

ORIGINAL ARTICLE

Autologous whole blood and autologous serum injections are equally effective as placebo injections in reducing disease activity in patients with chronic spontaneous urticaria: a placebo controlled, randomized, single-blind study

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Abstract

Background: Recent demonstration of circulating anti-IgG antibodies towards IgE and its receptor (FcεRI) has led to an interest in inducing tolerance to circulating histamine-releasing factors with autologous blood injections as a treatment option in chronic spontaneous urticaria (CU). The aim of the study was to assess the efficacy of autologous whole blood (AWB) and autologous serum (AS) injections in patients with CU compared to placebo. **Methods:** A total of 88 CU patients with (+) autologous serum skin test (ASST) (59) and (-) ASST (29) were randomized into three parallel subgroups and were treated with weekly injections of AWB, AS or placebo for 10 weeks. Clinical assessments included urticaria activity score (UAS) and dermatology life quality index. **Results:** In ASST (+) patients, the percentages of patients with >30% improvement in UAS and DLQI were 85% and 90% in AWB group, 65% and 65% in AS group and 79% and 90% in placebo group, respectively. In ASST (-) patients, these figures were 67% and 89% in the AWB group, 80% and 80% in the AS group and 60% and 70% in the placebo group. The intergroup difference for complete subsidence was not statistically significant. **Conclusions:** Even though we could not show a better efficacy than placebo, autohemotherapy resulted in a marked decrease in disease activity and improvement in quality of life scores in CU patients.

Key words: autoreactive urticaria, chronic urticaria, autohemotherapy, autologous serum injections, autologous whole blood injections, urticaria treatment

Introduction

Chronic spontaneous urticaria (CU) is characterized by the rapid and unprompted appearance of wheals or angioedema. It can result from many different causes such as chronic infections, food intolerance, non-infectious chronic inflammatory processes (gastritis, esophagitis) and autoreactive functional antibodies directed against the IgE receptor (1).

In 1980s, it was found that autologous serum (AS) injected into the skin could elicit a wheal response in some patients (the autologous serum skin test; ASST) and a serum histamine-releasing factor (HRF) was

postulated (2). During the 1990s, autoantibodies against the IgE receptor and IgE itself were detected in the serum from patients with CU. These antibodies were suggested to cross-link basophil or mast cell IgE receptors in the absence of IgE or antigen causing degranulation and histamine release and creating erythema and edema typical of urticaria (3). At least 30–50% of patients with CU have detectable functional anti-FcεRI or anti-IgE autoantibodies (4). It has been demonstrated that around a third of patients with CU show a positive response against their own serum in the ASST, and in some of these patients it is possible to identify autoantibodies against the

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high-affinity IgE-receptor (FcR1) or IgE. These functional autoantibodies can be detected by the basophil histamine release assay. All patients with a positive ASST can be subsumed to suffer from autoreactivity or autoreactive CU (5). Autoreactive urticaria is characterized by a long duration and high disease activity when compared with other forms of CU. Patients frequently exhibit concomitant autoimmune disorders such as autoimmune thyroiditis (1).

Autoreactive urticaria constitutes a therapeutic challenge since it is refractory to treatment. Removal of autoantibodies has been a target for treatments like plasmapheresis, cyclosporine and intravenous immunoglobulin which have been proven to be helpful but due to their high costs these treatments are suggested to be reserved for patients who are unresponsive to other forms of treatment (6). There have been efforts to treat autoreactive urticaria with "desensitization" protocols which use injections of autologous whole blood (AWB) or serum and have been reported to be beneficial (7,8).

AWB injection (autohemotherapy) is an ancient treatment method which has been used for allergic diseases, atopic dermatitis, circulatory disorders, viral diseases and cancer with a little evidence of scientific research (9,10). Hypothesizing that the circulating HRFs are responsible for the induction of symptoms in CU patients with positive ASST, autohemotherapy was regarded as a promising therapeutic option in this group of CU patients by Staubach et al. who performed a placebo-controlled clinical study to assess the efficacy of AWB injections in patients with CU (7). Later, Bajaj et al. suggested that HRFs are present in the serum and used AS to evaluate the efficacy of autohemotherapy in CU patients in a multicenter study (8).

