Brief Report

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Three-year real-world outcomes of lanadelumab prophylaxis in hereditary angioedema: Complete disease suppression and psychosocial benefits in two East Asian patients

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SUMMARY: Hereditary angioedema (HAE) is a rare, potentially life-threatening disorder characterized by recurrent, disabling episodes of subcutaneous or submucosal swelling. Lanadelumab, a monoclonal antibody targeting plasma kallikrein, is approved for long-term prophylaxis and has shown high efficacy in clinical trials. However, real-world data on its prolonged use, particularly from East Asia, remain scarce. This report evaluates 3-year clinical and patient-reported outcomes of lanadelumab prophylaxis in two Japanese patients with HAE type I. Both male patients (in their 30s and 70s) received subcutaneous lanadelumab, 300 mg, every 2 weeks, later extended to every 4 weeks following disease stabilization. Clinical efficacy was assessed by attack frequency. Patient-reported outcomes (PROs) included the Angioedema Control Test (AECT), Angioedema Quality of Life Questionnaire (AE-QoL), Hospital Anxiety and Depression Scale (HADS), and Treatment Satisfaction Questionnaire for Medication (TSQM-9). Safety and tolerability were also monitored. Both patients achieved complete or near-complete elimination of HAE attacks during the 156-week follow-up. AECT scores reached the maximum of 16 by week 12 and remained stable. AE-QoL scores improved by approximately 30 points, reflecting sustained quality-of-life benefits. HADS-Anxiety scores declined into the normal range, indicating reduced anticipatory anxiety. TSQM-9 global satisfaction remained above 90 out of 100, and no serious adverse events occurred; one patient experienced mild transient injection-site swelling. This case series presents the longest real-world follow-up of lanadelumab in East Asia. Findings confirm its sustained efficacy, safety, and psychosocial benefits, including enhanced quality of life and emotional recovery. These findings suggest that lanadelumab may play an important role in the long-term management of HAE in Asian clinical settings.

Keywords: hereditary angioedema, lanadelumab, patient-reported outcomes, quality of life, anxiety, kallikrein inhibitor, East Asian population

1. Introduction

Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by recurrent episodes of subcutaneous or submucosal swelling, most commonly caused by C1-inhibitor (C1-INH) deficiency (HAE type I) or dysfunction (type II), resulting in excessive bradykinin generation (*1*). Attacks typically affect the face, extremities, gastrointestinal tract, or airway, with laryngeal edema being potentially life-threatening. In addition to the physical burden, HAE imposes a substantial psychosocial impact—patients often live in chronic fear of unpredictable attacks, leading to anxiety, impaired quality of life, and reduced social functioning (*2,3*).

Lanadelumab, a fully human monoclonal antibody that inhibits plasma kallikrein, was approved in 2018 for the long-term prophylaxis of HAE. The pivotal HELP study demonstrated that lanadelumab reduced attack rates by approximately 87% compared to placebo, with sustained benefits confirmed in open-label extension studies (*4,5*). The standard dosing regimen is 300 mg subcutaneously every 2 weeks, with extension to every 4 weeks possible in patients with stable disease control (*6*).

Although the efficacy of lanadelumab has been well documented in Western populations (*7-12*), clinical trials and real-world data from East Asia remain limited (*13,14*). In Japan, lanadelumab became commercially available only in 2022, and most existing reports describe follow-up durations of one year or less (*15,16*). As prophylactic options expand globally, optimal strategies — including treatment duration, monitoring approaches, and tapering decisions — remain insufficiently defined.

Beyond preventing attacks, long-term prophylaxis plays a crucial role in alleviating the psychological burden of HAE, including anticipatory anxiety and fear

of asphyxiation. In this regard, patient-reported outcomes (PROs) such as the Angioedema Control Test (AECT) (*17*), Angioedema Quality of Life Questionnaire (AE-QoL) (*18*), treatment satisfaction measures (*19,20*), and the Hospital Anxiety and Depression Scale (HADS) (*21,22*) offer valuable insights into the broader benefits of sustained therapy (*23*).

