Induction of Remission in Chronic Urticaria by Immunotherapy Using Immunoglobulin/histamine Complex (Histobulin^{TM}): A Case Report

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Case report

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Abstract

Background: Symptom control is a major concern in chronic urticaria. Histobulin^{TM} is a histamine/immunoglobulin complex and has been reported to be effective for chronic urticaria.

Case Presentation: HistobulinTM was administered until remission was induced instead of fixing the number of administrations in four cases of chronic urticaria. Two patients showed an early response and finished treatment with 12 injections of Histobulin, and the other two patients showed a late response and were injected 43 times and 46 times. Remission was induced successfully in all four cases.

Conclusions: Hitobulin^{TM} is not only effective but also induces remission in CSU. The Histobulin^{TM} therapy protocol in CSU may be better if the treatment is continued until remission is achieved. Based on the responses of the patients, early responders and late responders were present. The progress of the disease during treatment consisted of a slow improvement phase and a rapid improvement phase. Uniquely, the appropriate allergy laboratory results, including blood eosinophil fraction, total IgE and eosinophil cationic protein level, were normal in all 4 cases. Further studies concerning the mechanisms of Histobulin^{TM} may be needed.

Background

Urticaria occurs in 0.5-5% of the general population [1]. Chronic urticaria (CU) is diagnosed when the episodes of urticaria last longer than six weeks [2]. Chronic urticaria is classified as chronic inducible urticaria (CIU) and chronic spontaneous urticaria (CSU). Histamine, which is released from mast cells, plays a major role in the pathogenesis of CU. The binding of FcεRI and IgE subsequently induces the degranulation of mast cells and the secretion of histamine and leukotriene. Currently, the treatment of chronic urticaria is focused mainly on effective symptomatic control, including the use of antihistamines, which are used for primary treatment. The disease is not controlled by antihistamines in many cases, and more advanced treatment is then needed [2, 3]. Recently, omalizumab, which is a monoclonal antibody to IgE that inhibits the binding of FcεRI and IgE, was used as a very effective therapeutic [4]. However, despite its effectiveness, recurrence of CSU is well documented with omalizumab treatment [5].

TNF-α inhibitors and intravenous immune globulin (IVIG) are also known to be effective therapeutics [6, 7]. However, these two drugs are not curative therapeutics and have a high cost and/or severe side effects. There is no causative treatment for CSU. The itching and skin lesions in CSU negatively affect the quality of life of patients [8]. Therapeutics for causative treatment in CUS as well as effective treatment for refractory CSU are needed.

Histobulin™ (Green Cross PD, Korea) is a histamine-fixed immunoglobulin preparation comprised of 0.15 μg of histamine dihydrochloride and 12 mg of IgG [9] and was developed from histamine-fixed serum [10], and it can inhibit antigen-induced histamine release from human peripheral blood basophils and rat peritoneal mast cells [11]. Histobulin is known to be effective in allergic rhinitis, bronchial asthma, and atopic dermatitis [12–15].

Immunoglobulin/histamine complexes have been reported to be effective in chronic urticaria for several decades without sufficient reports [16–18]. In a recent report, some patients showed remission, and the remission of chronic urticaria by Histobulin™ treatment was the focus [17]. In this report, Histobulin™ therapy was continued until remission was induced, which is a new therapeutic approach. Finally, remission was induced in all four cases, and two types of clinical courses are described in this report.

Case Presentation

Case 1

A 69-year-old Korean female patient visited the Department of Allergy and Clinical Immunology, Cheju Halla General Hospital, due to urticaria and itching for 5 months. She had no specific family history or past medical history. She was taking fexofenadine for 2 months every day before the visit to our clinic (Table 1a). There were no inducible factors, including stress, exercise, cold or sunlight exposure. Based on the diagnostic criteria for CSU, a diagnosis of chronic spontaneous urticaria (CSU) was made [2], and an urticaria activity score of 7 was given for the evaluation of the clinical severity [19]. The total score was 93 points. In the clinical severity scoring, the five points that the patient showed initial improvement, the reduction of medication (medication reduction), the state of medication free (medication free), the state of symptom-free (symptom free) and remission (continuous symptom-free more than 4 weeks) were documented.

