Original Article

A multicenter, open-label, uncontrolled, single-arm phase 2 study of tirabrutinib, an oral Bruton’s tyrosine kinase inhibitor, in pemphigus

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ABSTRACT

Background: The treatment of pemphigus is based on systemic corticosteroid use and adjuvant therapies, but some patients are resistant to conventional therapy. Tirabrutinib is a highly selective oral Bruton’s tyrosine kinase inhibitor that may be clinically effective in treating pemphigus by suppressing B-cell signaling.

Objective: We investigated the efficacy and safety of tirabrutinib in patients with refractory pemphigus.

Methods: This was a multicenter, open-label, single-arm phase 2 study of Japanese patients with refractory pemphigus receiving appropriate treatment with an oral corticosteroid and adjuvant therapies. Patients received postprandial oral tirabrutinib 80 mg once daily for 52 weeks. After 16 weeks of tirabrutinib treatment, the corticosteroid dose was tapered to ≤10 mg/day of prednisolone equivalent.

Results: In total, 16 patients were evaluated (mean age, 52.5 years; 50 % male). The complete remission rate after 24 weeks of treatment (primary endpoint) was 18.8 % (3/16; 95 % confidence interval, 6.6 %–43.0 %). By Week 52, eight patients (50.0 %) achieved complete remission and 10 patients (62.5 %) achieved remission. Over 52 weeks of treatment, the mean prednisolone dose decreased from 17.03 to 7.65 mg/day. Incidences of adverse events (AEs) and adverse drug reactions were 87.5 % and 43.8 %, respectively. A relationship with tirabrutinib was ruled out for all serious AEs and Grade ≥3 AEs.

Conclusion: Treatment with tirabrutinib enabled remission and reduced oral corticosteroid exposure over time and did not result in any major safety concerns in patients with refractory pemphigus. Thus, oral tirabrutinib may be a new treatment option for patients with refractory pemphigus.

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1. Introduction

Pemphigus is a rare and severe autoimmune disease caused by pathogenic immunoglobulin G (IgG) autoantibodies directed against adhesion proteins, desmoglein 1 (Dsg1) and Dsg3, located in the epidermis. IgG autoantibodies bind to Dsg, resulting in loss of epidermal keratinocyte adhesion (acantholysis) and intra-epidermal skin blistering and erosions in the involved sites [1–5]. Several types and subtypes of pemphigus have been described. The main subtypes are pemphigus vulgaris, characterized by painful oral erosions, and pemphigus foliaceus, characterized by...
exclusive skin lesions [4]. If left untreated, some types of the disease can be life-threatening.

The Japanese guidelines for the management of pemphigus recommend oral high-dose corticosteroids for first-line treatment during the induction period and tapering during the maintenance period [6]. In pemphigus, the goal of treatment is to maintain remission with a minimal oral steroid dose, namely, 0.2 mg/kg per day or 10 mg/day or less. In the consolidation phase, prednisolone is the first choice for initial therapy. If therapeutic effects are judged to be insufficient, consideration should promptly be given to using additional treatments such as immunosuppressants, high-dose intravenous immunoglobulin therapy, plasma exchange, and steroid pulse therapy. In the maintenance phase, corticosteroids are tapered to reduce the prednisolone dose to 0.2 mg/kg per day or less or prednisolone 10 mg/day or less.

However, there are refractory cases in which it is difficult to achieve remission despite the use of conventional treatments such as immunosuppressive agents, high-dose intravenous immunoglobulin, and plasma exchange. Moreover, many patients who do respond to conventional treatment often develop various side effects [7]. Recently, there have been reports on refractory cases treated with rituximab. However, not all patients benefit from rituximab due to potentially severe side effects [8] and continuous infusion over several hours requires considerable healthcare resources and is inconvenient for patients [9,10]. Therefore, other therapeutic options with alternative mechanisms of action are needed [4].

