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Lanadelumab demonstrates high efficacy in reducing the frequency of angioedema attacks in patients with severe HAE in real-life settings

Lanadelumab wykazuje wysoką skuteczność w zmniejszaniu częstości napadów obrzęku naczynioruchowego u pacjentów z ciężkim HAE w warunkach codziennej praktyki klinicznej

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Abstract

Introduction and objective: Evaluation of lanadelumab efficacy in preventing angioedema attacks in patients with severe hereditary angioedema due to C1-inhibitor deficiency in Poland and descriptive analysis of this group of patients. **Materials and methods:** Retrospective analysis of patients treated with lanadelumab in Poland. Data were acquired from the electronic database of the National Health Fund, compiled from 15 hereditary angioedema centres. Only patients with severe hereditary angioedema course (at least 12 severe – abdominal, pharyngeal or laryngeal – hereditary angioedema attacks per six months, requiring on-demand medications) initiated treatment. The patients received lanadelumab 300 mg every two weeks. The efficacy of the therapy was assessed after six months. **Results:** Lanadelumab was initiated in a total of 43 patients (group B). Twenty of them achieved the follow-up point after six months (group A). The mean age of the patients was 44 years. The majority (76.7%) were female and 79% had a family history of hereditary angioedema. Most patients (95.3%) had HAE-1 (absolute deficiency of C1-inhibitor). On average, within six months before treatment, group A patients experienced 19.7 (95% confidence interval, CI: 16.06–23.33) severe hereditary angioedema attacks. In the six months following treatment initiation, the number of attacks decreased to an average of 0.5 (95% CI: 0–1.0), with significant reductions in all types of hereditary angioedema attacks – abdominal ($p < 0.0001$), pharyngeal ($p < 0.005$), and laryngeal ($p < 0.05$). Utilisation of on-demand medications dropped from an average of 23.5 (95% CI: 16.7–30.3) to 0.5 standard therapeutic dose (95% CI: 0–1.1). **Conclusions:** The study highlights the therapeutic potential of lanadelumab in managing hereditary angioedema, usually offering patients a complete resolution of severe hereditary angioedema attacks and release from dependence on rescue medication. Our results support the current paradigm shift in hereditary angioedema treatment.

Keywords: lanadelumab, hereditary angioedema, prophylaxis, real-life study, C1-inhibitor

Streszczenie

Wprowadzenie i cel: Ocena skuteczności lanadelumabu w zapobieganiu napadom obrzęku naczynioruchowego (*hereditary angioedema*, HAE) u pacjentów z ciężkim HAE z powodu niedoboru inhibitora C1 w Polsce oraz analiza opisowa tej grupy pacjentów. **Materiał i metody:** Retrospektywna analiza pacjentów leczonych lanadelumabem w Polsce. Wykorzystano dane z elektronicznej bazy danych Narodowego Funduszu Zdrowia, zebrane z 15 ośrodków HAE. Tylko pacjenci z ciężkim przebiegiem HAE (co najmniej 12 ciężkich – brzusznych, gardła lub krtani – ataków HAE w ciągu 6 miesięcy, wymagających leków na żądanie) rozpoczęli leczenie. Pacjenci otrzymywali lanadelumab w dawce 300 mg co 2 tygodnie. Skuteczność terapii oceniano po 6 miesiącach. **Wyniki:** Leczenie lanadelumabem rozpoczęło 43 pacjentów (grupa B). 20 z nich osiągnęło punkt kontrolny po 6 miesiącach (grupa A). Średnia wieku wyniosła 44 lata. Większość (76,7%) stanowiły kobiety, a 79% miało rodzinną historię HAE. Większość pacjentów (95,3%) miała rozpoznane HAE-1. Średnio w ciągu 6 miesięcy przed rozpoczęciem leczenia pacjenci z grupy A doświadczyli 19,7 (95-procentowy przedział ufności, *95% confidence interval*, CI: 16,06–23,33) ciężkiego napadu HAE. W ciągu 6 miesięcy od rozpoczęcia leczenia liczba ataków zmniejszyła się średnio do 0,5 (95% CI: 0–1,0), przy znacznym zmniejszeniu wszystkich rodzajów napadów – brzusznych ($p < 0,0001$), gardłowych ($p < 0,005$) i krtaniowych ($p < 0,05$). Wykorzystanie leków na żądanie zmniejszyło się ze średnio 23,5 (95% CI: 16,7–30,3) do 0,5 standardowej dawki terapeutycznej (95% CI: 0–1,1). **Wnioski:** Wyniki badania wskazują na istotny potencjał terapeutyczny lanadelumabu w leczeniu HAE. Stosowanie tego leku u większości chorych doprowadziło do całkowitego ustąpienia ciężkich napadów HAE, z jednoczesną redukcją dawek przyjmowanych leków ratunkowych. Nasze wyniki potwierdzają konieczność zmiany paradygmatu leczenia HAE.

