Improvement of psoriasis-associated arthritis and skin lesions by treatment with molecular hydrogen: A report of three cases

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Abstract. Psoriasis, a chronic inflammatory skin disease, is caused by infiltrating lymphocytes and associated cytokines, including tumor necrosis factor (TNF)α, interleukin (IL)-6, and IL-17. Effective treatments, including pathogenesis-based biological agents against psoriasis, are currently under development. Although the role of reactive oxygen species (ROS) in the pathogenesis of psoriasis has been investigated, it remains to be fully elucidated; ROS-targeted therapeutic strategies are also lacking at present. Therefore, the objective of the present study was to assess whether H_2, a ROS scavenger, has a therapeutic effect on psoriasis-associated inflammation by reducing hydroxyl radicals or peroxynitrite in the immunogenic psoriasis cascade. Three methods were used to administer H_2: Drop infusion of saline containing 1 ppm H_2 (H_2-saline), inhalation of 3% H_2 gas, and drinking of water containing a high concentration (5-7-ppm) of H_2 (high-H_2 water). Treatment efficacy was estimated using the disease activity score 28 (DAS28) system, based on C-reactive protein levels, and the psoriasis area and severity index (PASI) score, determined at baseline and following each H_2 treatment. Furthermore, levels of TNFα, IL-6, and IL-17 were analyzed. The DAS28 and PASI score of the three patients decreased during H_2 treatment, regardless of the administration method. The psoriatic skin lesions almost disappeared at the end of the treatment. IL-6 levels decreased during H_2 treatment in Case 1 and 2. IL-17, whose concentration was high in Case 1, was reduced following H_2 treatment, and TNFα also decreased in Case 1. In conclusion, H_2 administration reduced inflammation associated with psoriasis in the three cases examined and it may therefore be considered as a treatment strategy for psoriasis-associated skin lesions and arthritis.

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Introduction

Psoriasis is a chronic skin disease affecting 2-3% of the population. Hyperproliferation of disordered epidermal keratinocytes leads to the formation of chronic erythematous plaques with inflammation on the thighs, joints, scalp and body trunk. 5-20% of patients with psoriasis have arthritis, and these patients often present with nail disorders typically featured by pits and yellowish changes in color (1). These complex symptoms, including pain and itchiness, considerably impair the quality of life, and the skin lesions affect physical health and mental wellbeing (2).

Although the etiology is unknown, T cells are thought to have a critical role in the pathogenesis of psoriasis. At the initial step, the pathogenic T cells recruited into the endothelium under the epidermis cause the dysregulation of cytokines, including TNFα, IL-1, IL-6 and IL-17 (3-6). They induce the expression of various adhesion molecules, including intracellular adhesion molecule 1 and leukocyte function-associated antigen 1, on endothelial cells and keratinocytes (1). This affects the rolling of leukocytes and induces the extravasation of the cells into the mesenchymal epithelium. Finally, the impaired angiogenesis is accompanied by increased levels of vascular endothelial growth factor (7) and a five-fold increased turnover of the basal layer results in the thickness of the skin lesions through inflammation. A number of biological drugs have successfully targeted these T-cell cytokine-associated or leukocyte adhesion-mediated molecular interactions (8-10).

Apart from the protein-based molecular mechanisms, reactive oxygen species (ROS) are thought to have an important role in the pathogenesis of psoriasis (11,12). Immune cells, including leukocytes that infiltrate into psoriatic lesions,

overproduce ROS and activate the redox-sensitive nuclear factor-κB-dependent positive feedback loop (13), which, in turn, increases the transcription of the abovementioned pro-inflammatory cytokines (14). Based on the involvement of ROS in the pathogenesis of psoriasis, anti-oxidant therapies have been tested, particularly in Germany, using fumaric acid esters that stabilize Nrf2, a transcriptional factor known to be an activator of intrinsic protective mechanisms against oxidative stress (15,16). However, direct evidence showing that ROS initiate psoriasis is currently lacking; furthermore, a therapeutic approach directly targeted to ROS has not been developed, yet. Among ROS, peroxynitrite, which is generated from the reaction of nitric oxide with superoxide, which are released from the endothelium, is likely to be involved in the pathogenesis of psoriasis, particularly in the development of plaque, with inflammation in the microcirculation of pathological angiogenesis. Another toxic type of ROS, the hydroxyl radical, may have a major role in the pathogenesis of psoriasis, as the absence of the specific scavenger of this species spontaneously causes oxidative states in chronic inflammation (14). Inert H_2 gas has the capability to scavenge the abovementioned ROS (17,18). H_2 has been safely used for the prevention of decompression sickness in deep divers (19). The therapeutic efficacy of H_2 in the treatment of rheumatoid arthritis (RA), an autoimmune disease associated with psoriasis via cytokine-mediated inflammation, was recently investigated (14); The prevalence of psoriatic arthritis was reported to be 19.5/100,0000 individuals in Japan in the 1990s (20). The present study examined the effect on H_2 treatment in three cases of psoriatic skin lesions as well as psoriatic arthritis. In addition to the administration method of drinking water containing dissolved H_2, which has been proven to reduce oxidative stress in the body (21) and infusion of saline containing H_2, which is currently being investigated for the efficacy in the treatment of RA (14), the inhalation of H_2 gas, which is a safe and painless method of H_2 administration, was also investigated, even though its efficacy in the treatment of arthritis has not been proven. The present study showed a reduction in inflammation associated with psoriasis by administration of H_2.

