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Abstract Book

1-P

Gene Sequencing of Angioedema with Normal C1-INH

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Rationale: Several new mutations co-segregating with individuals or families with a history of recurrent angioedema have been described in the last two decades, but the true prevalence of angioedema with normal C1-Inhibitor (HAE-nC1INH) is unknown. Factor 12 mutation (HAE-FXII) is the most commonly reported, albeit still extremely rare. Other endotypes associated with excessive bradykinin production (HAE-BK endotypes) are Plasminogen (HAE-PLN) and Kininogen-1 (HAE-KNG1) gene mutations. Mutations associated with intrinsic vascular-endothelium dysfunction (HAE-VE endotypes) include the Angiopoietin-1 (HAE-ANGPT1), Myoferlin (HAE-MYOF), and the Heparan sulfate-sulfotransferase (HAE-HS3ST6) mutations. Two new HAE-nC1INH mutations were just recently published. Apparently, variable family history and lack of specific biomarkers hamper these patients' correct diagnosis and management. Therefore, genetic evaluation is an unmet need for patients without a definitive diagnosis. We genotyped patients with clinical manifestations of recurrent angioedema with normal C1INH searching for the above mutations.

Methods: DNA was extracted manually from whole blood in patients with a history of recurrent angioedema, without hives, and with normal levels of C4, antigenic and functional C1INH. PCR was performed, and amplification was confirmed on agarose gel using primers of six known mutations. PCR products were then treated with Exo-SAP and Sanger-sequenced by a genetic analyzer.

Results: Sixty-one patients were analyzed (53 females, 8 males). Factor XII missense mutation [c.983C>A (p.Thr328Lys), NM_000505.4] was identified in 22 patients (diagnostic yield of 36%). All were females, and most of their attacks were related to exposure to estrogens. The mean age of this group was 41.7±13.6 years (range 19-65), and the mean age of onset was 19.7±4.6 years (range 7-29). Seventeen patients (77.3%) reported a positive family history of angioedema, accounting for ten patients from one family, two from two families, and one each from eight families (asymptomatic probands were not genotyped). The 38 yet-undiagnosed patients with HAE-nC1INH (30 Females, 8 Males), were tentatively assigned the AE-UNK diagnosis. None of the other five published mutations were expressed in this cohort.

Conclusions: Genetic analysis of a sub-population with recurrent angioedema and normal C4 and C1INH levels

discovered that 22 patients from 11 families could be classified as HAE-FXII.

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2-P

The Hereditary Angioedema (HAE) Attack Journey: A Conceptual Model of Patient Anxiety and On-Demand Treatment Burden During an HAE Attack

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Background: People with hereditary angioedema (HAE) experience a complex decision-making process during which anxiety can be associated with delays in on-demand treatment of HAE attacks.

Methods: The US Hereditary Angioedema Association recruited people with Type I or II HAE who had experienced 1 or more HAE attacks in their lifetime to complete a 20-minute, self-reported, online survey between September 6 and October 19, 2022. The survey investigated patient anxiety during attacks (on a numeric rating scale between 0-"not anxious" and 10-"extremely anxious") and factors influencing on-demand treatment of HAE attacks.

Results: Participants included 107 people with Type I or II HAE (80% female, mean age = 41 years). Respondents reported a mean (±SD) anxiety level of 4.2 (±3.4) on a 0 to 10 scale when anticipating the use of their current on-demand treatment and treated their HAE attack an average of 2.4 hours after recognizing the initial onset of the attack. Those who reported feeling extremely anxious (rating ≥7) when anticipating the use of on-demand treatment reported delaying treatment 4.3 hours (mean). Although respondents were able to recognize the initial onset of an attack, the majority (86%) chose to delay on-demand treatment administration. The most common reason respondents chose not to treat or delayed treating an attack was because they questioned whether the attack was severe enough to treat. Nearly all respondents (95%) reported that their level of anxiety decreases once they realize they are recovering from the HAE attack when asked "Do you agree with the following statement? My level

of anxiety decreases once I realize I am recovering from my HAE attack.

This survey, combined with previous insights from patients and healthcare providers, helped develop a conceptual model of the “HAE attack journey,” illustrating fluctuations in anxiety levels, starting with an increase at attack recognition, and subsiding with recovery.

Conclusions: Results from this survey show that some people with HAE have anxiety when anticipating parenteral on-demand treatment. People with HAE often delay administering on-demand treatment with longer treatment delays reported by those feeling moderately to extremely anxious. Anxiety is reduced when people realize they are beginning to recover from the attack.

3-P

Early Diagnosis of Hereditary Angioedema: A Key Point to Effective Management and Treatment

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Background: Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by recurrent, swelling due to C1 inhibitor deficiency. Children of affected patients face a 50% risk of inheriting the disease. Most patients are symptomatic during puberty, but clinical manifestations can occur during childhood. HAE might be triggered by trauma, medical procedures, stress, estrogens, and other drugs.

Case Report: A 5-year-old female with a known family history of HAE (mother, grandfather, and great-grandmother affected) presented to the emergency department (ED) with significant facial swelling following minor facial trauma. The patient had a previous history of recurrent episodes of abdominal pain without a clear cause and severe cutaneous swelling related to mosquito bites. Despite the positive family history and clinical manifestations suggestive of angioedema, the patient had not undergone prior diagnostic testing for HAE and an individualized treatment regimen had not been established.

Upon presentation to the ED, angioedema was not immediately recognized due to the lack of prior testing. However, the mother asked the ED physician to consult the angioedema specialist, given the clinical symptoms and family history. The specialist was available and after consultation the ED physician was more prone to recognize the swelling as an angioedema attack and to treat the attack *ex juvantibus* with intravenous plasma derived C1 inhibitor (pdC1INH). As the drug

was not available at the hospital, the grandfather provided the pdC1INH from home. The patient was then treated empirically with pdC1INH. Following the administration of pdC1INH the patient's facial swelling began to diminish noticeably. In the following days, the edema completely resolved, confirming the suspected diagnosis of HAE. No adverse reactions were reported after the treatment. After this acute episode, C1INH was measured and resulted below normal range. The patient was then diagnosed with HAE.

Conclusions: This case emphasizes the critical need for early diagnosis of HAE, especially in pediatric patients with a positive family history. Timely identification allows to establish appropriate management strategies. Enhanced awareness among healthcare providers regarding HAE and its familial patterns can lead to improve patient outcomes and prevent potentially severe complications associated with delayed or incorrect treatment.

4-P

Real Life (RL) Study of Efficacy and Safety of Long-Term Prophylaxis (LTP) with Lanadelumab in Patients with Angioedema Due to C1 Inhibitor Deficiency: Experience of a Referral Angioedema Centre

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Rationale: Angioedema with C1 inhibitor (C1-INH) deficiency is a rare pathology due to a congenital or acquired deficit of C1-INH. The disease is characterized by recurrent episodes of swelling of skin, gastrointestinal tract, or airways mucosa. Lanadelumab, a monoclonal antibody that inhibits plasma kallikrein, has been demonstrated to be a safe and effective LTP in reducing the attacks frequency. The aims of the study were to evaluate the safety and efficacy of Lanadelumab in real world setting, QoL, disease control, treatment satisfaction, and post-procedural attack in patients on Lanadelumab.

Methods: This retrospective, observational study analysed a cohort of 29 patients (26 with hereditary and 3 with acquired angioedema) from our referral Centre in Milan. Patients treated with Lanadelumab for at least 4 months were included. We collected data on AE and on frequency and severity of attacks. Questionnaires (AE-QoL, AECT, SGART) were used to evaluate QoL, disease

control, and treatment response. Post-procedural attacks were also reported.

Results: Follow up time was between 4 months and 7 years with a mean of 31,5 months. No severe AE were reported. No patient discontinued Lanadelumab for AE. 44,8% of the patients reported mild or transient AE: injection site reactions (31,0%), mild hyper-sensibility reactions (10,3%) and Myalgia (6,9%).

A significant reduction of the frequency of attack (P-Value<0,0001) after 1 year of Lanadelumab compared to baseline was found (78,5% mean attack reduction). The efficacy of LTP was sustained during follow up. 34,6% of patient were attack free for at least 10 months. No significant reduction in severity of attacks was found. Questionnaires resulted: AE-QoL mean was 29,9 (ranging from 17 to 85, lowest score means better QoL), AECT have shown in 93,1% of patients a controlled disease (>10pts), SGART mean was 3,41, with 93,1% of patients rating treatment response as good or excellent.

Lanadelumab showed a reduction of post-procedural attacks (p-value 0.014).

Conclusions: Our study confirms the safety and the efficacy of Lanadelumab with 10 months attack free period for over one-third of patients. AE-QoL, AECT and SGART demonstrated a high QoL, controlled disease, high treatment response in most of the patients. Lanadelumab LTP resulted protective from post-procedural attacks.

5-P

Hungarian Landscape of Long-Term Prophylaxis of Hereditary Angioedema Between 1979 and 2023

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Rationale: HAE-C1INH causes a significant emotional and physical burden for patients due to the unpredictability of HAE attacks. Therefore, one main goal of treatment is the prevention of these attacks. Attenuated androgens (e.g., danazol) and antifibrinolytics (e.g., tranexamic acid) were used to achieve this goal until recently, when modern medications, such as the replacement of C1INH or the kallikrein inhibitors (e.g., lanadelumab, berotralstat), were introduced. Since its establishment in 1979, the Hungarian Angioedema Center has been

regularly following up on Hungarian HAE-C1INH patients, keeping detailed records of their medications. Our aim was to analyze the types of long-term prophylactic (LTP) medications used in the Hungarian patient population throughout the years.

Methods: We collected data entered between 1979 and 2023 into the prospective registry of Hungarian HAE-C1INH patients. We analyzed the demographic parameters and the medications used for LTP.

Results: Altogether, 209 patients (114 female, 95 male) were followed up for a median of 17 years. The median age of patients was 22 years at diagnosis and 40 years at the last control visit in 2023. Until 1984, no LTP was used. Between the early 2000s and 2023, the proportion of patients receiving danazol gradually decreased from 60.5% to 13.6%, parallel to the gradual increase in the proportion of patients not receiving LTP from 15.1% to 72.7%. Meanwhile, tranexamic acid LTP usage shrank from 12.7% to 0.6%. Since 1999, twelve patients received off-label intravenous C1INH prophylaxis for some months (eight patients for pregnancy and/or breastfeeding and four patients because of their otherwise uncontrollable disease). Since 2014, eleven patients received LTP (subcutaneous C1INH, berotralstat, lanadelumab, or garadacimab) in the context of clinical trials. One patient still receives berotralstat as a post-trial access. In 2022, we introduced subcutaneous C1INH in four and lanadelumab in eight patients. In 2023, 13.6% of patients received danazol, 0.6% received tranexamic acid, 13.1% received modern LTP, and 72.7% received on-demand treatment only.

Conclusions: While in the early days most Hungarian HAE-C1INH patients received danazol or tranexamic acid for LTP, modern LTP options are gaining ground. The number of patients who can be managed only with on-demand treatment has also been increasing.

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Experiences with Oral Long-Term Prophylactic Treatment Among Patients with Hereditary Angioedema Participating in an Online Discussion and Survey

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Rationale: There are several approved first-line

therapies for long-term prophylaxis (LTP) for patients with hereditary angioedema (HAE). These therapies are administered orally, by intravenous infusion, or subcutaneous injection. This study aimed to understand patients' experience with and ease of using oral LTP for HAE.

Methods: Patients with HAE in the United States (US) were recruited to participate in an online discussion and survey about their experiences with berotralstat and other medications. Screening questions were administered before participation to ensure eligibility. Patients were eligible to participate if they resided in the US, were 18 years or older, had been diagnosed with HAE (any type) by a healthcare professional, and were currently taking berotralstat (oral medication) for LTP. Participants provided consent for their data to be used anonymously or in aggregate. The study was approved by WCG Institutional Review Board.

Results: Sixty-one patients answered questions about their medication routines. Most patients (79%) reported taking at least one concomitant non-HAE medication; all of these patients (100%) took at least one oral medication, and two-thirds of these patients took 3 or more concomitant medications. When asked about the ease or difficulty of following their overall medication regimen (including berotralstat) as prescribed, patients provided a mean rating of 5.9 on a 7-point Likert scale (1 being extremely difficult to 7 being extremely easy). Most patients reported having a routine for taking berotralstat, often taking it at a specific time of day, with other medications, or in conjunction with another daily activity. Participants were also asked to rate their agreement with statements about berotralstat (n=59) and prior LTP (n=34). None reported that storing or preparing their berotralstat was inconvenient (somewhat or strongly agreed). A few (7%) found their berotralstat inconvenient to administer. Conversely, the majority (59% and 53%) of patients agreed that their prior LTP was inconvenient to store/prepare or administer, respectively.

Conclusions: Patients with HAE taking berotralstat find it easy to take the medication every day. Berotralstat fits into their daily routine and is more convenient to store and administer than their prior LTP.

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7-P

Melkersson-Rosenthal Syndrome: A Case Report of Antihistamine-Refractory Orofacial Angioedema

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Background: In patients with angioedema (AE) unresponsive to antihistamines, identifying the underlying cause is crucial. Differential diagnoses mainly include AE-endotypes: Mast cell-mediated, Bradykinin-mediated, AE due to intrinsic vascular endothelium dysfunction, and AE-subtypes: Drug-induced, and AE of unknown cause.

Melkersson-Rosenthal syndrome (MRS) is characterized by a triad of symptoms including recurrent orofacial swelling (especially of the lips), facial paralysis, and a fissured tongue. The syndrome's exact etiology remains elusive, contributing to diagnostic complexities and varying management approaches across reported cases.

Case Report: We present the case of a 36-year-old woman with an 11-year history of lip and facial swelling. Recently, she developed swelling in both upper and lower lips, along with unilateral cheek swelling, cheek numbness, and recurrent painless facial paralysis. Increased doses of Antihistamine treatment proved ineffective. In the medical history, in addition to the edema, she also reported mild, recurrent paralysis of the right eye, totaling three episodes of exacerbation, initially diagnosed as trigeminal neuralgia. Examination revealed a fissured tongue similar to her sister's tongue geography. Diagnostic workup, including clinical lab tests, determination of IgE levels, and screening for antibodies against anti-nuclear antibodies (IFA), all returned normal results. The patient's clinical presentation and history led to a diagnosis of Melkersson-Rosenthal syndrome (MRS), subsequently confirmed by a neurologist. Frequently conditions such as Bell's palsy, Sarcoidosis, Crohn's disease, Cheilitis, Orofacial, and Wegener's Granulomatosis, Allergic reactions can mimic the symptoms of MRS. Patients with MRS may not present with all three classic symptoms simultaneously. Symptoms of MRS are often episodic and may resolve spontaneously between episodes, leading to an underestimation of the frequency and severity of the condition. Diagnosis is primarily clinical. A biopsy showing granulomatous inflammation can support the diagnosis of MRS but is not definitive, as similar findings can be present in other granulomatous conditions. Treatment focuses on symptom relief and improving quality of life through anti-inflammatory therapies targeting neurological manifestations.

Conclusion: In this case, systemic oral corticosteroids effectively relieved symptoms. Long-term management

under neurologic supervision is essential. Despite advances, further research is necessary to elucidate the underlying mechanisms and develop tailored therapeutic strategies for this rare neuroinflammatory disorder.

8-P

Significant Improvement in Angioedema for Patients with Chronic Spontaneous Urticaria (CSU) Treated with Barzolvolimab: Results from a Phase 2 Trial

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Rationale: Mast cells (MC) are key effector cells that drive the development of wheals and angioedema in chronic spontaneous urticaria (CSU). Barzolvolimab (an anti-KIT monoclonal antibody that depletes MCs) demonstrated encouraging clinical activity in a Phase 1b CSU study. In this ongoing 52-week, Phase 2 study in patients with antihistamine refractory CSU, barzolvolimab demonstrated clinically meaningful, statistically significant improvement in urticaria activity score 7 (UAS7) and was well-tolerated. Here we describe the effects of barzolvolimab through Week 12 on angioedema in this study (NCT05368285).

Method: This ongoing, double-blind, placebo-controlled trial randomized patients to receive barzolvolimab subcutaneously at 75mg Q4W, 150mg Q4W, 300mg Q8W or placebo during a 16-week placebo-controlled treatment phase followed by 36-weeks of active treatment, and 24-weeks of follow-up. The primary endpoint is mean change from baseline in UAS7 at Week 12. Key secondary and exploratory clinical endpoints include change from baseline (BL) for angioedema activity score over 7 days (AAS7) and angioedema-free days (AFD).

Results: Of the 208 patients enrolled, 149 patients had AAS7>0 at BL. The BL mean [Standard Deviation (SD)] AAS7 was 54.1 (24.7), 54.6 (27.8), 53.2 (28.9), and 56.3 (30.3) for 75mg, 150mg, 300mg, and placebo, respectively.

At Week 12, the Least Square mean [Standard Error (SE)] change in AAS7 from BL for this subgroup was -33.6 (3.7) (P=0.0039), -39.6 (3.9) (P<0.0001), -41.4 (3.6)

(P<0.0001) for the 75mg, 150mg, and 300mg arms respectively vs -16.0 (4.4) for placebo. Proportion of patients with an improvement of ≥ 8 points in AAS7 compared to BL was 82.9%, 87.1%, 85.0% and 57.1% for the 75mg, 150mg, 300mg and placebo, respectively. Mean (SD) of AFD from start of treatment to Week 12 for all treated patients was 54.1 (29.1), 64.1 (24.9), 68.8 (21.2), and 56.3 (33.1) days for 75mg, 150mg, 300mg and placebo, respectively.

Conclusions: The barzolvolimab Phase 2 study in patients with antihistamine refractory CSU met its primary endpoint of improvement in UAS7 at Week 12 and demonstrated statistically significant and clinically meaningful improvement in CSU symptoms, including angioedema. These results combined with a favorable safety profile warrant further development of barzolvolimab in CSU.

9-O&P

Long-Term Safety and Efficacy of Oral Deucricitbant, a Bradykinin B2 Receptor Antagonist, for Prophylaxis in Hereditary Angioedema: Results of the CHAPTER-1 Open-Label Extension Study

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Rationale: Deucricitbant is a selective, orally-administered antagonist of the bradykinin B2 receptor under development for on-demand and prophylactic treatment of hereditary angioedema (HAE) attacks. CHAPTER-1 (NCT05047185) is a 2-part Phase 2 study evaluating the efficacy and safety of deucricitbant for long-term prophylaxis of HAE attacks. In the double-blind, placebo-controlled part 1 (N=34 enrolled), the monthly attack rate was reduced by 84.5% (P=0.0008) in participants receiving deucricitbant 40mg/day (immediate-release capsule formulation; least squares mean [LSM]: 0.30; 95% CI: 0.11, 0.82) for 12 weeks vs placebo (1.94; 1.31, 2.87). In the ongoing part 2, participants receive open-label treatment with deucricitbant 40mg/day for long-term safety and efficacy assessments.

Methods: Eligible participants were aged ≥ 18 and ≤ 75 years, diagnosed with HAE-1/2, not receiving other prophylactic treatments at screening, and experienced ≥ 3 attacks within 3 months prior to screening or ≥ 2 attacks during screening (up to 8 weeks). All 30 participants who completed the double-blind placebo-controlled part 1 after randomizing into treatment groups with deucricitbant 20mg/day (N=11) or 40mg/day (N=10) or with placebo (N=9), enrolled into the ongoing part 2.

Results: This part 2 data snapshot (cut-off: June 2024) included 30 participants with a mean exposure to deucricitbant 40mg/day of longer than 12 months (up to a maximum of approximately 20 months). Mean age was 39.1 years at CHAPTER-1 part 1 randomization; 60.0% were female. Treatment with deucricitbant was well-tolerated, with no TEAEs leading to treatment discontinuation. The median monthly rate of "all" and "moderate and severe" investigator-confirmed attacks with deucricitbant 40mg/day in part 2 was 0.00 and 0.00, respectively.

Conclusions: Results of the ongoing CHAPTER-1 open-label extension study provide evidence on the long-term safety and efficacy of deucricitbant for prevention of HAE attacks.

10-P

Clinical Characteristics and the Burden of Disease of the Croatian Adult Patients with HAE – Nationwide Survey Analysis

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Rationale: Hereditary angioedema (HAE) is a rare disease characterized by unpredictable attacks of soft tissue swelling caused by the excessive production of bradykinin. Due to the nature of the disease, the majority of patients experience some kind of quality of life impairment and high burden of disease. According to the statistics, Croatia, a country of 3.8 million people, should have around 80 patients with HAE. Although the precise number is unknown, we assume the number is higher. The aim of our research was to analyse the epidemiological and clinical characteristics of HAE in Croatia and the effect of the disease on quality of life.

Methods: We conducted a nationwide survey analysis on adult (18+) HAE patients with the goal of collecting the demographics, epidemiological and clinical characteristics, severity of HAE and the treatment modalities. The patients filled out different HAE related questionnaires: general data, AECT, AE-QoL, FACIT-FATIGUE, SF36, EQ-5D-5L, WPAI:GH, Beck's Depression and Anxiety Inventory. We used descriptive statistics to analyse and summarize the data. The study was conducted before the first-line long-term prophylactic treatment with lanadelumab and berotralstat for HAE was available in Croatia. The patients requiring long-term prophylactic treatment were treated with second-line long-term prophylactic drugs.

Results: All patients included in the nationwide survey have an access to HAE expert, on demand, short- and long-term prophylactic treatment depending on the severity of HAE and according to the availability of the HAE drugs in Croatia. The majority reported high treatment satisfaction; an equal percentage reported a fear of dysfunctional social life and losing job security, death anxiety and passing the disease to their children. Patients with moderate to severe phenotype of HAE have an intermediate to high burden of disease and impaired quality of life. All patients are familiar with the existence of Croatian HAE patient organisation and the majority of them are members.

