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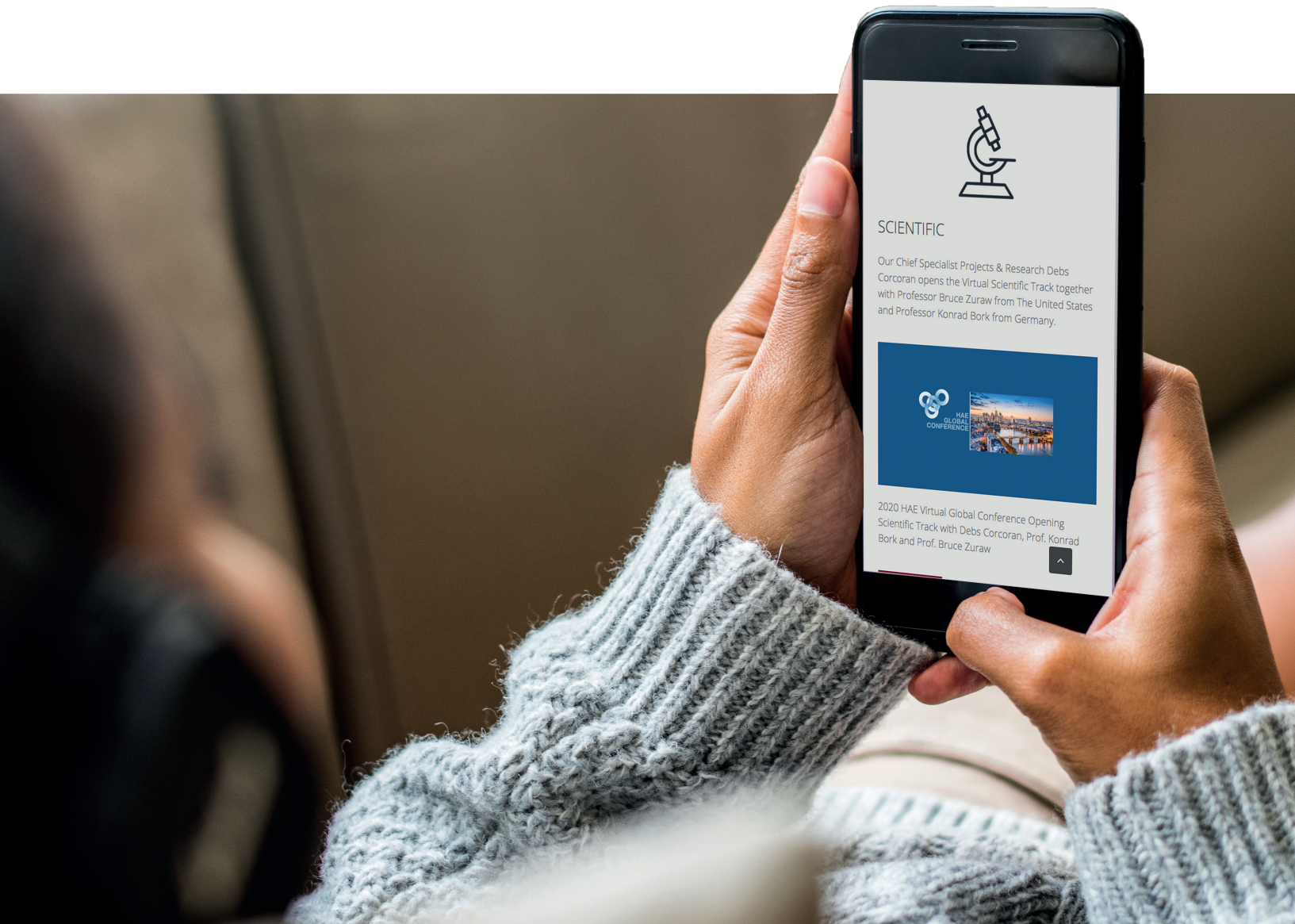

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Topic 1. Determining Better Pathways to Diagnosis and Management of HAE

Novel SERPING1 Gene Mutations and Clinical Experience in a Single Centre Cohort of Patients with Hereditary Angioedema from North India

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Background: There is paucity of literature on genetic profile and long-term follow-up of patients with Hereditary angioedema (HAE) from developing countries.

Methods: This is a retrospective analysis of the clinical and genetic profile of 52 patients (from 26 families) diagnosed to have HAE from January 1996 to December 2019. Data were retrieved from medical records of the Paediatric Immunodeficiency Clinic, Post Graduate Institute of Medical Education and Research, Chandigarh, India. The diagnosis was established based on symptoms consistent with HAE, low C4 and/or low C1-INH and/or a positive family history. SERPING1 gene mutation was identified using sanger sequencing.

