



Original Research Article

Single centre experience with histaglobin as an adjunctive treatment of chronic urticaria: A post marketing surveillance study



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ABSTRACT

Introduction: Chronic urticaria consists of itchy rash on most days for at least six weeks. It is caused by release of histamine and other mediators from degranulated cutaneous mast cells. Antihistamines, the current treatment mainstay, do not provide relief in many cases and necessitates the use of adjunctive treatment. Histaglobin, through the synthesis of histamine-neutralizing antibodies, can serve as an adjunct. The current study was aimed to evaluate the efficacy and safety of Histaglobin, as adjunctive therapy, in patients with chronic urticaria.

Materials and Methods: Patients with chronic urticaria were enrolled in this single-centre, prospective open-label study. Patients were administered 3 injections of Histaglobin (1ml), subcutaneously, at intervals of 7 days. Efficacy was assessed by grading the change in disease activity, measured using urticarial activity score (UAS 7) on days 0, 7, 14, 28 and 42. Adverse events (AEs) and concomitant medications were also recorded at each study visit.

Results: Thirty-seven of the 38 enrolled patients completed study by following-up on day 28. Thirty-four (91.9%) patients showed improvement; 21 (56.8%) showed 'moderate improvement' and 13(35.1%) showed 'clear cut improvement'. There was a significant ($p < 0.0001$) reduction in UAS from Day 0(15.8 ± 6.1) to Day 28(6.0 ± 6.2). There was one patient who developed redness at injection site. Half the patients on antihistamines and all those on steroid treatment were able to reduce/stop these treatments at the end of study.

Conclusion: Histaglobin treatment was found to be effective in the treatment of chronic urticaria. It was also well tolerated and reduced antihistamines and steroids pill burden. Histaglobin, is a safe, well-tolerated and valuable adjunct to antihistamines in the management of chronic urticaria.

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1. Introduction

Urticaria has been described by the Chinese as far back as in the 7th century. Chronic urticaria (CU) is well-defined as urticaria persisting daily or almost daily for more than 6 weeks.¹ The exact prevalence of CU is unknown. The lifetime prevalence of chronic urticaria is around 1.8% in adult population and 0.1 – 0.3 % in children.² It is characterized by dermal edema caused by vascular dilatation and fluid leakage into the skin resulting in the formation of hives.³ Although chronic urticaria is rarely

fatal, it is known to impact quality of life adversely resulting in absenteeism from school and work.² Chronic urticaria is classified into chronic spontaneous (idiopathic) and inducible urticaria (dermatographic, cold by contact, delayed pressure, heat by contact, solar, aquagenic, cholinergic, contact, and vibratory).⁴

Histologically, chronic urticaria lesions demonstrate dermal edema accompanied by presence of mononuclear cells, eosinophils, basophils, mast cells and activated macrophages. Some lesions show perivascularitis. The pathophysiology is based on mast cell degranulation and release of mediators. Of the many molecules identified, histamine is believed to be the most important.

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First in the treatment ladder start by means of non-sedating antihistamines, started at low doses. Escalation of the dosage of these mediators and adding a leukotriene antagonist are the subsequent strategies in the management. The use of immunomodulators such as cyclosporin, methotrexate, omalizumab, and dapsone is the last resort in treating this condition. Empirically, anti-histamine treatment is usually prescribed for 3–6 months. It is often not possible to control the disease with antihistamines alone.^{5,6}

Histaglobin (Histaglobulin) which is a sterile preparation of histamine and human gammaglobulin in strictly defined proportions (each ml, contains, Human Normal Immunoglobulin I.P 12 mg, Histamine Dihydrochloride B.P 0.15 mcg)⁷ is capable of eliciting an immunological response against histamine. The mechanism of action of this drug has not been elucidated completely. Some believe that Histaglobulin administered subcutaneously induces production of antibody against the histamine-immunoglobulin complex, which binds and inactivates histamine release during allergy. Repeated doses of histaglobulin increase this antibody titre.^{8,9} This single centre post marketing surveillance study was an effort to evaluate the efficacy and safety of Histaglobin and establish its role as an adjunct to antihistamines and/or steroids in the treatment of chronic urticaria.

2. Materials and methods

2.1. Study design and study centre

This was single arm, open label post marketing surveillance study conducted to evaluate efficacy and safety of subcutaneous Histaglobin as adjunctive therapy in patients with chronic urticarial. The study was conducted in dermatology clinic located at Nerul, Navi Mumbai, and a residential and commercial node of Navi Mumbai, with an estimated population of around 1 million.

2.2. Patient selection

Patients of either gender and more than 18 years of age diagnosed with chronic urticaria and on active treatment with antihistamines were eligible for enrolment. Those patients giving history of allergy to histoglob were excluded from the study. Pregnant and lactating women were also excluded from the study.

