Original research article

Evaluation of Autologous Serum Therapy in Patients with Chronic Idiopathic Urticaria

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Abstract

Background: Chronic urticaria (CU) is one of the important challenges faced by dermatologists. Chronic autoimmune urticaria (CAU, 45%) and chronic idiopathic urticaria (CIU, 55%), are the 2 main subtypes of CU, with a combined incidence of 0.5% in the general population. Patients with chronic urticaria who frequently exhibit histamine-releasing autoantibodies and who frequently experience wheals and flares in response to intradermal testing with their sera are referred to as having autoimmune urticaria. The current study aimed to evaluate the efficacy of Autologous Whole Blood Therapy, in Autologous Serum Skin Test (ASST) positive and ASST negative Chronic Idiopathic Urticaria (CIU) patients.

Methods: Group (S): n=25 positive ASST for eight weeks, deep intramuscular, gluteal injections of autologous whole blood were administered to CIU patients. The median cubital vein was used to draw blood, which was then immediately injected intramuscularly. Group I (N): n=25 ASST-negative CIU patients received treatment with an 8-week course of once-weekly deep intramuscular gluteal injections of autologous whole blood. Eight IM injections were given to each group. Each successive injection was 5 ml after the initial 2.5 ml dosage. At the 0^{th}, 6^{th}, 8^{th}, and 12^{th} weeks, each of the 50 patients were assessed. The Urticaria severity scale was used to underpin the clinical evaluation (USS).

Results: At the baseline at 0 weeks both groups have no cases in the mild category and the group (S) 68% were in a severe category as compared to 12% of the group (N) the p values were not found to be significant. At the end of 4 weeks, none of the cases were in the mild category however, cases in the severe category decreased from 68% at the starting point in Group (S) to 20% at the end of 4 weeks. In group (N) the decrease was from 12% in the severe category to 8% at the end of 4 weeks. At the end of weeks of treatment, no cases remained in the severe category of group (S) and group (N) the number of cases increased to 40% in the mild category from zero percent at the end of 4 weeks in the group (S). Similarly in group (N), no cases were present in the severe category and the maximum number of cases were in the moderate category. At the end of 3 months (12 weeks), 88% of cases in the group (S) and 80% of cases in group (N) were converted to the mild category of USS.

Conclusion: This study demonstrates that autologous whole blood treatment (AWBT) works well in CIU and only has mild side effects. The effectiveness of AWBT has been demonstrated in several previous studies, including this one. Individuals with urticaria who test positive for ASST respond to AWBT a little bit better than ASST-negative patients do. In

this study, we have found that people with urticaria who are ASST-positive get more benefits from AWBT/autohemotherapy than ASST-negative individuals.
Keywords: Chronic Idiopathic Urticaria (CIU), Autologous Serum Skin Test (ASST), Autologous Whole Blood Therapy (AWBT), Urticaria Severity Scale (USS)

