ijpbs 2025;doi10.22376/ijpbs.2025.16.1.p13-39

International Journal of Pharma and Bio Sciences

ISSN 0975-6299

Immunoglobulin/Histamine Complex in Allergic Diseases: A Systematic Review

Sivanandhan K[1], Kiran Godse[2], Carlton Pereira[3], Shalini Patodiya[4], Gautam Modi[5], Saswata Banerjee[6], and Hemal Patel[7*]

[1] *Consultant Pediatrician and Allergist, Asthma Research and Treatment Centre & Kishor Pharma Medical Services, Neyveli, TamilNadu*

[2] *D Y Patil Hospital, Navi Mumbai, Maharashtra*

[3] *Bosco ENT Nursing Home and Research Centre, Mumbai, Maharashtra*

[4] *Amber Clinics, Hyderabad, Telangana*

[5] *Modi Allergy Clinic, Patna, Bihar*

[6, 7] *Bharat Serums and Vaccines Limited, Mumbai, Maharashtra*

Abstract: Histaglobulin or immunoglobulin/histamine complex (IHC) has been used globally to treat allergic diseases for several decades. It is a sterile, non-allergen-specific immunotherapeutic agent made up of histamine dihydrochloride and human immunoglobulin as the main components. Histaglobulin effectively treats allergic rhinitis, bronchial asthma, chronic urticaria, atopic dermatitis, and many other allergic conditions. It can be given over a long period without any safety concerns. However, despite being used for several decades for chronic allergic conditions, no reviews or systematic reviews (SRs) comprehensively cover the efficacy and safety of histaglobulin/IHC in various chronic allergic conditions. The publicly available literature on its efficacy and safety in various chronic allergic conditions consists only of small open-label prospective studies, case reports, or case series. This systematic review was undertaken to provide a comprehensive view of the efficacy, safety, and dosing schedule of histaglobulin in common chronic allergic dermatological and respiratory conditions such as chronic urticaria, atopic dermatitis, allergic rhinitis, and bronchial asthma. Further, the SR explored the role of histaglobulin in other conditions such as psoriasis, cutaneous drug allergies, Pfeiffer-Weber-Christian disease with multiple food allergies/atopic dermatitis, and primary eosinophilic colitis. The SR also covers the role of histaglobulin in treating allergic psychiatric manifestations. This is the first SR that documented and concluded that histaglobulin could safely achieve a long-term symptoms-free state in chronic allergic conditions such as chronic urticaria, atopic dermatitis, allergic rhinitis, and asthma. The studies captured in the SR show that histaglobulin can be given for prolonged periods as weekly injections or more frequently (at intervals of 4 days) until completely symptom-free or with significant improvement from allergic symptoms. The SR also identified the need for large multicentre prospective, double-blind, randomized controlled trials, prospective well-designed open-label trials, and observational real-world studies to document the efficacy (including remission) and safety benefits of histaglobulin in various types of chronic allergic conditions not responding to conventional treatments.

Keywords: Histaglobulin, Histaglobin, Histobulin, Histadestal, immunoglobulin/histamine complex, allergy, urticaria, Human Normal Immunoglobulin/histamine dihydrochloride.

***Corresponding Author**

Hemal Patel , Bharat Serums and Vaccines Limited, Mumbai, Maharashtra

Date of Receiving 6 September 2024

Date of Revision 16 October 2024

Date of Acceptance 5 November 2024

Date of Publishing 10 January 2025

Funding Bharat Serums and Vaccines Limited paid for medical writing support. None of the authors are paid any honorarium.

Citation Sivanandhan K, Kiran Godse, Carlton Pereira, Shalini Patodiya, Gautam Modi, Saswata Banerjee, and Hemal Patel , Immunoglobulin/Histamine Complex in Allergic Diseases: A Systematic Review.(2025).Int J Pharm Sci.16(1), p13-39 http://dx.doi.org/10.22376/ijpbs.2025.16.1.p13-39

1. INTRODUCTION

Chronic allergic conditions, especially dermatological conditions such as chronic urticaria and atopic dermatitis, and respiratory conditions such as allergic rhinitis and asthma, are on the rise in India and globally.[1,2] Chronic allergic conditions affect all age groups, including children. The incidence and prevalence of these diseases are often under-reported.[1,2] However, approximately 25% of the population in developing countries have one or more chronic allergic conditions.[1]Chronic allergic conditions carry many of the same risk factors, *viz* environmental, genetic, food allergies, physical inactivity, obesity, and altered gut microbiome, and may run in families (increased incidence in those with family history).[1,2] Most treatments for these allergic conditions are aimed at symptomatic control. The curative treatments are lacking. Histaglobulin or immunoglobulin/histamine complex (IHC) is a sterile, non-allergen-specific immunotherapeutic agent consisting of histamine dihydrochloride and human immunoglobulin as the main components.[3–8] This IHC has been used globally to treat allergic conditions such as allergic rhinitis, bronchial asthma, chronic urticaria, and atopic dermatitis for several decades.[6–9] Literary evidence points towards its curative potential in these allergic conditions. Histaglobulin can be administered over a long period with no safety concerns. It is contraindicated in pregnancy and acute infectious states.[3] However, despite being used for decades for chronic allergic conditions, the efficacy and safety of histaglobulin have been extensively published through small open-label studies, case reports, or case series. No reviews or systematic reviews (SRs) shed light on the efficacy and safety of histaglobulin/IHC in chronic allergic conditions.

1.1. Histaglobulin: mechanism of action in chronic allergic conditions

An immunological sensitivity to an allergen and recurrent or continuous exposure contribute to chronic allergic conditions (Figure 2).[10,11] This immunological sensitivity is thought to be mediated via histamine release and other mechanisms (Figure 2).[12] The exact mechanism of action of histaglobulin/IHC in chronic allergy has yet to be completely understood. However, histaglobulin/IHC exerts a strong histaminopexic effect by producing highly potent antihistamine antibodies that neutralize allergen-induced histamine released from human peripheral blood basophils and mast cells, decreasing the clinical effect of histamine by increasing serum histamine binding capacity (SHBC); inhibiting NF-kappa B nuclear translocation and downregulating proinflammatory cytokine; altering cytokine production from T-helper cells thereby inhibiting interleukin-4 (IL-4) and IL-5 and decreasing immunoglobulin E (IgE) biosynthesis and eosinophil accumulation, respectively. (Figure 2).[8,12–15] Individuals with an allergic condition have 20% to 30% less or even lower SHBC than normal individuals.[15-16] Hence, the histamine released from mast cells in response to an antigen does not get neutralized in patients with allergic conditions due to extremely low SHBC. The free histamine acts on the H receptors in target organs such as the skin, lungs, and gut to produce allergic effects. Hence, an immunotherapy that inhibits histamine release and/or neutralizes histamine will likely produce sustained results and remission. Since histaglobulin increases SHBC significantly in patients with allergies, it helps to neutralize the free histamine in the serum produced in response to an antigen, and the patient becomes symptom-free. However, the histamine receptors are already sensitized in patients with allergies, and therefore, to increase the response to histaglobulin, patients can be administered antihistamines for five to seven days to desensitize the histamine receptors. The immune response triggered by Histaglobulin/IHC lasts long.[6,8,10,17] Repeated histaglobulin/IHC doses help raise and maintain the ideal antihistamine antibodies and SBHC for continued effect.[6,14] The immune response triggered by histaglobulin is long-lasting, with repeated doses helping to raise and maintain ideal antihistamine antibody levels and SHBC for continued effectiveness. Given these mechanisms, this study aims to evaluate the efficacy and safety of histaglobulin in allergic conditions through a systematic review of the literature

2. MATERIALS AND METHODS

This SR was conducted following a non-registered protocol and the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA)[18,19] Guidelines.

2.1. Inclusion criteria

The SR included any human clinical trial, case series, or case report investigating the efficacy and safety of histaglobulin in any allergic condition. Published English-language articles were included.

2.2. Exclusion criteria

The SR excluded all animal and laboratory preclinical studies and studies not using histaglobulin as a treatment strategy.

2.3. Search strategy

Two free literature databases, MEDLINE (PubMed) and Google Scholar, were independently searched by two researchers between April 1, 2024, and April 4, 2024, for English-language human clinical trials on histaglobulin. The search was carried out using the following search terms for histaglobulin: Histaglobulin, Histaglobin, Histobulin, Histadestal, immunoglobulin/histamine complex, human normal immunoglobulin with histamine dihydrochloride; and the following search terms for allergic conditions: cutaneous allergy, urticaria, atopic dermatitis, eczema, psoriasis, allergic rhinitis, chronic bronchitis, asthmatic bronchitis, hay fever, bronchial asthma, and spasmodic tracheitis. The search terms were combined by Boolean operators like “AND” and “OR” as appropriate. All literature, irrespective of year of publication, was considered. Five hundred and thirty-five records were retrieved. Two Researchers independently screened the retrieved records, and 50 duplicates were removed using a reference manager. Four hundred eighty five retrieved records were screened for eligibility, 459 were excluded after mutual discussion, and 26 were included in the SR. A decision was made to include abstracts if they had complete information on at least the efficacy of histaglobulin in a particular condition. The Protocol was modified accordingly. No abstracts published in the English language that had complete information were identified. There were 148 non-English language studies for which abstracts were unavailable and could not be included. Each researcher then scoured the bibliography of the 26 identified records to include any eligible study missed during the literature search. Only two records were included, one of which was a Congress poster. Ultimately, 28 records were included in the SR. Figure 1 outlines the records' detailed search and selection criteria

through the PRISMA flow chart. The details of the 28 studies included in the SR are captured in Table 1.