Słowa kluczowe: lanadelumab, dziedziczny obrzęk naczynioruchowy, profilaktyka, badanie *real-life*, C1-inhibitor

INTRODUCTION

Hereditary angioedema (HAE) due to C1-inhibitor (C1-INH) deficiency is a rare, genetically determined disease characterised by reversible attacks of oedema (angioedema) of the skin/subcutaneous tissue and mucous membrane/submucous tissue at various body sites. Globally, its incidence rate is estimated between 1:50,000 to 1:100,000[1]. In Poland, more than 400 patients have been diagnosed to date (patient registry, unpublished data), which means that potentially many patients remain undiagnosed. The condition results from a mutation in the *SERPING1* gene leading to two types of angioedema with C1-INH deficiency: HAE-1 with absolute deficiency of C1-INH and HAE-2 with functional deficiency. Lack of or impaired function of C1-INH leads to dysregulation of kallikrein activity and excessive production of bradykinin, leading to reversible capillary hyperpermeability with subsequent oedema of local tissues[2]. The effects can be very debilitating for patients, with often both disfiguring and painful skin swelling. In attacks affecting the abdomen, they are the cause of severe colic pain, often with vomiting, hypotension, and total disability for a day or longer[3]. Furthermore, HAE attacks can cause the obstruction of the airways, and one to every 20 patients may die from fatal laryngeal attack even with the availability of emergency medications[4]. All this results in a significant reduction in the quality of life of HAE patients[5].

There are different strategies in the management of HAE, addressing on-demand therapy, short-term (e.g. presurgical), and long-term prophylaxis. The currently recommended on-demand treatments include intravenous C1-INH

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replacement therapy [pd-C1-inh or recombinant human C-inh (rhC1-inh)], and subcutaneous bradykinin B2 receptor antagonist (icatibant)[6]. However, on-demand treatment does not result in complete cessation of attacks – they are shorter and less severe, but just as frequent. They can still be life-threatening, unpredictable, and debilitating, significantly reducing patients' quality of life. This is why in recent years so much attention has been paid to long-term prophylaxis, where the goal is to achieve full control of HAE attacks and normalisation of patients' lives[7]. It has a significant impact not only on improving the quality of life, but also patients' safety. In the past, there have been various trials of HAE prophylactic treatment with patients treated with androgens, antifibrinolytics (both off-label), or intravenous plasma-derived C1-INH (pdC1-inh). However, oral androgens have been found to cause numerous side effects, limiting their use in women and children, and demanding close monitoring of therapy[8], while antifibrinolytics have not been found to be effective[6]. In turn, the intravenous route of pdC1-inh administration limits the use of this treatment due to the venous access issues. In addition, the treatment is not adequately effective, with frequent occurrence of breakthrough attacks[9].

Over the past few years, three medications have been registered worldwide and are recommended by current guidelines for long-term prophylaxis of HAE: subcutaneous pdC1-inh, lanadelumab (human monoclonal antibody binding active plasma kallikrein) and berotralstat (small-molecule inhibitor of plasma kallikrein)[6]. However, the high price of these medications limits their use in many countries. In Poland, only lanadelumab is reimbursed and can be prescribed to patients aged 12 and above who have had a minimum of 12 severe HAE attacks in the past six months[10]. Lanadelumab is a fully human monoclonal antibody that binds to and inhibits the action of plasma kallikrein, thereby preventing the cleavage of high-molecular-weight kininogen and the production of bradykinin. However, lanadelumab does not inhibit the tissue kallikrein-kinin system, resulting in the lack of effect on important physiological functions of bradykinin, such as in the cardiovascular system. Due to its long half-life (~14 days) lanadelumab can be administered every 14–28 days[11]. The drug's safety and very high efficacy have been confirmed in a number of randomised clinical trials, including a pivotal phase 3 study accompanied by an open-label extension study[12–14], and the drug was registered in 2018 for the indication: "routine prophylaxis of recurrent attacks of HAE in patients 12 years of age and older"[15]. To date, there have been only a few publications describing lanadelumab treatment in the real-life setting, mainly in small groups of patients[16–19].

