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Предварительные результаты неинтервенционного одноцентрового исследования по оценке эффективности применения ланаделумаба в рутинной клинической практике в Российской Федерации

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АННОТАЦИЯ

Обоснование. Наследственный ангиоотёк с дефицитом С1-ингибитора — редкое заболевание, вызванное дефицитом и/или снижением функциональной активности С1-ингибитора, проявляющееся рецидивирующими ангиоотёками различной локализации. Согласно современной концепции лечения, его целью является не только купирование возникающих ангиоотёков и предотвращение летального исхода, но и достижение полного контроля симптомов заболевания и высокого качества жизни. Ланаделумаб — современный препарат для долгосрочной профилактики ангиоотёков у пациентов старше 12 лет.

Цель — оценка эффективности и безопасности терапии ланаделумабом в реальной клинической практике в Российской Федерации (IISR-2021-200085).

Материалы и методы. В исследование включено 16 больных наследственными ангиоотёками с дефицитом С1-ингибитора, которые получали терапию ланаделумабом. Из числа включённых в исследование пациентов подростки составили 19% (3/16); большинство участников исследования были женского пола (13/16; 81%); средний возраст 29,9 лет. Препараты долгосрочной профилактики, которые получали 11/16 (69%) пациентов до начала исследования, были отменены в связи с инициацией терапии ланаделумабом. Оценка эффективности проводилась путём сравнения частоты атак до терапии и на её фоне, а также с помощью специальных шкал и опросников, в частности AAS, AECT, AE-QoL, HAE-AS (только у взрослых пациентов). Для оценки безопасности регистрировали все нежелательные явления, возникшие на фоне терапии.

Результаты. Средняя частота атак до инициации терапии составляла до 10 в месяц на одного пациента, а количество использованных доз препаратов для купирования симптомов — 4,7 в месяц на пациента. На фоне терапии спустя полгода эти же показатели составили 0,26 и 0,09 соответственно (для обоих показателей разница была статистически значимой: p <0,001). У 10/16 (62,5%) пациентов за 6 месяцев с момента инициации терапии не зафиксировано ни одной атаки. Через 3 месяца от начала терапии контроль заболевания достигнут у всех пациентов: среднее значение показателей по опроснику AECT увеличилось с 5,6 до 14,2 (p <0,001). Среднее значение качества жизни по опроснику AE-QoL значительно улучшилось спустя 6 месяцев терапии: показатель снизился с 58 до 19 баллов (p <0,001). За весь период наблюдения не зафиксировано ни одного серьёзного нежелательного явления, связанного с приёмом ланаделумаба.

Заключение. Результаты исследования показали, что благодаря терапии ланаделумабом удалось не только снизить количество атак наследственных ангиоотёков и повысить контроль над заболеванием, но и улучшить качество жизни пациентов; также был продемонстрирован высокий профиль безопасности препарата.

Ключевые слова: наследственный ангиоотёк; НАО; ангиоотёк; С1-ингибитор; брадикинин; ланаделумаб.

Как цитировать

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Preliminary results of a non-interventional single-center study evaluating the efficacy of long-term use of lanadelumab in routine clinical practice in the Russian Federation

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ABSTRACT

BACKGROUND: Hereditary angioedema with C1 inhibitor deficiency is a rare disease caused by a deficiency and/or a decrease in the functional activity of the C1 inhibitor. The primary symptom of this condition is recurrent angioedema of various localizations. According to the modern concept of treatment, the therapy aims to stop emerging angioedema and prevent death as well as achieve complete control of the disease and a high quality of life. Lanadelumab is a modern medicine developed and used to prevent attacks in patients with hereditary angioedema aged ⩾12 years.

AIM: A retrospective study (IISR-2021-200085) was conducted to evaluate the efficiency and safety of lanadelumab in real-life practice in Russia.

MATERIALS AND METHODS: In all, 16 patients with hereditary angioedema and C1 inhibitor deficiency were enrolled at the initiation of lanadelumab treatment. The patients were predominantly female (81%; 13/16). The average age of patients was 29.9 years; 19% (3/16) of the patients were adolescents. The effectiveness was evaluated by comparing the patient-reported attack rates. The following PROs for the adults only were assessed initially and during the treatment: angioedema activity score, angioedema control test (AECT), angioedema quality of life questionnaire (AE-QoL), and hereditary angioedema activity score. The incidences of adverse events were evaluated.