Conclusions: Patients with moderate to severe phenotype of HAE have some unmet needs which should be discussed on follow-up visits with their HAE experts. Different kinds of treatment strategies should

be applied for different phenotypes of HAE patients to minimize the burden of disease.

Acknowledgments: Special acknowledgments and thanks to the president and members of the Croatian patient organisation HAE Croatia for participating in the nationwide survey, which led to this research.

11-P

Laryngeal Involvement in the Absence of Specific Treatments: A Study of 20 Tunisian Patients with Hereditary Angioedema

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Rationale: Upper airway edema is a rare but a serious complication of hereditary angioedema (HAE). It is often associated with significant morbidity and mortality in the absence of targeted therapies.

This study aims to evaluate the clinical characteristics of patients with upper airway edema (UAE) among those with HAE and to assess the efficacy of fresh frozen plasma (FFP) transfusion when targeted treatments are unavailable.

Methods: We conducted a retrospective study involving symptomatic HAE patients.

Data were extracted from the medical records at the Department of Internal Medicine B, Charles Nicolle Hospital.

Results: Among 50 patients diagnosed with type I HAE, at least one instance of UAE was observed in 20 cases. Most patients were female (70%). The most common symptoms were dysphonia (75%), dysphagia (75%), and dyspnea (60%). Diagnosis delay in patients with UAE attacks was 22.5 years on average. Reported triggers of UAE attacks were stress, dental treatment, scraping and infection. Fourteen patients (70%) received FFP transfusion, resulting in significant improvement within an average of 9.25 hours. However, four patients required emergency tracheotomy, and three deaths were attributed to treatment delay.

Conclusion: Symptoms isolated to the upper airway in HAE warrant urgent attention due to rapid progression and potential life-threatening outcomes. FFP transfusion is controversial due to delayed responses and associated side effects. However, it remains as the silver lining of patients in the absence of targeted therapies.

12-P

Genetic Characterization of Hereditary Angioedema Type 1 in a Tunisian Cohort

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Rationale: Hereditary angioedema type 1 is a rare, life threatening genetic disease with

autosomal dominant transmission leading to spontaneous edema of the submucosal and subcutaneous layers. It is caused by variants in the SERPING1 gene. We aimed to study the genetic spectrum of HAE type 1 in a Tunisian cohort.

Methods: We conducted a genetic study by sanger sequencing exons 3, 4, 5, 6,

7, and 8 of the SERPING1 gene in 14 patients (P1 to P14) from 11 families (F1 to F11). These patients were referred to the Department of Congenital and Hereditary Diseases at Charles Nicolle Hospital for molecular diagnosis of Hereditary Angioedema type 1.

Results: We established the molecular diagnosis in eight patients from five families

(F2, F3, F6, F7, F9) by identifying five pathogenic variants, four of which were previously described in the literature.

These four variants were: the c.889+1G>T p. ? identified in three individuals from F3, the c.816_818del (p.Asn272del) found in two patients from F9, the c.120_121del (p.Gly41Argfs*16) (F2) and the c.666_667del (p.Gln223Aspfs*33) (F7).

Additionally, a novel pathogenic variant was revealed : the c.169G>T (p.Glu57*) in F6.

All these mutations are predicted to cause significant changes in the protein structure, leading to decreased activity which explains our patient's phenotype.

Conclusions: We have confirmed the diagnosis of Hereditary Angioedema type 1 in five families, enabling precise genetic counseling and cascade screening. Our results emphasize the genetic heterogeneity of HAE type 1 and the importance of comprehensive genetic characterization for optimal disease management.

13-P

Impact of Delayed Treatment of Hereditary Angioedema Attacks on Quality of Life and Ability to Work

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Rationale: HAE guidelines recommend early on-demand treatment following recognition of an attack to limit disease morbidity and mortality. We examined the impact of the time to on-demand treatment on patients' quality of life (QoL) and ability to work.

Methods: People with HAE Type 1 or Type 2 were recruited through HAE UK to complete a 20-minute, self-reported, online survey between April and May 2023. Participants ≥ 12 years old, with ≥ 1 treated HAE attack using an approved parenteral on-demand therapy within 3 months prior to the survey, were included. The EuroQol Five-Dimensions Five-Level (EQ-5D-5L) assessed physical and mental QoL and a modified Hereditary Angioedema Quality of Life Questionnaire assessed physical and social QoL. A modified Work Productivity and Activity Impairment Questionnaire: General Health assessed participants' ability to work during seven days from attack start.

Results: Respondents included 46 adults with HAE (100% Type I), 54% of whom were receiving long-term prophylaxis at the time of their last treated attack. Most patients considered their attacks moderately severe (59%) or severe/very severe (28%). The median (interquartile range) reported time to treatment from attack onset to on-demand treatment was 2 (1-5) hours, with only 9% treating in < 1 hour. During the attack, mean EQ-5D-5L index score was 0.81 for patients who treated their attack in < 1 hour and between 0.44 (1- < 2 hours) to 0.24 (≥ 8 hours) for those who treated ≥ 1 hour. No participants who treated their attack in < 1 hour reported a severe impact on energy, sleep or activity level (based on HAE-QoL) compared to 48%, 17%, and 45% of participants, respectively, who treated in ≥ 1 hour. Among working participants (n=30), the average overall work impairment was 10% for those who treated in < 1 hour, and between 34% (5- < 8 hours) and 59% (≥ 8 hours) for all other participants.

Conclusions: Nearly all participants waited an hour or longer to treat their attacks. QoL and work productivity were worse for those who delayed treatment. Our findings highlight the need for more education on treating at the earliest recognition of an attack as recommended by clinical guidelines and proactively addressing barriers that contribute to treatment delays.

14-P

Impact of Hereditary Angioedema Attacks on Quality of Life and Ability to Work Among UK Patients Receiving Long-term Prophylaxis or On-demand Treatment Only

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Rationale: While long-term prophylaxis (LTP) has been shown to reduce the frequency of hereditary angioedema (HAE) attacks, the burden of these attacks and their impact on quality of life (QoL) have not been previously described. This analysis describes the ramifications of HAE attacks on QoL and ability to work in patients receiving on-demand therapy only or on-demand therapy plus LTP.

Methods: People with HAE Type 1 or Type 2 were recruited through HAE UK to complete a 20-minute, self-reported, online survey between April and May 2023. Participants ≥ 12 years old, with ≥ 1 HAE-treated attack using an approved parenteral on-demand therapy within 3 months prior to the survey, were included. QoL during last treated attack was assessed using modified EuroQol Five-Dimensions Five-Level (EQ-5D-5L) and Hereditary Angioedema Quality of Life Questionnaires (HAE-QoL). A modified Work Productivity and Activity Impairment Questionnaire: General Health assessed participants' ability to work during 7 days from attack start.

Results: Respondents included 46 adults, with 54% receiving LTP at the time of their most recent treated attack (plasma-derived C1 inhibitor: 40%, lanadelumab: 24%, berotralstat: 12%, danazol: 12%, tranexamic acid: 12%). Fifty-nine percent of patients considered their attacks moderately severe and 28% severe/very severe. EQ-5D-5L index scores were meaningfully lower

(minimal important difference: 0.08) during the attack (on-demand treatment only, mean [standard deviation] = 0.46[0.3]; on-demand + LTP, 0.43[0.4]) compared to current scores (on-demand only, 0.88[0.2]; on-demand + LTP, 0.75[0.3]). Thirty-three percent of participants receiving on-demand treatment only and 52% receiving on-demand + LTP reported severe impact on energy levels, with over 40% in both groups reporting severe impact on activity levels. Feeling socially isolated was reported by 65% of respondents (48% on-demand only; 80% on-demand + LTP) and feeling like a burden to people around them was reported by 44% (38% on-demand only; 48% on-demand + LTP). Among working participants (n=30), average overall work impairment was 44% (44% on-demand only; 46% on-demand + LTP). **Conclusions:** Patients receiving parental on-demand treatment only and those receiving parental on-demand treatment plus LTP experienced substantial burden during their last treated HAE attack, in terms of physical, mental, and social QoL, as well as work productivity.

15-P

Design of RAPIDe-3 Phase 3 Trial: Efficacy and Safety of the Oral Bradykinin B2 Receptor Antagonist Deucricitbant Immediate-Release Capsule in Treatment of Hereditary Angioedema Attacks

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Rationale: Hereditary angioedema (HAE) attacks are caused by excess bradykinin activating bradykinin B2 receptors. Deucricitbant is a potent, selective, orally administered antagonist of bradykinin B2 receptor under development for on-demand and prophylactic treatment of HAE attacks. In the RAPIDe-1 Phase 2 trial (NCT04618211), treatment with deucricitbant immediate-release (IR) capsule resulted in rapid onset of action and reduced time to substantial symptom relief and resolution of HAE attacks; treatment was well-tolerated.

Methods: RAPIDe-3 (NCT06343779) is a Phase 3 global, ongoing, randomized, crossover, double-blind, placebo-controlled trial of oral deucricitbant IR capsule for on-demand treatment of HAE attacks. The study is being conducted in approximately 30 countries. Participants are ≥ 12 – ≤ 75 years old, diagnosed with HAE-1/2, and had ≥ 2 HAE attacks in the three months before screening. Patients on long-term HAE prophylaxis are included.

Results: During the treatment phase, participants self-administer double-blinded study drug (deucricitbant IR capsule 20 mg or placebo, in a crossover fashion) to treat two qualifying attacks. Randomization is stratified according to age (≥ 12 to < 18 years, ≥ 18 years) and use of long-term prophylaxis (Yes/No). The primary objective of RAPIDe-3 is to evaluate the efficacy of deucricitbant IR capsule as an on-demand treatment on the onset of symptom relief during HAE attacks. The primary endpoint is time to onset of symptom relief, defined as a Patient Global Impression of Change (PGI-C) rating of at least “a little better” for two consecutive timepoints within 12 hours post-treatment. Secondary endpoints include assessments of end of progression of attack symptoms, substantial symptom relief, and symptom resolution as defined by PGI-C, Patient Global Impression of Severity (PGI-S), and Angioedema symptom Rating scale (AMRA), as well as use of rescue medication. Safety outcome measures include treatment-emergent adverse events (TEAEs); serious TEAEs; and changes in clinical laboratory tests, ECG, and vital signs. After RAPIDe-3 completion, participants can elect to continue deucricitbant IR capsule treatment in an open-label extension.

Conclusion: RAPIDe-3 is a global Phase 3 study designed to evaluate the efficacy and safety of oral deucricitbant IR capsule for treatment of attacks in adolescents and adults with HAE.

16-P

Integrated Safety and Efficacy of Garadacimab for Hereditary Angioedema Prophylaxis Across 3 Clinical trials: Phase 2, Pivotal Phase 3, and Open-Label Extension Studies

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Rationale: Hereditary angioedema (HAE) attacks are unpredictable and debilitating. We report integrated safety and efficacy across Phase 2, pivotal Phase 3, and open-label extension (OLE) studies evaluating garadacimab (anti-activated factor XII monoclonal antibody) for HAE prophylaxis.

Methods: Subcutaneous garadacimab was evaluated in an integrated analysis comprising Phase 2 (12-week placebo-controlled period with subsequent open-label period; 75/200/600 mg once-monthly or 400 mg once every 2 weeks), pivotal Phase 3 (6-month placebo-controlled period), and >12-month OLE studies (both 200 mg once-monthly). Endpoints included treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs), per protocol: thromboembolic/abnormal bleeding events, severe hypersensitivity/anaphylaxis) and efficacy.

Results: Overall, 172 patients received garadacimab (any dose; median [range] exposure 1.3 [0.2–4.2] years; 83.1% and 19.2% had ≥ 1 and ≥ 2 years' exposure, respectively). Of these, 148/172 (86%) experienced ≥ 1 TEAE (97.6% mild/moderate), an exposure-adjusted rate of 3.1 TEAE/patient-year. Seven patients experienced SAEs, none garadacimab-related. One AESI per protocol was experienced by 1 patient (Phase 2, 600 mg, epistaxis, not garadacimab-related). The most common garadacimab-related TEAEs were mild/moderate injection-site reactions.

Per integrated efficacy set, the mean (standard deviation) monthly attack rate in garadacimab 200 mg-treated patients (n=164) was 0.17 (0.40) versus 3.55 (2.40)

during run-in, corresponding to a 94.2% reduction. Over a median 1.2 years' observation, the majority of garadacimab-treated patients (94/164, 57.3%) remained attack-free. No placebo-receiving patients (n=25) were attack-free.

Conclusion: These data further corroborate the robust garadacimab efficacy over >1 year for long-term HAE prophylaxis along with the favorable and consistent safety profile so far observed.

17-O&P

Prediction of Hereditary Angioedema During Attacks in Patients with Recurrent Angioedema: Awareness at a Glance with the Hereditary Angioedema Prediction Score (HAEps)

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Rationale: Misdiagnosis of hereditary angioedema (HAE) resulted in inappropriate management of the patients in the emergency room (ER). A scoring system which anticipates the possible diagnosis of HAE can be beneficial for the physicians working in ER. Therefore, we aimed to develop a practical scoring system for the prediction of HAE in patients with recurrent angioedema (RAE) during acute attacks.

Method: Nine experts on HAE unanimously determined five predictive items (PIs) comprising absence of urticaria, presence of abdominal pain episodes and family history, early onset of attacks (before 18 years of age) and unresponsiveness to antihistaminergic treatments previously for the HAE depending on the literature to be included in the HAEps. 106 patients with HAE and 155 patients with non-HAE were questioned and their medical records were reviewed. A score was attributed to each significant PI according to OR value obtained in logistic regression analysis. Then, the cut-off point for the prediction of HAE and its sensitivity and specificity were determined with the ROC curve analysis.

Results: The median age of the patients was 41.5 (IQR=29-51) years and 65.8% of them were female. All items were significantly different between patients with HAE and non-HAE in univariate analysis. According to regression analysis, 23, 11, 9 and 53 points were

attributed to absence of urticaria, presence of abdominal pain episodes and family history and unresponsiveness to antihistaminergic treatments, respectively. No score was attributed to early onset of age ($p > 0.05$). In the ROC analysis the area under curve was 0.990 and a total score of ≥ 27 showed the best sensitivity (97.6%) and specificity (93.5%).

Conclusion: In this study we developed a predictive scoring system (HAEps) for the diagnosis of HAE in patients with RAE in ER. Equal or more than 27 points indicated the presence of HAE with a substantial sensitivity and specificity. Our findings should be validated with a comprehensive multicenter study and we believe that if HAEps will be very practical and useful if it's adapted to artificial intelligent.

18-P

HAE with Factor XII Mutation: More Common in Some Countries?

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Rationale: Hereditary Angioedema (HAE) is an underdiagnosed genetic disease, with autosomal dominant inheritance, incomplete penetrance and highly variable clinical expression. Although HAE with normal C1 inhibitor (HAEnC1-INH) is less frequent than HAE with C1INH deficiency, there is a significant prevalence of the former in some countries, especially for FXII mutation. We aimed to describe HAE genetic diagnosis and clinical-demographic features in patients with HAEnC1-INH followed up at a single tertiary-level center in Rio de Janeiro, Brazil.

Method: A descriptive, cross-sectional study with prospective data collection of 138 Brazilian patients with HAE was performed. From the total, 31 patients with HAEnC1-INH were selected. Data were assessed based on a specific questionnaire.

Results: Of 138 patients evaluated with HAE, thirty-one (22.5%) had HAEnC1-INH, from 6 unrelated families. The FXII mutation (exon 9 - Thr328Lys mutation, in heterozygosity, previously described), was found in all of them. Twenty-five of the 31 patients were female (80.6%) and six were male (19.4%). Mean age was 42.4 ± 16.4 years (range: 13-77 years). All of them had a familial history. There was a long delay (15.0 ± 13.7

years) between the onset of symptoms and diagnosis. Eight (25.8%) were asymptomatic and 19 patients (61,3%) had moderate to severe HAE attacks. There was a tendency for lip swelling (77%) to be more frequent in our series.

Conclusions: A long time between the first symptoms and the diagnosis of HAE was seen in our study, despite the presence of familial history, highlighting the importance of reinforcing the clinical criteria for the diagnosis of HAE, especially in the group of HAEnC1-INH. An important proportion of HAE-FXII patients (22,5%) were diagnosed, pointing to the possibility that, perhaps, HAE-FXII is more prevalent in our country. Screening family members, including asymptomatic ones, is essential for early diagnosis and better management, reducing the morbidity and mortality of HAE and improving the quality of life of patients and their families.

19-P

Efficacy of Attenuated Androgens in the Long-Term Prophylaxis of Hereditary Angioedema

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Rationale: Hereditary angioedema (HAE) is a rare genetic disorder characterized by episodes of subcutaneous and mucosal edema. Attenuated androgens have been used for over four decades to treat HAE. However, there have been significant advances in HAE treatment with the emergence of new medications. In developing countries, limited access to these medications means the use of androgens remains prevalent. This study aims to evaluate the long-term effectiveness and safety of prophylaxis with attenuated androgens over the past three years in an ACARE center in Brazil.

Methods: Fifteen patients with HAE from the Division of Allergy, Clinic Immunology and Rheumatology of the Federal University of São Paulo were selected. Seven patients were excluded: four due to loss of follow-up, two due to not undergoing long-term prophylaxis, and one due to the use of tranexamic acid. A retrospective analysis was conducted, collecting data on the number of HAE attacks before and during the past three years of using long-term prophylaxis, as well as treatment-related side effects.

Results: Of the eight patients included, all had HAE with C1 inhibitor deficiency (type 1). The maximum time between symptom onset and diagnosis was 23 years, with a median of 13 years. At the beginning of follow-

up, 25% (n=2) of patients had weekly attacks, 50% (n=4) had monthly attacks, and 25% (n=2) had attacks every three months, with frequent visits to the emergency room. After starting attenuated androgens, the average number of HAE attacks per year was 1.25, with a median of 1 (range 0-4 attacks/year). The severity of attacks was also reduced, with only three episodes requiring emergency room visits and no hospitalizations. No patients discontinued the medication due to side effects.

Conclusions: Although attenuated androgens are not the first-line treatment for HAE, they can be an option for patients with frequent HAE attacks where first-line medications are not yet available, as they reduce the frequency and severity of angioedema. The treatment of HAE should be individualized, using the minimum effective dose of medication and monitoring side effects.

O-20

Recapitulating Hereditary Angioedema Using a Personalized Expanded Potential Stem Cell (EPSC) Platform: Demonstrating C1-Inhibitor Retention and Signals of Liver Disease Among Hepatocytes Differentiated from Patient-Derived EPSC

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Rationale: The majority of hereditary angioedema (HAE) is caused by deficiency or dysfunction of C1-esterase inhibitor (C1-INH), caused by mutations of *SERPING1* – of which is predominantly expressed in hepatocytes. The exact pathomechanism of *SERPING1* mutations have not been fully elucidated, and previous studies have primarily focused only on circulating C1-INH. There has been increasing evidence demonstrating HAE to be more of a metabolic liver disorder, but studies on patient hepatocytes have been limited by difficulty to acquire relevant samples. In this study, we utilized our expanded stem cell (EPSC) platform to derive hepatocytes differentiated from individual HAE patients. Using this personalized disease model, we explored the pathomechanisms of *SERPING1* dysfunction of different type I and II HAE patients.

Methods: By using our well-established reprogramming platform, EPSCs from 5 unique HAE patients with different type I or type II HAE mutations were established and differentiated into patient-specific hepatocytes. Disease and individual-specific features were investigated on EPSC-derived hepatocytes.

Results: Patient EPSCs showed comparable pluripotency and trilineage differentiation capability as healthy controls. All EPSCs were able to be further differentiated

into hepatocytes which showed typical polygonal and binuclear hepatic characteristics and expressed critical hepatocyte markers, including *ALB*, *AFP*, *AIAT*, *ASGR1* and *HNFB4a*.

Patient EPSC-derived hepatocytes showed morphological abnormalities compared to controls, including ballooning, displaced nuclei, lipid deposition, and other apoptosis-like features. Hepatocytes from type I HAE patients demonstrated <50% expression of *SERPING1* at both RNA and protein levels, while those from type II HAE patients showed equal expression, compared to controls. Furthermore, patient-derived hepatocytes demonstrated retention of C1-INH within the cytoplasm, significantly more in type II than type I patients. Furthermore, bulk RNA sequencing showed patient-derived hepatocytes to significantly upregulate collagen-containing extracellular matrix and zinc finger protein (ZFP41), common hallmarks of chronic liver disease and hepatocellular carcinoma.

Conclusions: Our patient-derived EPSC platform was able to recapitulate and personalize disease models from individual HAE patients. EPSC-derived hepatocytes were able to accurately model *SERPING1* dysfunction and confirm that HAE is indeed a metabolic liver disorder – with hepatocytes demonstrating retention of C1-INH in their cytoplasm and expression of RNA markers typical of chronic liver disease.

21-P

Phase 3 KONFIDENT Trial of Oral Sebetralstat for Treatment of Hereditary Angioedema Attacks: Analysis of the European and US Patient Subgroups

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Rationale: KONFIDENT, an international, randomized, double-blind, placebo-controlled, 3-way crossover, phase 3 trial (NCT05259917) of an oral plasma kallikrein inhibitor, sebetralstat, for on-demand treatment of

hereditary angioedema (HAE-C1INH), met the primary endpoint (NCT04208412). In this analysis, we assessed the efficacy and safety of sebetralstat in the two largest geographic subgroups, European and US.

