CAT Assignment (Critically Appraised Topic)

Title: Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options

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1. Reference:


2. Clinical Question:

Does treatment with sofosbuvir for Hepatitis C genotype 2 or 3 patients for whom peginterferon and ribavirin treatment was not an option lead to a sustained virologic response at 12 week weeks after therapy?

PICO Parts:

P – Hepatitis C patients with genotype 2 or 3 for whom peginterferon and ribavirin treatment was not an option

I – Sofosbuvir

C – Trial 1: matching placebo; Trial 2: prior interferon therapy

O – Sustained virologic response at 12 weeks after therapy

3. Search Strategy

a. Database(s) searched: PubMed

b. Keyword Search Terms used: Hepatitis C, sofosbuvir

c. MeSH Search Terms used: hepatitis c, sofosbuvir, hepacivirus, humans

d. Limits used: English, humans, within last 5 years
4. Methods Description (setting, population, sample size, study design):

This multicenter study includes two blinded, randomized, phase 3 trials involving patients with chronic hepatitis C. Specifically, patients with two particular genotypes (2 or 3) were included in both trials. For trial one, patients were enrolled at 63 sites in the United States, Canada, Australia, and New Zealand from March 2012 through May 2012. For trial two, patients were enrolled at 67 sites in the United States, Canada and New Zealand from May 2012 through July 2012.

In trial one (“POSITRON”), 207 patients who had no prior treatment with peg-interferon, or who had to discontinue interferon therapy due to adverse effects, received oral sofosbuvir and ribavirin, while 71 patients without prior peg-interferon use received matching placebo, both for 12 weeks. In trial two (“FUSION”), 103 patients who previously did not respond to interferon therapy received sofosbuvir and ribavirin for 12 weeks, and 98 patients who also did not respond to interferon received sofosbuvir and ribavirin for 16 weeks.

5. Methods Interpretation (Validity):
   a. Was there an independent “blind” comparison with a reference standard? Yes. There were two separate trials included in this study. First, the POSITRON trial was a blinded, placebo-controlled study that compared sofosbuvir and ribavirin treatment for 12 weeks with a matching placebo in patients who had previously received and discontinued interferon treatment regimen due to severe
adverse effects, medical contraindications, or those who had decided against it. Second, the FUSION trial was a blinded, active-control study that selected patients who had received prior interferon treatment without a therapeutic response. There was no placebo control group in this trial. One group received sofosbuvir and ribavirin 12 weeks and another group received the same regimen for 16 weeks.

b. Did the sample include an appropriate spectrum of patients to whom the treatment will be applied in clinical practice?
The study enrolled patients from 63 and 67 sites throughout the United States, Canada, and New Zealand during a 3-month enrollment period for POSITRON and FUSION trials, respectively. In terms of generalizability for clinical practice, the study design takes into account the geographical variations, and attempts to minimize the effect by having a multinational, multicenter enrollment process. This can also have an added benefit of creating a potential larger sample population.

c. Did the results of the treatment being evaluated influence the decision to treat with the reference standard?
Although the patients in the study were blinded to the treatments they were receiving, it was unclear whether the physicians were blinded to the study design as well. A lack of double-blinding can introduce observer-expectancy bias, which suggests that physicians are more likely to document a positive outcome if they expect the treatment group to show signs of recovery.

d. Were the methods for performing the treatment described in sufficient detail to permit replication?
The study provides ample information regarding the study design such as sample selection and HCV RNA level measurement and subtyping. Additionally, it provides information about the data analysis information including the statistical tests used for each trial of the study, but failed to mention the statistical analysis software utilized in the study. It also included a disclosure regarding the sponsor who collected the data, monitored the study conduct, and completed the data analysis.
6. **Results:** In the first trial of patients for whom peginterferon was not an option, 12 or 16 weeks of treatment with sofosbuvir with ribavirin was effective with the rate of sustained virologic response of 78% (95% confidence interval (CI) 72-83) compared to 0% with placebo (p<0.001). In the second trial, patients previously treated unsuccessfully with peginterferon responded to sofosbuvir and ribavirin treatment with a rate of 50% in 12 weeks of treatment and 73% in 16 weeks of treatment (p<0.001). In both studies, response rates were lower among patients with genotype 3 than among those with genotype 2. Also, within genotype 3 patients, response rates were lower for patients with cirrhosis. The overall rate of discontinuation of sofosbuvir was low (1-2%) with most common adverse effects of headache, fatigue, nausea, and insomnia.

**Comments on Study Results:** To conclude, in patients with Hepatitis C genotype 2 or 3 unable to be treated with peginterferon, 12 or 16 week treatment with sofosbuvir and ribavirin was effective, especially amongst patients with genotype 2 infection and those without cirrhosis. Additionally, in patients previously treated with peginterferon without a response, 16 weeks of sofosbuvir treatment was significantly more effective than 12 weeks of treatment. However, the results are still unclear as to why there are lower rates of sustained virologic response among patients with HCV genotype 3 compared to those with genotype 2 variant.

7. **Translational applications (How does this study apply to your patients? Be specific regarding a T1-T4 level):**

The study is adequate with statistically significant results and are likely clinically significant. This is a phase 3 trial and therefore, the translational application level is T2 which is translation to patients with practice implications. The study indicates that there is no other effective treatment option that is currently available for HCV genotype 2 or 3 infection that do not have sustained virologic response to the current standard of care which is 24 weeks of peginterferon and ribavirin treatment. The study also indicates no effective alternate treatment for patients that have contraindications to interferon treatment or decided not to use this treatment. The study suggests 12 weeks of sofosbuvir and ribavirin treatment as the optional effective treatment for these patients. The study also recommends extending the duration of treatment to 16 weeks for patients with cirrhosis who were not responsive to prior interferon treatment.
Blinded, randomized studies of two trials were carried out and significant differences in the study groups are reported. The study is reproducible and the data interpretation is appropriate. For the patient conditions described above where sustained virologic response is not achieved with the standard of care treatment, the treatment option from this study is likely to be given clinical consideration. The lack of alternative treatment is indicated in the study and patients can benefit from the recommended effective treatment option from this study. This means that there is a potential for the change in clinical practice for these patients.