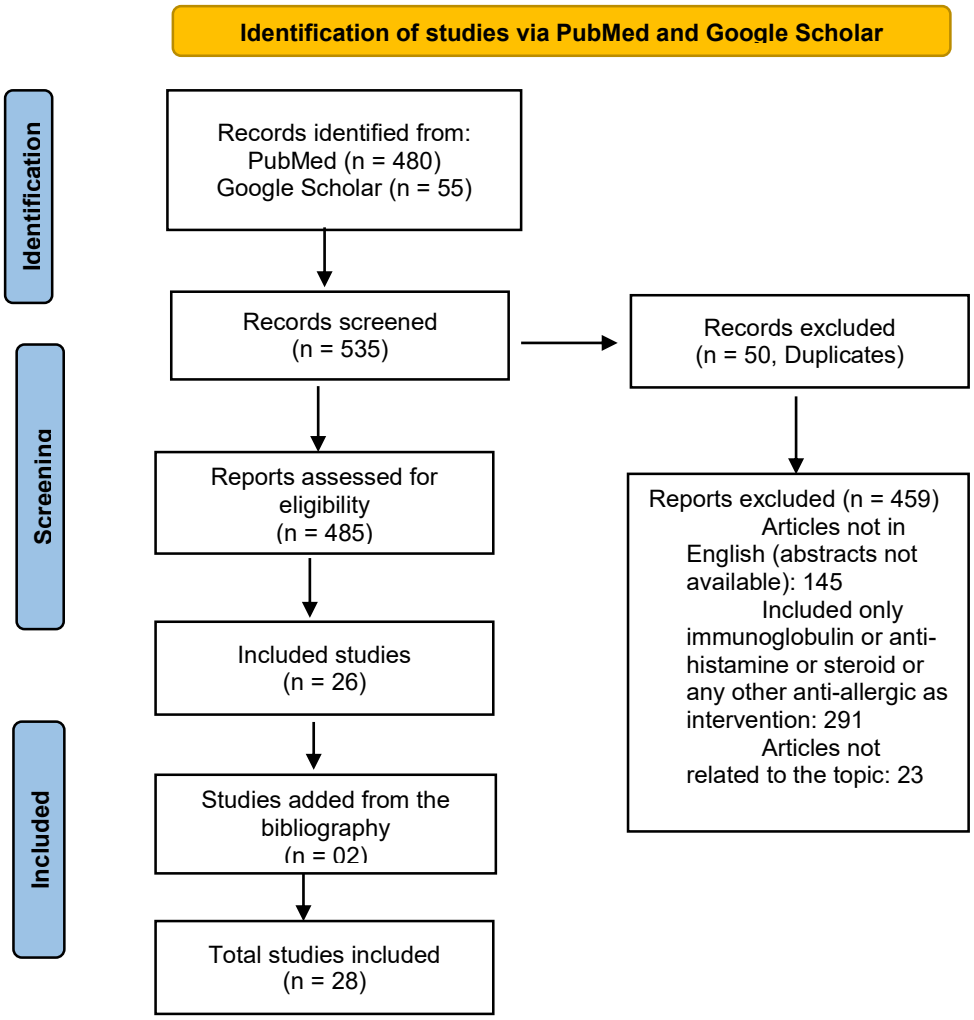

Fig 1: PRISMA flow chart of the literature review

Table 1: List of records included in the systematic review

S No	Title (Year)	Intervention (duration of treatment)	Condition	Study design	Duration of histaglobulin response in the study*
A	**Allergic, dermatological conditions**				
1	Effects of the immunoglobulin/histamine complex in chronic spontaneous urticaria focusing on remission induction (2022)[72]	12 weekly injections of Histaglobulin or H1 antihistamine	Chronic spontaneous urticaria	Retrospective cohort	Relapse-free during a mean follow-up of 30.5 months; only 2 patients relapsed at 12 and 14 months
2	Induction of remission in chronic urticaria by immunotherapy using immunoglobulin/histamine complex (Histobulin™): a case report (2021)[12]	Histaglobulin by subcutaneous route starting weekly and then by reducing frequency until in remission (no signs and symptoms for 4 weeks without medication)	Chronic spontaneous urticaria	Case series (4 cases)	Two patients showed an early response (completed treatment with 12 injections), and two showed a late response. Remission was achieved in all four patients
3	Efficacy of Injection Histoglob in Treatment of Chronic Urticaria-A Prospective Study (2019)[28]	1 mL histaglobulin subcutaneously weekly for 8 weeks	Chronic spontaneous urticaria	Prospective single-center open-label study	48.5% attained complete remission at 24 weeks follow-up
4	Weekly injection of histaglobulin produces long-term remission in chronic urticaria: A prospective clinical study (2016)[5]	1 mL histaglobulin subcutaneous for 8 consecutive weeks	Chronic spontaneous urticaria	Prospective single-center open-label study	45% attained complete remission at 24 weeks visit
5	Comparative Study of Positive Versus Negative Autologous Serum Skin Test in Chronic Spontaneous Urticaria and its Treatment Outcome[29]	Histaglobulin weekly injections subcutaneously for 5 weeks; 3rd month and 6th month	Chronic spontaneous urticaria	Prospective correlation study	6-month follow-up ASST+ve: 81.3% improved ASST-ve: 43.5% improved
6	Comparative evaluation of the therapeutic efficacy and safety of injected histaglobulin versus autologous serum therapy in chronic urticaria (2021)[4]	1 mL histaglobulin subcutaneously or 1 mL autologous serum intramuscularly for 6 consecutive weeks	Chronic idiopathic urticaria	Prospective single center	Significant improvement in histaglobulin vs. AST group at 24 weeks
7	A Comparative Study of Autologous Serum Therapy and Histaglobulin in Chronic Urticaria: Underutilized Modalities Revisited! (2023)[6]	1 mL histaglobulin subcutaneously or 2 mL autologous serum intramuscularly weekly for 8 weeks	Chronic urticaria	Prospective single center	Considerable improvement in histaglobulin and AST group at 8 weeks
8	Efficacy of Injection Histaglobulin in Treatment of Chronic Urticaria. (2021)[26]	1 mL histaglobulin subcutaneously weekly for 8 weeks	2021 Chronic urticaria	open-label, clinical study	80% attained complete remission at 24 weeks
9	Comparative study of the effectiveness of autologous serum and histaglobulin in autologous serum skin test positive and negative cases of chronic urticaria (2019)[30]	1 mL histaglobulin subcutaneously or 2 mL autologous serum intramuscularly weekly for 8 weeks	Chronic urticaria	Prospective, comparative, randomized controlled, single-blinded study	Significant improvement at 8 weeks
10	Single center experience with haptoglobin as an adjunctive treatment of chronic urticaria: a post-marketing surveillance study (2019)[27]	1 mL histaglobulin subcutaneously weekly for 3 weeks	Chronic urticaria	Prospective single-center open-label study	91.9% improved by Day 28; improvement persisted until Day 42
11	Immunotherapy using Histobulin in atopic dermatitis (2020)[8]	Histaglobulin weekly for 24 or 36 weeks	Atopic dermatitis	Case series (4 cases)	Case 1: AD remission at 36 weeks; URI symptom-free for 1 year Case 2, 3, and 4: Significant improvement in AD score at 24 weeks; no URI symptoms for 1 year

12	Treatment of atopic dermatitis with a combination of allergen-specific immunotherapy and a histamine-immunoglobulin complex (2008)[9]	Combination of histamine-immunoglobulin complex and allergen-specific immunotherapy for 12 months	Atopic dermatitis	Prospective single-center open-label study	Significant improvement at 1 year
13	Histobulin as a complementary but essential therapeutic for Intravenous Immune Globulin Therapy of Pfeiffer-Weber-Christian disease with multiple allergic diseases and its effects on allergic disease: A case report (2021)[35]	12 doses of histaglobulin given at varying frequency	Pfeiffer-Weber-Christian disease (PWCD) with multiple food allergies and atopic dermatitis	Case Report	Remission of AD, food allergies, allergic rhinitis, and free of URI symptoms after histaglobulin for 35 weeks, followed by 3 months IVIG followed by 12 histaglobulin doses
14	Intravenous Immune Globulin (IVIG) therapy after unsuccessful treatment with corticosteroid and Cyclosporine A in Pfeifer-Weber-Christian Disease: A Case Report (2021)[34]	12 doses of histaglobulin given at varying frequency	Pfeiffer-Weber-Christian disease (PWCD) with multiple food allergies and atopic dermatitis	Case Report	
15	Immunotherapy using Histobulin™ in psoriasis: A case report (2022)[7]	12 injections of histaglobulin	Psoriasis	Case Report	Relapse-free for >18 months
16	Prevention of multiple drug allergies by histaglobulin (2006)[14]	Histaglobulin 2mL subcutaneously at weekly intervals for three weeks Monthly booster doses at one, three, and six months Six monthly boosters thereafter	Cutaneous drug allergy	Case Report	Allergy-free on 6-monthly booster histaglobulin doses for 4-year
B	**Psychological conditions concurrent with chronic urticaria**				
17	Effects of the immunoglobulin/histamine complex on panic disorder concurrent with chronic spontaneous urticaria: a case report (2023)[31]	Histaglobulin (27 weekly injections) and hydroxyzine	Panic disorder concurrent with chronic spontaneous urticaria	Case Report	CSU and allergic rhinitis remission after 27 weekly injections Medications for panic disorder and insomnia were stopped
18	Effects of Histobulin (Immunoglobulin/Histamine Complex) on Depression and Anxiety in Chronic Urticaria: Psychiatric Manifestations or Psychiatric Comorbidities of Chronic Urticaria?: A Case Report (2021)[33]	Histaglobulin (12 weeks or 26 weeks of weekly injections)	Depression anxiety in chronic urticaria	Case series (3 cases)	Case 1: after 26 weekly injections, allergic rhinitis, and CSU remitted, depression and suicidal urges disappeared
19	Effects of Histobulin on Depression and Anxiety in Chronic Urticaria: Psychiatric Manifestations or Psychiatric Comorbidities of Chronic Urticaria?: A Case Report (2020)[32]	Histaglobulin (12 weeks or 26 weeks of weekly injections)	Depression anxiety in chronic urticaria	Case series (3 cases)	Case 2: Allergic and psychiatric manifestations disappeared after 12 weekly injections Case 3: Slight improvement in CSU and anxiety after 12 weekly injections
C	**Allergic respiratory conditions**				
20	A prospective study to compare the therapeutic effects of histaglobulin and nasal steroids in allergic rhinitis (2023)[37]	Histaglobulin (SC/week X 10 weeks >> once monthly booster dose X 3 months)versus Nasal steroids: Fluticasone (2 puffs)	Allergic rhinitis	Prospective single-center open-label	More significant improvement in the eosinophil count and IgE level with histaglobulin compared to the

21	Comparative study of therapeutic effect of histaglobulin with nasal steroids in allergic rhinitis: A hospital-based prospective study (2019)[36]	Histaglobulin (SC/week X 10 weeks >> once monthly booster dose X 3 months)versus Nasal steroids: Fluticasone (2 puffs)	Allergic rhinitis	Prospective single-center open-label	nasal steroid group at 3 months (end of study)
22	Effect of Histaglobulin in allergic rhinitis- a prospective study (2018)[10]	Histaglobulin (1 ml SC X 4 injections at 4 days' interval X 2 months>>1 injection/month X 3 consecutive months>> booster dose after 6 months)	Allergic rhinitis	Prospective single-center open-label	At 6 months: Complete response: 46% Poor response: 42% No response: 12%
23	Efficacy of histaglobulin on allergic rhinitis (1997)[3]	Histaglobulin (SC/week X 10 weeks>> monthly booster doses X three months in responding cases)	Allergic rhinitis	Prospective single-center open-label	Response at 3 months Histaglobulin: 59.6% Histaglobulin + terfenadine: 61.7% Histaglobulin + cetirizine: 56.9%
24	A novel method for treating bronchial asthma with newly designed histaglobulin therapy (2022)[15]	Histaglobulin in two phases (Phase 1: 6 primary doses of 1 mL at weekly intervals; Phase 2: three booster doses)	Bronchial Asthma	Prospective single-center open-label	97.8% were free of allergic symptoms at 5 years
25	Abstracts of the XX World Allergy Congress™ 2007 December 2-6, 2007, Bangkok, Thailand (2008)[39]	Histaglobulin in two phases (Phase 1: 6 primary doses of 1 mL at weekly intervals; Phase 2: three booster doses)	Bronchial Asthma	Prospective single-center open-label	15-year observation: 94.6% were free from asthma and allergic rhinitis symptoms for varying durations; 96% were free for >4 years
26	Experiences with Histaglobulin in Patients with Bronchial asthma[40]	Histaglobulin weekly for 3 weeks, followed by monthly maintenance	Bronchial Asthma	Prospective single-center open-label	58.3% were symptom-free (duration not known)
D	**Multiple allergic respiratory and dermatological conditions**				
27	Evaluation of histamine-gamma globulin (haptoglobin) in the treatment of various allergic conditions[17]	Histaglobulin weekly for 3 weeks followed by monthly maintenance (double-blind portion was versus placebo)	Asthma, allergic rhinitis, seasonal hay fever, atopic dermatitis, and urticaria	Prospective single-center **mixed design** (open-label and double-blind placebo-controlled)	Response persisted long without treatment (duration not known) Symptom-free: 66.7% Substantial improvement: 18.8% No improvement: 15%
E	**Other conditions**				
28	Treatment of primary eosinophilic colitis using immunoglobulin/histamine complex (2023)[41]	Histaglobulin Weekly 12 mg subcutaneously X 10 weeks	Eosinophilic colitis	Case report	Abdominal pain disappeared after 5 weeks, and response persisted at 16 months

*Reported as relapse-free, symptom-free, cure, remission, or improvement of disease symptoms

Abbreviations: AD, atopic dermatitis; AST, autologous serum therapy; ASST, autologous serum skin test; CSU, chronic spontaneous urticaria; IVIG, intravenous immunoglobulin; URI, upper respiratory infection

2.4. Data analysis and its limitations

The SR included prospective open-label single-center studies, only case series, case reports, studies (one study in multiple allergic conditions had a mixed design of open-label portion and a small double-blind placebo-controlled portion), and one randomized controlled trial (RCT). Physicians used 1mL or 2mL (12mg human normal immunoglobulin with histamine dihydrochloride 0.15µg) histaglobulin in different dosing schedules for the same allergic condition. Hence, direct comparisons of the studies were not possible. The authors, therefore, extracted relevant information from the included studies and synthesized the information with mutual discussion to reach a logical conclusion.