Materials and methods

The three patients with psoriatic arthritis gave their written informed consent to participate in the present study, where a therapy involving molecular hydrogen as an anti-inflammatory agent was used. The treatment protocol was approved by the Haradoi Hospital Ethics Committee (Fukuoka, Japan). Three methods were used to administer H_2: Drop infusion of saline containing 1-ppm H_2 (H_2-saline), inhalation of 3% H_2 gas, and drinking of water containing a concentration of 5-7 ppm H_2 (Hydrogen Water 7.0; Ecomo International, Co., Ltd., Iizuka-shi, Fukuoka, Japan). All methods were previously verified regarding their safety (21-25). H_2-dissolved saline was administered as described previously (21). Briefly, 250 ml saline in a soft bag was placed in a circulating water bath containing 1.6 ppm H_2 generated by an electrolysis instrument (MiZ Company, Fujisawa, Japan), and the concentration of H_2 in the saline was adjusted to 1 ppm prior to infusion. The concentration was confirmed by using the methylene blue-platinum colloid regent-based titration method (26). Although the present case study is not a clinical study, H_2-saline was used in a randomized double-blinded placebo-controlled manner in order to evaluate its effect on the patients objectively. Placebo saline, which was used in Case 3, was prepared in the same water bath without H_2. 500 ml H_2-saline or placebo-saline was administered over 40 min by drip intravenous infusion (DIV) prior to breakfast intake every day over five days.

The high-H_2 water was prepared according to the methods described previously (24). The high-H2 water (500 ml), which contains 2.5-3.5 mg H_2 was consumed every day during the administration period.

H_2 gas for inhalation was generated using a hydrogen gas supply apparatus (patent no. 5091364; Patent Gazette of Japan 2013; MiZ Company, Fujisawa, Japan) constituted by an electrolysis chamber, a membrane and electrode plates. H_2 gas generated from the cathode surface was mixed with air blown directly onto the cathode, so that the H_2 gas concentration was maintained at ~3%. The H_2 gas was inhaled via a cannula attached to the nose. The concentration of H_2 gas on the way out of the cannula was verified to be ~3% using a hydrogen gas meter (XP-3140; New Cosmos Electric Co., Ltd., Osaka, Japan). The H_2 gas was inhaled for 1 h prior to breakfast every day for 5 days

The improvements in the psoriatic skin lesions were estimated using the psoriasis area and severity index (PASI) score (27). The pruritus of the skin lesions was measured by the visual analog scale (VAS) for itching (28). Arthritis was estimated by changes in the disease activity score in 28 joints (DAS28) using C-reactive protein levels (29). Blood samples were collected at each time point, and levels of serum cytokines TNFα, IL-17 and IL-6 were measured using the MILLIPLEX Human Cytokine kit (Merck Millipore, Billerica, MA, USA).

Results

Case 1. A 55-year-old woman with multiple erythematous plaques accompanying a scaly eruption mainly on the lower limbs simultaneously experienced psoriatic arthritis on her wrists, hands, knees and shoulders; her condition had significantly affected her activities of daily life for seven years. She had been pathologically diagnosed as having psoriasis vulgaris and had been treated with corticosteroid and calcipotriol ointments. As her arthritis was consistent with the 2010 American College of Rheumatology criteria for RA (30), she had been treated with methotrexate (14 mg per week) for six months. During that period, her arthritis did not improve and adalimumab, approved for the treatment of RA and psoriasis in Japan, was introduced. The therapy was effective and was successfully continued for four months in addition to a reduced dose of methotrexate (8 mg per week). Following consultation of her physician, and due to financial considerations regarding the continuation of the drug therapy, the patient showed interest in H_2 treatment, which had been used in clinical trials for arthritis patients at Haradoi Hospital, particularly for RA patients (24). Her treatment with adalimumab and corticosteroid and calcipotriol ointments was suspended prior to commencing H_2 treatment. Only methotrexate was continued throughout the study. During the four-week washout period of adalimumab, the patient complained about recurring pain in her wrists and shoulders. The itching sensation and psoriatic

