Conclusion: Pharmacokinetic modeling of a 5WB regimen for icatibant suggests exposures closer to those in adults, with acceptable safety margins. The 5WB approach provides a safe and effective dosing strategy during HAE attacks in children and adolescents.

1424 | Short-term prophylaxis with recombinant human C1 inhibitor in 9 patients with hereditary angioedema: A case series

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Background: Recombinant human C1-inhibitor (rhC1-INH) is registered for intravenous treatment (IV) of hereditary angioedema (HAE) attacks. Short-term prophylactic treatment (STP) with C1-INH is recommended in patients who will undergo invasive, surgical or dental procedures, and/or stressful events, much likely to provoke a HAE attack. STP with rhC1-INH is currently not licensed, and usually not investigated in clinical trials, due to the rarity of the disease. Therefore, it is important to publish these cases as a basis for informed decision making in an otherwise complex disease.

Method: SPT with rhC1-INH was initiated to cover 11 interventions in 9 HAE Type 1 patients: 5 men, mean age 51 years (17 - 73 years); mean weight 80.7 kg (60 - 98 kg). Patients were planned for invasive medical procedures: 6 dental procedures, 2 colonoscopies, 1 quadrantectomy with axillar lymph node dissection for invasive breast carcinoma (during common anesthesia), 1 cervical conization (with local anesthesia), and 1 mountaineering adventure holiday. All of the patients were evaluated to have a fragile course of the disease with frequent and/or severe HAE attacks. After ethical implications were discussed, a decision for STP with either 1 or 2 vials of 2100 U rhC1-INH, in the day of the procedure was initiated. Patients were followed closely and post-procedural periods analyzed.

Results: All patients experienced a safe peri- and post-procedural period with no breakthrough HAE attacks. STP with rhC1-INH was introduced 60-360 minutes (mean 148 minutes) before deemed interventions. No adverse events from the drug and/or medical procedures were observed. The patient with breast surgery developed prodromal signs of an abdominal attack on day 3 after the surgical intervention, which was successfully prevented with a dose of rhC1-INH. The average dose of rhC1-INH used for STP was 46.85 U/kg. Referring to the summary of product characteristics (SPC), 4 patients followed the prescription regimen for up to 4200 U (for weight above 84 kg), 3 patients used a higher dose (up to 64.61 U/kg), 2 patients used a lower dose (up to 28.75 U/kg): overall, 7 patients used 2 vials and 2 patients—1 vial of rhC1-INH.

Conclusion: Short-term prophylactic treatment with rhC1-INH could be a safe and viable option for HAE patients. Based on the case series, the prophylactic treatment should occur within 6 hours of the procedure or event. The dose indicated in the SPC for treatment of acute HAE attacks seems suitable also for STP.

1425 | Reduction of attack severity with fixed-dose subcutaneous (SC) C1 inhibitor liquid in hereditary angioedema patients: Results from the phase 3 SAHARA study

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Background: Ready-to-use SC SHP616 liquid (2000 IU in 4 mL) was shown to be superior to placebo in reducing HAE attacks in a Phase 3 SAHARA study in adult and adolescent patients with HAE with C1 inhibitor deficiency. A secondary study objective was to assess HAE attack severity in patients who received SHP616 as long-term prophylactic treatment (LTP).

Method: Patients in the randomized, double-blind study (NCT02584959) were aged ≥12 years with ≥2 monthly attacks pre-screening or pre-LTP. In a partial crossover design, 80% of subjects were randomly assigned to placebo or SHP616 2000 IU every 3-4 days for 14 weeks and crossed over from active to placebo or vice versa for another 14 weeks. The remaining patients were randomized to receive SHP616 2000 IU every 3-4 days for 28 weeks. Icatibant was used for breakthrough attacks. Patients in crossover sequences with ≥1 post-baseline observation were analyzed for efficacy. Attacks were rated as mild, moderate, or severe. Cumulative attack severity was the sum of the maximum symptom severity score recorded for each HAE attack and cumulative daily severity was the sum of the maximum severity scores recorded for each day of symptoms across all body locations.

Results: Of 81 patients screened, 75 were enrolled; 60 were randomized to the crossover sequence and 15 to the 28-week SHP616 arm. The mean (SD) age of patients was 41.3 (14.6) years and the mean (SD) weight was 84.0 (26.5) kg. During 12 months before screening, 90.7% received HAE therapy and 50.7% had a history of LTP with C1-INH or androgens. Of 57 placebo-administered patients, 8.8% were attack-free and 5.3%, 22.8%, and 63.2% had HAE attacks of mild, moderate, and severe maximum severity, respectively. Of 56 SHP616-treated patients, 37.5% were attack-free and 8.9%, 26.8%, and 26.8% had attacks of mild, moderate, and severe maximum severity, respectively. Relative to placebo, there were statistically significant reductions in cumulative HAE attack severity and cumulative daily severity (normalized per month) with SHP616, with a median reduction of 83.3% (least squared mean difference [LSMD] of -4.9; $P < 0.0001$) and 85.1% (LSMD of -12.4; $P < 0.0001$), respectively.

