Abstract: P829

Title: EFFECTS OF ORAL IPTACOPAN MONOTHERAPY, INCLUDING INCREASED PAROXYSMAL NOCTURNAL HEMOGLOBINURIA RED BLOOD CELL CLONE SIZE, ARE SUSTAINED IN ANTI-C5-TREATED PATIENTS WITH ANEMIA: FINAL APPLY-PNH DATA

Abstract Type: Poster Presentation

Topic: Bone marrow failure syndromes incl. PNH - Clinical

Background:

In the 24-week (wk) randomized period of the Phase III APPLY-PNH trial (NCT04558918), iptacopan (a first-in-class, oral factor B inhibitor) showed superiority vs C5 inhibitors and was well tolerated in anti-C5-treated PNH patients (pts) with persistent anemia.

Aims:

We report final (48-wk) APPLY-PNH data, including PNH red blood cell (RBC) clone size and C3 fragment deposition, after a 24-wk extension period.

Methods:

Adult PNH pts (receiving anti-C5 for ≥6 months; mean hemoglobin [Hb] <10 g/dL) were randomized to receive iptacopan monotherapy 200 mg twice daily or continue anti-C5 for 24 wks. In an optional 24-wk extension, pts in the iptacopan arm continued iptacopan; pts in the anti-C5 arm switched to iptacopan monotherapy.

Results:

95 pts entered the extension (iptacopan arm n=61/62; anti-C5-to-iptacopan arm n=34/35). In the iptacopan arm, improvements at Wk 24 were sustained at Wk 48, including increased Hb, normal/near-normal mean Hb and transfusion avoidance. Rapid improvements in these outcomes were seen in the anti-C5-to-iptacopan arm, reaching values comparable to the iptacopan arm. In the iptacopan and anti-C5-to-iptacopan arms, mean Hb at Wk 48 was 12.2 and 12.1 g/dL (SD 1.6 and 1.4; includes post-transfusion data), and 91.9% of pts (Wks 2–48) and 94.1% (Wks 26–48) achieved transfusion avoidance, respectively. The adjusted mean change from baseline (BL) to Wk 48 in Hb, Functional Assessment of Chronic Illness Therapy–Fatigue score and absolute reticulocyte count was +3.35 g/dL, +9.80 and −106.26 × 109/L in the iptacopan arm and +3.36 g/dL, +10.96 and −107.95 × 109/L in the anti-C5-to-iptacopan arm, respectively. In both arms, mean lactate dehydrogenase at Wk 48 was consistent with BL.

In the iptacopan arm, the increase from BL to Wk 24 in total PNH RBC (type II and type III) clone size was sustained to Wk 48 (Wk 48 mean 90.9%; mean change from BL 26.2%), as was a reduction in C3 fragment deposition on PNH RBCs (Wk 48 mean 1.97%; mean change from BL −16.1%; **Figure**). In the anti-C5-to-iptacopan arm, PNH RBC clone size increased (Wk 48 mean 90.1%; mean change from Wk 24 to 48 30.3%) and C3 fragment deposition reduced (Wk 48 mean 0.12%; mean change from Wk 24 to 48 −16.9%) rapidly after switching treatment.

6/62 pts in the iptacopan arm had clinical breakthrough hemolysis (BTH; all mild or moderate) during 48 wks of therapy; in the anti-C5-to-iptacopan arm, clinical BTH occurred in 6/35 pts during 24 wks of anti-C5 and in one additional pt after switching to iptacopan. No BTH led to iptacopan discontinuation. Three iptacopan-treated pts had major adverse vascular events; none were considered treatment related. There were no deaths or treatment discontinuations due to treatment-emergent adverse events (TEAEs) with iptacopan. No serious hemolysis TEAEs or serious infections caused by *N. meningitidis, S. pneumoniae* or *H. influenzae* occurred with iptacopan.

Summary/Conclusion:

In APPLY-PNH, long-term iptacopan monotherapy led to durable responses and was well tolerated in anti-C5-treated PNH pts with anemia. Pts in the iptacopan arm had sustained improvements in several hematological and clinical parameters. An increase in PNH RBC clone size and decrease in C3 fragment deposition was maintained, indicating sustained control of intravascular hemolysis with resolution of extravascular hemolysis. Pts in the anti-C5-to-iptacopan arm had rapid improvements in outcomes after treatment switch. These data suggest that oral iptacopan monotherapy may be a practice-changing option for PNH pts with suboptimal response to anti-C5 therapy.

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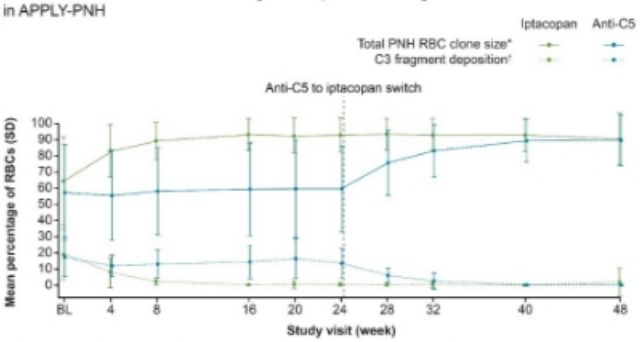
Figure. Total PNH RBC clone size* and C3 fragment deposition† during 48 weeks of treatment in APPLY-PNH



Pts with available total PNH RBC clone size* data (pts with available C3 fragment deposition† data)										
Iptacopan	62 (61)	57 (55)	57 (52)	56 (43)	53 (38)	60 (47)	60 (48)	56 (41)	60 (44)	61 (47)
Anti-C5 antibody	35 (34)	28 (28)	32 (31)	28 (28)	32 (31)	33 (31)	30 (27)	32 (25)	29 (21)	30 (16)

*Percentage of type II and type III PNH RBCs; †Percentage of type II and type III PNH RBCs that were C3d-positive
BL, baseline; PNH, paroxysmal nocturnal hemoglobinuria; pt, patient; RBC, red blood cell; SD, standard deviation

Keywords: Complement, Paroxysmal nocturnal hemoglobinuria (PNH), Hemolysis, Phase Ⅲ