Basic allergic tests (blood tests and the skin prick test) were conducted before and after treatment. In the patient, the 2nd laboratory test was not done. They had blood tests for complete blood counts with differentials, serum eosinophil cationic proteins, serum total IgE and IgE levels for specific allergens using a multiple allergosorbent test (MAST, Green Cross PD, Korea). In the MAST test, the specific IgEs for 41 allergens were evaluated, including *Dermatophagoides pteronyssinus* (Dp), *Dermatophagoides farina* (Df), cat, dog, egg white, milk, soybean, crab, shrimp, peach, mackerel, rye pollen, house dust mites, cockroach, *Clasporium herbarum*, *Aspergillus fumigatus*, *Alternaria alternata*, birch-alder mix, white oak, short ragweed, mugwort, Japanese hop, hazelnut, sweet vernal grass, Bermuda grass, orchard grass, timothy grass, reed, *Penicillium notatum*, sycamore, sallow willow, poplar mix, ash mix, pine, Japanese cedar, acacia, oxeye daisy, dandelion, Russian thistle, rod pig and weed. The test results showed the levels of specific IgE for each allergen, and a normal negative range was 0.000-0.349 IU/mL.

A skin prick test was also performed for 53 allergens. The allergens tested by the skin prick test were *Alternaria*, *Aspergillus fumigatus*, *Aspergillus nigre*, *Candida albicans*, *Cladosporium*, *Penicillium chrysogenum*, German cockroach, Dp, Df, dog, cat, gray elder/silver birch, grass mix, mugwort, short ragweed, black willow pollen, orchard grass, Bermuda grass, timothy, English plantain, English rye grass, Holm oak, Japanese cedar, cotton flock, milk mix, egg mix, chicken, beef, pork, cod, oyster, salmon, prawn, mackerel, tuna, almond, peanut, bean, carrot, cabbage, walnut, maize, peach, tomato, black pepper, spinach, wheat flour, rabbit, kapok, hop, F acacia, pine and poplar. Skin prick tests were performed on the upper back between the scapular spine and the area of the spine at L1. The area to be tested was cleaned

with alcohol and coded with a skin marker pen corresponding to the number of allergens being tested. The marks were placed 2 cm apart. A drop of allergen solution was placed beside each mark. A small prick through the drop was made through the skin using a Morrow Brown Needle→ (Morrow Brown Allergy Diagnostics, USA) by holding the needle perpendicular to the test site and placing the needle firmly through the testing extract and into the epidermis. The drop was removed immediately after the skin was pricked, and the needle was discarded immediately. Histamine hydrochloride 1 mg/ml was used as a positive control, and physiological saline was used as a negative control. The allergy results were measured using the wheal size. Reactions were read after 15 min and described as negative (0, no reaction), 1+ (reaction greater than the control reaction but smaller than half the size of the histamine reaction), 2+ (equal to or more than half the size of the histamine reaction), 3+ (equal to or more than the size of the histamine reaction) and 4+ (equal to or more than twice the size of the histamine reaction). The minimum size of a positive reaction was 3 mm.

Patients underwent laboratory tests and the skin prick tests before and after treatment. Characteristically, all patients had normal results in the classical allergy tests, including eosinophil fraction in white blood cell counts, basophil fraction in white blood cell counts, eosinophil cationic protein (ECP) and serum total IgE levels (Table 1b). However, the sensitization patterns in blood and skin were variable and different among the four cases (Table 1c).

Histobulin™ (Green Cross, Korea) is composed of 12 mg human immunoglobulin/0.15 μg histamine complex (2 ml in an ample). Histobulin was administered by subcutaneous injection in the deltoid areas of the upper arm every week. In all cases, patients were instructed to take levocetrizine when they were uncomfortable, or if the histamine injection interfered with normal living, working or sleeping.

The patient received 12 injection of Histobulin. Her initial clinical severity was 38 points. The clinical progress is shown in Fig. 1a. She showed initial clinical improvement after the second injection (initial improvement) (Fig. 1b, Table 1). The weekly medication frequency was reduced after the third injection (Medication Reduction). After the eighth injection, she no longer took medication (Medication Free). She was symptom-free (symptom free) continuously (remission) after the tenth injection. Remission was defined when symptoms and signs were not present for 4 weeks without medication. Her remitted state was maintained for more than 18 months until the present.

Case 2

A 63-year-old Korean female patient visited the Department of Allergy and Clinical Immunology, Cheju Halla General Hospital, due to urticaria and itching for 3 years. She had no specific family history or past medical history. There was no specific inducible factor for the development of urticaria. She was taking hydroxyzine for 3 years every other day before visiting our clinic (Table 1a). She met the diagnosis of CSU.

Histobulin™ was administered to her 12 times. Her initial clinical severity was 40 points (Fig. 1a). She showed an initial clinical improvement after the first injection (Fig. 1b, Table 1a). Weekly medication

frequency was reduced after the fourth injection (Medication Reduction). After the eighth injection, she took no longer took medication (Medication Free). She was symptom-free (symptom free) continuously (remission) after the eleventh injection. Her remission has been maintained for more than 4 years until the present.