This study aims to provide insights into HAE patients in Poland, which has been largely uncharted.

MATERIALS AND METHODS

This retrospective study utilised data from the electronic database of the National Health Fund (NHF), compiled from 15 HAE treatment centres in Poland (Supplementary Tab. 1S). Between December 2021 and August 2023, 44 HAE patients were evaluated for eligibility for lanadelumab treatment under the National Treatment Regime by the Ministry of Health's Coordinating Team for Rare Diseases. Patients had to meet all inclusion criteria and could not meet any of the exclusion criteria specified in the Polish drug access program dedicated to HAE patients and called "Preventive treatment of patients with recurrent attacks of severe hereditary angioedema" (Tab. 1). The most

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Tab. 1S. List of centres treating HAE patients with lanadelumab

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Inclusion criteria	1. Diagnosed HAE type I or type II 2. Age 12 years and older 3. Documented frequent occurrence of severe angioedema attacks – a minimum of 12 attacks (abdomen, larynx, throat) with documented use of rescue medication in the past six months
Exclusion criteria	1. Pregnancy or breastfeeding – the treating physician, in consultation with the Coordinating Team for Ultra-Rare Diseases, may decide to continue treatment in cases where discontinuation of therapy would carry a higher risk of adverse effects than its continuation 2. During the six-month treatment period, the monthly average incidence of life-threatening attacks did not decrease by at least 50% compared to the average incidence of attacks in the six-month period prior to treatment 3. Occurrence of symptoms of hypersensitivity to lanadelumab or any of the excipients

Tab. 1. Inclusion and exclusion criteria for lanadelumab treatment according to the regulations of drug access program (as of November 2021)

important criterion was the occurrence of at least 12 severe HAE attacks involving the abdomen, pharynx or larynx, requiring emergency medication in the six months prior to qualification. The diagnosis of HAE with C1-INH deficiency had to be established based on typical clinical presentation and confirmed by laboratory test results (C1-INH function, levels of C1-INH protein, and C4, according to the international guidelines[6]). Patients, whose first symptoms occurred above the age of 40 and without a family history, additionally required a C1q test.

From a group of 44 patients qualified for therapy, a total of 43 patients started the treatment and one patient dropped out due to logistic issues. The patients were treated with lanadelumab 300 mg every two weeks. At the discretion of the attending physician, the dose could be changed to 300 mg given every four weeks, but after a minimum of six months of therapy, so the dose was constant during the observational period. The first follow-up visit was scheduled six months after starting lanadelumab. Efficacy was assessed by tracking the number of severe attacks requiring emergency medication. Treatment success was gauged by a minimum 50% reduction in severe attacks. Data obtained from the NHF database included basic patient demographics and clinical information from six months before and six months after the initiation of lanadelumab treatment. Due to the retrospective character of the study, the consent of the Bioethics Committee or patients was not required.

Statistical analysis

To perform statistical analyses, Statistica (TIBCO Software Inc, version 13) was used[20]. For continuous variables with normal or non-normal distribution, respectively, means and 95% confidence intervals (CI) or medians and interquartile ranges (IQR) were computed. For nominal variables, the counts and percentages were analysed. To assess normal distribution, Shapiro–Wilk test was used. To compare independent groups, *t*-Student test was used. When normality assumptions were not met, non-parametric tests (*U* Mann–Whitney, Wilcoxon signed-rank) were applied. A two-sided *p*-value lesser than 0.05 was considered to be statistically significant.

