



Efficacy of Autologous Serum Therapy in Patients with Recalcitrant Chronic Urticaria and Positive Autologous Serum Skin Test

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Abstract

Background: Chronic urticaria (CU) is a common problem and negatively affects both work and social life because of its chronic relapsing course and poor response to therapy. Conventional therapies of CU sometimes fail to control the disease activity, especially in autologous serum skin test (ASST) +ve patients. More recent therapies that target the immune system are frequently limited by their high cost and/or aggressive side effects. Several lines of evidence have shown a possible therapeutic value of autologous serum therapy (AST) injection in the treatment of recalcitrant CU.

Objective: to evaluate the effect of autologous serum therapy in the treatment of CU patients with positive ASST

Methods: Our study is a randomized placebo-controlled, single-blind trial. 30 patients were given AST and 30 patients were given IM injection of normal saline (placebo). Both groups received the injections for 9 weeks then were followed up 12 weeks after the last injection. Urticaria activity score (UAS-7) and German version of Chronic Urticaria Quality of Life Questionnaire (CU-Q (2)oL) were used to evaluate the effectiveness of therapy

Results: we demonstrated a statistically significant improvement in UAS-7 score and (CU-Q(2)oL) Questionnaire in cases group after 9 weeks and after 12 weeks from last injection

Conclusion: The autologous serum therapy might prove to be a potent and probably curative treatment option for patients with chronic urticaria.

Key words: Autologous serum therapy, ASST, Chronic urticaria, UAS-7, CU-Q(2)oL

Introduction

Chronic idiopathic urticaria (CIU) is the most common type of chronic urticaria (CU), accounting for up to 90% of all cases of CU. It has been estimated that CIU affects between 0.6%⁽¹⁾ to 5%⁽²⁾ of individuals during their lifetime.

Approximately half of all cases of CIU may be caused by an autoimmune mechanism⁽³⁾. Diagnosing autoimmune urticaria (AU) can be rather challenging; diagnosis can be achieved either by in-vitro basophil-histamine release test, or by performing in-vivo autologous serum skin test (ASST)⁽⁴⁾.

It was observed that approximately 60% of CIU patients have a positive ASST represented as a wheal and flare reaction to intradermal autologous serum injections ⁽⁵⁾. The sensitivity of this test is estimated to be 65-81% and the specificity 71-78% ⁽⁶⁾.

Unfortunately, patients with AU are more treatment-resistant, and their disease runs a more aggressive course, than those with non-autoimmune CIU ⁽⁷⁾. Conventional approaches with high doses antihistamines are effective in about 50% of patients. Thus, there is an urgent need for novel and safer therapeutic modalities to improve the patients' quality of life.

Methods

Our study is a placebo-controlled single blind trial conducted on 60 patients with chronic autoimmune urticaria recruited from the allergy outpatient clinic at Ain Shams University hospitals. The study was approved by the Research Ethics Committee of Ain Shams University, and all participants gave informed consent to participating in the study.

All patients had a positive ASST according to the method by Sabroe et al. ⁽⁵⁾. Patients were randomized by block randomization (1:1 in 3 blocks of 20 patients) into two treatment groups:

Cases group (Autologous serum therapy (AST) group): 30 patients treated with deep intramuscular (IM) gluteal injection of 2ml autologous serum once weekly for 9 weeks. 5ml of venous blood was taken in a plain vacutainer, serum separated by centrifugation and 2 ml of the serum was injected intramuscularly to the patient. Cetirizine tablets 10 mg was taken 2 hours before the procedure to prevent side effects such as allergic reaction, hypotension, urticarial wheals and angioedema, and both groups were put under observation for 2 hours after the injection.

Control group: 30 patients treated with deep IM gluteal injection of 2 ml normal saline once weekly for 9 weeks. 5ml of venous blood was taken from the control group to ensure patients

were blinded as to which modality of therapy was administered.

All 60 patients were followed up after 12 weeks from the last (9th) injection.