The lack of a large number of placebo-controlled, blinded studies in this area promoted us to perform a clinical study to investigate the efficacy of autohemotherapy in CU. For this purpose, we designed a placebo-controlled, single-blind, parallel-group study which would compare the efficacy of AWB, AS and placebo injections in patients with CU.

Materials and methods

Patients

Patients with CU with wheals present for 3 days a week were considered for inclusion if aged between 18 and 70 years and gave informed consent for the study. Inclusion started on January 2009 and discontinued on August 2009. Information sheets included patients' age, duration of the disease and age of onset, previous therapies, family history of urticaria, atopy

history and total IgE levels. Exclusion criteria were pregnancy, physical urticaria, systemic corticosteroid or immunosuppressive therapy during the last 6 weeks and serious chronic systemic diseases.

The trial was designed as a prospective, randomized, placebo-controlled, single-blinded and parallel-group study and was approved by the local ethics committee.

ASST

All patients were subjected to ASST. The procedure of ASST was performed according to the guidelines which have been recently published (11). Short-acting antihistamines were withdrawn at least 72 h before testing; no patients had taken long-lasting antihistamines or immunosuppressive drugs for at least 2 months before testing.

Clinical assessment

Clinical assessment of the patients was performed by using a revised version of urticaria activity score (UAS) and dermatology life quality index (DLQI). UAS is a self-scoring system which has been described by O'Donnell et al. and Grattan et al. (12,13). We revised this scoring system like Staubach et al. (7) and patients recorded 11 symptoms of urticaria (number of wheals, size of wheals, duration of wheals, intensity of pruritus, duration of pruritus, number of erythema, size of erythema, duration of erythema, number of angioedema, size of angioedema and duration of angioedema) using score values between 0 and 3. This yielded daily scores between 0 and 33. The UAS was calculated at the beginning (week 0), immediately after the end of the treatment (week 10) and after 6 weeks of injection-free follow-up period (week 16). Only daily UAS scores could be calculated because of the incompatibility of the patients.

The DLQI is a quality of life (QoL) instrument that includes 10 items and has been validated as a reliable outcome in patients with CU (14). The DLQI was calculated on weeks 0, 10 and 16.

At the end of the study, the UAS and DLQI scores on weeks 10 and 16 were compared with UAS and DLQI scores at week 0. A decrease by >30% in UAS and an increase by >30% in DLQI were considered as improvement in all groups. We referred to Staubach et al. who has considered 30% to be a significant response in their recent study (7).

Randomization of the treatment groups

Eighty-eight patients were classified into two groups – ASST (+) ($n = 59$) and ASST (-) ($n = 29$) – according

to their ASST results. Each group was randomized into three treatment groups; the first group received AWB ($n = 29$, 33%), the second group received AS ($n = 30$, 34%) and the third group received placebo injections ($n = 29$, 33%) every week for 10 weeks. The treatment procedure was as follows: 1) 1 week of run-in period to record the symptoms (UAS); 2) 10 weeks of gluteal intramuscular injections (blood was taken from the cubital vein and injected immediately without centrifugation for AWB and with centrifugation for AS; first injection was 2.5 ml and the following injections were 5 ml, every week) and 3) 4 weeks of follow up without treatment. The patients were not allowed to take antihistaminics unless they could not bear the urticarial symptoms. The rescue antihistaminic was fexofenadine for all patients.

Patients were blinded to treatment; the injectors were wrapped by stickers so that patients could not see what was injected in. In the placebo group, the blood was taken but was discarded and saline was injected instead. The randomization procedure was performed using computer-generated random number tables. The study design is represented in Figure 1.

Statistical analyses

NCSS (Number Cruncher Statistical System) 2007 and PASS 2008 Statistical Software (Utah, USA) were used for statistical analyses. The following statistical methods were used for interpretation of the results: descriptive statistical methods (mean,

standard deviation, frequency) as well as Kruskal Wallis test for comparison of the data which do not show normal distribution and Mann Whitney U test for determining the parameters which cause discrepancies. Student t test was used to make group comparisons between parameters with normal distribution while Mann Whitney U test was used for parameters which do not show normal distribution. Chi-square and Fisher's Exact Chi-square tests were used to analyze qualitative data. $p < 0.05$ Was considered to be statistically significant.

Results

Patient characteristics and results of ASST

Ninety-four CU patients volunteered to participate in the study. Six patients were excluded because they quit the study after one or two injections. Patient characteristics were as follows: there were 58 females (66%) and 30 males (34%), the mean age was 39 ± 12 years (range 18–70), the mean age of onset was 34 ± 13 years (range 8–68) and the mean duration of the disease was 52 ± 87 months (range 2–408).