2.3. Investigations

Informed consent was obtained from the patients and baseline investigations were done. Demographic characteristics such as age, gender and weight were noted. The detailed past medical history and regarding the duration of signs and symptoms were also noted. This was followed by a clinical examination of the patient. Routine investigations such

as complete blood count with absolute eosinophil count, random blood sugar, urine routine examination, IgE test, thyroid profile, renal and liver function tests were done for patients.

2.4. Study Intervention

The patients were administered 3 subcutaneous injections of 1 ml Histaglobin (HISTOGLOB[®] manufactured by Bharat Serums and Vaccines Ltd, Maharashtra, India), which is a combination of human normal immunoglobulin (12 mg) and histamine dihydrochloride (0.15 mcg) in addition to the ongoing treatment. The injections were administered, one each, on days 0, 7 and 14.

2.5. Monitoring and follow-up

Each patient enrolled in the study was required to complete the study duration of 42 days, which included visits for administration of Histaglobin injection at Day 0, Day 7 and Day 14 followed by follow-up visits on day 28 and 42.

At each of these visits the disease activity was measured using the UAS7⁴, a unified, validated and simple scoring system. It is a sum of daily pruritus score (0 - none, 1 - mild, 2 - moderate, 3 - severe) and daily wheal score (0 - none, 1 - one to six wheals, 2 - seven to twelve wheals, 3 - more than twelve wheals). The sum of score (0 – 6) for each day is summarized over one week, with a maximum of 42. Higher scores indicate more severe disease. Safety of the product was assessed by the occurrence of Adverse Events (AEs). Details of concomitant medications were recorded at each visit.

2.6. Endpoints

For efficacy assessment the primary endpoint used was proportion of patients showing change in disease activity from baseline at Day 28. This change was graded using a 3-grade scale based on change in UAS7 scores. The grades were 1) 'no improvement' - if the UAS7 score worsened or remained unchanged, 2) 'moderate improvement' - if the score decreased but did not reach 0(zero) and 3) 'clear cut improvement' - if the score decreased to 0(zero).

Additionally, change in the requirement of other medications was also assessed based on whether there was dose alteration (increased/decreased) or complete stoppage.

2.7. Statistical analysis

Statistical analysis was performed using SAS[®], Version 9.4. Descriptive statistics such as mean, standard deviation, median, minimum and maximum were calculated for continuous variables, while frequency and percentage were calculated for categorical variables. All the patients who completed the study visit at Day 28 were considered for efficacy analysis. Wilcoxon signed rank test was used to

compare pre-treatment (Day 0) and post-treatment (Day 28) UAS.

3. Results

3.1. Study population

Thirty-eight patients were enrolled into the study, of which 37 patients completed the study at Day 28 and 27 patients completed the follow-up visit at Day 42. One patient was lost to follow up after Day 14 and hence not considered for efficacy analysis. Of the enrolled 38 patients, 23(60.53%) were male and 15(39.47%) were female. Mean (\pm SD) age of patients was 36.8(\pm 10.18) years and mean (\pm SD) weight was 62.8(\pm 10.70) kg. Mean duration of the disease was 1.95 \pm 2.84 years for the patients enrolled in study. Baseline demographic details of the study patients are given in Table 1.

3.1.1. Primary Efficacy Endpoint

A total of 34(91.89%) patients showed improvement in UAS 7 from Day 0 to Day 28. Twenty one (56.76%) patients showed 'moderate improvement' and 13(35.14%) patients showed 'clear cut improvement' based on UAS 7. The UAS 7 remained unchanged in 1(2.70%) patient and increased in 2(5.41%) patients at Day 28 ('no improvement'). Analysis of UAS 7 for 27 patients who completed follow-up visit at Day 42 showed 'clear cut improvement' in 12(44.44%) patients, 'moderate improvement' in 9(33.33%) patients and 'no improvement' in 6(22.22%) patients.

Mean UAS7 sequentially decreased from 15.8 at Day 0 to 9.7 at Day 7, 9.2 at Day 14 and 6.0 at Day 28. However, there was slight increase in mean UAS7 at Day 42(6.5) as compared to Day 28(6.0). The reduction observed in UAS7 from 15.8 \pm 6.06 at Day 0 to 6.0 \pm 6.22 at Day 28 was statistically significant ($p < 0.0001$). Table 2 shows summary of mean UAS7 by visits.

3.2. Additional endpoint

All patients were on antihistamines and 3 patients were also on steroid treatment at the beginning of study. Antihistamine use was stopped in 5.26% patients, decreased in 47.37% patients and remained unchanged in 47.37% patients at the end of study. In 3 patients on steroids, their use was stopped in 66.67% patients and decreased in 33.33% patients. Patients in whom antihistamines and steroids could be stopped, average treatment duration for these treatments were 22.5 days and 5 days, respectively Table 3.