Case 3

A 53-year-old Korean female patient visited the Department of Allergy and Clinical Immunology, Cheju Halla General Hospital, due to urticaria, itching and angioedema on the face every 15 days for 3 months. Urticaria and itching developed, and angioedema followed. The symptoms and signs persisted for 7 days. Recently, she took levocetirizine every other day for 2 months (Table 1a). She had no specific family history. In her past medical history, she was diagnosed with colon cancer and received surgical treatment 6 months prior. There was no specific inducible factor for urticaria, and her diagnosis was CSU.

Histobulin was given 46 times. Her initial clinical severity was 50 points (Fig. 1a). She showed an initial clinical improvement after the ninth injection (initial improvement) (Fig. 1b, Table 1a). The weekly medication frequency was reduced after the twenty-third injection (Medication Reduction). After the thirty-sixth injection, she no longer took medication (Medication Free). She was symptom-free (symptom free) continuously (remission) after the 41^{ST} injection. Her remission has been maintained for more than 6 months until the present.

Case 4

A 51-year-old Korean female patient visited the Department of Allergy and Clinical Immunology, Cheju Halla General Hospital, due to urticaria and itching for 4 months. She was taking levocetirizine every other day for 4 months (Table 1a). She had no specific family history or past medical history. She had no specific inducible factor for the development of urticaria. Her diagnosis was CSU.

Histobulin was given 46 times. Her initial clinical severity was 42 points (Fig. 1a). She showed an initial clinical improvement after the sixth injection (Fig. 1b, Table 1a). Medication frequency per week was reduced after the eleventh injection (Medication Reduction). After the fifteenth injection, she took medication no more (Medication Free). Her symptoms and signs were no longer present (symptom free) after the twenty-fourth injection, and her symptom-free status was maintained continuously (remission) after the thirty-fifth injection. Her remission has been maintained for more than 24 months until the present.

Discussion And Conclusions

Effectiveness of Histobulin™

The major points of this report are that remission was achieved by Histobulin™ in CSU and that Histobulin™ was effective. Despite the results that remission was observed in some patients in a previous

report [17], in this trial, the new concept was applied which consisted of continuing Histobulin™ treatment until remission was induced, rather than fixing the treatment frequency and period. The frequency of injection that led to the actual clinical improvement in a patient was 30 times that of injection in one case (Table 1a, Fig. 1b). In this case, Histobulin™ therapy may be ineffective only by 12 injections in another previous report [11]. Considering that symptomatic control is currently the major target of treatment of CSU in international guidelines [2], the induction of remission with Histobulin™ is the revolutionary result.

Omalizumab is used for refractory chronic urticaria [4]. It is also not a curative treatment. A high cost and the need for repetitive treatments due to recurrences [5] are the limitations of treatment. If Histobulin™ induces remission, it might be better that Histobulin™ therapy is considered an effective therapeutic in CSU. Histobulin™ therapy is indicated in several situations, including cases in which, due to quality of life, patients want to improve the suffering from chronic urticaria and to cease medication.

Laboratory Characteristics of Chronic Spontaneous Urticaria

The main pathogenesis of CSU is mast cell degranulation and histamine release, which are common in allergic diseases. In the classic pathway, allergy sensitization and provocation by exogenous allergens and subsequent mast cell granulation and allergen-specific Th2 activation result in Th2 cytokine production, including IL-4 and IL-5 production. Consequently, serum total IgE, allergen-specific IgE and blood basophil fraction are increased by IL-4 through repetitive allergen challenges. In particular, in atopic dermatitis, the blood eosinophil fraction and serum eosinophil cationic protein were increased by IL-5 through repetitive allergenic challenges. Therefore, representative allergy laboratory tests, including blood eosinophil and basophil fractions, serum eosinophil cationic protein, and serum total IgE levels, are possibly increased in allergic diseases. However, the immunopathogenesis of CSU does not follow the classic pathway bypassing the exogenous allergen-IgE-FcεRI pathway (Fig. 2a), and the representative allergy laboratory tests were likely all negative. In the four patients of this report, the laboratory results were all negative (Table 1b).

Exogenous allergens are not causes of CSU, and at least in some cases, the sensitization profile in the serum allergen-specific IgE test and skin prick test may be negative or their results may be not significant clinically. However, itching possibly changes the lesion site as Th2 polarization occurs through TSLP and IL-21 [20]. In this situation, allergen sensitization to exogenous allergens might occur. Due to itching and urticaria, patients may scrape, and invading allergens can be introduced. Allergen sensitization can occur in these conditions as it does in normal subjects without any allergic disease. Therefore, allergen sensitization profiles in the blood allergen-specific IgE test and the skin prick test will be positive for allergens, although the positive allergens are not directly related to chronic urticaria. Conclusively, all the allergy laboratory tests and the allergen sensitization profiles are conceptually negative in CSU. However, allergen sensitization profiles can show positive allergens according to the clinical conditions, as in this report (Table 1c).