Parameter	*n* (%)	Mean (95% CI)	Median (IQR)	Min–max
Age [years]	43 (100)	37.3 (32.8–41.8)	36 (25–47)	13–69
Gender	Male: *n* = 10 (23.25) Female: *n* = 33 (76.75)	–	–	–
Height [cm]	43 (100)	168.7 (165.9–171.5)	168 (164–173)	153–195
Weight [kg]	43 (100)	73.3 (68.3–78.3)	74 (62–83)	44–125
Body mass index – BMI [kg/m^2]	43 (100)	25.7 (24.1–27.3)	24.7 (22.8–28.4)	16.1–43.3
BMI categories	Emaciation 1 (2.3) Underweight 1 (2.3) Normal weight 21 (48.8) Overweight 11 (25.6) Obese I° 7 (16.3) Obese II° 1 (2.3) Extreme obesity 1 (2.3)	–	–	–
Footnotes: emaciation <17; underweight – 17–<18.5; normal weight – 18.5–<25; overweight – 25–<30; obese I° – 30–<35; obese II° – 35–<40; extreme obesity ≥40.				

Tab. 2. Demographics and basic characteristics – whole study group (B)

Parameter	*n* (%)	Mean (95% CI)	Median (IQR)	Min–max
Age [years]	20 (100)	39.8 (32.2–47.4)	37 (26.5–54.0)	16–69
Gender	Male: *n* = 4 (20) Female: *n* = 16 (80)	–	–	–
Height [cm]	20 (100)	168.35 (163.7–173.0)	166.5 (163.0–174.0)	154.0–195.0
Weight [kg]	20 (100)	76.7 (68.4–85.0)	75.5 (62.5–87.5)	56.0–125.0
Body mass index – BMI [kg/m^2]	20 (100)	27 (24.4–29.6)	24.7 (23.4–30.6)	19.6–43.3

Tab. 3. Demographics and basic characteristics – subgroup of patients treated for at least six months with lanadalumab (group A)

Parameter	*n* (%)	Mean (95% CI)	Median (IQR)	Min–max
Type of HAE	HAE-1: 41 (95.35) HAE-2: 2 (4.65)	–	–	–
C1-INH concentration [g/L]	HAE-1: *n* = 41 (95.35)	0.056 (0.050–0.062)	0.050 (0.042–0.070)	0.004–0.900
	HAE-2: *n* = 2 (4.65)	0.620 (0–1.255)	0.620 (0.570–0.670)	0.570–0.670
C1-INH function [%]	33 (76.7)	14.82 (11.96–17.68)	15.20 (8.00–20.90)	0.10–34.00
Time from the first symptoms to diagnosis [years]	43 (100)	18.3 (14.3–22.2)	18 (7–25)	0–47
Long-term prophylaxis ever in the past	Yes: *n* = 16 (37.2) No: *n* = 27 (62.8)	–	–	–
First-degree relatives diagnosed with HAE	Yes: *n* = 34 (79.07) No: *n* = 9 (20.93)	–	–	–
Number of severe* HAE attacks	43 (100)	18.7 (16.4–20.9)	15 (13–22)	12–40
Number of severe* abdominal attacks	43 (100)	15.02 (12.7–17.4)	13 (10–18)	4–36
Number of severe* pharyngeal attacks	43 (100)	2.1 (1.2–3.0)	1 (0–3)	0–10
Number of severe* laryngeal attacks	43 (100)	1,5 (0.7–2.3)	0 (0–2)	0–10
Number of on-demand medications standard therapeutic doses**	43 (100)	21.9 (17.6–24.8)	18 (14–24)	12–75
Number of icatibant standard therapeutic doses**	43 (100)	8.9 (6.0–11.9)	8,0 (0–13)	0–45
Number of pdC1-inh 1,500 IU standard therapeutic doses**	43 (100)	10.9 (7.8–13.9)	10 (2–18)	0–37
Number of pdC1-inh 500 IU standard therapeutic doses**	43 (100)	1.1 (0–2.7)	0 (0–5)	0–32
Number of rhC1-inh standard therapeutic doses**	43 (100)	0.3 (0–0.7)	0 (0–0)	0–10
* Severe HAE attacks are defined as involving the abdomen, pharynx or larynx and requiring the administration of an emergency treatment (icatibant, pdC1-inh, rhC1-inh). ** Used to treat HAE attacks.				