As a critical mediator of B-cell receptor (BCR) signaling, Bruton’s tyrosine kinase (BTK) inhibition suppresses BCR-stimulated proliferation, costimulatory molecule expression, and antibody production in B-cells [11–13]. BTK has been implicated in the pathology of pemphigus, as demonstrated by the successful treatment of B-cell depletion with rituximab [14,15]. A covalent reversible BTK inhibitor, PRN1008, which has been granted orphan drug designation for pemphigus vulgaris, is in clinical development (ClinicalTrials.gov Identifier: NCT03762265).

Tirabrutinib hydrochloride (ONO/GS-4059), herein referred to as tirabrutinib, is a highly selective oral BTK inhibitor recently approved for the treatment of central nervous system primary lymphoma [16], Waldenstrom macroglobulinemia [17], and plasma cell lymphoma in Japan [18]. Tirabrutinib inhibited stimulation-induced IgG production in human B-cells (unpublished data) and prevented further increases in anti-double stranded DNA antibody level in spontaneous lupus-prone mice [19]. Based on its mechanism of action, tirabrutinib is expected to inhibit the IgG autoantibody-mediated mechanism that plays a central role in the pathophysiology of pemphigus and may provide a new treatment option for refractory pemphigus. This study aimed to investigate the efficacy and safety of tirabrutinib in patients with refractory pemphigus.

2. Materials and methods

2.1. Study design and treatment

This open-label, uncontrolled, single-arm phase 2 study was conducted at six study sites in Japan. Patients were enrolled from 29 January 2019 to 20 December 2019. After registration, patients received postprandial oral tirabrutinib 80 mg once daily for 52 weeks (Fig. 1). This dosing regimen was selected based on the inhibition rate of CD69 expression on B-cells from a clinical pharmacological study in healthy adults (unpublished data). Patients who wished to continue treatment beyond 52 weeks were allowed to do so during the extension period until the marketing approval of tirabrutinib for refractory pemphigus.

After 16 weeks of treatment with tirabrutinib, the corticosteroid dose was tapered to <10 mg/day (prednisolone equivalent). Patients were followed-up for up to 28 days after the last dose of tirabrutinib.

This study protocol was approved by the Institutional Review Board of each participating study site, and the study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. The study was registered at the Japan Pharmaceutical Information Center (JapicCTI-184231).

2.2. Patients

The inclusion criteria were patients aged ≥20 years with refractory pemphigus, defined as a second increase in the...
pemphigus disease area index (PDAI) score [20] before oral corticosteroid tapering to 10 mg/day (prednisolone equivalent) despite appropriate treatment with an oral corticosteroid and a second-line treatment. Patients had to have an oral corticosteroid dose at registration of 15–30 mg/day (prednisolone equivalent).

The main exclusion criteria were patients with serious and uncontrolled organ dysfunction, with a disease other than pemphigus that required systemic corticosteroid administration within 12 weeks before the start of the observation period, with an active infection, who received an oral antibiotic within 2 weeks before the start of the observation period, with a history of serious infection after the start of immunosuppressant administration, who previously received tirabrutinib or any other BTK inhibitor (in an effort to reduce bias in the study assessments), who were pregnant or breastfeeding or those wishing to become pregnant, and those considered ineligible as judged by the investigators.

2.3. Efficacy

The primary endpoint was complete remission rate after 24 weeks of treatment. The 24-week endpoint was selected based on the results of previous studies on rituximab [21]. Complete remission was defined as the absence of blisters or new erythema due to pemphigus starting at Week 16, while on treatment with ≤10 mg/day of prednisolone equivalent or together with minimum adjuvant therapy [22]. Secondary endpoints were as follows: complete remission rates over time, remission rates over time, and changes in PDAI score [23], anti-Dsg1 and Dsg3 antibody levels, and oral corticosteroid exposure over time.