2.5. Quality of evidence and risk of bias

The literature search did not retrieve any review articles or systematic reviews. The 25 included records were mainly prospective small single-center open-label studies (n=13), case reports (n=7), case series (n=3), one retrospective cohort study, and one RCT. Hence, risk-bias assessment could not be performed using one assessment tool. The researchers agreed to assess the risk of bias using different methods. The two researchers used the Cochrane Collaboration's tool to assess the risk of bias in an RCT.[20,21] The tool assesses six domains of bias such as random sequence generation (selection bias), allocation concealment (selection bias), blinding participants and personnel (performance bias), blinding outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). The risk of bias is stratified as low, high, and unclear.[20,21] The RCT was a single-blinded (patient-blinded) study in which patients were randomized in a 1:1 ratio to receive either histaglobulin or autologous serum therapy (AST) through a computer-generated random number table. Both researchers concluded that the RCT had an unclear risk of bias. The small double-blind placebo-controlled portion of mixed design study [17] was not evaluated for the risk of bias as enough information was unavailable. The risk of bias in open-label studies is usually assessed using the "Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool."[22,23] The ROBIN-I tool assesses biases due to confounding and participant selection (pre-intervention biases); biases in the classification of interventions and deviations from intended interventions (at-intervention biases); and post-intervention biases such as biases due to missing data, measurement outcomes, and selection of reported results. The tool storifies the risk as low, moderate, serious, and critical.[22,23] This ROBINS-I tool was used independently by the researchers to assess the bias risk in 13 prospective open-label studies. Most records exhibited a moderate risk of bias as most investigations were retrospective, patients and treatment were non-randomized, and physicians modified the dosing schedules. Therefore, the results were susceptible to confounding and various other biases. There is no tool for reporting the risk of bias in case series and case reports. The two researchers concluded there was no bias in reporting individual case histories, presenting symptoms, past medical history, laboratory investigations, skin prick tests, multiple allergosorbent tests (MAST) for the detection of allergen-specific IgE levels, treatments provided, disease scoring before and after treatment, and clinical course of disease. However, the treatment dose and duration were determined by the treating physician.

3. RESULTS

3.1. Dermatological conditions

3.2. Urticaria

Chronic urticaria is defined as widespread, short-lived (<24 hours) wheals with pruritus occurring daily or almost daily for ≥6 weeks.[4,5] Chronic urticaria have different aetiologies such as chronic idiopathic urticaria (CIU; approximately 70% cases of chronic urticaria with no cause identified) or chronic spontaneous urticaria (CSU) and urticaria secondary to physical stress, infections, vasculitis or pseudoallergy. Autoimmune or autoreactive urticaria, a subgroup of CIU, is reported to have histamine-releasing immunoglobulin G autoantibodies.[4,24] Chronic urticaria usually fluctuates and requires prolonged treatment and patient compliance. Achieving long-term remission and reducing antihistamine use are felt needs in chronic urticaria management.[5]Histaglobulin is expected to disrupt the chronic urticaria pathway at various steps and can, therefore, provide long-term relief in chronic urticaria.[12]

3.3. Systemic review findings

The SR retrieved 10 studies evaluating the efficacy and safety of histaglobulin in chronic urticaria (Table 2). In all the studies, patients underwent routine investigations such as complete blood count (CBC) with differential count, thyroid profile, renal and liver function tests, urine routine examination, stool examination for ova and cysts, and IgE. Response to treatment was measured using urticaria activity score (UAS)[25] or UAS-7[5,26,27] (Table 2). Apart from UAS, Kumar et al (2021) also assessed quality of life using the Chronic Urticaria Quality of Life (CU-Q2oL) questionnaire.[4] The histaglobulin group had a more significant overall improvement in the CU-Q2oL scores than the AST group (52.51% vs. 46.74%).[4] Six studies divided patients based on an autologous serum skin test (ASST) into ASST +ve and ASST –ve subgroups.[4–6,26,28,29] The study by Kumar et al. (2016),[29]Rajesh et al. (2016), and Thota (2019) reported no significant difference in UAS score reduction/disease improvement between histaglobulin-treated ASST +ve and ASST –ve subgroups. Kumar et al. (2021) and Ravi et al. (2023) found that both AST and histaglobulin caused significant UAS reduction. Kumar et al. (2021) suggested that UAS reduction was probably more in ASST +ve patients because they had more ASST +ve patients in the histaglobulin than in the AST group. On the other hand, Ravi et al. (2023) reported that the histaglobulin group saw a more significant UAS reduction compared to AST only in the ASST –ve group. In their study, the ASST +ve e group demonstrated an insignificant difference in UAS reduction by histaglobulin and AST.[6] Contrary to these studies, Chaudhari et al. (2019) reported significant UAS reduction at week 8 in AST versus histaglobulin group (P = 0.0168). Although the AST group demonstrated better UAS reduction than histaglobulin at all other time points, the difference was insignificant.[30] At week 8, the mean between-group UAS reduction was significant in the ASST –ve group (P= 0.044, favoring AST) and insignificant in the ASST +ve group (P= 0.2800). Further research is required to understand histaglobulin response by ASST results. A case series of four histaglobulin-treated CSU patients reported a varying dosing schedule. Though the injection was started weekly, its frequency was reduced based on a decrease in signs and symptoms. This was continued until

the patient achieved remission (sign and symptom-free for ≥four weeks without medication).[12] None of the studies reported any major side effects with histaglobulin. All the studies reported a considerable decrease in the use of rescue antihistamines after histaglobulin therapy.

Table 2: Studies evaluating the efficacy and safety of histaglobulin in chronic urticaria

Authors (year); country	Study design (N)	Patient population	Dosing	Comparator/rescue medication	UAS[25]/UAS 7[5,26,27]
Vignesh Nambi et al. (2023); India[6]	Prospective open-label single center (N=80; 20 in each group) (**ASST positive patients**: Group A: AST and Group B: histaglobulin **ASST negative patients**: Group C: AST and Group D: histaglobulin)	Chronic urticaria	1 mL histaglobulin subcutaneously or 2 mL autologous serum intramuscularly weekly for 8 weeks	Autologous serum therapy/Levocetrizine 5 mg	**ASST positive** Group A (AST): UAS mean reduction from 18.55 to 2.3 Group B (histaglobulin): UAS mean reduction from 16.85 to 4.3 *P= 0.27*, indicating that both groups showed a good response **ASST negative** Group C (AST): mean reduction from 18.15 to 5.1 Group D (histaglobulin): mean reduction from 15.6 to 1.65 *P 0.002, Group D showed more reduction than Group C*
Kim and Noh (2022); Korea[72]	Retrospective cohort (N=134; 114 on IHC and 20 on H1 antihistamines; treatment chosen by patients)	Chronic spontaneous urticaria	12 weekly injections of Histaglobulin or H1 antihistamine	H1 antihistamine/ levocetirizine 5 mg	**Histaglobulin group**: Mean UAS reduced from 35.4 at baseline to 11.3 (P<0.001) **Antihistamine group**: Mean UAS changed from 36 to 36.2 points (P=0.826) 90 patients (78.9%) completed 12 weeks of histaglobulin, and 40% achieved remission; the Remission rate increased from 40% to 58.6% after 24 weeks to 65.5% after 36 weeks 24 patients (21.1%) stopped before 12 weeks
Kim and Noh (2021); Korea[12]	Case series of four cases	Chronic spontaneous urticaria	Histaglobulin by subcutaneous route starting weekly and then by reducing frequency until in remission	None/ one patient each on fexofenadine or hydroxyzine and two patients each on levocetirizine	Two patients received 12 histaglobulin injections and achieved complete remission after 10 and 11 injections, respectively.

			(no signs and symptoms for 4 weeks without medication)		Two patients received 46 injections; one achieved remission after 35 injections, and the other after 41 injections.
Khemani et al (2021); India[26]	Prospective open-label single center (N=40; 32 completed eight weeks dosage and final follow-up at 24th week)	Chronic spontaneous urticaria	1 mL histaglobulin subcutaneously weekly for 8 weeks	None/levocetirizine 5 mg	No difference in **UAS 7** reduction between males and females. ASST was negative in 9 (28%) and positive in 23 (72%) of patients who completed the study **UAS 7** reduction more in ASST-negative **ASST-positive**: From 13.28±3.95 at baseline to 3±2.26 at week 8 to 3.21+2.21 at week 24 **ASST-negative**: From 11±3.54 at baseline to 1.58±1.83 at week 8 to 1.83±0.93 at week 24 The difference in UAS reduction between ASST-positive and ASST-negative patients was insignificant at 8 weeks (P=0.06) and significant at week 24 (P= 0.04). Histaglobulin was effective in producing long-term remission.
Kumar et al. (2021); India[4]	Prospective open-label single center (N=96; 48 in each group; 62 completed six weeks of treatment and two follow-up visits)	Chronic idiopathic urticaria	1 mL histaglobulin subcutaneously or 1 mL autologous serum intramuscularly for 6 consecutive weeks; evaluation at 3 weeks and 6 weeks after treatment	Autologous serum therapy/ Ebastine 20mg as rescue medication	**Histaglobulin**: UAS Reduced from 24.5±5.3 at 1st week to 12.9±2.2 at 3 weeks (−11.78; P <0.001) and 11.8±4.2 at 6 weeks (−10.95'; P <0.001) **Autologous serum**: UAS reduced from 22.9±7.3 at 1st week to 14.01±6.7 at 3 weeks (−4.747; P <0.001) and 14.3±5.8 at 6 weeks (−4.880; P <0.001) Results by ASST were not reported. However, more histaglobulin than AST patients were in the ASST-positive group, suggesting that ASST-

					positive patients had better responses than ASST-negative patients. 20 patients dropped out before 6 weeks of treatment due to complete remission
Chaudhari et al. (2019); India[30]	Prospective, comparative, randomized controlled, single-blinded study (N=60; 30 in each group; 1:1 randomization)	Chronic urticaria with itching and wheals occurring daily or near-daily (≥3 times/week) for ≥6 weeks and had moderate and severe urticaria score	1 mL histaglobulin subcutaneously or 2 mL autologous serum intramuscularly weekly for 8 weeks	Autologous serum therapy/ levocetirizine	AST: mean reduction in UAS from 68.5% to 29% (from 12.3±1.66 at baseline to 5.23±2.97 at week 8) **Histaglobulin**: mean reduction in UAS from 69.4% to 39.4% (from 12.6±1.5 at baseline 7.1±2.77 at week 8) Significant reduction in both groups by 8 weeks; Insignificant intra-group differences at week 1 to 7; significant between-group differences favoring AST at week 8 (P = 0.0168)
Godse et al (2019); India[27]	Prospective open-label single center (N=38; 37 completed Day 28 follow-up)	Chronic urticaria on active treatment with antihistamines	1 mL histaglobulin subcutaneously weekly for 3 weeks, followed up to Day 42	None/second generation antihistamines as Levocetirizine, Desloratadine, Loratidine and third-generation antihistamines Fexofenadine	**UAS 7**: significant reduction from Day 0 (15.8 ±6.1) to Day 28 (6.0±6.2) (p<0.0001) By Day 28, 21 (56.8%) showed 'moderate improvement,' and 13(35.1%) showed 'clear-cut improvement.'
Thota (2019); India[28]	Prospective open-label single center (N=35; 26 completed eight weeks dosage and final follow-up at 24th week)	Chronic spontaneous urticaria	1 mL histaglobulin subcutaneously weekly for 8 weeks	None/levocetirizine 5 mg	Mean UAS decreased from 5.1 at baseline to 1.01 at week 24, an 80.2% reduction 17/35 patients (48.5%) attained complete remission at 24 weeks. **ASST-positive**: mean UAS reduced from5.4 to 1.02 (81.11% reduction) **ASST-negative**: mean UAS reduced from 4.8 to 1 (79.16% reduction) The difference between ASST positive and negative was not statistically significant.
Kumar et al. (2016)[29]	Prospective correlation study (N=110;) **ASST positive**: n=48 **ASST negative:** n=62	Chronic spontaneous urticaria	Histaglobulin weekly injections subcutaneously for 5 weeks; 3rd month and 6th month	None/ antihistamines + prednisolone 20 mg once daily for 1 week	**ASST-positive**: 81.25% showed improvement; 64.6% (31 of 48) showed significant improvement in disease activity **ASST-negative**: 43.54% showed improvement; 33 of 62 who failed to

					achieve remission on antihistamines showed significant improvement in disease activity when histaglobulin and prednisolone were added. The difference between ASST positive and negative was not statistically significant (P = 0.328)
Rajesh et al (2016); India[5]	Prospective open-label single center (N=52; 29 completed 8-week regimen)	Adults (>18 years) with chronic spontaneous urticaria: history of daily or almost daily widespread, itchy, spontaneous wheals for ≥6 weeks, with individual lesions lasting <24 hours	1 ml histaglobulin subcutaneous for 8 consecutive weeks; weekly evaluation and at 24 weeks	None/ levo-cetirizine 5 mg	Mean **UAS 7**: reduced from 18.9 ± 6.3 to 3.7 ± 5.4 by 8 weeks (80.4% reduction) **ASST-positive**: reduced from 19.8 ± 5.7 to 3.8 ± 5.8 (80.8% re-duction) **ASST-negative**: reduced from 17.80 ± 6.9 to 3.5 ± 4.9 (80.3% re-duction) (*P* = 0.85). Among 29 patients who completed 8 weeks: Complete remission (UAS = 0): 14 patients Excellent response (>75% reduction): 21 patients; Good response (51–75% reduction): one patient; moderate response (25–50% reduction): six patients; and poor response (<25% reduction): one patient Final assessment after 24 weeks: 23 (45%) patients had complete remission (of these, 17 patients had completed the study's 8 weeks of continuous therapy, and six patients had taken histaglobulin continuously for at least 4 weeks) Seven patients had complete resolution of symptoms within 4 weeks and withdrew from the study

ASST, autologous serum skin test; IHC, immunoglobulin-histamine complex

UAS, urticaria activity score[25]: Score 0 (no wheels no pruritus'); Score 1 (wheals: Mild: <20 wheels/24hours; pruritus: mild, present but not bothersome); Score 2: (Wheals: moderate: 20-50 wheals/24hour; pruritus: moderate: troublesome but does not interfere with sleep); Score 3: (Wheals: severe: >50 wheals/24hours; pruritus: severe: sufficiently troublesome to interfere with sleep); UAS total score: <6 as well controlled, 7-15 as mild, 16-27 as moderate and 28-42 as severe urticaria

UAS 7: 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 12 wheals). The sum of the score (0-6) for each day is summarised over one week, with a maximum of 42. Higher scores indicate more severe disease.

