Efficacy of autologous serum therapy in positive and negative autologous serum skin test patients in chronic urticaria in a tertiary care centre

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Abstract

Autologous serum therapy (AST) has been a recent therapeutic choice for a variety of chronic diseases such as allergic, inflammatory, infectious, and autoimmune disorders. However, evidence were not convincing of the beneficial effects of autologous serum therapy in treatment of Chronic urticaria (CU). CU is a common dermatological condition that is very disturbing to the patient as well as to the physician. A new observation was made about the abnormal type 1 reactions to intradermal autologous serum injections in some CU patients. This has led to the new subgroup of *autoimmune chronic urticaria*. The autologous serum skin test (ASST) is an intradermal test result in immediate hypersensitivity-type skin reactions in a subpopulation of CU patients and it's giving promising evidence of therapeutic and diagnostic benefit. Autologous whole blood injection has already been used as one of the old treatment modalities for chronic urticaria. The objectives of this study/reasearch are to analyse the efficacy of autologous serum therapy in patients with chronic urticaria and compare its results in ASST(+) and ASST(-) chronic urticaria patients. Approximately 5 mL of patients' blood was drawn in a plain vacutainer and centrifuged at 3000 r.p.m. for 10 min, separated 2.5 mL serum injected deep intramuscularly into gluteus muscle. Injections were repeated every week for about 9 weeks and a repeat follow up at 20 weeks was done. Out of a total of 20 patients, excellent improvement in terms of decrease in Urticaria assessment severity score was seen in 6 patients; whereas, 10 patients showed partial response, 2 patients showed no response and 2 patients lost the follow up. 10 patients with ASST(+) and 6 patients of ASST(-) showed little improvement in urticaria severity score. AST therapy is a cost-effective adjuvant modality to reduce the severity of symptoms of chronic urticaria. In some patients it's giving long term remission period and it decreases the updosing of antihistamines.

Introduction

Chronic urticaria (CU) is a common skin condition characterized by the appearance of evanescent wheals and itch for more than six weeks. Usually it occurs because of degranulation from cutaneous mast cells leading to extravasation of plasma in the dermis.[1] A diagnosis of Chronic Idiopathic Urticaria (CIU) is usually made after evaluating all the possible causes of urticaria. In 1993, Hide *et al.*[2] partially resolved this condition of urticaria when he reported that there are autoantibodies against the high-affinity IgE receptor, FcεRIα that results in release of histamine in a subset of CU patients. Further studies reported that 27-61% of CU patients,[3-6] had these circulating antibodies in their blood. Thus, chronic autoimmune urticaria (CAU, 45%) and chronic idiopathic urticaria (CIU, 55%) are the two subgroups classified, and the total incidence of both variants is 0.5%.[7] These above findings helps to explain why some patients with CU responded well to corticosteroids and other immunosuppressive drugs and very poorly to antihistaminics.

Autologous serum skin test (ASST) has been a simple opd basis method to screen a group of patients with chronic autoimmune urticaria (CAU).[8] Intradermal injection of autologous resulted in immediate hypersensitive type skin reactions characterised by developing wheal and flare response which indicates that the role of a circulating histamine-releasing factor. The ASST has been reported to be positive in 41~67% of all CU patients.[2,6,9]

Individual and combination treatments of antihistamines, anti-inflammatory drugs, immuno-suppressants, monoclonal antibodies directed to immunoglobulin E, and antidepressants have been used as treatment regimens for chronic urticaria.[10,11] However, few cases have been found refractory and most of the regimens were less cost effective. Autologous whole blood (AWB) therapy has been tried in treatment of diseases such as allergic, inflammatory, infectious, and autoimmune disorders.[12] A study by Staubach *et al.*[13] has shown that autologus whole blood therapy is effective in ASST-positive CU. Autologus Serum therapy (AST) is derived from AWB by centrifuging the cellular components of blood for intramuscular injections. After centrifuging, the blood obtained serum is injected which is less painful for the patients and easier to administer without reducing its efficacy.[14] The advantage of autologous serum in place of whole blood is the fact that the circulating autoimmune factor is present in the serum, not in the cellular components of blood. Also, finer needles can be used for injection which reduces the patient's discomfort and results in increasing compliance; moreover, the serum can be kept for a few hours, but whole blood has to be injected soon to prevent clots.[15,16]

We conducted the prospective, open label study of autologous serum therapy in patients with CU in both ASST(+) and ASST(-). Thus, we examined its effects on severity parameters and we compared the efficacy in both groups.