Results: Median age at the time of onset of symptoms and at the time of diagnosis was 9.5 years and 19.5 years respectively with a median delay in diagnosis of 11 years. Family history of angioedema was noted in 40 patients. SERPING1 gene sequencing could be carried out in 21/26 families till the time of this analysis. Novel pathogenic variants were identified in 3 families (2 missense and 1 nonsense mutation), 8 families had a previously reported mutation and 10 families had no mutation in the SERPING1 gene. All patients were managed with prophylactic attenuated androgens (stanazolol 2-4 mg/day) or tranexamic acid (30-50 mg/kg/day). Acute attacks of life-threatening angioedema were managed with plasma infusion. The total follow-up of entire cohort is 2784 patient months with mean follow-up 53 months. No disease related mortality was reported in the entire cohort; however, 2 families gave history of death of one family member each due to laryngeal oedema.

Conclusions: This is the largest single centre cohort of patients with HAE from India. In resource limited settings with non-availability of C1-INH therapy, patients with HAE can be managed using stanazolol, tranexamic acid and plasma infusions.

Topic 1. Determining Better Pathways to Diagnosis and Management of HAE

Short Term Prophylaxis in Patients with Hereditary Angioedema: Our Experience from Resource Constrained Settings

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Background: Short term prophylaxis for patients with Hereditary Angioedema (HAE) is required during surgical procedures as it may precipitate an acute attack. We report our experience with short term prophylaxis in resource constrained settings.

Case 1: M, a 6-year-old girl, was diagnosed to have type 1 HAE in 2015 (low C4, low C1INH and a suggestive family history). She was initiated on tranexamic acid [TA] (500 mg per day) and stanozolol (0.5 mg per day). She presented with dental pain in 2018 and was diagnosed to have mandibular cyst for which a radical excision was advised. The dose of stanozolol was increased to 0.5 mg two times a day. Fresh frozen plasma (FFP) [dose: 10 ml/kg] was infused twice daily for two days before surgery and one dose was given during perioperative period. She was electively intubated, was given general anesthesia and the mandibular cyst was excised uneventfully.

Case 2: S, a 29-year-old female was diagnosed to have HAE in 2001 when she presented with facial swelling and had a suggestive family history. She was found to have low C4, low C1-INH and a pathogenic variant in *SERPING1* gene (c.51+1G>A intron 2 splicing defect). She was treated with tranexamic acid and stanozolol. She continued to have intermittent episodes of mild angioedema. She conceived twice in 2017 and 2018 while she was taking TA. She had first trimester abortion on both occasions. TA was subsequently discontinued. She conceived again in 2018. She had uneventful pregnancy and had no episodes of angioedema even though she was not on any prophylaxis. She was planned for an elective cesarean section and was given 3 units of FFP before and during cesarean section and stanozolol 2 mg/day that was initiated a day before the cesarean section and continued for 5 days. She had an uneventful delivery and had no episodes of angioedema.

Conclusion:
Short term prophylaxis with FFP and stanozolol may be considered in patients with HAE when C1INH therapy is not available.

Topic 1. Determining Better Pathways to Diagnosis and Management of HAE

Role of Genetic Testing in Diagnosis of Hereditary Angioedema

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Introduction: Establishing a correct diagnosis of hereditary angioedema (HAE) is crucial for the patient's prognosis and quality of life. Complement test allows confirming or excluding the presence of hereditary C1-inhibitor (C1-INH) deficiency (HC1-INH-def). Molecular genetic methods are essential for establishing the diagnosis of HAE with normal C1-INH function (nC1-INH-HAE), preimplantation and prenatal diagnosis.

Methods: In Hungarian Angioedema Reference Center (HARC) genetic tests for *SERPING1*, factor XII (*F12)* and plasminogen (*PLG)* gene are available. Genotyping had been performed by conventional methodology and recently has been confirmed by the use of a validated custom and targeted NGS platform.

Results: 194 patients with HC1-INH-def, two patients with *F12* and two with *PLG* gene mutation are followed up at HARC. 70 families with HC1-INH-def, a family with *F12* and another one with *PLG* gene mutation have been diagnosed. We identified *SERPING1* gene mutations (1 insdel, 3 gross deletions, 10 deletions, 4 duplications, 22 missense variations, 6 splicing variants) in 61 families with HC1-INH-def, of these four novel. In 1/9 family where no defect had been detected by conventional genotyping, NGS recovered a pathogenic deep intronic mutation. In five cases with C1-INH deficiency, genetic testing helped to establish the diagnosis because of ambiguous complement results, in four cases HC1-INH-def was diagnosed by genetic testing from cord blood in newborns. In 8 families with HC1-INH-def mutation was not detected. In a family with nC1-INH-HAE, *F12* gene mutation was described. It was a novel mutation, a duplication of 18 base pairs (c.892_909dup). A family with PLG-HAE has been diagnosed recently.