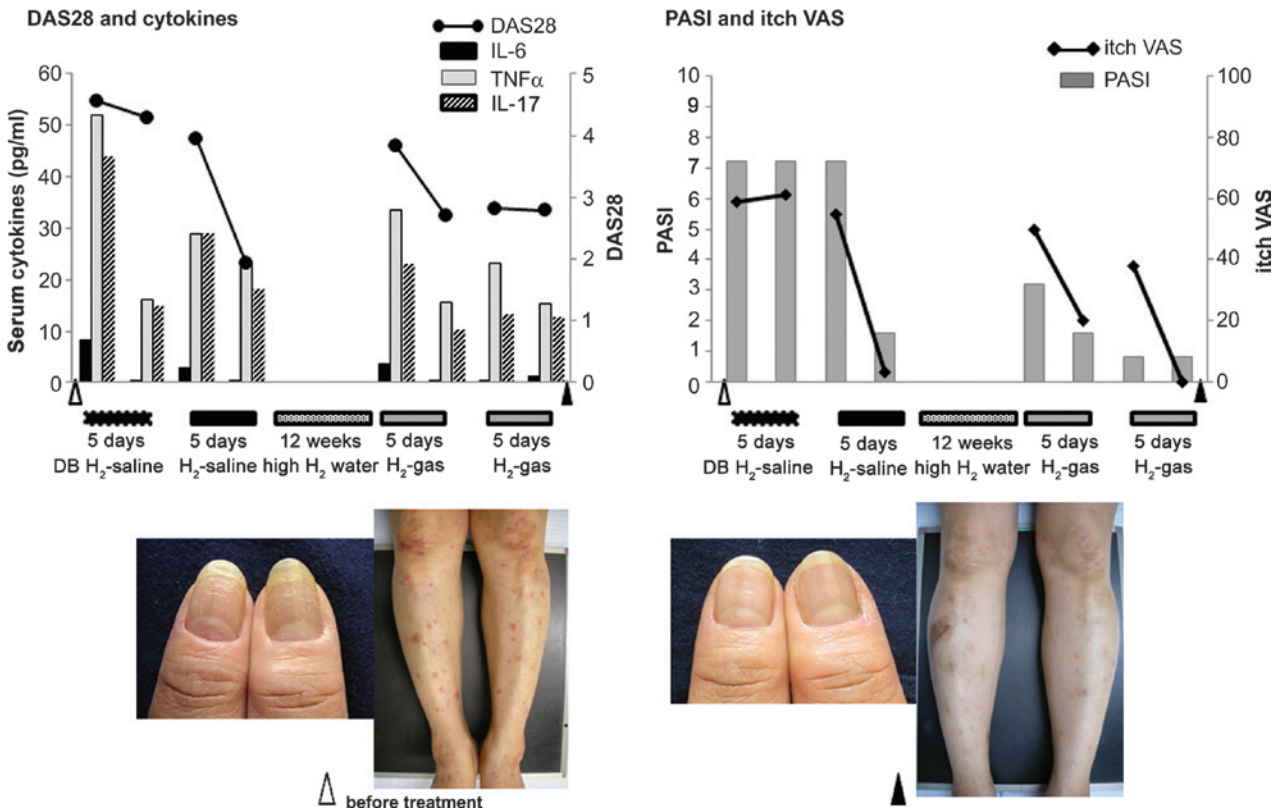

Figure 1. Case 1. Cytokines and DAS28 are shown in the upper left segment, and PASI and itch VAS are in the upper right segment. Images of the nails on the thumbs and lower thighs prior to and after the study are shown in the lower segment. Bars below the x-axis indicate the treatment periods. Black bars indicate H_2-saline. Gray bars indicate H_2-gas. Dotted bars indicate high H_2 water. Bars with broken lines indicate double-blinded (DB) administration. DAS28, disease activity score 28; PASI, psoriasis area and severity index; VAS, visual analogue scale.

skin lesions also recurred (Fig. 1; photos before treatment). She was administered an H_2-saline infusion daily for five days, first in a randomized, double-blinded manner. As shown in Fig. 1, she underwent treatment with double-blinded H_2-saline infusion, but neither DAS28 nor PASI score showed a remarkable decrease during this period. However, all of the three cytokines (IL-6, 8.33 pg/ml; TNFα, 52.0 pg/ml; and IL-17, 44.1 pg/ml at baseline) decreased, particularly IL-6, which decreased by 96% (reaching 0.3 pg/ml). Following a two-day treatment pause, she was treated with H_2-saline openly for another five days, after which the DAS28 and PASI score markedly decreased. Of note, the itching disappeared, and IL-6 decreased from 2.91 to 0.3 pg/ml.

