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CASE STUDY

Real-world effectiveness and safety of dupilumab in patients with moderate and severe atopic dermatitis: 2-year experience

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Abstract

Objective: Dupilumab has been deemed highly effective for atopic dermatitis (AD). However, there have been no reports performing a combination analysis with hematological data and improvement rates pertaining to the continued use of dupilumab for up to 2 years in real world. In this study, we evaluated the effectiveness and safety of using dupilumab for up to 2 years in 9 patients with AD at our hospital.

Methods: Thirty-six patients with moderate-to-severe AD treated by dupilumab, and 9 of them treated for 2 years. Changes in the severity scoring, pruritus numerical rating scale (NRS), patient-oriented eczema measure (POEM), serum levels of immunoglobulin E (IgE), thymus and activation-regulated chemokine (TARC), eosinophils, and lactate dehydrogenase (LDH) at Week 0, 2, 4, 16, 48, 72, and 96 of those patients were investigated, and we studied features of the patients who had any adverse events (AEs).

Results: Investigator's global assessment (IGA), eczema area and severity index (EASI), body surface area (BSA), NRS, POEM, and serum levels of LDH were significantly decreased from Week 4 onwards to Week 96 compared with baseline condition. Serum levels of TARC and LDH were significantly decreased from Week 4 onwards to Week 96. Regarding 9 patients who were treated with dupilumab for up to 2 years, serum levels of TARC and eosinophils decreased without statistical significance. The serum levels of IgE significantly decreased at Week 72, 96 compared with the baseline. Regarding as AEs, ocular symptoms were the most frequently observed (15/36, 41.2%), and there were no cases of discontinuation due to AEs.

Conclusions: Treatment with dupilumab was well tolerated and showed improvements in AD for at least 2 years.

Chisako Fujiwara and Akihiko Uchiyama contributed equally to this work.

1 | INTRODUCTION

Atopic dermatitis (AD) is a chronic-relapsing inflammatory dermatosis characterized by intense pruritus that has detrimental effects on quality of life.[1] Dupilumab, a fully human monoclonal antibody directed against the interleukin (IL)-4 receptor that blocks type-2 cytokines, IL-4, and IL-13 signaling, was approved for moderate-to-severe AD in 2018 in Japan. The efficacy and safety of dupilumab have been indicated in various clinical trials.[2,3] Moreover, there has been increasing evidence of the efficacy of dupilumab in real-world clinical practice.[4,5] However, there are no reports demonstrating the combination of hematological data and improvement rates with continued use of dupilumab for up to 2 years in the real world. We herein analyzed clinical data in patients who used dupilumab for 2 years at our hospital.

2 | CASE STUDY

We analyzed 36 patients with AD treated with dupilumab between July 2018 and July 2021 at the Gunma University Hospital, Japan. All patients fulfilled the criteria for AD according to Hanifin and Rajka.[6] Cases that could not be evaluated 4 weeks after initiating dupilumab treatment due to referral to another hospital were excluded. In total, we evaluated 36 patients (100%) for 1 month, 26 patients (72.2%) for 4 months, 17 (47.2%) for 1 year, and 9 (25.0%) for 2 years without any interruptions in our hospital. The reduction in the number of patients that reached each week of treatment was due to the fact that patients started treatment at different times and they did not achieve at each week of treatment at the moment of the publication of this paper. Furthermore, two patients were referred to other hospitals for the continuation of dupilumab after 4 months and one patient after 1 year. No cases were discontinued due to ineffectiveness.

The clinical score system (eczema area and severity index [EASI], investigator's global assessment [IGA], body surface area [BSA]), patient-reported symptoms (patient-oriented eczema measure [POEM], pruritus numerical rating scale [NRS]), and several serum markers were assessed at the baseline visit and at weeks 2, 4, 16, 48, 72, and 96. Changes in the index scores from baseline were analyzed in patients who completed each week follow-up; we used a paired-samples *t*-test. Differences between the two phenotype groups were compared using one-way analysis of variance followed by Bonferroni's post hoc test. χ^2 analysis was used to compare frequencies. $p < .05$ was considered statistically significant. Statistical analysis was performed by GraphPad Prism (version 9).

