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

There is no cure for psoriasis, but several treatment options exist, including topical corticosteroids, retinoids, coal tar preparations, dithranol, salicylic acid, and vitamin D analogs; phototherapy with ultraviolet (UV) B or UVA plus psoralen; and systemic immunosuppressants, such as oral corticosteroids, methotrexate, cyclosporin, and acitretin. Hydroxyurea, sulfasalazine, and tacrolimus have also been used in patients who fail to respond to more conventional therapies. The immunopathogenesis of psoriasis is now well understood, and biologics have been developed and trialed recently 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.

Histobulin™ (Green Cross PD, Korea) is a histamine-fixed immunoglobulin preparation comprising 0.15 μg of histamine dihydrochloride and 12 mg of immunoglobulin. This preparation was developed for the regulation of
blood serum levels by histaminoeptic effects and has been shown to be effective in treating patients with allergic rhinitis, bronchial asthma, chronic urticaria, and atopic dermatitis (AD). This case report describes the treatment of a patient with psoriasis with Histobulin™ therapy, and complete remission of psoriasis was observed. Therefore, Histobulin™ is suggested as a curative therapeutic.

2 | CASE REPORT

A 15-year-old Korean male patient visited the Department of Allergy and Clinical Immunology, Cheju Halla General Hospital, due to 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. Concerning allergic rhinitis, he had suffered from frequent rhinorrhea, sneezing, nasal congestion, and itching of the nose for several years as typical clinical manifestations of allergic rhinitis. The patient had taken 5 mg of levocetirizine once a day for the relief of allergic rhinitis symptoms when his daily life was affected. The development and progress of allergic rhinitis and psoriasis were not found to be related to each other in the medical history or clinical progression.

Basic allergy 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 levels. Specific IgE levels for the allergens were found using a multiple allergosorbent test (MAST, Green Cross PD, Korea). In the MAST, the specific IgE levels for 41 allergens were evaluated as described in a previous report (see the Supplementary material). The test results showed the specific IgE level for each allergen, and a normal negative range was between 0.000 and 0.349 IU/ml.

A skin prick test was also performed for 53 allergens as described in a previous report (see the Supplementary material). Histamine hydrochloride 10 mg/ml was used as the positive control, and physiological saline was used as the negative control. The wheal size was measured. 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 the histamine wheal), 2+ (equal to or more than half the size of the histamine wheal), 3+ (equal to or more than the size of the histamine wheal), and 4+ (equal to or more than twice the size of the histamine wheal). The minimum size of a positive reaction was 3 mm.

The severity score was evaluated using the Psoriasis Area and Severity Index (PASI). Four body regions were assessed according to erythema, infiltration, desquamation, and body surface area involvement. The degree of severity (per body region) was scored from 0 to 4. The surface involvement (per body region) was scored from 0 to 6. The PASI produces a numeric score ranging from 0 to 72. Skin biopsy was performed to confirm the diagnosis of psoriasis.

The patient underwent laboratory tests, a skin prick test, 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/µl). In the differential counts of WBCs, the 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 ng/ml). The total IgE level was normal at 203 before treatment and 297 after treatment (normal range: less than or equal to 350 IU/ml).

In the MAST, the specific IgE levels for Dermatophagoides pteronyssinus (Dp), Dermatophagoides farina (DF), cats, shrimp, and timothy grass were positive before treatment and decreased after treatment for all items (Table 1). In the skin prick test, the changes in reactions according to the allergens were variable and insignificant.

Skin biopsy was performed at the lesion site and an unaffected site on the back. The specimens were 0.4 × 0.3 × 0.5 cm. HE staining was performed. The pathological finding of the lesion site was suggestive of 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 are typical of psoriasis, were observed. The pathological diagnosis was psoriasis (Figure 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. The patient’s psoriasis progressed, and the PASI score increased from 14.5 to 18 points over 2 weeks, during which skin biopsy was performed and a pathological diagnosis was made. The patient did not take any other medication during Histobulin™ therapy. The clinical response to Histobulin™ therapy was rapid, and the patient’s symptoms and signs improved after the first injection of Histobulin™ (Figure 2). Although the
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. Treatment with the medication was stopped, and the patient did not experience recurrence for more than 18 months.