After a four-week washout period, the patient was made to drink the high-H_2 water for 12 weeks. DAS28 and PASI score as well as the VAS score for itching gradually increased during this period. The patient then inhaled 3% H_2 gas for five days, after which PASI score as well as the pain VAS and itch VAS were decreased. In addition, all of the cytokines were reduced during this period. In particular, IL-6 was reduced by 92% (from 3.64 to 0.3 pg/ml). After a three-week washout period, the patient inhaled the H_2 gas for another five days. All symptoms, particularly those regarding the nails and skin of the lower thigh (see images in Fig. 1), were improved at the end of the study.

Case 2. A 67-year-old man with multiple scaly erythematous plaques on the scalp, trunk and limbs was pathologically diagnosed as having psoriasis vulgaris >12 year prior to participation in the present study. He complained about arthritic pain in his wrists, knees and ankles. As radiography did not reveal any erosion or deformity of the bones despite repetitive recurrence of arthritis for >10 years, he was diagnosed as having psoriatic arthritis. In addition, he had experienced severe itching on the psoriatic lesions, which had been severely affecting his activities of daily living for >10 years. The skin on his entire body was frequently injured by scratching, although he had been treated with corticosteroid and calcipotriol ointments daily, and with narrow-band ultraviolet B (UVB) irradiation over one week at a frequency of two or three times yearly. He was interested in H_2 treatment, since he complained of severe pain and swelling in his wrists, left hand and right ankle, and was experiencing itching on the psoriatic lesions. Although he had been treated with corticosteroid and calcipotriol ointments on all the psoriatic skin, the psoriatic lesions had not improved, except for the partially reduced scale on the plaque (Fig. 2 photo, before treatment). Although treatment with drugs was recommended to him, he declined due to financial issues and requested H_2 treatment.

After continuous treatment with corticosteroid and calcipotriol ointments for one week (Fig. 2, image before treatment), he was treated by venous infusion of H_2 in a randomized, double-blinded manner. During the double-blinded infusion, treatment with the corticosteroid and calcipotriol ointments was continued. As shown in Fig. 2, the first five-day double-blinded infusion contained H_2, and the DAS28, PASI and itch VAS scores decreased during this period. Among the three cytokines (IL-6, 55.3 pg/ml; TNFα, 38.1 pg/ml; and