Concept of Treatment Protocol for Histobulin™

The clinical difference of this case report is the concept of the treatment protocol. In the previous treatment using immunoglobulin/histamine complex, the duration of treatment accordingly the numbers of treatment was fixed and the clinical results were evaluated. Fortunately, remission was observed in some patients in another previous report [17], and the possibility that the immunoglobulin/histamine complex induces remission in CSU was suspected. In this study, Histobulin™ treatment continued, and remission was induced in all 4 cases of CSU.

Clinically, the injection numbers until remission was achieved were different among the patients. Two cases responded early, and remission for them was also induced within 12 injections (Table 1a, Fig. 1a & b). The other two cases responded after more injections, and remission was also induced after more injections, some patients after 41 injections. Therefore, Histobulin™ treatment should be approached not by a fixed number of injections or periods but by waiting for remission with whatever numbers of injections are required because according to the patients, the response to Histobulin™ treatment was different.

Characteristics of Clinical Progress in Histobulin™ Therapy: Clinical Landmarks

From the results, the clinical progress of Histobulin™ therapy was characterized as five steps. First, the initial improvement (initial improvement) could be observed (Table 1a, Fig. 1b). Second, the medication frequency was reduced (medication reduction), and third, patients ceased to take medication at the end (medication free) without being bothered by the symptoms and signs of CSU. Fourth, patients reached symptom-free status for a week during treatment (symptom free) without medication. Fifth, if the symptoms and signs of the patients were free for more than 4 weeks without any medication or treatment, most patients maintained remission status for a long time (remission). These four cases have not shown recurrence up until the present. If patients showed remission, the treatment was stopped.

Detection of initial improvement is very important because, if patients showed initial improvement clinically, it may be expected that Histobulin™ is possibly effective and patients may achieve remission at the end. The point of the initial improvement was also different among the patients from 1 to 9 injections. In case 3, the patient felt and described the improvement after the ninth injection; namely, the initial improvement was shown 9 weeks after the beginning of treatment. In this case, both the patient and physician wondered if Histobulin™ was effective. In the treatment protocol of 12 injections, this patient may be classified as an ineffective case.

Medication frequency per week was reduced during treatment. The interval of medication was directly related to the medication frequency. After the interval of medication was 6 days, patients did not take any more medication. Namely, a medication interval of 7 days or more was not present, and a medication-free status was reached. If the medication interval was 6 days, the physician may have predicted that medication-free status would come. From these results, Histobulin™ also seems to have the effects of symptomatic relief. Among several immunologic actions for the therapeutic effects of Histobulin™, histaminopexy reduces the blood histamine level. Through a mechanism of histaminopexy, Histobulin™ is enough to temporarily improve the clinical symptoms and signs of CSU.

At the beginning of this study, it was questionable whether remission was achieved by Histobulin™ therapy. As a result, in all cases, remission was achieved through the symptom-free stage.

Two Kinds of Responders to Histobulin™

Based on the mechanisms of action of Histobulin™, the therapeutic effects of Histobulin™ should be assessed step by step and revised systemically (Fig. 2b). Step 1 is autoantigen-specific IgE and autoantigen binding (step 1a) [21]. Another step 1 is the IgG or IgM autoantibody binding to IgE (step 1b). Step 2 is binding of the autoantigen-IgE complex or anti-IgE IgG/IgM antibody-IgE complex to FcεR1 (step 2a). Another step 2 is binding of the anti-FcεR1 autoantibody to FcεR1 (step 2b) [22]. Step 3 is histamine release with mast cell degranulation. Step 4 is a high level of histamine binding to the histamine receptor, which leads to clinical manifestations of allergies.

Histobulin™ was developed for the effects of histaminopexy and decreases serum histamine levels [10] (Fig. 2b). Moreover, Histobulin™ induced antibodies to histamine [16, 23]. With the effects of histaminopexy and/or antihistamine antibody, Histobulin™ seems to reduce the histamine level at step 4. Histobulin™ inhibits antigen-induced histamine release from human peripheral blood basophils [11] and seems to be effective in step 3. Recently, Histobulin™ decreased specific IgE clinically [24] and may be effective in step 1a.

IVIG suppresses NFκB activation [25], and Histobulin™ also inhibits NFκB nuclear translocation [26]. IVIG affects Th1/Th2 imbalance [27], and Histobulin™ modulates Th1/Th2 bias [28]. Histobulin™ seems to have the effects of IVIG. The main constituent of Histobulin™ is immunoglobulins, and Histobulin™ seems to have a small quantity of IVIG. IVIG effects was possibly expected in Histobulin™. IVIG is effective in autoantibody-mediated autoimmune diseases such as idiopathic thrombocytopenic purpura (ITP), in which anti-platelet antibody is positive [29]. Histobulin™ was reported to possibly be effective in autoimmune disease [24]. From this viewpoint, Histobulin™ may be effective in level step 1a (IgE antibody to autoantigens), step 1b (IgE and IgM autoantibody to IgE) and step 2b (autoantibody to FcεR1). Overall, Histobulin™ seems to be effective in CSU by affecting most of the level of immunopathogenesis of CSU.

