Pegcetacoplan for post-transplant recurrent C3 glomerulopathy or immune complex membranoproliferative glomerulonephritis in NOBLE: 52-week patient evolution

SA-PO800

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CONCLUSIONS

- ✓By inhibiting C3 and C3b, pegcetacoplan achieved meaningful histology improvements for 8 of 9 (88.9%) patients while also improving disease parameters, increasing serum C3, and decreasing plasma sC5b-9
- ✓The phase 3 VALIANT (NCT05067127) trial is evaluating the safety and efficacy of pegcetacoplan in patients with native kidney or post-transplant C3G or primary IC-MPGN

BACKGROUND

- C3G and primary IC-MPGN are rare chronic kidney diseases caused by overactivation of the classical and alternative pathways of the complement system[1]
- This overactivation causes high levels of C3 breakdown products to be deposited in the kidneys, which can result in kidney damage and culminate in kidney failure[1,2]
- Pegcetacoplan, a targeted C3 and C3b inhibitor, showed preliminary efficacy and safety in transplant-naive patients with C3G in the 48-week phase 2 DISCOVERY trial (NCT03453619)[3]
- Results of the phase 2 NOBLE trial (NCT04572854) extended these efficacy findings to patients with post-transplant recurrent C3G or primary IC-MPGN by showing that 50% (5 of 10) of patients who received pegcetacoplan had ≥2 orders of magnitude reduction in C3c staining after 12 weeks (primary endpoint); pegcetacoplan was also found to be well tolerated[4]
- The NOBLE study continued 40 weeks beyond the week 12 primary endpoint, during which all patients received pegcetacoplan in addition to SOC[4]

OBJECTIVE

To report the efficacy and safety outcomes for patients with post-transplant recurrent C3G or primary IC-MPGN who received pegcetacoplan for 52 weeks in the phase 2 NOBLE trial

METHODS

- As previously reported, NOBLE is a prospective, phase 2, multicenter, open-label, randomized controlled trial of pegcetacoplan versus SOC for post-transplant patients with recurrent C3G or primary IC-MPGN[4]
- After a 12-week randomized period, all patients received subcutaneous pegcetacoplan 1080 mg twice weekly plus SOC for 40 weeks[4]
- We present the post hoc analysis results for patients with the most extensive experience with pegcetacoplan in the NOBLE study; this includes patients who received pegcetacoplan plus SOC for 52 weeks and had laboratory results at week 52 (n=9), as well as a subgroup of these patients who had ≥80% adherence (treatment completers) (n=7)

RESULTS

- All of the 10 patients randomized to pegcetaoplan in NOBLE completed the 12-week RCP
- Laboratory data at week 52 were available for 9 of these patients; these 9 were included in the current analysis
- Seven patients in this analysis completed NOBLE through week 52 with ≥80% adherence and are considered treatment completers
- At week 52, 5 of 9 (55.6%) patients had reduced C3c staining (P = .0423 vs baseline) and 7 of 9 (77.8%) had decreased histology activity scores compared with baseline (**Table 1**, **Figure 1**)
- Two of 8 (25.0%) evaluable patients had absent electron microscopy deposits at week-52 biopsy (**Table 1**) and 4 of 8 (50.0%) had absent podocyte effacement
- Patients with proteinuria ≥1 g/g at baseline (n=4) had a median 56.4% decrease in proteinuria (**Table 1**)
- Seven of 9 (77.8%) patients had stable/improved eGFR

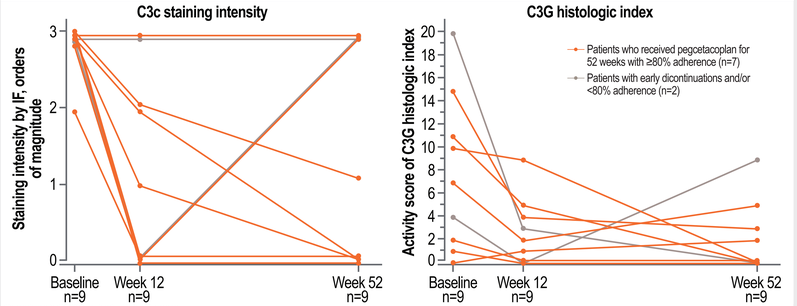
Table 1. Histological, clinical, and biomarker parameters of disease activity for patients who received 52 weeks of pegcetacoplan