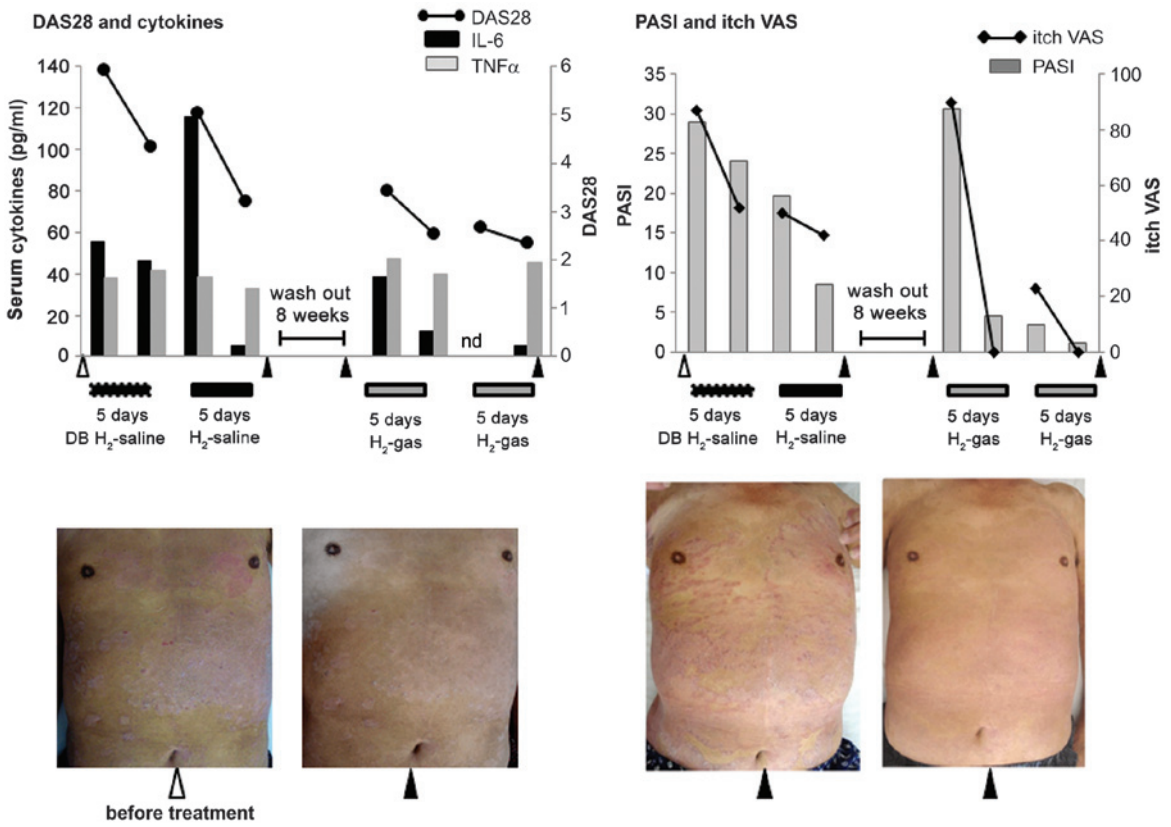

Figure 2. Case 2. Cytokines and DAS28 are shown in the upper left segment, and PASI and itch VAS are in the upper right segment. Photos of the trunk at the indicated time-points are shown in the lower segment. Bars below the x-axis indicate the treatment periods. Black bars indicate H_2-saline. Gray bars indicate H_2-gas. Bars with broken lines indicate double-blinded (DB) administration. nd, no data for cytokines; DAS28, disease activity score 28; PASI, psoriasis area and severity index; VAS, visual analogue scale.