Mean total IgE levels were 188 ± 261 (range 5–2001). Twelve (13%) of the patients had family history of urticaria, while 20 (23%) had family history of atopy and 10 (11%) had atopy history by her/himself.

ASST was negative in 29 (33%) and positive in 59 (67%) of the patients. There were no statistically significant differences between ASST (+) and ASST

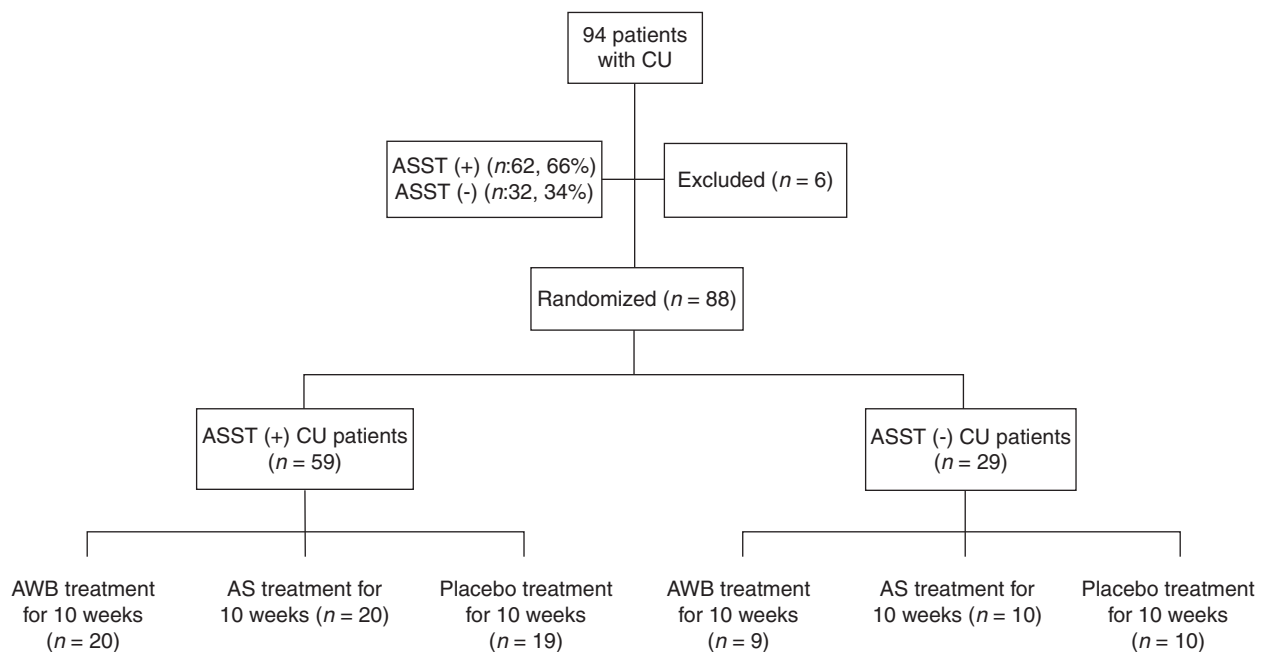


Figure 1. Study design.

(-) patients with regard to age, gender, age of onset and duration of the disease, family history of urticaria and atopy and personal atopy history (Table I). ASST results showed insignificant differences with respect to number, size and duration of the wheals ($p > 0.05$) and UAS and DLQI scores before treatment, week 10 and week 16 ($p > 0.05$).

The mean UAS score at baseline was 16 ± 7 (range 0–30), at week 10 was 8.6 ± 6.6 (range 0–24) and at week 16 was 7 ± 7 (range 0–26). The mean DLQI score at baseline was 10 ± 6 (range 0–27), at week 10 was 4 ± 5 (range 0–9) and at week 16 was 4 ± 5 (range 0–22).

In ASST (+) patients, DLQI scores of AWB group were significantly higher than AS group ($p: 0.005$; $p < 0.01$) and placebo group ($p: 0.037$; $p < 0.05$) at baseline. There were no differences between the DLQI scores of AS and placebo groups before treatment ($p: 0.147$; $p > 0.05$). In ASST (-) patients, the DLQI scores of treatment groups did not differ from each other at baseline, at week 10 and week 16 ($p > 0.05$).