Introduction

Itching is a common symptom of urticaria, a temporary eruption of erythematous or oedematous swelling of the dermis. Heberden first described urticaria (which is derived from the Latin word (Urtica, which means nettle), or nettle rash, in 1772, saying that "the little elevations on the skin in the 'nettle' rash often appear involuntarily, especially if the skin be rubbed, or scrubbed, and seldom stay for many hours in the same place, and sometimes not many minutes. Angioedema may accompany wheals in almost all clinical patterns of urticaria, but the presence of isolated angioedema (without wheals) is significant since some of these individuals will lack a C1 esterase inhibitor (C1 INH). A particular physical stimulation can cause repeatable wheezing in people with physical urticarias, a subtype of urticarias. The appearance of wheals can take many hours after the physical stimulation in a few types of physical urticaria, such as delayed dermographism, delayed pressure urticaria, and the uncommon delayed cold urticaria. Urticaria is frequently a symptom of anaphylaxis, even though it seldom advances to that state. In addition to the best medication therapy, effective management of urticaria requires a full understanding of the etiologies, triggers, and exacerbating variables. A prevalent and difficult dermatosis known as chronic urticaria (CU) is defined by the emergence of transient wheals on most days for more than six weeks. Even though the word is frequently used interchangeably with chronic ordinary urticaria, chronic urticaria of at least six weeks' length can also be physical or urticarial vasculitis. It is a clinical diagnosis that calls for extensive history-taking, pertinent testing, and the exclusion of physical, drug-induced, and infection-related urticaria. Previously autoimmunity was identified as the cause, most sufferers were thought to have "idiopathic" urticaria. Clinical evidence reveals that chronic urticaria is frequently a complex illness and that an endogenous cause works in concert with extrinsic aggravating variables to define its daily activity. Hide et al., [1] showed that autoantibodies against the high-affinity IgE receptor, FcRI, produce histamine release in a subset of individuals with CU, this problem was largely overcome. According to further studies, 27–61% of CU patients have these circulating antibodies in their blood, depending on the type of antibody testing. [2-5] The autologous serum skin test was shown to be the most straightforward screening technique to detect this group of individuals with what was known as chronic autoimmune urticaria (CAU) (ASST). [6] Chronic urticaria in certain people seems to be a symptom of a particular autoimmune condition. No histamine-releasing factor can be found in vivo or in vitro in the remaining 50% of patients, and the causes of this are still unknown. Other non-antibody variables can also be at play. The presence of histamine-releasing autoantibodies in cholinergic or physical urticaria has not been shown. These patients' immediate-type wheals and flares in response to intradermal injection of autologous serum indicated the existence of circulating histamine-releasing factors. According to reports, these CAU patients had more wheals with a broader distribution, more intense pruritus, and more regular systemic symptoms. [7] These studies contributed to the understanding of why certain CU patients reacted favorably to corticosteroids and immunosuppressive medications but poorly to H1 antagonists. The effectiveness of autologous whole blood treatment (AWBT) in CAU, where patients get weekly intramuscular injections of whole blood, was recently reported by Staubach et al., [8] Recently, this method of therapy was widely used to treat several disorders, including atopic

dermatitis, CU [9] and others, but it has mostly been abandoned as being "unscientific." This study aims to evaluate the effectiveness of autologous whole blood treatment (AWBT) in patients with chronic urticaria who are ASST positive and ASST negative.

Material and Methods

The present study was conducted in the Department of Dermatology, Osmania Medical College and Hospital, Hyderabad, Telangana State. Institutional Ethical approval was obtained for the current study. Written consent was obtained from all the participants of the study after explaining the nature of the study in the local language with all possible outcomes. Only those voluntarily willing to participate in the study were included.

Inclusion criteria

1. Chronic idiopathic urticaria
2. Males and females
3. Aged 18 years of age or older

Exclusion criteria

1. Physical Urticaria
2. Urticarial Vasculitis
3. Pregnancy and Lactation
4. Immunocompromised patients
5. Patients on Systemic corticosteroid or immunosuppressive drugs used in the
6. past 6 weeks
7. H/O Bronchial Asthma

All the patients who met the requirements for inclusion underwent thorough systemic, dermatologic, and general physical examinations as well as meticulous history collection. Blood tests were done to rule out systemic diseases, collagen vascular diseases, immunosuppression, infestation and infections, and pregnancy. The tests were done when suspected by relevant history. Antihistamines were stopped for 3 days and then on the fourth day, an "Autologous serum skin test" was done to categorize the CIU patients into ASST-positive and ASST-negative cases. A total of n=50 cases were included they were divided into two groups. Group (S): n=25 positive ASST for eight weeks, deep intramuscular, gluteal injections of autologous whole blood were administered to CIU patients. The median cubital vein was used to draw blood, which was then immediately injected intramuscularly. Group I (N): n=25 ASST-negative CIU patients received treatment with an 8-week course of once-weekly deep intramuscular gluteal injections of autologous whole blood. Eight IM injections were given to each group. Each successive injection was 5 ml after the initial 2.5 ml dosage. The Urticaria Activity Score (USS) was used to determine disease severity and response to treatment. [10] based on the scores it was graded as Mild (USS 1-6), Moderate (USS 7-12), and Severe (USS 13-18). Post administration of AWBT, the patient was put under observation for 30 min to look for immediate adverse effects. The patients were advised to take the antihistamines only if they developed significant breakthrough urticaria. The antihistamine advised was Tab Fexofenadine 180 mg in all the patients. At the 0^{th}, 6^{th}, 8^{th}, and 12^{th} weeks, each of the n=50 patients was assessed. Side effects of pain and injection site changes in skin and soft tissue were observed

Results

A total of n=50 patients were enrolled in this study based on the inclusion and exclusion criteria n=25 Group (S): n=25 positive ASST and Group I (N): n=25 ASST negative cases.