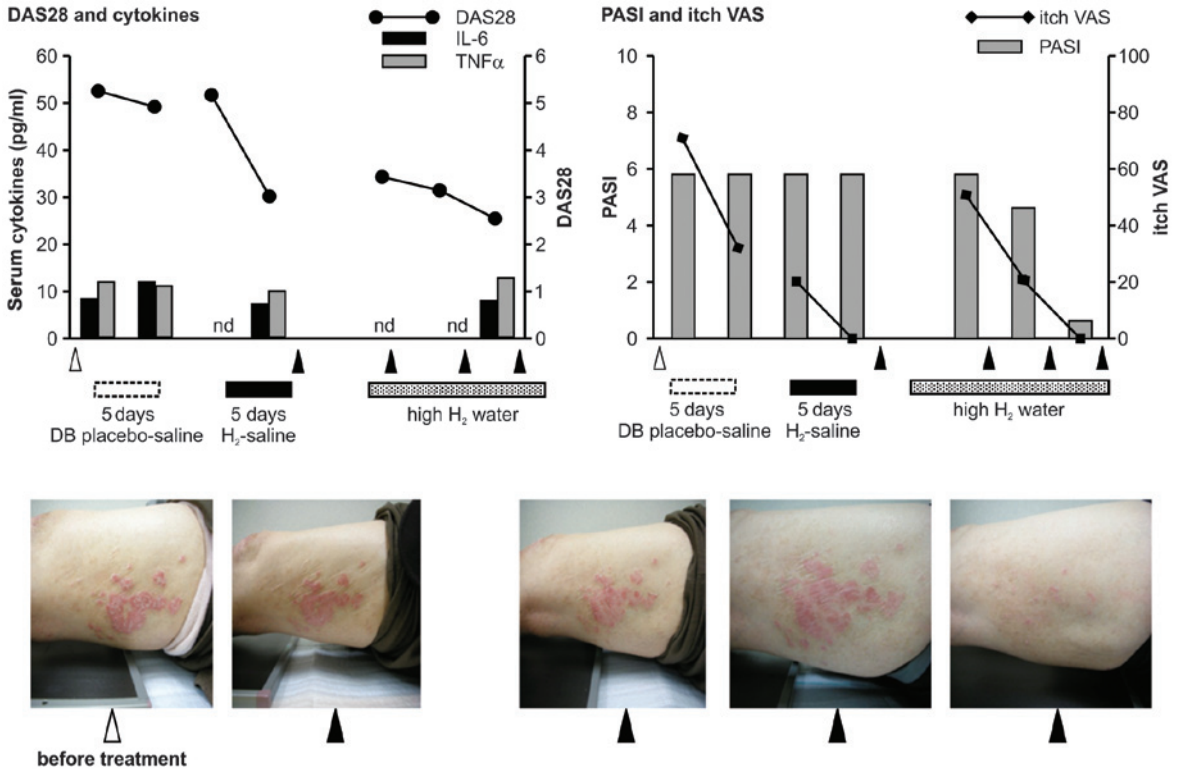

Figure 3. Case 3. Cytokines and DAS28 are shown in the upper left segment, and PASI and itch VAS are in the upper right segment. Photos of the left femoris at the indicated points are shown in the lower segment. Bars below the x-axis indicate the treatment periods. Black bars indicate H_2-saline. Dotted bars indicate high H_2 water. Bars with broken lines indicate double-blinded (DB) administration, and blank bars indicate placebo. nd, no data for cytokines; DAS28, disease activity score 28; PASI, psoriasis area and severity index; VAS, visual analogue scale.

Table I. Summary of three cases.

Parameters	Case 1	Case 2	Case 3
Age (years)/Gender	55/F	67/M	81/F
Disease duration (years)	7	12	20
Family history	Positive	Negative	Negative
Treatment for arthritis prior to H_2	Methotrexate, 8 mg/week Adalimumab, 40 mg/2 weeks	NSAIDs	NSAIDs
Treatment for skin lesions prior to H_2	Corticosteroid and calcipotriol ointment	Corticosteroid and calcipotriol ointment UVB irradiation, 2-3 times/year	Corticosteroid and calcipotriol ointment
Concomitant drug with H_2	Methotrexate	Corticosteroids partially[a] and calcipotriol ointment	
		UVB[b] irradiation on the left side of the trunk	Corticosteroid ointment
Therapeutic efficacy			
H_2-infusion	Effective	Effective	Effective
H_2-inhalation	Effective	Effective	nd
H_2-drink	Partially effective	nd	Effective

[a]Corticosteroid ointment was used during the double-blinded infusion of H_2-saline and during the washout period prior to the double-blinded inhalation of H_2. [b]UVB was irradiated during the open-labeled infusion of H_2-saline. nd, no data available; NSAIDs, non-steroidal anti-inflammatory drugs; UVB, narrow-band ultraviolet B irradiation; F, female; M, male.

IL-17, 0.97 pg/ml at baseline), the serum levels of IL-17 were below the standard value (4 pg/ml) throughout the study. The skin lesion improvement during this period may have been due to the conventional ointment treatment, while the amelioration of arthritis and decrease of IL-6 was thought to be the effect of the H_2-saline infusion. The corticosteroid and calcipotriol ointment treatment was then discontinued; after a one-week washout period, the patient was treated with H_2-saline openly for another five days. During this period, the left half of the body trunk was UVB-irradiated. At the end of this period, DAS28, PASI and itch VAS score were further improved. There was no difference in the psoriatic lesions of his trunk between the left side (with UVB irradiation) and right side (without the UVB irradiation), both of which showed remarkable improvement (Fig. 2, second image from the left). TNFα showed no remarkable change, whereas IL-6, which had recurred during the washout period, was markedly decreased by 95%. Improvements in arthritis and skin lesions were thought to be the effect of H_2. After the H_2-saline treatment, the patient was recommended continuous drinking of the high-H_2 water, but he refused to drink 500 ml of water every day.

During an eight-week washout period, the skin lesions and arthritis recurred, and the patient requested additional H_2 therapy. During the washout period, although he had self-administered corticosteroid and calcipotriol ointments, the psoriatic arthritis and particularly the skin lesions exacerbated (Fig. 2, third image from the left), with the PASI and itch VAS score increased. The corticosteroids were discontinued, and the patient was made to inhale 3% H_2 gas. The DAS28 and PASI score decreased by the fifth day. Of note, the itching sensation disappeared and IL-6 was reduced by 31.0%. After a one-week washout period, the patient inhaled H_2 gas for another five days, after which all symptoms were improved (Fig. 2, right image). Among the cytokines, IL-6 showed the highest reduction (by 90% as compared with the baseline value).