Conclusion: LTP with a fixed dose (2000 IU in 4 mL) of ready-to-use SHP616 led to fewer severe attacks, a higher proportion of attack-free patients, and a clinically meaningful and statistically significant reduction in cumulative attack severity and daily severity in HAE patients relative to placebo.

1426 | Management of German hereditary angioedema patients: comparison to other regions in the icatibant outcome survey

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Background: The Icatibant Outcome Survey (IOS; NCT01034969) is a Shire-sponsored, international, observational study monitoring safety and effectiveness of icatibant, a bradykinin B2 receptor antagonist approved for the acute treatment of adults with hereditary angioedema with C1 inhibitor deficiency (HAE-C1-INH). We report IOS data comparing demographic and icatibant-treatment outcomes in HAE-C1-INH patients from Germany to HAE-C1-INH patients from other IOS countries.

Method: A descriptive, retrospective, comparative analysis of data from of a total of 685 IOS patients with HAE-C1-INH from seven centers in Germany (n = 93) vs centers from Austria, Brazil, Czech Republic, Denmark, France, Greece, Israel, Italy, Spain, Sweden and the United Kingdom (n = 592, July 2009—January 2017). Icatibant treatment outcomes were retrieved from patients with complete attack outcome data for time to treatment, time to resolution and attack duration (160 attacks in 93 German patients and 1442 attacks in 592 patients from other IOS countries).

Results: German patients reported significantly fewer severe or very severe attacks (38.7% vs 57.5%, respectively) ($P < 0.0001$). The proportion of attacks treated with a single icatibant injection was significantly higher in German patients (97.1% vs 91.6%, $P = 0.0003$). The median time to treatment (0.0 hour vs 1.5 hours), time to resolution (3.0 hours vs 7.0 hours), and attack duration (4.3 hours vs 10.5 hours) in German patients vs other IOS countries, were all significantly shorter (all $P < 0.0001$). Overall, German patients did not use rescue medication at a higher rate ($P = 0.138$), however they did report significantly more use of C1 INH as rescue medication (129/576 attacks, 22.4%) than patients from other IOS countries (325/4303 attacks; 7.6%, $P < 0.001$). No meaningful differences were identified between patients from Germany and other countries, respectively, with regard to sex (62.4% vs 57.9% females), median age at enrollment (42.8 years vs 39.0 years), median age at symptom onset (11.0 years vs 12.0 years) and median age at diagnosis (21.9 years vs 20.8 years).

Conclusion: German IOS patients share similar demographic characteristics to patients from other IOS countries yet treat their attacks with icatibant significantly earlier and have markedly fewer severe or very severe attacks. Factors including regional access to and availability of icatibant may drive these outcomes and warrant further investigation.

1427 | Early vs late administration of icatibant in patients with hereditary angioedema

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Background: The relationship of the timing of icatibant self-treatment to demographic and treated attack characteristics for patients with hereditary angioedema due to C1-inhibitor deficiency are poorly understood.

Method: The Icatibant Outcome Survey (IOS, NCT01034969) is an ongoing, international, prospective, observational study designed to monitor the safety and effectiveness of icatibant treatment in the real-world setting. IOS data from patients in 11 countries were used to evaluate early vs late icatibant self-treatment (patients with median time-to-first injection <1 hour vs ≥1 hour from attack onset, respectively).

Results: Of 301 patients analyzed, 119 (39.5%) had median time-to-first injection <1 hour (median [Q1, Q3] for 829 icatibant-treated attacks, 0.3 hour [0.0, 0.6]) with no difference observed between early and late treating groups when comparing males and females. Early self-treatment varied across countries, ranging from 79.1% (Germany) to 11.1% (France). Early treaters vs late treaters treated attacks localized to skin, abdomen and larynx at a similar rate ($P = 0.814$, $P = 0.506$, and $P = 0.862$ respectively). No statistically significant difference between early vs later treater groups was observed based on pooled-attack severity (very mild/mild/moderate vs severe/very severe; $P = 0.135$). Comparing early vs late treatment, respectively, a significant reduction ($P < 0.001$) in median (Q1,Q3) time to resolution [4.2 hours (1.0, 10.0) vs 9.0 hours (3.5, 24.3)] and median (Q1,Q3) attack duration [5.0 hours (1.5, 11.0) vs 14.7 hours (6.5, 33.0)] was observed (269 patients; 1693 attacks with complete information on time to treatment, time to resolution and duration of attack).