

Immunotherapy Using Histobulin™ In Psoriasis: A Case Report

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Case report

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Abstract

Background: There is no cure for psoriasis. Early treatment using biologics is recommended to improve skin manifestations and reduce systemic inflammation, which leads to comorbidities in various organs.

Case Presentation: Histobulin™ therapy was performed on a psoriasis patient who developed the disorder due to allergic rhinitis. Psoriasis was confirmed pathologically by skin biopsy. The patient responded rapidly, and the skin manifestations began to improve after just the first injection. Although the patient showed some temporary aggravation after the third injection, the clinical symptoms and signs improved continuously thereafter and disappeared after the eighth injection. Remission was induced and was evident when the patient showed no symptoms and signs during the subsequent 4 weeks during which time the patient received 4 more injections; afterwards, Histobulin™ therapy was ceased. After treatment, psoriasis did not recur for more than 6 months.

Conclusions: Histobulin™ is effective and induces remission in psoriasis patients. Histobulin™ is suggested for curative therapeutics in psoriasis patients, and further basic research and clinical evaluation are necessary.

Key Clinical Message

Histobulin™ therapy was effective and induced remission in a psoriasis patient.

Background

Psoriasis is a chronic immune-mediated inflammatory disease that affects 2–4% of the population worldwide [1]. Psoriasis is an immune-mediated disease, and a complete cure is difficult to achieve as patients experience progressive recurrence [2]. It is a relapsing and remitting condition that may be exacerbated by environmental factors such as trauma, stress and infection [3].

There is no cure for psoriasis, but several treatment options exist [4], including topical corticosteroids, retinoids, coal tar preparations, dithranol, salicylic acid and vitamin D analogues; phototherapy with ultraviolet (UV) B or UVA plus psoralen; and systemic immunosuppressants, such as oral corticosteroids, methotrexate, cyclosporin and acitretin. Hydroxyurea, sulphasalazine, and tacrolimus have also been used in patients who fail to respond to more conventional therapies. Recently, the immunopathogenesis of psoriasis has been well understood, and biologics have been developed and tried with good effects. Most importantly, psoriasis is understood as a systemic disease. To prevent systemic comorbidities, early systemic treatment with biologics, including etanercept, adalimumab, certolizumab infliximab certolizumab and ustekinumab, is recommended due to the centrality of their targets in disease pathogenesis [5].

Histobulin™ (Green Cross PD, Korea) is a histamine-fixed immunoglobulin preparation comprising 0.15 µg of histamine dihydrochloride and 12 mg of IgG [6]. This preparation was developed for the regulation of

blood serum levels by histaminopexy effects [7] and has been known to be effective in treating patients with allergic rhinitis, bronchial asthma, chronic urticaria and atopic dermatitis (AD) [8–11]. In this report, a case of a psoriasis patient who achieved complete remission with Histobulin™ was described.

Case Presentation

A 15-year-old Korean male patient visited the Department of Allergy and Clinical Immunology, Cheju Halla General Hospital, due to having allergic rhinitis for several years and the presence of round and scaly skin eruptions on the whole body for 2 months. He had no specific family history or past medical history. The patient felt slight itching on the skin lesion sites.

Basic allergic tests (blood tests and a skin prick test) were conducted. He underwent blood tests for a complete blood count (CBC) with differential serum eosinophil cationic protein and serum total IgE. Specific IgE levels for allergens were found using a multiple allergosorbent test (MAST, Green Cross PD, Korea). In the MAST, 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, goldenrod and pigweed. The test results showed the level 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 alternaria*, *Aspergillus fumigatus*, *Aspergillus nigre*, *Candida albicans*, *Cladosporium*, *Penicillium chrysogenum*, German cockroach, Dp, Df, dog, cat, grey 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 and L1 spinal levels. 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 2 cm apart. A drop of allergen solution was placed beside each mark. A small prick is made in the skin through the drop using a Morrow Brown Needle[→] (Morrow Brown[□] Allergy Diagnostics, USA) by holding the needle perpendicular to the test site and punching firmly through the test 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 results were measured as the wheal size. Reactions were read after 15 min and described as negative (0, no reaction), 1+ (reaction greater than a 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 was 3 mm.