Case 3. An 81-year-old woman had experienced psoriasis vulgaris with multiple erythematous scaly plaques mainly on the lower limbs with simultaneous psoriatic arthritis on her wrists, hands and knees for >20 years. She had been treated with topical corticosteroid and calcipotriol ointment. Despite continuous treatment with corticosteroids, her psoriatic lesion on her lateral femoris had been intractable throughout (Fig. 3, image before treatment). Although the psoriatic lesion was restricted to her limbs by continuous treatment with corticosteroid and calcipotriol ointments, her PASI score, which had been relatively low, remained unchanged, and the itching on the psoriatic lesions and the pain on her wrists, hands, shoulders and knees had severely affected her quality of life. When she expressed her interest in H_2 therapy, she complained of pain and swelling on her wrists and hands. Since radiography did not reveal any erosion or deformity of the bones despite persistent arthritis for >20 years, her arthritis was not classified as RA. The corticosteroid and calcipotriol ointments were used until the itching was reduced during the period she drank the high-H_2 water after the infusion study. As shown in Fig. 3, the first infusion was double-blinded placebo saline. There was no remarkable change in the DAS28 and PASI score. Only the itching sensation was reduced by the placebo effect. Among the three cytokines (IL-6, 8.36 pg/ml; TNFα, 11.9 pg/ml; and IL-17, 1.16 pg/ml at baseline), IL-6 increased and showed no remarkable change during this period. IL-17 decreased, but the serum levels were below the standard value (4 pg/ml) throughout the study (data not shown). After a two-day treatment pause, H_2 was infused openly for an additional five days.

Although the range of the femoral psoriatic lesions appeared nearly unchanged during this period, the scaling was improved (Fig. 3, second image from the left) and the itching disappeared at the end of the infusion therapy. The DAS28 also decreased during this period.

The patient was not willing to inhale H_2 gas; however, she continuously drank the high-H_2 water for 16 weeks. During the first four weeks, there was no reduction in the PASI score (Fig. 3, third image from the left). The itch VAS score gradually increased during this period. At eight weeks, the PASI score was slightly reduced (Fig. 3, right image). The itching and DAS28 scores also decreased, and the patient discontinued the treatment with corticosteroid and calcipotriol ointments. After 16 weeks of drinking high-H_2 water, the PASI score was markedly reduced with the disappearance of the psoriatic lesions on her lateral femoris (Fig. 3, right image). The itching also disappeared. At the end of the study, cytokine levels showed no significant change from those at the beginning of the study.

The results are summarized in Table I. No adverse effects have been observed in any of the cases presented in the present study.

Discussion

Psoriasis is known as a representative disease that shows the orchestrated mechanisms of chronic inflammation (2). In the present report, the treatment effects of three psoriasis cases with H_2 appeared to demonstrate the participation of ROS in chronic inflammation and also the therapeutic possibilities and preventive potential of H_2, free from adverse effects.

In the present study, each of the three methods used for H_2 administration had their respective advantages. The effect of H_2-saline infusion on the autoimmune-based and ROS-associated arthritis, such as RA, was investigated in the present study. The high-H_2 water method does not require hospitalization and is suitable for the daily intake of H_2; however, evidence of cytokine-based improvement was not obtained in the present study. The third method, H_2 inhalation, is expected to produce a higher concentration of H_2 in the arterial blood (21); however, there is no evidence concerning its efficacy in the treatment of arthritis or psoriatic skin lesions. Among these methods, the infusion method, which is currently being investigated for its therapeutic efficacy against RA, was applied first, as the psoriatic arthritis in Cases 1 and 2 also fulfilled the diagnostic criteria of RA; however, continuous treatment using the infusion method is difficult due to the pain caused by the injection and the inconvenience of hospitalization; therefore, following establishment of the proof of principle regarding the efficacy of H_2 in the treatment of arthritis and psoriasis, other forms of administration were employed subsequently. After the period of H_2-saline infusion, H_2 was observed to continue to be efficacious. When the symptoms recurred, it was estimated that the washout period of H_2 administered by infusion of H_2-saline was completed. The intake of H_2 was then continued by drinking high-H_2 water daily. The patient in Case 1 reported a higher efficacy of the H_2-saline than that of high-H_2 water, while the patient in Case 2, who refused drinking water as prescribed, requested periodic treatment with H_2-saline. Although there was no clear evidence for the efficacy of the inhalation of H_2 gas, patients in Case 1 and 2 requested to try the H_2 gas inhalation method.

H_2-saline infusion in a double-blinded manner effectively reduced DAS28 and PASI score in Case 2. In addition, the open-labeled infusion suggested beneficial effects of H_2 infusion in the treatment of psoriatic skin lesions as well as psoriatic arthritis in all three cases. In particular, the marked reduction of IL-6 observed in Case 1 and 2 demonstrates the anti-inflammatory effects of H_2. IL-17, which is involved in the pathogenesis of psoriasis as well as RA, was reduced following infusion of H_2-saline in Case 1, which was the only case in which IL-17 was above the standard value. In Case 1, TNFα was also reduced following administration of H_2-saline. The results of all of the three cases suggested a potential therapeutic effect of H_2-saline on psoriasis.