3.4. *Psychological conditions occurring concurrently in urticarial*

The SR retrieved seven case reports (two case series of three cases each and one case report) demonstrating the effective treatment of psychological conditions (panic disorder, depression, and anxiety) occurring concurrently with chronic urticaria.[31–33] Allergic conditions like chronic urticaria are known to be associated with psychiatric manifestations.[31–33] These conditions are often referred to as 'allergic psychiatric manifestations (APM)' or 'histamine-mediated psychiatric manifestations (HmPM). Histamine plays a role in balancing the neuroimmunomodulation.[31] Therefore, histamine H1 receptor antagonists such as chlorpheniramine and hydroxyzine have been used to treat APM due to their ability to inhibit serotonin reuptake.[31] Histaglobulin helps in treating APM such as panic disorder, depression, and anxiety by exerting an effect similar to the antagonism of all the four histamine receptors (Figure 2).[33]

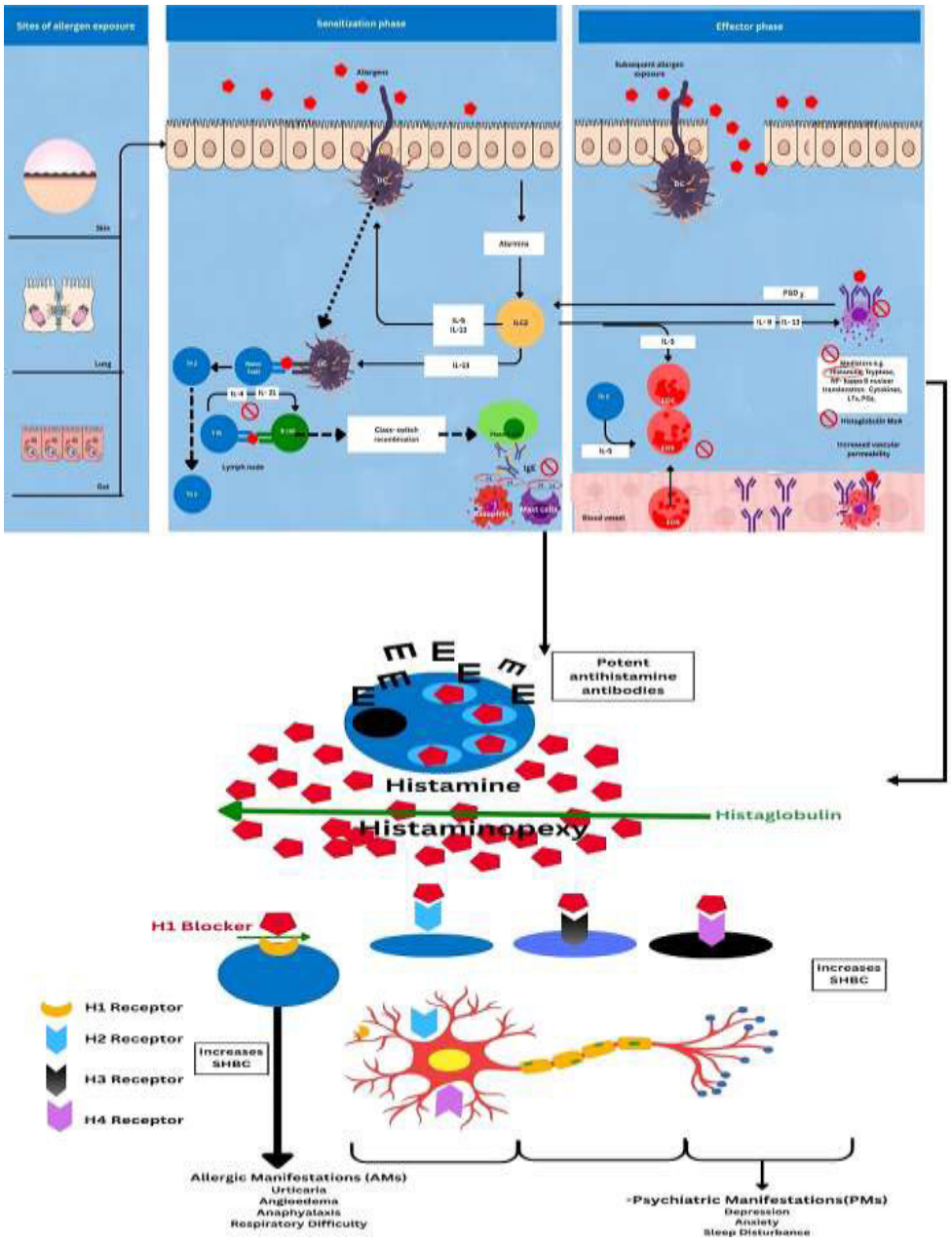

Fig 2: Histaglobulin: mechanism of action in chronic allergic conditions.[8,11–15,33]

Histaglobulin exerts three effects in chronic allergic conditions. 1. Histaminopexic effect: produce highly potent antihistamine antibodies that neutralize allergen-induced histamine released from human peripheral blood basophils and mast cells and increase serum histamine binding capacity (SHBC); 2. Inhibiting NF-kappa B nuclear translocation and downregulating proinflammatory cytokine; 3. Altering cytokine production from T-helper cells: inhibiting IL-4 and IL-5, and hence, decreasing IgE biosynthesis and eosinophil accumulation, respectively. Psychiatric manifestations of chronic allergic diseases are probably controlled by blocking histamine receptors. Abbreviations: B, B lymphocyte; BAS, basophil; DC, dendritic cell; EOS, eosinophil; IL, interleukin; ILC2, type 2 innate lymphoid cell; LT, leukotrienes; MC, mast cell; PG(D2), prostaglandin (D2); sIgE, allergen-specific immunoglobulin E; Tfh, T follicular helper cell; Th naïve/2, T helper lymphocyte naïve/type 2; TSLP, thymic stromal lymphopoietin.

3.5. *Systemic review findings*

A case report of a 52-year-old female with CSU and concurrent panic disorder that developed and persisted simultaneously for 23 years was effectively and safely treated with histaglobulin and hydroxyzine. Her CSU and panic disorder remitted after 27 injections, and there was an improvement in allergic rhinitis and symptoms of upper respiratory infections (URIs) .[31] There was significant improvement in the Beck Depression Inventory (BDI-2) for

depression, the State-Trait Anxiety Inventory (STAI) for anxiety, and the Beck Hopelessness Score (BHS). There were two published reports of the same case series of three cases. The case series reported remittance of depressive symptoms and urticaria after weekly histaglobulin in two Korean female patients (a 30-year-old treated for 12 weeks and a 28-year-old treated for 26 weeks).[32,33] The BDI, STAI status, and STAI trait score became normal in both patients. In another case where a 50-year-old female Korean patient had significant improvement in urticaria after 12 weeks of histaglobulin treatment, but there was no improvement in depression and anxiety. Her BDI score was 38 (severe), and her STAI status score improved slightly from severe (62) to moderate at 57, but the STAI trait score was normal at 53 after treatment.[32,33]

3.6. Atopic dermatitis

Atopic dermatitis is usually treated with symptomatic relief medications (systemic corticosteroids, mycophenolate mofetil, or cyclosporin A). However, these medications produce disappointing results, and long-term use raises the risk of toxicity and side effects.[9] Though allergen-specific immunotherapy treats atopic dermatitis, its clinical usefulness is debatable.[9] The clinical efficacy of allergen-specific immunotherapy is dose-dependent. Still, higher doses are associated with an increased risk of side effects such as generalized urticaria, respiratory distress, dizziness, and shock.[9] Hence, there is a felt need for non-specific immunotherapeutic agents with low-side effect profiles in atopic dermatitis.[3,9]

3.7. Systematic review Findings

The literature search retrieved two studies from Korea evaluating the efficacy and safety of histaglobulin in atopic dermatitis. One was a prospective single-center study (Nahm et al., 2008), and the other was a case series of four cases treated at a single center (Noh, 2020).

3.8. Prospective pilot single-center study

The study from Korea enrolled 20 patients with atopic dermatitis and hypersensitivity to house dust mites not effectively controlled by standard medical therapies.[9] The subjects were treated with IHC and allergen-specific immunotherapy for 12 months. Of the 18 subjects who completed 12 months of study, the SCORAD (clinical severity scoring system for atopic dermatitis) values significantly decreased from 43.6 ± 15.9 at baseline to 27.8 ± 18.3 at 6 months and 18.3 ± 14.9 at 12 months ($P < 0.001$). After 12 months of treatment, there was a decrease in the SCORAD value of ≥30% and ≥ 50% from baseline in 94.4% and 55.6% of the subjects, respectively.[9] The SCORAD values at 6 and 12 months also reduced significantly in nine subjects with severe atopic dermatitis (SCORAD values ≥40) ($P = 0.01$ and $P = 0.008$, respectively). In these subjects, a decrease in the SCORAD value of ≥30% and ≥ 50% from baseline occurred in 88.9% and 33.3%of the subjects, respectively. Rescue treatment with oral corticosteroids was taken by two of the nine subjects.[9] The study concluded that long-term use of histaglobulin was feasible and effective in atopic dermatitis and had no significant side effects.[9]

3.9. Case series

The case series presented four cases of atopic dermatitis from a single center in Korea treated with histaglobulin (12mg human immunoglobulin/0.15µg histamine complex) subcutaneously (deltoid area of the upper arm) every week for 24 or 36 weeks (Table 3).[8] All patients stopped antihistamine therapy for at least a week before receiving histaglobulin. Case 1 (19 years, female) achieved remission after 36 injections; Cases 2 and 3 (both 15 years, male) and Case 4 (20 years, female) showed significant clinical and symptomatic improvement after 24 injections. All patients showed a significant decrease in URI frequency as well. The case series showed that histaglobulin is effective and safe as long-term therapy in atopic dermatitis with the additional benefit of reducing URI frequency.