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Materials and Methods

All the clinically diagnosed cases of urticaria after excluding the causes of urticaria were having almost daily appearance of wheals for ≥6 months, age >18 and <70yrs with willingness for weekly follow-up and injections included in the study. The patients having history of predominantly physical urticaria, systemic corticosteroid or immunosuppressive drug use in the past

6 weeks, pregnancy, other systemic illnesses and HIV positive/HBsAg positive and those who are not willing for consent were excluded.

Demographic details were recorded and detailed history of disease including history of atopy was taken. A total of 20 patients with CU were taken up for study after taking all the criteria into consideration with informed and written consent. They were screened for ASST test following which they were advised nine weekly intramuscular injections and at least one post treatment follow-up after the ninth injections. Long acting antihistamines were withdrawn at least 3 weeks before and short-acting ones 48 hrs before ASST testing. The procedure of autologous serum skin tests follows. Approximately 5 mL of blood in a plain vacutainer was centrifuged at 3000 r.p.m. for 10 min. After serum was separated 0.1 mL of autologous serum and normal saline were injected intradermally at least 5 cm apart on the volar aspect of the forearm. The results were measured at baseline and after 30 mins. ASST was considered positive when the average of diameters of the autologous serum wheal was ≥1.5 mm more than the normal saline wheal. Rescue short acting antihistamine was permitted as in the run-in period; no other drugs were permitted. Disease activity and severity were recorded on a 0-3 scale (Table 1) at baseline (0 week), end of treatment (9 weeks) and follow-up (20 weeks).[17] All statistical analysis was done using percentage and bar graphs and Chi-Square test to assess the therapeutic response.

Results

The median age of patients was 25 years (range 21-30 years). There was equal distribution of 10 ASST(+) and 10 ASST(-) in the study population. Patients in both groups showed a downward trend in Urticaria Activity Score (UAS) from baseline to the end of treatment. There was partial improvement seen in 10 patients (50%) and complete response in 6 (30%) patients, seen in terms of decrease in UAS, whereas 2 patients (10%) showed no response and 2 patients (10%) lost for follow up. Chi-square test showed a significant P value of 2.80. Hence there was a strong statistical significance seen. Out of 10 ASST(+) patients 5 patients (50%) showed complete response and 5 patients (50%) showed partial response. Out of 10 ASST(-) patients, 1 patient (10%) showed complete response and 5 patients (50%) showed partial response, 2 patients showed no response at all and 2 patients were lost for follow up. Mean response was significant at nine weeks and continued even after the injections were stopped in both groups. The fall was 100% at the 9th week in ASST(+) patients *versus* a fall of only 60% in ASST(−) patients. The response to therapy in both groups of patients is depicted in a pie chart (Figure 1). A mixed response was noticed at the 20th week follow up, out of 13 patients who came for follow-up, only 4 patients were satisfied with the therapy. 9 patients needed antihistaminic supplementation intermittently but with reduced severity.

Discussion

Autologus serum therapy brings us one step closer to relieving the patient of this unwanted condition the patient is suffering from. As we know mast cell degranulation is the key factor in the pathogenesis of urticaria, the reason for degranulation is a mystery, and the term *idiopathic* is used in this type of urticaria. Further research have shown antibody to high-affinity IgE receptor (FcεRI) is found to degranulate the mast cell with binding to the IgE receptors.

In our study population, 50% (10 out of 20) were found to be suffering from autoimmune urticarial which were similar to most previous studies.[4,5] Still the gold standard test to diagnose the antibodies to FcεRI is basophil histamine release assay only and the *in-vivo* analogue of this test is ASST.[18] At present, these tests are only carried out in a few laboratories and are not available in all set ups. ASST test is a simple easy non-specific screening test which finds the presence of serum histamine-releasing factors of any type and to detect the autoantibodies against the IgE receptor.[19,20]

Chronic urticaria patients with positive ASST are usually associated with HLA DR4; some of them have a autoimmune thyroid disease, a more long and refractory disease course and may be more resistant and recalcitrant to H1-antihistamine treatment than patients with a negative ASST.[10]

Till date antihistamines and leukotriene inhibitors are a drug of choice for urticaria management . In some cases immunosuppressive agents are needed for controlling urticaria symptoms and mainly they work by preventing the degranulation by averting the antibody formation. The immunosuppressive agents have more side effects and it's very difficult to manage the addictive and more serious adverse reactions. The main objectives in the treatment of urticaria are neutralizing the effects of degranulation and preventing mast cell degranulation.