RESULTS: Before lanadelumab, 69% (11/16) of the patients received alternative long-term prophylaxis, which was canceled after the start of lanadelumab treatment. The average number of attacks per month and treated attacks per month prelanadelumab were 10 and 4.7 per patient, respectively. After 6 months of treatment, these values were 0.26 and 0.09, respectively (10 patients were symptom free at 6 months after the initiation of the treatment). After 3 months of treatment, the mean AECT values improved from 5.6 to 14.2 (p <0.001), and all patients showed adequate disease control. After 6 months of treatment, AE-QoL decreased from 58 to 19 (p <0.001). No serious adverse events related to lanadelumab were observed.

CONCLUSION: Our study demonstrated that the composite effect of lanadelumab minimizes the attack rate and improves the quality of life in patients with hereditary angioedema. A good safety profile of lanadelumab is shown.

Keywords: hereditary angioedema; HAE; angioedema; C1-inhibitor; bradykinin; lanadelumab.

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BACKGROUND

Hereditary angioedema (HAE) caused by C1-inhibitor deficiency is a rare disorder resulting from mutations in the SERPING1 gene, leading to reduced C1-inhibitor enzyme levels or activity [1–3]. The primary symptom of this condition is recurrent angioedema (AO) affecting the skin and mucous membranes, which often persists despite antihistamine and systemic corticosteroid treatments. The primary mediator of edema in HAE is bradykinin.

HAE attacks vary unpredictably in frequency, severity, and duration, imposing serious physical, social, and psychological burdens that negatively affect the daily life of patients, even during asymptomatic periods [1–3]. Airway edema and abdominal attacks are potentially fatal, with the latter causing extreme pain and necessitating unnecessary medical interventions.

HAE management revolves around three main principles: long-term prophylaxis, short-term prophylaxis, and acute attack management. Historically, there were no drugs indicated for HAE treatment. Approaches like attenuated androgens, fibrinolysis inhibitors, progestins, and fresh frozen plasma emerged in the mid-20th century. Later, pathogenetically-grounded medications were introduced, such as human C1-esterase inhibitor concentrate (administered intravenously) extracted from healthy donor plasma [4] and icatibant, a bradykinin receptor antagonist (administered subcutaneously) [5]. These advancements addressed acute attacks (icatibant and C1-esterase inhibitor) and short-term prophylaxis (human C1-esterase inhibitor). While on-demand therapy reduced mortality risk and hospitalizations, patients still grappled with fear of unpredictable attacks, intense pain, and significant limitations on social and daily activities.

The subsequent therapeutic advancement aimed to prevent edema development using a C1-esterase inhibitor. While successful in some cases, the inconvenience of the dosing regimen (intravenous administration 2–3 times weekly [6]), suboptimal symptom control for certain patients, and challenges in administering therapy without venous access prompted the search for improved long-term prophylaxis options.

In the past five years, three novel long-term prophylaxis drugs for Hereditary Angioedema (HAE) have gained global registration: subcutaneous self-administered C1-esterase inhibitor concentrate (Haegarda) [4], subcutaneous monoclonal antibodies targeting kallikrein lanadelumab (Takhzyro) [7], and oral plasma kallikrein inhibitor berotralstat [8]. Distinguished from previously used agents like androgens, fibrinolysis inhibitors, and progestins, these new drugs offer significantly improved efficacy and safety. Thus, they have become the first-line therapy for HAE patient management of patients as per WAO/EAACI (World Allergy Organization/European Academy of Allergy and Clinical Immunology) guidelines in 2021 [9].

This influx of new drugs has revolutionized the approach to HAE treatment. The focus has shifted from merely preventing patient mortality via drugs for acute attack management and short-term prophylaxis, to achieving comprehensive symptom control and a quality of life comparable to that of the general population. Both lanadelumab and subcutaneous human C1-esterase inhibitors have been registered in Russia along with modern pathogenetic drugs for long-term prophylaxis for HAE patients. Both drugs are featured in the most recent federal clinical guidelines [10]. However, in routine practice, only lanadelumab is available, as a subcutaneous C1 inhibitor has not been imported into Russia.

Lanadelumab, a fully human monoclonal antibody administered subcutaneously, inhibits plasma kallikrein activity (IgG1/κ-light chain). Its registered indication covers long-term HAE prophylaxis, excluding acute attack treatment. At the start of therapy, lanadelumab is prescribed at a dose of 300 mg every two weeks, with the possibility of extending to four-week intervals upon achieving symptom control (no attacks) [11–13].

