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Oral Iptacopan Monotherapy Increases Paroxysmal Nocturnal Hemoglobinuria (PNH) Red Blood Cell Clone Size Via Control of Intra- and Extravascular Hemolysis in Anti-C5-Treated PNH Patients With Anemia

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Abstract

Background: Anemia caused by C3-mediated extravascular hemolysis (EVH) commonly occurs in patients with PNH receiving standard-of-care (SOC). Iptacopan is an oral complement factor B inhibitor. In the 24-week randomized period of the Ph-3 APPLY-PNH trial (NCT04558918), iptacopan monotherapy had superior efficacy to SOC. We report the total PNH red blood cell (RBC) clone size and C3-deposition from the 24-week randomized period of APPLY-PNH.

Methods: Adults with PNH (N=97) with mean hemoglobin <10g/dL on stable SOC (eculizumab/ravulizumab) for ≥6mo were randomized 8:5 (stratified by SOC and RBC transfusions [RBCTs] in the preceding 6 mo) to take iptacopan 200 mg twice-a-day (n=62) or continue SOC (n=35). Primary endpoints were defined as a ≥2g/dL hemoglobin increase from baseline and hemoglobin ≥12g/dL without RBCTs. A prespecified testing procedure adjusted for multiplicity; unadjusted, 2-sided P-values are reported for significant endpoints. Total PNH RBC clone size and C3-deposition were exploratory endpoints.

Results: Iptacopan was superior to SOC for both primary endpoints: 82.3% of iptacopan-treated vs. 2.0% of SoC-treated patients had a ≥2g/dL hemoglobin increase from baseline (P<.0001); 68.8% vs. 1.8% achieved hemoglobin ≥12g/dL, respectively (P<.0001). Iptacopan was superior for RBCT avoidance (+70.3%; P<.0001), adjusted mean changes from baseline in hemoglobin (+3.63g/dL; P<.0001), FACIT−F score (+8.29; P<.0001) and absolute reticulocyte count (-116.26×10^9/L; P<.0001), and annualized clinical breakthrough hemolysis (BTH) rate (rate ratio: 0.10; P=.0118). In the iptacopan arm, the mean total PNH RBC clone size (baseline, 64.6%) increased by wk4 and stabilized through week 24 (93.2%). Mean C3-deposition (baseline, 19.2%) reduced by wk4 and became negligible through week 24. Through week 24, both were comparable to the baseline in the SOC arm. Headache/diarrhea was more commonly reported with iptacopan. Two SOC-treated patients experienced serious hemolysis; none for iptacopan.

Conclusions: Iptacopan significantly improved hemoglobin levels vs SOC without RBCTs. By controlling intravascular hemolysis and reducing C3-deposition-mediated EVH, iptacopan led to an expected increase in PNH RBC survival to comprise >90% of the total RBC population. Clinical BTH rate and severity appeared lower with iptacopan. Iptacopan may become a practice-changing outpatient treatment for patients with PNH with a suboptimal response to eculizumab/ravulizumab and a preferred option for patients with hemolytic PNH.

Keywords

MDS, paroxysmal nocturnal hemoglobinuria, iptacopan, complement inhibitor, hemolysis, Phase III