Efficacy analysis

There was a marked improvement in both UAS and DLQI scores of the groups at the end of the study.

The mean UAS scores and mean DLQI scores of patients were improved by 55% and 60% at the end of the study (16 weeks), respectively. The mean decrease in DLQI scores (between baseline and week 16) were -10, -3 and -8 for ASST (+) patients, and -6, -4 and -6 for ASST (-) patients receiving AWB, AS and placebo, respectively. These differences were exceeding the minimally important difference for DLQI (2.24–3.1) as reported by Shikier et al. (15). When we compared the responses to treatment in ASST (+) patients, we found that >30% improvement in DLQI scores was achieved by a significantly higher number of patients treated with AWB than AS ($p < 0.05$) but not than placebo ($p > 0.05$). This difference between groups was lost at week 16. In ASST (-) patients, we found no difference between treatment groups when we compared the improvement in DLQI scores at weeks 0, 10 and 16 ($p > 0.05$) (Figure 2).

The mean UAS scores at baseline, at week 10 and week 16 did not differ significantly among AS, AWT and placebo groups ($p > 0.05$). There was no statistically significant difference by means of >30% improvement in UAS scores between treatment groups (AWB, AS and placebo) at weeks 0, 10 and 16 ($p > 0.05$) (Figure 3). In AWB group, the number of patients with >30% improvement in UAS scores at week 10 was higher in ASST (+) patients than ASST (-) patients ($p < 0.05$), but this difference was lost at

Table I. Patient characteristics with respect to ASST results.

	ASST (+)	ASST (-)	
	mean $\pm$ SD	mean $\pm$ SD	<i>p</i>
+Age	39.36 $\pm$ 11.95	39.07 $\pm$ 14.13	0.919
+Age at onset of disease	34.15 $\pm$ 13.56	34.03 $\pm$ 14.28	0.969
++Duration of disease (months)	56.10 $\pm$ 88.40	57.83 $\pm$ 113.03	0.553
	<i>n</i> (%)	<i>n</i> (%)	
Gender			
Male	24 (40.7)	6 (20.7)	0.063
Female	35 (59.3)	23 (79.3)	
	mean $\pm$ SD	mean $\pm$ SD	++ <i>p</i>
UAS before treatment	18.07 $\pm$ 5.31 (17)	16.52 $\pm$ 5.78 (15)	0.175
DLQI before treatment	11.10 $\pm$ 5.89 (11)	10.07 $\pm$ 5.83 (9)	0.353
	<i>n</i> (%)	<i>n</i> (%)	* <i>p</i>
Family history of CU	10 (16.9)	2 (6.9)	0.196
Family history of atopy	11 (18.6)	9 (31.0)	0.192
Atopy history	6 (10.2)	4 (13.8)	0.615

*Student *t* test.

++Mann Whitney U test.

*Chi-square test.

ASST = autologous serum skin test; CU = chronic spontaneous urticaria; DLQI = dermatology life quality index; SD = standard deviation; UAS = urticaria activity score.

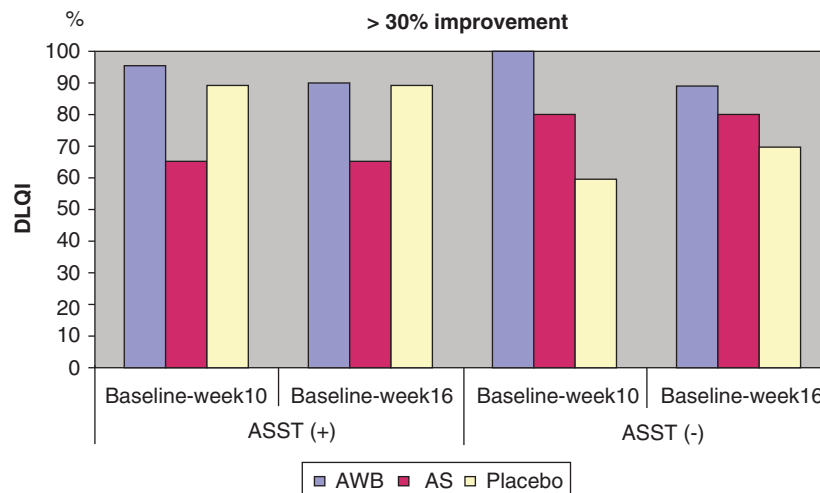


Figure 2. The >30% improvement rates in DLQI scores between treatment groups at baseline, week 10 and week 16. DLQI = dermatology life quality index.