According to the Board of Experts resolution [14] and the latest revision of the draft federal clinical guidelines for the management of patients with HAE (the planned date for the release of approved updates is 2023) [10], lanadelumab prescription is recommended for severe cases unresponsive to other long-term prophylaxis options or when contraindications exist. Lanadelumab is the first-line therapy in children aged above 12 and is preferred for young women aged 18 to 45 (except during pregnancy or breastfeeding due to lacking safety data).

Lanadelumab's effectiveness and safety were validated in the multicenter, randomized, double-blind, placebo-controlled phase III clinical trial HELP (Hereditary Angioedema Long-term Prophylaxis) including 125 patients, which is a fair number for an orphan disease [15]. Further, the open-label extended-phase study HELP OLE confirmed its long-term efficacy and safety [13].Currently, ongoing analyses of lanadelumab's real-world efficacy and safety are in progress [16–19], although limited by the disease's rarity. However, no studies to date have examined its efficacy and safety in the Russian population.

Several practical aspects of lanadelumab usage remain unaddressed, including:

1) transitioning patients already on long-term prophylaxis to lanadelumab;
2) adjusting short-term prophylaxis for patients with full symptom control on lanadelumab;
3) prolonging intervals between lanadelumab injections post-symptom control;
4) determining the maximum interval duration;
5) evaluating the therapy's duration of effect after discontinuation.

Given these gaps, a two-year non-interventional retrospective/prospective study focusing on lanadelumab's long-term effectiveness in routine clinical practice in Russia is of paramount importance.

Our study aims to assess both the efficacy and safety of the long-term use of lanadelumab in real-world clinical practice in the Russian Federation.

MATERIALS AND METHODS

Study Design

This study adopts a non-interventional, retro-prospective approach and is conducted at a single center. It involves patients with C1 inhibitor-deficient HAE who started lanadelumab treatment according to current usage guidelines [3]. The plan aimed to follow up 30 patients for 24 months. The study includes interim findings derived from six months of data analysis for 16 patients.

Eligibility Criteria

To be included, participants need to be aged ⩾12 and willingly provide signed and dated written informed consent for study participation, either personally or via a legal representative. Their use of lanadelumab should align with the drug's current guidelines, and the decision to use lanadelumab should have been made before any involvement in the study. Additionally, data on HAE attacks from the prior six months are required for inclusion.

For retrospective inclusion, the mentioned criteria are supplemented with the availability of data on the assessed indicators, adverse events, and medical interventions since starting lanadelumab treatment.

Participants are excluded if they fail to provide signed and dated written informed consent, have contraindications to lanadelumab treatment according to the current drug guidelines, are pregnant or breastfeeding, or are currently participating or planning to participate in other interventional studies.

Terms and Conditions

This study is conducted on the basis of the NRC "Institute of Immunology" FMBA of Russia Clinic in Moscow. This clinic is a certified reference center within the ACARE international network catering to patients with AO.

Given the vast expanse of the Russian Federation and the resultant remote patient locations, the study is carried out with the support of experts experienced in HAE patient management from other centers. These include Moscow Center of Allergy and Immunology of City Clinical Hospital № 52, the Moscow Ministry of Health (Moscow Reference Center for Assistance to Patients with AO of the ACARE International Network), Saratov State Medical University named after V.I. Razumovsky of the Ministry of Health of Russia, National Medical Research Center of Pediatric Hematology, Oncology and Immunology named after Dmitry Rogachev of the Ministry of Health of Russia, Healthcare institution of the Vologda region "Vologda Regional Clinical Hospital," and FSBSI "Research Institute of Fundamental and Clinical Immunology."

Data Sources

Retrospective data are sourced from ambulatory patient records, while prospective data collection takes place during follow-up visits in adherence to the study protocol. All information is entered into individual registration cards.

Study Duration

The study started in December 2021 and is currently ongoing. Patient follow-up is designed to last for 24 months. Follow-up assessment points are set at 3 months, 6 months, 12 months, and 24 months (except in cases of early termination of participation in the study). This article presents data on the first 16 patients who were followed up over six months.

Description of Medical Intervention

This non-interventional study included patients who were prescribed lanadelumab as a part of standard clinical practice. The first 16 patients, meeting the inclusion criteria, were enrolled in December 2021. At this point, all patients were already undergoing lanadelumab therapy and detailed medical records were maintained for each of them, allowing for the use of retrospective data.