Baseline demographics and clinical characteristics are summarized in Table 1. In total, 35 Japanese and 1 Spanish patients (22 males, 14 females; mean age ± standard deviation [SD], 36.1 ± 12.9 years) were included. Adult-onset AD was defined by the cutoff value of 18 years. The rate of patients with pruritic papules was 33.3%, and 17 (47.2%) patients were severe (IGA = 4). Cyclosporine A (CsA) and systemic corticosteroids were used in nine (25.0%) and three (8.3%) patients, respectively. Thirty-five patients used topical corticosteroids of strong class or higher, and five used tacrolimus ointment. Thirty-one patients (86.1%) had atopic diseases, including 7 (19.4%) with asthma, 12 (33.3%) with

TABLE 1 Demographics and baseline disease characteristics

Characteristic	Total patients (*n* = 36)
Age, years	
Mean (SD)	36.1 (12.9)
Range	17–69
Gender	
Male	22 (61.1%)
Female	14 (38.9%)
Onset time	
Early	34 (94.4%)
Adult	2 (5.6%)
Clinical phenotype	
Prurigo	12 (33.3%)
Others	24 (66.7%)
IGA	
4	17 (47.2%)
3	19 (52.8%)
EASI	
Mean (SD)	27.0 (11.9)
Range	2.4–58.3
EASI, head-and-neck	
Mean (SD)	1.6 (1.3)
Range	0–3.5
BSA, %	
Mean (SD)	45.2 (25.1)
Range	10–85
NRS	
Mean (SD)	7.1 (2.3)
Range	2–10
POEM	
Mean (SD)	19.9 (6.3)
Range	8–28
Any previous treatment	
H1-antihistamines	29 (80.1%)
Cyclosporin A	9 (25.0%)
Systemic corticosteroids	3 (8.3%)
Any other atopic condition	31 (86.1%)
Asthma	7 (19.4%)
Food allergy	12 (33.3%)
Allergic rhinitis	19 (52.8%)
Allergic conjunctivitis	4 (11.1%)

Abbreviations: BSA, body surface area; EASI, eczema area and severity index; IGA, Investigator's global assessment; NRS, pruritus numerical rating scale; POEM, patient-oriented eczema measure; SD, standard deviation.

food allergy, 19 (52.8%) with allergic rhinitis, and 4 (11.1%) with allergic conjunctivitis.

IGA/EASI and POEM/NRS decreased significantly compared with the baseline condition at week 4, and they continued to decrease gradually until week 48 (Figure 1A,B). Serum levels of thymus and activation-regulated chemokine (TARC) and lactate dehydrogenase (LDH) were significantly decreased from week 4 onwards to week 48. Serum levels of immunoglobulin E (IgE) and eosinophils were significantly decreased at week 48 (Figure 1C). The EASI-75 response was 58.3% (21/36), 76.9% (20/26), and 100% (17/17) at 4, 16, and 48 weeks, respectively. Pertaining to the EASI response for the head-neck area, the EASI-75 response was 46%