### TABLE 1 Sensitization profiles to exogenous allergens by a multiple allergosorbent test (MAST, Green Cross PD, Korea) and a skin prick test (SPT)

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

Note: For the MAST, the test results show the level of the specific IgE for each allergen, and a normal negative range is between 0.000 and 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 the histamine wheal), 2+ (equal to or more than half the size of the histamine wheal), 3+ (equal to or more than the size of the histamine wheal), and 4+ (equal to or more than twice the size of the histamine wheal). The minimum size of a positive reaction is 3 mm.

### FIGURE 1 Photographs and pathological findings. The patient showed scaly round skin eruptions on the whole body, which is typical for psoriasis. The pathological findings of the lesions were suggestive of subacute spongiotic dermatitis. The lesions 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 X 100). Club-shaped epidermal ridges (HE X 200) and elongated dermal papillae containing dilated capillaries (HE X 400), which are typical of psoriasis, were observed. The pathological diagnosis was psoriasis.

### DISCUSSION

Psoriasis is a common dermatological disease. Moreover, other systemic diseases, including rheumatic disease, arthritis, colitis, diabetes, and hypertension, are frequently associated with psoriasis. Nevertheless, there is currently no cure for psoriasis, and conventional treatments are symptomatic. Many biologics have been developed and suggested for the treatment of psoriasis.
These biologics have their own associated side effects. Histobulin™ is a biologic therapeutic similar to IVIG. Histobulin™ has been used for several decades with considerable safety and without serious side effects. Moreover, Histobulin™ is not expensive, especially compared with other biologics.

Histobulin™ was effective in treating the psoriasis patient presented in this report. Moreover, the clinical response was very rapid, and complete remission was induced and maintained (Figure 2). This was the first episode of psoriasis for the patient. Regarding the clinical progression of psoriasis, the pathological findings indicated that the disease was in an early stage, and the clinical severity was mild to moderate. This case report involves early intervention in mild to moderately severe psoriasis. The rapid improvement seemed to be possible
due to the mild to moderate severity of psoriasis in this patient. 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. This case report in which Histobulin™ was used describes early and systemic intervention for psoriasis. Early intervention seemed to be very effective in this patient.

Histobulin™ is an anti-allergic therapeutic agent. A relationship between allergies and psoriasis has been reported. Immunoallergic reactivity has been reported in patients with psoriasis. In particular, the relationship between psoriasis and AD has been reported. Although psoriasis and AD are clearly independent diseases according to clinical criteria, psoriasis and AD share a common immunopathogenesis. AD and psoriasis have even been suspected to be part of one spectrum. Recently, Histobulin™ was reported to be an effective treatment and to induce complete remission in AD patients. Considering the common immunopathogenesis of psoriasis and AD, Histobulin™ is naturally hypothesized to be effective in the treatment of psoriasis. However, with only one case, the relationship between allergic rhinitis and psoriasis could not be determined.

The intake of histamine-rich foods was reported to lead to the development of various disorders in many organs with dermatological sequelae, including psoriasis. In psoriasis, tryptase- and chymase-positive mast cells were activated early in developing lesions, and the cells later increased in number in the upper dermis with concomitant expression of cytokines and TNF superfamily ligands. Antihistamines for histamine receptor (HR) 1 were suggested as a treatment option for the symptom of itching in psoriasis. HR 2 antagonists were reported to have a clinical effect on psoriasis. In addition, histamine receptor 4 (HR 4) was reported to play a role in psoriasis. An action of histamine in the development of psoriasis has been suggested. Histaminopexy is the main anti-allergic mechanism of Histobulin™. Considering that histamine participates in the pathogenesis of psoriasis, Histobulin™ may be effective in the treatment of psoriasis.

Psoriasis is a chronic inflammatory autoimmune disease characterized by the excessive aberrant hyper-proliferation of keratinocytes. The pathogenesis of psoriasis is complex, and a strong proinflammatory stimulus leads to chronic inflammation in psoriasis patients. Histaglobulin (the same immunoglobulin/histamine complex as Histobulin™) inhibits NF-kappa B nuclear translocation and downregulates proinflammatory cytokines. The anti-inflammatory effects of Histobulin™ were described in AD patients and patients with Pfeiffer-Weber-Christian disease. Histobulin™ may be effective in the treatment of psoriasis through anti-inflammatory effects.