All the patients completed the study and were available for final assessment at 12 weeks after 4 weeks of follow-up. Most of the cases belonged to the age group 21 – 30 years with a combined strength of n=23(66%) followed by the age group 31 – 40 years with a total strength of n=16(36%). This indicated that the ASST was more common in the younger age group as compared to the older ages. The age-wise and group-wise distribution of the cases included in the study has been depicted in table 1.

Table 1: showing the age-wise distribution of the cases included in the study

Age group (years)	***Group (S)***		***Group (N)***		*Total*	
	Frequency	*percentage*	*Frequency*	*percentage*	*Frequency*	*percentage*
21 – 30	11	44.00	12	48.00	23	66.00
31 – 40	10	40.00	08	32.00	18	36.00
41 – 50	03	12.00	05	20.00	08	16.00
51 - 60	01	04.00	00	00.00	01	04.00
Total	25	100	25	100	50	100.00

The sex-wise distribution of the cases showed in Group (S) out of n=25 cases n=15(60%) were males and n=10(40%) were females. Similarly in Group (N) out of n=25 cases, n=14(66%) were males and n=11(44%) were females. There were no significant differences in gender of the patients found between ASST positive Group (S) and ASST negative Group (N) cases as the p-values were found to be greater than 0.05.

Table 2: Showing the duration of diseases in two groups of patients in the study

Disease duration	***Group (S)***		***Group (N)***	
	Frequency	*percentage*	*Frequency*	*percentage*
1 – 6 months	2	08.00	9	36.00
7 – 12 months	4	16.00	6	24.00
1 – 3 years	8	32.00	7	28.00
3 – 4 years	6	24.00	2	08.00
> 4 years	5	20.00	1	04.00
Total	25	100.00	25	100.00

A critical analysis of table 2 revealed that ASST Positive (Group S) cases had the disease which is of longer duration 3 – 4 years in 44% of cases whereas a similar comparison of ASST Negative (Group N) cases the disease was less than one year in duration in 60% of cases.

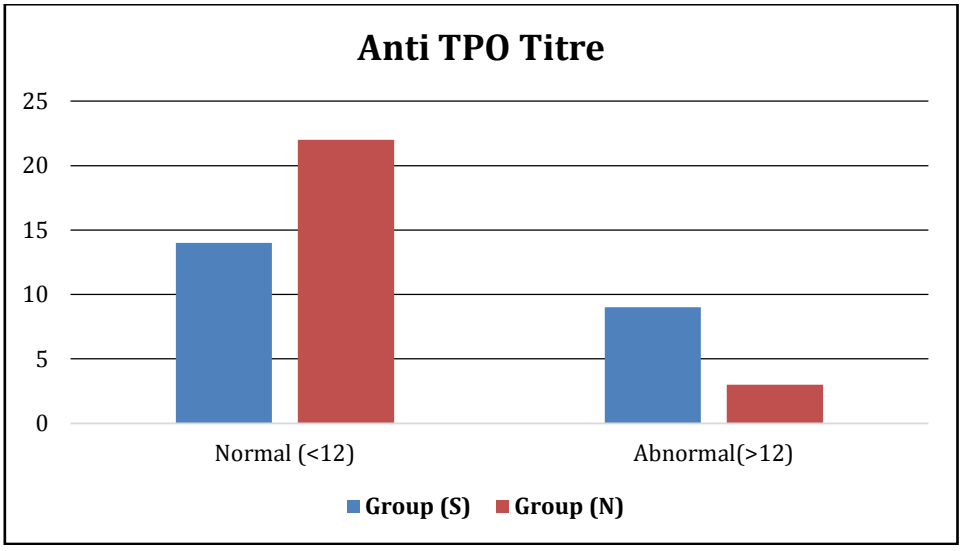

Figure 1: Levels of Anti-TPO titers in the cases of study

Out of n=50 cases in the study n=9(36%) in Group (S) and n=3(12%) in Group (N) were found with high anti-thyroid peroxidase (TPO) antibodies. There was a significantly higher association of Anti-thyroid peroxidase antibodies in the group (S) ASST positive cases as compared to the group (N) ASST negative cases. The p values were calculated to be <0.012 and hence considered significant depicted in figure 1.