Exclusion criteria included patients with urticaria < 6 weeks, patients with other allergic disorders as asthma, atopic dermatitis, allergic rhinitis, positive skin prick test, secondary causes of urticaria, patients on aspirin or steroids, associated renal, liver disease, pregnant and lactating females.

ASST was done as follows:

Venous blood was placed in sterile plastic tubes and allowed to clot at room temperature for 30 minutes. Then the serum was separated by centrifugation at 500 x g for 15 minutes and kept in aliquots for use in the ASST. Sample (50 µl) of autologous serum and 0.9% sterile saline (for negative control) were separately injected intradermally into the volar aspect of the patient's forearm skin with 27G needles, leaving gaps of at least 3cm. Intradermal test with histamine (10 µg/µl) was used as a positive control. Areas in which wheals had appeared in the last 24 hours before the test were avoided. Skin prick tests with histamine were interpreted after 15 minutes. Wheals and flare responses were measured after 30 minutes. A positive ASST was defined as a serum-induced wheal which is both red and has a diameter of 1.5 mm or more than the saline-induced response at 30 minutes ⁽⁸⁾.

Clinical Assessment

For all patients, severity of urticaria was assessed on basis of

1. Urticarial activity score (UAS-7) ⁽⁹⁾ at baseline, at 9 weeks and at 12 weeks of follow up after completion of therapy. Daily intensity of pruritus (range: 0 none to 3 severe) and number of hives ratings (range: 0 none to 3 more than 12 hives) are summed to create a daily UAS score (range: 0-6 points/day); daily UAS scores are summed over a week to create the UAS7 (range: 0-42) ⁽¹⁰⁾. According to the sum of the UAS-7 in one week, severity of urticarial was graded into:

Mild urticaria: UAS7=7-15, moderate urticaria: UAS7=16-27, severe urticaria: UAS7=28-42⁽¹¹⁾

2. German version of Chronic Urticaria Quality of Life Questionnaire (CU-Q(2)oL)⁽¹²⁾ which is further analyzed into 6 scales namely functioning, sleep, itching & embarrassment, mental status, swelling & eating and limitation of looks.

Data management and statistics

The clinical data were collected, verified, revised, coded, edited on a personal computer and analyzed using SPSS version 20. Descriptive analysis was done followed by inferential statistics. Level of significance of 0.05 was considered. The tests performed were mean, standard deviation (SD), t-test for independent samples, chi Square test, ANOVA test. ($p > 0.05$ = Non-significant, $p < 0.05$ = Significant, $p < 0.01$ = Highly significant)

Results

Tale 1 shows baseline characteristics of study population. The two studied groups were matched regarding gender, age and duration of urticaria.

In our current study AST was well-tolerated and only a few patients reported minor side effects in the form of rash, itching and dizziness just after the first injection in 6 cases (20%). Postural

hypotension for 12 to 24 hours was encountered in 3 cases (10%) white flashes of light were experienced in 2 cases immediately at time of injection and lasted for a few seconds (6%). As regard controls only one patient reported postural hypotension after injection. We did not notice any bruising at injection sites.

We found no statistically significant difference in UAS-7 between the two studied groups at baseline, and we demonstrated a statistically significant improvement in UAS-7 score in cases group after 9 weeks and after 12 weeks from last injection (figure 1).

For cases group, the mean CU-Q (2)oL score at baseline was 71 ± 24 (range 36-91), at week 9 was 48 ± 16 (range 30-82) and at week 12 from the last injection was 41 ± 14 (range 25-70). For control group, the mean CU-Q (2)oL score at baseline was 76 ± 11 (range 60-94), at week 9 was 67 ± 10 (range 50-82) and at week 12 from the last injection was 56 ± 8 (range 42-69). Although there was no statistically significant difference between the two studied groups at baseline, there was statistically significant improvement of the CU-Q(2)oL score at 9 weeks and at 12 week of follow up, denoting that AST was superior to placebo in improving the quality of life of enrolled subjects (figure 2).