The severity score was evaluated using the Psoriasis Area and Severity Index (PASI) [12]. Over 4 body regions (head [h], trunk [t], upper [u] and lower [l] extremities) were assessed according to erythema (E), infiltration (I), desquamation (D), and body surface area involvement (A). The degree of severity (per body region) value was given as 0 for no symptoms, 1 for slight symptoms, 2 for moderate symptoms, 3 for marked symptoms, and 4 for very marked symptoms. The surface involvement (per body region) value was given as 1 for 10%>, 2 for 10%-29%, 3 for 30%-49%, 4 for 50%-69%, 5 for 70%-89% and 6 for 90%-100%. Because the head, upper extremities, trunk, and lower extremities corresponded to approximately 10%, 20%, 30%, and 40% of body surface area, respectively, the PASI score was calculated by the formula $PASI = 0.1(Eh + Ih + Dh)Ah + 0.2(Eu + Iu + Du)Au + 0.3(Et + It + Dt) At + 0.4(El + Il + Dl)Al$. Skin biopsy was performed to confirm the diagnosis of psoriasis.

The patient underwent laboratory tests, skin prick tests and PASI scoring before and after treatment. White blood cell (WBC) counts were normal at 5.57 before treatment and 7.99 after treatment (normal range: 3.9–11.0 1000/ μ l). In the differential counts of WBCs, neutrophil, lymphocyte, eosinophil and basophil fractions were within the normal range. Blood eosinophil cationic protein levels were as high as 37.9 before treatment and decreased to 35.5 after treatment (normal range: 0–24 (ng/ml)). After Histobulin™ therapy, the serum IgA level was evaluated for selective IgA deficiency and was normal at 95.7 (normal range 70–400 mg/dL). The total IgE level was normal at 203 before and 297 after treatment (normal range: less than or equal to 350 IU/ml).

In the MAST, specific IgEs for Dp, Df, cat, shrimp and timothy grass were positive before treatment and decreased after treatment in all items (Table 1). In the skin test, the changes in reactions according to the allergens were variable and insignificant .

Skin biopsy was performed at the lesion site and a normal site on the back. The specimens were 0.4x0.3x0.5 cm. H&E stain was performed. The pathologic finding of the lesion site was suggestive subacute spongiotic dermatitis. The results showed acanthosis, a microscopic focus of spongiosis with overlying microscopic parakeratosis and the absence of keratohyalin granules. Acanthosis with elongated epidermal ridges was observed (HE X100). Club-shaped epidermal ridges (HE X 200) and elongated dermal papillae containing dilated capillaries (HE X 400), which is typical of psoriasis, were observed. The pathologic diagnosis was psoriasis (Fig. 1).

The final diagnosis was allergic rhinitis and psoriasis. Histobulin™ therapy for allergic rhinitis was initiated, and the clinical severity of psoriasis was evaluated simultaneously. Psoriasis progressed, and the PASI score increased from 14.5 to 18 points over 2 weeks, during which skin biopsy was performed and the pathologic diagnosis was made.

The clinical response was rapid, and the patient improved after just the first injection of Histobulin™ (Fig. 2). Although the patient temporarily showed some aggravation 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 time 4 subsequent injections were administered. Medication ceased, and the patient did not experience recurrence for more than 6 months.

Discussion

Histobulin™ was effective in treating psoriasis patients. Moreover, the clinical response was very rapid, and complete remission was induced and maintained (Fig. 2). This was the first episode of psoriasis for the patient. The clinical progress of psoriasis indicated that the disease was in an early stage considering the pathologic findings, and the clinical severity was mild to moderate. This is a case of early intervention in psoriasis with mild to moderate severity. The rapid improvement seemed to be possibly due to mild to moderate severity in this case. Notably, systemic inflammation accompanies psoriasis and recently, early systemic treatment was recommended not only to improve cutaneous symptoms but also to reduce systemic inflammation, improving long-term outcomes by mitigating comorbidity progression [13]. This case report using Histobulin™ describes the early and systemic intervention of psoriasis. Early intervention seems to be very effective in this case.