Table 3: USS recorded in two groups at different intervals of the study

Week	*USS grade*	*Group (S)*		*Group (N)*		*P value*
		Frequency	*percentage*	*Frequency*	*percentage*	
0 week	***Mild***	**0**	**00.00**	**0**	**00.00**	**0.958**
	Moderate	**8**	**32.00**	**22**	**88.00**	
	Severe	**17**	**68.00**	**3**	**12.00**	
4 weeks	***Mild***	**0**	**00.00**	**0**	**00.00**	**0.521**
	Moderate	**20**	**80.00**	**23**	**92.00**	
	Severe	**5**	**20.00**	**2**	**08.00**	
8 weeks	***Mild***	**10**	**40.00**	**4**	**08.00**	**0.171**
	Moderate	**15**	**60.00**	**21**	**84.00**	
	Severe	**0**	**00.00**	**0**	**00.00**	
12 weeks	***Mild***	**22**	**88.00**	**20**	**80.00**	**0.026***
	Moderate	**3**	**12.00**	**5**	**20.00**	
	Severe	**0**	**00.00**	**0**	**00.00**	

*** Significant**

At the baseline, at 0 weeks both groups have no cases in the mild category and the group (S) 68% were in a severe category as compared to 12% of the group (N) the p values were not found to be significant. At the end of 4 weeks, none of the cases were in the mild category however, cases in the severe category decreased from 68% at the starting point in Group (S) to 20% at the end of 4 weeks. In group (N) the decrease was from 12% in the severe category to 8% at the end of 4 weeks. At the end of weeks of treatment, no cases remained in the severe category of group (S) and group (N) the number of cases increased to 40% in the mild category from zero percent at the end of 4 weeks in the group (S). Similarly in group (N), no cases were present in the severe category and the maximum number of cases were in the moderate category. At the end of 3 months (12 weeks), 88% of cases in the group (S) and

80% of cases in group (N) were converted to the mild category of USS. The details have been depicted in table 3.

Table 4: Improvement in USS score after treatment in both groups

Improvement of USS score	***4 weeks***	***8 weeks***	***12 weeks***
Group (S)			
Poor (<25%)	**13**	**4**	**0**
Satisfactory (26 – 50%)	**12**	**16**	**2**
Good (51 – 75%)	**0**	**4**	**20**
Excellent (> 76%)	**0**	**0**	**3**
Group (N)			
Poor (<25%)	**23**	**12**	**3**
Satisfactory (26 – 50%)	**2**	**13**	**19**
Good (51 – 75%)	**0**	**0**	**3**
Excellent (> 76%)	**0**	**0**	**0**
p-value	**0.225**	**0.041***	**0.002***

*** Significant**

The percentage improvement in USS score was evaluated from 0 weeks which was considered as the baseline. Based on it, they were classified as Poor (<25% improvement), Satisfactory (26-50%), Good (51-75%), and Excellent (> 76%). In group (S) at 4 weeks, n=13 cases showed poor improvement n=12 showed satisfactory improvement similarly, at the end of 8 weeks n=20 showed good improvement and n=4 cases were still showing poor improvement. At the end of 12 weeks, n=23 cases showed good and excellent improvements, and n=2 cases were having satisfactory improvement as depicted in table 4. In group (N) at the end of 4 weeks, n=23 cases were showing poor improvement and n=2 cases were having satisfactory improvements. Similarly, at the end of 8 weeks, n=13 cases were showing satisfactory improvement, and n=12 cases still with poor improvement. At the interval of 12 weeks, n=22 cases were showing good and excellent improvement and n=3 cases were showing satisfactory improvement. The p-value analysis at the end of 4 weeks remained insignificant however, at the end of 8 weeks and 12 weeks the values were found to be significant as given in table 4.

Rescue antihistaminics were given to both negative and positive individuals to treat the symptoms. Patients have been prescribed 1 to 3 tabs of Fexofenadine 180 mg daily, while others only needed it once or twice a week. Out of N=25 patients of the group (S) at baseline evaluation, 56% of cases required 3 tabs of rescue fexofenadine every day, 40% required 2 tablets, and 4% required a single dose. At the end of 4 weeks, 2 doses were required in 80% of cases and three doses in 4% of cases. At the end of 8 weeks, none of the cases required 3 doses, and 68% of cases required only a single dose. At 12 weeks 72% of cases required a single dose and 28% required 2 doses depicted in figure 2. A similar trend of decrease in dose requirement of antihistaminics was observed in the group (N) as the duration of the treatment progressed and at the end of 12 weeks, 84% required a single dose, and 16% required 2 doses given in figure 2.