Remission rate was defined as the proportion of patients who achieved complete or partial remission. Partial remission was defined as the presence of transient new lesions that healed within 1 week while the patient was receiving minimal therapy for 8 weeks, while on treatment with ≤10 mg/day of prednisolone equivalent or together with minimum adjuvant therapy [22]. Titers of IgG autoantibodies against Dsg1 and Dsg3 were analyzed by indirect fluorescent antibody technique or enzyme-linked immunosorbent assay.

2.4. Safety

The incidences of adverse events (AEs), serious AEs, and adverse drug reactions (ADRs) were evaluated. Immunological testing was also performed (IgG, IgM, CD19+ B-cells, and CD3+ T-cells).

2.5. Statistical analysis

The target sample size was 14 patients with an expected dropout rate of 10 % based on the following assumptions: the spontaneous remission rate was predicted to be <10 % based on infliximab data [24] and the opinions of pemphigus specialists; and the expected remission rate at Week 24 was predicted to be 40 % in reference to clinical data on rituximab [23]. Thus, assuming a threshold complete remission rate of 10 % and a complete remission rate of 40 %, and based on the probability that the lower limit of the confidence interval (CI) (Wilson method with a one-sided significance level of 2.5 %) would exceed the threshold, a sample size of 12 was determined to be large enough to have a power of ≥80 %.

Efficacy was assessed in the full analysis set, which comprised patients who met the eligibility criteria, received the study drug, and completed at least one post-baseline efficacy evaluation. Safety was evaluated in the safety set, which comprised patients who received at least one dose of the study drug.

Descriptive statistics were used for baseline characteristics, with n (%) for categorical variables and mean ± standard deviation (SD) for continuous variables. The complete remission rate at 24 weeks after starting the study drug and its two-sided 95 % CI were calculated using the Wilson method. Similar statistical methods were used for secondary efficacy endpoints. Patients with missing data on the oral corticosteroid dose and/or the PDAI score any time between Weeks 16 and 24 and patients who received rescue therapy before Week 24 were handled as non-responders. AEs were classified by MedDRA/J version 23.1 System Organ Class and Preferred Term. Statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA).

### Table 1

Baseline demographic and clinical characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD or n (%)</th>
<th>N = 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td>52.5 ± 8.8</td>
</tr>
<tr>
<td>Sex, Male</td>
<td>8 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>73.04 ± 12.90</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.89 ± 5.15</td>
<td></td>
</tr>
<tr>
<td>Type of pemphigus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>8 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Pemphigus foliaceus</td>
<td>6 (37.5)</td>
<td></td>
</tr>
<tr>
<td>Pemphigus vegetans</td>
<td>2 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Duration of morbidity, months$^a$</td>
<td>57.00 ± 56.66</td>
<td></td>
</tr>
<tr>
<td>Total PDAI</td>
<td>9.9 ± 7.1</td>
<td></td>
</tr>
<tr>
<td>Anti-desmoglein profile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>16 (100)</td>
<td></td>
</tr>
<tr>
<td>Anti-desmoglein 3 positive only</td>
<td>7 (43.8)</td>
<td></td>
</tr>
<tr>
<td>Anti-desmoglein 1 positive only</td>
<td>7 (43.8)</td>
<td></td>
</tr>
<tr>
<td>Anti-desmoglein 1 and anti-desmoglein 3 positive</td>
<td>2 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Desmoglein 1 antibody, U/mL</td>
<td>408.44 ± 310.89$^a$</td>
<td></td>
</tr>
<tr>
<td>Desmoglein 3 antibody, U/mL</td>
<td>518.78 ± 394.93$^a$</td>
<td></td>
</tr>
<tr>
<td>Prednisolone dose, mg/day</td>
<td>17.03 ± 3.90</td>
<td></td>
</tr>
<tr>
<td>Minimum adjuvant therapy</td>
<td>4 (25.0)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12 (75.0)</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Duration of morbidity (months) × (“date of the first dose” – “date of disease diagnosis” + 1) / 30.4375.