The efficacy and safety were assessed using questionnaires filled out at control points. These surveys encompass various aspects including attack frequency, usage of AO management medications, adverse events, and medical interventions were recorded. PRO (patient-reported outcome) tools are used as additional metrics (Table 1).

- **AE-QoL Questionnaire:** Assessing the quality of life in patients with AO over four weeks, it comprises 17 questions, each with five response options (scoring from 0 to 4 points). The total score is converted to a hundred-point scale, ranging from 0 to 100 (higher scores indicate greater disease burden) [10].

Table 1. Comparative characteristics of scales and questionnaires used to assess the severity of hereditary angioedema [10]

Characteristic	AAS28	HAE-AS	AECT	AE-QoL
Title	Angioedema activity score 28	HAE activity score	Angioedema control test	Angioedema quality of life
Estimated period	4 weeks	6 months	4 weeks / 3 months	4 weeks
Filling method	Prospective	Retrospective	Retrospective	Retrospective
Subject of evaluation	AO frequency and duration	AO frequency and duration	Disease control	Impact on quality of life

Note: HAE: hereditary angioedema; AO: angioedema.

- **AAS28 (Angioedema Activity Score 28):** A daily questionnaire where patients record AO presence or absence within the last 24 hours. For recurring AO, five supplementary questions are answered, each graded from 0 to 3 points. The daily score ranges from 0 to 15 points, with a 4-week summary (AAS28) aiding in gauging disease activity [10].
- **HAE-AS (HAE Activity Score):** Designed for retrospective disease assessment, it spans six months. The questionnaire comprises 12 questions, with each response corresponding to a point value. Scores can range from 0 to 30 points, reflecting disease activity [10].
- **AECT Questionnaire (Angioedema Control Test):** Consisting of four questions, each with five response options (scoring from 0 to 4 points), the maximum score is 16 points. A control threshold of 10 exists; a score ⩾10 is deemed good control, while <10 is considered inadequate [10].

The Primary Outcome of the Study

The study group underwent a clinical assessment, evaluating the disease activity before and during therapy. An algorithm for extending the intervals between administrations of the study drug was developed, alongside documentation of medical interventions during therapy and adverse events. Additionally, the possibility of patient self-injection was evaluated.

Subgroup Analysis

No subgroup analysis was conducted as a part of this study.

Outcome Registration Methods

We analyzed patient medical records covering the six months before lanadelumab therapy initiation and the period post-therapy initiation. All studied parameters were recorded in individual registration cards.

Ethical Review

Approval for the study was granted by the local ethics committee of the NRC "Institute of Immunology" FMBA, Protocol No. 12 dated June 12, 2021.

Statistical Analysis

Descriptive and comparative statistical analyses of the data were performed using software for statistical data processing, such as IBM SPSS Statistics (USA), RStudio (USA), and MS Excel (USA). The findings were presented in the form of summary tables and graphs. Comparative analysis of quantitative data was performed using the Wilcoxon rank test, with statistical significance set at $p < 0.05$. Given the rarity of HAE and the limited presence of HAE patients in the general population, the sample size could not be pre-calculated.

RESULTS

Participants of the Study

Sixteen patients were included in the study, comprising 13 (81%) female patients and 3 (19%) male patients. The average age of patients at the start of therapy was 29.9 years, ranging from a minimum of 13 years to a maximum of 47 years. Among the participants, 13 (81%) were adults and 3 (19%) were adolescents aged between 12 and 17 years. All included patients were diagnosed with HAE type I characterized by C1 inhibitor deficiency. A detailed breakdown of the patient cohort is presented in Table 2.

Main Results of the Study

In the lead-up to the study, all enrolled patients were previously on various long-term prophylaxis regimens. These included tranexamic acid as the sole prophylactic treatment for three patients, while nine individuals received two different drugs for long-term prophylaxis. Additionally, three patients were using three distinct long-term prophylaxis drugs, and one patient was managing their condition with four different long-term prophylaxis medications. Before lanadelumab therapy initiation, 11 (69%) patients received long-term prophylaxis with one of the previously mentioned drugs. Detailed specifics are presented in Table 3.

Transition from Initial Treatment

All enrolled patients discontinued their previous treatment upon initiating lanadelumab. For most patients, this shift was driven by the ineffectiveness of their initial treatment. In 4 patients, the transition occurred immediately upon lanadelumab initiation, and only one patient experienced AO on the fourth day, which was alleviated using icatibant. In ¾ of the patient, the instantaneous transition to lanadelumab did not cause AO.