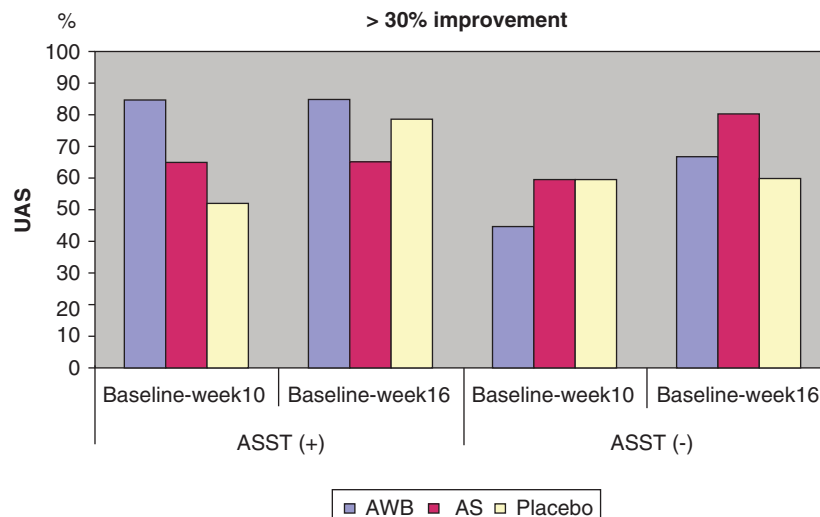


Figure 3. Percentage of patients with >30% improvement in UAS at baseline, week 10 and week 16. UAS = urticaria activity score.

week 16. In AS and placebo groups, we found no difference between >30% improvement rates in UAS scores of ASST (+) and (-) patients at weeks 0, 10 and 16 ($p > 0.05$).

In all treatment groups, there was no significant difference between ASST (+) and ASST (-) patients regarding >30% improvement in DLQI and UAS scores between weeks 10 and 16 ($p > 0.05$).

The UAS scores were completely improved in ASST (+) and ASST (-) groups in 4 (20%) versus 1 (11%) patients in AWB group, 4 (20%) versus 2 (20%) in AS group and 5 (26.3%) versus 1 (10%) in placebo group, respectively. There was no statistically significant difference among treatment groups regarding the number of patients who completely improved (Table II).

Discussion

Our current study was aimed at assessing the efficacy of autohemotherapy in CU patients. ASST was positive in 62% of our patients which was consistent with other authors' data. We could not show any difference with respect to age, gender, age of onset and duration of the disease, family history of atopy and urticaria, personal history of atopy, number, size and duration of the wheals, UAS and DLQI scores between ASST (+) and ASST (-) patients which was concordant with the findings of Nettis et al. (16).

Staubach et al. included a total of 56 CU patients (35 ASST (+) and 21 ASST (-)) to their placebo-controlled, single-blinded study. The study group was divided into two separate subgroups to be treated with

Table II. Complete improvement rates between treatment groups.

		ASST (+)	ASST (-)
		<i>n</i> (%)	<i>n</i> (%)
Complete improvement	UAS		
	AWB	4 (20)	1 (11.1)
	AS	4 (20)	2 (20)
	Placebo	5 (26.3)	1 (10)
Total		13 (66.3)	4 (41.1)

AS = autologous serum; ASST = autologous serum skin test; AWB = autologous whole blood; UAS = urticaria activity score.

AWB or placebo injections each week for 8 weeks. After 12 weeks of follow-up period, ASST (+) patients were found to have a more profound decrease in activity scores and antihistaminic use and increase in QoL scores than the ASST (-) patients. Placebo injections were ineffective in both groups. The response to AWB and placebo injections in ASST (+) and (-) patients did not significantly differ from each other and this was attributed to the limited number of patients who enrolled in the study (7).