$^b$n = 9, anti-desmoglein 1-negative patients were excluded.

$^c$n = 9, anti-desmoglein 3-negative patients were excluded.

BMI: body mass index, PDAI: pemphigus disease area index, SD: standard deviation.
3. Results

3.1. Patients

In total, 18 patients were enrolled. Of these, 16 received tirabrutinib and were included in this study. Two patients were excluded from the analysis because they met the exclusion criteria (Fig. 1).

The baseline demographic and clinical characteristics of patients are shown in Table 1. The mean ± SD age of patients was 52.5 ± 8.8 years, and 50% were male. The most common type of pemphigus was pemphigus vulgaris (50.0%), followed by pemphigus foliaceus (37.5%) and pemphigus vegetans (12.5%). Six out of eight patients with pemphigus vulgaris were only positive for anti-Dsg3, and the other two were anti-Dsg1 and anti-Dsg3 positive. All six patients with pemphigus foliaceus were only positive for anti-Dsg1. One out of two patients with pemphigus vegetans was only positive for anti-Dsg1 and the other was only positive for anti-Dsg3. No patients were anti-Dsg1 and anti-Dsg3 negative. The mean ± SD PDAI score at baseline was 9.9 ± 7.1.

3.2. Efficacy

After 24 weeks of treatment (primary endpoint), the complete remission rate was 18.8% (3/16 patients; 95% CI, 6.6%–43.0%). The lower limit of the 95% CI was lower than the threshold of 10%.
The cumulative complete remission rate and the cumulative remission rate up to 52 weeks of treatment were 50.0 % (8/16 patients; 95 % CI, 28.0–72.0 %) and 62.5 % (10/16 patients; 95 % CI, 38.6–81.5 %), respectively. The changes in cumulative complete remission rate and cumulative remission rate are shown in Fig. 2A, Table S1, and Table S2. At Week 52, the complete remission rate was 50.0 % (7/14 patients; 95 % CI, 26.8–73.2 %); partial remission rate, 14.3 % (2/14 patients; 95 % CI, 4.0–39.9 %); and remission rate, 64.3 % (9/14 patients; 95 % CI, 38.8–83.7 %). In patients with pemphigus vulgaris, foliaceus, and vegetans, at Week 52, the complete remission rates were 57.1 % (4/7 patients), 33.3 % (2/6 patients), and 100.0 % (1/1 patient), respectively (Table S1); and the respective remission rates were 57.1 % (4/7 patients), 66.7 % (4/6 patients), and 100.0 % (1/1 patient) (Table S2).

The mean ± SD PDAI score decreased from 9.9 ± 7.1 at baseline to 5.5 ± 7.3 at Week 8 (mean percent change: −58.9 %), and to 1.3 ±

![Graph A](image1.png)

**Fig. 3.** Changes over time in anti-desmoglein 1 and 3 antibody levels (A), and percent change from baseline in anti-desmoglein 1 and 3 antibody levels and IgG (B). Data are mean (standard deviation). Anti-desmoglein 1 antibody, n = 9, 8, 9, and 8 for baseline–Week 8, Week 12, Weeks 16–20, and Weeks 24–52, respectively. Anti-desmoglein 1-negative patients were excluded.

Anti-desmoglein 3 antibody, n = 9 and 8 for baseline–Week 12 and Weeks 16–52, respectively. Anti-desmoglein 3-negative patients were excluded.

IgG, n = 16, 15, and 14 for baseline, Week 12, Week 24, and Weeks 36–52, respectively.