Patient Self-Injection Ability

The ability of patients to self-inject was analyzed. During the first administration of lanadelumab, 8 (50%) patients, including one adolescent, were trained in self-administration. They were able to independently carry out the injections following instructions and continued doing so at home for six months. Patients ensured proper transportation (three transportations by plane, three transportations by car, and two transportations by train), adhering to recommended storage conditions during transit (transportation of the drug should be carried out via cold chain).

Maintenance of Drug and Regimen Adherence

There were no instances of drug loss among the patients. Only one deviation from the prescribed administration regimen was noted, where a patient forgot about the scheduled date. Among the remaining 8 patients, the drug was received at the clinic due to regulations that prohibit direct distribution to the patient in certain cities.

Table 2. Data about patients enrolled in the study

Patient	Center	Age*, years	Sex	Type	Height, sm	Weight, kg	BMI, kg/m^2
01	Moscow	42	f	I	1.65	73	26.81
02	Moscow	22	f	I	1.75	65	21.22
03	Novosibirsk region	47	f	I	1.59	76.5	30.26
04	Khabarovsk region	17	m	I	1.73	62	20.72
05	Moscow region	44	f	I	1.63	93	35.00
06	Tver region	30	f	I	1.64	83	30.86
07	Saratov region	13	f	I	1.64	49	18.22
08	Saratov region	37	m	I	1.81	85	25.95
09	Tambov region	22	f	I	1.68	84	29.76
10	Kaliningrad region	19	f	I	1.68	53	18.78
11	Moscow region	38	f	I	1.73	62	20.72
12	Krasnodar region	14	f	I	1.68	50	17.72
13	Vologda region	47	f	I	1.74	87	28.74
14	Novosibirsk region	29	f	I	1.61	53	20.45
15	Stavropol region	23	f	I	1.65	57	20.94
16	Moscow	34	m	I	1.83	90	26.87

Note: * Age at the time of therapy initiation. BMI: body mass index.

Table 3. Analysis of baseline and prior long-term prophylaxis in patients prior to initiation of lanadelumab therapy

Patient	The effect of long-term prophylaxis					
	Initial		Previous			
	The drug at the time of inclusion into the study	Cancellation of therapy after the initiation of lanadelumab	Tranexamic acid	Danazol	Progestins	Human C1-esterase inhibitor
01	None	n/a	None	None	Insufficient	Insufficient
02	Human C1-esterase inhibitor 1000 IU 2 times a week	Immediately	None	None	-	Insufficient
03	Danazol 200 mg per day	Immediately	None	Insufficient	-	Insufficient
04	Human C1-esterase inhibitor 1000 IU 2 times a week	Immediately	None	-	-	Insufficient
05	Danazol 200 mg per day	Gradually	None	Insufficient	-	-
06	None	n/a	None	-	Insufficient	-
07	Tranexamic acid 1500 mg 3 times a day	Immediately	Insufficient	-	-	-
08	Danazol 200 mg per day	Gradually	Insufficient	Insufficient	-	-
09	None	n/a	None	-	None	-
10	Human C1-esterase inhibitor 1000 IU once a week	Gradually	None	-	-	Insufficient
11	Tranexamic acid 2250 mg per day	Gradually	Insufficient	-	None	-
12	Tranexamic acid 2000 mg per day	Gradually	Insufficient	-	-	-
13	Tranexamic acid 1500 mg per day	Gradually	Insufficient	-	-	-
14	None	n/a	None	-	None	-
15	None	n/a	None	-	None	-
16	Human C1-esterase inhibitor	Gradually	None	None	-	None

Note: n/a: not applicable; dashes indicate that the patient has never received this therapy.

Three patients experienced protocol deviations due to external factors: (1) the first patient could not visit the clinic due to an exacerbation of a concurrent disease (gout), (2) the second patient missed treatment due to the clinic's work schedule on public holidays, and (3) the third patient could not adhere due to personal work commitments.

All study patients were initially prescribed a lanadelumab regimen of 300 mg once every 14 days, irrespective of immediate effects. One patient could not receive an injection due to clinic closure on public holidays. Efforts were made to extend injection intervals upon achieving disease control. Given the study's real-world clinical context and the absence of specific guidelines for interval extension in the drug's instructions, the protocol for altering administration was tailored. Among eight patients, the interval between injections was instantly extended by seven days.

