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HEREDITARY ANGIOEDEMA: BASIC MECHANISM AND TREATMENT MODALITIES

1420 | Novel SERPING1 mutations in bulgarian patients revealed by a targeted next generation sequencing platform

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Background: Hereditary angioedema (HAE) is a rare autosomal dominant disease characterized by swelling of the face, lips, tongue, larynx, genitalia, or extremities, with abdominal pain caused by intra-abdominal edema. HAE is caused by mutations affecting the C1 inhibitor gene (SERPING1), resulting in low levels of C1 inhibitor (Type I HAE) or normal levels of ineffective C1 inhibitor (Type II HAE).

Method: Genotyping was performed by means of a targeted next generation sequencing platform of the SERPING1 in 30 C1-INH-HAE type 1 patients, belonging to 13 HAE families. The newly developed and validated custom NGS platform targets the entire 11q12-q13.1 loci, including the promoter, coding, intron-exon boundary as well as intronic regions of the SERPING1 gene. Complement fractions and clinical symptoms were analyzed in relation to revealed gene mutations. Consent was obtained from all of the patients.

Results: This is the first genetic study of the Bulgarian HAE patients. Genetic defects were identified in 10 HAE families are: 3 nonsense, 2 splice-site defects, 2 frameshift mutations, 1 indel non frameshift, 1 missense, and 1 large deletion of exon 4. Novel mutations, not previously reported in human gene mutation databases were discovered, and were predicted to be deleterious due to the expected effect on DNA transcript and protein.

Conclusion: We identified 10 mutations of the SERPING1 gene in 13 HAE Type I families form the Bulgarian population (comprising 50% of the diagnosed HAE families in the country), revealing novel mutations, causative for C1-INH deficiency. A recently developed and validated targeted NGS platform was used for SERPING1 genotyping, presenting excellent potential for the future of HAE genetic diagnostics.

1421 | Improved health-related quality of life in pediatric patients with hereditary angioedema (HAE): a phase 3 study of C1 inhibitor for attack prevention

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Background: Patients with HAE have recurrent episodes of subcutaneous and submucosal tissue edema that negatively affects their quality of life (QoL). C1 inhibitor (C1-INH; Shire, Lexington, MA, USA) is currently approved to treat and prevent pre-procedure angioedema attacks in patients ≥2 years old (EU), and to routinely prevent attacks in patients aged ≥6 (EU) and ≥12 years (US). The QoL of children aged 6-11 years who received C1-INH for the routine prevention of angioedema attacks was assessed.

Method: Children in a multicenter single-blind study (NCT02052141) were required to have an average of ≥1.0 angioedema attacks/month that were moderate, severe, or required acute treatment during a 12-week baseline observation period (BOP). Patients received 500 U or 1000 U intravenous (IV) C1-INH, every 3-4 days for 12 weeks in a crossover design. Patients completed the youth version of the EuroQol 5-dimensional (EQ-5D-Y) descriptive system and Visual Analogue Scale (VAS) questionnaire at screening, weeks 5 and 9 of the BOP, and weeks 1, 5, and 9 of both consecutive 12-week treatment periods. Descriptive statistics were used to summarize the EQ-5D-Y descriptive system responses and VAS scores by treatment and visit.

Results: Twelve patients with HAE type I and a median (range) age of 10.0 (7-11) years were enrolled, 7 (58.3%) of whom were female. During BOP, treatment with 500U C1 INH, and 1000U C1-INH, ≤33.3%, ≤22.2%, and none of the patients, respectively, reported having problems with mobility, self-care, doing usual activities, pain or discomfort, and feeling worried, sad or unhappy. The mean [SD] EQ-5D VAS scores increased from 78.3 (13.8) at baseline (average of all pre-dose visits during the BOP) to 92.9 (17.7) at week 9 of treatment with 500U C1-INH and 98.5 (1.6) with 1000U C1-INH, indicating better overall health. The mean (SD) change in the VAS score from baseline to week 9 of treatment with 500U and 1000U C1-INH was 10.4 (19.0) and 21.6 (13.4), respectively, suggesting an overall improvement in QoL, particularly with the higher dose.

Conclusion: These data in 12 children aged 6-11 years indicate that treatment with both 500U and 1000U IV C1-INH (but particularly with 1000U C1-INH) for the routine prevention of HAE attacks improved patients' overall health status or QoL as measured by the EQ-5D-Y.