Histobulin™ is an anti-allergic therapeutic. The relationship between allergies and psoriasis has been reported. Immunoallergic reactivity was reported in patients with psoriasis [14]. In particular, the relationship between psoriasis and AD has been reported. Although psoriasis and AD are clearly separable diseases using clinical criteria [15–16], psoriasis and AD share immunopathogenesis [17]. AD and psoriasis were even suspected to be part of one spectrum [18]. Recently, Histobulin™ was reported to be an effective treatment and to induce complete remission in AD patients [11]. Considering the immunopathogenesis of psoriasis and AD, Histobulin™ is naturally considered to be effective in psoriasis.

The intake of histamine-rich foods was reported to lead to the development of various disorders in many organs with dermatologic sequelae, including psoriasis [19]. In psoriasis, tryptase- and chymase-positive mast cells were activated early in the developing lesions, and later, the cells increased in number in the upper dermis with concomitant expression of cytokines and TNF superfamily ligands [20]. Antihistamines for histamine receptor (HR) 1 were suggested as a treatment option for itch in psoriasis [21]. HR 2 antagonists were reported to have a clinical effect on psoriasis [22]. Additionally, histamine receptor 4 (HR 4) was reported to play roles in psoriasis [23]. The action of histamine in the development of psoriasis was suggested [22, 24]. Histaminopexy is the main anti-allergic mechanism of Histobulin™ [25]. Considering that histamine participates in the pathogenesis of psoriasis, Histobulin™ may be effective in treating psoriasis.

Psoriasis is a chronic inflammatory autoimmune disease characterized by excessively aberrant hyperproliferation of keratinocytes [26–27]. The pathogenesis of psoriasis is complex, and a strong proinflammatory stimulus leads to chronic inflammation in psoriasis patients [26, 28]. Histaglobulin (the same immunoglobulin/histamine complex as Histobulin™) inhibits NF-kappa B nuclear translocation and

downregulates proinflammatory cytokines [29]. The anti-inflammatory effects of Histobulin™ were described in AD patients and patients with Pfeifer-Weber-Christian disease [11, 30]. Histobulin™ may be effective in treating psoriasis through anti-inflammatory effects.

Intravenous immune globulin (IVIG) is well known to be effective in treating autoimmune disease [31], and IVIG is effective in psoriasis patients [4, 32]. The major constituent of Histobulin™ is immunoglobulin and it may have a small amount of IVIG. Histobulin™ possibly has effects on autoimmune disease. Recently, Histobulin™ was suspected to be effective in treating autoimmune disease patients [30]. The anti-autoimmune effects of Histobulin™ possibly improved and induced complete remission in psoriasis in this case. The mechanisms of action of Histobulin™ in psoriasis are listed as histaminopexy, anti-inflammatory and anti-autoimmune effects as described above. The histaminopexy and anti-inflammatory effects may be symptomatic and temporarily lead to the rapid improvement of clinical manifestations. However, anti-autoimmune effects may be causative, which may induce complete remission without recurrence in this case.

Psoriasis is a common dermatologic disease [33]. Moreover, other systemic diseases, including rheumatic disease, arthritis, colitis, diabetes and hypertension, are quite frequently associated with psoriasis [34]. Nevertheless, there is currently no cure for psoriasis, and conventional treatments are symptomatic [26]. Many biologics have been developed and suggested for the treatment of psoriasis [35, 36]. These biologics have their own set of side effects [26]. Histobulin™ is a biologic therapeutic similar to IVIG [37]. Histobulin™ has been used for several decades and is considerably safe without serious side effects. Moreover, Histobulin™ is not expensive, especially compared with other biologics.

Conclusions

Histobulin™ is effective and induces remission by early intervention in patients with mild to moderate psoriasis. Curative treatments for psoriasis are lacking, and the development of safe and efficacious novel therapeutics is urgently needed for psoriasis; Histobulin™ is suggested as a safe and inexpensive therapeutic in addition to its considerable clinical effects as indicated in this report. Histobulin™ is suggested as a curative therapeutic in psoriasis patients, and further basic research and clinical evaluation of Histobulin™ are necessary.