Chronic urticaria is a condition with variable course and the treatment has to be continued till the patient goes into remission. Symptom-free period and reducing the pill burden have been patients' demands and clinicians' targets for a long time. Still, there is a need for newer therapeutic modality along with the antihistamines and leukotriene inhibitors. Many cost-effective adjuvant and innovative therapy have been under trials. Our study explores the use of serum instead of the use of whole blood which has been tried for various conditions including Chronic urticaria.

Our study has shown that AST was an effective adjuvant treatment in both ASST(+) and ASST(−) patients. In our study, there was partial improvement seen in 10 patients (50%) and complete response in 6 (30%) patients, seen in terms of

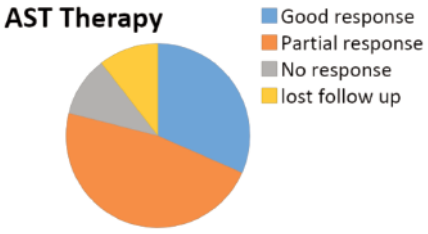

Figure 1. Response to autologous serum therapy (AST).

Table 1. Urticaria severity assessment score.[15]

Score	Wheals	Pruritus
0	None	None
1	Mild (<20 wheals/24 hr)	Mild (present but not annoying or troublesome)
2	Moderate (20-50 wheals/24 hr)	Moderate (troublesome but does not interfere with sleep)
3	Intense (>50 wheals/24hr or large confluent areas of wheals)	Severe (interferes with sleep)

decrease in UAS, whereas 2 patients(10%) showed no response and 2 patients(10%) lost for follow up. Out of 10 ASST (+) patients, 5 patients (50%) showed complete response and 5 patients (50%) showed partial response. Out of 10 ASST(-) patients, 1 patient (10%) showed complete response and 5 patients (50%) showed partial response, 2 patients showed no response at all and 2 patients were lost for follow up.

A study by Staubach, *et al.*[13] showed that ASST positive patients markedly improved UAS after AWB therapy (41%), as compared to ASST positive patients who received placebo (18%) or ASST negative patients that had been treated with AWB (21%) or placebo (11%).The quality of life in ASST positive, AWB treated CIU patients improved after therapy.[2]

A study by Bajaj *et al.*[16] showed in that in an ASST positive group, 35.5% of patients were completely asymptomatic at the end of the follow up, while an addition of 24.2% were markedly improved. In the ASST negative, these figures were only 23%. The *inter* group difference for complete subsidence was statistically significant ($P<0.05$).[3]

In their study, Patil *et al.*[14] gave autologous serum therapy to 20 ASST positive patients. There was an excellent improvement in 9 patients wheareas 6 patients did not show a satisfactory response and 5 patients showed no response at all. This study is not followed-up by specific parameters over a time period.[5]

Jonathan Te-Peng Tseng *et al.* showed 8 (88%) of the 9 ASST(+) patients with CU responded to treatment with AWB injection. Only 2 (25%) of the 8 ASST(–) patients showed response to the treatment.

However, recent therapy for refractory and resistant chronic urticaria is biologics. The omalizumab has been showing promising results by giving long term remission and other drugs off label such as dupilumab, reslizumab, mepolizumab, and benralizumab. But cost effective and maintenance parameters are not in favour of using this with poor patients.[21,22] The omalizumab treatment is currently the best option for chronic urticaria, which is resistant to antihistaminics. In ASST positive urticaria, usage of omalizumab does show significant difference in therapeutics response compared to ASST negative patients. In developing and economical poor countries, AST therapy is still a better option compared to biologics.[23]

Thus, in our study, we found that improvement in urticaria symptoms was evident in both autoimmune and non-autoimmune urticarial patients, nevertheless more efficiently in the autoimmune group. It has been a satisfactory effort in reducing the monetary burden with less hazards and in maintaining a symptom-free period in chronic urticaria patients. However, the time duration till this therapy effect lasts is yet uncertain and it needs further trials. A significant drawback of this study was its uncontrolled and unblinded nature. The placebo group was not chosen, as most cases were the once refractory to conventional therapy. A larger placebo-controlled study with unselected CIU patients is warranted to assess the utility of this therapy in our patients. The duration until when the therapy is going to be effective was not determined.