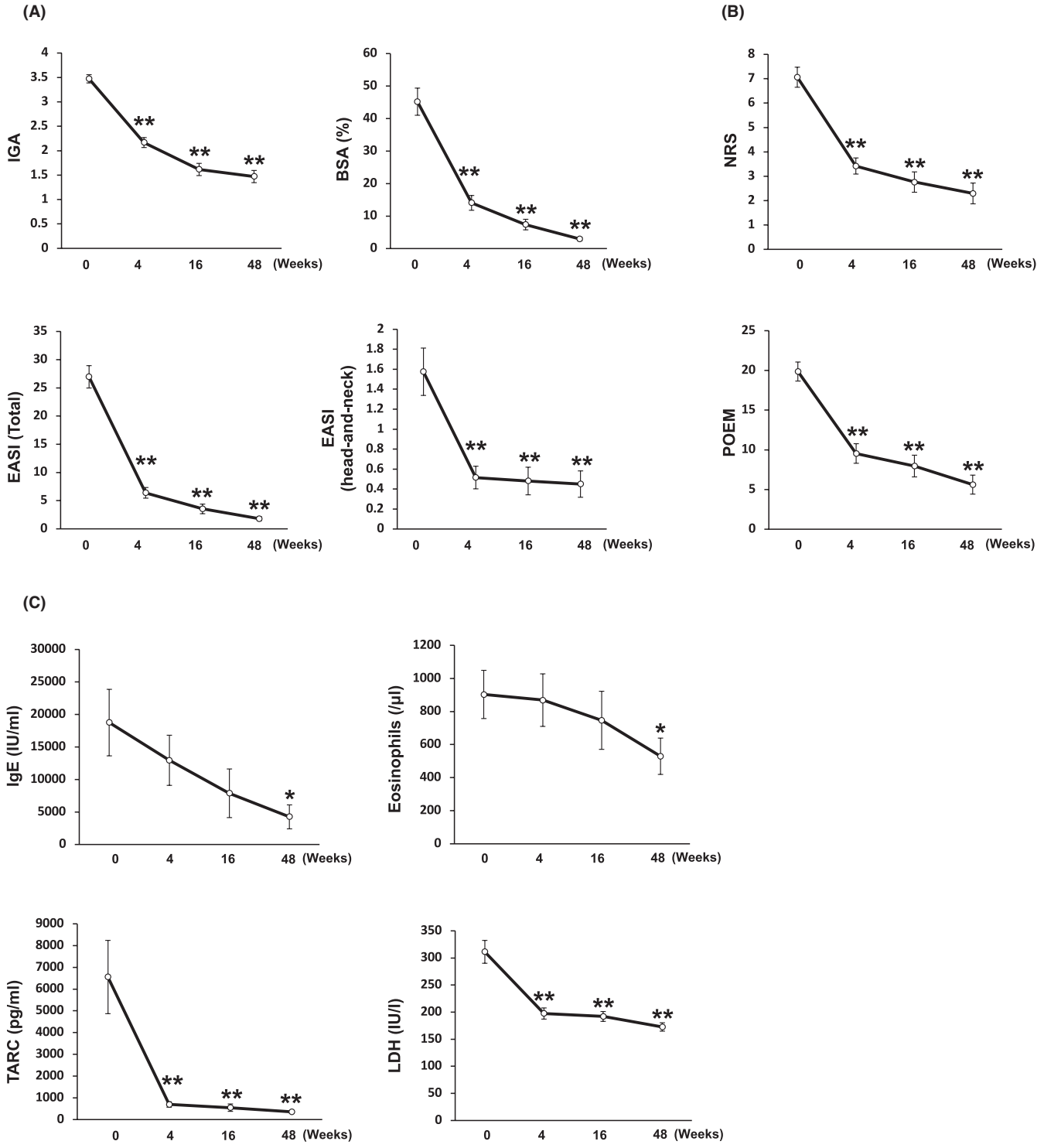

FIGURE 1 Mean clinical data up to 48 weeks. The effect of dupilumab on skin severity (IGA, BSA, EASI total, and EASI head-and-neck) (A), NRS, POEM (B), and laboratory data (IgE, eosinophils, TARC, and LDH) (C) from baseline to 1 year after initiating dupilumab treatment. Values represent mean ± SEM. *$p < .05$; **$p < .01$

(13/28), 65% (15/23), and 54% (7/13) at 4, 16, and 48 weeks. All patients, who used CsA or systemic corticosteroids, were able to discontinue these therapies.

Next, nine patients were investigated regarding changes in skin severity using uninterrupted laboratory data from the baseline up to 2 years. After 48 weeks, there was no deterioration in IGA/EASI/BSA and POEM/NRS (Figure 2A,B). The response rate was 100% (9/9) for EASI-75 and 88.9% (8/9) for EASI-90 at 96 weeks. Regarding the EASI response for the head-neck area, EASI-75 and EASI-90 responses were 85.7% (6/7) and 57.1% (4/7) at 96 weeks. Serum levels of LDH decreased significantly at week 4, and they continued to decrease gradually until week 96. Serum levels of TARC and eosinophils