Methods: Participants aged ≥ 12 years with HAE-C1INH treated up to 3 eligible attacks (any location) with 1 or 2 doses of sebetralstat 300 mg, sebetralstat 600 mg, or placebo (in 1 of 6 treatment sequences). Primary endpoint: time to beginning of symptom relief (Patient Global Impression of Change rating of at least "A Little Better" for 2 time points in a row) within 12 hours of first study drug administration. Safety was assessed primarily through collection of adverse events.

Results: Overall, 110 participants from 17 countries treated 264 attacks. In the European subgroup, 58 participants (median age 40.0 years; 48% female; 86% White; median BMI 25.4; 95% HAE-C1INH-Type 1; 7% receiving long-term prophylaxis) treated 141 attacks. In the US subgroup, 34 participants (median age 39.5 years; 79% female; 91.2% White; median BMI 29.3; 82% HAE-C1INH-Type 1; 47% receiving long-term prophylaxis) treated 78 attacks. Mucosal attacks, (abdomen or larynx) occurred in 40% and 55% of European and US participants, respectively. In the European subgroup, 25% of attacks were severe/very severe, compared to 10% in the US subgroup. Median (interquartile range [IQR]) time from attack onset to treatment was 48 minutes (6-205) for European participants and 38 minutes (5-124) for US participants. Median (IQR) time to beginning of symptom relief for European and US subgroups, respectively were: 1.8 hours (1.0-9.3) and 1.3 hours (0.8-3.1) with sebetralstat 300 mg; 1.8 hours (1.0-3.3) and 1.8 hours (1.3-3.9) with sebetralstat 600 mg, and 5.5 hours (1.3->12) and 6.2 hours (2.3->12) with placebo. No serious treatment-related AEs and no AEs leading to trial discontinuation were reported in either subgroup.

Conclusions: While certain demographic factors, such as BMI, HAE-type, and prophylaxis use and attack characteristics including, location and severity, differed between the European and US subgroups, the efficacy and safety of sebetralstat were similar.

22-P

Prophylactic Treatment with Oral Deucricitbant Improves Health-Related Quality of Life of Patients with Hereditary Angioedema

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Rationale: Hereditary angioedema (HAE) attacks are caused by excess bradykinin activating bradykinin B2 receptors. Deucricitbant is a potent, selective, orally administered antagonist of the bradykinin B2 receptor under development for on-demand and prophylactic treatment of HAE attacks.

Methods: CHAPTER-1 (NCT05047185) is a two-part Phase 2 study evaluating the efficacy and safety of deucricitbant for long-term prophylaxis of HAE attacks. In part 1, participants received double-blind treatment with placebo or deucricitbant 20 mg/day or 40 mg/day (immediate-release capsule formulation) for 12 weeks. In the ongoing part 2, participants have the opportunity to continue treatment with open-label deucricitbant 40 mg/day. Thirty-four participants were enrolled across Europe, the United Kingdom, and North America. Health-related quality of life (HRQoL) was assessed using pre-defined endpoints: Patient Global Assessment of Change (PGA-Change), which measures change in how the participant's HRQoL has been impacted by their HAE since starting study treatment; and the Angioedema QoL questionnaire (AE-QoL), a tool developed for recurrent angioedema and validated in

HAE (higher scores indicate greater impairment).

Results: In part 1, treatment with deucricitbant resulted in substantial improvement in PGA-Change at week 12 compared with baseline, with 8/10 and 7/9 participants feeling “much better” in the deucricitbant 20 mg/day and 40 mg/day groups, respectively, vs 1/8 in the placebo group. All (9/9) participants receiving deucricitbant 40 mg/day reported improvement in PGA-Change, whereas 5/8 placebo group participants experienced “no change”. Furthermore, the mean AE-QoL total score improved from baseline to week 12 by 19.0 and 25.9 points in participants receiving deucricitbant 20 mg/day and 40 mg/day, respectively, vs 11.9 points in the placebo group. The AE-QoL domains that showed the greatest improvement with deucricitbant treatment were “fear/shame” and “functioning”.

Conclusions: Analyses of CHAPTER-1 trial data demonstrate that prophylactic treatment with oral deucricitbant for 12 weeks resulted in clinically meaningful improvement in HRQoL for people living with HAE.

23-P

Propensity Score-Matched Comparison of Outcomes for Deucricitbant vs Standard of Care in People Living with Hereditary Angioedema

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Rationale: To compare outcomes between the cohort of a clinical study of deucricitbant for treatment of hereditary angioedema (HAE) attacks with those of an observational study cohort treating HAE attacks with standard of care (SOC).

Methods: RAPIDe-2 (NCT05396105) is an ongoing Phase 2/3 open-label extension study evaluating outcomes of long-term use of deucricitbant immediate-release capsule for treatment of HAE attacks. An observational mixed methods study (MMS) assessed outcomes among people with HAE who treated their attacks with SOC. During an HAE attack, participants in both studies completed the Patient Global Impression of Change (PGI-C) and Severity (PGI-S) assessments. Kaplan-Meier estimates were calculated for time to PGI-C reaching “a little better” or “better” at 2 consecutive timepoints and time to PGI-S 1-level improvement. A propensity score matching (PSM) method was used to compare RAPIDe-2

and MMS cohorts using the following parameters: maximum of 10 consecutive attacks included for each participant; all attacks included for each participant; and attacks matched with replacement.

Results: At the cutoff date of March 1, 2024, RAPIDe-2 included 17 participants (65% female; mean [range] age 43 [20-71]) who had reported 258 non-laryngeal attacks. MMS included 29 participants (69% female; mean [range] age 41 [18-70]) who reported 98 non-laryngeal attacks, with attacks most often treated with icatibant (60.2%) or C1-INH concentrate (31.7%). Among 73 attacks matched between the two cohorts, median estimates for time (hours) to PGI-C “a little better” and “better” and to PGI-S 1-level improvement were shorter for RAPIDe-2 vs MMS, with values of 1.07 (0.98-1.89) vs 2.38 (1.68-3.10, $p < 0.0001$) for PGI-C “a little better”; 2.66 (1.98-3.55) vs 4.49 (3.09-6.18; $p = 0.0006$) for PGI-C “better,” and 2.14 (1.93-2.94) vs 4.02 (3.15-5.19; $p < 0.0001$) for PGI-S 1-level improvement.

Conclusions: This PSM analysis provides evidence that a cohort of participants with HAE in a clinical study treated with deucricitbant had more favorable outcomes on PGI-C and PGI-S assessments compared with a cohort treated with SOC in an observational study.

24-P

Self-Reported Treatment Preferences of Patients Switching from Prior Prophylactic Therapies to Donidalorsen for the Treatment of Hereditary Angioedema: Results from the Phase 3 OASISplus Study

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Rationale: Hereditary angioedema (HAE) is a rare and potentially life-threatening disorder caused by C1 inhibitor deficiency or dysfunction leading to kallikrein-kinin system disinhibition and subsequent tissue swelling. In the phase 3 OASIS-HAE study (NCT05139810), donidalorsen, an investigational ligand-conjugated antisense oligonucleotide targeting production of prekallikrein, significantly reduced the HAE attack rate and was generally well tolerated. We report safety, Angioedema Control Test (AECT), HAE attack rate, and treatment preference results from patients who switched from long-term prophylactic therapies to donidalorsen 80 mg in the phase 3 OASISplus study.

Methods: In this ongoing open-label phase 3 study,

patients with HAE on a stable dose (≥ 12 weeks) of lanadelumab, berotralstat, or C1-inhibitor replacement switched directly onto donidalorsen 80 mg subcutaneous (SC) every 4 weeks using a predefined algorithm. The primary endpoint was the incidence/severity of treatment-emergent adverse events (TEAEs). Other endpoints included changes in the AECT, HAE attack rate, and responses to a treatment preference survey at week 17. Interim data are reported from a February 2024 data cut-off.

Results: Sixty-four patients switched from lanadelumab (n=31), berotralstat (n=11), or C1 inhibitor (n=22) to donidalorsen. As of the data cut-off, 7 dosed patients (10.9%) had terminated the study early, 57 (89.1%) were ongoing, 58 (90.6%) completed 17 weeks, and 12 (18.8%) completed 1 year of treatment. Patient mean age was 42 years; 59.4% were female and 89.1% were White. Mean donidalorsen exposure was 218.7 days. Fifty of 64 dosed patients (78.1%) reported TEAEs, most of which were unrelated to study drug. One patient permanently discontinued treatment due to a non-drug-related TEAE. At Week 17, the proportion of patients with well-controlled symptoms (AECT ≥ 10) increased from 67% at baseline to 93%, and the mean HAE attack rate decreased by 62% overall. Of the 55 patients who completed the treatment preference survey at week 17, 84% preferred donidalorsen over their prior therapy, 11% reported no preference, and 5% preferred their original therapy.

Conclusions: At week 17 in this interim analysis, donidalorsen was generally well tolerated, HAE symptom control increased among patients switching from prior prophylaxis to donidalorsen, and most patients preferred donidalorsen over their previous treatment.

25-P

ASIA Syndrome Associated Angioedema: Can We Predict the Onset by Genetic Testing

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Rationale: ASIA - autoimmune/inflammatory syndrome induced by adjuvants. Symptoms can be multifacial and the recurrent angioedema is one of the dominant. Genetic screening is discussed as a preemptive option. The following alleles of genes - HLA type II (DRB1*0301 or in combination with HLA-B*08, DRB1*01, and DRB4), as well as the Arg620Trp polymorphism in the PTPN22 are discussed as a causative reason responsible for the development of autoimmune diseases, including ASIA

syndrome [1,2].

Methods: A single center observation of 11 patients with clinical criteria of ASIA syndrome and 10 controls (hyaluronic fillers with adjuvants during 2 years or more). Genetic screening was performed in 9(11) patients from the ASIA group and 10 patients from the control group.

Results: All patients with ASIA are young women (Me 29 years). In 8 cases the hyaluronic fillers are considered as a potential trigger, in 1 - combination of filler and breast implant, in 1 - calcium hydroxyapatite and in 1 - pure follicle-stimulating hormone and human chorionic gonadotropin and hyaluronic filler. As symptoms, 10 patients had angioedema with the most frequent facial localization (at the site of drug administration), one had a concomitant combination of chronic spontaneous and heat urticaria, 2 had arthralgias, myalgias combined with lymphadenopathy. Autoimmune response was presented by antibodies to myeloperoxidase, cathepsin, C1q, citrullinated protein/peptide, antinuclear factor and detected in 7 of 11 patients. Treatment considerations: on hydroxychloroquine (2 patients), 1 - danazol, 1 tranexamic acid, 5 patients are on Ahs (1 at standard dose, 4 escalated to 4 tablets/day), 1 patient has a combination of hydroxychloroquine and omalizumab, 2 patients do not receive any treatment by their own choice. In 2 patients a combination of 2 factors was found: DRB1*0301, B1*08 (in one patient additionally Arg620Trp polymorphism). An isolated Arg620Trp polymorphism was found in 4 patients. Thus, genetic factors increasing the risk of autoimmune conditions were found in 6 out of 9 patients.

No genetic findings in the control group.

Conclusions: More than half of patients with ASIA syndrome have genetic factors associated with autoimmunity. Further studies are needed to create reliable diagnostic and treatment algorithm.

References: [1] Borba V. et al. *Biomolecules*. 2020 Oct 12;10(10):1436. doi:10.3390/biom10101436. [2] Watad A, et al. *Lupus*. 2017 Jun;26(7):675-681. doi:10.1177/0961203316686406. Epub 2017 Jan 6.

26-P

Challenges of Diagnosis and Treatment of Recurrent Angioedema from Nepal – The Unseen Struggle in Resource-Constrained Settings

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Rationale: Angioedema is often missed or mistreated in a less privileged world. With the availability of a single immunologist, there is a rise in the etiological diagnosis of recurrent angioedema (RAE). We describe the challenges and struggles of the journey of diagnosing cases of RAE.

Methods: Case sheets of patients diagnosed (as per internationally acclaimed criteria) as various etiologies of RAE from August 2020 to February 2024 were analyzed. We also implemented community-directed interventions (CDIs) from January 2022 up to May 2023, like health camps, media promotions, articles, videos, television interviews, awareness talks, college classes, and society formation.

Results: RAE was mistreated as urticaria/allergy with antihistamines. Among >100 cases with RAE, only 29 patients could do the biochemical tests and 7 could afford commercially available genetic tests. Among 29, Angiotensin-converting enzyme inhibitor- and ibuprofen-related acquired angioedema were diagnosed in 6 and 3 patients, respectively. Fifteen patients were diagnosed with hereditary angioedema with median age of onset and diagnosis of 8.5 and 23 years, respectively. Thirteen of them had low C4 and C1-esterase inhibitor (C1-INH). One patient had elevated C1-INH whereas the remaining one had normal C1-INH. Among 7 genetic diagnoses, 6 had a mutation in the SERPING1 gene (e.g., p.Gly17Arg, p.Arg494Ter) and 1 in rare kininogen (KNG1) gene (p.Met379Lys). Among phenocopies, a girl had autoantibody to C1 inhibitor whereas another was found to have autoantibodies to factor H. In a web-based survey, HAE awareness among physicians was low. All patients with RAE were treated with antihistamines and steroids before visiting us. After CDIs, the rate of visiting patients with RAE doubled. Post-diagnosis, all patients were kept on long-term prophylaxis with tranexamic acid and/or attenuated androgens. Patients with laryngoedema or tongue swelling were also treated with fresh-frozen plasma infusions. One patient has recently availed of C1-INH therapy for her treatment. Others could not procure it due to non-affordability. Occasional angioedema accompanied urticaria in 14.5% (n = 40) of patients.

Conclusions: This is the first report on RAE from Nepal. Lack of awareness and resources have resulted in misdiagnosis, mistreatment, and poor outcomes in resource-constrained settings.

27-P

Clinical Characteristics and Outcomes in Disease Control and Quality of Life in Patients with Hereditary Angioedema in a Colombian Healthcare Institution

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Rationale: Patients with HAE suffer from unpredictable, recurrent swelling episodes that are painful, functionally disabling, potentially life-threatening, and have a negative impact quality life.

The Objectives are describing the demographic

and clinical characteristics of patients with HAE in Colombia and to develop a comprehensive real-world understanding of the patient perspective on the humanistic burden of HAE, including disease control and quality life in a transdisciplinary care model.

Methods: Retrospective and descriptive observational study. Descriptive observational study with a time frame from August 2022 to May 2024, including patients with a confirmed diagnosis of hereditary angioedema, treated in a specialized medical care center in Bogota D.C.

Results: There are currently 175 patients in the cohort, with an average age of 37 years (4-85), with a predominance of females (62%), which agrees with the hypothesis of Bork et al. Hereditary angioedema due to C1-inhibitor deficiency was the most frequent (90%), followed by hereditary angioedema due to C1-inhibitor dysfunction (6%), and unclarified cases (4%). The average age of diagnosis was 22 years. 86% of the crises have been moderate and 7% laryngeal. In 98.3% of patients, icatibant was prescribed for on-demand management. Long-term prophylaxis was required in 21% of patients, in a higher proportion with lanadelumab. Since the beginning of the program, a significant improvement has been observed in the quality of life measured by AEQoL, with an average impact of 4% currently. After 13 months of adherence to the program, almost absolute control of the disease is achieved as measured by AECT with an average value of 15 points.

Conclusions: Hereditary angioedema is considered an rare disease, difficult to diagnose and access adequate treatment, especially in developing countries, which limits achieving good health results. We present the clinical characteristics of 176 patients closely managed in a health program directed by allergists, evidencing the excellent results in disease control and improvement in quality of life after 21 months of adherence to the program. Based on these positive results, we sincerely encourage the replication of our health care model to improve the well-being of patients affected by this disease.

28-P

Beyond Angioedema: Recognizing Mimickers in Patients with Facial Swellings

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Background: Angioedema is a common clinical presentation characterized by rapid swelling of the deeper layers of the skin, often affecting the eyelids, lips, and face. However, not all facial swellings are due to

angioedema, and misdiagnosis can lead to inappropriate treatment and management. This poster highlights the importance of distinguishing angioedema from its mimickers through the presentation of four clinical cases.

Case Report: Four patients presented to the clinic with acute swelling of the eyelids, lips, and face, initially presumed to be angioedema. Detailed patient histories, physical examinations, and further diagnostic evaluations revealed alternative diagnoses:

1. Case 1: A 34-year-old female presented with sudden unilateral eye swelling accompanied by pain and erythema. She was diagnosed with a hordeolum (stye), an acute infection of the eyelid's sebaceous glands, confirmed by ophthalmologic evaluation.

2. Case 2: A 47-year-old female presented with diffuse facial edema with pronounced periorbital swelling after using hair dye. She was diagnosed with an allergic reaction to paraphenylenediamine (PPD), a common allergen in hair color products, confirmed through allergy testing.

3. Case 3: A 37-year-old female with persistent swelling of the upper lip was diagnosed with cheilitis granulomatosa, a rare inflammatory condition, confirmed by lip biopsy.

4. Case 4: A 58-year-old female with diffuse facial and neck swelling was diagnosed with superior vena cava syndrome secondary to breast carcinoma, revealed through imaging studies and oncologic assessment.

Each case demonstrated the necessity of considering a broad differential diagnosis when evaluating patients with facial swelling to avoid misdiagnosis of angioedema.

Conclusions: Facial swellings that mimic angioedema require careful clinical evaluation to identify the true underlying cause. These cases illustrate the diverse etiologies that can present with similar symptoms and emphasize the importance of thorough diagnostic workup.

29-O&P

Hereditary Angioedema Severity and Poor Quality of Life Are Strong Predictors on Occurrence of Sleep Disorders: Insights from the HAE SLEEP Study

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Rationale: The relationship between Hereditary Angioedema (HAE) severity, quality of life (QoL), and the occurrence of various sleep disorders has been an underexplored area of research. Understanding this relationship is critical for developing comprehensive care strategies for patients suffering from HAE. This study aims to evaluate the impact of HAE severity and QoL, on the probability of developing different sleep disorders.

Methods: We conducted a logistic regression analysis using a sample of 139 individuals diagnosed with HAE. The primary predictor variables were the severity of HAE (severe vs. not severe) assessed by the HAE-AS, and QoL domains from the AE-QoL questionnaire. The outcomes were the presence of various sleep disorders. Odds ratios (OR) and their standard errors were calculated to determine the strength of associations, with statistical significance assessed at $p < 0.1$, $p < 0.05$, and $p < 0.01$ levels.

Results: The results indicated significant associations between severe HAE and the increased likelihood of certain sleep disorders. Specifically, severe HAE was strongly associated with Insomnia (OR = 2.620, $p < 0.01$), OSA (OR = 2.400, $p < 0.05$), RLS (OR = 5.854, $p < 0.01$). Gender differences were notable in Insomnia, with males showing a lower probability compared to females (OR = 0.459, $p < 0.05$). The AE-QoL domains significantly affected the odds of developing sleep disorders, Fatigue/Mood domain significantly increased the likelihood of Insomnia (OR = 1.087, $p < 0.01$), Hypersomnolence (OR = 1.069, $p < 0.01$), RLS (OR = 1.054, $p < 0.01$), and OSA (OR = 1.040, $p < 0.01$). Additionally, the Fears/Shame domain was a significant predictor for Insomnia (OR = 1.034, $p < 0.01$), RLS (OR = 1.036, $p < 0.01$), and OSA (OR = 1.014, $p < 0.1$).

Conclusions: The severity of HAE and the level of impact on quality of life, are significant predictors of multiple sleep disorders, indicating the necessity for targeted screening to improve the management of sleep issues in this population.

30-P

The MENPHYS study: MENTAL Burden in PHYSICIANS Who Treat Patients with Chronic Urticaria, Angioedema, Or Atopic Dermatitis

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Rationale: Chronic urticaria (CU), atopic dermatitis (AD), and recurrent angioedema (RAE) are chronic, disabling diseases that significantly impair patients' quality of life. Providing care for patients with chronic inflammatory diseases can affect the psychological well-being of treating physicians. Consequences include physician mental health issues and the risk of patients experiencing medical errors, subpar care delivery, and diminished treatment satisfaction. As of now, the impact of providing care for patients with CU, AD, or RAE on treating physicians is unknown. The goal of our study is to evaluate and characterize the mental burden experienced by physicians who treat patients with these diseases.

Methods: MENPHYS (Mental Burden in Physicians Who Treat Patients with Chronic Urticaria, Angioedema, Or Atopic Dermatitis) is an observational cross-sectional study by the GA2LEN centers of references and excellence networks for urticaria (UCARE), atopic dermatitis (ADCARE), and angioedema (ACARE). UCARE, AACARE, and ACARE physicians and other physicians who treat patients with CU, AD, and /or RAE will complete an online questionnaire that includes the Depression Anxiety Stress Scale (DASS-21) and the Maslach Burnout Inventory.

Results: The MENPHYS study will assess: 1) Physician demographic profiles (age, sex, country, specialty, years of experience, type of practice), 2) Patient populations treated by physicians, in CU, AD, and RAE, including numbers of patients and experience with their treatment, 3) Access to therapies for of CU, AD, and/or RA medication, 4) Physician health status including

immunological and mental conditions, as well as CU, AD, and RAE. In physicians with CU, AD, or RAE, we will determine disease duration and control with patient-reported outcome measures. In physicians who see patients with RAE, we will assess if they see patients when they have acute attacks.

Conclusions: The MENPHYS study will provide first insights on the impact of treating patients with CU, AD, and RAE on physicians. Our findings may help to develop strategies aimed at mitigating the mental burden on physicians, thereby improving the care of patients.