Table 3: Case series in atopic dermatitis treated with histaglobulin

Case presentation	SCORAD (total score: 103)		MAST (41 allergens; normal negative range for each allergen: 0.000-0.349 IU/mL)		SPT (53 allergens; +ve test at ≥3 mm)		IgE (IU/mL) (normal range: ≤350)		Eosinophil fraction (%) (normal range: 0-5)		TEC (normal range: 0-500)		ECP (normal range: 0-24)		URI frequency (times/year)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Case 1: 19 years; female; h/o AD; presented with oozing and severe eczematous lesions, mainly on the face	42.5	0	0	0	1	1	96.5	25.7	4	1	250	50	7.17	2.72	2	0
Case 2: 15 years male; h/o AD since infancy, aggravated in the past year; presented with erythematous lesions on the face, neck, and elbow	29	16.5	10	9	6	7	967	1790	9.6	5.3	480	300	23.3	39.6	4	0
Case 3: 15 years, male; h/o AD since infancy, aggravated in the past week; presented with vesiculopapular eruptions on the face and neck	26.1	14.2	2	2	0	0	240	390	3.3	4	240	260	33.5	32.7	24	0
Case 4: 20 years; female; h/o AD since infancy; presented with eczematous lesions on the posterior neck, flexure area of the elbow, and popliteal area	32.9	5	7	13	10	7	1362	1281	3.6	5.5	350	440	44.7	52.8	12	2

Note: all patients fulfilled the Haniffin and Rajka criteria; all had been symptomatically treated (e.g., antihistamines and steroids) and had persisting fluctuating signs and symptoms despite treatment

Abbreviations: AD, atopic dermatitis; ECP, Eosinophil cationic protein; h/o, history of; IgE, immunoglobulin E; MAST, multiple allergosorbent test; SCORAD, clinical severity scoring system for atopic dermatitis; SPT, skin prick test; TEC, total eosinophil count; URI, upper respiratory infection

3.10. Cutaneous drug allergy

Only one case report from India highlighting the role of histaglobulin in preventing multiple drug allergies was retrieved. The author used histaglobulin to prevent drug allergy in a few patients and published a detailed case report of a 40-year-old male with multiple drug allergies (Figure 3).[14]

The case report was based on only clinical presentations. Laboratory reports and allergy-specific tests were not reported. Blood, urine, and stool tests were performed at the first presentation, but the nature of the tests or their values were not incorporated in the case report. The author concluded that since histaglobulin has been used to treat recurrent urticaria, its use in cutaneous drug allergy should be explored.[14]

Fig 3: Case presentation of a 40-year-old male with multiple cutaneous drug allergies treated with histaglobulin. Many of the drugs the patient was allergic to were reintroduced after treatment without any allergic reactions[14]

3.11. Psoriasis

The systematic review retrieved only one case report from Korea highlighting the curative effects of histaglobulin in biopsy-confirmed psoriasis in a 15-year-old with scaly skin eruptions and concurrent allergic rhinitis.[7] In the past, his symptoms of allergic rhinitis were controlled by once-daily 5 mg levocetirizine. He underwent a detailed allergy evaluation. The psoriasis severity score was evaluated using the Psoriasis Area and Severity Index (PASI). The skin lesions and clinical manifestations started improving after the third histaglobulin injection and disappeared completely after the eighth injection. Thereafter, four weekly histaglobulin injections were continued, and the patient showed no signs or symptoms of psoriasis during four weeks. After this, histaglobulin was stopped, and the patient was psoriasis-free for more than 18 months. The case report did not mention the histaglobulin injection dose and schedule, except for the 12 injections. However, the laboratory tests before and after treatment were captured (Figure 4) and showed a decrease in allergic reactions. The authors concluded that histaglobulin started early in patients with mild to moderate psoriasis can induce remission. However, larger trials are required to test its therapeutic and curative efficacy in psoriasis.[7]

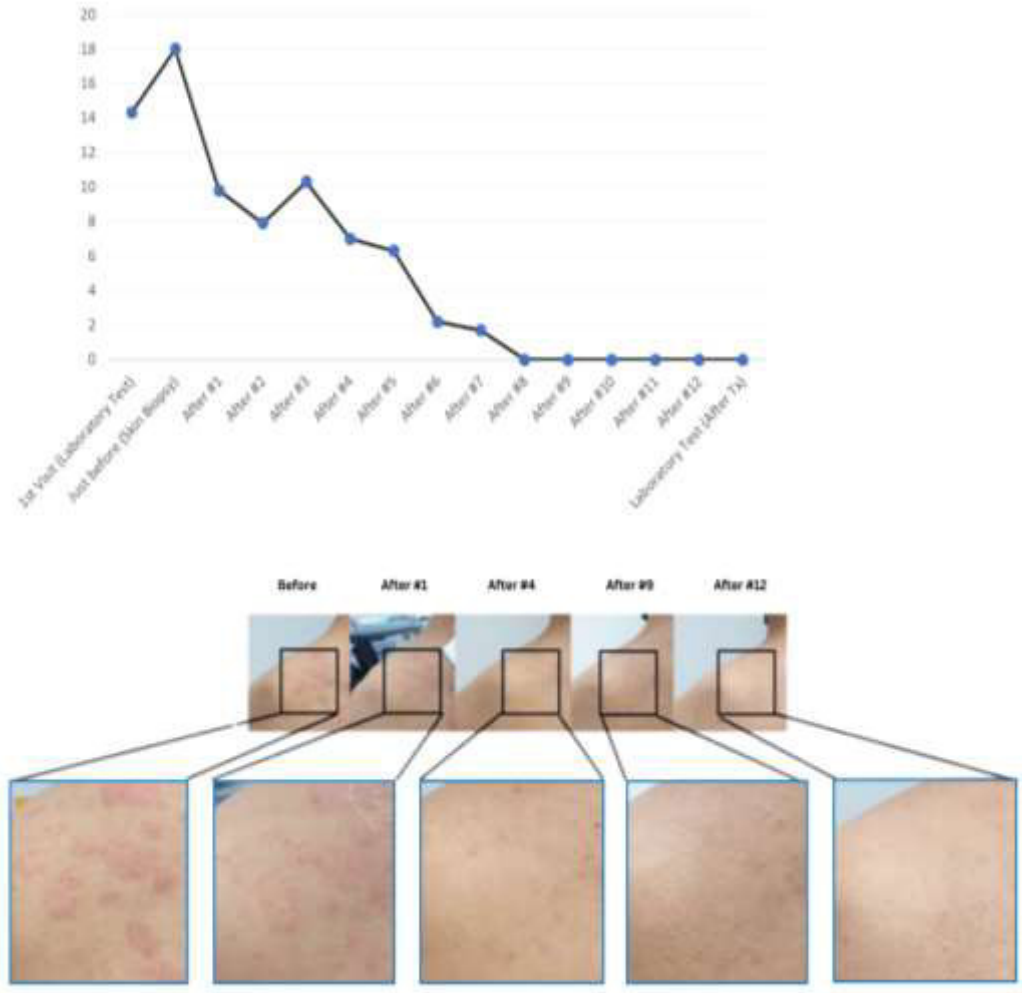

Fig 4: Laboratory tests and results before and after treatment of psoriasis with histoglobulin[7]

Clinical progression of Histaglobulin therapy in a psoriasis patient: The patient's psoriasis progressed, and the PASI score increased from 14.5 to 18 points over 2 weeks, during which laboratory tests and skin biopsy were performed. The clinical response was rapid, and the patient's symptoms and signs improved after the first injection. Although the patient temporarily showed some irritation after the third injection, the clinical manifestations, including skin lesions, improved continually and completely disappeared after the eighth injection. The patient showed no symptoms or signs of psoriasis for 4 weeks, during which 4 subsequent injections were administered (from the ninth to the twelfth injection). The patient stopped taking medication, and the patient did not experience recurrence for more than 6 months.

3.12. Pfeiffer-Weber-Christian disease (PWCD)

Pfeifer-Weber-Christian disease (PWCD) is also known as idiopathic nodular panniculitis.[34] It is a rare condition characterized by lobular relapsing panniculitis of adipose tissue with multiple organ involvement and systemic symptoms (recurrent fever, malaise, systemic inflammation, and cutaneous nodules). There is no consensus on effective PWCD therapy. Still, it usually responds to corticosteroids and immunosuppressive agents such as cyclosporine A.[34] There is a felt need for an effective treatment/cure for PWCD.

3.13. Systematic review: Findings

The filtered literature retrieved two publications on the same case from Korea, highlighting the role of sequential histaglobulin and intravenous immunoglobulin (IVIG) in steroid- and cyclosporine A-resistant PWCD.[34,35] A 35-year-old female presented with excruciatingly painful breast mass and multiple allergic conditions, as depicted in Figure 5. Her atopic dermatitis fulfilled the Hanifin and Rajka criteria, and its severity was measured before and after treatment using SCORAD. She underwent detailed evaluation for allergic diseases, including specific IgE levels for 41 allergens, which were tested using a MAST, skin prick test for 53 allergens, CBC with differential counts, and serum eosinophil cationic protein. Medical knowledge and literature could not explain the improvement in breast mass size and pain during the first histaglobulin injection. It was suspected that the benefits were due to the immunoglobulin in histaglobulin. Hence, sequential IVIG was started, as shown in Figure 5. Previous literature had shown that IVIG alone was not sufficient for PWCD remission.[35] Hence, it could be concluded that histaglobulin was essential for remission.The patient achieved PWCD remission with sequential histaglobulin and IVIG. After the second course of histaglobulin, atopic dermatitis and allergic rhinitis were remitted, and food allergies disappeared. However, further trials are required to establish the role of histaglobulin with or without IVIG in the management of PWCD and in achieving remission.

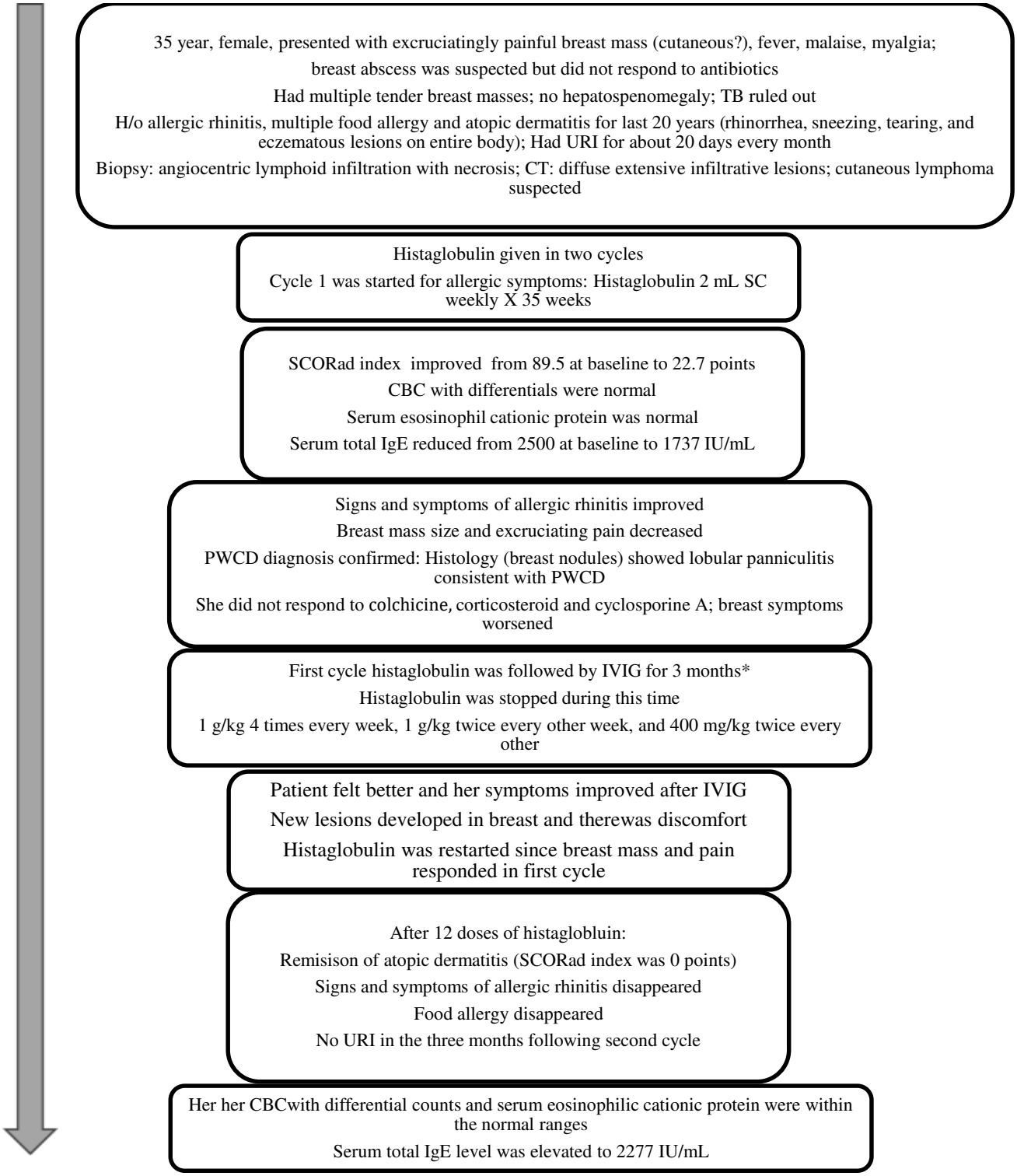

Fig 5: Case presentation of a 35-year-old female treated with sequential histaglobulin and intravenous immunoglobulin (IVIG) in steroid- and cyclosporine A-resistant Pfeiffer-Weber-Christian disease (PWCD)[34,35]

