Глекапревир и Пибрентасвир у пациентов с ВГС и тяжелым почечным повреждением

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ORIGINAL ARTICLE

Glecaprevir and Pibrentasvir in Patients with HCV and Severe Renal Impairment

Edward Gane, M.D., Eric Lawitz, M.D., David Pugatch, M.D., Georgios Papatheodoridis, M.D., Norbert Bräu, M.D., Ashley Brown, M.D., Stanislas Pol, M.D., Ph.D., Vincent Leroy, M.D., Ph.D., Marcello Persico, M.D., Christophe Moreno, M.D., Ph.D., Massimo Colombo, M.D., Eric M. Yoshida, M.D., David R. Nelson, M.D., Christine Collins, Ph.D., Yang Lei, Ph.D., Matthew Kosloski, Ph.D., and Federico J. Mensa, M.D.

BACKGROUND

- Chronic hepatitis C virus (HCV) infection is more prevalent among patients who have chronic kidney disease than among those who do not have the disease.
- Patients with chronic kidney disease who also have HCV infection are at higher risk for progression to end-stage renal disease than those who have chronic kidney disease without HCV infection.
- Patients with both HCV infection and advanced chronic kidney disease have limited treatment options.

METHODS

- We conducted a multicenter, open-label, phase 3 trial to evaluate the efficacy and safety of treatment with the combination of the NS3/4A protease inhibitor glecaprevir and the NS5A inhibitor pibrentasvir for 12 weeks in adults who had HCV genotype 1, 2, 3, 4, 5, or 6 infection and also had compensated liver disease (with or without cirrhosis) with severe renal impairment, dependence on dialysis, or both.

- Patients had stage 4 or 5 chronic kidney disease and either had received no previous treatment for HCV infection or had received previous treatment with interferon or pegylated interferon, ribavirin, sofosbuvir, or a combination of these medications.

- The primary end point was a sustained virologic response 12 weeks after the end of treatment.

Patient Population

- Patients were screened between December 21, 2015, and March 25, 2016, at 30 trial centers in Australia, Belgium, Canada, France, Greece, Italy, New Zealand, the United Kingdom, and the United States.
- We enrolled adults 18 years of age or older who had chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection and compensated liver disease with or without cirrhosis.
- Patients were required to have an estimated glomerular filtration rate at screening of less than 30 ml per minute per 1.73 m2 of body-surface area.

Baseline Demographic, Disease, and Clinical Characteristics

Characteristic	Value
Number of patients enrolled	104
Male sex — no. (%)	79 (76)
Race — no. (%)	
White	64 (62)
Black	25 (24)
Asian	9 (9)
Other	6 (6)
Mean age (range) — yr	57 (28–83)
Median body-mass index (range)	26 (18–45)
eGFR in patients not undergoing hemodialysis — ml/min/1.73 m2	20.6±8.0
Median HCV RNA level — log10 IU/ml (range)	5.9 (3.4–7.5)
HCV genotype — no. (%)	
1	
1a	23 (22)
1b	29 (28)
Other	2 (2)
2	17 (16)
3	11 (11)
4	20 (19)
5	1 (1)
6	1 (1)

Characteristic	Value
HCV treatment history — no. (%)	
None	60 (58)
Interferon and pegylated interferon with or without ribavirin	42 (40)
Sofosbuvir and ribavirin with or without pegylated interferon	2 (2)
Compensated cirrhosis — no. (%)	
No	84 (81)
Yes	20 (19)
Chronic kidney disease stage — no. (%)	
Stage 4	14 (13)
Stage 5	90 (87)
Hemodialysis — no. (%)	85 (82)
Polymorphisms — no./total no. (%)	
Any polymorphism	28/96 (29)
NS3 only	1/96 (1)
NS5A only	24/96 (25)
Both NS3 and NS5A	0/96

Table 2. Sustained Virologic Response Rate.

Time of measurement	Value
On-treatment response — no./total no. (%)*	
Week 1	37/101 (37)
Week 2	77/100 (77)
Week 4	98/103 (95)
Week 8	103/103 (100)
Final treatment	104/104 (100)
Posttreatment response — no./total no. (%)†	
Sustained virologic response at posttreatment week 4	103/104 (99)
Sustained virologic response at posttreatment week 12	102/104 (98)
Sustained virologic response at posttreatment week 24	100/104 (96)‡

* A positive on-treatment or posttreatment response was defined as an HCV RNA level of less than 15 IU per milliliter.
‡ Two patients who were reported to have a sustained virologic response at 12 weeks but not at posttreatment week 24 were lost to follow-up between posttreatment weeks 12 and 24.

Table 3. Adverse Events and Selected Laboratory Abnormalities.*

Event	Value
	no. of patients (%)
Any adverse event	74 (71)
Serious adverse event	25 (24)
Adverse event leading to discontinuation of trial drug	4 (4)
Adverse event reported in at least 10% of patients	
Pruritus	21 (20)
Fatigue	15 (14)
Nausea	12 (12)
Death†	1 (1)
Alanine aminotransferase >3× ULN, grade ≥2	0
Total bilirubin >3× ULN, grade ≥3‡	1 (1)
Hemoglobin <8.0 g/dl, grade ≥3‡	5 (5)

* ULN denotes the upper limit of the normal range.

† One patient died due to an adverse event of cerebral hemorrhage, which was assessed by the investigator as being unrelated to trial drug.

RESULTS

- Among the 104 patients enrolled in the trial, 52% had genotype 1 infection, 16% had genotype 2 infection, 11% had genotype 3 infection, 19% had genotype 4 infection, and 2% had genotype 5 or 6 infection.
- The sustained virologic response rate was 98% (102 of 104 patients; 95% confidence interval, 95 to 100). No patients had virologic failure during treatment, and no patients had a virologic relapse after the end of treatment.
- Adverse events that were reported in at least 10% of the patients were pruritus, fatigue, and nausea. Serious adverse events were reported in 24% of the patients. Four patients discontinued the trial treatment prematurely because of adverse events; three of these patients had a sustained virologic response.

CONCLUSIONS

Treatment with glecaprevir and pibrentasvir for 12 weeks resulted in a high rate of sustained virologic response in patients with stage 4 or 5 chronic kidney disease and HCV infection. (Funded by AbbVie; ClinicalTrials.gov number, NCT02651194.)

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