31-P

A Snapshot of Angioedema Mimics at a Tertiary Setting

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Rationale: Suspected angioedema is a common referral for patients presenting with swelling of a body part to immunology/allergy and dermatology services. While there are hallmark features that help distinguish angioedema from angioedema masqueraders, the heterogeneity of various cutaneous and systemic conditions adds to the layer of complexity in reaching a diagnosis.[1],[2]

Method: A review of suspected angioedema cases referred to immunology/allergy and dermatology service at a tertiary hospital was conducted. Patients with alternative diagnoses mimicking angioedema were identified. Nature and location of symptoms, concurrent drug use, underlying co-morbidities including atopic background, relevant biochemical parameters, radiological findings and management plans were recorded and summarised.

Results: These cases had been referred for further evaluation for "angioedema" involving the eye, lip, cheek or face. All cases had no history of angiotensin-converting enzyme inhibitor or nonsteroidal anti-inflammatory drug use. Serum tryptase, C4 and C1 esterase inhibitor function levels were normal in the cases identified, where relevant. All cases had persistent swelling instead of episodic occurrence. Conditions identified included (1) cheilitis granulomatosa (orofacial granulomatosis) manifesting with lip swelling; (2) Morbihan disease with persistent eye and facial swelling; (3) allergic contact dermatitis presenting with facial and marked eye swelling; (4) dust mite allergy with characteristic periorbital swelling and concurrent nasal symptoms worse in the morning; (5) Sjögren

syndrome with salivary gland swelling and (6) drug rash with eosinophilia and systemic symptoms (DRESS) with facial swelling. All cases achieved symptomatic improvement when the right diagnosis was established, except a case that was lost to follow-up hence outcome was unknown.

Conclusions: Angioedema or swelling is a common referral from the community or other in-patient specialties. However, not all cases referred for angioedema are angioedema. Differential diagnoses must be considered when history and physical examination do not suggest so, or when standard treatment for angioedema fails to achieve symptom control. Establishing the right diagnosis may be challenging due to complexity of presentation, and having a multi-disciplinary approach in discussion provides appropriate management plan, therefore greatly improving patient outcome.

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32-P

AAE Kaleidoscope: The Clinical Heterogeneity of AAE presentations

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Rationale: Acquired angioedema (AAE) with C1-esterase inhibitor (C1-INH) deficiency is a rare condition that typically presents after 40, eventually unraveling underlying lymphoproliferative disease or monoclonal gammopathy. It has an estimated prevalence of 1:500,000. Misdiagnosis as anaphylaxis or allergy is common when patients present to emergency department. Given rarity of this condition and lack of consensus on effective management plan, there is an unmet need to further characterise this disease to address patients' needs and improve physicians' awareness and understanding. Here, we present a case series of AAE at two tertiary health institutions in metropolitan Melbourne.

Methods: Retrospective data collection at allergy/immunology clinics was carried out to identify cases diagnosed with AAE. Age of onset, location of angioedema attacks, underlying disease, background C4, C1q and C1-INH levels, acute and long-term management plans as well as treatment outcome were recorded.

Results: A total of 6 cases were identified, with 3 female

and 3 male. All cases were diagnosed after the age of 60, except one case who presented in his 40s. All had low C4 and C1q levels. There were 2 cases of splenic marginal zone lymphoma, 3 cases of monoclonal gammopathy and a case of T-cell lymphoma. The cases of splenic marginal zone lymphoma were siblings, one with recurrent airway angioedema successfully treated with on-demand icatibant and cycles of rituximab, while the other sibling had biochemical evidence of C1q and C1-INH deficiency without clinical angioedema. Both had secondary hypogammaglobulinaemia on immunoglobulin replacement. Two cases with monoclonal gammopathy demonstrated symptom improvement with long term tranexamic acid, further reducing frequency and severity of airway, facial and genital swelling. Both continue to use icatibant when the needs arise. One case with monoclonal gammopathy achieved complete symptom control with lanadelumab. The remaining case with lymphoma had episodic ocular and facial swelling alongside low C1q level with further plan to repeat C1-INH level given the first sample demonstrated normal level in the early course of disease.

Conclusions: This case series highlights the clinical heterogeneity of AAE with C1-INH deficiency. Long-term treatment plans must be tailored to patient's circumstances or needs, as well as availability of and access to specific medications.

33-P

Patient-Reported Benefits of Early On-Demand Treatment of HAE Attacks

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Background: Hereditary angioedema (HAE) is characterized by painful and debilitating attacks of tissue swelling in various locations. The objective of this survey was to understand whether people living with HAE have different behaviors and experiences based on whether they treat attacks early or whether they delay on-demand treatment.

Methods: Patients with Type I or II HAE who were recruited by the US Hereditary Angioedema Association completed a 20-minute, self-reported, online survey from September 6 to October 19, 2022.

Results: Total respondents included 107 Type I or II HAE patients, 80.4% female, with a mean age of 41 years.

When asked the question, “How long do you wait before you initiate on-demand treatment?” 46 (43%) patients stated that they treated their attacks in <1 hour; these patients reported carrying on-demand treatment with them 70.5% of the time (vs 58.9% for patients who waited to treat their attack \geq 1 hour). Patients who treated their attacks <1 hour reported gaining control of their attacks in 1.4 hours (vs 2.9 hours for those who waited to treat their attack \geq 1 hour) and achieved full recovery in 1.3 days (vs 1.9 days for those who waited to treat their attack \geq 1 hour). Only 23.8% of patients who treated their attacks in <1 hour reported experiencing an attack return (vs 34.9% of patients who delayed treatment). None (0%) of the patients who treated their attacks in <1 hour reported feeling embarrassed to carry their on-demand treatment (vs 20.9% of those who delayed treatment). Despite the anxiety that patients reported when anticipating parenteral on-demand treatment, patients who treated attacks in <1 hour reported feeling less anxious (3.4 on a scale of 0-11 vs 4.9 for those who delayed treatment) and treated more attacks overall (27.4% vs 9.7% for those who delayed treatment).

Conclusions: Results from this survey highlight that people living with HAE who treat their attacks early are more likely than those who delay treatment to carry their on-demand treatment with them, treat more attacks, feel less anxious when anticipating on-demand treatment, and recover more quickly from HAE attacks.

34-P

A Concise Summary of the Hereditary Angioedema (HAE) Registry and Activities of the Immunology, Asthma and Allergy Research Institute for the HAE Patients in Iran

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Rationale: The Immunology, Asthma and Allergy Research Institute (IAARI) affiliated with Tehran University of Medical Sciences, serves as the main referral center for Inborn Errors of Immunity, in Iran. To improve Hereditary Angioedema (HAE) patient care, IAARI implements public awareness campaigns, early diagnosis initiatives and individualized treatment plans. The institute established the Iranian Hereditary Angioedema Registry (IHAR) to collect epidemiological, clinical, and laboratory data on HAE patients. This is the updated report from IAARI activities about HAE.

Methods: Patients with HAE from across the Iran are

referred to IAARI for evaluation. Following confirmed diagnosis by clinical and laboratory evaluations, they are enrolled in IHAR.

Results: Educational Initiatives: IAARI actively promotes awareness through annual events for healthcare providers and patients and their families on International HAE Day. To enhance patient education, IAARI is translating the “Understanding the HAE” book into Persian.

Guidelines and Advocacy: The national HAE management guideline was updated in 2022, and an online version is available on the IAARI website. In collaboration with HAE International (HAEi), 100 emergency room posters were distributed nationwide to improve HAE recognition. In addition, IAARI's membership as an accredited Angioedema Center of Reference and Excellence (ACARE) center was confirmed in late 2023. **Patient Registry and Research:** IHAR established in 2006 in IAARI. The IHAR has enrolled 140 patients with HAE types 1 and 2 over 17 years. IHAR data has contributed to over 21 abstracts and 5 full research papers.

Policy and Support: IAARI collaborated with Iran's Ministry of Health to register Icatibant, a crucial HAE medication in Iranian pharmacopeia.

IAARI supported the establishment of the Immune Deficiency Patients Advocacy (IDPA) NGO, which provides educational, financial and emotional support for patients with inborn errors of immunity including Hereditary Angioedema.

Conclusions: The development of comprehensive databases containing epidemiological, clinical and laboratory data on HAE patients is instrumental in furthering our understanding of the disease's clinical presentation and optimizing its management. This rich repository of information holds the potential to improve patient care, inform future treatment strategies, and ultimately contribute to a reduction in HAE-related mortality.

35-O&P

Human Plasma-Derived C1 Inhibitor (C1-INH) for Short-Term Prophylaxis in Hereditary Angioedema with Normal C1-INH

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Rationale: Hereditary Angioedema (HAE) is a disease with autosomal dominant inheritance, initially identified in patients with C1 esterase inhibitor (C1-INH) deficiency and later described with normal C1-INH. The accumulation of bradykinin is responsible for mucosal and submucosal edema, mainly affecting the subcutaneous tissue, gastrointestinal tract and upper airways, which is a well-known pathomechanism for HAE-C1INH, however not always for HAE-nC1-INH. The most frequently reported triggers are stress, trauma, infection and dental, surgical or endoscopy procedures. The use of human plasma-derived C1-INH (pdC1-INH) is well established for short-term prophylaxis (STP) in HAE-C1INH, however not defined for HAE-nC1INH. The aim of this study is to evaluate the STP in this population.

Method: This is a multicenter, observational, retrospective study, in patients over 12 years old, with a confirmed diagnosis of HAE who underwent high-risk procedures after receiving pdC1-INH as STP. Data collection was carried out using a questionnaire with personal information, diagnosis, and medication in use. The patients were divided in three groups according to their diagnosis: G1 (HAE-C1INH), G2 (HAE-FXII), G3 (HAE-UNK).

Results: Seventy-three infusions were evaluated in 44 patients (70F:3M, median age: 39 years, range 13 to 67) in three groups: G1) HAE and C1-INH deficiency (37 infusions), G2) HAE-FXII (22 infusions) and G3) HAE-UNK (14 infusions). The indications for STP were: dental procedure (G1=12; G2=3; G3=2); diagnostic procedure (G1=8; G2=5; G3=5); elective surgery (G1=9; G2=5; G3=6); cesarean section (G1=5; G2=7; G3=1); normal birth (G1=2; G2=2; G3=0); others (G=1). Edema after the procedure occurred in 4/37 (10.8%) for G1, 2/22 (9%) for G2 and 3/14 (21.4%) for G3.

Conclusions: The study demonstrated the effectiveness of pdC1-INH in short-term prophylaxis, which is less successful in patients with HAE-UNK when compared to HAE-FXII and HAE-C1INH. The procedures which

provoked more attacks were diagnostic procedures and elective surgery. The doses used were considered adequate and, therefore, these events were not dose-dependent. This is the first study of short-term prophylaxis in patients with HAE-FXII and HAE-UNK.

36-P

A Case of Atypical nC1-INH-HAE or Capillary Leak Syndrome?

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Background: Painful episodic swellings on different body parts or mucosa may be histamine or bradykinin mediated and has to be clarified as treatment options are different. Diseases associated with diffuse body swellings with weight gain are the so-called episodic angioedema associated with eosinophilia, EAE, or capillary leak syndrome again responding to completely different treatment modalities.

Case report: Here we report a 57 years-old man presented firstly with cholinergic urticaria ongoing for 3-4 years and small fiber neuropathy, SFN, as an underlying condition which was treated with IVIG monthly. Methacholine skin and physical ergometer test confirmed the diagnosis and antihistaminics controlled his cholinergic urticaria. In the following, he developed painful plantar swellings after hiking, that expanded with time to lower legs, fingers, hands and face without physical effort. Additionally, he developed dizziness, headache, fatigue, abdominal pain, diarrhea, and shortness of breath from time to time, despite IVIG treatment for his SFN. He was prescribed omalizumab for more than 6 months without any effect. His check-up included and resulted in normal serum total IgE and negative screening for specific IgE on inhalant allergen panel, complete blood count without any eosinophilia, C1-INH-Ag and activity, C3, C4 within normal range. Immunologic tests were negative for ANA, Subsets, anti-ds-DNA, anti-Thyroid-antibodies including C1q. WES for all known mutations for nC1-INH-HAE resulted negative too. So, we could rule out histaminergic, drug induced, C1-INH or acquired angioedema and EAE but could not differentiate between nC1-INH-HAE and capillary leak syndrome. We used icatibant SC during an acute swelling phase with rapid relief of swelling and pain. This prompted us to long-term prophylaxis with pd-nf-C1-INH 1000 IU SC twice weekly to the full satisfaction of the patient.

Conclusion: Even if successful treatment with pd-nf-C1-INH does not allow to discriminate between an atypical nC1-INH-HAE and capillary leak syndrome.

37-P

The Combination of Two Oral Kallikrein Inhibiting HAE-Therapies for LTP and On-Demand Treatment in a Teenager

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Background: Hereditary angioedema, HAE, is typically characterized by recurrent swellings of the skin and mucous membranes and abdominal pain.

Case report: Here we report a young boy, born 2010 in a family with known HAE type I. HAE was diagnosed at birth and confirmed with 12 months. He developed his first attack at 4 years of age on the hands, followed by severe peripheral and abdominal attacks. As the father was on on-demand pdC1INH IV therapy the boy also received this treatment applied by the father. He learned IV self-administration at the age of 10 y. In the last 2 years, he suffered from severe abdominal attacks at least twice a week. In the meantime, his father was taking berotralstat as participant of APeX-2 study and was attack-free. He also wanted to take berotralstat orally but with 11 years of age he was too young for the ongoing study. In July 2022, after market introduction, we started berotralstat-LTP. Soon, his attack rate decreased from at least 10 to 2-3 attacks/month. He was happy since he needed much less IV on-demand therapy. In April 2023, we were recruiting for oral on-demand KONFIDENT-S study for adolescents and adults for HAE I/II. In May 2023 he started the study per protocol and since then he is treating his few attacks with on-demand KVD900.

The patient and his parents are happy no longer to need any injections for his attacks since more than 1 year.

Conclusion: Berotralstat-LTP was very effective for him but he still needed some on-demand treatment. Additional oral on-demand treatment closed this gap. Combination of 2 oral kallikrein inhibiting small molecules (LTP and on-demand) enabled him a life without injections and was well-tolerated without any side effects.

Rational: The objective of the present study was to thoroughly delineate the genetic spectrum associated with Hereditary Angioedema (HAE) type I and type II within the Iranian patient. The exploration of the genetic landscape of HAE in this study aimed to contribute valuable insights and enhance our knowledge of the genetic factors influencing the manifestation of HAE in Iranian patients.

Methods: A cohort of seventy-two patients exhibiting a clinical phenotype characterized by recurrent edematous attacks in various anatomical regions, including the face, upper and lower limbs, hands, and upper airway, were enrolled in the study. The genetic analysis focused on identifying mutations in the SERPING1 gene through Polymerase Chain Reaction (PCR) and Sanger Sequencing techniques. Furthermore, to detect large deletions or duplications in cases where initial screening yielded negative results, Multiplex Ligation-dependent Probe Amplification (MLPA) was employed in conjunction with Sanger sequencing.

Results: Among the seventy-two patients included in the study, fifty-four individuals were clinically diagnosed with Hereditary Angioedema (HAE) type I, while eighteen were classified as having HAE type II. Through genetic analysis, a total of thirty-two distinct pathogenic variations, encompassing frameshift, missense, nonsense, and splicing defects, were identified in sixty-three patients. Notably, in nine cases, no pathogenic mutations were detected despite thorough screening.

Conclusions: Final diagnosis with mutation analysis of HAE after clinical evaluation and assessment of C1INH level and function can prevent potential risks and life-threatening manifestations of the disorder. In addition, genetic diagnosis can play a significant role in facilitating early diagnosis, pre-symptomatic diagnosis, early diagnosis of children, asymptomatic cases, and those patients who have the borderline biochemical results of C1-INH deficiency and/or C4.

38-P

Genetic Study of Hereditary Angioedema Type I and Type II in Iranian Patients

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39-O

CRISPR-Based Gene Editing of KLKB1 Resulted in Long-Term Plasma Kallikrein Protein Reduction and Decreased Attack Rate in Patients with Hereditary Angioedema: Updated Results From a Phase 1 Study

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Rationale: Hereditary angioedema (HAE) is a rare

genetic disease associated with unpredictable attacks of swelling due to dysregulated bradykinin production. Kallikrein is a clinically validated target for long-term prophylactic treatment of HAE. NTLA-2002 is an investigational, in vivo CRISPR-based therapy targeting KLKB1, with the goal of rebalancing the disease pathway by decreasing bradykinin production, leading to prevention of HAE attacks after a single dose.

Methods: NCT05120830 is a phase 1/2 study of NTLA-2002 in adults with HAE. Phase 1 dose escalation is complete (25 mg, n=3; 50 mg, n=4; 75 mg, n=3). The Phase 1 primary endpoints were safety and tolerability; other endpoints included pharmacokinetics, pharmacodynamics, and clinical efficacy. Phase 2 is a randomized, double-blind, placebo-controlled study of NTLA-2002 25 mg and 50 mg, which has completed enrollment and is ongoing.

Results: As of February 12, 2024, the 25 mg, 50 mg, and 75 mg cohorts have a median of 24, 18, and 20 months of follow-up, respectively. The most common (>50%) adverse events (AEs) were infusion-related reactions, fatigue, and COVID-19. No serious AEs, Grade ≥ 3 AEs, or clinically significant laboratory findings were observed. Dose-dependent reductions in plasma kallikrein protein were demonstrated, with mean reductions from baseline to latest assessment of 60% (25 mg, Week 88), 88% (50 mg, Week 72), and 95% (75 mg, Week 88). From the time of administration of NTLA-2002 to the latest assessment, a mean reduction from baseline in monthly attack rate of 98% was observed across all dose levels, and of 97% for attacks requiring acute therapy. From Week 16 to the latest assessment, the mean reduction from baseline in monthly attack rate across all dose levels was 99%, with 8 out of 10 participants remaining attack-free since the end of the primary observation period (Week 16).

Conclusions: A single-dose of NTLA-2002 infusion was well tolerated, and led to significant, dose-dependent, and durable reductions in total plasma kallikrein protein and attack rates for more than 1.5 years, with clinically significant reduction in attack rate observed to date.

40-O

Chronic Recalcitrant Urticaria in Adolescent with HAE-C1INH a Case Vignette

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Background: Hereditary Angioedema (HAE) due to C1-inhibitor deficiency (HAE-C1INH) is characterized by recurrent subcutaneous or submucosal swelling episodes. The underlying pathomechanism is vascular endothelial hyperpermeability owing to Bradykinin

(BK), produced downstream of the Kallikrein-Kinin cascade. In contrast, Urticaria (URT) is considered a distinct entity, manifested by wheals and erythema (wheal & flare, hives), accompanied by intense pruritus, and mediated by mast-cell (MC) degranulation products. So far, few cases of urticaria have been reported among HAE-C1INH patients, most of which were temporary or relapsing. Interactions between MC products and BK-mediated mechanisms of vascular permeability have been demonstrated by Oschatz et al. in the rodent model. [1] Antihistamines were shown to inhibit BK-induced cutaneous wheal-and-flare [2], and BK analog (icatibant) released histamine from isolated skin MCs and elicited skin reactions attenuated by antihistamines. [3] MC degranulation may release Heparin and other negatively charged polyanions that can trigger the FXII-activated cascade. [4] Recently the role of the MRGPRX2 MC receptor was also stated as a putative link. [5]

Case report: We present an intriguing case of a 17-year-old female with an established diagnosis and wide family history of HAE-C1INH-type 1. Her grandfather, mother, and four siblings are also affected. Along with recurrent angioedema attacks, she has developed from early childhood typical urticaria accompanied by pruritic flushing. Lately, she also experienced acral cyanosis resembling the Raynaud Phenomenon involving the tips of her fingers and skin of the lower extremities. Laboratory investigation revealed antigenic C1INH= 6.0 mg/dl, C4 <2.9 mg/dl, positive anti-nuclear antibodies (1:320, nucleolar pattern) but negative dsDNA antibodies, but absence of any nuclear or nucleolar specific autoimmune markers. Hematology, coagulation, biochemistry, and immunology panels are normal. Serum Tryptase (baseline) was normal at 6.6 mcg/L. Attempted therapies included: C1INH, icatibant, antihistamines, montelukast, and corticosteroids. Long-term prophylaxis with either Omalizumab or Kallikrein inhibitors is considered.

Conclusion: This case suggests the coexistence of bradykinin-mediated (HAE-BK) with mast-cell-mediated urticaria/angioedema (HAE-MC, URT) and a plausible cross-talk between the two phenotypically distinct entities.

Acknowledgments: Permission to present the case without any identifying details was received by the parents.

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41-P

Rationale and Design of the ALPHA-SOLAR Clinical Trial of STAR-0215 250

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Rationale: HAE caused by C1-INH deficiency results in uncontrolled activation of plasma kallikrein that initiates potentially life-threatening HAE attacks. STAR-0215 is an investigational humanized YTE-modified IgG1kappa monoclonal antibody with an estimated half-life < 127 days and potent and durable (at least 84 days) reduction of plasma kallikrein activity demonstrated in healthy adult subjects. The ALPHA-SOLAR clinical trial (NCT06007677) is assessing the long-term safety and efficacy of STAR-0215 in patients with HAE, which may be administered every 3- or 6-months.

Methods: ALPHA-SOLAR is an open-label, phase 2 clinical trial open to participants in the ongoing Phase 1b/2 ALPHA-STAR trial (adults, HAE type I or II) who meet eligibility requirements. This trial will enroll up to approximately 56 participants globally with an anticipated treatment exposure of up to 5 years. Enrolled participants will receive a subcutaneous loading dose and either 300 mg SC Q3 Months or 600 mg SC Q6 Months of STAR-0215. The primary endpoint will be assessment of the long-term safety and tolerability of STAR-0215. Secondary endpoints will include evaluation of the frequency, severity, and duration of HAE attacks and pharmacokinetic/pharmacodynamic parameters. The study will also evaluate disease biomarkers and quality-of-life endpoints.