Current Regimen Adherence

As of the six-month mark (post-therapy initiation), 5 (31.25%) patients continue to receive treatment once every 14 days. The remaining 11 (68.75%) successfully extended the interval between administrations from 17 to 36 days.

Attack Frequency and Treatment Need

Before lanadelumab therapy, the average monthly attack frequency per patient was 10 (with a minimum of 1 and a maximum of 17). The need for AO management drugs averaged 4.7 per patient per month (with a minimum of 1 and a maximum of 8). After 6 months of therapy, the average attack frequency dropped significantly to 0.26 per month per patient (with a minimum of 0 and a maximum of 0.83), and the need for AO management drugs diminished to 0.09 per patient per month (with a minimal of 0 and a maximal of 0.33). Statistically, these reductions were significant ($p < 0.001$). Ten patients remained entirely free of HAE attacks within six months after the initiation of therapy.

Patient-Reported Outcome (PRO) Values

Among patients aged >18 years ($n = 13$), PRO values were assessed before therapy initiation and three months and six months after initiation. The mean HAE-AS score after six months from therapy initiation decreased from 16.2 points (with a minimum of 5 points and a maximum of 23 points) to 2.3 points (with a minimum of 0 points and a maximum of 6 points). ($p < 0.001$), signifying substantial improvement. The mean AECT score also saw positive changes, increasing from 5.6 points before therapy initiation (with a minimum of 0 points and a maximum of 13 points) to 14.2 points after 3 months ($p < 0.001$) and stabilizing at 15.1 points after 6 months. There was no statistically significant difference between the results at the control point of 3 months and 6 months ($p = 0.077$). This reflects good disease control in all 13 patients at both assessment points. Notably, 7 out of 13 adult patients achieved complete control over disease activity (16 out of 16 possible points) after six months of therapy (Fig. 1).

Improvement in Quality of Life

The study demonstrated a significant enhancement in quality of life based on the AE-QoL questionnaire. After 6 months from therapy initiation, the mean score decreased from 68 points (with a minimum of 17 points and a maximum of 82 points) to 19 points (with a minimum of 1 point and a maximum of 54 points) ($p < 0.001$) (Fig. 2).

Impact of Medical, Dental, and Cosmetic Interventions

Over the course of 6 months from therapy initiation, 7 (43%) patients underwent various medical, dental, and cosmetic interventions, all of which could potentially trigger HAE. This accounted for a total of 21 interventions across these 7 patients. Notably, no instances of AO were reported following these interventions. It is worth noting that

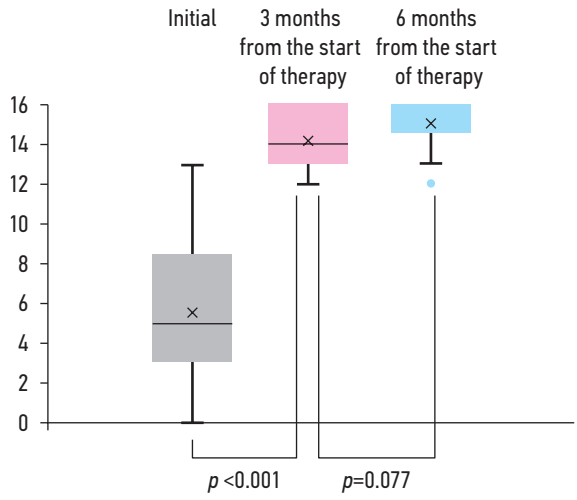

Fig. 1. Assessment of disease control with AECT before and during therapy with lanadelumab (n=13).

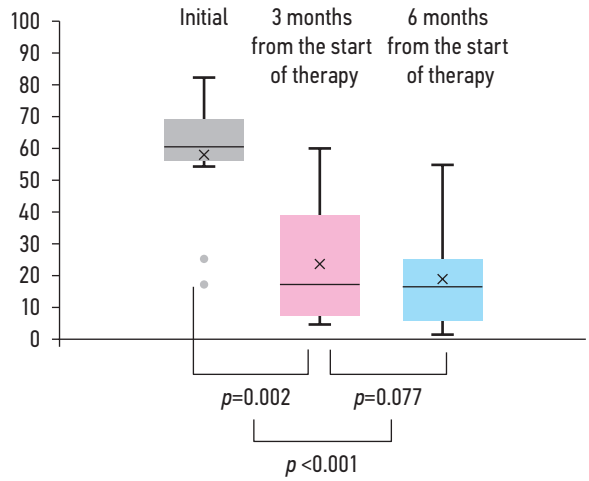

Fig. 2. AE-QoL value before and during therapy with lanadelumab.

short-term prophylaxis using human C1-esterase inhibitor 1000 IU intravenously was administered only to 1 patient. Further details are presented in Table 4.

