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 preciously
    - 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

- Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl JMed. 2014;370(20):1879-88.

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9/26/2014