Therapeutic depletion of myeloid lineage leukocytes in patients with generalized pustular psoriasis indicates a major role for neutrophils in the immunopathogenesis of psoriasis

Shigaku Ikeda, MD,[a] Hidetoshi Takahashi, MD,[b] Yasushi Suga, MD,[c] Hikaru Eto, MD,[d] Takafumi Etoh, MD,[e] Keiko Okuma, MD,[a] Kazuo Takahashi, MD,[f] Takeshi Kanbara, MD,[g] Mariko Seishima, MD,[h] Akimichi Morita, MD,[i] Yasutomo Imai, MD,[j] and Takuro Kanekura, MD[k]
Tokyo, Asahikawa, Chiba, Yokohama, Gifu, Nagoya, Hyogo, and Kagoshima, Japan

Background: Generalized pustular psoriasis (GPP) is a chronic autoimmune disease characterized by fever, erythema, and neutrophilic pustules over large areas of the skin. GPP does not respond well to pharmacologic intervention.

Objective: We sought to assess efficacy of selectively depleting the myeloid lineage leukocytes in patients with GPP.

Methods: Fifteen patients with persistent moderate to severe GPP despite conventional therapy were included. Eligible patients had more than 10% of their skin area covered by pustules. Treatment with oral etretinate, cyclosporine, methotrexate, prednisolone, and topical prednisolone/vitamin D3 was continued if had been initiated well in advance of study entry. Five sessions of adsorptive granulocyte and monocyte apheresis (GMA) with the Adacolumn (JIMRO Co Ltd, Takasaki, Japan) were administered (1 session/wk over 5 weeks) to selectively deplete Fcγ receptor and complement receptor bearing leukocytes. Efficacy was assessed by measuring the skin areas covered by pustules at baseline and 2 weeks after the last GMA session.

Results: One patient did not complete the first GMA session. Based on the GPP severity scores relative to entry, the overall scores improved (n = 14, $P = .0027$), and the area of erythroderma ($P = .0042$), pustules ($P = .0031$), and edema ($P = .0014$) decreased. Likewise, Dermatology Life Quality Index improved ($P = .0016$), reflecting better daily function and quality of life. Twelve patients were judged as responders (85.7%), and 10 patients maintained the clinical response for 10 weeks after the last GMA session without any change in medication.

Limitations: This study was unblinded and without a placebo arm.

Conclusion: GMA in this clinical setting was safe and effective, suggested a major role for granulocytes/monocytes in the immunopathogenesis of GPP. (J Am Acad Dermatol 2013;68:609-17.)

Key words: Dermatology Life Quality Index; edema; erythroderma; generalized pustular psoriasis; granulocytapheresis; granulocyte and monocyte adsorption apheresis; granulocytes and monocytes; neutrophilic pustules.

From the Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine, Tokyo[a]; Department of Dermatology, Asahikawa Medical University[b]; Department of Dermatology, Juntendo University Urayasu Hospital, Chiba[c]; Department of Dermatology, St Luke's International Hospital, Tokyo[d]; Department of Dermatology, Tokyo Teishin Hospital[e]; Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine[f]; Department of Dermatology, Yokohama City University Medical Center[g]; Department of Dermatology, Gifu University Graduate School of Medicine[h]; Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences[i]; Department of Dermatology, Hyogo College of Medicine[j]; and Department of Dermatology, Kagoshima University Graduate School of Medical and Dental Sciences.[k]

Sponsored by JIMRO Co Ltd.
Conflicts of interest: None declared.
Accepted for publication September 23, 2012.

Reprint requests: Shigaku Ikeda, MD, Department of Dermatology and Allergology, Juntendo University Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. E-mail: ikeda@juntendo.ac.jp.