Conclusion: Genetic test is essential for distinguishing the different types of HAE. It is useful for differentiating angioedema with C1-INH-deficiency in selected cases where complement results are ambiguous, in infants because of immature complement system in these ages.

Topic 1. Determining Better Pathways to Diagnosis and Management of HAE

Pregnancy in Patients with Hereditary Angioedema and Normal C1 Inhibitor (HAEnlC1INH)

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Background: HAE with normal C1 inhibitor was first identified in 2000 and estrogens have been described as trigger factors of attacks. Women are more symptomatic and this bradykinin mediated edema could worsen during the pregnancy. Previous studies with HAE and C1-INH deficit show a variable course of this period. We aim to evaluate the course of pregnancies in women with confirmed HAEnlC1INH.

Methods: We evaluated women with confirmed HAEnlC1INH. We applied a questionnaire collecting data from previous clinical history and course of pregnancies. Ethical Committee approved the protocol and patients signed forms authorizing the study.

Results: A total of 37 pregnancies out of 26 women were included (7 with factor 12 mutation). Mean age of the women was 42.5 years old and at the pregnancy was 27.4. Mean onset of symptoms and diagnosis were 20.2 and 34.6 years old. Abortion was reported in 8/45 (17.8%) pregnancies. First attacks were reported in 18/26 before pregnancy, 2/26 during and 6 after the pregnancy (mean onset 2.5 years). There was no difference in onset of symptoms according to presence of *F12* mutation. Attacks occurred at the 1st trimester in 41.7%; 2nd in 12.5%; 3rd in 20.8%; 1st and 3rd in 4.2% and during the whole period in 20.8%. 15/18 patients had attacks before and maintained during the 1st pregnancy with worsening in 9; improvement in 4; no change in 1 and 1 didn't respond. Regarding localization of attacks, extremities and abdomen were more affected (53.3%) and upper airways was reported by 26.7%.

Conclusions: Onset of HAEnlC1INH rarely occurred during pregnancy. Abortion occurred with similar frequency as expected for not affected women. The 1st trimester was more symptomatic and pregnancies did not influence the course of disease. Although there is strong relevance of estrogens in HAEnlC1INH, pregnancy can't be inputted as more dangerous for women than the disease per se. In addition, pregnancies had a similar influence as observed for HAE with C1-INH deficit.

Topic 1. Determining Better Pathways to Diagnosis and Management of HAE

Next-Generation Sequencing (NGS) Provides More Information for Diagnosis Patients with Hereditary Angioedema (HAE) and Mixed Clinical Manifestations

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Introduction: The classification of angioedema without urticaria distinguishes acquired and hereditary forms of the disease. It is important to separate them due to the treatment differences.

Methods: For patients with angioedema without wheals we performed C3c, C4, C1-INH, C1q, IgE, HMWK, ANA, C1-INH function tests; Sanger sequencing of *SERPING1* gene; NGS of *SERPING1* gene in its full length (all exons, introns, promoter, 5′-,3′-UTRs) using Nextera XT (Illumina). All clinically significant variants are confirmed by Sanger sequencing, MLPA or EQT technology.

Results: We identified 68 genetically confirmed C1-INH-HAE patients (13 (19%) with Type II HAE) belonging to 27 families. In our report, we didn't include one family with suspicious HAE patients with an intron change in the *SERPING1* gene. The proband (5y.o. boy, patient №1, first attack at 5) had histamine associated swelling. His mother (28y.o., patient №2, first attack at 24) and grandmother (53y.o., patient №3, first attack at 21) were diagnosed as patients with idiopathic histaminergic acquired angioedema (IH-AAE) and with acquired angioedema related to angiotensin converting enzyme inhibitors (ACEi-AAE) in another Centre before. Patients №1-3 had normal C3c, C4 and C1-INH levels; IgE was 4 times higher in patient №1 and normal in patients №2-3. HMWK and C1-INH function tests showed for patients №2-3 similar results to C1-INH-HAE. In patients №2-3 we found one heterozygous change in the *SERPING1* gene (c.1029+689T>C; gAD_EUR-0,0000%; rs192076424). The patient №1 didn't have such variant. We have not demonstrated yet the full effect of this SNV on C1-INH function. Additionally, we found a heterozygous compound in the *KNG1* gene for patient №3, which can explain her early hypertension.

Conclusion: We can provide a perspective on how NGS can be implemented effectively in clinical settings and can help to disclose a disease. This would help patients receiving adequate therapy and improve patients' life quality.