Here, we present two Japanese patients with HAE who received continuous lanadelumab prophylaxis for 156 weeks (~3 years) — to our knowledge, the longest real-world follow-up reported in East Asia. Along with clinical outcomes, we evaluated multiple PROs to assess long-term disease control, quality of life, and emotional well-being. This case series aims to inform clinical practice by illustrating how prolonged lanadelumab therapy can achieve not only physical remission but also meaningful psychosocial recovery in the management of HAE.

2. Patients and Methods

2.1. Patients and setting

This observational case series included two adult male patients with HAE type I, diagnosed based on low antigenic and functional levels of C1-INH. Both patients were managed in our dermatology department and had longstanding histories of frequent angioedema attacks prior to initiating prophylactic therapy. Patient 1, a man in his 30s, was diagnosed with HAE at age 20. Initially, he experienced infrequent attacks (approximately one facial or abdominal episode per year), but in the five years preceding prophylaxis, his attack frequency increased to monthly peripheral swellings and abdominal attacks requiring on-demand treatment, significantly impairing his daily life. Patient 2, in his 70s, had experienced HAE symptoms since adolescence and was diagnosed at age 30. He suffered multiple severe episodes, including facial and tongue edema, and was hospitalized at least six times for trauma-induced angioedema (*e.g.*, following dental procedures or spinal anesthesia). In the year before starting prophylaxis, he experienced approximately two attacks per month and lived with persistent fear of laryngeal involvement.

2.2. Lanadelumab prophylaxis

Both patients began lanadelumab prophylaxis between 2019 and 2020 through a compassionate use program prior to local commercial availability. The initial regimen consisted of lanadelumab 300 mg administered subcutaneously every two weeks. Patients received injection training, with initial doses administered under medical supervision. After achieving sustained attack-free status for 6–12 months, dosing was extended to every four weeks in both patients, in accordance with product labeling and through shared decision-making. Lanadelumab prophylaxis continued uninterrupted throughout the observation period (156 weeks for Patient 1; 152 weeks for Patient 2). On-demand C1-INH was used only in the event of breakthrough attacks.

2.3. Outcome assessments

Patients were followed regularly — every 4–8 weeks in the first year, and every 3–6 months thereafter. At each visit, the number and frequency of attacks since the previous visit were recorded based on patient interviews and medical records. The following validated PRO instruments were administered at baseline and periodically during treatment:

i) Angioedema Control Test (AECT): A 4-item tool assessing disease control over the prior 4 weeks (score range: 0–16; ≥ 12 indicates good control). AECT was evaluated at baseline, at 12 weeks, and annually thereafter.

ii) Angioedema Quality of Life Questionnaire (AE-QoL): A 17-item HAE-specific QoL measure covering four domains, with a total score range of 0 to 100 (higher scores indicate worse QoL). AE-QoL was administered at baseline and approximately at months 3, 6, 12, 24, and 36.

iii) Hospital Anxiety and Depression Scale (HADS): A 14-item questionnaire measuring anxiety (HADS-A) and depression (HADS-D), each scored from 0–21. Scores ≥ 11 suggest clinically significant distress. HADS was assessed at baseline and at multiple time points to track anxiety related to fear of attacks.

iv) Treatment Satisfaction Questionnaire for Medication (TSQM-9): A 9-item tool assessing effectiveness, convenience, and global satisfaction (scores range: 0–100). TSQM-9 was administered at follow-up visits starting from month 3 onward.

2.4. Ethics statement:

This case report was conducted at Saitama Medical Center, Japan, in accordance with the ethical principles of the Declaration of Helsinki (1975). Written informed consent was obtained from all patients for the publication of this report, including relevant clinical details and anonymized data. According to the institutional policy, case reports involving one or two patients that do not contain identifiable information are exempt from formal review by the institutional review board (IRB). Therefore, IRB approval was not required for this publication.