Despite just 4 cases, there were two kinds of responders: early responders and late responders. These seem to be related to the mechanisms of action of Histobulin™ and the pathogenesis of CSU. Histamine plays a central role in the clinical manifestations of CSU, including itching and urticarial eruption. The basic effect of Histobulin™ is histaminopexy, which is enough to improve the initial symptoms. The frequencies of injections until patients showed initial improvement were different in the four cases, which may be because the severity of CSU through the effects of histamine also seems to be different among the patients. This may be related to the sensitivity of patients to histamine and/or the level of histamine in the circulation or tissues.

However, the histaminopexy effects of Histobulin™ are inevitably temporary. It is well known that autoimmune mechanisms participate in the pathogenesis of CSU. In this circumstance, without the resolution of these autoimmune mechanisms, remission induction is impossible in CSU. However, long-

term remission was induced, and there was no recurrence in any of the four cases. Autoimmune mechanisms in the cases of this report seem to be solved by Histobulin™.

Two Phases of Improvement in Histobulin™ Therapy

In particular, in the late responders, two phases of clinical courses were observed: the early slow improvement phase and late abrupt improvement phase. In the early slow improvement phase, patients showed slow or steady or even no change after initial improvement until the 35th injection in case 3 and the 14th injection in case 4 (Fig. 1a). In the late rapid improvement phase, rapid improvement was observed between the 36th and 41st injections in case 3 and between the 15th and 24th injections in case 4.

The main action mechanisms of Histobulin™ were suspected to be different in the early slow improvement phase and late abrupt improvement phase. It is suspected that histaminopexy may theoretically be related to the early slow improvement phase and that the resolution of autoimmune mechanisms may be related to the late rapid improvement phase.

The early responders mainly showed only the rapid improvement phase, which is similar to the curve of the late rapid improvement phase of the late responders in which the autoimmune mechanisms seem to be resolved just after Histobulin™ treatment. From the clinical courses, the immunopathogenesis of CSU related to the rapid improvement phase seems to be the essential point to be solved in the disease for remission induction and causative treatment.

New concept of allergy: Classification of allergic disease

Considering the immunopathogenesis of CSU, basically the general allergic laboratory test and the skin prick test are normal, as the laboratory results in all 4 cases of this report, because CSU is occurs via an alternative allergy pathway rather than the classic pathway in which allergic sensitization to exogenous allergens is occurred and allergy provocation by sensitized allergens is followed (Fig. 2a). From these points, CSU is a histamine-mediated disease with skin manifestations and is nonallergen-specific. Additionally, from a therapeutic perspective, Histobulin™ therapy is a nonallergen-specific immunotherapy. Accordingly, allergies might be classified as allergen-specific allergies and nonallergen-specific allergies.

Antihistamine, steroids and other immunosuppressants, including cyclosporine A and omalizumab, are also nonallergen-specific treatments, but they are temporary symptomatic treatments that mask terminal actions in disease pathogenesis rather than curative or causative treatments.

However, several curative/causative nonallergen-specific treatment agents that improved the immunopathogenesis have been reported recently, such as IFN-γ, which results in polydesensitization effects in allergic diseases **[30]**. Nonallergen-specific polydesensitization effects of Histobulin™ have been reported [24]. Based on the action mechanisms of Histobulin$^{TM, it}$ may need to be classified as a nonallergen-specific histamine-mediated disease.

Conclusively, Hitobulin™ is not only effective but also induces remission in CSU. The Histobulin™ therapy protocol in CSU continues the treatment until remission is achieved. According to the patients, early responders and late responders were present. The progress of treatment consisted of a slow improvement phase and a rapid improvement phase. Uniquely, the representative allergy laboratory results, including blood eosinophil fraction, total IgE and eosinophil cationic protein level, were normal in all 4 cases. Further studies concerning the mechanisms of Histobulin™ may be needed.

List Of Abbreviations

CSU, Chronic spontaneous urticaria; Dp, Dermatophagoides pteronyssinus; Df, Dermatophagoides farina

Declarations

- Ethics approval and consent to participate

IVIG therapy in this case was approved by the IRB of Cheju Halla General Hospital (IRB No 2020-M07-01).

- Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

- Availability of data and materials

Not applicable.

- Competing interests

The authors declare that they have no competing interests.

- Funding

None.

- Author’s contributions

GN do all works for this report.