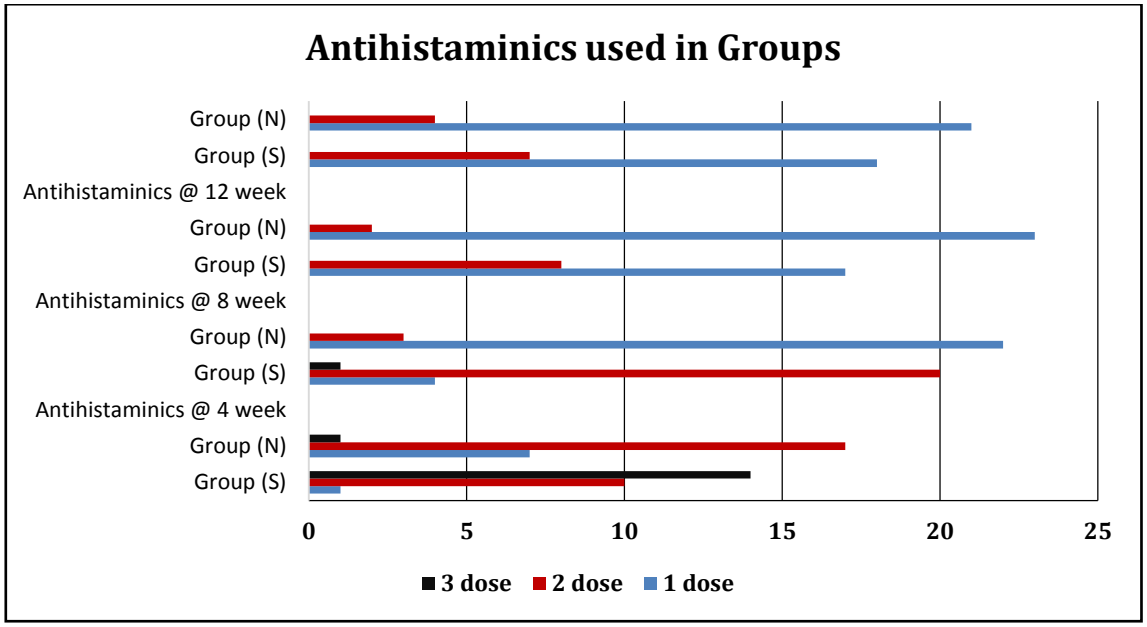

Figure 2: Anti-histaminics used in both the groups of cases at various intervals

Adverse Effects: Few incidences of adverse effects seen in both Group (S) and Group (N) were pain at the injection site and an increase in symptoms. In group (S) 16% of patients had injection site pain and one patient saw an increase in urticaria symptoms. In group (N) pain at the injection site was present in 20% of cases and 8% found a transient increase in symptoms in the duration of the first 4 weeks which gradually disappeared subsequently.

Discussion

The unpleasant dermatosis known as Chronic Idiopathic Urticaria (CIU) is frequently seen in dermatology outpatient clinics. There is a range of clinical manifestations and reasons for CIU. The anxious patient often changes dermatologists in the hopes of finding a treatment. Despite a dermatologist's best efforts, most of the time there is no cause. The high-affinity IgE receptor FcRI on basophils and mast cells or, less frequently, antibodies to IgE, are targets of circulating histamine-releasing autoantibodies in around 45% of individuals with CIU. Patients with CIU that is ASST positive experience severe, protracted disease. To regulate their symptoms, they need a large dose of antihistamines. For ASST-positive CIU, well-established therapeutic options include Steroids, Cyclosporine, and Omalizumab. Most of the cases belonged to the age group 21 – 30 years with a combined strength of n=23(66%) followed by the age group 31 – 40 years with a total strength of n=16(36%). This indicated that the ASST was more common in the younger age group as compared to the older ages. The age of the patients in this research varied from 21 to 52 years for Group (S) and from 21-53 years for Group (N). Most of the cases belonged to the age group 21 – 30 years with a combined strength of n=23(66%) followed by the age group 31 – 40 years with a total strength of n=16(36%). This indicated that the ASST was more common in the younger age group as compared to the older ages. The results are in concordance with the findings of Bajaj et al., [11] who carried out a multicentre, prospective, open-label study of autologous serum treatment in individuals with chronic urticaria. In Group (S), the mean age was 24.12 years, while in Group (N), the mean age was 24.5 years. We found CIU more common in males. The gender distribution of the CIU depends on the geographic location and the population of the sample derived. This was similar to an Indian study, a double-blind, parallel-group, randomized, controlled study in CIU by P. Debbarman et al., [12] they found Males outnumbered females. Males were 61% and females 39%. Similarly in this study