Adverse Events

Throughout the study, 4 adverse events were registered. Among these, 3 were considered to be probably drug-related, although all of them were classified as mild and aligned with descriptions outlined in the instructions for use. Additionally, one patient had a serious adverse event that was not attributed to the treatment. Notably, none of the reported adverse events led to therapy discontinuation. More details are presented in Table 5.

DISCUSSION

Summary of Main Study Results

The study confirmed the efficacy of lanadelumab for long-term prophylaxis in C1-inhibitor-deficient HAE patients. A marked reduction in attack frequency decreased need for acute attack therapy, and improved patient quality of life were demonstrated. Furthermore, the safety of lanadelumab treatment was confirmed by the absence of serious adverse events associated with its usage.

Discussion of Main Study Results

The efficacy and safety of lanadelumab had previously been validated in a double-blind, randomized trial, wherein the optimal dosing regimen was determined as 300 mg subcutaneously once every 14 days [11].

While double-blind trials provide rigorous evaluation, real-world evidence contributes a practical dimension. Countries such as Canada, Germany, and France have already shared their experiences with lanadelumab in actual clinical settings [18, 20]. Our study fills a notable gap by examining the usage of lanadelumab within a Russian cohort for the first time in literature.

The preponderance of female patients (81%) in the study is significant. This shift in gender ratio may be attributed to the historical usage of danazol, particularly better tolerated by males [21]. In females, the use of danazol is associated with a high risk of developing adverse events. Therefore, in patients with HAE, even with a severe course of the disease, danazol was administered with caution [9].

The study cohort exclusively consisted of patients with type I HAE, a choice influenced by the relative rarity of type II HAE occurrences. Notably, type II HAE was not employed as an exclusion criterion in the study.

A significant observation arises from the study's analysis of previous long-term prophylactic treatments. The consistent reduction in attack frequency and enhancement in disease control for all patients underscores a crucial finding: the ineffectiveness of prior prophylactic options is not indicative of potential lanadelumab failure. This insight holds valuable implications for clinical decision-making and therapeutic strategies.

Transitioning from prior long-term prophylactic treatments to lanadelumab presents its own set of challenges and has no solution to date. A case example in our study involving a patient on tranexamic acid therapy who experienced uterine bleeding upon discontinuation highlights the complexity of this transition. Therefore, further data collection and analysis on the discontinuation of tranexamic acid, including optimal discontinuation timing, gradual dose reduction, and assessment of adverse events, is required.

Table 4. Medical, dental and cosmetologic interventions performed during 6 months during lanadelumab therapy

Type of intervention	Number of interventions	Before short-term prophylaxis therapy	Angioedema
Dental procedures	16	0	0
Esophagogastroduodenoscopy	3	1	0
Cosmetic (facial cleansing, permanent make-up)	2	0	0

Table 5. Reported adverse events

Adverse events after lanadelumab administration	Patient	Severity	Association with the drug	Outcome	Note
Small papular rash appearing the day following the injection	07	Mild	Probably related	Continues and reappears	-
Hyperemia at the injection site	15	Mild	Probably related	Reappears	-
Uterine bleeding	22	Severe (hospitalization)	Not related	Hospitalization	Probably due to tranexam discontinuation
Headache on the day of injection	02	Mild	Probably related	Reappears	-

To address the dilemma of discontinuation, the SHAERPA study has been initiated. This is to collect data and formulate guidelines for discontinuing attenuated androgen treatments, like danazol, in HAE patients. Notably, Fain et al.'s subgroup study [18] corroborated the finding that previous long-term prophylactic interventions do not affect the efficacy of lanadelumab.

Lanadelumab is designed for self-administration according to the provided guidelines. In this study, patients who were eligible based on regional drug supply regulations were trained in the technique of self-preparing and self-administering lanadelumab. all participants successfully executed the procedure on their initial attempt and consistently managed subsequent administrations. Importantly, no instances of drug loss during transportation were reported.

Remarkably, the study demonstrates the advantages of self-administration. There was only one deviation (1 out of 8) from the prescribed administration schedule (the patient missed the day of injection) among administering the treatment at home. Conversely, a larger number of deviations (3 out of 8) were documented among the injection in a medical. Thus, this variance signifies that self-administration aligns with a lower frequency of protocol deviations.