Results: Results from this trial will add to the long-term safety and efficacy profile of STAR-0215 administered every 3 or 6 months.

Conclusion: The goal of the ALPHA-SOLAR long-term open-label trial is to evaluate the long-term safety and efficacy of STAR-0215 as a potential long-acting preventative therapy for HAE designed to normalize the lives of people with HAE.

42-P

HAE in Ukraine: An Update on Diagnostics and Treatment

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Rationale: To update the data about HAE diagnostics, treatment and current patient's needs in Ukraine.

Methods: The data are based on the reports of immunologists all over Ukraine and the patient organization information. To collect social aspects and patient needs a google form questionnaire was distributed among patient organization members.

Results: To date, 94 patients with HAE have been diagnosed in Ukraine, of which 77 are adults and 17 are children, 47.8% of whom were diagnosed during 2021-2024. Median age is 37,5 years (range: 6-72) and 61,2% are female. Patients are represented from all regions of Ukraine, some of them had to change their place of residence due to the beginning of the war, 14% moved to another region of Ukraine, 4% went abroad. In most patients, the disease manifested in childhood (average age 10.4 years), while the average age of diagnosis is 26.5 years. Until 2021, diagnostics were available almost exclusively at patients' own expense. A sponsored project allowed a free diagnosis in 2021-2024 for 44 new patients.

The only treatment available is C1-inhibitor concentrate. 90% of patients have access to on-demand treatment, 62% of patients can self-administer the drug. Only 23% indicated the use of C1-inhibitor for each attack, 31.8% strive for this, and 40% use the drug only for abdominal or laryngeal attack. Reasons for not administering the drugs are: delays in the purchase of drugs and disruption of access to medical facilities due to rocket attacks and blackouts, fear of addiction, avoidance of injury to veins. 72.3% of patients noted a deterioration in the course of the disease after the start of full-scale Russian-Ukrainian war in an increasing the frequency and/or severity of attacks. 48% of patients receive prophylactic treatment with C1-inhibitor concentrate with varying regularity.

Conclusions: Over the past few years, the diagnosis and access to treatment of HAE has significantly improved in Ukraine. Availability of laboratory diagnostics is essential for the detection of new patients. Compliance to treatment is quite low, the war also has a significant impact on the patients' well-being meaning the migration, additional attack triggers and access to medical facilities.

Acknowledgements: The authors express their gratitude

to all immunologists of Ukraine, as well as patients, for participating in the survey.

43-P

Being Attack-Free is Associated with Improved Quality of Life for Patients with Hereditary Angioedema Treated with Garadacimab: Post Hoc Analysis from the Pivotal Phase 3 (VANGUARD) Study

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Rationale: Recurrent, unpredictable, and potentially life-threatening hereditary angioedema (HAE) attacks impact patient quality of life (QoL). Per guidelines, HAE treatment goals are to achieve complete disease control and to normalize patients' lives. Garadacimab (fully human anti-activated factor XII monoclonal antibody) prophylaxis significantly reduced monthly attack rate vs placebo (mean [95% confidence interval] 0.27 [0.05–0.49] vs 2.01 [1.44–2.57]; $P < 0.0001$) in the pivotal Phase 3 (VANGUARD) study; overall, 62% of patients receiving garadacimab and no patients receiving placebo were attack-free. Consistent with efficacy, substantial and clinically meaningful improvements in QoL were observed. This post hoc analysis further explores the impact of being attack-free with garadacimab prophylaxis on QoL in the pivotal Phase 3 (VANGUARD) study.

Methods: Eligible patients with HAE (aged ≥ 12 years with baseline monthly attack rate ≥ 1) were randomized 3:2 to receive garadacimab 200 mg subcutaneously once monthly after a 400 mg loading dose or volume-matched placebo up to Day 182 (6 months). Angioedema QoL questionnaire (AE-QoL) scores were collected (across four domains [Functioning, Nutrition, Fatigue/mood, Fear/shame] and total score) in patients aged ≥ 18 years. An AE-QoL item-based subgroup analysis compared AE-QoL scores in patients who were attack-free vs not attack-free.

Results: Overall, 33 garadacimab-treated patients and 20 placebo-receiving patients provided AE-QoL scores

at Day 182. Of the garadacimab-treated patients, mean (standard deviation [SD]) AE-QoL total score at Day 182 was improved for attack-free ($n=19$; 6.6 [8.9]) vs not attack-free patients ($n=14$; 18.4 [20.5]). All placebo-receiving patients experienced ≥ 1 attack by Day 182 (mean [SD] AE-QoL total score 40.5 [24.7]).

In Functioning and Nutrition AE-QoL domains, all attack-free patients reported that they never experienced any QoL impairment at Day 182. In Fatigue/mood and Fear/shame AE-QoL domains, most attack-free patients reported that they never or rarely experienced any QoL impairment at Day 182, with a minority reporting they occasionally experienced QoL impairment.

Conclusions: In this post hoc analysis of the pivotal Phase 3 (VANGUARD) study, garadacimab was associated with QoL improvement in patients with HAE, with attack-free patients experiencing the greatest improvement. Most attack-free patients had normalized QoL (never experiencing QoL impairment).

44-P

Efficacy and Safety of Oral Deucricitbant, a Bradykinin B2 Receptor Antagonist, in Prophylaxis of Hereditary Angioedema Attacks: Results of CHAPTER-1 Phase 2 Trial

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Rationale: Hereditary angioedema (HAE) attacks are caused by excess bradykinin activating bradykinin B2 receptors. Deucricitbant is a potent, selective, orally administered antagonist of the bradykinin B2 receptor under development for on-demand and prophylactic treatment of HAE attacks.

Methods: CHAPTER-1 (NCT05047185) is a two-part Phase 2 study evaluating the efficacy and safety of deucricitbant for long-term prophylaxis of HAE attacks. In part 1, participants received double-blind treatment with placebo or deucricitbant 20 mg/day or 40 mg/day (immediate-release capsule formulation) for 12 weeks. In the ongoing part 2, participants have the opportunity to continue treatment with open-label deucricitbant 40 mg/day. Eligible participants were aged ≥ 18 and ≤ 75 years, diagnosed with HAE-1/2, not receiving other prophylactic treatments at the time of screening, and experienced ≥ 3 attacks within the last 3 months prior to screening or ≥ 2 attacks during screening (up to 8 weeks). Thirty-four participants were enrolled at Sites in Canada, Europe, the United Kingdom, and the United States.

Results: The primary endpoint was met, with monthly angioedema attack rate reduced by 79.3% ($p=0.0009$) and 84.5% ($p=0.0008$) in participants receiving deucricitbant 20 mg/day (least squares mean [LSM]: 0.40; 95% CI: 0.17, 0.92) and 40 mg/day (0.30; 0.11, 0.82), respectively, vs placebo (1.94; 1.31, 2.87). In analyses of secondary endpoints, deucricitbant 20 mg/day and 40 mg/day reduced the monthly rate of "moderate and severe" attacks by 82.8% and 92.3%, and the monthly rate of attacks treated with on-demand medication by 75.1% and 92.6%, respectively. Participants treated with deucricitbant showed consistent reduction in monthly attack rate regardless of baseline attack rate. Both doses of deucricitbant were well-tolerated. Four treatment-related treatment-emergent adverse events (TEAEs) were reported by 4 participants: 1 receiving placebo, 2 deucricitbant 20 mg/day, and 1 deucricitbant 40 mg/day. All 4 treatment-related TEAEs were mild in severity. There were no serious TEAEs, no severe TEAEs, and no TEAEs leading to treatment discontinuation.

Conclusions: Results of the CHAPTER-1 trial provide evidence on efficacy and safety of deucricitbant for the prevention of HAE attacks and support its further

development as a potential prophylactic therapy for HAE.

45-P

Clinical and Psychosocial Characterization of Patients with Hereditary Angioedema in Ecuador: Impacts on Quality of Life, Work Productivity, and Clinical Management Strategies

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Rationale: Hereditary Angioedema (HAE), a rare hereditary condition, causes severe swelling affecting patients' quality of life. HAE's incidence in Ecuador, is unknown but ranges from 1:50,000 to 1:100,000 worldwide. For this reason, we aim to present the first registry of Ecuadorian HAE patients and to describe their demographic, clinical, and psychosocial characteristics for the first time.

Methods: A cross-sectional study was conducted involving 28 HAE patients from Ecuador. Data collection included demographics, clinical and laboratory characteristics, comorbidities, treatment modalities, and patient-reported outcomes using the AECT, AE-QoL, HAE-AS, Work Productivity and Activity Impairment (WPAI) questionnaire, Hospital Anxiety and Depression Scale (HADS), and Generalized Anxiety Disorder (GAD-7) scale.

Results: The study included 28 patients with a mean age of 35.0 years (SD = 16.8). The cohort comprised 54% females; 48% were employed full-time and 19% unemployed. Comorbidities were present in 71% of patients, with allergic rhinitis (53%) and high blood pressure (40%) being the most common. Most patients had Type 2 HAE (86%). Attack locations included the abdomen (86%), legs/arms (71%), and face (38%), with stress (76%) and trauma (62%) being the primary triggers. Long-term prophylaxis was used by 33% of patients, exclusively with androgens. On-demand treatments were used by 52% of patients, with antihistamines being the most common (64%). ICU admission was necessary for 1% of patients. The AECT overall score was 9 (SD = 4.9), with 62% of patients reporting uncontrolled disease. The HAE-AS overall score was 9 (SD = 4.7), with 19% classified as having severe disease. The AE-QoL overall score was 42 (SD = 23.1), indicating a moderate impact on quality of life. The WPAI showed a mean overall work impairment of 84% (SD = 30.5) and activity impairment of 54% (SD = 31.7). HADS scores

revealed a mean overall score of 20 (SD = 10.1), with 43% experiencing anxiety. GAD-7 scores indicated mild to severe anxiety in 48% of patients.

Conclusions: This is the first study to present the profile of patients with HAE in Ecuador and its impact on QoL and work productivity, evidencing the need for effective and tailored interventions, and comprehensive support systems for HAE patients in Ecuador.

46-P

Breast Augmentation Surgery in Hereditary Angioedema Patients: No Increase in Attack Frequency – A Report of Two Cases

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Background: Hereditary Angioedema (HAE) is a rare genetic disorder characterized by recurrent and unpredictable episodes of swelling. Surgical procedures in HAE patients are often approached with caution due to the risk of trauma-induced attacks and complications associated with foreign bodies, such as implants. This case report examines the impact of breast augmentation surgery on the frequency of HAE episodes in two female patients.

Case Report: We report two cases of female patients diagnosed with HAE who underwent breast augmentation surgeries. Patient one, a 23-year-old, had an average of two attacks per month. Patient two, a 35-year-old, had an average of three attacks per month. Both patients were on on-demand treatment with intravenous plasma-derived C1 inhibitor.

Each surgeon discouraged the patients from proceeding with the surgery due to the risks associated with trauma and the presence of a foreign body. Despite these warnings, both patients chose to undergo the procedure. The surgery for patient one was performed using texturized breast implants with an inframammary approach and subfascial placement. Patient two had surgery using texturized breast implants with an inframammary approach and submuscular placement. Each procedure lasted 50-60 minutes and was completed without complications.

Patient one received a local anesthetic and a brachial plexus block, avoiding orotracheal intubation to minimize trauma. Patient two underwent general anesthesia with orotracheal intubation. One hour before surgery, each patient received prophylaxis with 1,500 IU of plasma-derived C1 esterase inhibitor intravenously. Following the surgeries, patient one was monitored for four years, and patient two for nine months. Neither patient experienced an increase in the frequency of HAE attacks during the follow-up periods.

Conclusions: Our report of two cases indicates that

breast augmentation surgery did not lead to an increase in the frequency of HAE attacks. The presence of the foreign body (breast implants) did not activate the contact system and was not associated with an increase in attack frequency. This suggests that, with appropriate prophylactic measures, breast augmentation surgery can be safely performed in HAE patients.

47-P

Comparison of Clinical Features of Patients Aged 65 and Over and Under 65 Years of Age with Hereditary Angioedema

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Rationale: Hereditary angioedema (HAE) is a rare disease characterized by sudden and often unprovoked episodes of swelling that can be potentially life-threatening when it involves the upper airways. There is limited data on the clinical characteristics of elderly patients with HAE-C1-INH. The aim of the present study was to characterize the clinical features of elderly patients.

Methods: In this retrospective study, seventy-six patients who have been followed up at a tertiary ACARE center were included. All patients had been diagnosed with HAE –C1-INH. The clinical characteristics of patients aged 65 and over have been compared with those of younger patients.

Results: A total of 9 (12%) patients were ≥ 65 years, 7 (77%) of whom were female. The median age at the time of diagnosis was higher in the elderly group (58 vs. 28 years, $p < 0.001$), whereas the median age at the first symptom was similar (20 vs. 19 years, $p = 0.33$). There was a significant delay in diagnosis time in the elderly group (42 vs. 4 years, $p = 0.002$). Hypertension was the most frequent (77%) comorbidity among elderly patients. The median number of angioedema attacks in the last year was 6 (range, 2–36), and similar to 10 (range, 2–48) patients < 65 years ($p = 0.82$). Angioedema control in the last three months was lower in older patients (56% vs. 84%, $p = 0.047$). The rate of laryngeal edema was similar (STP) in patients < 65 years and older patients ($p = 0.48$). The use of STP was higher in the elderly group (33% vs. 9%, $p = 0.04$), whereas the use of long-term prophylaxis was similar (11% vs. 39%, $p = 0.10$). The most commonly used treatment for acute attacks was pdC1-INH (92% vs. 89%, $p = 0.60$). Two (22%) patients in the elderly group did not benefit from danazol. No adverse events with icatibant, pdC1-INH, danazol, or tranexamic acid were encountered among patients.

Conclusions: Compared to patients younger than 65 years of age, annual attack rates and the number of emergency admissions were similar, whereas elderly

patients had lower angioedema control for the last three months. The use of STP rates was higher among elderly patients.

48-P

The Relationship Between Surgical Procedures and Angioedema Attacks in Hereditary Angioedema

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Rationale: Hereditary angioedema (HAE) is a rare and life-threatening disease caused by deficiency or dysfunction of C1 inhibitor (C1-INH). Surgical interventions are known to trigger angioedema attacks. This study aims to assess the incidence of perioperative attacks and identify associated risk factors.

Methods: The study included patients diagnosed with HAE between 1999 and 2024 at a tertiary care adult allergy clinic. Patients were retrospectively examined for information regarding type of surgical procedures and the occurrence of perioperative angioedema.

Results: In total, 28 out of 102 HAE patients were excluded from the study due to incomplete data. The sample comprised of 74 patients, of whom 46 (62.1%) were female. A total of 53 patients underwent 94 surgical procedures. In 81 (79.3%) procedures general anesthesia was used, 7 (6.9%) procedures had spinal anesthesia, and 4 (3.9%) procedures had local anesthesia. The most common were 27 (28.7%) gynecological, 27 (28.7%) abdominal, and 16 (17.0%) ear, nose, and throat procedures. Out of 54 surgical procedures performed before diagnosis of HAE, abdominal surgeries were the most common (n=23, 42.5%). Of the total 27 abdominal surgeries, 23 (85.1%) were performed in patients presenting with gastrointestinal angioedema attacks before the diagnosis of HAE. Preoperative HAE prophylaxis was not administered in 63 (67.0%) procedures, and 52 (82.5%) of them occurred before the diagnosis of HAE.

The most commonly used prophylactic agent was plasma-derived C1-inhibitor (pdC1-INH) (n=24). Perioperative angioedema was observed in 28 (29.8%) surgeries, with a median recovery duration of 48.0 hours. In surgeries performed after the HAE diagnosis, attacks occurred in 7 out of 31 surgeries (22.6%) who received prophylaxis, compared to 2 out of 9 surgeries (22.2%) who did not receive prophylaxis.

Within gynecological surgeries, the most commonly reported procedure was cesarean sections (n = 22). Among a total of 22 cesarean sections, no significant difference in attack frequency was observed between the 11 cesarean sections who received prophylaxis and the 11 who did not (n= 3, 27.3%, and n=2, 18.2%,

respectively, p=0.611).

Conclusions: HAE may present with an abdominal attack which may result in unnecessary invasive abdominal procedures. It was noteworthy that prophylaxis did not affect the frequency of attacks in cesarean sections in our cohort.

49-O&P

Effective Use of Mass Spectrometry for Bradykinin Detection to Confirm Activation of the Plasma Kallikrein-Kinin System in Hereditary Angioedema

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Rationale: The etiology of recurrent angioedema can be either bradykinin-mediated angioedema (BK-AE) or, more commonly, due to mast cell activation. Hereditary angioedema (HAE) can be potentially fatal in undiagnosed, untreated, or mismanaged cases, leading to acute laryngeal attacks and asphyxiation. Establishing an accurate and precise diagnostic measurement of bradykinin for recurrent angioedema patients can distinguish between the two pathways, even allowing for optimized therapeutic management. This study aimed to use liquid chromatography-tandem mass spectrometry (LC-MS/MS) to quantitatively measure bradykinin (BK) levels in patients with hereditary angioedema (HAE) and non-histaminergic angioedema with normal C1-inhibitor levels (nl-C1INH HAE) compared to healthy subjects.

Methods: Whole blood samples were obtained from patients with chronic recurrent non-histaminergic angioedema with C4 and C1-Inhibitor function test results (sorted into two groups: HAE and nl-C1INH HAE) and healthy subjects (no history of angioedema). Quantification of bradykinin and its metabolites (BK 1-5, 1-7, 1-8, 1-9) was performed using a LC-MS/MS laboratory-validated test procedure after cold activation preparation of the samples over a time course of up to 5 days. The established BK reference interval (normal range) is <9.1 ng/ml.

Results: LC-MS/MS was performed on a total of 198 patient samples: HAE (n=78), nl-C1INH HAE (n=57), Healthy (n=63). The mean total BK results are as follows; the Reference Interval (RI-healthy group) was 2.1 ng/ml (standard error mean-SEM=0.35), HAE group: 189.9 ng/ml (SEM=25.04), nl-C1INH HAE group: 27.1 ng/ml (SEM=15.67). The comparison p-values between nl-C1INH HAE and RI is 0.0161, between HAE and RI is <0.0001, and between HAE and nl-C1INH HAE is <0.0001.

Conclusions: The results revealed significant levels of bradykinin (BK) in many patients previously diagnosed

with nI-C1INH HAE, confirming the etiologic nature of their recurrent angioedema attacks, although their overall mean BK levels were lower than those in the HAE group. Collecting blood samples during prodromal or acute angioedema attacks may provide additional BK findings in this group. As expected, HAE patients generally exhibited high levels of BK. The LC-MS/MS measurement of BK is a valuable tool in the diagnostic workup of all types of non-histaminergic angioedema cases.

50-P

Patient Support Groups for Hereditary Angioedema Associated with Improved Access to Diagnosis and Treatment: An Asia-Pacific Perspective

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Rationale: Hereditary angioedema (HAE) is a potentially life-threatening disorder where early diagnosis and treatment can improve outcomes. Patient support groups (PSG) advocate for improved access to diagnosis and treatment, but their impact remains unknown. This study aims to evaluate the impact of PSG on longitudinal HAE prevalence and medication access in the Asia Pacific (APAC).

Methods: An electronic questionnaire was distributed to representative HAE-knowledgeable physicians with national HAE organization(s) or PSG recognized by HAE International in the APAC. Regions were classified into

either advanced or emerging economies, and outcomes were analysed.

Results: Eleven of 15 (73.3%) representative countries participated (Advanced: 5, Emerging: 6). The establishment of PSG was associated with increased availability of HAE medication in regions with emerging economies (0% to 66.7%). Similarly, there was an overall increase in reported prevalence of 0.12 per million (63.0%, $p=0.008$), with a statistically significant increase in regions with emerging economies (0.12 to 0.19 per million, $p=0.028$) after establishment of PSG. The majority (72.7%) of representatives reported that "PSG made a positive difference in education and awareness" and reported use of PSG resources. Almost half (45.4%) agreed that "it was easier to find or gain access to tests since gaining support from HAE PSG", and more than one-third (36%) agreed "PSG made connections to find routes to diagnostic testing easier".

Conclusions: Findings of this study underscore the significance of PSG in addressing the challenges of HAE in regions with emerging economies, including improving access to HAE diagnosis and treatment in the APAC region.

51-P

Predicting Hereditary Angioedema Prognosis with a Next-Generation Sequencing Angioedema Panel

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Background: Hereditary Angioedema (HAE) is a rare autosomal dominant genetic disease often caused by mutations in the C1 inhibitor gene SERPING1, leading to dysregulated kallikrein-kinin system (KKS) activity and excessive bradykinin production. While numerous pathogenic mutations in SERPING1 and other KKS pathway genes have been identified, genetic diagnosis remains challenging for patients with HAE-like symptoms but unknown mutations. Additionally, potential genetic modifiers influencing disease severity require further investigation. Next Generation Sequencing (NGS) interrogates many targets at simultaneously on a large scale with the potential for clinical applicability. In our study, we conducted molecular diagnosis of HAE patients using a targeted 77-gene NGS panel focusing on genes involved in angioedema including coagulation, complement, and tissue-kallikrein pathways.

Methods: Genomic DNA was extracted from peripheral blood samples which underwent DNA fragmentation via amplicon assay, then a semiautomated library preparation process, followed by sequencing performed using Illumina flow cell technology. Bioinformatics

analysis and data interpretation were conducted using cloud-based commercial software. Large duplications or deletions were verified using multiplex ligation-dependent probe amplification (MLPA) or Sanger sequencing. The impact of identified variants was assessed using a combination of commercial and publicly available computational tools.