Intravenous immune globulin (IVIG) is well known to be effective in the treatment of autoimmune diseases, and IVIG is effective in the treatment of psoriasis patients. The major constituent of Histobulin™ is immunoglobulin, and Histobulin™ may contain a small amount of IVIG. Histobulin™ may have effects on autoimmune disease. Recently, Histobulin™ was suspected to be effective in the treatment of patients with autoimmune diseases. The anti-autoimmune effects of Histobulin™ possibly improved and induced complete remission in psoriasis in the patient presented in this case report. The mechanisms of action of Histobulin™ in psoriasis are listed as histaminopexic, anti-inflammatory, and anti-autoimmune effects as described above. The histaminopexic and anti-inflammatory effects may be symptomatic and temporarily lead to the rapid improvement of clinical manifestations. However, the anti-autoimmune effects may be causative, which may have induced complete remission without recurrence in the patient presented in this case report.

Conclusively, Histobulin™ is effective and induces remission through 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 the treatment of psoriasis. Histobulin™ is suggested as a safe and inexpensive therapeutic with considerable clinical effects, as indicated in this report. Histobulin™ is also suggested as a curative therapeutic for psoriasis patients, and further basic research and clinical evaluation of Histobulin™ are necessary.

**AUTHOR CONTRIBUTIONS**

GN performed the work for the clinical aspects of this report. HSK performed the work for the pathogenesis evaluation.

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**CONFLICT OF INTEREST**

The authors declare that they have no competing interests.

**DATA AVAILABILITY STATEMENT**

There are no conflicts of interest for the authors.
ETHICAL APPROVAL
This case was approved by the IRB of Cheju Halla General Hospital (IRB No 2020-M07-01).

CONSENT
Written informed consent was obtained from the patient for the 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.

