non-responder	14 (63.6)	5 (71.4)	9 (60.0)
Complete remission‡	2 (9.1)	0	2 (13.3)

Values are presented as number (%). AWB: autologous whole blood, CSU: chronic spontaneous urticarial, CAU: chronic autoimmune urticaria, CIU: chronic idiopathic urticaria. Analysis of group differences (CAU vs. CIU) were done by using Fisher's exact test, *$p>0.05$, †>30% improvement of UAS after repeated AWB injection, ‡complete remission defined as no occurrence of wheals during follow-up.

pregnant or lactating, patients with any severe systemic disease, and patients who had taken any immunosuppressive agent within 4 weeks of entry were excluded from the study. The patients were classified into two groups after autologous serum skin test (ASST): positive (CAU) and negative (CIU). After the cessation of antihistaminic treatment for at least 3 days, ASST was performed. A wheal with a diameter at least 1.5 mm greater than that of a saline-induced wheal at 30 min was considered positive. We took venous blood samples and immediately administered a gluteal intramuscular AWB injection. The volume of injection was 2.5 ml at week 0, and 5 ml/week for the subsequent injections. All patients underwent laboratory examinations before treatment, including complete blood count, liver and renal function tests, urinalysis, and D-dimer analyses. Only antihistamines were allowed during the AWB injection phase for worsening pruritus or wheals. The outcome measures were pruritus intensity; wheal number, size, and duration; and sleep and daily activity interference by using score values from 0 to 3. The sum of all six severity parameters were calculated to obtain the urticaria activity score (UAS)[7] every week, and the UAS at week 0 and week 8 was compared between responders and non-responders. The consumption of antihistamines was calculated at the endpoint. A "responder" was defined as a patient with >30% improvement of UAS after repeated AWB injections[5].

In total, 8 of 22 patients (36.4%) with CSU were responders to AWB injection; 2 of 7 (28.6%) CAU and 6 of 15 (40.0%) CIU patients were considered responders (Table 1). There was no significant difference in responder ratios between the CAU and CIU groups. The antihistamine consumption at week 8 did not show any significant differences compared with baseline (data not shown). Between responders and non-responders, we found

Table 2. Comparison between responders and non-responders to autologous whole blood injection among 22 CSU patients

	Responder (n=8)	Non-responder (n=14)	*p*-value*
UAS at baseline, range (0~18)	14.4±1.51	12.8±3.57	0.019
UAS at week 8, range (0~18)	7.1±2.1	10.7±4.27	0.050
Duration of CSU (mo)	14.9±12.3	50±95.31	NS
Sex (male:female)	0:8	4:10	NS
Age (yr)	47.28±17.30	48.86±17.84	NS
ASST (positive/negative)	2:6	5:9	NS
D-dimer (μg/mg)	0.53±0.28	0.29±0.22	NS
CRP (mg/dl)	0.08±0.07	0.21±0.45	NS

Values are presented as mean±standard deviation or number only. CSU: chronic spontaneous urticaria, UAS: urticarial activity score, ASST: autologous serum skin test, CRP: C-reactive protein; NS: not significant ($p>0.05$). *PASW Statistics 18 (Quarry Bay, Hong Kong) was used for statistical analysis, $p<0.05$ was considered to indicate statistical significance of differences.

that CSU patients with a high baseline UAS improved markedly after repeated AWB injections ($p=0.019$); however, there was no difference with respect to disease duration, sex, age, ASST result, D-dimer, and C-reactive protein level (Table 2). No patients experienced serious adverse events; however, minor adverse events such as bruising and injection pain were noted.

Although desensitization with repeated AWB injections theoretically provided better efficacy in patients with CAU than in those with CIU, our results showed that there were no significant differences between groups at the endpoint. Mori and Hashimoto[8] reported that an ASST-positive patient was completely cured after AWB injections; however, the patient remained ASST positive. These findings suggest that the underlying mechanism of AWB injections is attributed to other pathogenetic factors. Unlike in previous reports[5,8], AWB injection did not cause a dramatic response in patients with antihistamine-resistant CSU regardless of the skin test results to autologous serum. Nevertheless, the most important finding of this study is that AWB injection might be more efficient in treating patients with CSU who had high disease activity at baseline. Therefore, AWB injections may be an option in treating patients with antihistamine-resistant CSU who have high disease activity. Further studies are required to reinforce the current results concerning AWB injection in patients with CSU, and evaluate its efficacy, duration, treatment interval, and dose.

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