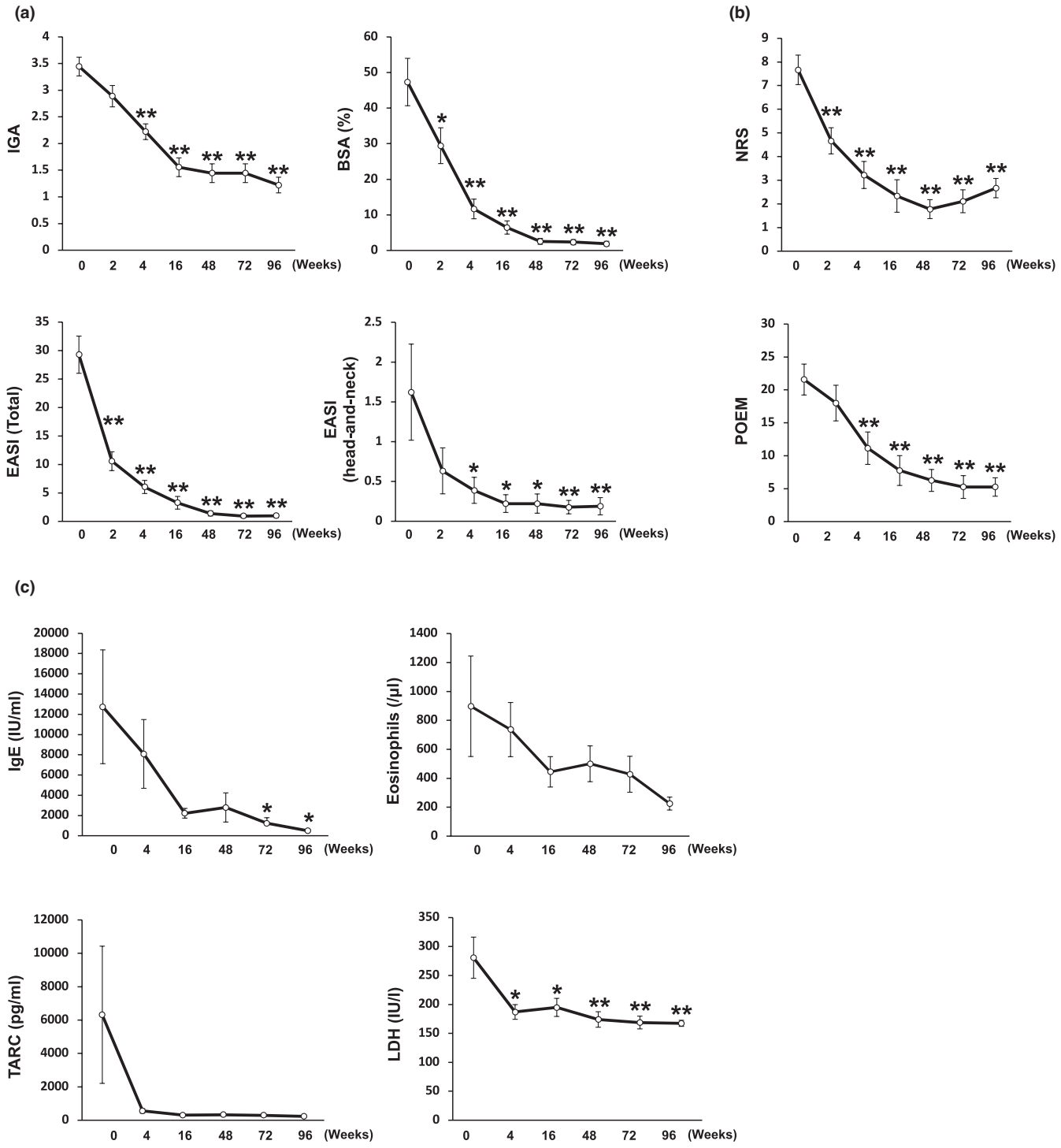

FIGURE 2 Mean clinical data up to 96 weeks. The effect of dupilumab on skin severity (IGA, BSA, EASI total, and EASI head-and-neck) (A), NRS, POEM (B), and laboratory data (IgE, eosinophils, TARC, and LDH) (C) from baseline to 2 years after initiating dupilumab treatment ($n = 9$). Values represent mean ± SEM. *$p < .05$; **$p < .01$