IgG: immunoglobulin G.
3.5 at Week 52 (mean percent change: −90.2 %) (Fig. 2B). The changes in prednisolone doses showed a similar trend. The mean prednisolone dose decreased from 17.03 mg/day at baseline to 7.65 mg/day after 52 weeks of treatment. Fig. 3A shows the actual changes over time in anti-Dsg1 and Dsg3 antibody levels. The mean percent change from baseline in anti-Dsg1 and Dsg3 antibody titers was −55.75 % and −39.39 % at Week 8, and −89.34 % and −60.41 % at Week 52, respectively (Fig. 3B). Anti-Dsg1 and Dsg3 antibody titers decreased from baseline while IgG levels were maintained.

3.3. Safety

The incidence of AEs was 87.5 % (14/16 patients), and that of ADRs was 43.8 % (7/16 patients) (Table 2). AEs found in two or more patients were nasopharyngitis (5 patients), influenza (3 patients), pemphigus (3 patients), hypertension (3 patients), folliculitis (2 patients), oral candidiasis (2 patients), and hepatic enzyme increased (2 patients). The only ADR seen in two or more patients was nasopharyngitis (3 patients), and all ADRs were Grade 1 or 2. No deaths were reported.

The incidence of serious AEs was 18.8 % (3/16 patients), and these included pemphigus in two patients; and pharyngitis, cerebral infarction, and gastric cancer in one patient each. The incidence of Grade 3 AEs was 25.0 % (4/16 patients), and these included pemphigus in two patients; pharyngitis, hypertension, cerebral infarction, steroid diabetes, gastric cancer, and blood alkaline phosphatase increased in one patient each. No Grade ≥4 AEs were reported.

In all instances of serious AEs and Grade 3 AEs, a relationship with tirabrutinib was ruled out. The incidence of AEs leading to discontinuation was 12.5 % (2/16 patients), which included pemphigus (1 patient) and gastric cancer (1 patient), none of which were considered related to tirabrutinib.

Regarding immunological examinations, Fig. 4 shows the actual changes over time in the levels of IgG, IgM, CD19+ B-cell count, and CD3+ T-cell count. The mean percent change from baseline in IgG, IgM, peripheral CD19+ B-cell count, and CD3+ T-cell count at Week 52 of treatment was −4.22 %, −26.4 %, −10.5 %, and 69.6 %, respectively.

**Table 2** Summary of AEs and ADRs (safety analysis set).

<table>
<thead>
<tr>
<th>AEs</th>
<th>ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>14 (87.5)</td>
</tr>
<tr>
<td>Any Grade 3 AE</td>
<td>4 (25.0)</td>
</tr>
<tr>
<td>Any Grade ≥4 AE</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>Any ADR</td>
<td>7 (43.8)</td>
</tr>
<tr>
<td>Any Grade ≥3 ADR</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Serious ADR</td>
<td>0 (0)</td>
</tr>
<tr>
<td>ADR leading to discontinuation</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

### Events occurring in ≥2 patients

<table>
<thead>
<tr>
<th>Category</th>
<th>AEs</th>
<th>ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5 (31.3)</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>Influenza</td>
<td>3 (18.8)</td>
<td>0</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>2 (12.5)</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>2 (12.5)</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pemphigus</td>
<td>3 (18.8)</td>
<td>0</td>
</tr>
<tr>
<td>Angiopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (18.8)</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>Laboratory test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic enzyme increased</td>
<td>2 (12.5)</td>
<td>0</td>
</tr>
</tbody>
</table>

ADR: adverse drug reaction, AE: adverse event.

**Fig. 4.** Changes over time in the levels of IgG (A), IgM (B), CD19+ B-cell count (C), and CD3+ T-cell count. The mean percent change from baseline in IgG, IgM, peripheral CD19+ B-cell count, and CD3+ T-cell count at Week 52 of treatment was −4.22 %, −26.4 %, −10.5 %, and 69.6 %, respectively.

Data are mean (standard deviation).

n = 16, 15, and 14 for baseline, Week 12, and Weeks 36–52, respectively.