3. Results and Discussion

This case series provides the longest real-world follow-up to date of lanadelumab prophylaxis in East Asian patients with HAE, suggesting sustained clinical remission, improved psychosocial well-being, and favorable

safety over a 3-year period. Both patients demonstrated a rapid and lasting resolution of angioedema attacks following the initiation of lanadelumab. Patient 1 became completely attack-free after the first month of therapy, while Patient 2 experienced only one mild episode of localized swelling at the injection site — likely attributable to a transient injection-triggered response — which resolved spontaneously without recurrence. Neither patient required acute treatment or hospitalization throughout the 3-year follow-up, indicating robust long-term disease control (Figure 1A). We also conducted a PubMed-based search (terms: "lanadelumab" AND "hereditary angioedema" AND "real-world" AND "Asia"), which yielded no other reports with follow-up durations of ≥ 3 years in East Asian populations. While not exhaustive, this search supports the novelty of our observations.

Prior to treatment, Patient 1 reported an estimated 15–20 attacks annually, while Patient 2 experienced around 24 episodes. Under lanadelumab prophylaxis, Patient 1 remained entirely attack-free, and Patient 2 experienced only one mild episode in the first year, followed by complete remission — corresponding to a 100% and > 95% reduction in attack frequency, respectively. These outcomes exceed those reported in pivotal trials such as the HELP study and its extension, where lanadelumab reduced attack rates by ~87% and maintained remission for up to 33 months in some patients (*4,5*). Moreover, our findings are consistent with recent real-world data from Germany and China (*12,14*), which may further support lanadelumab's durable efficacy.

Regarding patient-reported outcomes, both individuals achieved maximum AECT scores (16/16) by Week 12, sustained through Week 156, indicating complete disease control (Figure 1B). AE-QoL scores improved markedly, with Patient 1's total score decreasing from 42 to 10 and Patient 2's from 62 to 30 (Figure 2). The largest improvements were observed in the "Fear/Shame" and "Fatigue/Mood" domains. This pattern may suggest that lanadelumab not only reduces physical symptoms but also alleviates psychosocial distress associated with unpredictability and perceived stigma. In East Asian contexts, such burdens may be differentially perceived, as suggested by prior studies (*14,16*). Notably, while our patients showed maximal improvement in "Fear/Shame", Japanese real-world data have reported "Functioning" as the most responsive domain (*16*), suggesting potential cultural variation.

Psychological recovery was further supported by reductions in HADS scores. At baseline, Patient 2 presented with moderate anxiety (HADS-A: 14), and Patient 1 with borderline abnormal anxiety (HADS-A: 8). By Week 156, both scores had fallen into the normal range (2 and 4, respectively), with no clinically significant depressive symptoms observed throughout the study period (Figure 3). These findings suggest that long-term prophylaxis with lanadelumab may contribute to improved emotional well-being, complementing the physical control of disease.

Treatment was well tolerated. No serious adverse events, hypersensitivity reactions, or abnormal laboratory findings were reported. The sole adverse event was a mild injection-site reaction in Patient 2. Notably, both patients successfully extended dosing intervals from biweekly to monthly regimens after 6–12 months of disease stability, without any resurgence of attacks. This approach aligns with product labeling and current clinical practice in Europe and China (*6,14*) and may enhance convenience and adherence, especially in older patients or those with limited healthcare access.