Results: A total of 92 previously diagnosed patient samples were sequenced by NGS, including 59 HAE, 30 non-HAE, and 3 healthy controls. Pathogenic SERPING1 mutations were found in all 59 HAE samples (100%), including a gross heterozygous deletion of exons 1-6 identified by MLPA and a novel 56 bp deletion in exon 6 detected by Sanger sequencing. Multiple additional variants identified by our NGS angioedema 77-gene panel met computational and segregation analysis criteria. These variants potentially impact genotype-phenotype correlations, as observed in two large family pedigrees, suggesting that angioedema-associated mutations may have a possible HAE disease-modifying clinical effect.

Conclusions: The detection of SERPING1 mutations by NGS correlated well with the clinical symptoms and signs of HAE. The additional findings of angioedema-associated mutations may modify the clinical severity of the primary SERPING1 phenotype. We designed and clinically validated an HAE molecular diagnosis workflow that has the potential to enhance clinical diagnosis and assist in selecting treatment options for patients with hereditary angioedema.

52-P

Impact of Attacks on Quality of Life in HAE Patients: Insights from a 2024 German Survey

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Rationale: Current HAE treatment guidelines emphasize achieving complete control over attacks to normalize patients' lives. HAE Vereinigung e.V. aimed to determine quality of life differences between patients with complete and incomplete control.

Methods: An online survey of HAE patients was conducted in May-June 2024. An independent t-test and ANOVA were used to define significant differences in quality of life by therapy type and attack frequency over the past six months.

Results: Sample: 122 patients participated, 56% on LTP, 44% on on-demand therapy. HAE Management: Despite

80% of patients expressing satisfaction with their treatment, complete control remains difficult to achieve: 31% of patients had 0 attacks, 28% had 1-3 attacks, and 41% had over 3 attacks in the past six months. Significant differences were observed: on-demand therapy patients had more frequent attacks, with 17% attack-free compared to 42% on LTP ($p < .001$). Physical Impact: 32% of patients reported physical limitations; on-demand therapy patients face more restrictions ($p = .05$). Those with 1-3 attacks had greater limitations compared to no attacks ($p < .001$). Work and school activities were less disrupted in patients with 0 attacks compared to those with 1-3 attacks ($p < .001$) and more than 3 attacks ($p < .001$). Emotional Impact: On-demand therapy patients experienced more anxiety, with over half fearing unexpected attacks. Conversely, 45% of long-term prophylaxis patients reported no fear of sudden attacks. Furthermore, patients with zero attacks felt significantly less burdened by their HAE compared to those with 1-3 attacks ($p < .001$) and those with over 3 attacks ($p < .001$). Social Impact: Patients with more than three attacks felt significantly more uncomfortable in public ($p < .001$) and avoided public appearances more ($p < .001$) than those with fewer attacks. Even those with 1-3 attacks cancelled more social events compared to those with no attacks ($p < .001$).

Conclusions: Patients with complete control over their attacks (0 attacks) reported significantly better outcomes in managing HAE compared to those with 1-3 or more than 3 attacks. Continuous adjustment based on patient-reported outcomes is essential to ensure that treatment plans address medical needs and quality of life aspects.

53-P

HAE nC1-INH: Treatment of Acute Attacks in Canada

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Rationale: Hereditary angioedema (HAE) is a severely debilitating and life-threatening rare disease presenting as unpredictable, recurrent/intermittent angioedema attacks in various parts of the body. There are three types of HAE. Types 1 and 2 result from deficiency and/or dysfunction of C1 inhibitor and HAE with normal C1 levels (HAE nC1-INH previously Type 3). HAE nC1-INH patients have limited access to acute treatment other than plasma-derived (pd) C1INH in Canada. This study was initiated to understand the effectiveness and impact of icatibant use for these patients.

Methods: HAE Canada (HAEC) conducted a national

survey in 2020 and extracted from that survey responses from patients with HAEnC1-INH. Also, in April 2024, HAEC conducted a survey of 103 patients with a diagnosis of HAEnC1-INH to better understand their acute treatment experience.

Results: Responses were obtained from 45 patients in 2020 and 27 in 2024. In 2020, medications used to treat acute attacks included pdC1-INH (39%), icatibant (30%) and tranexamic acid (5%). The remaining 27% responded other or not applicable. 65% used C1-INH >12 times a year; the remainder (35%), 1 to 6 times a year. 15% used icatibant >12 times a year, 23% 7 to 12 times, and 62% used it 1 to 6 times. In 2024, 22/27 respondents treated an acute attack with icatibant and 95% (21/22) found it effective. Of the 17/22 that provided information on time to relief, 14/17 had immediate (10-90 minutes) relief. Written comments about the use of icatibant included: ease of use, rapid action, lifesaving, reduced length and severity of attacks, ability to self-manage attacks, reduced fear and anxiety, and improved quality of life.

Conclusions: Canadian HAE nC1-INH patients treat acute attacks mainly with pdC1INH and icatibant. HAEnC1-INH patients who used icatibant to treat attacks found it effective, although it is not approved by Health Canada for this indication. Frequency of use differs for icatibant and pdC1-INH possibly due to access to the treatment. Having better access to a treatment for acute attacks that is self-injected, subcutaneously administered, and rapidly effective could reduce stress and health care costs and improve quality of life for patients with HAEnC1-INH.

54-P

Garadacimab Provides Early Onset of Protection Against HAE Attacks from Week 1 After First Administration

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Rationale: Hereditary angioedema (HAE) attacks impart a substantial disease burden. Garadacimab (anti-activated factor XII monoclonal antibody) demonstrated durable efficacy with a favorable long-term safety profile across the pivotal Phase 3 (VANGUARD) and Phase 3 open-label extension (OLE) studies. Early onset and durability of protection are critical to optimize HAE control and establish treatment confidence. This post hoc analysis elaborates on the early onset of efficacy and durable protection from HAE attacks demonstrated by garadacimab.

Methods: In the pivotal study, patients aged ≥12 years with HAE with C1-inhibitor deficiency/dysfunction received garadacimab 200 mg subcutaneously once monthly after a 400 mg loading dose (n=39) or placebo (n=25). In the OLE study, all patients who rolled over from prior studies and were newly enrolled (n=69) received garadacimab 200 mg once monthly. Newly enrolled patients received a 400 mg loading dose. Time-normalized monthly number of attacks at weekly (Weeks 1–4) and monthly intervals were analyzed in both studies. Pharmacokinetic (PK) parameters were evaluated after the loading dose in a representative subset of newly enrolled patients (n=15) in the OLE.

Results: In the pivotal study, garadacimab substantially reduced the mean (95% confidence interval [CI]) monthly number of attacks as early as Week 1 vs run-in (0.11 [-0.11–0.34] vs 3.07 [2.41–3.73], respectively), and compared with placebo (1.81 [0.74–2.88] vs 2.52 [2.13–2.91], respectively). Similarly, in the OLE, mean (95% CI) monthly number of attacks were reduced as early as Week 1 vs run-in (0.25 [0.01–0.50] vs 3.41 [2.79–4.04], respectively) for newly enrolled patients. Garadacimab had durable efficacy in both studies (mean monthly number of attacks reduced by ≥85% through Month 6 in the pivotal study and ≥87% through Month 14 for newly enrolled patients in the OLE). Garadacimab concentrations reached steady-state exposure after the loading dose and remained consistent over time.

Conclusions: Garadacimab provides early onset of protection from HAE attacks from Week 1 after first administration and durable protection. This is supported by consistent evidence from the pivotal and OLE studies and PK data from the OLE. These attributes contribute toward optimizing HAE control and provide confidence in the treatment effect of garadacimab.

55-P

Assessing the prevalence of sleep disorders among severe and uncontrolled patients with Hereditary Angioedema in Ecuador

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No presenter

Rationale: The prevalence of sleep disorders among patients with hereditary angioedema (HAE) is currently unknown. Nevertheless, their existence could influence their quality of living and general well-being, as shown in other medical conditions. The objective of this study was to describe for the first time the prevalence of sleep problems in Ecuadorian patients with HAE by employing several diagnostic methods.

Methods: This study was conducted to assess 21 Ecuadorian participants with HAE using the SATED, STOP BANG, Epworth Sleepiness Scale, and the Global Sleep Assessment Questionnaire (GSAQ). The participants were classified into two groups: controlled and uncontrolled per AECT, as well as severe and not severe groups per HAE-AS. This study investigated and compared the occurrence of good quality sleep, risk of OSA, sleepiness, and particular sleep disorders among different groups using descriptive analysis.

Results: Approximately 40% of the participants did not experience a good sleep quality based on the SATED evaluation. Within the uncontrolled and severe group, 38% and 25% respectively experienced poor sleep quality. The STOP BANG findings revealed that 62% of the individuals were classified as having an intermediate risk for OSA. Within the uncontrolled group, 54% had an intermediate level of risk. Within the severe group, 50% of individuals had intermediate-high risk. The Epworth Sleepiness Scale indicated that 31% in the uncontrolled group and 50% in the severe group experienced sleepiness. According to the GSAQ, OSA and Insomnia were the most prevalent sleep disorders, with rates of 57.1% and 48% respectively. These diseases were more common among the uncontrolled group.

Conclusions: This study demonstrates that individuals with HAE in Ecuador experience elevated frequencies of sleep disorders and bad quality of sleep. The research indicates that individuals with HAE require customized interventions for sleep problems to enhance their quality of life and overall health. Further research using bigger sample sizes is necessary to validate these conclusions and investigate potential underlying mechanisms.

56-O&P

Angioedema in Patients with Chronic Spontaneous Urticaria

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Rationale: Angioedema is a common and distressing symptom in patients with Chronic Spontaneous Urticaria (CSU). Understanding its prevalence and impact on disease severity can lead to improved patient management and quality of life. This study aims to enhance the understanding of angioedema in CSU, contributing to more effective approaches.

Methods: This study was conducted at the Dermatology Department of City General Hospital "8th September", Skopje North Macedonia. 230 CSU patients were included and angioedema was recorded. The Weekly Urticaria Activity Score (UAS7) was employed to evaluate disease activity by assessing CSU symptoms over seven consecutive days. Autoimmune status (categorized positive or negative) was determined based on a personal history of concomitant autoimmune disease or the presence of at least one type of autoantibodies. The Autologous Serum Skin Test (ASST) (categorized positive or negative) was performed by injecting the patient's own serum intradermally into the volar part of the forearm.

Results: Angioedema was present in 40% of CSU patients, occurring more frequently in: patients with a severe activity CSU compared to a moderate severe activity CSU (82.32% vs. 65.38%, $p=0.026$); patients with a severe activity CSU compared to a mild clinical activity CSU (82.32% vs. 65.96%, $p=0.0360$); and patients with a severe activity CSU compared to well-controlled disease (82.32% vs. 45.45%, $p=0.0004$). The association of autoimmune status and angioedema was statistically significant ($p=0.025$), patients with positive autoimmune status were significantly more likely to have angioedema compared to patients with negative autoimmune status (75.17% vs. 61.18%). Angioedema was noted more in patients with positive ASST compared to negative ASST patients ($p=0.38$); 72.14% of patients with a positive ASST test and 66.67% of patients with a negative ASST test had angioedema. The duration of CSU was significantly longer in patients with angioedema compared to those without angioedema ($p=0.000012$). Patients with angioedema had a mean CSU duration of 61.7 ± 46.2 months and a median disease duration of 54 months.

Conclusions: Our study brings more findings that underscore the complexity of CSU, particularly in patients with angioedema, and the need for comprehensive management strategies that consider disease activity, autoimmune status, and duration.

57-O

ALPHA-STAR, a Phase 1b/2 Clinical Trial of Single and Multiple Doses of STAR-0215 in Patients with Hereditary Angioedema: Initial Safety and Efficacy Results

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Rationale: STAR-0215 is an investigational humanized immunoglobulin G1 monoclonal antibody inhibitor of plasma kallikrein with long-lasting activity enabled by a YTE-modified Fc domain. ALPHA-STAR (NCT05695248) is an ongoing Phase 1b/2 clinical trial in patients with HAE, evaluating the safety, tolerability, efficacy, pharmacokinetics, pharmacodynamics, and immunogenicity.

Methods: Adults (n=16) with HAE Type 1 and 2, reporting ≥ 2 HAE attacks during the 8-week run-in period, were sequentially assigned to receive STAR-0215 subcutaneously. Participants were recruited into 3 dose cohorts, Cohort 1: 450 mg (day 1); Cohort 2: 600 mg (day 1), 300 mg (day 84); Cohort 3: 600 mg (day 1), 600 mg (day 28) and followed for 6 months after the last injection. Results reported here are from an initial analysis (data cut-off 13-Mar-2024).

Results: The mean age (SD) of study participants across all three cohorts was 46 (20) years, 56% were female, and 88% had Type 1 HAE. Safety and efficacy outcomes are based on 6.5 patient years (PY) of accumulated follow-up. Treatment-emergent adverse events (TEAEs) occurred in 13 (81%) participants and related TEAEs occurred in 2 (13%) participants who received STAR-0215. No moderate, severe, or serious TEAEs and no treatment discontinuations were reported. In Cohort 1 (n=4), mean/median) baseline attack rate per month was 2.7/2.9 and decreased to 0.22/0.18 post treatment, the mean/median percent reduction from baseline was 84%/94%. In Cohort 2 (n=6), mean/median baseline attack rates decreased from 2.3 /1.9 to 0.13/0.0, the mean/median percent reduction from baseline was

93%/100%. In Cohort 3 (n=6), mean/median baseline attack rate was 1.8/1.7 which decreased to 0.16/0.0 post STAR-0215 treatment, the mean/median percent reduction from baseline was 90%/100%. For the first 3 months, 50%, 67%, and 50% of participants with available follow-up were attack free in Cohorts 1-3, respectively. There were no severe HAE attacks during the treatment phase.

Conclusions: STAR-0215, a monoclonal antibody inhibitor of plasma kallikrein, has the potential to offer effective long-acting prevention of HAE attacks sustained for up to 6 months, supporting progression into Phase 3 to evaluate effectiveness of every 3- and 6-month administration.

58-P

Impact of Oral Sebetralstat on Anxiety Associated with Hereditary Angioedema Attacks in the Phase 3 KONFIDENT Trial

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Rationale: Many patients with HAE-C1INH experience severe anxiety during attacks, which may relate to the need to inject on-demand treatment. This analysis investigated attack-associated anxiety in the absence of injectable therapy in the phase 3 KONFIDENT trial and impact of sebetralstat on anxiety, compared with placebo.

Methods: In KONFIDENT (NCT05259917), participants (≥ 12 years) with HAE-C1INH treated ≤ 3 attacks with oral sebetralstat 300mg, 600mg, or placebo. Prior to administering study medication and for 24h after, participants self-reported anxiety using a Modified Generalized Anxiety Numeric Rating Scale (GA-NRS) from 0 (not at all anxious) to 10 (extremely anxious). Pearson correlation was used to determine the coefficients between GA-NRS and baseline demographics and attack characteristics. Cumulative GA-NRS was calculated as the area under the curve over 12h (AUC0-12) or 24h (AUC0-24) from administration. Least squares mean

(LSM) changes in GA-NRS from baseline through 12h post-baseline were calculated. Cohen's kappa analysis was used to determine agreement of a ≥ 2 -point reduction in GA-NRS within 12h, with time to beginning of symptom relief within 12h (primary endpoint).

Results: Of 264 treated attacks, 250 (sebetralstat 300mg: 83; sebetralstat 600mg: 87; placebo: 80) included GA-NRS records through 24h. Median baseline GA-NRS was 3.0. Among baseline variables, Patient Global Impression of Severity ("Very Severe" to "None") demonstrated the strongest correlation with GA-NRS. AUC0-12 and AUC0-24 were reduced with sebetralstat 300mg ($P=0.004$ and $P=0.022$, respectively) and 600mg ($P=0.0008$ and $P=0.0012$) versus placebo. For participants with moderate-to-extreme anxiety (4-10; median 5.0 for 300mg and 6.0 for 600mg and placebo), LSM change from baseline (95% CI) at 4h was -2.8 (-3.6 , -1.9) for each sebetralstat group and -1.3 (-2.2 , -0.4) for placebo and at 12h was -3.5 (-4.3 , -2.6) with sebetralstat 300mg, -4.3 (-5.2 , -3.5) with 600mg, and -1.7 (-2.6 , -0.8) with placebo. GA-NRS reductions of ≥ 2 points moderately agreed with the beginning of symptom relief (kappa: 0.47).

Conclusions: In the absence of injectable on-demand treatment, greater baseline attack severity was associated with greater baseline anxiety. Compared with placebo, sebetralstat significantly reduced anxiety, including in participants with moderate-to-extreme anxiety, and anxiety reduction was correlated with beginning of symptom relief.

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59-O

First Insights from the Global ACARE SHAERPA Study on Androgen Discontinuation in HAE Patients, An Interim Analysis

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Background: Managing Hereditary Angioedema (HAE) focuses on achieving complete disease control and a normal quality of life, primarily through long-term prophylaxis (LTP). Since the late 1970s, androgens like danazol have been used for LTP in HAE. However, due to significant adverse events such as weight gain, virilization, and depression, androgens are no longer recommended as first-line LTP.

Rationale: In recent years, safer and more effective LTP therapies have emerged, prompting a shift from androgen therapy to modern LTP. As of now, it remains unclear how androgens are best discontinued, i.e. by tapering or stopping all at once.

Methods: The global network of Angioedema Centers of Reference and Excellence (ACARE) launched the SHAERPA study (Stopping Androgen Treatment in Patients with HAE – Characterization of Rationale, Protocols, and Development of Advice for Patients and Physicians). SHAERPA uses two detailed questionnaires: a 55-question patient survey and a 23-question physician survey. The patient survey covers androgen type, dosage, adverse effects, treatment duration, and reasons for discontinuation. The physician survey focuses on reasons and protocols for discontinuation, as well as subsequent medication choices. SHAERPA is ongoing and aims to enroll 500 patients.

Results: Of 155 HAE patients (80 females; mean age 52 years) who discontinued androgen therapy, all had used danazol, for an average of 9.6 years (range 0.25-43 years). Key reasons for discontinuation included side effects ($n=25$), lack of efficacy ($n=15$), fear of side effects ($n=11$), and availability of alternative treatments ($n=11$). Common side effects were weight gain, altered libido, depression, headaches, menstrual irregularities, mood changes, and fatigue.

Two of three patients (67%) stopped androgen treatment all at once, and 37% tapered the dose. The most commonly used LTP treatments, after stopping androgen treatment, were lanadelumab ($n=21$), tranexamic acid ($n=14$), and C1 inhibitor ($n=10$). Sixteen physicians, with an average of 17 years of experience (range 5-35), reported treating 5-840 HAE patients, with 30% of their patients (range 0-100) still on androgen

therapy.

Conclusions: The SHAERPA study highlights that different protocols are used for the discontinuation of androgen treatment in HAE. The inclusion of further patients in SHAERPA is encouraged and can be expected to provide more insights on how androgen treatment is best continued.

60-O

Lanadelumab Effectiveness and Safety in Adolescent Patients with Hereditary Angioedema Aged 12 to <18 Years: Pooled Results From the Real-World ENABLE and EMPOWER Studies

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Rationale: Data on long-term prophylaxis (LTP) outcomes in adolescents with hereditary angioedema (HAE) are scarce. ENABLE (NCT04130191) and EMPOWER (NCT03845400) are observational, real-world, Phase IV studies evaluating the long-term (≤ 3 years) effectiveness and safety of lanadelumab LTP in patients ≥ 12 years of age with HAE. This post hoc analysis uses pooled ENABLE and EMPOWER study data to assess lanadelumab treatment outcomes among adolescent patients in clinical practice.

Methods: Adolescents (12–17 years) with HAE Type I/II who were receiving open-label lanadelumab LTP in the ENABLE and EMPOWER studies were included in this analysis. Effectiveness (based on patient-reported [via smartphone application] and routine clinic visit data) and safety (treatment-emergent adverse events [TEAEs]) were analyzed in patients new to lanadelumab (< 4 lanadelumab doses before enrollment [i.e. before attainment of lanadelumab steady-state]; 'new patients') and patients established on lanadelumab (≥ 4 lanadelumab doses before enrollment; 'established patients').

Results: Overall, 13 new patients (mean \pm SD age: 15.2 \pm 2.0 years, mean \pm SD weight: 77.4 \pm 32.3 kg, female: 53.8%, HAE

Type I: 76.9%) and 7 established patients (mean \pm SD age: 15.7 \pm 1.4 years, mean \pm SD weight: 87.8 \pm 34.8 kg, female: 71.4%, HAE Type I: 85.7%) were included; all patients were White. HAE attack rate (model estimated) in new patients decreased by 87% post-lanadelumab, from 3.99 (95% CI 2.19–7.25) attacks/month at baseline (pre-enrollment) to 0.53 (95% CI 0.25–1.14) attacks/month post-lanadelumab (incidence rate ratio [IRR] 0.13, 95% CI 0.08–0.24), and by 90% (IRR 0.10; 95% CI 0.06–0.17) during lanadelumab steady state (Day 70 onward). In established patients, mean \pm SD HAE attack rate during the overall study period was 0.0 \pm 0.03 attacks/month. Most HAE attacks were of mild/moderate intensity, were treated with on-demand medications (most frequently C1-esterase inhibitors or icatibant) and did not require visits to healthcare facilities. There were 42 treatment-emergent adverse events (TEAEs; mild/moderate: 88.1%, non-serious: 92.9%) in 9/13 new patients and 10 TEAEs (all mild/moderate and non-serious) in 6/7 established patients. No injection-site reactions or lanadelumab-related TEAEs were reported.