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REFERENCES
1. Raychaudhuri SP, Farber EM. The prevalence of psoriasis in the world. J Eur Acad Dermatol Venereol. 2001;15:16-17.
2. Rendon A, Schäkel K. Psoriasis pathogenesis and treatment. Int J Mol Sci. 2019;23:1475-1502. doi:10.3390/ijms20061475
3. Krueger GG, Duvic M. Epidemiology of psoriasis: clinical issues. J Invest Dermatol. 1994;102:14-18.
4. Germain N, Mediwick R, Fernando M, et al. Psoriasis: response to high-dose intravenous immunoglobulin in three patients. Br J Dermatol. 2002;147:554-557.
5. Korman NJ. Management of psoriasis as a systemic disease: what is the evidence? Br J Dermatol. 2020;182:840-848. doi:10.1111/bjd.18245
6. Kim JH, Shin IS, Lee YK, Oh HJ, Ban SJ. Improved HPLC method using 2,3-naphthalenedicarboxaldehyde as fluorescent labeling agent for quantification of histamine in human immunoglobulin preparations. Osong Public Health Res Perspect. 2011;2:127-134.
7. Parrot JL, Laborde C. The histamine-fixing power of blood serum; its modification after an injection of normal human serum or of an azoprotein of histamine. J Physiol Paris. 1954;46:492-495.
8. Narayana J, Shianthi T, Bharadwaj S. Efficacy of histaglobulin on allergic rhinitis. Indian J Otolaryngol Head Neck Surg. 1997;49:77-79.
9. Jankowska R, Małolepszy J, Nowak I. Influence of histaglobulin therapy on skin tests and clinical symptoms in patients with atopic bronchial asthma. Pneumonol Alergol Pol. 1992;60:69.
10. Rajesh G, Keerthi S, Karthikeyan K, et al. Weekly injection of histaglobulin produces long-term remission in chronic urticaria: a prospective clinical study. Indian J Pharmacol. 2016;48:292-297.
11. Noh G. Immunotherapy using Histobulin in atopic dermatitis. Clin Case Rep. 2020;9:113-117.
12. Fredriksson T, Pettersson U. Severe psoriasis-oral therapy with a new retinoid. Dermatologica. 1978;157:238-244.
13. Christophers E. Psoriasis-epidemiology and clinical spectrum. Clin Exp Dermatol. 2001;26:314-320. doi:10.1046/j.1365-2230.2001.00832.x
14. Cabrijan L, Kehler T. Association of psoriasis with other disease. Acta Med Croatica. 2015;69:59-63.
15. Deng Y, Chang C, Lu Q. The inflammatory response in psoriasis: a comprehensive review. Clin Rev Allergy Immunol. 2016;50:377-389. doi:10.1007/s12016-016-8535-x
16. Conrad C, Gilliet M. Psoriasis from pathogenesis to targeted therapies. Clin Rev Allergy Immunol. 2018;54:102-113. doi:10.1007/s12016-018-8668-1
17. Boehncke WH, Brembilla NC. Unmet needs in the field of psoriasis: Pathogenesis and treatment. Clin Rev Allergy Immunol. 2018;55:295-311. doi:10.1007/s12016-017-8634-3
18. Fathi R, Armstrong AW. The role of biologic therapies in dermatology. Med Clin North Am. 2015;99:1183-1194. doi:10.1016/j.mcn.2015.07.008
19. Girolomoni G, Griffiths CE, Krueger J, et al. Early intervention in psoriasis and immune-mediated inflammatory diseases: a hypothesis paper. J Dermatolog Treat. 2015;26:103-112.
20. Borisenko KK. Immunologic reactivity of patients with psoriasis. Sov Med. 1975;3:34-39.
21. Guttmann-Yassky E, Nogales KE, Krueger JG. Contrast pathogenesis of atopic dermatitis and psoriasis — part I: clinical and pathologic concepts. J Allergy Clin Immunol. 2011;127:1110-1118.
22. Guttmann-Yassky E, Nogales KE, Krueger JG. Contrast pathogenesis of atopic dermatitis and psoriasis — part II: immune cell subsets and therapeutic concepts. J Allergy Clin Immunol. 2011;127:1420-1432.
23. Sun L, Liu W, Zhang J. The role of toll-like receptors in skin host defense, psoriasis and atopic dermatitis. J Immunol Res. 2019;14:1824624. doi:10.1155/2019/1824624
24. Guttmann-Yassky E, Krueger JG. Atopic dermatitis and psoriasis: two different immune disease or one spectrum? Curr Opin Immunol. 2017;48:68-73. doi:10.1016/j.coi.2017.08.008
25. Lugović-Mihić L, Seserko A, Duvancić T, et al. Histamine intolerance—possible dermatologic sequences. Acta Med Croatica. 2012;66:375-381.
26. Harvima IT, Nilsson G, Suttle MM, et al. Is there a role for mast cells in psoriasis? Arch Dermatol Res. 2008;300:461-478. doi:10.1007/s00403-008-0874-x
27. Komiya E, Tominaga M, Kamata Y, et al. Molecular and cellular mechanisms of itch in psoriasis. J Mol Sci. 2020;9(21):8406. doi:10.3390/jmcn21218406
28. Nielsen HJ. Histamine and histamine type-2 receptor antagonists in psoriasis. Mechanisms and speculations. Dan Med Bull. 1991;38:478-480.
29. Schaper-Gerhardt K, Rossbach K, Nikolouli E, et al. The role of the histamine H(4) receptor in atopic dermatitis and psoriasis. Br J Pharmacol. 2020;177:490-502. doi:10.1111/bph.14550
30. Sandoval-Talamantes AK, Gómez-González BA, Uriarte-Mayorga DF, et al. Neurotransmitters, neuropeptides and their receptors interact with immune response in healthy and psoriatic skin. Neuropeptides. 2020;79:102004. doi:10.1016/j.npep.2019.102004
31. Hawkes JE, Chan TC, Krueger JG. Psoriasis pathogenesis and the development of novel targeted immune therapies. J Allergy Clin Immunol. 2017;140:645-653. doi:10.1016/j.jaci.2017.07.004
32. Baker BS, Laman JD, Powles A, et al. Peptidoglycan and peptidoglycan-specific Th1 cells in psoriatic skin lesions. J Pathol. 2006;209:174-181.
33. Ayoub M, Mittenbühler K, Sütterlin BW, et al. The anti-allergic drug histaglobulin inhibits NF-kappa B nuclear translocation and down-regulates proinflammatory cytokines. Int J Immunopharmacol. 2000;22:755-763.
34. 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. Clin Case Rep. 2020;9:966-972.

35. Imbach P, Morell A. Idiopathic thrombocytopenic purpura (ITP): immunomodulation by intravenous immunoglobulin (IVIg). Int Rev Immunol. 1989;5:181-188.

36. Jolles S, Hughes J. Use of IGIV in the treatment of atopic dermatitis, urticaria, scleromyxedema, pyoderma gangrenosum, psoriasis and pretibial myxedema. Int Immunopharmacol. 2006;6:579-591. doi:10.1016/j.intimp.2005.11.017

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