Bajaj et al. tried to refine autohemotherapy by removing the cellular components of blood because they suggested that the HRFs are present in the serum and this would lead to a less painful injection. They designed their study with a total of 75 patients (ASST (+) 62 and ASST (-) 13) who were scheduled to be given AS injections each week for 9 weeks. After 12–16 weeks of follow-up period, 35.5% of ASST (+) and 23% of ASST (-) patients were found to be completely symptom-free while 24.2% of ASST (+) and 23% of ASST (-) patients significantly improved. In conclusion, ASST (+) patients benefited statistically more from AS injections (8).

In our study, at the end of 16th week, >30% improvement in UAS scores was 85% for ASST (+) patients who were given AWB injections and 65% of ASST (+) patients who were given AS injections at the end of 16th week. In ASST (-) group, at the end of 16th week, >30% improvement in UAS scores was found in 67% of patients in AWB group, 80% of patients in AS group and 60% of patients in placebo group. We found better improvement rates in UAS scores when we compared our results with the other two studies in both ASST (+) and ASST (-) patients. But at the level of significance, we could not show any difference among the three treatment groups ($p > 0.05$) (7,8).

In ASST (+) patients, >30% improvement in DLQI scores at the end of 16th week was found in 90% of patients in AWB group, 65% in AS group and 90% in placebo group. In ASST (-) patients, the DLQI scores significantly improved in 89% of patients in AWB

group, 80% in AS group and 70% in placebo group. Even though in our study higher percentages of improvement in DLQI scores were achieved with AWB and AS treatments in both ASST (+) and ASST (-) patients compared to Staubach et al., we could not find statistically different improvement among treatment groups: AWB, AS and placebo ($p > 0.05$).

At the end of the study, the UAS scores were completely improved in ASST (+) and ASST (-) groups in 4 (20%) versus 1 (11%) patients in AWB group, 4 (20%) versus 2 (20%) in AS group and 5 (26.3%) versus 1 (10%) in placebo group, respectively. Bajaj et al. reported complete improvement in 35.5% of ASST (+) patients and 23% of ASST (-) patients receiving AS injections (8).

To our knowledge, this study is the only study that evaluates the efficacy of AWB and AS injections in a placebo-controlled, single-blind and prospective design. The outcomes of our study do not seem to corroborate recent findings of other studies. AWB and AS injections were found to provide a significant decrease in disease activity and increase in QoL, but placebo could also provide a comparable efficacy. We found that AWB injections provided better improvement in UAS scores in ASST (+) patients than ASST (-) patients during the treatment period, but at the end of 16 weeks there were no significant differences between groups with respect to UAS and DLQI scores. We also found that AWB injections resulted in a better improvement of DLQI scores in ASST (+) patients when compared to AS but was not better than placebo.

We agree with Staubach et al. who suggest that urticarial symptoms could be decreased by repeated challenge with circulating HRFs but cannot agree that this treatment method might represent a means of inducing specific tolerizing immune responses similar to those seen in specific immunotherapy; because the effect of treatment was pronounced during the injection period and after the injections were discontinued, the difference between ASST (+) and ASST (-) patients was lost and we could not show that AWB or AS injections were more effective than placebo.

The most important finding of our study was even though they rarely got rescue antihistaminics, there was a marked decrease in disease activity and improvement in QoL scores of patients in all groups. In studies investigating the efficacy of conventional antihistaminic therapy in CU, rupatadine was found to reduce the urticaria scores by an average of 60% compared to 44% for placebo and desloratadine by 74% compared to 48.7% for placebo (17,18). When we looked at our results, we saw that at the end of 10th week, AWB reduced the UAS by 67% and placebo

reduced UAS by 42% in ASST (+) patients; these figures were 30% versus 31% in ASST (-) patients. The percent of patients with complete improvement was 20% in ASST (+) patients who were treated with AWB; this finding is similar to the result of a study which reported total disappearance of symptoms with levocetirizine in 24% of CU patients (19). Autohemotherapy with a very low cost and few side effects seemed to provide comparable results to conventional antihistaminic therapy.

Based on our results, we cannot recommend autohemotherapy as a treatment strategy for CU but we believe it could be an adjuvant to decrease urticaria activity. Clinicians who perform urticaria policlinics in a specialized setting would agree that CU patients who have been using antihistaminics for a long period of time would seek different treatment modalities when they are referred to a center which is specialized on urticaria. Because other treatment modalities such as plasmapheresis, cyclosporine and intravenous immunoglobulin are very expensive and have serious side effects, AWB injections but not AS might be tried for those patients with long-lasting, unremitting urticaria who have a positive ASST.

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