Topic 1. Determining Better Pathways to Diagnosis and Management of HAE

Whole Exome Sequencing Identified Novel Candidate Genes Associated with Hereditary Angioedema of Unknown Origin

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Introduction: The prevalence of hereditary angioedema of unknown origin (U-HAE) is extremely low and accounts for about 1% of all cases of HAE. In the Next-Generation Sequencing (NGS) era, identifying genes whose changes can lead to edema has become more affordable. But the more we perform NGS for suspicious U-HAE, the more questions arise.

Methods: The study included 5 individuals from 2 unrelated families with clinical and laboratory characteristics of nC1NH-HAE, for whom we initially performed NGS for amplicons of 18 genes (including *FXII, PLG, ANGPT1, KNG1*) and the results were questionable. We thus performed Exome Sequencing (WES) using Nextera Exome Kit (Illumina). After variant calling, quality control and filtering (population frequency<1%) we identified some variants potentially disease associating. The uniqueness of variants was checked among other DNA samples and donors. All clinically significant variants were confirmed by Sanger sequencing.

Results: Analysis of WES in family 1 revealed one heterozygous change segregating with the phenotype in the CPA3 gene (NM_001870:c.509T>G;p.F170C), not previously described and with no data about population frequency. This gene encodes a member of the carboxypeptidase A family that is released by mast cells and is involved in the degradation of endogenous proteins. Among its related pathways are agents acting on the renin-angiotensin system. Analysis of NGS in family 2 revealed heterozygous changes common to the two affected members whose frequency in the general population is too high for them to be clear cut candidate to be causative variant. Among them a variant in the ANGPT1 gene (c.454-22T>C; rs200470101; AF_ALL 0.003), a gene already associated with nC1NH-HAE.

Conclusion: The next step in our work will be to examine all available symptomatic and asymptomatic relatives for these changes and to test the activity of the encoded proteins in plasma samples to validate their association with HAE.

Topic 1. Determining Better Pathways to Diagnosis and Management of HAE

The FXII c.-4T>C Variant as a Disease Modifier in Patients with Hereditary Angioedema due to the Thr309Lys FXII Mutation

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Background: Clinical variability and incomplete penetrance are challenging features of HAE-FXII that difficult the diagnosis and management of the disease. The c.-4T>C Kozak polymorphism is recognised as the only common variation accounting for the variability in the FXII plasma levels and has been previously shown to exert some impact on the course of HAE due to C1-Inhibitor deficiency.

Methods: We investigated the genotype frequency distribution of the c.-4T>C polymorphism in 39 non-related Spanish HAE-FXII index patients diagnosed at Hospital La Paz (Madrid) and its association with the severity of HAE symptoms and the activation status of the plasma contact system during remission.

Results: In the studied cohort, the c.-4CC genotype was significantly (pvalue:0.001) overrepresented: 71% were CC-homozygous (expected frequency: 59%) and 21% were CT-heterozygous (expected frequency: 39%). HAE-FXII patients with a c.-4CC genotype exhibited significantly higher kallikrein-like activity values (0.9659±0.1136) than those with a c.-4TC genotype (0.7645±0.1235) (pvalue:0.024) and their corresponding age- and sex-matched controls with either c.-4CC (0.6978±0.1361; pvalue: 0.001) or c.-4TC genotypes (0.5863±0.07;pvalue:0.0001). Moreover, the c.-4T>C status also modified the clinical course of the disease, the c.-4CC genotype being significantly associated to higher severity scores (c.-4CC: 4.43 ± 2.28 versus c.-4TC: 2.0 ± 1.15; pvalue: 0.006). We found no evidence ofassociation between the polymorphism and the degree of estrogen dependence or the time until remission.

Conclusions: Our results indicate that the c.-4T>C polymorphism acts as a genetic disease modifier partially determining the degree of contact system activation and the clinical severity of HAE-FXII patients with the p.Thr309Lys mutation. Moreover, in consideration of its clinical impact and overrepresentation in the studied cohort, c.-4T>C in turn possibly influences the diagnostic rates of the disease.

Topic 1. Determining Better Pathways to Diagnosis and Management of HAE

In Search of an Association Between Genotype and Phenotype in Hereditary Angioedema due to C1 Inhibitor Deficiency (C1-INH-HAE)

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Background: Hereditary angioedema due to C1-inhibitor deficiency (C1-INH-HAE) is a rare autosomal dominant disease caused by mutations affecting the *SERPING1* gene. Our aim was to describe the phenotypic characteristics of C1-INH-HAE according to a classification of the *SERPING1* gene mutations.

Methods: Adult patients with C1-INH-HAE followed-up in the Allergy Department from Hospital La Paz between April 2016 and April 2018 were included. We used the classification of *SERPING1* gene mutations proposed *by Bos et al (2002)* based on the alteration of the reactive center loop (RCL) of the gene. In addition, we classified as zero the mutations that did not generate protein. Demographic, clinical and laboratory data were studied.