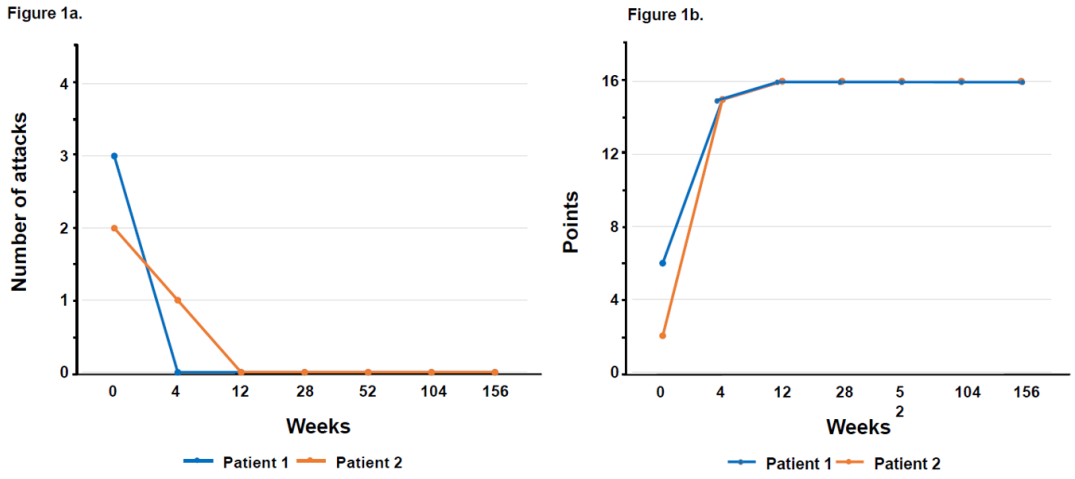

Figure 1. (A) Attack frequency at baseline reflects approximate yearly rates prior to treatment. Patient 1 (blue) and Patient 2 (orange) both experienced near-complete elimination of attacks over 156 weeks of lanadelumab use. Patient 2 had one mild attack in Year 1 (localized angioedema at the injection site) and remained attack-free thereafter. This illustrates the sustained, long-term efficacy of lanadelumab in preventing HAE attacks. **(B)** Angioedema Control Test (AECT) scores from baseline to Week 156. Both patients achieved the maximum score of 16 by Week 12, indicating optimal disease control, which was maintained throughout follow-up.

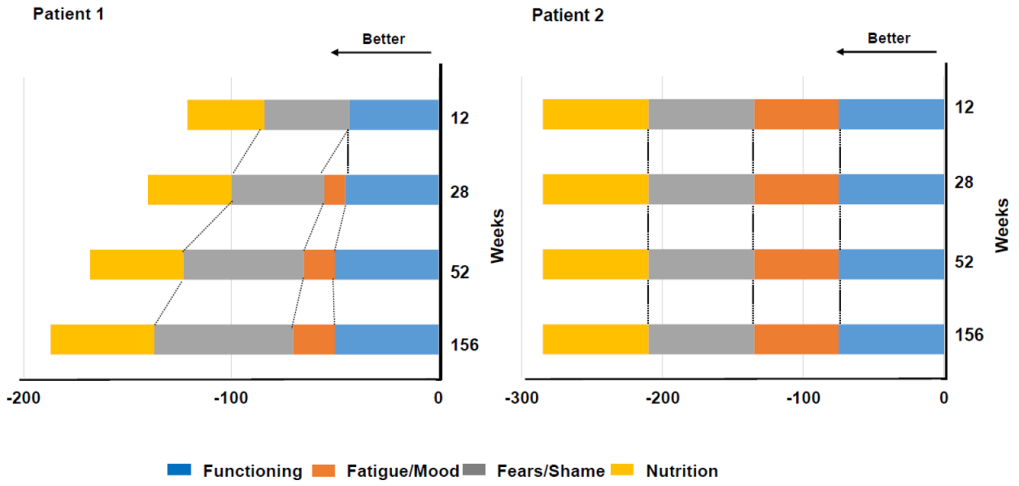

Figure 2. Angioedema Quality of Life Questionnaire (AE-QoL) total scores over time (lower scores reflect better quality of life). Both patients showed approximately 30-point reductions from baseline to Week 156, indicating significant and sustained improvement.