Patients who continued with antihistamines received second generation antihistamines as Levocetirizine, Desloratadine, Loratidine and third generation antihistamine Fexofenadine. Majority of the patients received treatment once daily (OD).

Only one adverse event (redness at site of injection) was reported during the study. Overall, Histaglobin injection was found safe and well tolerated by study patients.

4. Discussion

Management of chronic urticaria involves treatment of identifiable cause, avoidance of aggravating factors and antihistamines. Antihistamines are the first line of treatment for all patients with chronic urticaria. If patients do not respond to usual dosage then the dosage may be increased. Despite using maximally tolerated doses of antihistamines, many patients do not respond adequately and require adjunctive therapies. Non-responders to antihistamines may be as high as 40% of all chronic urticaria patients.¹⁰ Multiple immunological agents like oral corticosteroids, cyclosporine, methotrexate, intravenous immunoglobulin, omalizumab, tacrolimus, etc. are used in such cases, but with limited success and safety concerns. Different immunotherapies including autologous serum/whole blood therapies have also been used with moderate success.

Histaglobin, a sterile preparation of histamine dihydrochloride coupled to active protein fraction extracted from human blood (gamma globulin) is a useful adjunctive therapy in resistant cases and has shown therapeutic response in various allergic diseases. Histaglobin has antigenic properties due to presence of histamine coupled to gamma globulin and leads to production of antihistamine antibodies. These antibodies formed are expected to neutralize the released histamine to allergic reaction.¹¹ Serum histamine binding capacity in normal individual is 20 to 30% and in allergic patients it is only 0 to 5%. Histaglobin treatment decreases IgE levels and it is hypothesised that the serum binding capacity of patient to histamine increases.¹² Clinical efficacy of Histaglobin is established in allergic disorders such as allergic rhinitis, allergic asthma, chronic recurrent urticaria and other allergic skin diseases.¹³

In this study, we included 38 adult patients (23 male and 15 female) with chronic urticaria with a mean age of 36.8(\pm 10.18) years. Although chronic urticaria is more common in females, in our study male patients were more than females.¹⁴ This may be due to small sample size and single-centre study design.

There was significant ($p < 0.0001$) reduction in mean UAS7 from Day 0 to Day 28. Improvement in UAS7 was seen in 91.89% patients with 35.14% patients showing complete improvement (UAS 7 'zero') at the end of treatment.

In their study, Gushchin et al. reported improvement in chronic urticaria in 82.5% patients and complete improvement in 15% patients with Histaglobin using similar clinical scoring. In two other studies, Histaglobin showed complete resolution of chronic urticaria in 10.8% (Rudzki et al.) and 48.3% (Rajesh G et al.) patients at the end

Table 1: Baseline demographic characteristics of the patients

Characteristic	Descriptive statistics	Baseline Value
Age (Years)	n	38
	Mean (SD)	36.8 (10.18)
	Median	36.0
	Min, Max	20, 60
Gender, n (%)	Male	23 (60.53%)
	Female	15 (39.47%)
Weight (kg)	n	24
	Mean (SD)	62.8 (10.70)
	Median	62.5
	Min, Max	36, 87

(n=number; SD=Standard Deviation; Min=Minimum; Max=Maximum)

Table 2: Summary of mean urticaria activity score (UAS7)

Visit	Descriptive Statistics	UAS7
Day 0	n	38
	Mean (SD)	15.8 (6.06)
	Median	15.0
	Min, Max	3, 28
Day 7	n	38
	Mean (SD)	9.7 (7.68)
	Median	7.0
	Min, Max	0, 36
Day 14	n	38
	Mean (SD)	9.2 (8.74)
	Median	7.0
	Min, Max	0, 42
Day 28	n	37
	Mean (SD)	6.0 (6.22)
	Median	4.0
	Min, Max	0, 22
Day 42	n	27
	Mean (SD)	6.5 (7.54)
	Median	3.0
	Min, Max	0, 21