Tab. 4. Medical history of HAE (whole study group – B)

Parameter	*n* (%)	Mean (95% CI)	Median (IQR)	Min–max
Type of HAE	HAE-1: 20 (100) HAE-2: 0 (0)	–	–	–
C1-INH concentration [g/L]	20 (100)	0.058 (0.048–0.068)	0.055 (0.047–0.079)	0.004–0.090
C1-INH function [%]	12 (60)	16.58 (8.12–25.05)	13.50 (5.45–24.00)	3.0–43.3
Time from the first symptoms to diagnosis [years]	20 (100)	21.03 (14.7–27.36)	20.50 (12.5–32)	0–43
Long-term prophylaxis ever in the past	Yes: 10 (50) No: 10 (50)	–	–	–
First-degree relatives diagnosed with HAE	Yes: 16 (80) No: 4 (20)	–	–	–
Six months before lanadelumab treatment				
Number of severe* HAE attacks	20 (100)	19.7 (16.1–23.33)	16.5 (13.5–24.5)	12–40
Number of severe* abdominal attacks	20 (100)	15.4 (11.6–19.1)	13.5 (11–19)	4–32
Number of severe* pharyngeal attacks	20 (100)	2.2 (0.7–3.6)	1.0 (0–2)	0–10
Number of severe* laryngeal attacks	20 (100)	2.2 (0.6–3.8)	0 (0–5)	0–10
Number of on-demand medications standard therapeutic doses**	20 (100)	23.5 (16.7–30.3)	19 (15–25)	12–75
Within six months after initiation of lanadelumab treatment				
Number of severe* HAE attacks	20 (100)	0.5 (0–1.0)	0 (0–0)	0–4
Number of severe* abdominal attacks	20 (100)	0.4 (0–0.9)	0 (0–0)	0–4
Number of severe* pharyngeal attacks	20 (100)	0	0 (0–0)	0–0
Number of severe* laryngeal attacks	20 (100)	0.1 (0–0.2)	0 (0–0)	0–1
Number of on-demand medications standard therapeutic doses**	20 (100)	0.5 (0–1.1)	0 (0–0)	0–4
* Severe HAE attacks are defined as involving the abdomen, pharynx or larynx and requiring the administration of an emergency treatment (icatibant, pdC1-inh, rhC1-inh). ** Used to treat HAE attacks.				

Tab. 5. Medical history of HAE – subgroup of patients treated for at least six months with lanadalumab (group A)

RESULTS

By August 2023, data was available for 43 patients. Demographics and patient characteristics are presented in Tabs. 2 and 3 separately for the whole group ($n = 43$; group B) and the subgroup ($n = 20$; group A), evaluated after six months of treatment. The mean age of enrolled patients was 44 years. The majority (76.7%) were female and 79% had a family history of HAE. 37.2% had been on long-term prophylaxis using either tranexamic acid or androgens (off-label) in the past. Only one continued such treatments during the six-months' qualification period for lanadelumab. One patient had previously used berotralstat during a clinical trial, and one patient had been treated with lanadelumab under another form of funding, but had to discontinue treatment for eight months to meet the eligibility criteria for the drug program. Most patients (95.3%) had HAE-1, as evidenced by reduced C1-INH levels. Only

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three adolescents aged between 13–16 years participated; hence, there was no separate analysis for this age group. Similarly, a separate analysis was not done for HAE-2 patients since they made up only 4.6% of the study group. The mean time from symptom onset to HAE diagnosis was 18.3 years (95% CI: 14.3–22.2). In our study group, that time was longer in women than in men [19.6 (95% CI: 15.0–24.2) vs. 13.4 (95% CI: 4.7–22.1), respectively], though the difference was not statistically significant. On average, within six months before lanadelumab treatment, each patient experienced 18.7 (95% CI: 16.4–20.9) severe HAE attacks and required 21.2 (95% CI: 17.6–24.8) standard therapeutic doses of rescue medications, like icatibant, pd-C1-inh, or rhC1-inh.

All 43 patients received at least one dose of lanadelumab. Twenty of these patients (group A) reached the six-month follow-up time point. The characteristics of this subgroup closely mirrored those of the entire group, implying a consistent patient sample. Notably, after starting lanadelumab, there was a significant reduction in the number of severe attacks. The majority of patients did not experience any attack after their first dose. Overall, only four out of the 20 patients had a few attacks, mostly abdominal. The mean number of attacks went down from an average of 19.7 (95% CI: 16.1–23.33) and median number of 16.5 (IQR 13.5–24.5) during the six months before treatment to an average of 0.5 (95% CI: 0–1.0) and median number of 0 (IQR 0–0) in the six months post-treatment ($p < 0.0001$). There were also significant reductions across all types of attacks – abdominal ($p < 0.0001$), pharyngeal ($p < 0.005$), and laryngeal ($p < 0.05$). Additionally, the usage of rescue medications dropped significantly from a mean number of 23.5 (95% CI: 16.7–30.3) and median number of 19 (IQR 15–25) standard therapeutic doses to an average of 0.5 (95% CI: 0–1.1) and median number of 0 (IQR 0–0) within six months after starting lanadelumab treatment ($p < 0.0001$). Medical history of HAE is presented in Tabs. 4 and 5 separately for the groups B and A.

