Long-term prophylaxis for hereditary angioedema: Initial experiences with garadacimab and lanadelumab

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Background: With no approved long-term prophylaxis (LTP) for the prevention of hereditary angioedema (HAE) attacks in Hong Kong, patients rely on compassionate use programs and drug trials. Moreover, studies regarding the use and efficacy of LTP in Asia are lacking.

Objectives: Our aim was to assess 2 LTP medications for HAE in Hong Kong: lanadelumab and garadacimab.

Methods: A prospective study was performed. Adult patients with a diagnosis of type I or type II HAE with 1 or more expert-confirmed attacks per month were consecutively recruited. The patients had been receiving treatment for at least 6 months. Clinical data were obtained, and questionnaires were administered before treatment periodically for at least 6 months following initiation of LTP.

Results: Almost one-third of the patients with HAE experienced frequent attacks and began receiving LTP (8 of the 11 received garadacimab and 3 of the 11 received lanadelumab). At baseline, the time-normalized number of HAE attacks was 2.5 plus or minus 1.3 per month. At month 6, there was an overall reduction of time-normalized number of attacks per month of –2.4 attacks per month (95% CI = –3.3 to –1.5. [$P < .01$]). The time-normalized number of HAE attacks at month 6 was 0.1 plus or minus 0.1 per month. More than 70% of the patients (8 of 11) were completely attack-free during the 6-month period while receiving LTP, and no patients required hospitalization. LTP improved patients' scores of the Angioedema Quality-of-Life Questionnaire ($P < .001$) and reduced activity impairment due to health ($P = .008$). Patients experienced significant improvement across all dimensions of the Treatment Satisfaction for Medication Questionnaire (54.5%-76.8% [$P = .002$]), and no adverse events were reported.

Conclusion: The patients receiving LTP with garadacimab and lanadelumab experienced a significant reduction in number of HAE attacks and improvement in quality of life, and they were satisfied with treatment. (J Allergy Clin Immunol Global 2023;2:100166.)

Key words: *Asia, Chinese, lanadelumab, garadacimab, hereditary angioedema, Hong Kong, prophylaxis, quality of life*

INTRODUCTION

Hereditary angioedema (HAE) is a rare but potentially fatal condition characterized by recurrent bradykinin-mediated angioedema.[1] The symptoms are variable and unpredictable, and currently, there are no reliable biomarkers. International guidelines have outlined the need for on-demand HAE-specific medications for all patients. For selected patients, long-term prophylaxis (LTP) is recommended to reduce the frequency and burden of angioedema attacks.[2] Various LTP therapies have been shown to improve HAE outcomes, reduce attack frequency and severity, reduce hospitalizations, and alleviate psychological burden.[3] Many emerging countries still lack access to LTP despite having a substantial proportion of patients who experience severe and frequent attacks, and Asian HAE research remains limited.[4]

The prevalence of HAE in Hong Kong increased almost 4-fold in the past 4 years (an incidence of ~1 in 166,000) owing to improved recognition, diagnostics, and a comprehensive family screening program.[5] As a result, more patients have been identified and indicated for treatment. After years of lobbying, on-demand HAE treatment finally became available in 2023. However, there is still an unmet need for LTP among patients experiencing more frequent attacks. Moreover, studies regarding the use of LTP of HAE among Asian populations are lacking. Currently in Hong Kong, patients have access to LTP only via compassionate use programs sponsored by drug companies or by participating in clinical trials.

We conducted this prospective study to assess the efficacy and safety of 2 HAE-specific LTP medications (garadacimab and lanadelumab) in Hong Kong. Lanadelumab is an mAb that inhibits kallikrein, an important protease in the kallikrein-kininogen cascade responsible for ultimate formation of bradykinin, a mediator resulting in vasodilation and angioedema. Garadacimab is a newer mAb targeting activated factor XII, an initiator of the kallikrein-kininogen cascade, thereby decreasing bradykinin production. At the time of writing of this report, patients had been recruited into a phase III garadacimab trial (ClinicalTrials.gov identifier NCT04739059) or had been granted access to lanadelumab through a compassionate-use program (for adults only). Between July 2021 and July 2022, patients with HAE who experienced frequent attacks (defined as ≥3 attacks within 3 months) began receiving either garadacimab or lanadelumab and were prospectively followed for 6 months. Patients with non–HAE-specific prophylactic agents (eg, androgens or antifibrinolytics) were excluded. Clinical data, including age at diagnosis, type of HAE, laboratory parameters, age at first HAE attack, site of