However, while self-administration displays clear benefits, the shift towards a more flexible treatment regimen necessitates implementing dynamic monitoring systems. Such systems should assess disease activity and the patient's quality of life, enabling treatment adjustments. Conversely, administering the drug in a medical setting introduces potential disruptions stemming from factors like appointment scheduling, which can disrupt the prescribed regimen. Such external factors may compromise the consistency of vital therapy.

Initially, the recommended administration schedule for lanadelumab is 300 mg every 14 days. However, the product instructions indicate the potential to extend this interval up to 28 days. Remarkably, real clinical practice studies have even shown the feasibility of extending the interval up to 1 month and even 90 days [18].

Despite these findings, a standardized scheme for extending intervals between lanadelumab injections remains absent. A study by Howevertgereit et al. [20] outlines their approach: the first three injections are performed at 14-day intervals, and subsequently, assuming complete remission, the intervals are extended for three days with each subsequent injection.

A personalized administration schedule was developed to ensure the effectiveness of each patient's therapy. We introduced interval extension after the initial six injections. This approach was underpinned by the equilibrium concentration of the active substance being attained by the 70th day (except for the previously mentioned cases of deviation from the recommended administration protocol). Accordingly, intervals were extended by 7 days (in the case of complete remission), and then by another 7 days, ultimately reaching a maximum of 28 days. Currently, ongoing efforts are directed at refining this personalized approach, and the results will be reported in future publications.

The most important objective of our study centered on assessing the effectiveness of lanadelumab as a long-term prophylactic treatment. In congruence with prior research endeavors, we were able to demonstrate the high efficacy of lanadelumab. This remarkable efficacy was registered after only three months from the start of therapy and persisted for the next three months until the next visit.

Notably, our study unveiled a significant reduction in the frequency of AO, with 10 patients even attaining complete remission. This achievement bears substantial long-term advantages despite the high cost of the drug. The advantages lie in the fact that these patients did not need the drugs to stop acute attacks, did not miss work and school due to their temporary disability, did not visit medical institutions, and did not require hospitalization. We speculate that the heightened disease control achieved through lanadelumab therapy might subsequently minimize the costs of short-term prophylaxis, and more crucially, ensure the safety of emergency invasive procedures, which could otherwise carry a risk of fatal consequences in the absence of necessary prophylactic measures. However, the comprehensive validation of these observations necessitates further clarification.

Our study reveals a statistically significant improvement in the level of control over disease symptoms after three months of initiating lanadelumab therapy as indicated by the AECT scores (Fig. 1). Importantly, this heightened control remained consistent between the 3rd and 6th months of therapy, suggesting that lanadelumab rapidly establishes disease management and sustains this level of control over time. Notably, the patients' quality of life exhibited a more profound improvement by the 6th month of therapy (Fig. 2). This outcome can be attributed to the fact that the patients' quality of life is affected not only by the direct influence of AO but also the anticipation of such attacks, as documented in patients' diaries.

In line with prior studies, our investigation affirms that lanadelumab maintains a high safety profile [11, 13]. The recorded adverse events align with those specified in the instructions and have been classified as mild. Importantly, these events do not hinder the patients' ability to self-administer therapy, a significant aspect of maintaining treatment adherence and patient autonomy.

Study Limitations

Considering that HAE is an orphan disease, a preliminary sample size calculation was not feasible due to the scarcity of cases. Consequently, the study enrolled all eligible patients with HAE and C1 inhibitor deficiency who met the inclusion criteria. This approach does pose a constraint on the study's ability to offer a truly representative sample, which limits the ability to extrapolate the results and their interpretation to the general population of patients with similar conditions beyond the study cohort.

CONCLUSION

In conclusion, the current guidelines for the treatment of HAE define the goals of treatment: as achieving complete absence of attacks, complete disease control, and maintaining patients' quality of life. With its convenient administration and excellent safety profile, lanadelumab approved globally in 2017 and in Russia in 2021, has demonstrated its potential to fully realize these objectives.

Our study is the first to investigate lanadelumab in routine clinical practice in Russia. This article presents the intermediate results gathered from monitoring 16 patients over a six-month therapy period. These results reaffirm the previously established efficacy and safety of lanadelumab while shedding light on methods to extend drug administration intervals, interventions performed during therapy, and the possibility of self-administration at home. We are actively continuing data collection, having enrolled 30 patients to date.

ADDITIONAL INFORMATION

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