Ig: immunoglobulin.
Discussion

Tirabrutinib is the first BTK inhibitor to be evaluated in a clinical study in patients with refractory pemphigus. There are refractory cases in which it is difficult to achieve remission despite the full use of conventional treatments. This study was conducted in patients with refractory pemphigus in whom the prednisolone dose could not be reduced to ≤10 mg/day.

In the present study, complete remission and remission rates increased over time, reaching 50.0 % and 62.5 %, respectively, at 52 weeks of treatment, and other secondary endpoints (PDAI score, anti-Dsg1 and Dsg3 antibody levels, oral corticosteroid exposure) also showed improvement after tirabrutinib administration. These findings indicate that the tirabrutinib action persisted during the 52 weeks of exposure.

The complete remission rate in the present study is comparable to that of a multicenter open-label study of rituximab (50 %) in patients with refractory pemphigus and pemphigoid [23]. However, unlike rituximab, which depletes B-cells, tirabrutinib maintained peripheral B-cell counts. These results suggest that tirabrutinib suppresses B-cell development and activation through its inhibition of BTK in the BCR cascade without B-cell depletion.

Based on these results, tirabrutinib can be expected to achieve remission in patients with refractory pemphigus. The incidences of AEs (87.5 %) and Grade ≥3 AEs in the present study (25.0 %) were not notably higher than those in a retrospective study in which patients received treatment based on the Japanese guidelines for the management of pemphigus (79.7 % and 45.2 %, respectively) [25]. Moreover, no Grade ≥3 ADRs of hepatic/renal impairment and bone marrow depression (known ADRs associated with immunosuppressants [6]), nor Grade ≥4 ADRs of infections (known ADRs associated with rituximab [8]), were reported in the present study.

Anti-Dsg1 and Dsg3 antibody titers appeared to decrease from baseline without a marked reduction in IgG. These results suggest that tirabrutinib may reduce pathogenic autoantibody titers while maintaining total IgG levels. CD19+ B-cell counts increased transiently at Weeks 12 and 24. This may be due to the release of B-cell into the circulation resulting from B-cell homing suppression by BTK inhibition [26]. The increase in CD3+ T-cell counts by almost 70 % at Week 52 may be attributed to reduced cell-mediated immune suppression by tapering of the corticosteroid dose [27].

In addition, tirabrutinib is expected to mitigate corticosteroid-induced ADRs by lowering oral corticosteroid exposure. Furthermore, it is surmised that the pharmacological action of tirabrutinib dissipates quickly as its half-life has been reported to be 6.5–8 h [28]. Tirabrutinib also exhibits its pharmacological action while preserving B-cells, unlike rituximab that induces long-term B-cell depletion. Based on this, we expect that if an ADR such as infection occurs, the event could be managed promptly.

From the perspective of convenience, tirabrutinib is an oral agent that is taken once daily. Therefore, it would not negatively impact daily life in terms of treatment administration, which may alleviate the patient’s physical and mental strain. In the present study, there were no major safety-related concerns with tirabrutinib treatment.

The present study has some limitations, including those inherent to its open-label, uncontrolled, single-arm design. This study is also limited by its small sample size (n = 16) and short duration of exposure (1 year).

In conclusion, treatment with tirabrutinib enabled remission and reduced oral corticosteroid exposure over time and did not result in any major safety concerns with preservation of B-cells in patients with refractory pemphigus. Thus, oral tirabrutinib may be a new convenient and well-tolerated treatment option for patients with refractory pemphigus for whom it is difficult to achieve remission despite management with conventional treatments.

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Data sharing statement

Qualified researchers may request Ono Pharmaceutical Co., Ltd. to disclose individual patient-level data from clinical studies through the following website: https://ClinicalStudyDataRequest.com. For more information on Ono Pharmaceutical Co., Ltd.’s Policy for the Disclosure of Clinical Study Data, please see the following website: https://www.ono.co.jp/eng/rd/policy.html.