Table (1): Comparison between the two studied groups regarding age, sex & duration of CU

	Cases		Control		P
Age in years					
Range	18-60		29-60		
Mean	39.95		45.2		0.087
S.D.	12.93		10.89		
Sex	No.	%	No.	%	
Male	9	30	15	50	0.089
Female	21	70	15	50	
Duration of CU in years					
Range	2-8		1-7		
Mean	4.25		3.65		0.254
S.D.	2.65		1.65		

Abbreviations: CU, chronic urticarial; S.D, standard deviation; UAS-7, Urticaria activity score.

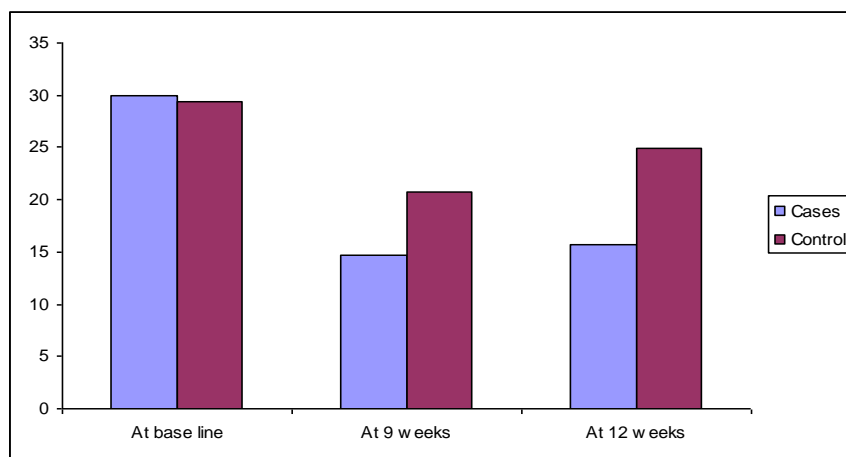


Fig. (1): Comparison between the two studied groups regarding UAS7 at different periods of follow up.'

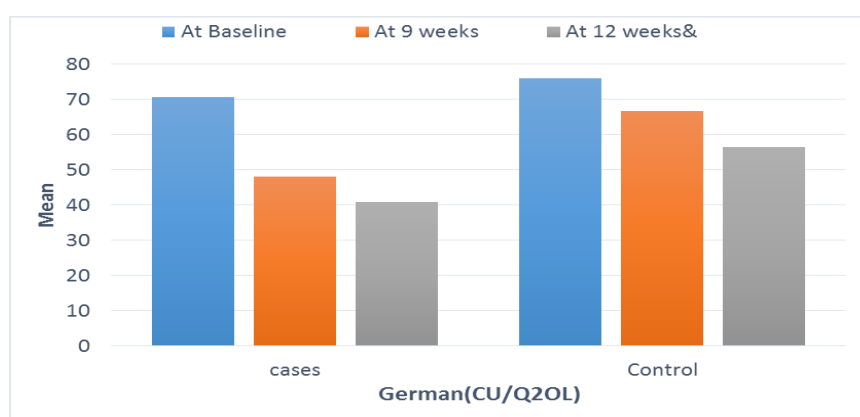


Fig. (2): Comparison between the two studied groups regarding German (CU/Q2OL) at different periods of follow up.

Discussion

Chronic urticaria (CU) is a common problem and negatively affects both work and social life because of its chronic relapsing course and poor response to therapy. Autohemotherapy, i.e. repeated intramuscular injections of autologous whole blood (AWB), was commonly used to treat patients with CU (before the development and introduction of antihistamines) with little evidence of scientific research. But several lines of evidence show that autohemotherapy is claimed to have therapeutic value in autoimmune diseases, circulatory disorders, viral diseases, cancer and atopic dermatitis⁽¹³⁻¹⁵⁾. AWB use in the treatment of CU was first documented by Fleck⁽¹⁶⁾ and was re-introduced by Staubach et al.⁽¹⁷⁾, in separate studies and the later use of serum in the treatment of urticaria was highlighted by Bajaj et al.⁽¹⁸⁾,

who emphasised the fact that the circulating autoreactive factors are present in the serum, not in the cellular components of blood. Moreover, bruising of injected skin has been reported by Staubach et al. with whole blood injections, which might have negatively affected the patients' compliance and hindered patients from completing long injection periods.