Conclusions: In keeping with findings from pivotal studies in mixed adult/adolescent HAE populations, data from real-world settings indicate that lanadelumab has sustained effectiveness and is well tolerated in adolescents.

61-O&P

Long-Term Efficacy and Safety of Oral Deucricitibant, a Bradykinin B2 Receptor Antagonist, in Treatment of Hereditary Angioedema Attacks: Results of the RAPIDE-2 Extension Study

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Rationale: Hereditary angioedema (HAE) attacks are caused by excess bradykinin activating bradykinin B2 receptors. Deucricitbant is a selective, orally administered antagonist of the bradykinin B2 receptor under development for on-demand and prophylactic treatment of HAE attacks. In the RAPIDe-1 Phase 2 trial (NCT04618211), deucricitbant immediate-release (IR) capsule reduced time to onset of symptom relief and to resolution of HAE attacks and reduced use of rescue medication compared with placebo; treatment was well-tolerated.

Methods: RAPIDe-2 (NCT05396105) is an ongoing Phase 2/3 extension study evaluating long-term efficacy and safety of orally administered deucricitbant IR capsule for the treatment of HAE attacks. Part A of this study enrolls adult (≥ 18 years) participants who completed RAPIDe-1 and meet the eligibility criteria. Participants continue self-administering the same double-blinded dose of deucricitbant IR capsule (10 mg, 20 mg, or 30 mg) received in RAPIDe-1 to treat qualifying non-laryngeal attacks as well as laryngeal attacks presenting without breathing difficulties.

Results: This Part A data snapshot (cut-off: 01 March 2024) included 265 qualifying attacks treated with deucricitbant IR capsule by 17 participants (combined dose group results reported). Participants' mean age was 43.9 years at RAPIDe-1 enrollment; 61.1% were female. Median time to onset of symptom relief, defined as PGI-C "a little better", was 1.1 hours (95% CI, 1.0–1.2), with 98.5% of attacks achieving onset of symptom relief by 12 hours. Median time to reduction in attack severity, measured as PGI-S ≥ 1 point reduction, and to complete resolution, measured as PGI-S "none", was 2.6 (2.0–2.9) and 11.5 (11.0–13.0) hours, respectively. In total, 84.5% of attacks achieved complete resolution within 24 hours, with 90.2% of these attacks achieving this milestone with a single dose of deucricitbant IR capsule. One of 265 attacks was treated with rescue medication after 2 doses of deucricitbant IR capsule. Deucricitbant IR capsule was well-tolerated with no new safety signals observed.

Conclusions: Results of the RAPIDe-2 extension study provide evidence on the long-term efficacy and safety of deucricitbant IR capsule for treatment of HAE attacks. The vast majority of attacks achieved early onset of symptom relief and complete resolution with a single dose of deucricitbant IR capsule.

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Treatment of HAE Attacks with Anticipated Future Oral On-demand Therapies as Reported by Patients

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Rationale: While self-administered, parenteral on-demand treatments (currently only subcutaneous or intravenous) are available for hereditary angioedema (HAE) attack management, oral therapies presently in development may provide patients alternatives to current on-demand treatment options.

Methods: Patients with Type I or II HAE who were recruited by the US Hereditary Angioedema Association completed a 20-minute, self-reported, online survey from September 6 to October 19, 2022. Data collected on anticipated behavior related to potential oral on-demand treatments was assessed.

Results: Respondents included 107 Type I or II HAE patients, 80.4% female, with a mean age of 41 years. When asked the question "What percent of the time do you think you would carry an effective HAE on-demand pill/tablet with you when traveling outside your home?" patients reported that they anticipated carrying an oral on-demand treatment 95.1% of the time on average compared with a baseline of 63.9% with current parenteral on-demand treatment. When asked "What percent of attacks do you think you would treat with an HAE on-demand pill/tablet?" patients reported that they would treat 88.5% of their attacks on average with an oral on-demand treatment (96.1% of attacks for patients 24 years of age or younger) compared with a baseline of 80.3% with current parenteral on-demand treatment (72.5% of attacks for patients 24 years of age or younger). When asked "Would you treat your attacks faster/earlier with an HAE on-demand pill/tablet versus your current on-demand treatment?" 75.7% of patients reported that they would plan to treat their attacks earlier with an oral on-demand treatment vs parenteral, including 100% (n=14) of patients 24 years of age or younger. Of the patients who answered "yes" 82.9% were extremely anxious about parenteral on-demand treatment, and of those, 80% reported that they would have less anxiety when anticipating using an oral on-demand treatment.

Conclusions: Based on this survey, people living with HAE currently using parenteral on-demand treatment may treat more of their attacks and treat earlier with an oral on-demand treatment option if approved, and are likely to experience less anxiety when anticipating administration of an oral on-demand treatment.

63-P

The Chronic Angioedema REgistry (CARE): Rationale, Methods, and Implementation

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Background: Different types of recurrent angioedema must be better characterized and understood, partly because each subtype requires different treatments. Disease registries enable us to evaluate features of angioedema in real life. CARE, the Chronic Angioedema Registry, was initiated in 2023 by the global network of Angioedema Centers of Reference and Excellence (ACAREs). It is the first medical registry for all types of recurrent angioedema.

Rationale: CARE aims to gather knowledge about different types of angioedema by collecting and analysing patient data, thereby improving disease understanding and patient care. CARE is a web-based, international, investigator-initiated, observational, open-ended registry driven by its investigators' academic and scientific interests (<https://chronic-angioedema-registry.com>). CARE collects real-life data on different types of recurrent angioedema, e.g., mast cell-mediated angioedema with and without wheals, bradykinin-mediated angioedema, hereditary angioedema, drug-induced angioedema, and angioedema of unknown origin. CARE aims to collect data without intentional selection or exclusion criteria and is open to all physicians treating patients with recurrent angioedema.

Methods: CARE plans to enrol at least 1,000 patients in the first three years to generate a comprehensive database for diverse sub-analyses. Core variables will be assessed at baseline and every follow-up visit; they include demographic data, disease duration, disease course, frequency, underlying causes, comorbidities, triggering factors, treatment responses, disease activity, disease control, quality of life impairment, and direct healthcare costs. CARE core variable data will be analysed twice yearly, and specific analyses will be performed for investigator-proposed research questions.

Conclusions: CARE is the first international registry to enrol patients with all types of angioedema to monitor core factors and assess sociodemographic and clinical factors that will bridge knowledge gaps regarding managing angioedema, which marks a milestone in our knowledge. Collecting real-life data will equip physicians and researchers with better information on managing, monitoring, and improving patient care in angioedema.

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Garadacimab Improves Quality of Life in Patients with Hereditary Angioedema: Results From the Phase 3 Open-Label Extension Study

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Rationale: Hereditary angioedema attacks are unpredictable, recurrent, potentially life-threatening, and substantially impair quality of life (QoL). The goal of treatment is to completely control disease and normalize patients' lives, per current guidelines. Garadacimab (anti-activated factor XII monoclonal antibody) reduced mean attack rate in the pivotal Phase 3 (VANGUARD) study (87% vs placebo) and ongoing long-term Phase 3 open-label extension (OLE) study (NCT04739059; 95% vs run-in). Garadacimab was also associated with substantial QoL improvements in both studies. This post hoc analysis reports categorized AE-QoL scores and treatment satisfaction from the long-term OLE.

Methods: Patients received garadacimab 200 mg subcutaneous once monthly. The patient population comprised previous garadacimab exposure (GPE; n=71; who received garadacimab in prior Phase 2 or 3 studies) and garadacimab-naïve (GN; n=90; who received placebo in prior Phase 3 study or were newly enrolled) cohorts. Change from baseline and degree of impairment in AE-QoL was evaluated at Month 12. A ≥ 6 -point decrease from baseline in mean total AE-QoL score was defined as minimal clinically important difference (MCID). Degree of impairment was categorized by mean total AE-QoL score: none (≤ 23 points), small (24–38 points), moderate/large (≥ 39 points). AE-QoL OLE baseline measures for GPE patients were equivalent to prior study last measurement. Treatment Satisfaction Questionnaire for Medication II (TSQM II) was completed at Month 12 (perfect satisfaction = mean score of 100).

Results: Overall, AE-QoL data from 49 GPE and 63 GN patients were analyzed. Due to QoL improvements in prior studies, most GPE patients (83.7%) reported no impairment at OLE baseline, which was sustained to Month 12. Per MCID, 81.6% of GPE patients experienced QoL stability (from prior study) or further improvement. Of GN patients, 92.1% achieved MCID in AE-QoL total score at Month 12. In total, 73.0% of GN patients reported moderate/large QoL impairment at baseline which improved at Month 12 to 81.0% reporting no QoL impairment. Of note, both GPE and GN cohorts reported high treatment satisfaction up to Month 12 (TSQM II mean scores 96.6 and 92.7, respectively).

Conclusions: Garadacimab elicited clinically meaningful, long-term improvements in QoL. Most patients reported no QoL impairment at Month 12 and high treatment satisfaction.

65-P

Evaluation of Adherence to Berotralstat in Patients with Hereditary Angioedema: A Prospective Survey in Community Pharmacies

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Rationale: Medication adherence is crucial for effective management of chronic diseases. This prospective study evaluates the impact of monthly follow-up and therapeutic monitoring by community pharmacists on adherence to berotralstat, a first line, once-daily (QD)

oral prophylactic treatment for hereditary angioedema (HAE).

Methods: A survey was administered to eligible patients with HAE in France upon the second dispensing of berotralstat and monthly thereafter for up to 12 months. Medication adherence was assessed using the Morisky questionnaire (primary endpoint); scores range from 0-8 (poor adherence if ≤ 6). HAE attacks and treatment-emergent adverse events (TEAEs) were also collected. Fisher's exact test was used to determine an association between adherence to berotralstat and HAE attacks or TEAE occurrence. Here, we report interim results through June 15, 2023.

Results: Forty-seven patients initiated berotralstat 150 mg QD in this study; 23 completed 6 months of treatment, of which 20 completed the Morisky questionnaire monthly through 6 months. At Month 6, 14/20 (70%) patients had a Morisky score of 8 (high adherence) and the median monthly HAE attack rate was 0 attacks/month (mean \pm SD=0.82 \pm 1.15; n=23). Overall, TEAEs were reported in 23/47 (49%) patients. The most common TEAEs were bloating/flatulence (27%), diarrhea (26%), upper abdominal pain (15%), and abdominal pain (15%). Discontinuations due to TEAEs occurred in 5/47 (10.5%) patients. High adherence to berotralstat was associated with no HAE attacks ($p < 0.005$), but not with TEAE occurrence ($p = 0.8$).

Conclusions: High adherence to berotralstat and consistently low attack rates were observed in patients with monthly follow-up and monitoring by community pharmacists. Moreover, adherence to berotralstat was significantly associated with effectiveness.

66-P

Clinical Features of Hereditary Angioedema: The First Tunisian Survey

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Rationale: No published data presently exist concerning hereditary angioedema (HAE) in Tunisia. The aim of this study was to establish the clinical and immunological characteristics of hereditary angioedema in our country.

Methods: A cross-sectional study including patient enrolled at the Internal Medicine department B of Charles Nicolle hospital in Tunisia. The study period was 2 years (2022-2024).

Results: A total of 50 patients diagnosed with HAE were identified. Male to female ratio was 0.9. The patients

were divided into eleven families.

The mean age of the patients was 35.7 years ranging from 6 to 70 years old. The mean age at the time of the first angioedema-related symptom was 10.8-year-old and the age of diagnosis was 31 years. Diagnosis delay was 20.2 years on average.

All subjects had type I HAE. A family history of angioedema symptoms was noted in 90% of cases. Triggering factors such as stress, trauma and infection were reported in 82% of cases. The presence of prodromes was noted in 68% of cases.

Clinical presentation included cutaneous swelling involving the extremities in 72% and the face in 46% of the cases. Acute abdominal pain was reported by 74% of the patients.

At least one laryngeal attack was observed in 40% of the patients resulting in 3 deaths.

Long-term prophylaxis was conducted in 58% of patients using Tranexamic acid or Danazol.

Conclusions: Our study showed that the clinical features of Tunisian HAE patients were consistent with previously described patterns of this rare disease. The most noteworthy feature identified was a significantly long diagnosis delay. The absence of targeted therapy was at the origin of the three reported deaths.

67-P

Ecological Momentary Assessment for Patients with Hereditary Angioedema: A Feasibility and Acceptability Controlled Study

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Rationale: Hereditary Angioedema (HAE) is a rare disease characterized by unpredictable swelling, impacting quality of life. Symptoms and emotional state monitoring using Ecological Momentary Assessments (EMAs) method could identify unmet needs, useful to structure personalized care. This approach enables ecological collection of experiences and psychological states, overcoming the limitations of paper-and-pencil questionnaires, and providing a dynamic understanding of mental phenomena. The potential of EMAs in HAE is unexplored. This study aims to assess EMAs feasibility and acceptability in HAE patients for the evaluation of momentary affective states.

Methods: HAE patients from the Italian Network of Hereditary and Acquired Angioedema (ITACA) cohort and healthy individuals with access to technological devices, were recruited. EMA prompts were weekly administered

for 16 weeks. Surveys were distributed via email using the REDCap™ platform on different days and times of day, asking participants to answer within 1.5 hours. The EMAs consisted of ten items that assessed affective states using the Positive Activation, Negative Activation and Valence scale (PANAVA-KS), using sliders with a pair of validated emoticons positioned at the edges to represent opposite emotional states (e.g. Stressed-Relaxed or Enthusiastic-Bored). Feasibility was assessed through recruitment, response, and completion rates, as well as survey completion time and return time. Participants were ultimately interviewed with a 7-item questionnaire, featuring 0 to 100 sliders, to examine EMA acceptability.

Results: Twenty-eight eligible individuals were contacted. Twelve HAE patients (age: 50 [22] years, 5 males) and 14 healthy subjects (age: 30 [32] years, 6 males) agreed to participate (93% recruitment rate). Response rates were 92% and 93% for HAE and healthy groups, respectively. Completion rates exceeded 96% in both groups. No significant differences were observed in survey completion time (1' 28" [0' 29"] vs 1' 15" [0' 15"], $P=0.274$), with 96% of EMAs completed in less than 3 minutes. Most participants responded within 1.5 hours throughout the study period. EMAs were generally deemed acceptable, with HAE patients finding the study more thought-provoking than controls (67.0 [33.0] vs 50.0 [23.0], $P=0.046$).

Conclusions: EMAs proved to be a feasible and acceptable method for continuous affective activation monitoring in HAE, providing ecological, unobtrusive, and continuous data.

68-P

Ecological Momentary Assessment of Affect: A Complementary Tool for Enhancing QoL Evaluation in Hereditary Angioedema

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Rationale: Disease-specific quality of life (QoL) questionnaires for Hereditary Angioedema (HAE) assess the overall burden of the disease, without capturing affect fluctuations. Ecological Momentary Assessment (EMA), a novel tool for monitoring individuals' experiences in natural settings, could be adopted to outline patients' affect and complement the traditional QoL assessments in the HAE scenario. This study aims to examine the differences in affective states using EMA between HAE patients and healthy individuals.

Methods: HAE patients from the Italian Network of

Hereditary and Acquired Angioedema and healthy individuals were recruited to complete EMAs weekly for 16 weeks via electronic devices. Each EMA included ten items investigating affect in terms of positive activation (PA), negative activation (NA), and valence (VA) based on the PANAVA-KS scale with validated emoticons. Each item was composed of a slider ranging from -3 to +3, with two emoticons at the extremities representing opposite emotional states (e.g., Stressed-Relaxed, Enthusiastic-Bored, etc.). HAE patients also completed the AngioEdema-QoL (AE-QoL) and Angioedema Control Test (AECT). PA, NA, and VA scores were compared between the two groups using the Wilcoxon Mann Whitney test and correlated with the clinical scales using Spearman's rho.

Results: Twelve HAE patients (age: 50 [22] years, 5 males, AECT: 15 [2.3], AE-QoL: 28 [13.5]) and fourteen healthy subjects (age: 30 [32] years, 6 males) were recruited. No significant differences in PA (0.6 [1.3] vs 0.1 [1.0], $p=0.165$) and NA (-0.7 [1.8] vs 0.2 [0.6], $p=0.181$) were found. A significant difference was noticed in VA (1.1 [1.2] vs 0.3 [0.7], $p=0.016$).

PA showed a negative correlation with AE-QoL (-0.78, $p=0.003$), as well as with almost all its domains ($\rho \leq -0.58$, $p < 0.05$). VA showed a negative correlation with AE-QoL ($\rho = -0.68$, $p=0.014$) and its Fatigue/Mood subscale ($\rho = -0.65$, $p=0.022$).

Conclusions: HAE patients do not differ from healthy individuals regarding emotional arousal, but their emotions are perceived as more positive. The correlations between PA, VA, and AE-QoL suggest that affect monitoring through EMAs is a complementary tool for enhancing QoL assessment in HAE. Therefore, affect monitoring proved to be a useful nonspecific tool for comparing patients with a rare and chronic disease with healthy individuals, and enhancing QoL assessment.

69-P

Real-World Effectiveness of Lanadelumab in Patients with HAE Type I/II: Data across the Four Countries from the INTEGRATED Study

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Rationale: Hereditary angioedema (HAE) is characterized by recurrent angioedema associated with

bradykinin pathway gene mutations. Lanadelumab is a long-term prophylaxis (LTP) treatment (tx) indicated for routine prevention of recurrent attacks of HAE in patients aged ≥ 2 years according to the EU label. A starting dose of lanadelumab 300 mg every 2 weeks (Q2W) is recommended for patients aged ≥ 12 years. In patients who are stably attack-free on the Q2W scheme, the physician can reduce the frequency to once every 4 weeks (Q4W). The INTEGRATED real-world evidence study aimed to assess the effectiveness of Q2W lanadelumab, and lanadelumab dose interval adjustments, in preventing HAE attacks.

Methods: A European historical cohort study utilizing medical chart data from HAE type I/II patients ≥ 12 years in Germany, France, Austria, and Greece). Patients initiated lanadelumab commercially or according to Authorization for Temporary Use (ATU; France only) between Aug 2018 - May 2021. Data were collected from lanadelumab initiation (index event) to earliest of discontinuation, death, loss to follow-up, or chart abstraction initiation (end of follow-up). Patient and tx history were collected 12 months (mos) pre-index.

Results: A total of 198 patients were included (Germany: 76, France: 86 [49/86 enrolled from the ATU], Austria: 14 and Greece: 22). 118 (59.6%) patients used LTP pre-index. Median duration of lanadelumab tx varied from 25.1 mos (Greece) to 29.9 mos (Germany). During the study period, 144 patients (72.7%) had ≥ 1 increase in dosing interval (highest for Austria; 100% and lowest for Greece; 40.9%). Mean (SD) time to first interval increase ranged from 5.5 (2.24) mos (Germany) to 10.9 (5.72) mos (France) post-index. All patients experienced HAE attacks pre-index; patients without attacks in the first 12 mos post-index (cumulative attack-free rate [AFR]) varied from 40.9% (Greece) to 69.9% (France). Over the entire post-index period, the cumulative AFR ranged from 28.6% (Austria) to 48.8% (France). Patients with interval increases showed improved cumulative AFR post-index (50.0%) compared to pre-index (0%).

Conclusions: Despite different LTP strategies pre-index, lanadelumab LTP improves the AFR in HAE type I/II patients in Germany, France, Austria and Greece, whether the patient is on Q2W or has dose interval increases.

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70-P

Global Frequency and Diagnosis of Hereditary Angioedema with Normal C1INH: A Real World ACARE Survey

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Rationale: The pathophysiology of hereditary angioedema (HAE) Type 1 (HAE-C1INH-Type1) and 2 (HAE-C1INH-Type2) is well characterized; however, HAE associated with normal C1-INH activity (HAE-nC1INH) is most often of unknown etiology. A global standardized algorithmic diagnostic approach is lacking, limiting precise prevalence estimates to inform management, including treatment. The current study aimed 1) to assess the global frequency of presumptively diagnosed HAE-nC1INH; and 2) to characterize the diagnostic pathway of patients with HAE-nC1INH, including types of testing and time to diagnosis.

Methods: Board-certified HAE-treating physicians, practicing at accredited Angioedema Centers of Reference and Excellence (ACAREs) completed a 27-item online survey based on personal recall between December 2022 and April 2023.

Results: Thirty physicians from 30 global ACAREs in 15 countries reported a mean treatment volume of 71 patients with all types of HAE within the previous 12 months (min: Argentina n=11; max: Netherlands n=148). On average, 24% of patients with HAE were diagnosed with HAE-nC1INH, compared to 66% with HAE-C1INH-Type1 and 10% with HAE-C1INH-Type2. The mean duration of symptoms prior to HAE-nC1INH diagnosis was 9 years, ranging from 2 years in the UK to 30 years in Peru. Most (88%; range: 33%-100%) patients with HAE-nC1INH were adults (≥ 18 yrs), and 12% were pediatric (range: 0%-67%), with proportions varying by country. On average, 9 (range: 5 [Argentina and Russia] to 14 [Austria]) criteria were used to diagnose HAE-nC1INH; leading criteria included family history (90%), plasma C4 levels (90%), C1 function and quantitative levels (87% each), Factor XII (83%), response to antihistamines (73%), and response to HAE-specific medication (70%). Icatibant (91%) and intravenous plasma-derived C1 inhibitor (10%-52%) were the most common treatments for confirming diagnosis. Utilization of genetic testing (other than Factor XII) for diagnosis was highly variable across countries.