The rationale was that breast symptoms improved due to the immunoglobulin component of histaglobulin
Abbreviations: CBC, complete blood count; IgE, immunoglobulin E; IVIG, intravenous immunoglobulin; SCORAD, clinical severity scoring system for atopic dermatitis

3.14. Respiratory Conditions

3.15. Allergic rhinitis

Allergic rhinitis can be treated with anti-allergic drugs and anti-inflammatory agents.[36] Intra-nasal steroids are commonly used to treat allergic rhinitis.[36,37] However, long-term use of intra-nasal steroids can cause dryness, nasal irritation, bleeding, altered taste and smell, headache, and rarely septal perforation. Long-term use can also cause habituation, and steroid withdrawal can cause recurrence. Immunomodulators like histaglobulin can overcome these limitations, possibly treat the condition, and prevent its recurrence through immune modulation. [37]

3.16. Systematic review: Findings

The literature search retrieved four studies from India[3,10,36,37] (Table 4) evaluating the efficacy and safety of histaglobulin in allergic rhinitis. Of these, one was a histaglobulin monotherapy

study of 50 patients with allergic rhinitis, of which 23 had a complete response, 21 had a fair, and six had a poor response.[10] Two single-center, prospective, open-label studies of identical study design from India compared the efficacy and safety of long-term use of histaglobulin versus intra-nasal steroids in allergic rhinitis.[36,37] Both steroids and histaglobulin significantly reduced the eosinophil and IgE antibody levels and shifted patients from severe "Rhinorrhoea, Nasal congestion and Sneezing" (RNS) scores to moderate scores. However, patients receiving histaglobulin showed more significant improvement compared to intra-nasal therapy steroids and reduced the recurrence rate compared to steroids.[36,37] Also, histaglobulin therapy had no major adverse effects, whereas long-term use of intra-nasal steroids was associated with adverse effects, as discussed above. The two studies concluded that long-term use of histaglobulin in patients with allergic rhinitis was effective and safe.[36,37] Another study compared histaglobulin monotherapy with histaglobulin in combination with antihistamines such as terfenadine or cetirizine; the study found no significant therapeutic advantage of combining antihistamines with histaglobulin.[3] The results of the four studies show that histaglobulin is effective in both treatment-naïve allergic rhinitis and chronic allergic rhinitis not controlled with conventional treatment.

Table 4: Studies evaluating the efficacy and safety of histaglobulin in allergic rhinitis

Authors (year); country	Study design (N)	Patient population	Dosing	Comparator	Rescue	Signs and symptoms	Eosinophil count (cells/mL)	IgE (IU/mL)	Safety
Prasenajith (2023)[37]; India	Prospective open-label single center (N=64; 32 in each group)	Treatment naïve with symptoms of one-week duration;18-50 years	SC/week X 10 weeks >> once monthly booster dose X 3 months	Nasal steroids: Fluticasone (2 puffs)	Montelukast and levocetirizine and nasal spray containing Azelastine hydrochloride and Fluticasone propionate	**Histaglobulin vs nasal steroids**			
						RNS score: A number of patients changed from severe at baseline to moderate at the end of the study in the histaglobulin group (P<0.05)	From 115 at baseline to 55 at end of study vs 120 at baseline to 85 at end of study (P<0.04)	80 at baseline to 40 at end of study vs 85 at baseline to 70 at end of study(P<0.04)	No safety issues were reported. Reduced recurrence Helped overcome side effects of steroids
Madhukar (2019)[36]; India	Prospective open-label single center (N=60; 30 in each group)	Treatment naïve with symptoms of one-week duration;18-50 years	SC/week X 10 weeks >> once monthly booster dose X 3 months	Nasal steroids: Fluticasone (2 puffs)	Montelukast and levocetirizine and nasal spray containing Azelastine hydrochloride and Fluticasone propionate	**Histaglobulin vs nasal steroids**			
						RNS score: A number of patients showed improvement between baseline and end of the study in the histaglobulin group (P<0.05)	The Histaglobulin group showed more significant improvement at the end of the study vs baseline.	Histaglobulin groups more significant improvement at the end of the study vs baseline	No safety issues were reported Reduced recurrence Helped overcome side effects of steroids
Verma et al. (2018)[10]; India	Prospective single center (N=50)	Long-duration allergic rhinitis is not responding to conventional treatments; 16-50 years	1 ml SC X 4 injections at 4 days interval X 2 months>>1 injection/month X 3 consecutive months>> booster dose after 6 months	None	None	Significant decrease in hypertrophic changes on PNS (P<0.05) 44 patients showed significant improvement in symptoms vs. 6 patients who did not show significant improvement (P< 0.001)	Increased eosinophil count was seen in 44 vs 7 patients before and after therapy(P<0.05)	Increased IgE was seen in 47 vs. 3 patients before and after therapy (P<0.05)	No adverse effects were reported.

Narayana et al (1997)[3]; India	Prospective single center (N=54; 18 subjects each were on histaglobulin alone, Histaglobulin + terfenadine, and Histaglobulin + cetirizine)	11 to 57 years	SC/week X 10 weeks>> monthly booster doses X three months in responding to cases.	Histaglobulin alone versus histaglobulin + antihistamines terfenadine (60 milligram O.D) or cetirizine (10 milligram O.D)	None	**Response** Histaglobulin alone: 59.61% Histaglobulin + terfenadine: 61.69% Histaglobulin + cetirizine: 56.86%	No significant difference in pre versus post-therapy (values not reported)	No significant difference in pre versus post-therapy (values not reported)	No adverse effects reported

OD, once daily; RNS, Rhinorrhea, Nasal congestion and sneezing; SC, subcutaneous

3.17. Bronchial asthma with or without allergic rhinitis

Low SHBC is implicated as the cause of allergic diseases. SHBC is reduced by 20-30% or more in patients with allergies compared to normal individuals.[15,38] There is no effective cure for bronchial asthma, and most treatment options focus on disease pathogenesis intending to provide symptomatic relief.[15] It is hypothesized that if SHBC can be raised in patients with bronchial asthma (±allergic rhinitis) by histaglobulin administration, it may lead to a cure for these allergic conditions.[15,39]

3.18. Systematic review: Findings

The literature search retrieved three records evaluating the efficacy and safety of histaglobulin in bronchial asthma. The first was a prospective single-center study from India[15]. The study evaluated the changes in IgE and SHBC levels in allergic patients (bronchial asthma and/or allergic rhinitis) after histaglobulin treatment. It also evaluated whether SHBC levels significantly differed between allergic and non-allergic individuals. The study identified 67 normal and 135 allergic persons (majority >40 years) based on total serum IgE (ELISA) (normal: <100 IU/mL; allergic: >200 IU/mL). The 135 allergic patients were first administered antihistamine, mast cell-membrane stabilizers, anti-inflammatory, and bronchodilator drugs for 5-7 days, followed by subcutaneous histaglobulin injection in two phases. In phase 1, patients received six primary doses of 1 mL at weekly intervals; in phase 2, they received three booster doses of 1 mL each, first 15 days after the last primary dose, second at one month after the first booster, and third at two months after the second booster dose. Histaglobulin was well tolerated, and there were no adverse side effects. During the five-year follow-up after histaglobulin treatment, 132 patients (97.8%) were free from allergic manifestations.[15]The average before-treatment SHBC of allergic patients was 83.6 µg/mL, 39% lower than the average SHBC of normal persons of 116 µg/mL. After histaglobulin treatment, the SHBC level was raised by an average of ~33% to 111.6 µg/mL in 122 (90.4%) allergic patients. A concomitant decrease in total IgE level was seen in most allergic patients.[15] The second record was a poster obtained during the bibliography search of an article by Sivanandhan and Dhanalakshmi (2022). This poster, presented by the same author at the 2007 World Allergy Congress, recruited 161 allergic patients (bronchial asthma with or without allergic rhinitis) for 15 years.[39] Patients were administered six primary and three booster doses of histaglobulin following preparation with drugs and according to the schedule described in the Sivanandhan and Dhanalakshmi (2022) study. After histaglobulin administration, a complete cure of clinical symptoms of bronchial asthma and allergic rhinitis was seen in 152 (94.6%) patients; 96 patients were symptom-free for over four years.[39] Of the 61 patients for whom IgE levels were estimated, 55 patients (90.2%) showed a significant reduction in IgE ($P<0.0001$) and were clinically free of asthma. The author concluded that histaglobulin could be an effective and safe option for treating bronchial asthma with or without allergic rhinitis. However, according to the author, the cure is possible only if the novel histaglobulin administration schedule is followed after preparing the patients with antihistamine, mast cell-membrane stabilizers, anti-inflammatory, and bronchodilator drugs for 5-7 days.[15,39] However, this method should be validated through larger randomized and real-world studies. The third record was a small old study by Tanaka (1977)[40] (N=13). The study showed that irrespective of the concurrent medications, histaglobulin treatment was effective in alleviating the symptoms of bronchial asthma in 58.3% of patients; histaglobulin was very effective in three cases, effective in four, and ineffective in five cases.

3.19. Multiple dermatological/respiratory allergic conditions

The SR included one old study by Gelfand et al. (1963)[17] that evaluated the role of weekly histaglobulin in multiple allergic conditions (asthma, allergic rhinitis, seasonal hay fever, atopic dermatitis, and urticaria). Of the patients recruited, 47 patients were treated with histaglobulin in an open-label manner, and 14 patients received either histaglobulin or placebo (n=7 in each group) in a double-blind setting. Six patients in the double-blind group had two allergic conditions. Histaglobulin was least effective in hay fever but very effective in all other conditions. Patients on histaglobulin improved significantly compared to those on placebo; 66.7% were essentially symptom-free, 18.8% showed substantial improvement, and 15% showed no improvement. Even those treated in an open-label design showed improvement in the symptoms of their allergic condition. The response to histaglobulin was slow and appeared over weeks, but once achieved, it persisted for a long without further treatment with histaglobulin.[17]

3.20. Other allergic conditions

3.21. Primary eosinophilic colitis

Primary eosinophilic colitis (PEC) is diagnosed by exclusion of other painful abdominal conditions. It is characterized by excessive eosinophilic infiltration of the colon in the absence of an underlying cause such as helminthic infestation, food allergies, etc.[41] PEC is usually treated according to the suspected underlying cause through diet change, antihelminthics, glucocorticoids, and immunomodulatory drugs. However, these medications are seldom effective since PEC's cause is unknown. PEC is considered a histamine-mediated gastrointestinal syndrome. Antihistamines are usually given for symptomatic control. However, antihistamines are not curative. Histaglobulin, an immunoglobulin/histamine complex (IHC), has anti-allergy properties mainly mediated through histaminopexy.[41]

3.22. Systematic review: Findings

The literature search filter retrieved one case report of a 49-year-old female from Korea that demonstrated that IHC was effective and curative in PEC (Figure 6).[41] PEC was diagnosed because of her history of allergy, abdominal pain, eosinophilic infiltration of the colon on pathology and the elimination of other possible underlying diseases through a battery of tests. Though the abdominal pain was controlled with steroids and antihistamines, it recurred frequently over the last nine years. Post histaglobulin therapy, she was symptom-free during the follow-up of 16 months. Monosodium glutamate (MSG) was suspected to cause hypersensitivity, ameliorated by histaglobulin. Histamine was suspected to be the cause of abdominal pain, and IHC (histaglobulin) seemed to have antinociceptive effects against histamine-mediated pain.

