Ledipasvir-sofosbuvir administered for 8 vs. 12 weeks: Multicenter Randomized Controlled Open Label Study

BACKGROUND:
- More than 3 million people in the US are chronically infected with the hepatitis C virus
- HCV related morbidity and mortality are projected to continue rising for another 20 years
- ½ - ¾ of people currently infected have not received a diagnosis and are untreated

OBJECTIVE:
- To determine if single tablet regimen of ledipasvir-sofosbuvir administered for 8 weeks has sustained virologic response as compared to known options

METHODS
- Multicenter, controlled experimental, open label.
- Duration: 24 weeks
- Inclusion criteria
  - HCV genotype I infection without cirrhosis
  - Anyone age 18 or older than hasn’t been treated previously
  - RNA level of at least 10^4 IU/ml
  - Alanine and aspartate aminotransferase levels of no more than 10 times the upper limit of the normal range
  - Platelet count of more than 90000 per cubic millimeter
  - Hemoglobin level of at least 11g/deciliter in women or at least 12g/deciliter in men
- Exclusion
  - Presence of cirrhosis
  - Clinically significant illness that may interfere with subject treatment
  - GI disorder/condition that may interfere with drug absorption
  - Clinical hepatic decompensation
  - Solid organ transplantation
  - Malignancy within 5 years prior to screening
  - Hepatitis B infection
  - Drug/alcohol abuse
  - Pregnant/nursing females
  - Immunosuppressant use
- 647 patients were stratified, randomized and treated
  - 215-Intervention group-ledipasvir (400mg)- sofosbuvir (90mg) for 8 weeks daily
  - 216-Control 1 –Ledipasvir-sofosbuvir plus ribavirin (1000mg daily if body weight of <75kg, 1200mg daily if body weight of ≥75kg) for 8 weeks
  - 216-Control 2 -ledipasvir (400mg)- sofosbuvir (90mg) for 12 weeks daily
- Outcome measures (efficacy and safety)
  - Primary efficacy end point- HCV RNA levels of less than 25IU/milliliter at 12 weeks after the end of therapy (intent to treat)-was compared to calculated historical response rate of 60%
  - Secondary efficacy end point - non inferiority of 8 weeks of intervention group to control
- Power -90% with an alpha of at least 0.05, to determine at least 30% point improvement in the rate of sustained virologic responses as compared with a calculated control rate of 60%
- Data handling method: intend to treat

RESULTS
- Number of patients that completed the study
  - Intervention group-215
  - Control 1 -213
Control 2 -211
Total number of patients-639

- Findings and statistical results for each outcome measure
  - The criterion for the primary end point was met in all three treatment groups
    - Rates of sustained virologic response that were superior to the adjusted historical control rate of 60% (P<0.001 for all comparisons)
      - Intervention-94%
      - Control 1 -93%
      - Control 2 -95%
  - Secondary end point
    - 8 weeks of ledipasvir–sofosbuvir vs the rate in the group that received 12 weeks of ledipasvir–sofosbuvir was 1 percentage point higher (97.5% CI, −4 to 6) and the rate in the group that received 8 weeks of ledipasvir–sofosbuvir with ribavirin was 1 percentage point lower (95% CI, −6 to 4)

- Authors stated conclusions
  - 8 week treatment of single tablet regimen of ledipasvir-sofosbuvir resulted in a high rate of sustained virologic response. Uniformly high rates of response in all the patient subgroups suggest the efficacy of this regimen across a broad range of previously untreated patients with HCV genotype 1 infection without cirrhosis that were not previously treated.

- Strengths
  - Large multi-center study
  - Controlled, stratified, randomized
  - Power
  - Statistically sound
  - Intend to treat

- Limitations
  - Potential for bias-authors were consulting for Gilead
  - Open label
  - Historical control was used
  - Control groups didn’t include current standard therapy for HCV

CONCLUSIONS
- The study showed that 8 week therapy of single tabled regimen of ledipasvir-sofosbuvir results in similar rates of response compared to control groups
- 8 weeks of treatment is more cost effective compared to 12 weeks of therapy and doesn’t have as many side effects as therapy with ribavirin.
- Future research
  - Future research is needed to duplicate the results and ensure that shorter therapy duration is indeed non-inferior to current regiments or longer regiments.
  - Studies that are doubled blinded, double dummy would be best to conduct in the future
  - With more studies to ensure these results, this therapy duration can potentially take place of longer therapies without compromising efficacy of treatment.

REFERENCE

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