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TABLE I. Baseline characteristics of all patients with frequent HAE attacks (n = 11)

Characteristic	All patients (n = 11)	Patients taking garadacimab (n = 8)	Patients taking lanadelumab (n = 3)
Age (y), mean (SD)	42.5 (13.4)	39.0 (9.0)	40.9 (8.7)
18 to <65	9 (81.8)	8 (100)	1 (33.3)
≥65	2 (18.2)	0	2 (66.6)
Female sex, no. (%)	6 (54.4)	4 (50)	2 (66.6)
Male sex, no. (%)	5 (45.5)	4 (50)	1 (33.3)
Chinese race, no. (%)	11 (100)	8 (100)	2 (66.6)
HAE type, no. (%)			
Type I	9 (81.8)	7 (87.5)	2 (66.6)
Type II	218.2)	1 (12.5)	1 (33.3)
Age at symptom onset (y), mean (SD)	18.5 (4.2)	19.3 (4.6)	16.7 (2.9)
History of laryngeal attacks, no. (%)	8 (72.7)	7 (87.5)	1 (33.3)
Availability of on-demand treatment, no. (%)	11 (100)	8 (100)	3 (100)
Ever prior use of LTP, no. (%)*	5 (45.5)	4 (50)	1 (33.3)
Oral kallikrein inhibitor	5 (45.5)	4 (50)	1 (33.3)
Androgen	3 (27.3)	2 (25)	1 (33.3)
Antifibrinolytics	3 (27.3)	3 (37.5)	0

*All LTP medications were stopped for at least 2 months before patients began taking garadacimab or lanadelumab.

involvement, frequency of symptoms, attack duration, and hospital admissions, were anonymized and collected. Questionnaires (including the Angioedema Quality of Life [AE-QoL] questionnaire; Hospital Anxiety and Depression Scale, Work Productivity and Activity Impairment Questionnaire: General Health, version 2.0; and Treatment Satisfaction Questionnaire for Medication, version II) were administered just before initiation of LTP and repeated after 6 months.