The inhalation of 3% H_2 gas also showed potential therapeutic efficacy in Case 1 and 2. Five days of treatment effectively improved arthritis and skin lesions of psoriasis. The marked decrease of IL-6 (Case 1 and 2), TNFα (Case 1), and IL-17 (Case 1) supports the therapeutic potential of H_2 gas. It should be noted that the influence of H_2 on the itching sensation of psoriasis was significant, whether it was by venous infusion or by inhalation.

The effects of continuous consumption of water containing 5-7 ppm H_2 on psoriasis was also marked. Although the effect was limited in Case 1, all of the parameters, including DAS28, PASI, itch VAS and cytokine levels, remained below the baseline during the treatment period. In Case 3, the therapeutic potential of the continuous consumption of high-H_2 water was obviously demonstrated, as at 16 weeks, the patient became almost free of the inveterate psoriatic skin lesions that had not been improved by the long-term treatment with glucocorticoid.

Although concomitant treatment was used for the skin lesions as shown in Table I, the treatment of arthritis was monotherapy with H_2, and the severity of arthritis was reduced in Case 2 and 3. As the psoriatic arthritis was improved by monotherapy with H_2, which was not due to the external use of corticosteroids, it appears that the improvement of the skin lesions was caused, to a certain extent, by H_2 treatment. Furthermore, regarding Case 1, it should be noted that the dosage of methotrexate concomitantly used for treating arthritis was not effective in combination with adalimumab prior to participation in the present study, whereas the arthritis was improved by the treatment with H_2, while adalimumab treatment was discontinued. Although the possibility that the skin lesion improvements were caused by methotrexate treatment cannot be excluded, it is indicated that they were in part owing to the intake of H_2 alongside the H_2-mediated improvements of psoriatic arthritis.

The involvement of ROS in the pathogenesis of psoriasis is partially explained by the function of the skin as a barrier against UV irradiation from sunlight or other environmental oxidative stressors. On the contrary, UVB irradiation is used for the treatment of psoriasis, and environmental factors may not be sufficient to induce arthritic psoriasis. It is likely that in the generation of psoriasis, the intrinsically produced ROS were able to overcome the initiating hurdle formed by the activated immune system in individuals with inherent or genetic susceptibility for the disease. The downregulation of

the cytokines that have crucial roles in the pathogenesis of psoriasis observed in the present case report indicates the involvement of intrinsically generated free radicals in the development of psoriatic lesions as well as the therapeutic efficacy of H_2.

Regarding the present study, it should be noted that the itching sensation was markedly reduced in all cases. Although it is known that cutaneous nerves are rich in psoriatic lesions and >50% of the patients with psoriasis experience chronic itchiness (31,32), a more substantial contribution of the nervous system to the pathogenesis of psoriasis, including nerve growth factor and its receptor, has been suggested (33,34). The influence of H_2 on the itching sensation suggests the presence of neurogenic inflammation associated with ROS in the psoriatic lesion and the possibility of a therapeutic approach similar to that for neurological inflammatory disorders. Among the three methods of H_2 intake, H_2 gas inhalation appeared to be particularly efficient for psoriatic skin lesions. This may be due to the uptake of H_2 into the arterial blood in the lungs, since it is able to circulate through the body and is released through the skin.

Recently, a compulsory anti-inflammatory approach using biological drugs, including antibodies and chimeric proteins, has been emerging in the treatment of psoriasis, and it is expected to become one of the major therapeutic strategies due to the unmet requirements of conventional therapies. These effective drugs are, however, accompanied by side effects, recurrence after discontinuation of the drugs, and high cost. More convenient, safe and widely effective treatments are required to emerge.

The findings presented in this study have limitations, as only three individual cases are reported, where improvement of symptoms of psoriasis was observed following H_2 therapy. However, the present study provided preliminary findings strongly indicating that H_2 possesses therapeutic properties against psoriasis. Large-scale clinical trials should be performed to evaluate the therapeutic effect of H_2. Since the safety of H_2 is established by its intrinsic production in the human body and as H_2 is inert against biogenic components, it may be considered for the treatment of psoriasis. The daily consumption of water containing 5-7 ppm H_2, which is commercially available, may show efficacy in the treatment of psoriasis.

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