Results: Thirty-two (36.8%) out of 88 patients had class 0 mutations, four (4.6%) had class 0 and class 3, two (2.3%) had class 1, one (1.1%) had class 1 and class 3, three (3.4%) had class 2, three (3.4%) had class 2 and class 3, twenty-two (25.3%) had class 3 and 21 patients had unclassifiable mutations. From the 67 patients who could be classified, 66 corresponded to type I HAE and 1 patient to type II. The mean age at onset of symptoms and at diagnosis were lower in patients with class 2 mutations. The highest average of angioedema attacks was observed in class 1, being more frequently peripheral and abdominal attacks. Similar C4 levels were found in all classes. C1 inhibitor levels were higher in class 1 and functional C1 inhibitor levels in class 2. Attenuated androgens were more frequently used as long-term prophylaxis in class 0 and these patients had a higher prevalence of arterial hypertension, allergies and tumor diseases. A higher score for the HAE-AS questionnaire (scale 0-30) was obtained in class 1.

Conclusions: The results suggest that there could be differences between the phenotypic characteristics and the classes of *SERPING1* gene mutations.

Topic 1. Determining Better Pathways to Diagnosis and Management of HAE

Treatment of Hereditary Angioedema Attacks: An Interim Analysis of Data from the European Registry of Recombinant Human C1 Esterase Inhibitor

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Background: Recombinant human C1 esterase inhibitor (rhC1-INH) is approved in multiple countries for the treatment of hereditary angioedema (HAE) attacks. An ongoing European treatment registry was established to examine the efficacy and safety of rhC1-INH.

Methods: Individuals with HAE due to C1 inhibitor deficiency (C1-INH-HAE) were enrolled in the registry following written informed consent and a decision to treat with rhC1-INH. Medical history and baseline HAE data were obtained at screening. Treatment decisions were at the discretion of the health care professionals (HCPs) involved in the patients' care. Using a web- based questionnaire, HCPs entered data about patients' attacks, response to therapy, and adverse events (AEs) posttreatment.

Results: In this analysis (01 Jul 2011 through 31 Jan 2020), 85 patients with C1-INH-HAE (34 male/51 female; mean age, 47.1 y; age range, 15-79 y) in 9 countries reported 2543 attacks and were treated with rhC1-INH. The mean age at HAE diagnosis was 25.2 y (range, 3-70 y). Before registry enrollment, patients, including 24 (28.2%) who were on prophylaxis at registry enrollment, experienced a mean of 30 HAE attacks/y. There were 1168 (45.9%) abdominal, 992 (39.0%) peripheral, 364 (14.3%) oro-facial-pharyngeal, 88 (3.5%) urogenital, and 68 (2.7%) laryngeal attacks; of these, 123 attacks involved 2 locations and 7 involved 3 locations. The mean rhC1-INH dose was 3287 IU (42.9 IU/kg). Patients reported resolution of 96.9% of HAE attacks 2 (2465/2543) with rhC1-INH within 4 hours; most HAE attacks (99.8%;538/2543) required only 1 dose of rhC1-INH. Five HAE attacks were treated with a second dose (total rhC1-INH administered to treat attack, 4200 IU). No hypersensitivity or thrombotic/thromboembolic events were reported. No patients had any drug-related serious AEs.

Conclusion: This interim registry analysis has provided real-world data on the treatment of 2543 HAE attacks and supports the efficacy and safety of rhC1-INH.

Topic 1. Determining Better Pathways to Diagnosis and Management of HAE

A Multicenter, Randomized, Double-Blind, Dose-Ranging Phase 2 Study Investigating the Efficacy, Pharmacokinetics (PK) and Safety of Prophylaxis with the Anti-Factor XIIa Monoclonal Antibody Garadacimab (CSL312) in Patients with Hereditary Angioedema (HAE)

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Background: HAE attacks result from incomplete inhibition of the contact system, of which activated Factor XIIa (FXIIa) is the key initiator. Garadacimab (CSL312), the first fully human immunoglobulin G4 monoclonal antibody that inhibits FXIIa, is under investigation for prophylactic HAE treatment. A first-in-human Phase 1 study confirmed in 2017 that garadacimab was well tolerated with good bioavailability and a favorable safety profile.