Initial presentation	Presentation to the clinic	Other relevant history	IHC (Histaglobulin)	Outcome
Sudden acute abdominal cramping pain with eosinophilia Initial treatment: high-dose oral methylprednisolone (60 mg) as pulse therapy (pain disappeared) Took 2.5 mg methylprednisolone daily for 9 years without a diagnosis being made (sudden bouts of abdominal pain now and then) No parasitic	Itching and skin rash Rhinorrhoea Sneezing Eosinophilia Abdominal pain No diarrhea No weight loss Steroids stopped Basic immunological evaluation* Basic rheumatologic tests** Stool test and parasite antibodies:	heavy alcohol drinker Smoked a half-pack of cigarettes/day X >10 years anaphylactic reaction to contrast media 9 years prior Diazepam allergy: urticaria and itching 4 years prior No history of intestinal obstruction, colonic perforation, or surgery.	Weekly 12 mg subcutaneously X 10 weeks Levocitrazine 5 mg within 30 minutes of abdominal cramping and pain Abdominal pain well controlled after 3 weeks of histaglobulin Abdominal pain disappeared after 5 weeks of histaglobulin	The PEC remitted completely with 5 weeks of IHC therapy MSG was strongly suspected as the cause of the PEC Urticaria remitted after 8 weeks of IHC No abdominal pain after MSG rechallenge at 16 months

Fig 6: Case presentation of a 49-year-old female from Korea with primary eosinophilic colitis[41]

**** complete blood count with differential, serum eosinophil cationic protein, serum total IgE and IgE levels for 41 specific allergens using a multiple allergosorbent test(MAST), Serum IgG, A. M, D, and IgG subclass levels, skin prick test for 53 allergens***
***** ANA, anti-citrullinated peptide antibody, rheumatoid factor, and C-reactive protein***
 # Clonorchis sinensis, Paragonimus westermani, Cysticrcosis, Sparganum and Toxocara cannis
Abbreviations: ANA, anti-nuclear antibody; Ig, immunoglobulin; IHC, immunoglobulin/histamine complex; MSG, monosodium glutamate; PEC, primary eosinophilic colitis

4. DISCUSSION

This systematic review showed that histaglobulin could be an effective and safe treatment for allergic, dermatological conditions such as chronic urticaria (including CIU and CSU), atopic dermatitis, cutaneous drug allergies; allergic respiratory conditions such as allergic rhinitis and bronchial asthma; and other allergic conditions such as PWCD with multiple food allergies and atopic dermatitis and primary eosinophilic colitis. The treatment was curative or of curative intent in all these conditions, with remission evident in RCT, open-label prospective studies, mixed design studies (open-label and a double-blind placebo-controlled portion), and case series/case reports. The systematic review also showed that despite its use in allergic conditions for decades, literature on histaglobulin/IHC is largely lacking. The freely available literature published in English is either from India or Korea. Most studies included were from 2016 to 2023, with three studies published before that in 2008[9], 2006[14], and 1997[3], and a poster published in 2008[39] (Table 1). None of these studies had a placebo-controlled design. Usually, placebo-controlled trials are published early during drug development, and histaglobulin is an old molecule. These must have been published long ago and in languages other than English. Hence, literature covering placebo-controlled trials was unavailable in publicly available repositories such as MEDLINE (PubMed) and Google Scholar. Some old literature (n=148) in languages other than English investigated the role of histaglobulin/IHC in several dermatological and respiratory allergic conditions. None of these articles had an abstract or full text available on PubMed or Google Scholar. These included predominantly Russian language articles investigating the role of IHC in eczema; allergic dermatitis; occupational allergic dermatitis and eczema; dermatoses; chronic urticaria and occupational dermatoses; pediatric eczema; chronic relapsing urticaria; pediatric bronchial asthma and allergic bronchitis; vasomotor rhinitis; and bronchial asthma.[42–57]. Other articles were published in Polish (chronic urticaria, prurigo, and pruritus'; paediatric bronchial asthma; atopic bronchial asthma; recurrent obstructive respiratory tract infections)[58–62], Ukrainian (paediatric bronchial asthma; paediatric allergic diseases)[63,64], Italian (intradermal histaglobulin in paediatric asthmatic syndromes; allergic diseases including bronchial asthma, headaches, and allergic dermatoses)[65,66], German (bronchial asthma)[67], French (recurrent inflammatory states of the respiratory tract in atopic children; chronic otitis of allergic origin)[68,69] and Japanese language (allergic rhinitis)[70]. These articles show that apart from the allergic conditions discussed in this SR, histaglobulin has been used to treat eczema, allergic dermatitis, dermatoses, vasomotor rhinitis, recurrent obstructive respiratory tract infections, chronic otitis of allergic origin, and paediatric allergic conditions of skin and respiratory tract. However, histaglobulin has been used for decades to treat chronic urticaria, atopic dermatitis, allergic rhinitis, and bronchial asthma. The review also showed that histaglobulin treatment may or may not decrease the IgE levels and eosinophil counts, which are implicated in the pathogenesis of allergic conditions. Patients with allergic conditions may have normal serum IgE level/eosinophil counts. Further, serum IgE level/eosinophil counts may be increased due to several non-allergic conditions in the patient.[71] Hence, IgE level/eosinophil counts should not be considered as the sole markers of improvement after Histaglobulin therapy. Rather, disease activity scores and clinical improvement should be considered. All studies in the SR showed marked improvement in disease activity score and marked relief in clinical symptoms after histaglobulin therapy. The SR also suggests that histaglobulin monotherapy alone is as effective as histaglobulin plus antihistamines[3]. However, this must be validated in larger trials across multiple allergic conditions.

There were a total of seven case reports demonstrating improvement in APM (panic disorder depression and anxiety) in patients with chronic urticaria treated with histaglobulin.[31–33] Similar findings with APM improving or remitting with histaglobulin have not been reported with other allergic conditions. Though histamine antagonism plays a role in neuroimmunomodulation, histamine antagonists are always unsuccessful in treating APM.[32] However, since histaglobulin indirectly antagonizes all four histamine receptors and has improved or remitted APM, its role in APM should be investigated in larger, well-designed trials across various allergic conditions that respond to histaglobulin. The SR also captured that histaglobulin can be given for prolonged periods as weekly injections or more frequently (at intervals of 4 days) until complete remission or significant improvement in allergic symptoms. Authors reported remission in urticaria for 12 to 24 months after stopping histaglobulin. Drug allergies could be prevented with yearly booster doses. Authors also reported that patients could be free of symptoms of bronchial asthma during the follow-up period of about 5 years after histaglobulin therapy. None of the studies reported any side effects with histaglobulin. Histaglobulin can be easily given as an outpatient treatment due to its subcutaneous mode of delivery at 4 days or weekly intervals.

5. STRENGTHS AND LIMITATIONS

Literature was searched using only free resources such as MEDLINE (PubMed) and Google Scholar. Hence, the SR will lack some important articles published on the paid sites. All the retrieved articles are small open-label prospective studies, case reports, or case series. There was only one RCT and one mixed-design study of an open-label portion and a double-blind placebo-controlled portion. Since allergic conditions are prevalent in India, and because histaglobulin has been used to treat them for decades, the authors had expected a significant amount of literature, including large real-world studies, on this topic. However, very few articles could be retrieved. This could be because the authors struggled to create an all-encompassing search string. Also, a full literature search could not be carried out for these articles in PubMed and Google Scholar as the terms "immunoglobulin-histamine complex," "immunoglobulin/histamine complex," or "human normal immunoglobulin with histamine dihydrochloride" pulled up many irrelevant articles. Hence, these terms had to be combined with histaglobulin or its various trade names to achieve a filterable search number. The searches retrieved old literature published in languages other than English. Abstracts for these were unavailable, so they could not be included in the systematic review. Further, a complete literature search in languages other than English was not feasible. Hence, the literature search could have missed several articles. Despite these shortcomings, this is the first SR to capture the efficacy and safety of histaglobulin/IHC in many allergic conditions. The authors expect this will create awareness regarding the important role of histaglobulin/IHC in these allergic conditions amongst treating physicians/specialists who treat chronic allergy cases in India. Authors of several case studies and small trials included in the SR noted disease remission with histaglobulin. However, it is important to carry out large multicentre prospective blinded RCTs or prospective well-designed open-label trials and observational real-world studies to document the efficacy (including remission) and safety benefits of histaglobulin in various types of chronic allergic conditions not responding to conventional treatments.

6. CONCLUSION

In conclusion, the systematic review (SR) demonstrates that histaglobulin/IHC, administered subcutaneously at 4 days or weekly intervals, is an effective and safe treatment for various allergic conditions. This dosing regimen has been shown to control disease activity, reduce severity, decrease the reliance on anti-allergic medications and their associated adverse effects, and improve patients' quality of life. However, variability in dosing schedules among physicians suggests that further standardization may enhance treatment outcomes. The literature supports the potential for histaglobulin to achieve long-term symptom-free states in conditions such as chronic urticaria, atopic dermatitis, allergic rhinitis, and asthma. Nonetheless, larger, well-designed trials are necessary to validate these findings and assess the generalizability of histaglobulin's benefits across broader populations. Promising results in psoriasis, cutaneous drug allergies, and primary eosinophilic colitis highlight its broader therapeutic potential. At the same time, further exploration into its role in treating allergic psychiatric manifestations is warranted.

7. AUTHORS CONTRIBUTION STATEMENT

All authors conceptualized and designed the systemic review of the literature. They reviewed methodology, data analysis and interpretation, and edited the manuscript. All authors approved the final version of the manuscript.

8. FUNDING

'Bharat Serums and Vaccines Limited paid for medical writing support. None of the authors are paid any honorarium.'

9. ACKNOWLEDGMENT

The authors thank Dr. Kokil Mathur and Dr. Punit Srivastava of Mediception Science Pvt. Ltd (www.mediception.com) for providing medical writing support in the preparation of this publication.

10. CONFLICT OF INTEREST

Dr. Saswata Banerjee and Dr. Hemal Patel are employees of Bharat Serums and Vaccines Limited. The authors declare that their affiliation with the company does not influence the objectivity, analysis, or interpretation of the data presented in this article. The study was conducted independently, adhering to ethical research standards, and any potential conflicts of interest have been disclosed transparently.

11. REFERENCES

1. Doll RJ, Joseph NI, McGarry D, Jhaveri D, Sher T, Hostoffer R. Epidemiology of Allergic Diseases. In: Allergy and Asthma: The Basics to Best Practices [Internet]. Cham: Springer International Publishing; 2019 [cited 2024 May 4]. p. 31–51. Available from: https://doi.org/10.1007/978-3-030-05147-1_2
2. Krishna MT, Mahesh PA, Vedanthan PK, Mehta V, Moitra S, Christopher DJ. The burden of allergic