Table 3: Summary of concomitant medication during the study

Drug Class	No. of patients on treatment at baseline	Ongoing/unchanged (%)	Decreased (%)	Stopped (%)
Antihistamines	38	18 (47.37%)	18 (47.37%)	2 (5.26%)
Steroids	3	0 (0%)	1 (33.33%)	2 (66.67%)

of treatment period. Thus, complete resolution of chronic urticaria reported in our study is higher than that reported by Guschin et al. and Rudzki et al., but lower than that reported by Rajesh et al.^{13–15} The observed difference in treatment responses in these studies may be attributed to differences in treatment schedule and patients' profile. In our study, mean UAS was reduced by 62% at 28 days after 3 weekly injections of Histaglobin while it was reduced by 80.4% after 8 weekly Histaglobin injections in a study done by Rajesh et al.¹⁴ Thus, prolonging the treatment beyond 3 doses may confer additional efficacy benefit in

chronic urticaria. Summary analysis of different studies involving around 2000 patients treated with Histaglobin had shown occurrence of adverse events (e.g., weakness, malaise, headache and local reactions) in about 0.5% cases.¹³ In this study also, Histaglobin was found safe and well tolerated, with only one patient reporting redness at the site of injection. In this study, 52.63% and 100% patients were able to reduce/stop antihistamine and steroid treatment, respectively, which may be attributed to therapeutic effectiveness of Histaglobin.

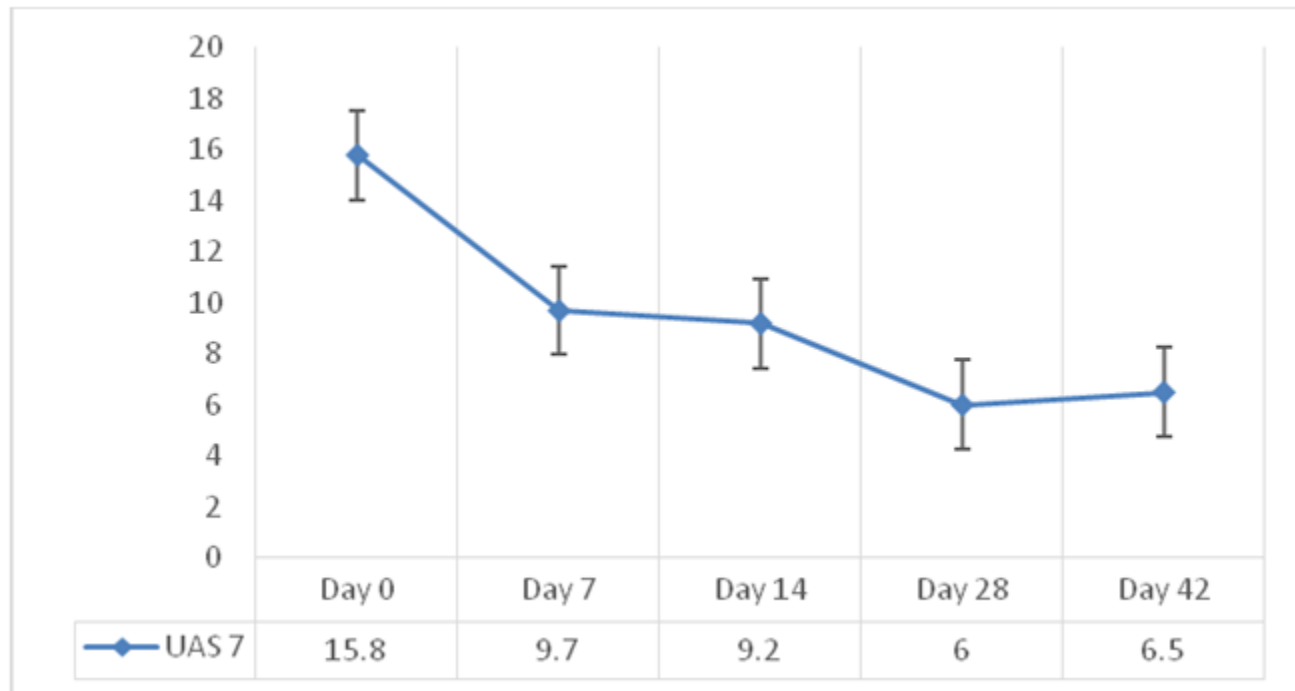


Fig. 1: UAS 7 over study period

4.1. Limitations

Being a single arm study, efficacy of Histaglobin could not be compared with placebo or a standard treatment. Any possible investigator-bias could not be eliminated because of open label treatment allocation. Also, since the study was conducted at a single centre only, centre-bias cannot be excluded from the results of the study. Despite these limitations, we believe this work serves to establish the efficacy and safety of Histaglobin as an adjuvant treatment of chronic urticaria.

5. Conclusion

Histaglobin was found to be helpful in providing relief to chronic urticaria patients receiving antihistamines, as identified by the significant reduction in disease activity. Histaglobin also lead to reduced requirement of antihistamines and/or steroids in these patients. Histaglobin, thus, may be a safe, well-tolerated and valuable adjunct to antihistamines in the management of chronic urticaria.

6. Source of Funding

None.

7. Conflict of Interest

Injection Histaglobin vials were provided for the study by Bharat Serums and Vaccines Ltd, Maharashtra, India.

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