Methods: This Phase 2 study (CSL312_2001; NCT03712228) was designed to determine the efficacy, safety, and PK/pharmacodynamics profile of garadacimab. The primary endpoint was the number of HAE attacks/month. Secondary endpoints included proportions of responders (≥50% relative reduction in the number of attacks/month), patients free of HAE attacks, rate of HAE attacks, HAE attacks treated with on-demand medication, safety, and PK. Eligible patients aged ≥18 to ≤65 with type 1 or 2 HAE were randomized 1:1:1:1 to receive subcutaneous 75, 200 or 600 mg garadacimab or placebo every 4 weeks (q4wk). After 13 weeks of double-blind, placebo-controlled treatment, patients were re-randomized to receive one of two open-label garadacimab doses q4wk for the rest of the study. C1 normal patients with an HAE-associated FXII or plasminogen (PLG) gene mutation (HAE-FXII/PLG) were also enrolled, and received open-label garadacimab dose q4wk.

Results: Overall, 32 patients have completed the blinded, dose-ranging treatment period; results will be presented in 2020. The open-label treatment periods are ongoing and will collect further efficacy and safety data.

Conclusions: If the efficacy and safety of garadacimab can be demonstrated in this study and confirmed in Phase 3 studies, it could support the approval of garadacimab. This novel recombinant monoclonal antibody may provide the HAE community with a new option for long-term prophylaxis.

Topic 2. Creating a Path to Normalisation of HAE Patients' Lives

Study of the Prevalence of Patients with Hereditary Angioedema Registered at Guillermo Grant Benavente Hospital in Concepción, Chile

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Background: This research is a descriptive cross-sectional observational study of patients with Hereditary Angioedema (HAE), a rare disease, registered at Guillermo Grant Benavente Hospital in Concepción, Chile. HAE is a genetic disease that causes episodes of swelling or edema of some parts of the body, such as the skin or mucous membranes (throat, urinary tract or intestine). The frequency and intensity of attacks are very variable and depends on each person or situation. It requires maximum attention to any swelling of the area of the face, neck or throat since there is a risk of suffocation.

Objective: To determine the prevalence of patients with HAE in the Bío-Bío and Ñuble regions.

Methods: The data were obtained by reviewing the clinical record of patients with HAE registered in the bronchopulmonary clinic of the Regional Hospital, with prior informed consent from the patients involved. The project was evaluated and approved by the Scientific Ethics Committee of the Concepción Health Service. The tabulation and analysis of the data was performed in InfoStat, including descriptive statistics, measures of central tendency and dispersion and relative frequencies.

Results: The preliminary results are of the 17 patients registered, with an average age of 39, 11 women and 6 men, with an average of 13 crises in 17 months, being the maximum of 53 and the minimum of 1. There is a patient who died from a crisis, corresponding to 6% of the total patients.

Conclusions: The study reflects the prevalence of patients with HAE, sociodemographic characteristics and clinical aspects, which favors the survival and quality of life of patients.

Topic 2. Creating a Path to Normalisation of HAE Patients' Lives

Psychological Impact of HAE led to the Creation of the BITTEN Model of Trauma Informed Healthcare

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Background: HAE patients can experience psychological impacts secondary to their HAE. Institutional betrayal (IB) may be a pathway to these impacts. IB occurs when an individual's trust in an institution is betrayed through the commission of negative behavior or the absence of expected care. HAE patients may experience healthcare system IB by: 1) having their symptoms dismissed/misdiagnosed, 2) insurance denials, 3) barriers accessing rarely prescribed or stocked medications, and 4) hospital system or structure failures due to unfamiliarity with HAE. Also, the severity and unpredictability of HAE episodes puts patients at risk for experiencing acute medical trauma. Yet, few healthcare providers (HCP) are prepared to address the impact of pre-existing IB and medical traumas on the HAE patient's current healthcare needs and expectations. Failure to address previous healthcare traumas likely results in trust ruptures between HAE patients and HCPs, thereby negatively impact healthcare services. Thus, the BITTEN Model of Trauma Informed Care (TIC) was developed through the lived experiences of a nurse-scientist with HAE and a clinical health psychologist with a different chronic health condition.

Methods: A mixed method design is used to describe the development of BITTEN and its current application. A schematic analysis of the first author's lived experience will be presented to show the BITTEN model as a frame to help HCPs provide HAE care. Actual care experiences will be shown as well as potential intervention points for BITTEN-sensitive HCPs.

Results: The BITTEN (Betrayal, Indicator for healthcare, Trauma history, Trust in provider, patient Expectations and Needs) Model of TIC was created to provide a best practice framework.

Conclusions: The BITTEN model helps HCPs realize, recognize, and respond to trauma to resist patient retraumatization. Providers managing HAE in outpatient settings could benefit from integrating mental health care to better assist HAE patients.

Topic 2. Creating a Path to Normalisation of HAE Patients' Lives

Coping Strategies as Predictors of Stress and Anxiety in Family Members and Caregivers of HAE Patients

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Background: The unpredictability and fear of potentially life-threatening attacks influence the occurrence and manifestation of anxiety in HAE patients' family members. Anxiety limits the psychosocial functioning and has a strong impact on QoL.