Declaration of Competing Interest

Jun Yamagami has received research funding, consultancy fees, lecture fees, and travel expenses from Ono Pharmaceutical Co., Ltd. for this study; and lecture and consultancy fees from Ono Pharmaceutical Co., Ltd., lecture fees from Japan Blood Products Organization and Nihon Pharmaceutical Co., Ltd., and a research grant from Japan Agency for Medical Research and Development (AMED Practical Research Project for Rare / Intractable Diseases) outside the submitted work. Hideyuki Ujiie has received research funding and travel expenses from Ono Pharmaceutical Co., Ltd. for this study; and research grants from Novartis Japan, Takeda Science Foundation, Bristol-Myers Squibb, Kobayashi Foundation, and Torii Pharmaceutical Co., Ltd.; research grants and personal fees (lecture fees) from Mitsubishi Tanabe Pharma and Maruho Co., Ltd.; and personal fees (lecture fees) from Ono Pharmaceutical Co., Ltd., Japan Blood Products Organization, Taiho Pharmaceutical Co., Ltd., Kyowa Kirin Co., Ltd., Kowa Pharmaceutical Co., Ltd., Sanofi S.A., Medical & Biological Laboratories Co., Ltd., Daiichi Sankyo Co., Ltd., and Nihon Pharmaceutical Co., Ltd. outside the submitted work. Yumi Aoyama has received research funding, consultancy fees, and travel expenses from Ono Pharmaceutical Co., Ltd. for this study; and research funding from Kanabo Cosmetics and Maruho Co., Ltd. outside the submitted work. Norito Ishii has received research funding, consultancy fees, and travel expenses from Ono Pharmaceutical Co., Ltd. for this study. Chihiro Tateishi has received research funding and travel expenses from Ono Pharmaceutical Co., Ltd. for this study; and grants and personal fees from Maruho Co., Ltd., Novartis Pharma K.K., Mitsubishi Tanabe Pharma Corporation, Eisai Co., Ltd., Celgene Corporation, Taiho Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Sanofi K.K., AbbVie K.K., Kyowa Kirin Co., Ltd., Jimro Co., Ltd., and Minophagen Pharmaceutical Co., Ltd., and Sun Pharma Japan Ltd.; grants from Pfizer Japan Inc., Boehringer Ingelheim International GmbH, UCB Japan Co., Ltd., Bristol-Myers Squibb Company, Pfizer R&D Japan K.G., Nippon Kayaku Co., Ltd., Tsumura Co., Ltd., Kotaro Pharmaceutical Co., Ltd., Torii Pharmaceutical Co., Ltd., Pola Pharma Co., Ltd., Taisho Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Smith & Nephew K.K., Nihon Pharmaceutical Co., Ltd., Ezaki Glico Co., Ltd., Nippon Zoki Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Co., Ltd., MSD K.K., EA Pharma Co., Ltd., Kyowa CritiCare Co., Ltd., Kaken Pharmaceutical Co., Ltd., Teijin Pharma Limited, Nippon Shokubai Co., Ltd., Nobelpharma Co., Ltd., SBI Pharmaceuticals Co., Ltd., Kao Corporation, Tokiwa Pharmaceutical Co., Ltd., Amgen K.K., and Parexel International Inc.; and personal fees from Janssen Pharmaceutical K.K., Medical & Biological Laboratories Co., Ltd., LEO Pharma K.K., and Chugai Pharmaceutical Co., Ltd. outside the submitted work. Akira Ishiko has received research funding and travel expenses from Ono Pharmaceutical Co., Ltd. for this study; and research funding from Sato Yakuhin Kogyo Co., Ltd., Sun Pharmaceutical Industries Ltd.,
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Shunsuke Hagihara: Formal analysis, Methodology, Writing – original draft, Writing – review and editing.

Koji Hashimoto: Conceptualization, Writing – original draft, Writing – review and editing.

Masayuki Amagai: Project administration, Supervision, Writing – original draft, Writing – review and editing.

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Appendix A. Supplementary data

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