Published online January 21, 2013.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2012.09.037

Psoriatic skin lesions are chronic autoimmune disorders, affecting about 2% of the global population.[1,2] In addition to psychologic morbidity, the conditions are often complicated by comorbidities such as rheumatoid arthritis, inflammatory bowel disease (IBD), cardiovascular disorders, and uveitis.[2-5] Currently, the causes and factors that perpetuate psoriasis are not understood well. In generalized pustular psoriasis (GPP), histologically, the entire skin may be affected by neutrophilic pustules in the epidermis, and clinically by erythroderma with sterile pustules.[6-8] However, psoriasis may be considered a model autoimmune disease, which does not respond well to pharmacologic interventions.[1,2,5,6] A dysregulated immune profile involving elevated myeloid lineage leukocytes (neutrophils and monocytes/macrophages) appears to be a major factor in the immunopathogenesis of GPP.[6-16] Accordingly, biopsy specimens from psoriatic lesions, notably from patients with GPP, reveal extensive neutrophil infiltration into the epidermis that causes Kogoj spongiotic pustules.[6-8] Hence, the elevated/activated neutrophils might be appropriate targets for therapeutic intervention in these patients.[7,8-15]

CAPSULE SUMMARY

- Generalized pustular psoriasis is a neutrophilic skin disease that does not respond well to pharmacologic intervention.
- Selective depletion of elevated/activated granulocytes and monocytes by adsorptive apheresis as a nonpharmacologic intervention was associated with significant improvement of generalized pustular psoriasis lesions.
- The findings of this study indicate that activated myeloid lineage leukocytes are major pathologic factors in generalized pustular psoriasis. The elevated leukocytes can be normalized by granulocytapheresis.

In light of the above background, we thought that patients with GPP should respond favorably to selective depletion of elevated neutrophils. Further, recently an adsorptive type extracorporeal granulocyte and monocyte apheresis (GMA) system has been developed (Adacolumn, JIMRO Co Ltd, Takasaki, Japan) for selective depletion of myeloid lineage leukocytes.[17] GMA in patients with inflammatory skin lesions including severe pyoderma gangrenosum and subcutaneous neutrophilic abscesses,[18-22] and patients with IBD[23-29] has shown good efficacy in the majority of the treated patients. In addition, GMA procedure has shown an excellent safety profile. Serious adverse side effects have rarely been reported. Here we report on the efficacy of GMA in patients with GPP, in a multicenter setting (albeit in a small cohort of patients).

METHODS

Patients and objective

The major objective of this study was to evaluate the efficacy of therapeutic depletion of myeloid lineage leukocytes by GMA in patients with GPP. Fifteen patients with moderate to severe GPP in spite of receiving conventional medications listed in Table I were included. To be eligible, more than 10% of the patient's skin had to be covered by pustules (Table II). Medications that these patients had received included oral etretinate, cyclosporine, methotrexate, prednisolone, and topical prednisolone/vitamin D3. These interventions were allowed to continue if they had started well in advance of entry to this study, but without any change in the dosage. Patients who had participated in another clinical investigation or had received extracorporeal therapy within the past 6 months were not eligible. Similarly, patients who had received a biologic agent within the past 8 weeks or had received phototherapy within 2 weeks before entry were ineligible. The study was conducted in a multicenter setting involving all institutes listed as authors' affiliations. The study design is outlined in Fig 1, *A* and *B*.

Determination of GPP severity and treatment efficacy

In this study, we had to adhere to officially set guidelines for assessing GPP severity and efficacy outcomes. The score system introduced by the practice guidelines for the treatment of pustular psoriasis, which is approved by the Japan Ministry of Health Research Group for Rare and Intractable Dermatological Diseases, was used. Based on this scoring system (Table II), the total GPP severity score ranges from 0 to 17 points: 6 or fewer = mild, 7 to 10 = moderate, and 11 to 17 = severe. These scores were translated from subscores of the GPP severity listed in Table II. In the subscoring system, the extent (percent of total body surface area) of erythroderma, pustules on erythematous background, and edema is given a score of 0 to 9 points with 3 points (maximum) each reflecting 75% or more erythroderma, 50% or more erythema with pustules, or 50% or more edema, whereas 0 indicates normal-appearing skin (Table II). Other relevant variables including body temperature, white blood cell counts, serum albumin