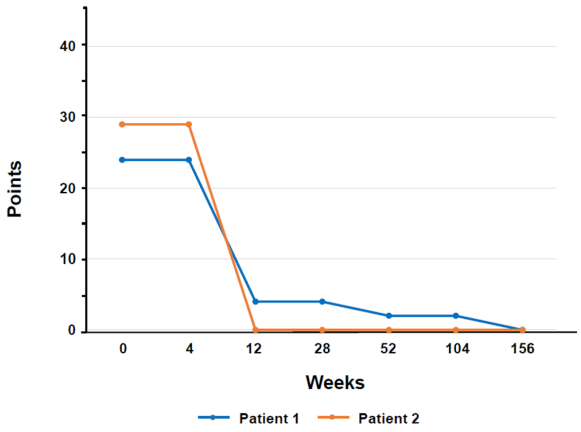

Figure 3. Hospital Anxiety and Depression Scale (HADS) subscale scores. Anxiety levels steadily declined during treatment; by Week 156, both patients' scores had normalized (≤ 7, indicated by shaded gray line), reflecting substantial relief from HAE-related anxiety. HADS scores are interpreted as follows: 0–7 = normal; 8–10 = borderline; 11–21 = clinically significant anxiety or depression.

Both patients expressed high satisfaction with therapy, with TSQM-9 Global Satisfaction scores exceeding 85 by Month 3 and remaining above 90 thereafter (Figure 4). Neither required dose adjustment nor discontinued therapy. These long-term outcomes indicate not only clinical efficacy but also patient acceptability and sustained adherence.

While limited by the small sample size and male-only cohort, this case series offers valuable insight into individualized trajectories of recovery and suggests a potential role for lanadelumab in East Asian clinical settings. The consistent responses observed across patients of different ages and clinical backgrounds suggest broad applicability of prophylactic treatment. However, further studies are warranted to examine long-term outcomes in female patients, where hormonal factors may influence disease dynamics.

In conclusion, this 3-year real-world experience demonstrates that lanadelumab prophylaxis offers more than just attack suppression — it may facilitate emotional recovery, restore daily functioning, and significantly improve quality of life. A comprehensive, patient-centered strategy incorporating preventive therapy, emergency preparedness, and psychological support is essential to fully leverage the long-term benefits of lanadelumab in managing HAE.

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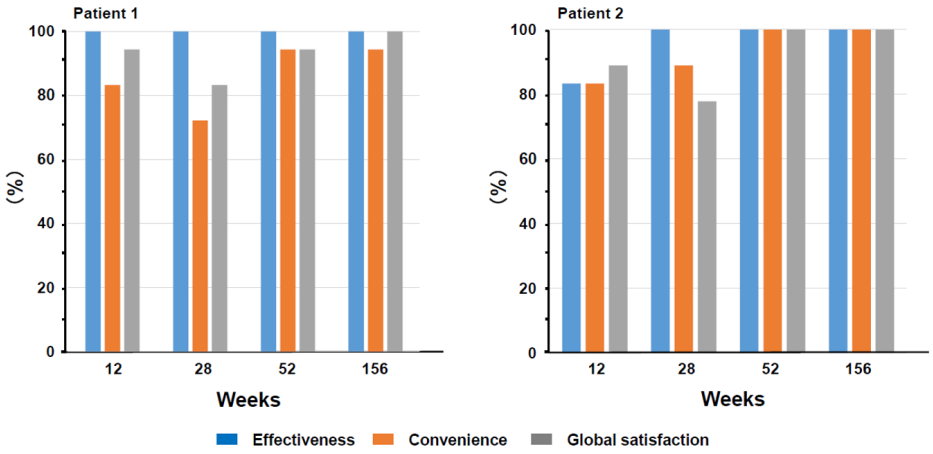

Figure 4. Treatment Satisfaction Questionnaire for Medication (TSQM-9) scores at Weeks 12, 28, 52, and 156 across three domains (effectiveness, convenience, and global satisfaction). Higher scores indicate greater treatment satisfaction. Both patients reported consistently high satisfaction throughout treatment. Note: Error bars are not shown, as data reflect individual case trajectories.

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