DISCUSSION

In line with the current medical standards, the goal of treatment in HAE is to achieve full control of the disease and normalise patients' lives. This can be achieved with long-term prophylaxis that completely eliminates HAE attacks. Indications for the inclusion of long-term prophylaxis should include not only the number and severity of HAE attacks, but also the quality of life, access to health care resources, or inability to achieve sufficient control with on-demand treatment[6]. Currently, the first-line medications for LTP are subcutaneously administered pdC1-inh, lanadelumab and berotralstat. In Poland, at the moment, only lanadelumab treatment is reimbursed, but the drug can be used in a remarkably limited group of patients with frequent (patients must have a historical baseline attack rate of at least 12 per six months) and severe HAE attacks (requiring an on-demand treatment) involving certain locations: the abdomen, pharynx or larynx[10]). With such strict eligibility criteria, this group differs from those described in other studies, in which the most common inclusion criterion was the occurrence of even just one HAE attack over a four-week period in the run-in period, regardless of its severity and location[12,21]. This is also the reason why our analysis is solely concerned with this limited group of patients without additional information on the attacks of swelling at other locations (e.g. peripheral swelling) or those not requiring on-demand medications.

The main objective of the analysis reported here was to determine the efficacy of lanadelumab therapy based on the reduction in the number of severe HAE attacks and the utilisation of on-demand medications. Our results show that long-term prophylaxis with lanadelumab resulted in a significant reduction in HAE attacks in all treated patients, with the average reduction in the number of HAE attacks from 18.7 [median 16.5 (IQR 13.5–24.5)] in the six months preceding treatment to an average of 0.5 [median 0 (IQR 0–0)] in the six months after treatment initiation (Fig. 1). As many as 80% of patients achieved remission of severe HAE symptoms just after the first dose of the drug, meaning that they did not have a single severe HAE attack requiring rescue medication. Only four patients had a total of nine severe breakthrough HAE attacks, with one patient's swellings occurring due to the accidental administration of an ACE inhibitor in the hospital emergency department as a treatment for elevated blood pressure. This significant reduction in HAE attacks following the introduction of lanadelumab was also combined with a marked decrease in the utilisation of rescue medications from an average of 23.5 to 0.5 standard therapeutic doses, thus further attesting to the efficacy of the studied kallikrein inhibitor. These benefits not only improve the patients' quality of life but might also imply a cost-saving advantage in the long run.

The results of our observations cannot be directly compared with the findings of randomised clinical trials (RCTs) or real-life studies due to the selection of the patient group. Nonetheless, it is important to emphasise the tremendous efficacy of this therapy in this strictly defined group of patients as well, with a 97.7% reduction in the number of severe HAE attacks. In comparison, in the HELP study, the HAE attacks reduction was 92.5% from the run-in period[12]. On the other hand, in a Canadian paper describing the effects of real-life treatment in a group of 12 patients, the efficacy was significantly lower, with a reduction in the number of attacks requiring emergency medication reaching 62%[16]. This good treatment effect among our patients may be, at least partly, linked to the fact that only one patient had used another form of long-term prophylaxis (tranexamic acid) in the six months prior to therapy and, therefore, the baseline HAE control in our patients was worse than, for example, in the Canadian group, in which 80% of patients were