Abbreviations

Dp, *Dermatophagoides pteronyssinus*; Df, *Dermatophagoides farina*; AD, Atopic dermatitis; HR, Histamine receptor

Declarations

-Ethics approval and consent to participate

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. Sensitization profiles to exogenous allergens by a multiple allergosorbent test (MAST, Green Cross PD, Korea) and a 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. The SPT results are described as negative (0, no reaction), 1+ (reaction greater than a 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.

MAST (Normal Range 0.35 IU/ml>)			SPT (Grade)		
Allergens	Before Tx	After Tx	Allergens	Before Tx	After Tx
Dp	6.17	2.95	Dp	0	4+
Df	3.35	2.53	Df	0	3+
Cat	1.26	1.02	Cat	0	3+
Timothy grass	0.57	0.39	Timothy grass	3+	3+
Shrimp	0.63	0.00			
			Grass mix	4+	4+
			Orchard	4+	3+
			English rye grass	0	4+
			Japanese cedar	0	3+

Figures

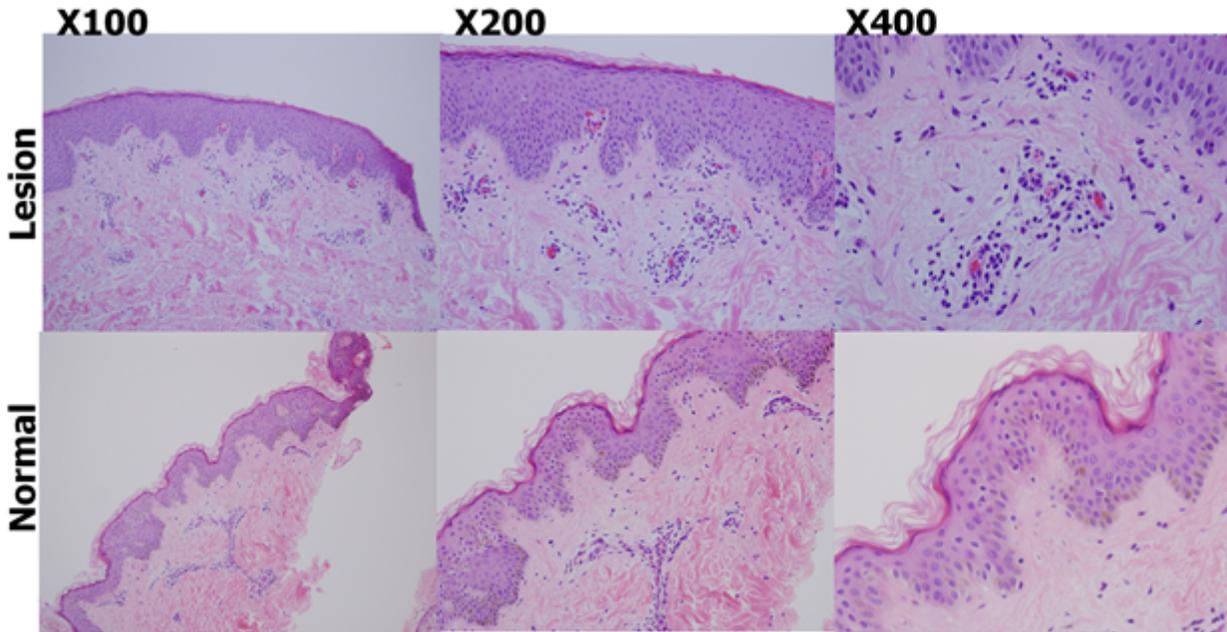


Figure 1

Photograph and pathologic findings. Patients showed scaly round skin eruptions on the whole body, which is typical for psoriasis. The pathologic findings of the lesions were suggestive subacute spongiotic dermatitis. The lesions showed acanthosis, a microscopic focus of spongiosis with overlying microscopic parakeratosis and absence of keratohyalin granules. Acanthosis with elongated epidermal ridges was observed (HE X100). Club-shaped epidermal ridges (HE X 200) and elongated dermal papillae containing dilated capillaries (HE X 400), which is typical of psoriasis, were observed. The pathologic diagnosis was psoriasis.

