

Outcome of combination antiviral therapy in hepatitis C virus infected patients with sickle cell disease

To the Editor

We read with great interest the recent published outstanding article by Ayyub et al¹ on the treatment of chronic hepatitis C virus (HCV) infection with Peginterferon alpha-2a and ribavirin in patients with sickle cell disease (SCD). The authors treated 8 SCD patients with combination therapy for 48 weeks duration. All patients attained early viral response. One patient developed breakthrough, and 2 patients relapsed after cessation of combination therapy and ultimately 5 patients achieved a sustained virological response (SVR). The interesting aspect of this study was no treatment withdrawal and no need for transfusion in these patients. We want to address some points that merit more attention. As the authors have explained, hydroxyurea by increasing hemoglobin F can decrease transfusion need, resultant iron overloading, and chance of anemia in patients with congenital hemoglobinopathies.² However in another comparative study on 6 SCD patients without oral hydroxyurea serum hemoglobin of patients did not also drop during treatment so, attribution of non-transfusion need in these patients to oral hydroxyurea administration is under-question.³ At present, there are evidences that intensive iron chelation and lowering of liver iron content such as administration of oral deferoxamine or phlebotomy can significantly enhance sustained viral response in hyper transfused patients however, the therapeutic role of hydroxyurea as adjuvant to ribavirin and interferon in polytransfused patients is not investigated yet.^{4,5} There are evidences that genotype 4 might be more responsive to combination anti-viral therapy than genotype 1 infection.⁶ Recently, Ferenci et al⁷ has indicated that genotype 4 infected patients who are receiving 24 weeks of PEG-IFN alpha 2a plus ribavirin 1000-1200 mg/day after achieving a rapid virological response (RVR) had SVR rate as high as 86.7%.⁷ Hence, the patients in Ayyub et al's¹ study had HCV RNA level $\leq 2 \times 10^6$ copy/ml and reasonable probability of attaining RVR the investigator could evaluate PCR results after 4 weeks of treatment and then adjust the treatment duration according to PCR results. Recently in a meta-analysis on 429 HCV infected thalassemic patients, we determined that ribavirin did not increase treatment discontinuation or major adverse events whereas increased transfusion needs by 30-50% that would return to pretreatment level during 2 months of post treatment cessation. We also indicated that genotype 1 infected thalassemic individuals significantly

took benefit from ribavirin (OR 0.46, 95% CI 0.22-0.95 for monotherapy and OR 1.7, 95% CI 0.46-6.04 with combination therapy in genotype 1 versus non-genotype 1 patients).⁸ In our center, we have treated 51 thalassemic patients with chronic hepatitis C infection with PEG-IFN for duration of 48 weeks between 2006-2009, 42 subjects completed the treatment schedule. Eighty-eight percent (37/42) attained early and end of treatment response however, 15 subjects relapsed after treatment cessation and finally 22 (52%) reached SVR (these results have not officially published yet). Khuroo et al⁹ in a meta-analysis of randomized clinical trials have determined that patients receiving PEG interferon alpha in combination with high-dose (1000-1200 mg/day) ribavirin have significantly higher rate of SVR than the patients who receiving low-dose (800 mg/day) ribavirin (72% versus 45.8%. There are also evidences that the response rate in similar genotype may be different in different countries.¹⁰ It is believed that discrepancies in viral kinetic decay curve in different races can yield different sustain viral response.¹¹

In conclusion, we can say that ribavirin in patients with hemoglobinopathies is safe and significantly improve treatment outcome by reducing relapses in these kind of patients.

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Reply from the Author

We appreciate the valuable comments of Dr Alavian, and Dr Tabatabaei about our recently published article. Indeed, in our series of sickle cell disease (SCD) patients, hydroxyurea was given along with the combination treatment of HCV. Hydroxyurea is known to increase the production of hemoglobin F and thus, may decrease the tendency towards sickling.^{12,13} In the face of the relative concerns about possible hematological effects of ribavirin, it was considered appropriate to keep the patients on hydroxyurea for the whole study period. Nevertheless, hydroxyurea itself may have its own hematological effects, like leucopenia. Having the patients under regular follow up made it reasonable to continue the drug, knowing that any such side-effects could be spotted early enough. None of our patients discontinued hydroxyurea. Therefore, it is difficult for us to tell what would have been the course of events without hydroxyurea.

We are impressed by the meta-analysis results presented by Dr Alavian and Dr Tabatabaei. The results of this meta-analysis confirm our impression that ribavirin can be safely administered in patients with various hemoglobinopathies. This is particularly true in patients with SCD. In our series, none of the patients required transfusion, discontinuation or alteration of therapy due to any hematological side-effects. With the small number of patients we have studied, it is not possible for us to comment on the difference of response between HCV Genotype 1 and Genotype 4 patients with SCD. The study design in our case series did not include measurement of HCV PCR 4 weeks after initiation of therapy, primarily because the study was started in the year 2003 and at that time the concept of rapid virological response (RVR) had not been evolved. Hence, we are unable to comment on the issue of RVR and any possible adjustment of treatment duration that could have been made accordingly.

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