Parameter		Pegcetacoplan Weeks 0–52 (n=9)	Pegcetacoplan Weeks 0–52 Treatment Completers (n=7)
C3c staining intensity on renal biopsy[a]	Patients with a decrease by ≥2 orders of magnitude compared to baseline, n (%)	5 (55.6) P = .0423[b]	5 (71.4) P = .0423[b]
	Patients with zero staining intensity, n (%)	4 (44.4)	4 (57.1)
Absent EM deposits, n (%)		2 (25.0; n=8)[c]	2 (33.3; n=6)[c]
Absent podocyte effacement, n (%)		4 (50.0; n=8)[d]	4 (66.7; n=6)[e]
Histology activity index	Patients who decreased from baseline, n (%)	7 (77.8)	6 (85.7)
	Score of zero, n (%)	5 (55.6)	4 (57.1)
	% change from baseline, median (IQR)	–100 (–100.0, –54.3)	–100 (–100.0, –80.0)
Proteinuria, % change from ≥1 g/g baseline, median (IQR; n=4)		–56.4 (–84.63, –25.86)[f]	–56.4 (–84.63, –25.86)[f]
Serum C3, % change from baseline, median (IQR)		347.37 (272.00, 1154.76)[g]	347.37 (272.00, 1154.76)[g]
Plasma sC5b-9, % change from baseline, median (IQR)		–64.1 (–67.0, –48.1)	–64.1 (–67.0, –48.1)
eGFR change from baseline, mL/min/1.73m², median (IQR)		16.0 (–12.0, 26.0)	22.0 (3.0, 27.0)

C3c, complement 3c; eGFR, estimated glomerular filtration rate; EM, electron microscopy; IQR, interquartile range; sC5b-9, soluble complement C5b-9.
[a]Study inclusion requires ≥2 orders of magnitude in C3c staining. [b]Analysis by Cochran-Mantel-Haenszel test. [c]At baseline, all patients (n=8 for whole group and n=6 for treatment completers; 100%) with available data had EM deposits present. [d]At baseline, 3/8 (37.5%) patients with available data had absent podocyte effacement. [e]At baseline, 2/6 (33.3%) patients with available data had absent podocyte effacement. [f]For this outcome, the 2 groups consisted of the same patients. [g]Post hoc 1-sample t test at 52 weeks compared to baseline *P*≤.05.

RESULTS (*continued*)

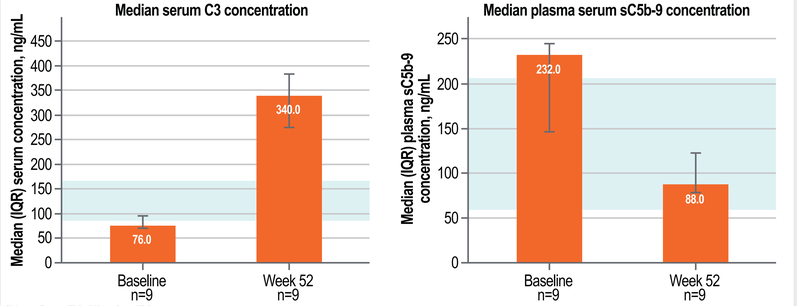
Figure 1. C3c staining and C3 histologic activity for patients who received 52 weeks of pegcetacoplan



C3c, complement 3c; C3G, C3 glomerulopathy; IF, immunofluorescence.
P value for change in C3c staining compared with baseline, *P*=.0143. *P* value for change in C3G histologic index compared with baseline, *P*=.0238.

- Eight of 9 patients (88.9%) had favorable biomarker results (ie, increased C3 and decreased sC5b-9 concentrations); all patients with ≥80% adherence (n=7) had favorable results (**Table 1**, **Figure 2**)
- Likewise, treatment completers (n=7) had favorable efficacy results (**Table 1**, **Figure 1**)

Figure 2. Serum C3 and plasma sC5b concentrations for patients who received 52 weeks of pegcetacoplan[a]



IQR, interquartile range; sC5b-9, soluble complement C5b-9.
[a]Blue boxes indicate normal concentration ranges.

- No meningitis cases, graft losses, or deaths were reported
- Non-serious rejection episodes were reported for 2 of 9 (22.2%) patients
- One of the 9 patients in this analysis discontinued the study due to physician's decision

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Abbreviations: C3G, C3 glomerulopathy; C3c, complement 3c; eGFR, estimated glomerular filtration rate; EM, electron microscopy; IC-MPGN, immune-complex membranoproliferative glomerulonephritis; IF, immunofluorescence; IQR, interquartile range; RCP, randomized controlled period; sC5b-9, soluble complement C5b-9; SOC, standard of care.

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