Conclusions: These findings highlight variable clinical

approaches and substantial delays in the diagnosis of HAE-nC1INH. HAE-nC1INH may be more prevalent than previously reported; however, the development of reliable, validated, and easily accessible biomarkers are needed to improve accurate diagnosis and clinical management of people living with HAE-nC1INH.

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71-P

Real-World Effectiveness and Safety of Lanadelumab for Hereditary Angioedema Attack Prophylaxis: A 3-Year Interim Analysis of the ENABLE Study

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Rationale: ENABLE (NCT04130191) is an ongoing Phase IV noninterventional, prospective, multicentre study evaluating lanadelumab long-term effectiveness in patients with hereditary angioedema (HAE) in real-world clinical practice. Interim analysis (11 December 2019-17 April 2023) results expand on previously reported 24-month data.

Methods: Patients aged ≥ 12 years with HAE Type I/II who initiated lanadelumab treatment per approved product labelling are recruited from 18 sites across Austria, Germany, Israel, Italy, Kuwait, Spain and Switzerland. Patients are followed up for up to 24 months (if enrolled on/after 1 March 2021) or 36 months (if enrolled before 1 March 2021). The primary effectiveness outcome is the incidence rate ratio of on-treatment HAE attacks after lanadelumab initiation compared with the 3 months before lanadelumab use (baseline). Safety is evaluated by treatment-emergent adverse events (TEAEs).

Results: Of the 140 patients enrolled (HAE Type I, 129; Type II, 10; undifferentiated Type I/II, 1), 2 did not receive lanadelumab within 7 days of their baseline visit. Patient age (mean \pm SD) was 41.0 \pm 14.4 years, 62.3% were female, 97.8% White, 68.1% had a medical history event at any time before enrolment. Mean \pm SD time

from HAE symptom onset to diagnosis was 8.8 \pm 11.2 years. Mean \pm SD time on lanadelumab treatment was 603.6 \pm 289.1 days. Most (97.1%) patients initiated lanadelumab with every 2 weeks dosing; by month 36, 43.1% reduced dosing frequency to every 4 weeks. HAE attack rate decreased from a mean 3.70 (95% CI, 3.19-4.28) attacks/month at baseline to 0.35 (95% CI, 0.27-0.46) on treatment; 86 (65.2%) patients had $\geq 90\%$ HAE attack rate reduction versus baseline. Most (84.0%) of the 505 TEAEs (reported in 98 [71.0%] patients) were unrelated to lanadelumab, mild (55.8%) or moderate (38.4%), and nonserious (97.2%). There were no deaths due to TEAEs and no serious lanadelumab-related TEAEs; 1 (0.2%) TEAE (unrelated to lanadelumab) led to study discontinuation. By MedDRA System Organ Class, the most frequent treatment-related TEAEs were general disorders and administration site conditions (65 events in 26 patients) and nervous system disorders (5 events in 5 patients).

Conclusions: These results demonstrate lanadelumab long-term effectiveness in reducing HAE attacks in real-world patients with HAE aged ≥ 12 years, and a safety profile consistent with previous studies.

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72-P

Prevalence of Autoimmune Diseases in Iranian Patients with Hereditary Angioedema

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Rationale: Hereditary angioedema (HAE) is a rare genetic disorder characterized by recurrent episodes

of severe swelling. Recent studies have suggested a potential link between HAE and autoimmune diseases but the prevalence remains debated. This study aimed to investigate the prevalence and types of autoimmune diseases in a cohort of Iranian patients with HAE.

Methods: We retrospectively analyzed the data of 141 patients with HAE registered in the Iranian HAE Registry (IHR) database. Patients with documented autoimmune diseases were identified, and the types of autoimmune diseases were recorded.

Results: Out of the 141 HAE patients, 11 patients (7.8%) exhibited manifestations of autoimmune diseases. Among these patients, 8 were female and 3 were male. 9 had HAE type I (81.8%) and 2 had HAE type II (18.2%). 7 patients (63.6%) had more than one autoimmune disease. The autoimmune diseases observed included rheumatoid arthritis in 7 patients, hypothyroidism in 5 patients, systemic lupus erythematosus (SLE) in 4 patients, psoriasis in 2 patients, discoid lupus erythematosus (DLE) in 1 patient and vitiligo in 1 patient.

Conclusions: Our findings suggest a potential association between HAE and certain autoimmune diseases, particularly rheumatoid arthritis and hypothyroidism. In addition, our study highlights the importance of screening HAE patients for autoimmune comorbidities, as the coexistence of these conditions can worsen disease severity and complicate management. Further large-scale studies are needed to confirm this relationship and elucidate the underlying mechanisms. Early recognition and management of comorbid autoimmune conditions may improve the overall health and quality of life of patients with HAE.

73-P

Adverse Health Outcomes and Patient and Physician Perspectives of Attenuated Androgen Use in Hereditary Angioedema

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No presenter

Rationale: Attenuated androgens (AAs) have historically been used as long-term prophylaxis (LTP) in hereditary angioedema (HAE) and are still used in certain countries due to limited access to newer treatments. This systematic literature review (SLR) builds upon previous research to better characterize the outcomes of AAs, including adverse events, comorbidities, cardiovascular

(CV) risk, and patient and physician perspectives of the risks associated with AAs.

Methods: MEDLINE and EMBASE were searched to identify studies published between January 1980 and July 2023 that reported quantitative outcomes associated with AA use in patients with HAE with no geographic or language restrictions. Prospective and retrospective studies, case series/reports, and surveys were included; the reference lists of literature reviews were screened for additional primary literature.

Results: A total of 108 studies were included, with 4 clinical trials, 43 observational studies, 37 case reports/series, and 24 reviews. Most studies were conducted in Europe (n=39) and the United States (n=19). Several adverse outcomes emerged with AA use, including increased body weight, menstrual irregularities, virilization, myalgia, acne, and liver damage. Hepatocellular carcinoma, increased coagulation activation, hypertension, and hypercholesterolemia were reported with prolonged AA use (≥ 5 years); even at low doses (danazol 100-300 mg/day). Changes in CV risk factors such as lipid profile (elevated low-density lipoprotein-cholesterol [LDL-C] and non-high-density lipoprotein-cholesterol [non-HDL-C], and low HDL-C), inflammation markers, and endothelial dysfunction were reported. Patients and physicians cited concerns with the use of AAs related to tolerability, fear of adverse events, and long-term adherence. In a 3-part survey, the percentage of clinicians unwilling to prescribe AAs increased from 18% in 2010 to 60% in 2019, likely reflective of alternative prophylactic treatments available.

Conclusions: Our findings point to a sizeable body of evidence on commonly reported and serious adverse outcomes of AAs for HAE prophylaxis and increased reluctance of physicians to use them in clinical practice. The risk benefit profile of AAs highlights the importance of access to targeted therapies in patients currently receiving AAs, in line with current WAO/EAACI guidelines for first-line LTP therapy. Further research is needed to understand the long-term CV outcomes associated with AA use in patients with HAE.

74-P

Reduction in Plasma Kallikrein by CRISPR-Based Gene Editing of KLKB1 Did Not Alter Coagulation in the Phase 1 Study of Patients With Hereditary Angioedema

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Rationale: Hereditary angioedema (HAE), a rare genetic disorder characterized by severe and unpredictable swelling attacks, results from a dysregulated contact activation pathway and increased bradykinin production. Kallikrein inhibition is clinically validated as a therapeutic target for treatment of HAE. Individuals with congenital prekallikrein deficiency (Fletcher factor syndrome) are reported to be healthy aside from observed prolongation of activated partial thromboplastin time (aPTT); this is not associated with increased risk of hemorrhage. NTLA-2002 is an investigational, in vivo CRISPR-based therapy administered as a one-time treatment to reduce total plasma kallikrein protein levels by permanently editing the KLKB1 gene to prevent angioedema attacks. We describe effects of KLKB1 reduction on aPTT in NTLA-2002-treated patients.

Methods: A phase 1/2 study of adults with HAE is ongoing (NCT05120830). Phase 1 dose escalation is complete; primary endpoints were safety and tolerability. Patients received a single dose of NTLA-2002: 25 mg (n=3), 50 mg (n=4), or 75 mg (n=3). aPTT was measured utilizing standard silica-based mechanical detection methods.

Results: At the time of analysis, median follow-up duration was 20.1 months. The most frequent adverse events (AEs) were infusion-related reactions and fatigue. No treatment-emergent serious AEs or Grade ≥ 3 AEs were observed. No patients experienced thromboembolic or bleeding events. A dose-dependent reduction in total plasma kallikrein was observed, with mean reductions from baseline to latest assessment of 60%, 88%, and 95% at the 25 mg, 50 mg, and 75 mg doses, respectively, without prolongation of aPTT. At latest assessment, aPTT ranged between 24.6-32.1 seconds, within the laboratory reference range of 20.4-35.1 seconds. A mean reduction of 98% from baseline to latest assessment was observed in monthly angioedema attack rate in all patients.

Conclusions: A single dose of NTLA-2002 was well tolerated. Treatment resulted in a significant, dose-dependent reduction in total plasma kallikrein and a durable reduction of angioedema attacks without apparent clinical consequence as related to the coagulation pathway.

75-P

Anxiety Associated with Parenteral On-Demand Treatment for Hereditary Angioedema Attacks

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Rationale: Patients with hereditary angioedema (HAE) often experience anxiety due to unpredictable, painful, and debilitating attacks. Currently, all approved on-demand treatments for managing these attacks require parenteral administration, which can be painful and challenging to administer, and may contribute to this anxiety. The current study aimed to characterize anxiety in patients about treating their HAE attacks with parenteral on-demand therapy.

Methods: People from Italy with Type 1 or Type 2 HAE were recruited between September 2023 and January 2024 by the Italian Network for Hereditary and Acquired Angioedema (ITACA) to complete an online quantitative survey. Participants were ≥ 12 yrs old and had to have treated ≥ 1 HAE attack with an approved on-demand therapy within 3 months prior to the survey. Participants were asked to rate their anxiety about using on-demand treatment during their last attack on a scale of "0 "not anxious" to 10 "extremely anxious".

Results: This interim analysis included 56 respondents (48 adults and 8 adolescents [< 18 years]), with 55% receiving prophylaxis at the time of their last treated HAE attack. Icatibant was the most commonly used on-demand therapy for the last attack (55%), followed by pdC1INH (43%). Anxiety was the second most common comorbid condition, with 13% (7/56) of participants diagnosed by a physician (females 9%; males 17%; adults 15%; adolescents 0%). Forty-five percent

(25/56) of participants felt moderately (anxiety: 4-6) or extremely anxious (anxiety: 7-10) about treating their last attack with on-demand treatment, including 75% of adolescents (6/8), and 86% (6/7) of those diagnosed with anxiety. The mean anxiety rating among all participants was 3.7 (SD 3.1). Among the 43 patients (77%) who reported feeling anxious, the primary reasons for anxiety were related to concerns around treatment efficacy (40% of respondents), administration burden/pain/side effects (35%), and cost/access (21%).

Conclusions: A substantial proportion of respondents in the survey experienced moderate to extreme anxiety due to anticipated use of on-demand treatment, particularly adolescents and those previously diagnosed with anxiety. Reasons for anxiety were most commonly related to treatment effectiveness, administration burden/side effects, and cost/access. Effective alternatives to current parenteral on-demand treatments are needed to address treatment-related anxiety associated with HAE attacks.

76-O&P

CSU Patients with Standalone Angioedema are More Similar than Different to CSU Patients with Both Wheals and Angioedema with Regard to Basic and Specialized Tests for the Underlying Cause of the Disease

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Background: Chronic spontaneous urticaria (CSU) can come with spontaneous wheals (W) and/or recurrent angioedema (AE) for more than 6 weeks.

Rationale: It remains largely unclear how similar or different CSU AE with and without W is regarding their pathophysiology.

Methods: CSU AE (n=43, 67% female) and CSU W+AE (n=36, 69% female) patients were compared with regard to their clinical manifestations, results of differential blood count as well as specialized tests including the basophil histamine release assay (BHRA) and total IgE levels. Moreover, disease control (Angioedema Control Test, AECT) and disease-related quality of life (Angioedema Quality of Life Questionnaire, AE-QoL) of both groups were compared.

Results: 40% and 20% of CSU AE and CSU W+AE patients were BHRA+, 70% and 58% had low (<40kU) total IgE levels and 67% and 20% were BHRA+ status and had low total IgE levels, respectively. In both CSU groups, BHRA+ patients showed lower eosinophil counts than

BHRA- patients, which was statistically significant ($p < 0.05$) in the CSU AE group. Disease onset in BHRA+ CSU AE patients was at higher age, but lower in BHRA+ CSU W+AE patients compared with their BHRA- counterparts. In CSU W+AE patients, BHRA+ status was linked to shorter AE duration, higher AECT total scores and lower AE-QoL total scores. No association between BHRA status, localizations of AE, gender and body mass index could be found in both CSU groups.

Conclusions: Our results show that CSU AE patients are more similar than different to CSU W+AE patients in their autoimmune profile supporting the concept that they belong to the same disorder.

77-P

Reduction of Burden of HAE Treatment Results in Better Disease-Related Quality of Life

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Background: Lanadelumab, a monoclonal antibody against plasma-kallikrein, is administered subcutaneously at two to four-week intervals for long-term prophylaxis in hereditary angioedema (HAE).

Rationale: Whether longer treatment intervals result in improved disease-related quality of life (QoL) remains elusive. We aimed to compare disease control and disease-related QoL impairment in patients who use lanadelumab treatment intervals of equal or less than 28 days ($L \leq 28$) and more than 28 days ($L > 28$).

Methods: The last documented treatment interval (in days) from patient records were extracted as well as individual levels of disease control and QoL impairment, as assessed with the Angioedema Control Test (AECT) and the Angioedema Quality of Life Questionnaire (AE-QoL)

Results: In total, 56 patients with HAE due to C1 inhibitor deficiency were included, 23 patients (70% female) with $L \leq 28$ treatment intervals and 33 (64% female) with $L > 28$. In the $L \leq 28$ group, the mean AECT was 14 points, the AE-QoL score was 24 points and the domain scores for functioning, fatigue/mood, fears/shame and nutrition were 14, 30, 25 and 22 points, respectively. In the $L > 28$ group, the median AECT was 15.5 points, the AE-QoL was 11.6, and the domain scores for functioning, fatigue/mood, fears/shame and nutrition were 1, 26, 10, and 3, respectively. In the $L \leq 28$ group, 10 patients had complete disease control (43%, AECT=16), 2 patients had poorly controlled disease. In the $L > 28$ group, 23 had complete control (70%), no patient had poorly controlled disease.

Conclusions: Lower frequency of treatment application is linked to better disease-related QoL.

78-P

A Case of Splenic Marginal Zone Lymphoma (SMZL) Manifesting as Acquired Angioedema with Decreased C1INH Level (AAE-C1INH)

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Background: Acquired angioedema due to C1 inhibitor deficiency (AAE-C1INH) is a rare disease which can be a manifestation of underlying pathology, such as lymphoproliferative disorder.

Case Report: A 46-year-old female was referred to allergist in Dec 2022 due to recurrent angioedema affecting face, upper and lower limbs, with abdominal discomfort and pain. She also experienced one episode of throat swelling. The patient has never been treated with ACE-inhibitors or any other possible angioedema elicitors. Her mother had abdominal pain but was never followed up. Decreased levels of C1 concentration and activity (0.05g/L and 6%, respectively), C4 (<0.02 g/L) and C1q (1.6mg/dl) were noted. Lymphocytosis (up to 4510 cells/ μ L) and chronic splenomegaly were seen on several independent examinations. Other test have not revealed any abnormalities. A diagnosis of AAE-C1INH was established. Angioedema attacks kept recurring irregularly and responded well to subcutaneous Icatibant. The patient was referred for hematological assessment with suspected lymphoproliferative disease as possible cause of AAE. After hematological assessment a diagnosis of SMZL was established. The patient did not present any general symptoms (significant weight loss, drenching night sweats, unexplained fever); the peripheral blood counts were normal, and splenomegaly was neither massive nor symptomatic. It was deemed that the angioedema episodes were due to the lymphoma and treatment with rituximab monotherapy 375 mg/m² weekly for four weeks was commenced in December 2023. Patient responded well to rituximab and remains free from angioedema since January 2024.

Conclusions: This case exemplifies the possibility of

late onset angioedema with decreased C1INH being a manifestation of underlying lymphoproliferative disorder. Therefore, a thorough differential diagnostics is required in angioedema, in particular the one with late onset and inconclusive family history.

79-O

Donidalorsen for the Treatment of Hereditary Angioedema: Results from a Phase 3, randomized, placebo-controlled trial (OASIS-HAE) and open-label extension OASISplus Study

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Rationale: Hereditary angioedema (HAE) is characterized by potentially life-threatening tissue swelling resulting from dysregulation of the kallikrein-kinin system. We report efficacy and safety results from the phase 3 OASIS-HAE (NCT05139810) and OASISplus open-label extension (OLE; NCT05392114) studies in patients with hereditary angioedema treated with donidalorsen, an investigational ligand-conjugated antisense oligonucleotide targeting prekallikrein.

Methods: In the OASIS-HAE double-blind, placebo-controlled study, patients were randomized to receive donidalorsen 80 mg or placebo subcutaneously once-every-4 weeks (Q4W) or 8-weeks (Q8W) over 24 weeks. The time-normalized number of HAE attacks/month (HAE attack rate) from weeks 1-25 (primary endpoint) and weeks 5-25 (secondary endpoint), and safety were assessed.

In OASISplus OLE, patients receiving donidalorsen 80 mg or placebo Q8W in OASIS-HAE received donidalorsen 80 mg Q8W; if not attack-free for \geq 8 weeks, patients received donidalorsen Q4W. All other patients received donidalorsen Q4W during OLE. The primary endpoint was incidence and severity of treatment-emergent adverse events (TEAEs; 02/2024 interim data).

Results: In OASIS-HAE, 90 patients were dosed (donidalorsen Q4W: n=45; donidalorsen Q8W: n=23; pooled placebo: n=22). Donidalorsen treatment significantly reduced HAE attack rate by 81% (Q4W, p<0.001; primary endpoint) and 55% (Q8W, p=0.004) vs placebo over weeks 1-25; median reduction from baseline was 90% (Q4W) and 83% (Q8W) vs 16% (placebo). Reduction in HAE attack rate over weeks 5-25 was 87% (Q4W; p<0.001) and 60% (Q8W; p=0.004) vs placebo; median reduction from baseline was 100% (Q4W) and 90% (Q8W) vs 14% (placebo). Sixty-five (72.2%) patients reported TEAEs, with headache and

nasopharyngitis being the most common (13% each); of TEAEs $\geq 5\%$ frequency, 11% had treatment-related injection-site reactions. One patient (Q8W) discontinued due to a drug-related TEAE, and 1 (placebo) had a serious adverse event (non-treatment-related) but did not discontinue.

The OLE included 83 patients from OASIS-HAE receiving 80 mg donidalorsen (Q4W: n=69; Q8W: n=14). Fifty-six (81.2%, Q4W) and 10 (71.4%, Q8W) patients reported TEAEs; most were non-treatment-related. Both Q4W and Q8W groups had a mean 92-93% reduction in HAE attacks from OASIS-HAE baseline.

Conclusions: Donidalorsen markedly reduced HAE attack rate and had an acceptable safety profile in OASIS-HAE, and demonstrated sustained efficacy and safety in the OLE study.

80-O

A Physician-Based Brazilian Registry for Hereditary Angioedema: Relevance of Genetic Diagnosis

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Rationale: Hereditary angioedema (HAE) is a rare disease with autosomal dominant inheritance. It is estimated that there would be approximately 4,000 patients with HAE in Brazil. Registry-based data may contribute to improving management of the disease.

Methods: A Brazilian registry for HAE was established, with demographic, clinical, treatment and genetic data included in the REDCap platform by the treating physicians.

Results: Of 704 patients enrolled (66.3% female), 549 (78%) have HAE with C1 Inhibitor deficiency (HAE-C1INH) and 155 (22%) HAE with normal C1INH with identified F12 disease-causing variants (HAE-FXII). Sixty-two HAE-nC1INH patients undergoing genetic evaluation were not included in the analysis. Among the 549 HAE-C1INH patients, 117 underwent genetic analysis, and 31 distinct variants in SERPING1 gene were identified; of those, 16 were missense variants and 15 were insertions, deletions, duplications, nonsense variants, and intronic variants leading to splicing defects. Among HAE-FXII patients, the c.983C>A (p.Thr328Lys) variant in exon 9 of F12 gene was found in 153 patients (98.7%), whereas the c.971_1018+24del72 variant was present in only 2 patients from a single family (1.3%). Other previously identified variants linked to HAE-nC1INH were not yet identified among Brazilian



patients with HAE. Patients 18 years-old and younger presented shorter time for diagnosis, as compared to patients older than 18 years-old (1.7 versus 14.8 years, $p < 0.01$). Regarding treatment, of 637 patients treated for HAE attacks, 369 (57.9%) received first-line therapies (Icatibant or plasma-derived C1INH concentrate), whereas only 36/537 (6.7%) of patients on long-term prophylaxis were treated with first-line therapies (lanadelumab or pdC1INH concentrate iv or sc). 242/576 (42%) of patients are currently on long term prophylaxis with attenuated androgens.

Conclusions: Genetic analysis is an important component of the diagnostic workup of patients with HAE, particularly those with HAE-nC1INH, allowing for precise diagnosis and early treatment in these patients. Both novel and previously identified variants in SERPING1 were present in patients and families with HAE-C1INH Type 1 and Type 2. The c.983C>A (p.Thr328Lys) variant in exon 9 of F12 was predominant among Brazilian patients with HAE-nC1INH. Diagnosis of HAE and treatment of acute attacks appear to be improving in Brazil, however effective long-term prophylaxis is still an unmet need.



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