decreased without statistical significance. The serum levels of IgE significantly decreased at weeks 72 and 96 compared with the baseline (Figure 2C). Twelve (33.3%) patients had prurigo, and there was no significant difference in both the demographics and clinical features of patients with AD achieving EASI-50/75/90 and EASI responses between the prurigo type and other types (Table S1A,B, and Figure S1). Baseline demographics and clinical features of patients with early and adult onset were summarized in Table S2.

Regarding adverse events (AEs), ocular symptoms ($n = 15$, 41.2%) were the most frequent AEs noted followed by herpes zoster ($n = 1$, 2.8%), hyperhidrosis ($n = 1$, 2.8%), joint pain ($n = 1$, 2.8%), and weight gain ($n = 1$, 2.8%). All ocular symptoms appeared within the second month after initiating dupilumab treatment. The severity of AEs, including ocular symptoms, was mild, and there were no cases of discontinuation due to AEs.

3 | DISCUSSION

A recently published open-label study showed that dupilumab could provide favorable safety and sustained efficacy for up to 3 years.[7] This retrospective observational study demonstrated the efficacy and safety of dupilumab in patients with moderate-to-severe AD in real-world clinical practice for up to 2 years. Our data showed that disease severity, patient-reported symptoms, and laboratory data, especially TARC and LDH, were significantly decreased within just after initiating dupilumab treatment.

Serum TARC and LDH levels are known as useful biomarkers of AD severity,[8,9] and serum total IgE level has been considered to be an indicator of allergic predisposition.[10] Uchida et al.[11] reported a significant decrease in serum total IgE levels at 3 months after initiating dupilumab treatment. Our study revealed a decreasing trend of IgE, without significant differences at 16 weeks, but with significant differences after 48 weeks. These results may indicate that LDH and TARC are sensitive indicators of the efficacy of AD treatment, and IgE is an indicator of long-term control.

In clinical trials, improvement of AD with dupilumab occurs equally across different anatomical regions at 4 and 16 weeks.[12] In contrast, several studies reported that the EASI improvement rate was lower in the head and neck areas than other bodily areas.[11,13] In our study, we did not compare the rate of improvement between the neck and head area with other parts of the body. However, we identified significant improvements in patients who continued their treatment for 1 year (after 4 weeks) and in patients who continued their treatment for 2 years (after 4 weeks), and the effects were sustained. These results might suggest that dupilumab therapy was also effective for the head and neck areas. It has been reported that improvement is slower in prurigo and nummular eczema types than in the other types.[8] However, in our study, the improvement of AD with dupilumab was equally effective in both prurigo and other types.

Similar to previous studies, ocular symptoms were the most common AE, and which tended to occur after 1–4 doses.[11,14] A previous clinical trial revealed that patients with high severity of AD at baseline were associated with the development of more symptoms of conjunctivitis during treatment.[14] In our study, there was a tendency for more ocular symptoms to appear in patients with high EASI. Using an EASI score of 35 as a cutoff value, six out of 8 (75.0%) patients with higher EASI score than cutoff value and nine out of 28 (32.1%) patients who had lower developed ocular symptoms ($p = .030$).

There are several limitations in this study. This is a nonblinded, noncontrolled, nonrandomized retrospective observational study with small number of subjects. These high levels of improvement might be caused by the difference in topical treatment, including the strength of topical corticosteroids and combination of moisturizers.

In conclusion, we demonstrated the safety and efficacy of continuous treatment with dupilumab for a period of 2 years using a combination of physical examinations and laboratory findings with real-world data. Further studies are needed to evaluate the safety and efficacy of dupilumab for long-term use.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DECLARATION SECTION

Approval of the research protocol: This retrospective cohort study was approved by the institutional review board of the Gunma University (no. 1545) and conducted according to the principles of the Declaration of Helsinki.

Informed Consent: Yes.

Registry and the Registration No. of the study: N/A.

Animal Studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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