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LETTER TO EDITOR

Peginterferon Alpha-2a versus Alpha-2b in Chronic Hepatitis C

Soo Ryang Kim

Department of Gastroenterology, Kobe Asahi Hospital, 3-5-25 Bououji-cho, Nagata-ku, Kobe, Japan

Dear Editor,

A combination of weekly administered subcutaneous injections of long-acting pegylated interferon (PEG-IFN) and oral ribavirin is the current standard treatment for hepatitis C virus (HCV) infection, according to the practice guidelines of the American Association for the Study of Liver Diseases. Currently, two licensed products, PEG-IFN alpha-2a (Pegasys, Hoffmann-La Roche) and PEG-IFN alpha-2b (PegIntron, Schering-Plough Corporation) are used. Lately, there has been considerable controversy over which product is more effective. A recent randomized controlled trial published in the New England Journal of Medicine has concluded that the two products are comparable with regard to benefits and drawbacks [(1)]. Accordingly, clinicians have no clear perception regarding the selection of PEG-IFN (alpha-2a or alpha-2b) for the clinical management of patients with chronic hepatitis C, especially those with high viral loads of genotype 1 that is resistant to treatment.

Findings from a single randomized controlled trial, even a very large one, are rarely definitive, and caution should be exercised in insuring their reproducibility. Systematic reviews and meta-analyses comprising all relevant trials are considered the highest level of evidence that provides valuable information on the quality and reliability of the available data.

Alavian, *et al.* [(2)] have described the advantages and disadvantages of dual therapy with PEG-IFN alpha-2a and with PEG-IFN alpha-2b, based on the results of head-to-head randomized controlled trials with the use of the DerSimonian and Laird method of conducting meta-analysis. In 7 randomized controlled trials, 3518 patients received PEG-IFN alpha-2a + ribavirin (n=1762) or PEG-IFN alpha-2b + ribavirin (n=1756). Early virological response (EVR), early treatment response (ETR), and sustained virological response (SVR) were greater among patients treated with PEG-IFN alpha-2a, with an odds ratio (OR) of 1.38 (95% confidence interval [CI] 1.11-1.71), 1.67 (95% CI 1.24-2.24), and 1.38 (95% CI 1.02-1.88), respectively. In the subset of naïve patients with genotype 1/4 and 2, the OR of SVR was 1.38 (95% CI 1.02-1.88) and 4.06 (95% CI 1.67-9.86), respectively. PEG-IFN alpha-2a demonstrated a significantly higher rate of neutropenia, OR=1.50 (95% CI 1.25-1.79), but the pooled OR for withdrawal rates was not significant [OR=0.78 (95% CI 0.47-1.29)]. The report concluded that PEG-IFN alpha-2a with similar safety is more effective than PEG-IFN alpha-2b. A longer duration of maximum serum concentration (168 *vs.* 48-72 h.) yields a greater SVR and higher neutropenia in PEG-IFN alpha-2a than in PEG-IFN alpha-2b recipients. The report is very informative for clinicians engaged in the management of patients with chronic hepatitis C.

Nonetheless, several problems need to be clarified. First, the randomized controlled trials were carried out in the United States and European countries. Those carried out in Asian countries such as China,

*** Correspondence:**
Soo Ryang Kim, M.D.
Department of Gastroenterology, Kobe Asahi Hospital,
3-5-25 Bououji-cho, Nagata-ku, Kobe, 653-0801, Japan.

Tel/Fax: *+81 78 612 5151*

E-mail: *asahi-hp@arion.ocn.ne.jp*

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Korea and Japan, where a large number of chronic hepatitis C patients are treated with PEG-IFN + ribavirin, also need to be analyzed. In Japan, a head-to-head randomized trial is under way.

Second, analysis of adverse events is wanting, due partly to the paucity of cases and partly to the short observation period. A post hoc optimal information size calculation geared to detecting a minimally important difference of a 10% relative risk reduction (based on the assumption of an average population risk rate of 10%) and using a 5% maximum type I error and 80% power, has suggested that a minimum of 27,000 patients would need to be randomized for a conclusive meta-analysis of adverse events [3]. The current number of patients in the meta-analysis of adverse events is approximately 3,500 (less than 15% of the requisite number). Randomized controlled trials need to publish clinical practices, clinical outcomes such as the risk of liver failure, hepatocellular carcinoma, and mortality in order to foster greater interest in patients and clinicians; moreover, a follow-up of at least 5 years is required.

Third, the nonstandardization of the ribavirin dose given across trials raises some concern. The weight-based dose of ribavirin ranges between 800 and 1,400 mg, whereas the weight cutoff varies among trials as well as within the same trial. For example, in the largest trial [1], 3 patients weighing 40-65 kg received a lower dose of ribavirin (800 mg) in the PEG-IFN alpha-2b group compared with a higher dose (1,000 mg) in the PEG-IFN alpha-2a group; however, the former achieved a higher SVR than the latter (46% *vs.* 43%). Also, patients weighing more than 105 kg received a higher dose of ribavirin in the PEG-IFN alpha-2b group (1,400 mg) than those in the PEG-IFN alpha-2a group (1,200 mg), yet, patients in the former achieved higher SVR than those in the latter (42% *vs.* 39%).

It is too early to conclude that PEG-IFN alpha-2a is superior to alpha-2b in the management of chronic hepatitis C patients. Future trials need to further the correlation between achieving SVR and clinically relevant outcomes such as risk of cirrhosis, hepatocellular carcinoma, and mortality.

References

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Alavian *et al.* reply:

We are thankful to Dr. Kim for his attention and astute comments.

First of all, during a literature review we could not find any randomized trial from Asian countries and we think that as soon as these trials become available, results of this meta-analysis should be updated accordingly.

Secondly, we completely agree with Dr. Kim regarding the very low confidence that we can place in the comparative safety profile of peginterferon alpha-2a and alpha-2b we found in our meta-analysis, but conducting a mega trial with a huge subject population of 27000 people, or even 10 trials with 2700 subjects would not seem to be possible in the near future. As far as cost-benefit is concerned, we would soon discover so much that could change current practice, as a result, we have no option but to judge according to the best current evidence available.

Thirdly, the higher dose of ribavirin in the peginterferon alpha-2b recipient group underscores our finding of a higher SVR in alpha-2a over alpha-2b, and shows that the superiority of peginterferon alpha-2a over alpha-2b is underestimated and is even greater than we have found. For other studies the protocol for dose adjustment of ribavirin was similar in the two arms of treatment, and this is what is needed to obtain pure effect size of peginterferon alpha-2a *vs.* alpha-2b: there has not been exactly the same protocol across all studies, although this would have been ideal.

Fourthly, if these patients are followed up, their data will be available till 2015, so that valid data would then be available regarding the comparative clinical benefit of peginterferon alpha-2a *vs.* alpha-2b, but for current use we can guess that given the higher SVR rate of peginterferon alpha-2a over 2b, long-term liver-related mortality, liver failure, cirrhosis and hepatocellular carcinoma of peginterferon alpha-2a is equal to that of 2b, if not significantly better. It is noteworthy that interferon therapy can reduce the incidence of HCC even in patients who do not clear of HCV viremia [1].

References

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