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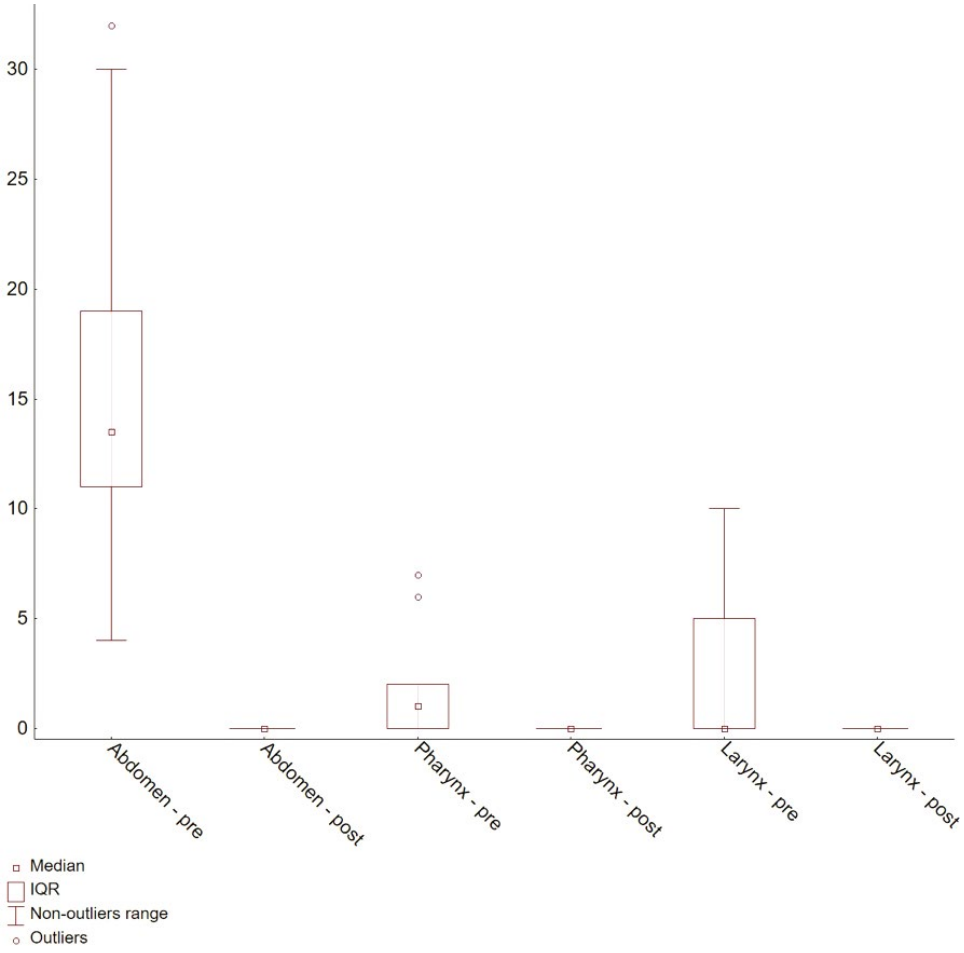

Fig. 1. Number of abdominal, laryngeal and pharyngeal severe HAE attack before and during lanadelumab treatment (group A)