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Tables

Table 1. a) The clinical profiles of disease and treatment progress. The clinical progress of Histobulin^{TM} therapy was characterized as five steps: initial improvement (initial improvement), reduction in medication frequency per week (medication reduction), cessation of medication (medication free), free from the symptoms and signs of CSU, free of symptoms without medication (symptom free) and persistence of symptom-free status for more than 4 weeks without any medication or treatment (remission). b) Basic profiles of representative allergic laboratory results, including blood eosinophil and basophil fractions, serum total IgE levels, and serum eosinophil cationic protein levels.

c) Sensitization profiles to exogenous allergens by a multiple allergosorbent test (MAST, Green Cross PD, Korea) and the skin prick test (SPT). For MAST, the test results show the level of specific IgE for each

allergen, and a normal negative range is 0.000-0.349 IU/mL. SPT was described as negative (0, no reaction), 1+ (reaction greater than control reaction but smaller than half the size of histamine), 2+ (equal to or more than half the size of histamine), 3+ (equal to or more than the size of histamine) and 4+ (equal to or more than twice the size of histamine). The minimum size of a positive reaction is 3 mm.

a)

		Case 1	Case 2	Case 3	Case 4	Unit
Disease Profiles	Duration of Disease	5	36	3	4	Months
	Duration of Latest Medication	2	36	2	4	Months
	Medication	Fexofenadine	Hydroxyzine	Levocetrizine	Levocetrizine	
	Medication Frequency per a week	7 (Everyday)	7 (Everyday)	7 (Everyday)	7 (Everyday)	Days/Week
	Anigoedema	(-)	(-)	(+)	(-)	
	Initial Severity	38	40	50	42	Points
Treatment Progress Profiles	Numbers of Injection	12	12	46	46	Times
	Initial Improvement	2	1	9	6	Times
	Medication Reduction	3	4	23	11	Times
	Medication Free	8	8	36	15	Times
	Symptom Free	10	11	41	24	Times
	Remission	10	11	41	35	Times
	Recurrence	No	No	No	No	
	Remission Duration	22 months	52 months	10 months	24months	Months

b)

	Case 1		Case 2		Case 3		Case 4		
	Before	After	Before	After	Before	After	Before	After	Normal Range (Unit)
WBC	6.61	7.53	4.63	5.51	7.26	6.67	4.8	5.0	3,900~11,000 (1,000/ul)
EOS %	2.1	1.2	4.1	4.2	2.1	4.0	2.7	0.8	0~5 (%)
BASO %	0.8	0.4	0.8	0.7	0.6	0.6	0.6	0.6	0~1 (%)
ECP	15.1	11.1	5.5	13.7	6.7	-	4.89	11.04	0~24 (ng/ml)
TIgE	84.4	89.1	43.5	41	-	-	320	278	0~350 (IU/ml)

c)

	Case 1			Case 2			Case 3			Case 4		
	Allergens	Before	After	Allergens	Before	After	Allergens	Before	After	Allergens	Before	After
MAST	Rye ollen	0.64	0.46	Milk	0.64	0				Dp	18.89	28.14
	Sweet vernal	1.15	0.39							Df	2.7	5.5
	Bermuda grass	0.73	0.6							Crab	2.39	2.58
	Orchard grass	0.93	0.61									
	Timothy grass	0.64	0.41									
	Reed	1.16	0.4									
	Russian thistle	3.34	0.52									
	Pigweed	0.65	0									
SPT	Dp	0	1	Alternaria alternaria	2	2	Grey Elder	1	0	Candida albicans	1	0
	Bermuda grass	0	1	Aspergillus fumigatus	1	0	Silver Birtch	1	0	German cockroach	0	2
				Cladosporim	1	0				Dp	2	2
				German cockroach	1	0				Df	2	2
				Dp	2	0				Grass mix	1	3
				Df	1	2				Orcard grass	1	3
				Dog	1	0				Timothy	2	2
				Short Ragweed	0	2				English Rye grass	1	3
				Black Willow	0	2				English Plantain	1	0
				Bermuda grass	1	0				Prawn	0	1
				Timothy	1	0						
				English Rye grass	1	2						
				Holm oak	0	2						
				Beef	1	2						
				Pork	1	2						
				Cod	1	0						
				Cabbage	0	2						
				Peach	0	2						
				Balck Pepper	0	2						
				Hop	0	2						
				Rabbit	1	0						
				Kopok	1	0						
				Pine	1	0						