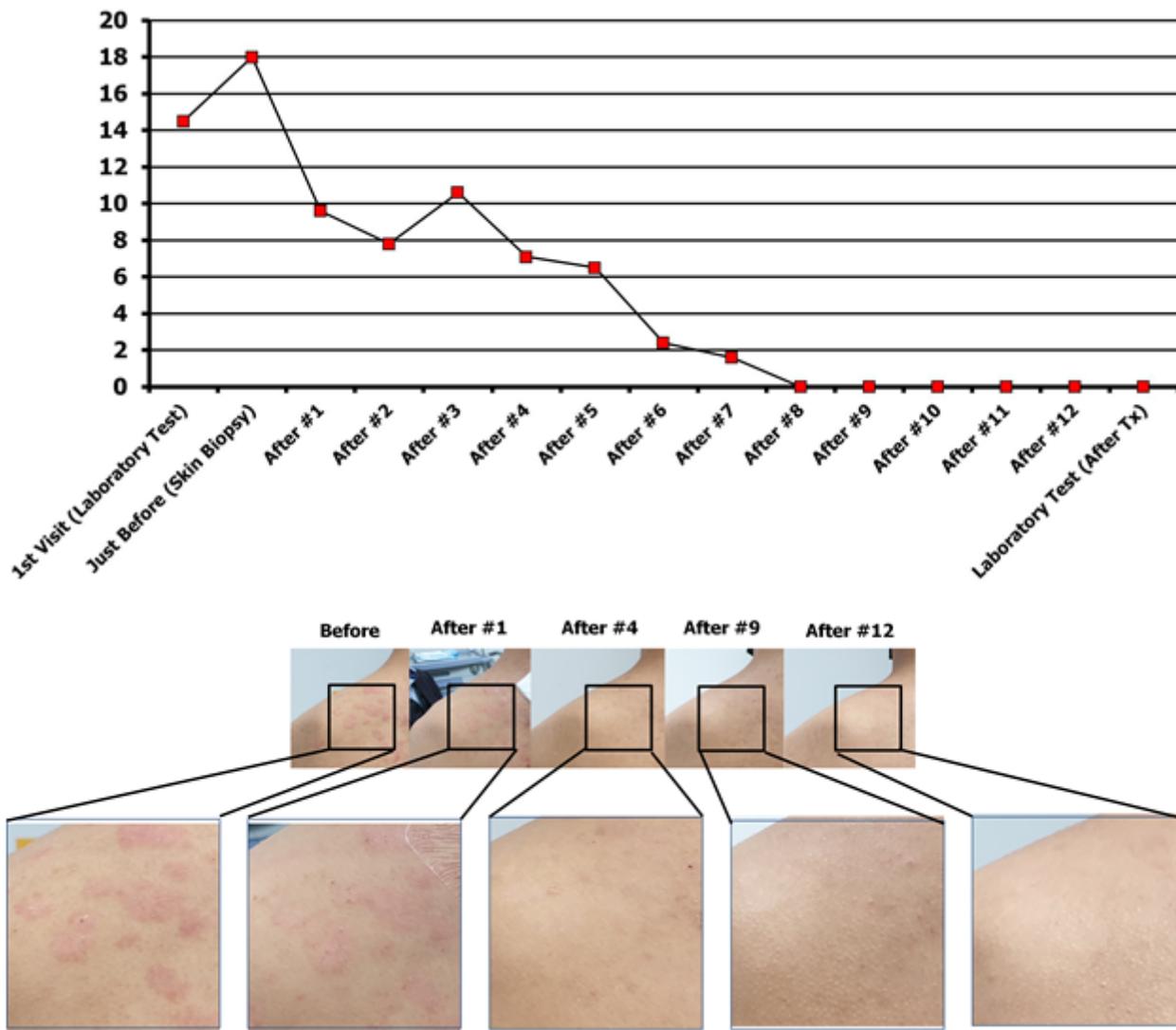


Figure 2

The clinical progress of Histobulin™ therapy in psoriasis patients. Psoriasis progressed, and the PASI score was increased from 14.5 to 18 points over 2 weeks of laboratory tests and skin biopsy. The clinical response was rapid, and the patient improved after just the first injection of Histobulin™. Although the patient temporarily showed some aggravation 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 twelfth injections). The patient ceased taking medication, and the patient did not experience recurrence for more than 6 months.