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Shortened therapy for genotype 1 hepatitis C virus. The final answer?

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Article commented:

Christophe Moreno, Pierre Deltenre, Jean-Michel Pawlotsky, Jean Henrion, Michael Adler,

Philippe Mathurin. Shortened treatment duration in treatment-naive genotype 1 HCV patients with rapid virological response: A meta-analysis. Journal of Hepatology 2010; 52: 25-31.

Original Abstract

Background & Aims. In hepatitis C virus genotype 1 (HCV-1) patients with a rapid viral decline within the first month of therapy, a 24-week course of pegylated interferon (PEG-IFN) alpha and ribavirin treatment has been claimed to be as efficient as the standard 48-week duration. **Methods.** We performed a meta-analysis of 7 randomized controlled trials comparing less than 48 weeks to 48 weeks PEG-IFN alpha/ribavirin treatment in 807 HCV-1 patients with rapid viral decline. **Results.** SVR was significantly less frequent with short treatment duration than with 48 weeks of therapy, with a mean difference of -13.6% (95% CI: -22.8% to -4.4%, p = 0.004). This difference was related to a higher relapse rate (mean difference: 9.9%, 95% CI: 4.1–15.7%, p < 0.001). In a sensitivity analysis restricted to studies using only a weight-based ribavirin regimen, shorter therapy was also less efficient. In the subgroup of patients with undetectable HCV-RNA at week 4 and a low baseline HCV-RNA level (£ 400,000 IU/mL), there was no significant difference in SVR rates between 24 and 48 weeks of treatment (mean difference: -3.10%, 95% CI: -8.6% to 2.4%, NS). **Conclusions.** In HCV-1 patients with a rapid virological response, 24 weeks of combination therapy with PEG-IFN alpha and ribavirin should be considered only in subjects with low baseline viral load. However, the optimal cut-off defining low baseline viral load and the impact of the presence of other factors capable of altering treatment response, remain subject to debate.

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Comment

The article by Moreno, *et al.,* is an important contribution to elucidate the optimal length of therapy for treatment naïve genotype 1 hepatitis C virus infected patients. The question of how safe is shortening HCV therapy and which subgroup of patients may benefit from this modality of treatment is greatly clarified with this meta-analysis. The foremost result shows that patients with rapid virological decline defined as 2-log HCV-RNA drop or undetectable HCV-RNA within the first 4 weeks of therapy who receive 24 weeks of therapy had higher relapse rates than patients who received 48 weeks therapy. In the subgroup analysis, both subgroups – patients with rapid virologic response (RVR) defined as undetectable HCV-RNA at week 4 and patients who receive weight adjusted ribavirin therapy– had lower sustained virologic response (SVR) with shortened treatment. The only subgroup of patients who had similar SVR with 24 weeks of therapy compared with 48, were patients with low baseline viral load (< 400,000 IU/mL) and RVR.

HCV is an important world wide health problem. 130 million of people are infected with HCV[1] and 40% of them are candidate to therapy. Current therapy

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with peginterferon and ribavirin for 48 weeks has a 55-60% of sustained virologic response, while viral genotype determines dramatically effectiveness of therapy (genotype 2 or 3: 70-80% SVR; genotype 1: 30-40% SVR).[2] Unluckily, genotype 1 represents 70% to 80% of chronic HCV infections in the United States, more than 60% in Europe and Asia,[3] and even a greater proportion in Latin America (e.g. 88% in Chile).[4] New specifically targeted antiviral therapies for hepatitis C (STAT-C) are under development to optimize genotype 1 viral treatment response. HCV serine protease inhibitor telaprevir in combination with peginterferon and ribavirin for 24 weeks has shown an SVR as high as 61%.[5] Thus, future therapies will significantly improve chronic HCV genotype 1 response rates by shortening treatment duration or increasing response in difficult to treat patients. On the other hand, adverse effects of antiviral therapy constitutes a major problems with antiviral therapy: 50-60% present adverse effects related to antiviral therapy and 10-14% of patients suspend therapy for serious adverse effects (e.g. rash, pruritus, arthralgia, nausea, diarrhea, thyroid disease, depression or anemia).[2,6] Shortening therapy could minimize these adverse effects, reducing costs of therapy and increasing compliance to HCV therapy.

The meta-analysis presented has a very thorough design with a well structured clinical question, broad research for randomized trials (including Medline, Cancerlit, Embase, manual searches and congress abstracts), appropriate inclusion criteria, two reviewers (although not independent), moderately adequate quality of trials included (even though intention-to-treat analysis was not specified) and inclusion of heterogeneity test. The meta-analysis has adequate internal validity and the results can be properly applied in clinical practice.[7]

Unfortunately the results didn't support shortened therapy for chronic HCV. It is remarkable to consider that the subgroup of patients with low basal viral load and RVR received shortened therapy with similar results to 48 weeks therapy. These results are in accordance with the European Medicines Agency (EMEA) recommendation, though the basal viral load approved by EMEA was < 600.000 IU/mL instead of < 400,000 IU/mL.

It is important to consider other factors when defining length of therapy, particularly liver fibrosis, which has clearly been demonstrated to influence response to therapy.[8] This factor could not be explored on this meta-analysis but its role should be elucidated in the future. Although some concern could arise from the definition of RVR in this meta-analysis (< 50 IU/mL at 4 weeks), the authors argue that it is improbable that the main message of this metanalysis will change using an RVR defined with more sensitive tests (limit of detection 15 IU/mL). The success of re-treatment after relapse in patients who received shortened therapy has not been evaluated, although a low response rate to re-treatment is observed in patients with genotype 1.[2,8]

A better definition of additional factors associated with response, such as the recently described IL28B[9] mutation and newer STAT-C agents will certainly modify the way we tailor the optimal length of treatment. In the meantime, the results of Moreno, *et al.,* strongly support that physicians continue treating genotype 1 HCV infected patients for 48 weeks, with the exception of patients with low baseline viral load and RVR, who may benefit from shortened therapy.

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