724 Intravenous C1-INH [C1-INH(IV)] Use Among Patients with Hereditary Angioedema (HAE) in the United States (US) and Associated Health Care Resource Utilization (HCRU)

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RATIONALE: Limited data are available regarding C1-INH(IV) treatment for HAE in the US. We characterized HAE medication consumption and HCRU in patients treated for HAE using a large US claims database.

METHODS: Retrospective cohort design using LifeLink™ Health Plan database records between 1/1/06 – 12/31/14. Subjects with HAE (ICD-9 code 277.6), ≥1 claim for an HAE-specific medication, and continuous insurance enrollment for ≥3 months following first (index) HAE prescription claim were included. Subjects included in a separate HCRU analysis were required to have enrollment data for ≥3 months pre- and ≥1 month post-index date.

RESULTS: 434/631 (68.8%) HAE patients used C1-INH(IV) (Cinryze® and/or Berinert®) during follow-up. 521/631 (82.6%) were included in the HCRU analysis, 336/521 (64.5%) of whom had claims for C1-INH(IV) treatment at any time. In unadjusted analyses, 68/336 (20.2%) of patients using C1-INH(IV) were hospitalized and 191/336 (56.8%) visited the emergency department (ED), compared to 11/185 (5.9%) and 80/185 (43.2%), respectively, of patients using only subcutaneous (SC) HAE medications. In the HCRU analyses, 18 patients had a central venous access device (CVAD) placed; 5/18 (27.7%) required hospitalization and 14/18 (77.7%) required an ED visit, compared to 79/521 (15.2%) and 271/521 (52.0%), respectively, among patients without a CVAD. The adjusted RR risk of hospitalizations and/or ED visits with a CVAD was 2.6 (95% CI: 0.17, 39.23) compared with no CVAD.

CONCLUSIONS: This study found high HCRU among C1-INH(IV) patients compared to patients using SC HAE medications, suggesting that venous access for HAE medication is associated with treatment complications in US HAE patients.

725 Recombinant Human C1 Inhibitor (rHC1INH) Is Efficacious and Well Tolerated As Prophylaxis for Prevention of Hereditary Angioedema (HAE) Attacks: A Randomized, Phase 2 Trial

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RATIONALE: rhC1INH is currently administered for the treatment of acute HAE attacks. Repeat rhC1INH treatment for recurrent attacks during open-label extension studies have maintained efficacy while being well tolerated, supporting a potential role for rhC1INH in prophylaxis.

METHODS: A randomized, double-blind, 3-period, crossover study was conducted in patients ≥13 years of age with functional C1INH levels <50% of normal and ≥4 HAE attacks during the previous 3 months. Patients received rhC1INH 50 IU/kg (max, 4200 IU) once or twice weekly or placebo in three, 4-week periods; each treatment was separated by 1 week and symptoms monitored by a daily diary. Primary endpoint was number of HAE attacks per 4-week period. Additional endpoints included percentage of patients with ≥25%, ≥50% (clinical response), or ≥75% reduction in number of HAE attacks versus placebo and number of days with HAE symptoms.

RESULTS: Thirty-two patients were randomized (mean age, 45.9 years [range, 16.9–73.5 years]). Mean number of HAE attacks was reduced from 7.2 (placebo) to 4.4 (rhC1INH once weekly; $P=0.0004$) and 2.7 (rhC1INH twice weekly; $P<0.0001$). Percentage of patients with ≥25%, ≥50%, and ≥75% reduction in HAE attacks versus placebo was 64.5%, 41.9%, and 19.4% for rhC1INH once weekly and 80.6%, 74.2%, and 41.9% rhC1INH twice weekly, respectively. Number of days with HAE symptoms was lower with rhC1INH twice weekly (5.1 days) and once weekly (8.0 days) versus placebo (10.2 days).

CONCLUSIONS: rhC1INH was efficacious for the prevention of HAE attacks and data support continued investigation of rhC1INH as prophylaxis.

726 Hereditary Angioedema with Normal C1 Inhibitor: An Italian Case Series

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RATIONALE: Hereditary angioedema with normal C1-inhibitor (nC1-INH-HAE) with and without factor XII mutations (FXII-HAE and U-HAE respectively) are familial disorders. We present the genetic and clinical features of patients with nC1-INH-HAE followed up in centers of the Italian Network for Angioedema (ITACA).

METHODS: 97 patients with personal or family history of angioedema and normal plasma levels of C1 inhibitor were studied. All patients were investigated for mutations in the whole *F12* gene coding region by direct DNA sequencing.

RESULTS: 80 patients had angioedema symptoms. Of these patients, 20 females (median age 42.2 years, range 12-78), belonging to 8 unrelated families, had the same mutation in *F12* gene, leading to the most common disease-causing aminoacid substitution, p.Thr309Lys. They were diagnosed as FXII-HAE. The haplotype analysis by using intragenic SNPs confirmed the hypothesis of a common founder. 17 subjects (9 males) in 7 FXII-HAE families were asymptomatic carriers of the same mutation.
60 patients (38% males; median age 45 years, range 12-81) had history of angioedema in their 36 families and no mutation in *F12* gene. They were diagnosed as U-HAE. Sequencing analysis revealed the presence of different SNPs that have been previously described as not affecting protein activity or function.
Accordingly, the minimum prevalence of FXII-HAE and U-HAE in Italy in 2016 is 37:59.394.000 inhabitants and 60:59.394.000 respectively, equivalent to 1:1.605.243 for FXII-HAE and 1:989.900 for U-HAE.

CONCLUSIONS: This nationwide survey of C1-INH-HAE provides for Italy a prevalence lower than in other European countries. We hyphotesize a disomogeneous geographical distribution of nC1-INH-HAE among European countries.