Figures

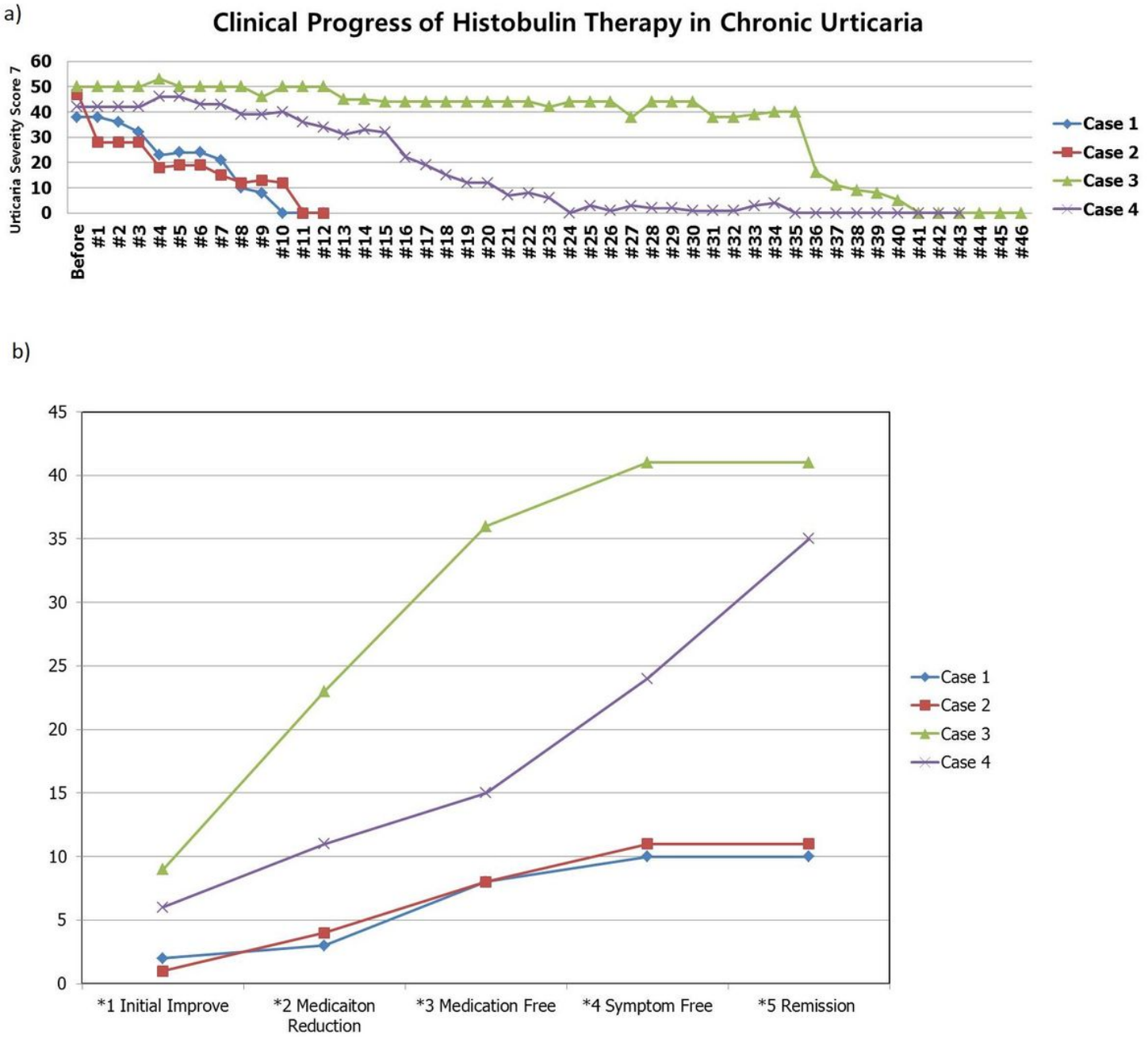

Figure 1

The clinical progresses of HistobulinTM therapy in CSU. a) Clinical progress. b) Five steps of clinical progress in HistobulinTM therapy: initial improvement (initial improvement), reduction in medication frequency per week (medication reduction), cessation of medication (medication free) without bothering from the symptoms and signs of CSU, free of symptoms without medication (symptom free) and persistence of symptom-free status for more than 4 weeks without any medication or treatment (remission).

