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A randomized double-blind trial of intravenous immunoglobulin for bullous pemphigoid

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Abbreviations: ADR, adverse drug reactions; BPDAI, bullous pemphigoid disease area index; FAS, full analysis-set; IVIG, intravenous immunoglobulin; jBPAS, japanese bullous pemphigoid activity score; PDAI, pemphigus disease area index.

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ABSTRACT

Background: Patients with steroid-resistant bullous pemphigoid (BP) require an appropriate treatment option.
Objective: A multicenter, randomized, placebo-controlled, double-blind trial was conducted to investigate the therapeutic effect of high-dose intravenous immunoglobulin (IVIG; 400 mg/kg/day for 5 days) in BP patients who showed no symptomatic improvement with prednisolone (≥0.4 mg/kg/day) administered.
Methods: We evaluated the efficacy using the disease activity score on day15 (DAS15) as a primary endpoint, and changes in the DAS over time, the anti-BP180 antibody titer, and safety for a period of 57 days as secondary endpoints.
Results: We enrolled 56 patients in this study. The DAS15 was 12.5 points lower in the IVIG group than in the placebo group ($p = 0.089$). The mean DAS of the IVIG group was constantly lower than that of the placebo group throughout the course of observation, and a post hoc analysis of covariance revealed a significant difference ($p = 0.041$). Furthermore, when analyzed only in severe cases (DAS ≥ 40), the DAS15 differed significantly ($p = 0.046$). The anti-BP180 antibody titers showed no difference between the two groups.
Conclusion: IVIG provides a beneficial therapeutic outcome for patients with BP who are resistant to steroid therapy.

1. Introduction

Bullous pemphigoid (BP) is an autoimmune disease characterized by subepidermal blisters caused by IgG autoantibodies targeting the hemidesmosomal components of the epidermal basement membrane zone (BMZ). In the treatment of BP, most patients respond to systemic steroid therapy; however, some patients show inadequate improvement with steroids alone or are not amenable to steroid therapy due to coexisting conditions such as diabetes, osteoporosis, and gastrointestinal disease, or because of the risk of infection.

Although some guidelines or consensus statements [1–5] and several case reports [6–16] have suggested the effectiveness of high-dose intravenous immunoglobulin (IVIG) [6], there is no evidence to demonstrate the efficacy of IVIG in BP. We previously demonstrated the efficacy of IVIG in patients with pemphigus in a randomized, double-blind, placebo-controlled clinical study [17]. In this study, we performed a similar randomized, double-blind, placebo-controlled clinical study to evaluate the therapeutic benefit of IVIG in patients with BP who showed no symptomatic improvement with prednisolone administered at a dose of ≥0.4 mg/kg/day.

2. Material and methods

2.1. Patients

This study was conducted at 53 medical institutions in Japan with affiliated dermatologists who specialized in autoimmune blistering diseases. Patients were given a confirmed diagnosis of BP based on our national diagnostic criteria, as follows: BP was diagnosed when the clinical and histological findings and at least one item from the immunological findings, or when the clinical findings and both items from the immunological findings, were satisfied.

(1) Clinical findings
- Multiple pruritic erythema and tense blisters of the skin;

(2) Histological findings
- Subepidermal blisters with infiltration of eosinophils;

(3) Immunological findings
- IgG or complement 3 deposition in the BMZ of the patient's skin, as detected by direct immunofluorescence;

(4) Anti-epidermal basement membrane antibodies (BP antibodies) in the blood identified by indirect immunofluorescence or an enzyme-linked immunosorbent assay.

To be enrolled in the study, patients were required to meet all of the following inclusion criteria and none of the exclusion criteria.

1. 1) Inclusion criteria: patients aged 20 years or older who provided written informed consent to participate in the study and who met all of the following:
   (i) treatment with any steroid at a dose ≥ 0.4 mg/kg/day (prednisolone equivalent);
2. patients on a stable treatment regimen for BP;
3. a disease activity score (DAS) (Supplementary Fig. 1) of at least 10;
4. patients who experienced no improvement in the DAS for 10 to 21 days before the commencement of study treatment (the pre-treatment observation period) or who had an increase in the DAS of at least 10 or an increase of at least 2 in the Japanese BP activity score (jBPAS) (Table 1) after a pre-treatment observation period of at least 7 days;