Methods: 17 family members and caregivers of HAE patients that were diagnosed less than 6 months ago (group A1), and 67 family members and caregivers of HAE patients that were diagnosed more than 6 months prior to the study (group A2) were included. Group B1 (control) included 12 family members of patients with severe food allergy manifesting with AE diagnosed less than 6 months ago and 82 family members of patients diagnosed more than 6 months prior to the study (B2).All participants underwent semi-structured interviews specialized for the purpose of the study, Ways of Coping Questionnaire, and the HAMA Scale.

Results: The least frequently used strategies for coping in group A2 were distancing (12%), confrontation (9%) and avoidance (13%). However, in group A1, confrontation was more pronounced (53%), especially during the initial phase of facing with the HAE diagnosis. The most common strategies in group A2 were strategies for planned problem solving, seeking social support and positive evaluation of the state. A high level of anxiety was diagnosed in group A1, where it was found that the coping strategies and the high level of anxiety interfere with the quality of life. The most frequent coping strategies in group B1 were confrontation (42%), as well as distancing and isolation. The most frequently used strategies in group B2 were problem-solving coping strategy and attitude and positive evaluation of the state.

Conclusion: The participants with a functional, positive and proactive coping style have a reduced level of stress and anxiety related to the disease itself and the therapy. The adherence to health care professional's advice is better and there is a positive effect on the patient's overall health and QoL.

Topic 2. Creating a Path to Normalisation of HAE Patients' Lives

Safety and Tolerability of Once Daily Oral Berotralstat (BCX7353) in Patients with Hereditary Angioedema (HAE): APeX-2 Study Results

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Background: Berotralstat, an oral once-daily highly selective inhibitor of plasma kallikrein, is in development for prophylaxis of HAE attacks. The efficacy and safety of berotralstat was evaluated in a randomized, double-blind, placebo-controlled Phase 3 study (APeX-2, NCT03485911).

Methods: 121 patients with HAE Type 1 or 2 and ≥2 investigator-confirmed attacks in the first 56 days of the run-in period were randomized 1:1:1 to receive berotralstat 150mg: berotralstat 110mg: placebo for 24 weeks (Part 1). Adverse events (AEs) were recorded and assessed by the investigator for severity and relatedness to study drug. Gastrointestinal (GI) abdominal AEs were prospectively defined. The incidence of GI abdominal AEs was analyzed overall and by month of onset. Safety was assessed over 24 weeks.

Results: AEs were reported for 82.9%, 85.0%, and 76.9% of patients in the 110mg, 150mg, and placebo groups, respectively. Drug-related AEs (ie, adverse reactions) were reported for 41.5%, 37.5%, and 33.3% of patients in the 110mg, 150mg, and placebo groups, respectively. Four patients reported serious AEs (SAEs), 1 on 110mg and 3 on placebo; none were drug related. Discontinuations due to AEs were uncommon: 3 patients on 110mg (7.3%), 1 patient on 150mg (2.5%), and 1 patient on placebo (2.6%). The most common adverse drug reactions were vomiting, diarrhea, abdominal pain, and back pain. GI abdominal AEs were predominantly mild, generally resolved without the use of medication and rarely resulted in discontinuation of berotralstat (1 patient on 110mg, 1.2%).

Conclusions: Berotralstat was safe and generally well tolerated at both the 110-mg and 150-mg doses. No drug-related serious AEs occurred. Rates of study discontinuation due to AEs were low and similar between patients in the berotralstat 150mg and placebo groups. The most common type of adverse reactions were mild GI abdominal AEs.

Topic 2. Creating a Path to Normalisation of HAE Patients' Lives

Evaluation of Efficacy of Oral Prophylaxis with Berotralstat (BCX7353) in Patients with Hereditary Angioedema (HAE): Results of the APeX-2 Study

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Background: Berotralstat is an oral once-daily inhibitor of plasma kallikrein in development for prophylaxis of HAE attacks. APeX-2 (NCT03485911), a randomized, double-blind, placebo-controlled, Phase 3 study, evaluated the efficacy and safety of berotralstat.

Methods: 121 patients with HAE Type 1/2 and ≥2 investigator-confirmed attacks in the first 56 days of the run-in period were randomized 1:1:1 to receive berotralstat 150mg: 110mg: placebo for 24 weeks (Part 1). Randomization was stratified by baseline attack rate (<2/month vs ≥2/month). Patients recorded HAE attacks in a diary and were to treat any HAE attacks in accordance with their usual treatment plan. Investigator-confirmed attacks (primary), treated attacks (prespecified), and standard of care (SOC) on-demand medication use (ad-hoc) were analyzed over 24 weeks. The rate of attacks and rate of SOC on-demand medication use were evaluated using negative binomial regression. Responder status (exploratory endpoint: ≥50% prespecified, ≥70% ad-hoc) was evaluated using logistic regression. Results for the 150mg dose are presented.