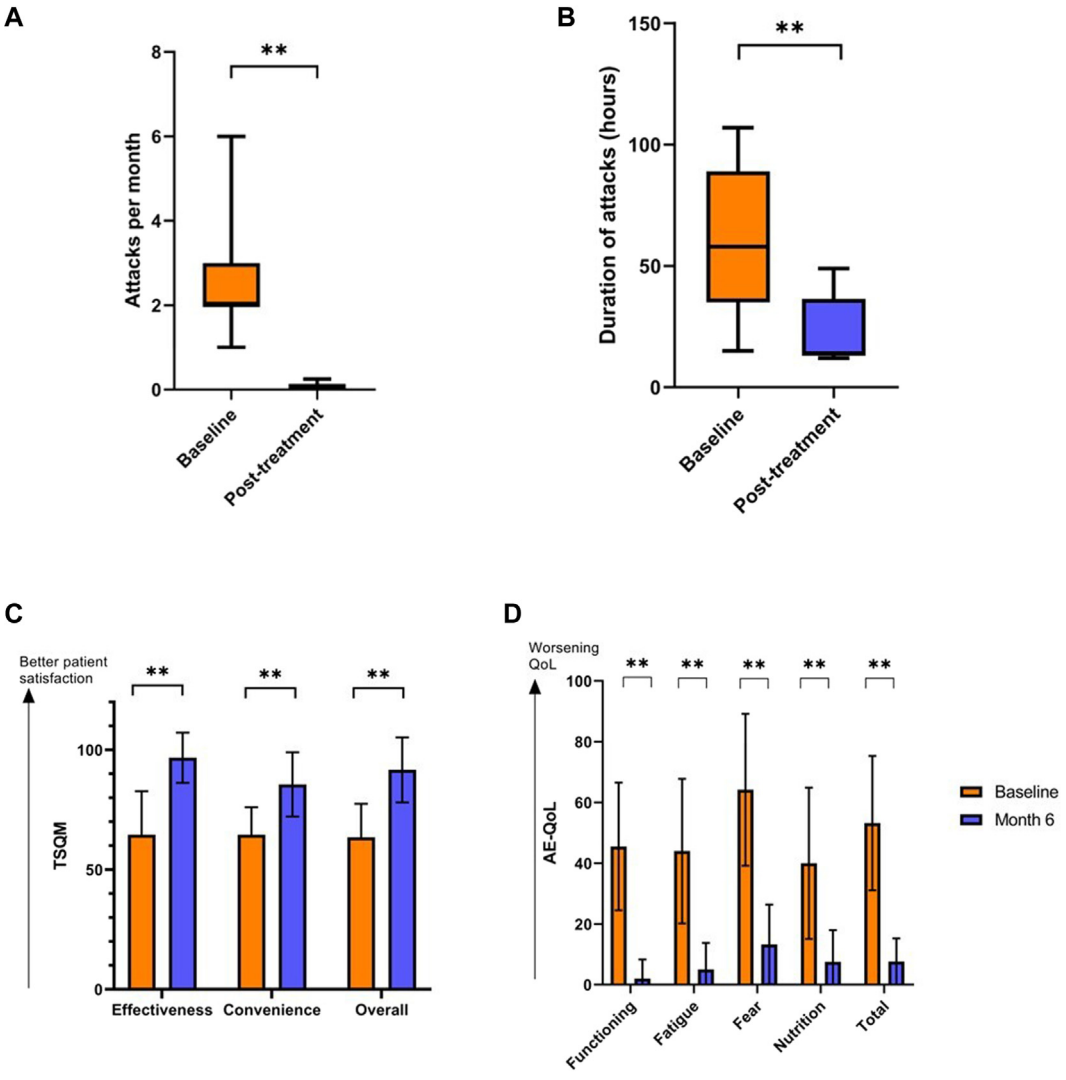
RESULTS AND DISCUSSION

Of all 36 adult patients with HAE in Hong Kong who were recruited during the study period, 30.5% (11 of 36) experienced frequent HAE attacks. All 11 began LTP: 8 began taking garadacimab (a 400-mg loading dose followed by 200 mg every 4 weeks subcutaneously), and 3 began taking lanadelumab (300 mg every 2 weeks subcutaneously). All of the patients received LTP, and no dosage adjustments were made. Demographics and baseline characteristics are shown in Table I. At baseline, the time-normalized number of HAE attacks was 2.5 plus or minus 1.3 per month. At month 6, there was an overall reduction of time-normalized number of attacks per month of –2.4 attacks per month (95% CI = –3.3 to –1.5. [$P < .01$]). The time-normalized number of HAE attacks at month 6 was 0.1 plus or minus 0.1 per month (Fig 1, *A*). More than 70% of the patients (8 of 11) were completely attack-free during the 6-month period. Among the minority of patients who still experienced attacks, the duration of each attack was significantly reduced (from 61.0 ± 28.6 hours to 22.6 ± 15.5 hours [$P < .01$]) (Fig 1, *B*). At baseline, the duration of hospitalization was 2.6 plus or minus 4.2 days, the number of admissions was 1.2 plus or 1.6, and the length of stay was 1.0 plus or minus 1.2 days per year. After prophylaxis, no patients required hospitalization during the 6-month period.