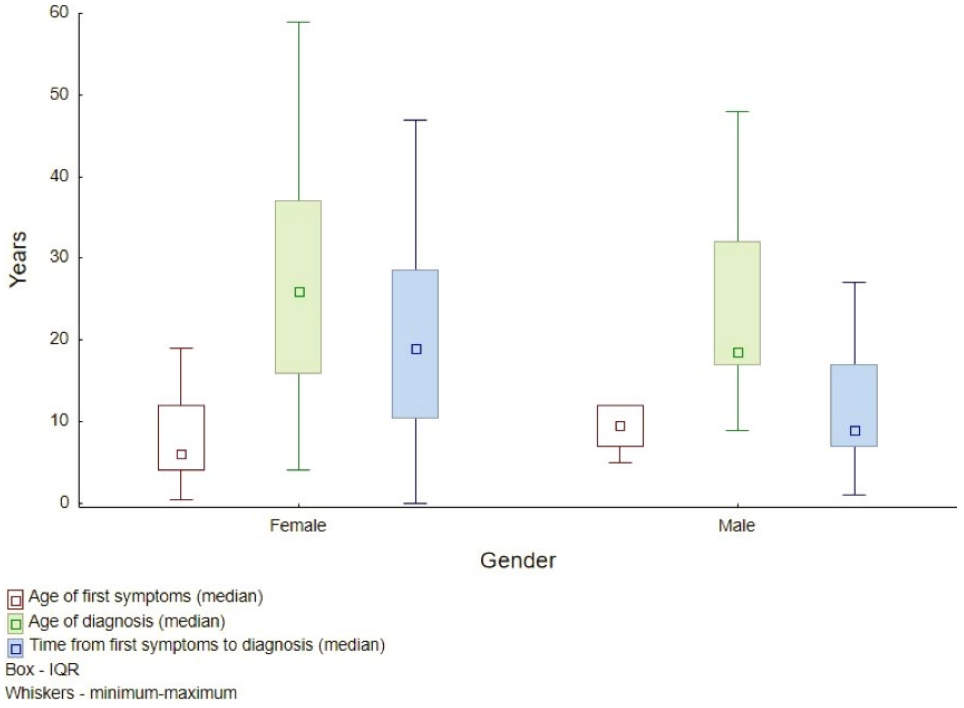

Fig. 2. Age of onset of symptoms, age of diagnosis, and time from onset of symptoms to diagnosis by patient gender

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switched, due to insufficient efficacy, from long-term prophylaxis with pdC1-inh to lanadelumab. Finally, it should be highlighted that, so far, no patient who started treatment has discontinued it, including for safety reasons.

The paramount efficacy of lanadelumab in reducing severe HAE attacks is indeed revolutionary. A near cessation of attacks post its administration can transform the therapeutic landscape for HAE. This reduction can translate to improved patient quality of life, reduced healthcare costs associated with emergency interventions, and an overall decrease in morbidity and potential mortality.

Other objectives of our study were to describe the group of patients treated with LTP. Our cohort predominantly consisted of women (76.7%), reflecting a trend observed in all HAE studies, related to the well-recognised effect of oestrogen on the number and severity of HAE attacks. We also noted an alarming delay in the diagnosis of HAE. The lag between the onset of symptoms and formal diagnosis of HAE remains a significant concern, averaging 18.3 years, especially since it is significantly longer than in other studies, which, depending on the country, ranged from two to 16.3 years[16,22,23]. This delay, which is even more pronounced in women than in men (Fig. 2), suggests a diagnostic challenge within the clinical practice, which may be due to the overlapping of symptoms with other conditions or potential under-recognition of HAE's clinical manifestations. Such a long time to establish a diagnosis in Poland may also be a result of the lack of broad availability of tests such as C1-INH concentration and function, although the situation has improved significantly in recent years. This protracted gap not only poses therapeutic challenges but may have psychosocial implications, given the chronic nature of the disease and the associated morbidity.

The reported analysis has its constraints. The results need to be interpreted in light of the study's retrospective nature and its focus on a specific population subset, with certain subgroups underrepresented, especially adolescents and HAE-2 patients. Because the data collected involved only a select group of the most severely ill patients, it is not possible to assess the effect of treatment on milder HAE attacks, which can also be debilitating for patients. Within the drug access program, the patients did not complete the AE-QoL (angioedema quality of life) questionnaire, so assessing the impact of treatment on patients' quality of life was not possible. Moreover, given the rarity of the condition, the sample size, though significant for such a study, is still limited.

CONCLUSION

Hereditary angioedema remains a significant clinical challenge, primarily due to the potential for severe and life-threatening attacks and the associated morbidity. Lanadelumab emerges as a promising therapeutic intervention, demonstrating a robust ability to reduce the number and severity of HAE attacks in a real-life setting. This study provides compelling evidence in favour of the drug's efficacy in these difficult-to-treat HAE patients.

Further longitudinal studies with larger sample sizes and spanning multiple geographic regions are warranted to validate these findings. Given the current evidence, clinicians should consider lanadelumab as a frontline prophylactic therapy for HAE, bearing in mind the criteria for eligibility and the patients' individual clinical profiles. The hope is that with improved awareness, timely diagnosis, and effective treatments like lanadelumab, the prognosis and quality of life for HAE patients can be significantly improved.

Conflict of interest

The authors report no financial or personal relationships with other individuals or organisations that could adversely affect the content of the publication and claim ownership of this publication.

Author contributions

Original concept of study: AK. Collection, recording and/or compilation of data: AK, KG, AJ, MK, KK, MŁ, TM, MP, RP, MSo, MStm MTŁ, ETP, MT, MZ, AZ. Analysis and interpretation of data: AK. Writing of manuscript: AK. Critical review of manuscript: GP, MR, MW, KJR. Final approval of manuscript: KJR.

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