Glecaprevir/Pibrentasvir in Patients with Hepatitis C Virus Genotype 1 or 4 and Past Direct-Acting Antiviral Treatment Failure

BACKGROUND:

- Once a patient has been treated for hepatitis C and has virological failure, the options for retreatment are limited based on their initial treatment.
- Three types of chronic hepatitis C medications, called direct-acting antivirals, are NS5A replication inhibitors, NS5B polymerase inhibitors, and NS3/4A protease inhibitors. Most effective treatments contain a NS5A inhibitor but if patients develop virological failure on a NS5A or NS3/4A containing regimen, resistance associated substitutions (RAS), changes in the RNA sequence, can occur which decreases the efficacy of future treatment.
- Previous therapies have been tested but cannot be always be used in certain populations so treatments are needed to successfully retreat patients with previous virological failure.

OBJECTIVE:

- Determine the efficacy and safety of ribavirin-free glecaprevir/pirbrentasvir (Mavyret) in patients with chronic HCV GT1, 4 5 or 6 with past treatment failure with a NS5A inhibitor, NS3/4A protease inhibitor or both, with or without compensated cirrhosis in 12 weeks of therapy compared to 16 weeks.

METHODS

- **Type of study design:** Randomized, parallel, open label, experimental, multicenter phase III study
- **Study duration**: 12 weeks vs 16 weeks
- **Inclusion criteria**: >18 years old; genotype 1, 4, 5, or 6; meet criteria for chronic hepatitis C; history of virologic failure with NS5A inhibitors or NS3/4A protease inhibitors or both; with or without compensated cirrhosis
- **Exclusion criteria**: HCV RNA <1,000 IU/mL; coinfection with hepatitis B, HIV or multiple genotype hepatitis C; positive urine drug screen; abnormal lab values (CrCl, AST/ALT, albumin, INR, etc); discontinuation of previous DAA treatment for reason other than virologic failure; previous exposure to glecaprevir or pibrentasvir.
- **Patient Screening**: 122 patients screened; 91 enrolled
    - Glecaprevir/pibrentasvir. 3 pills (100 mg/40 mg each: total 300/120 mg)
        - 44 received glecaprevir/pibrentasvir 300/120 mg once daily for 12 weeks
        - 47 received glecaprevir/pibrentasvir 300/120 mg once daily for 16 weeks
- **Primary Outcom**e: Percentage of patients with sustained virological response at 12 weeks post treatment (SVR12)
- **Secondary Outcomes**: Percentage of patients with on-treatment virologic failure and percentage of patients with virologic relapse
- **Data handling method**: Intent to treat

RESULTS

Primary Endpoint SVR12		
Response	**12 weeks n=44**	**16 weeks (n=47)**
Overall	**89%** (39/44 patients; 95% CI 76-95)	**91%** (43/47 patients; 95% CI 80-97)
On-treatment virological failure	2% (1/44 patients))	9% (4/47 patients)
Virologic relapse	9% (4/44 patients)	0% (0/47 patients)

- **Past treatment with NS3/4A protease inhibitor only**:
  - 100% achieved SVR12 in 12 and 16 week treatment groups
- **Past treatment with NS5A inhibitors only:**
  - 12 weeks: 88% achieved SVR12 (14 of 16; 95% CI, 64-97)
  - 16 weeks: 94% achieved SVR 12 (17 of 18; 95% CI, 74-99)
- **Past treatment with both NS5A and NS3/4A**
  - 12 weeks: 79% achieved SVR12 (11 of 14; 95% CI, 52-92)
  - 16 weeks: 81% achieved SVR12 (13 of 16; 95% CI, 57-93)
- **Authors conclusions**
  - 16 weeks of G/P treatment achieved a high SVR12 rate in patients with HCV GT1 infection and past failure to regimens containing either NS5A inhibitors or NS3 protease inhibitors but past treatment with both NS5A and NS3/4A was associated with lower SVR12 rate.
    - 16 week treatment may be required for patients with NS5A experience alone
  - G/P was safe and tolerated well regardless of the treatment time

STRENGTHS

- Stratified randomization allowed for comparable treatment groups
- No dropouts
- Efficacy in curing hepatitis C after treatment failure seen
- Wide variety of patients (age, location, w/ or w/o compensated cirrhosis), but analyses of individual subtypes not possible due to small sample size
- Appropriate treatment dosing and duration

LIMITATIONS

- No control therapy
- Small sample size
- No data on compliance which is crucial to sustained cure
- Only applies to one genotype (GT1); not enough genotype 4 patients enrolled
- No clearly stated objective regarding 12 weeks vs. 16 weeks
- No p-values listed to assist the reader in determining significance
- No power calculated – if low, risk of type II error could mean missing treatment significance

CONCLUSIONS

- Although there were not p-values listed to show statistical significance, the efficacy of G/P in achieving SVR12 in genotype 1 hepatitis C patients with previous treatment failure using NS5A inhibitors and NS3/4A protease inhibitors was seen in this trial through achievement of SVR12.
- With the small sample size, the results of this trial may not be applicable to the patients being re-treated who are genotype 1 or 4 but the 16 week treatment provides an option for prescribers who are not seeing efficacy with other treatments.
  - G/P is not currently indicated for treatment failure with both NS5A inhibitors and NS3/4A protease inhibitors and is not the first line treatment for for previous treatment with NS5A alone so in the future that could change with further studies and reaseach
- Further analysis and studies need to be completed with a larger sample size, formal hypothesis and p-values listed to determine if G/P should be the first line option in patients with previous treatment failure. This would be especially important in previous treatment failure with NS5A inhibitors alone as well as combined with previous NS3/4A protease inhibitor. Further analysis is also needed to compare G/P to other regimens approved for retreatment.

Poordad F, Pol S, Asatryan A, et al. Glecaprevir/Pibrentasvir in patients with hepatitis C virus genotype 1 or 4 and past direct-acting antiviral treatment failure. Hepatology. 2018 Apr;67(4):1253-1260.

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