No adverse events were reported, and there was significant improvement in treatment satisfaction (Fig 1, *C*). There were significant improvements across all dimensions of the AE-QoL questionnaire, and improvement in overall score exceeded the minimal clinically important difference (Fig 1, *D*). Hospital Anxiety and Depression Scale scores were within the normal range both at baseline and after LTP. Marked improvements in work productivity were reflected in several domains of the Work Productivity and Activity Impairment Questionnaire: General Health before treatment, including an 8.5% reduction in work time missed, a 68.6% reduction in impairment while working, a 59.1% reduction in overall work impairment, and a 55.7% reduction in activity impairment. There was a significant reduction of activity impairment after use of LTP (from 55.7% to 15.7% [$P < .01$]). A further breakdown of the change in work productivity and activity impairment is shown in Fig E1 (in the Online Repository at www.jaci-global.org).

This is the first study examining the efficacy and safety of LTP among Chinese patients with HAE. It is also the first study investigating the use of lanadelumab and garadacimab in Asia. Previous Asian studies focused largely on the use of off-label and non–HAE-specific prophylactic agents such as androgens and fibrinolytics.[6] Previously, the only other Asian studies investigating US Food and Drug Administration–approved LTP drugs were conducted in Japan that demonstrated a reduction in attack frequency and improvement in AE-QoL questionnaire score with berotralstat and C1-inhibitors.[7,8] We also found that LTP significantly reduced the frequency and duration of HAE attacks, rendering the majority of patients completely attack-free. LTP also significantly improved scores on all dimensions of the AE-QoL questionnaire and reduced impairment of work productivity and activity. Both lanadelumab and garadacimab demonstrated excellent safety profiles, with no adverse events reported during the study period. Our findings were consistent with those of previous HAE LTP studies for lanadelumab among cohorts outside Asia.[9]

The main limitation of this study is its small sample size, which is inherent to all studies of rare diseases, although ours is the largest cohort of Chinese patients evaluating use of US Food and Drug Administration–approved LTP in HAE thus far. The relatively short follow-up period warrants further longitudinal studies. Because this was an observational study, there was also potential for selection bias, although patients were recruited into the garadacimab trial (which was available first) or the lanadelumab compassionate use program (which became available after the end of garadacimab trial recruitment) because of medication



	Pre	Post	Difference	*p* value
Effectiveness	65.2±15.3	97.0±10.0	31.8±18.6	**<0.01**
Convenience	62.1±10.5	85.9±12.8	23.7±13.4	**<0.01**
Overall	64.4±11.8	92.4±13.2	28.0±13.6	**<0.01**

	Baseline	Month 6	Difference	*p* value
Functioning	42.7±22.0	1.8±6.0	-40.9±23.0	**<0.01**
Fatigue	40.0±26.2	4.5±8.5	-35.5±25.8	**<0.01**
Fear	58.2±30.6	12.1±13.1	-46.2±35.4	**<0.01**
Nutrition	36.4±26.5	6.8±10.3	-29.5±25.8	**<0.01**
Total	48.9±25.7	7.0±7.7	-42.0±27.3	**<0.01**

FIG 1. Clinical and psychological outcomes before and after the start of LTP for hereditary angioedema. **A,** Attacks per month. **B,** Duration of attacks. **C,** Treatment satisfaction. **D,** Quality of life. All data are expressed as mean percentages ± SDs.

access at the time rather than on the basis of individual patient characteristics.

This study clearly demonstrated the safety and effectiveness of LTP in patients with HAE who experienced frequent attacks, with significant improvement in clinical and psychological parameters, as well as in work productivity and activity. Although it is difficult to compare the 2 LTP medications given the small number of patients, we believe that garadacimab will be increasingly popular given the superior frequency of administration (every 4 weeks in the case of garadacimab vs every 2 weeks in the case of lanadelumab). However, this will depend on the cost and availability of the drugs. Cost-effectiveness studies are needed and are under way. In line with international recommendations, our initial experience supports an urgent need for LTP medications to be approved and made available for underserved patients with HAE who experience frequent attacks in Asian countries and beyond. Although further multicenter studies are needed to confirm generalizability to other Asian populations, the international immunology community needs to work together to provide universal access to effective and safe treatment for all patients with HAE beyond our own borders and across the globe.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Clinical implications: Access to LTP for HAE is lacking in many Asian countries. This is the first study demonstrating the safe use of LTP in Chinese patients with HAE and showing reduced attack frequency and duration, leading to improved quality of life.

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