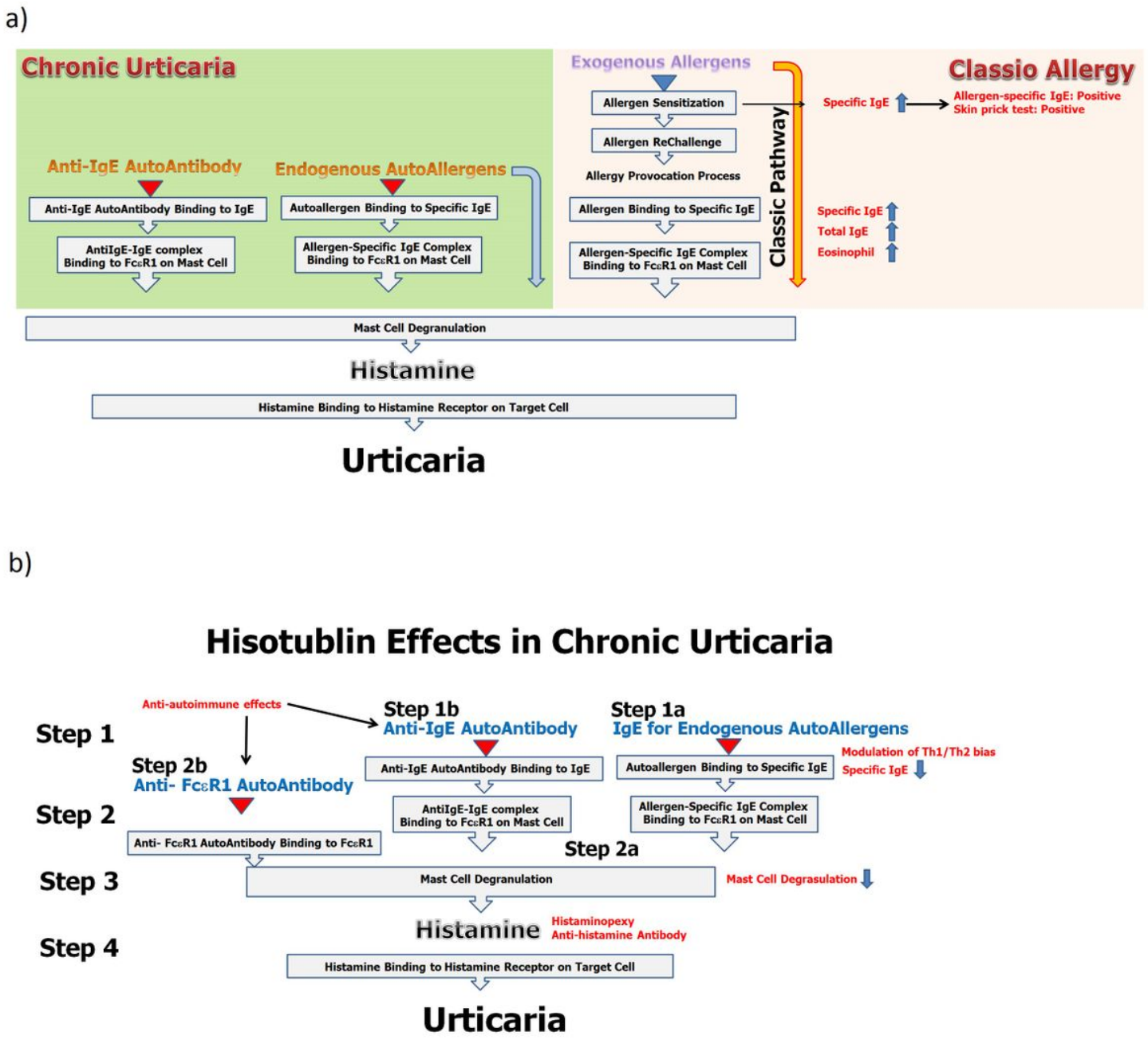

Figure 2

a) Laboratory characteristics in CSU. In the classic allergic pathway, allergy sensitization and provocation by exogenous allergens and subsequent mast cell granulation and allergen-specific Th2 activation result in an increase in allergen-specific IgE (SIgE), serum total IgE (Total IgE), blood eosinophil fraction and serum eosinophil cationic protein. However, the immunopathogenesis of CSU bypasses the exogenous allergen-IgE-FcεRI pathway, and the representative allergy laboratory tests were possibly all negative. b) Revised action mechanisms of HistobulinTM in CSU. The immunopathogenesis of CSU was revised step by step as autoantigen-specific IgE and autoantigen binding (step 1a), the IgG or IgM autoantibody binding to IgE (step 1b), binding of autoantigen-IgE complex or anti-IgE IgG/IgM antibody-IgE complex to

FcεR1 (step 2a), binding of anti-FcεR1 autoantibody to FcεR1 (step 2b), histamine release with mast cell degranulation (step 3) and high level of histamine and binding to histamine receptor which leads to clinical manifestations of allergy (step 4). HistobulinTM has the effects of histaminopexy and induces antihistamine antibodies. HistobulinTM possibly decreases serum histamine levels at step 4. HistobulinTM inhibits antigen-induced histamine release from human peripheral blood basophils at step 3. HistamineTM decreases specific IgE clinically and affects step 1a (IgE antibody to autoantigens). The main constituent of HistobulinTM is immunoglobulins, and IVIG effects were possibly expected in HistobulinTM. HistobulinTM may be effective in step 1b (IgG and IgM autoantibody to IgE) and step 2b and step 2b (autoantibody to FcεR1).