Results: The rate of HAE attacks was significantly reduced in the berotralstat 150mg treatment group compared to placebo (150mg, -44.2%, p<0.001). The rate of attacks requiring treatment (150mg, -49.2%, nominal p<0.001) and the rate of use of SOC on-demand medications (150mg, -53.6%, nominal p<0.001) were also significantly reduced compared to placebo. 57.5% of patients assigned to the 150mg dose group had a ≥50% relative reduction in baseline attack rate (nominal p=0.005, odds ratio [OR]=3.913) and 50.0% had ≥70% relative reduction in baseline attack rate (nominal p=0.002, OR=5.630).

Conclusions: Berotralstat treatment significantly reduced rates of HAE attacks, attacks requiring treatment, and SOC on-demand medication use relative to placebo. 50.0% of patients receiving berotralstat 150mg had a ≥70% relative reduction in baseline attack rate.

Topic 2. Creating a Path to Normalisation of HAE Patients' Lives

The Appliance of the Psychodynamic Life Narrative Method in Work with Anxiety and Compulsive Thoughts after a Laryngeal Attack in a Patient with a Hereditary Angioedema.

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Background: A review of research aimed at studying the mental health of HAE patients has shown a correlation between the disease burden and levels of anxiety and depression (Fouche A.S. et al., 2014). The psychological distress is also one of the attack triggers. Swellings of the upper airways make the disease life-threatening and are associated with a severe anxiety level. However, there were no research found describing the use of psychocorrective approaches managing the anxiety associated with life-threatening attacks. Our aim is to demonstrate the relevance of the psychodynamic life narrative method in work with HAE patients' anxiety related to laryngeal attacks.

Patients and methods. A case analysis of an HAE patient (a 37 years old female) who received psychological assistance at the Dmitry Rogachev NRC PHOI. Among complaints: strong anxiety and compulsive thoughts related to an anticipation of laryngeal attack recurrence. Psychological assistance using the psychodynamic life narrative (Viederman M., 1983) was provided through online consultations (3 sessions in total), once a week.

Results: The case analysis showed that laryngeal attacks are related to severe death anxiety, a lack of life control, feeling dependent on physicians, as well as uncertain about medical help accessibility. The current life circumstances were defined, which the patient connected with the psychological distress associated with the swelling occurrence. The current life circumstances were placed into the life story of the patient and were interpreted as past traumatic situation recurrence. The creation and comprehension of this life narrative led to a compulsive thought reduction and a substantial decline in anxiety.

Conclusions: The use of psychodynamic life narrative permits a rapid relief of psychopathological symptoms and a reinforced life control. Further research on using psychodynamic life narrative seems promising for the correction of anxiety and depressive disorders in HAE patients.

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Fear of Attacks Reduces Quality of Life for Canadian HAE Patients

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Background: Hereditary angioedema is a rare inherited disorder characterized by recurrent episodes of severe swelling in different parts of the body often with no known trigger.

Methods: In 2019, HAE Canada conducted 2 online surveys to assess challenges faced by HAE patients and caregivers and to gain insight into experience with the newest prophylactic therapies: subcutaneous C1 esterase inhibitor, and lanadelumab a subcutaneous monoclonal antibody plasma kallikrein inhibitor.

Results: The first survey had 73 respondents: 68 (92%) individuals with HAE, and 6 (8%) caregivers. Attacks were experienced more than once a month by 29.4% (20/68) and more than once a week by 16.2% (11/68). They occurred in the GI tract in 89.6% of patients (60/67), as facial swelling in 79.1% (53/67) and in the upper airway in 71.6% (48/67). 74% (50/68) of respondents indicated they feared unpredictable, debilitating attacks which led to generalized anxiety in 63.3% (31/49) and a desire for control of swelling and treatment plans in 59.2% (29/49).
Eight participants (13%) had been treated with lanadelumab, mainly through participation in a clinical trial. Five considered it extremely effective in preventing attacks. Reported adverse events [headache (2/8) and injection site pain (7/8)] were tolerable to very tolerable. The second survey, intended to obtain information about the C1 inhibitor, had 19 respondents, 3 of whom had received the treatment. It was “extremely effective” for all 3 respondents and significantly reduced attacks for 2 of them. Reported adverse events [headache (1/3) and injection site reaction (2/3)] were tolerable to very tolerable.

Conclusion: Unpredictable painful or life-threatening HAE attacks are feared by HAE patients and lead to generalized anxiety. The newest medications are effective in reducing attacks. Positive results by survey respondents describe the impact of new drug therapies on reducing the fear and improving quality of life of Canadian HAE patients.