In our study injections were administered weekly for a period of 9 weeks, and both groups were reassessed after 12 weeks of receiving the last injection to detect development of tolerance. We specifically chose a 3-4 times longer follow-up duration than Staubach and co-workers⁽¹⁹⁾ did to accurately assess the longevity of the suppressive effect of this form of treatment. Patients were followed up 12 weeks after the last injection to

determine sustained tolerance after discontinuation of therapy.

In the cases group, 18 (59.9%) showed significant decrease in UAS score at 9 weeks enrollment compared to baseline. Moreover, a statistically significant difference was detected in UAS-7 score at the study completion (12 weeks) compared with UAS-7 score at baseline, indicating that subjects receiving autologous serum injections showed tolerance even after discontinuation of injections.

In our study, all six scales of CU/Q2OL were significantly lowered in the last follow up visit compared to baseline in both groups, and there was better improvement in CU/Q2OL in cases than controls.

Our study is consistent with Bajaj et al.⁽²⁰⁾ whose results indicate that almost 60% of ASST +ve patients showed a significant improvement in their signs and symptoms after 9 weekly ASI was given. More importantly, the study group has shown that improvement is sustained for at least 3-4 months after the last injection. However, the fore mentioned study used a different scoring system for assessing urticarial severity, the urticaria total severity score (USS) and also the study included ASST –ve patients.

Debbarman et⁽²¹⁾ al recently also stated that AST has enormous potential in the treatment of urticaria, as they demonstrated significant reduction in symptoms of urticaria (measured by TSS score) by 5th week of initiation of therapy that was superior to on-demand antihistamines and was accompanied by improvement of quality of life (measured by DLQI). The improvement that was evident from 5 th week of therapy continued even at six months which speaks for itself the usefulness of this therapeutic modality.

Similar to allergen immunotherapy, which induces clinical and immunological tolerance defined by persistence of clinical benefit and associated long-term immunological parameters after discontinuation of treatment⁽²²⁾, our data suggest a sustained benefit of AST in cases group as score values for virtually all outcome measures

remained unchanged for 12 weeks after cessation of treatment. Clinical improvement persisting after treatment discontinuation could account for long-term clinical tolerance. However, it might suggest that the study period may have been too short and that future trials should include follow-up assessments at later time points after the end of treatment. One possible mechanism is the stimulation of anti-idiotypic production against autoantibodies, which could block their binding to the high affinity IgE receptor FcεRI of mast cells or basophils. The second possibility could be tolerance induction to IgE or FcεRI. The third possible mechanism could be tolerance induction to other blood autoantigens or even foreign allergens. With autologous serum therapy, antigens, like a vaccine, are processed and presented to the immune system by muscular dendritic cells, with a different immune response priming potential that may convert a previously disease-causing antigen into a regulatory antigen that activates regulatory T cells, which could suppress effector T cells^(23,24).

Conclusion

We have demonstrated that the autologous serum therapy might prove as a potent and probably a curative treatment option for patients with chronic urticaria. Sterile injection technique is recommended, with proper labeling and careful injection technique advised to avoid transfer of infections. Although we do not know exactly how or when it works, AST could prove of great benefit especially if larger scale trials are conducted as it is economical, cost-effective and does not involve use of various expensive and hazardous drugs like cyclosporine and omalizumab. Further trials evaluating immunological biomarkers of tolerance, namely T-regulatory cells, with longer follow up periods are needed to confirm our findings.

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