diseases in the Indian subcontinent: barriers and challenges. The Lancet Global Health. 2020 Apr 1;8(4):e478–9.
3. Narayana J, Shanthi T, Bharadwaj S. Efficacy of histaglobulin on allergic rhinitis. Indian J Otolaryngol Head Neck Surg. 1997 Jan;49(1):77–9.
4. Kumar S, Dhillon SS, Brar B, Singh A. Comparative Evaluation of the Therapeutic Efficacy and Safety of Injected Histaglobulin versus Autologous Serum Therapy in Chronic Urticaria. J Clin Aesthet Dermatol. 2021 Mar;14(3):38–41.
5. Rajesh G, Keerthi S, Karthikeyan K, Venkatesan M. Weekly injection of histaglobulin produces long-term remission in chronic urticaria: A prospective clinical study. Indian J Pharmacol. 2016;48(3):292–7.
6. Vignesh Nambi R, Gurusamy S, Danny G, Nagaraju S. A Comparative Study of Autologous Serum Therapy and Histaglobulin in Chronic Urticaria: Underutilized Modalities Revisited! Medical Journal of Dr DY Patil University [Internet]. 2023 Oct 11 [cited 2024 Apr 10]; Available from: https://journals.lww.com/mjdy/abstract/9000/a_comparative_study_of_autologous_serum_therapy.99891.aspx
7. Kim HS, Noh G. Immunotherapy using Histobulin™ in psoriasis: A case report. Clin Case Rep. 2022 May 12;10(5):e05831.
8. Noh G. Immunotherapy using Histobulin in atopic dermatitis. Clin Case Rep. 2020 Nov 11;9(1):113–7.
9. Nahm DH, Lee ES, Park HJ, Kim HA, Choi GS, Jeon SY. Treatment of atopic dermatitis with a combination of allergen-specific immunotherapy and a histamine-immunoglobulin complex. Int Arch Allergy Immunol. 2008;146(3):235–40.
10. Verma A, Sachan A, Singh A, Sachan S. Effect of histaglobulin in allergic rhinitis- a prospective study. Journal of Evidence based Medicine and Healthcare. 2018 Dec 10;5(50):1–7.
11. Jutel M, Agache I, Zemelka-Wiacek M, Akdis M, Chivato T, del Giacco S, et al. Nomenclature of allergic diseases and hypersensitivity reactions: Adapted to modern needs: An EAACI position paper. Allergy. 2023;78(11):2851–74.
12. Kim HS, Noh G. Induction of remission in chronic urticaria by immunotherapy using immunoglobulin/histamine complex (Histobulin™): a case report. Allergy Asthma Clin Immunol. 2021 Nov 12;17(1):116.
13. Liebhart J, Zak-Najmark T, Małolepszy J, Nadobna G, Liebhart E. Changes of histaminopexy in patients with bronchial asthma and chronic urticaria after histaglobin administration. Arch Immunol Ther Exp (Warsz). 1986;34(4):385–9.
14. Mohanty M, Mohapatra S, Pattnaik K, Swain T. Case Report- Prevention of multiple drug allergy by histaglobulin. Indian Journal of Pharmacology (ISSN: 0253-7613) Vol 38 Num 1. 2006 Jan 1;38.
15. Sivanandhan K, Dhanalakshmi S. A Novel Method for Treating Bronchial Asthma with Newly Designed Histaglobulin Therapy. Int J Pharm Bio Sci [Internet]. 2022 [cited 2024 Apr 12];13(3). Available from: http://ijpbs.net/abstract.php?article=7092
16. Kirtchev P, Frankland AW. The Histamine Binding Power of Human Serum from Allergic and Non-Allergic Subjects. Allergy. 1965;20(3):153–9.
17. Gelfand HH, Cinder JC, Grant SF, Soiffer M. Evaluation of histamine-gamma globulin (histaglobin) in the treatment of various allergic conditions. Ann Allergy. 1963 Mar;21:150–5.
18. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29;n71.
19. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021 Mar 29;n160.
20. Higgins J, Savović J, Page M, Elbers R, Sterne J. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). In: Cochrane Handbook for Systematic Reviews of Interventions version 64 (updated August 2023) [Internet]. Cochrane; 2023 [cited 2023 Dec 5]. Available from: https://training.cochrane.org/handbook/current/chapter-08
21. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011 Oct 18;343:d5928.
22. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016 Oct 12;355:i4919.
23. Sterne J, Hernán M, McAleenan A, Reeves B, Higgins J. Chapter 25: Assessing risk of bias in a non-randomized study. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). In: Cochrane Handbook for Systematic Reviews of Interventions version 64 (updated August 2023) [Internet]. Cochrane; 2023 [cited 2024 Apr 11]. Available from: https://training.cochrane.org/handbook/current/chapter-25
24. Sachdeva S, Gupta V, Amin SS, Tahseen M. CHRONIC URTICARIA. Indian J Dermatol. 2011;56(6):622–8.
25. Godse KV. Urticaria Meter. Indian J Dermatol. 2012;57(5):410–1.
26. Khemani UN, Sajgane AA. Efficacy of Injection Histaglobulin in Treatment of Chronic Urticaria. JCDR [Internet]. 2021 [cited 2024 Apr 10]; Available from: https://jcdr.net/article_fulltext.asp?issn=0973-709x&year=2021&volume=15&issue=4&page=WC09&issn=0973-709x&id=14825
27. Godse K, Tare D, Gawali R. Single centre experience with histaglobin as an adjunctive treatment of chronic urticaria: A post marketing surveillance study. IP Indian Journal of Clinical and Experimental Dermatology. 2019;5(3):243–8.
28. Thota S mangadevi. Efficacy of Injection Histoglob in Treatment of Chronic Urticaria-A Prospective Study. IOSR-JDMS. 2019;18(3):57–62.
29. Kumar YHK, Bhaskar S, Shankar K. Comparative Study of Positive Versus Negative Autologous Serum Skin Test in Chronic Spontaneous Urticaria and its Treatment Outcome. N Am J Med Sci. 2016 Jan;8(1):25–30.
30. Chaudhari A, Mehta H, Agrawal N. Comparative study of effectiveness of autologous serum and histaglobulin in autologous serum skin test positive and negative cases of chronic urticaria. Indian Journal of Allergy, Asthma and Immunology. 2019 Jun;33(1):25.

31. Kim HS, Noh G. Effects of the immunoglobulin/histamine complex on panic disorder concurrent with chronic spontaneous urticaria: a case report. Journal of Medical Case Reports. 2023 Jul 28;17(1):341.
32. Noh G, Cho S. Effects of Histobulin on Depression and Anxiety in Chronic Urticaria: Psychiatric Manifestations or Psychiatric Comorbidities of Chronic Urticaria?: A Case Report [Internet]. 2020 [cited 2024 Apr 26]. Available from: https://www.researchsquare.com/article/rs-94970/v1
33. Kim HS, Noh G. Effects of Histobulin (Immunoglobulin/Histamine Complex) on Depression and Anxiety in Chronic Urticaria: Psychiatric Manifestations or Psychiatric Comorbidities of Chronic Urticaria?: A Case Report. Journal of Clinical & Experimental Immunology. 2021 Nov 30;6(6):390–6.
34. Noh G, Han CW. Intravenous Immune Globulin (IVIG) Therapy After Unsuccessful Treatment with Corticosteroid and Cyclosporine A in Pfeifer-Weber-Christian Disease: A Case Report. Am J Case Rep. 2021 Jan 4;22:e929519-1-e929519-7.
35. Noh G. Histobulin as a complementary but essential therapeutic for Intravenous Immune Globulin Therapy of Pfeiffer-Weber-Christian disease with multiple allergic diseases and its effects on allergic disease: A case report. Clinical Case Reports. 2021;9(2):966–72.
36. Madhukar M, Paparaja S. Comparative study of therapeutic effect of histaglobulin with nasal steroids in allergic rhinitis: A hospital based prospective study. MIJOENT [Internet]. 2019;11(2). Available from: https://www.medpulse.in/ENT/Article/Volume11Issue2/ENT_11_2_1.pdf
37. Prasenajith L. A prospective study to compare the therapeutic effects of histaglobulin and nasal steroids in allergic rhinitis. J Cardiovasc Dis Res [Internet]. 2023;14(7). Available from: https://www.jcdronline.org/admin/Uploads/Files/64b8cb1c48fca3.75769622.pdf
38. Fuchs E, Gronemeyer W, Brückner-de Velliet M. The Possibility of Affecting Allergic Reactions by Histamine-Gamma-Globulin Compound. International Archives of Allergy and Applied Immunology. 2009 Jul 30;66(Suppl. 1):291–2.
39. Sivanandhan K. Abstract No 459, Asthma - a curable disease in Abstracts of the XX World Allergy Congress™ 2007 December 2-6, 2007, Bangkok, Thailand. World Allergy Organ J. 2008 Nov 15;1(Suppl 3):A1–1013.
40. Tanaka Z. Experiences with Histaglobulin in patients of bronchial asthma. PMJ. 1977;15(3).
41. Kim HS, Noh G. Treatment of primary eosinophilic colitis using immunoglobulin/histamine complex. Clinical Case Reports. 2023;11(1):e6885.
42. Nikitina NM. [Histaglobin in the treatment of eczema and neurodermatitis in children]. Pediatriia. 1966 Mar;45(3):38–41.
43. Karagezian MA. [Treatment of allergic dermatitis with repeated courses of injection of histaglobin]. Sov Med. 1967 Sep;30(9):136–7.
44. Karagesian MA. [Treatment of occupational allergic dermatitis and eczema with histaglobin]. Sov Med. 1974 Jul;0(7):122–5.
45. Skripkin IK, Kashtanova MG, Somov BA, Butov IS, Putintseva SV. [Use of histoglobin in the treatment of some dermatoses]. Sov Med. 1971 Jan;34(1):124–6.
46. Butovetskiĭ LD, Bannikov VK. [Treatment of some dermatoses with histoglobin]. Sov Med. 1971 Jan;34(1):126–9.
47. Shevliakov LV. [Histaglobin treatment of chronic urticaria and occupational dermatoses]. Vestn Dermatol Venerol. 1973 Feb;47(2):62–3.
48. Niamdorzh T. [Histaglobin treatment of children with eczema]. Vestn Dermatol Venerol. 1972 Nov;46(11):71–3.
49. Iskakov TK. [Experiences in the use of histaglobin in young children, suffering from bronchial asthma and asthmatic bronchitis]. Pediatriia. 1966 Jul;45(7):23–7.
50. Sokolova TS, Fedotova AM, Iskakov TK. [Treatment of bronchial asthma in children with histaglobin and its effect on several aspects of histamine metabolism]. Vopr Okhr Materin Det. 1968 Aug;13(8):32–6.
51. Kondrat'ev GG, Sergeev VP. [Treatment of eczema with histaglobin]. Vestn Dermatol Venerol. 1968 Aug;42(8):65–7.
52. Tikhomirova NV. [Effect of histaglobin therapy on the antihistamine factor in chronic relapsing urticaria]. Vestn Dermatol Venerol. 1970 Aug;44(8):24–7.
53. Fiveĭskiĭ VD. [Local use of histaglobin in vasomotor rhinitis]. Zh Ushn Nos Gorl Bolezn. 1974;0(2):31–5.
54. Rapoport ZZ, Shvetskaia AF, Zinov'eva LI. [Use of histaglobin in the treatment of bronchial asthma]. Sov Med. 1973 Jul;36(7):139–40.
55. Borodin IP, Egorova-Mezhevalova AG. [THE USE OF A COMBINATION OF GAMMA-GLOBULIN WITH HISTAMINE (HISTAGLOBIN) FOR THE TREATMENT OF ALLERGIC DISEASES]. Sov Med. 1963 May;26:74–9.
56. Germanets II, Rezenkina LD, Anton'ev AA. [Complex therapy of occupational allergic dermatoses with pyrogenal and histaglobin]. Gig Tr Prof Zabol. 1974 Feb;18(2):22–5.
57. Stadchenko NA, Teliiants SN. [Experience in the use of Histaglobin in allergic diseases]. Sov Med. 1966 Aug;29(8):73–6.
58. Rudzki E, Czubalski K. [Results of treatment of chronic urticaria, prurigo and pruritus with histaglobin]. Przegl Dermatol. 1967;54(5):571–4.
59. Chmielewska-Szewczyk D, Szczypiorski K. [Histaglobin treatment of bronchial asthma in children]. Pediatr Pol. 1970 Jul;45(7):807–14.
60. Jankowska R, Małolepszy J, Nowak I. [Influence of histaglobin therapy on skin tests and clinical symptoms in patients with atopic bronchial asthma]. Pneumonol Alergol Pol. 1992;60(11–12):69–72.
61. Krawczuk J. [Histaglobin in the prevention and treatment of recurrent obturative respiratory tract infections in children]. Pediatr Pol. 1974 Dec;49(12):1525–9.
62. Chyrek-Borowska S, Bogdanikowa B, Droxd J. [Histaglobin in treatment of allergic diseases with reference to serum protein determination]. Pol Tyg Lek. 1971 Sep 13;26(37):1432–5.
63. Tikhiĭ AK, Levchenko LM. [Use of apizatron and histaglobin in the overall treatment of bronchial asthma in children]. Pediatr Akus Ginekol. 1974;(1):11–3.
64. Bezrukov LA, Boriakovskiĭ VG, Dziuba OL, Kozachek VI, Lasitsa OI. [Histaglobin treatment of allergic diseases in children]. Pediatr Akus Ginekol. 1977;(1):18–9.
65. Berardi G, Fornaci M, Rossi R. [Our experience in the treatment of asthmatic syndromes in children with

intradermal histaglobin and gamma globulin]. Minerva Pediatr. 1970 Mar 24;22(12):556–9.
66. Morini V. [Preliminary note on the clinical trial of a combination of histamine, human gamma globulin and serotonin for the radical desensitizing therapy of allergic diseases, with special reference to bronchial asthma, headaches and allergic dermatoses. I]. Clin Ter. 1969 Sep 15;50(5):465–73.
67. Schrádi A, Bene J. [Results in the therapy of bronchial asthma using histaglobine]. Z Erkr Atmungsorgane Folia Bronchol. 1972;136(3):337–45.
68. Buczylko K, Latkowski B, Zalewski P. [Histaglobin in the treatment of recurrent inflammatory states of the respiratory tract in atopic children]. Rev Laryngol Otol Rhinol (Bord). 1988;109(2):191–4.
69. Latkowski B. [Histaglobin in the treatment of chronic otitis of allergic origin]. Rev Laryngol Otol Rhinol (Bord). 1980;101(5–6):235–40.
70. Matsui T, Sato F, Takenouchi S. [Clinical effects of histaglobin on allergic rhinitis]. Jibiinkoka. 1970 Nov;42(11):971–2.
71. Laurent J, Noirot C, Ansquer JC, Laurent G, Kestenbaum S, Lagrue G. [How to define the normal level of serum IgE in adults?]. Ann Med Interne (Paris). 1985;136(5):419–22.
72. Kim HS, Noh G. Effects of the immunoglobulin/histamine complex in chronic spontaneous urticaria focusing on remission induction. Allergy. 2022 Sep;77(9):2846–8.