References

1. Kaplan AP, Greaves M. Pathogenesis of chronic urticaria. Clin Exp Allergy 2009; 39:777-87.
2. Hide M, Francis DM, Grattan CE, et al. Autoantibodies against the high affinity IgE receptor as a cause of histamine release in chronic urticaria. N Engl J Med 1993;328:1599-604
3. Godse KV. Autologous serum skin test in chronic idiopathic urticaria. Indian J Dermatol Venereol Leprol 2004;70: 283-4.
4. Fiebiger E, Maurer D, Holub H, et al. Serum IgG autoantibodies directed against the alpha chain of Fc epsilon RI: A selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? J Clin Invest 1995;96: 2606-12.
5. Ferrer M, Kinet JP, Kaplan AP. Comparative studies of functional and binding assays for IgG anti Fc epsilon Riα (α-subunit) in chronic urticaria. J Allergy Clin Immunol 1998;101:672-6.
6. Piconi S, Trabattoni D, Iemoli E, et al. Immune profiles of patients with chronic idiopathic urticaria. Int Arch Allergy Immunol 2002;128:59-66.
7. Kaplan AP. Urticaria and Angioedema. In: Wolff K, Goldsmith LA, Katz SI, et al., eds. Dermatology in General Medicine. 7th ed. New York: McGraw-Hill; 2008. pp 330-43.
8. Sabroe RA, Grattan CE, Francis DM, et al. The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. Br J Dermatol 1999;140:446-52
9. Asero R, Tedeschi A, Lorini M, et al. Chronic urticaria: novel clinical and serological aspects. Clin Exp Allergy 2001;31:1105-1110, 2001.
10. Konstantinou GN, Asero R, Maurer M, et al. EAACI/GA2LEN task force consensus report: the autologous serum skin test in urticaria. Allergy 2009;64:1256-68.
11. Grattan CE, Humphreys F. Guidelines for evaluation and management of urticaria in adults and children. Br J Dermatol 2007; 157:1116-23.
12. Behl PN. Practice of Dermatology. 7th edition. New Delhi: Oxford Blackwell Scientific publications; 1990. Autohaemotherapy; p. 76.
13. Staubach P, Onnen K, Vonend A, et al. Autologous whole blood injections to patients with chronic urticaria and a positive autologous serum skin test: a placebo-controlled trial. Dermatology 2006; 212:150-9.
14. Bajaj AK, Saraswat A, Upadhyay A, et al. Autologous serum therapy in chronic urticaria: old wine in a new bottle. Indian J Dermatol Venereol Leprol 2008;74:109-13.
15. Maurer M. Chronic urticaria, Chapter 5.2. Urticaria and angioedema. In: Zuberbier T, Grattan C, Maurer M., Eds. New York: Springer International 2010. pp. 45–54.
16. Patil S, Sharma N, Godse K. Autologous serum therapy in chronic urticaria. Indian J Dermatol 2013;58: 225-6
17. Schoepke N, Doumoulakis G, Maurer M. Diagnosis of urticaria. Indian J Dermatol 2013;58: 211-8
18. Grattan CE, Sabroe RA, Greaves MW. Chronic urticaria. J AmAcad Dermatol 2002;46:645-57.
19. Zuberbier T, Asero R, Bindslev-Jensen C, et al. EAACI/GA2LEN/EDF/WAO guideline: Management of urticaria. Allergy 2009;64:1427-43.
20. Zuberbier T, Bindslev-Jensen C, Canonica W, et al.: EAACI/GA2LEN/EDF guideline: definition, classification and diagnosis of urticaria. Allergy 2006;6:316-20.
21. Kolkhir P, Altrichter S, Munoz M, et al. New treatments for chronic urticaria. Ann Allergy Asthma Immunol. 2020 Jan;124:2-12.
22. Wedi B. Emerging treatments for chronic urticaria. Expert Opin Investig Drugs. 2022;31:281-90.
23. Metz M, Vadasz Z, Kocatürk E, Giménez-Arnau AM. Omalizumab updosing in chronic spontaneous urticaria: an overview of real-world evidence. Clin Rev Allergy Immunol 202;59:38-45.