patients were young adults or middle-aged (mean age ranged from 25 to 43). We found CIU with ASST positivity group (S) and had prolonged illness duration (table 2). Similar findings were reported by Staubach et al., [59] group (S) patients reported having had their condition for longer than group (N) ASST negative. According to Bajaj et al., [11], patients in group (S) had urticaria for 6 months to 32 years, whereas those in the group (S) had urticaria for 6 months to 10 years. In our study, the group (S) at baseline demonstrated severe USS has severe 68% followed by 32% with moderate USS. In group (N) at the baseline, 88% were with moderate USS and 12% were with severe USS none of the cases in both groups had mild USS at the baseline (table 3).

Bajaj et al., [11] found a significantly higher proportion of ASST-positive patients were classified as having severe urticaria compared to the ASST-negative group at baseline (91.9 vs. 69.2%; P = 0.02). Hence, we found the duration of the disease was longer, and more severe in patients with positive ASST than in patients with negative ASST CIU, as was seen in studies done by Krupashankar DS et al., [14] and ZA Azeem Sabroe et al., [15] Both the group (S) and group (N) CIU showed improvement following therapy. Group (S) ASST positive CIU improved by 68%, whereas group (N) ASST negative CIU improved by 48%. No illness return occurred, and the improvement persisted even during the study's 4-week follow-up period after the eighth treatment. After receiving nine weekly autologous serum skin injections, at least 60% of patients in group (S) and 46% of cases in the group (N) had appreciable improvements in their signs and symptoms. After the final injection, this improvement persisted for at least three to four months. These findings were consistent with our research. Similar outcomes were seen in further trials carried out by Staubach, et al., [13] and Debbarman, et al., [12] We found in this study that there was a gradual decline in the requirement of antihistaminics as the duration of treatment increased represented in the figure 2. In a comparative retrospective investigation of AWBT in ASST-positive and negative CIU, Jonathan Te-Peng Tseng, et al., [16] discovered a gradual decline in rescue antihistamines in the ASST-positive group. Staubach, et al. reported that 12 weeks after the start of therapy, ASST-positive patients needed less than half the amount of antihistaminic rescue medicine they had previously taken (-52%, p = 0.005) in a randomized placebo-controlled study in ASST-positive and negative CIU. In the current study, we found n=9(36%) in Group (S) and n=3(12%) in Group (N) with high anti-thyroid peroxidase (TPO) antibodies. There was a significantly higher association of Anti-thyroid peroxidase antibodies in the ASST positive group (S) cases as compared to the ASST negative group (N) cases. According to Leznoff et al., [17] thyroid autoimmunity might contribute to the development of chronic urticaria and angioedema. In research by N Bakos et al., [18] it was discovered that autoimmune thyroiditis and autoimmune urticaria are related. Similar to our analysis, the authors of the majority of studies indicated that a few patients complained of temporary (24 hr) discomfort and/or bruising at the injection site. Such side effects were more frequent in individuals getting higher dosages, according to Chen, et al., [19]

Conclusion

This study demonstrates that autologous whole blood treatment (AWBT) works well in CIU and only has mild side effects. The effectiveness of AWBT has been demonstrated in several previous studies, including this one. Individuals with urticaria who test positive for ASST respond to AWBT a little bit better than ASST-negative patients do. In this study, we have found that people with urticaria who are ASST-positive get more benefits from AWBT/autohemotherapy than ASST-negative individuals. Based on these findings, it may be assumed that autohemotherapy is worthwhile for ASST-positive individuals before

contemplating drugs other than antihistamines that have less proof of their efficacy, are more expensive, and carry a larger risk of serious side effects.

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