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Optimizing dosage and duration therapy for chronic hepatitis C «difficult-to-treat patients»

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Article commented:

Fried MW, Jensen DM, Rodríguez-Torres M, Nyberg LM, Di Bisceglie AM, Morgan TR, et al. Improved outcomes in patients with hepatitis C with difficult –to-treat characteristics: randomized study of higher doses of Peginterferon a-2a and ribavirin. *Hepatology* 2008; 48: 1033-43. (Reprinted with permission).

Abstract

Treatment response remains suboptimal for many patients with chronic hepatitis C, particularly those with genotype 1 and high levels of viremia. The efficacy of high-dose regimens of peginterferon α-2a and ribavirin was compared with conventional dose regimens in patients with features predicting poor treatment responses. Eligible treatment-naïve adults with genotype 1 infection, hepatitis C virus (HCV) RNA > 800,000 IU/mL and body weight > 85 kg were randomized to double-blind treatment with peginterferon α-2a at 180 or 270 microg/week plus ribavirin at 1,200 or 1,600 mg/day for 48 weeks (four regimens were evaluated). The primary endpoint was viral kinetics during the first 24 weeks of therapy. Among patients receiving peginterferon α-2a (270 microg/week) the magnitude of HCV RNA reduction was significantly greater than for patients randomized to the conventional dose of peginterferon α-2a (180 microg/week) for the pairwise comparison for ribavirin at 1,600 mg/day (P = 0.036) and numerically greater for the pairwise comparison for ribavirin at 1200 mg/day (P = 0.060). Patients randomized to the highest doses of peginterferon α-2a (270 microg/week) and ribavirin (1,600 mg/day) experienced the numerically highest rates of sustained virologic response (HCV RNA < 50 IU/mL) and the lowest relapse rate (47% and 19%, respectively). The arm with the higher doses of both drugs was less well-tolerated than the other regimens. *Conclusion:* Higher fixed doses of peginterferon alfa-2a (270 microg/week) and ribavirin (1600 mg/day) may increase sustained virologic response rates compared with lower doses of both drugs in patients with a cluster of difficult-to-treat characteristics.

Comment

The main factor that influences the results of current therapy for chronic hepatitis C is viral genotype. Results are good for genotype 2, acceptable for genotype 3 and clearly insufficient for genotypes 1 and 4. Patients infected with genotypes 1 and 4 should receive a 48 week therapy consisting of ribavirin in a weight-adjusted dose combined with weekly pegylated interferon α-2a (Pegasys, 180 μg) or α-2b (Peg-intron, 1.5/μg/kg).[1] The chance of obtaining sustained viral response (SVR) – defined as non detectable HCV-RNA 24 weeks after the end of therapy- does not reach 50% in the majority of the published series, including the first large pivotal trials, and many groups have reported still poorer results in their clinical practice. Current guidelines indicate to stop therapy in those patients not achieving an early viral response (EVR) at week 12, defined as undetectable HCV-RNA or at least $\geq$ 2 $\log_{10}$ drop in viral loal (12-week stopping rule),[2] and in those not achieving non-detectable HCV-RNA after 24 weeks of therapy (24-week stopping rule).[3] In these circumstances, therapy should be interrupted because it has been clearly demonstrated that these patients have very few possibilities of reaching SVR indeed if they obtain a non-detectable viremia afterwards during therapy.

Several baseline factors that influence the probability of obtaining SVR after combined antiviral therapy in genotype 1-infected patients have been identified. It is clearly demonstrated that a high viral load [the best cut-off being, probably, < 400,000 IU/mL[4]] and an advanced fibrosis stage in liver biopsy both reduce significantly the chance of reaching SVR, whereas black race, insulin resistance (and/or overweight) and age over 60 are also associated with a lower rate of SVR,[5-8] although these factors may be at least in part interelated.

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Therefore, it is posible to identify a subgroup of «difficult-to-treat patients» among subjects infected with genotype 1 (and 4). These patients have a high probability of suffering therapeutic failure, mainly in the form of relapse after transient viral response . This is one of the more difficult experiences both for chronic hepatitis C patients and for their doctors. Several strategies have been proposed to improve the results of therapy in these patients. Firstly, as it is obvious, to obtain the best adherence to the current treatment, that is symbolized by the 80-80-80 rule.[9] Two more challeging approaches are to increase the doses of pegylated interferon and/or RVB or to extend the duration of therapy.

Fried et al.[10] have reported the results of a randomized trial comparing four different schemes consisting of standard or high doses of both pegylated interferon α-2a and RBV in naïve patients infected with genotype 1, high viral load (> 800.000 i.u./mL) and overweight. One hundred and seventy seven patients were included and distributed in four groups assigned to high (180 μg/week) or standard (120 μg/week) doses of pegylated interferon α-2a, each with 1,600 or 1,200 mg/day of RBV. The four groups were matched for sex, age, race, viral load, percentage of cirrhotics (< 20%) and steatosis in the liver biopsy but it is not reported if they were matched for earlier fibrosis stages. The highest rate of SVR was obtained in the group with the higher doses of both drugs (46.8%), whereas the group with the two standard doses obtained only a 28.3% of SVR. Results in the other two groups were intermediate (36.2% and 31.9% for high-dose PEG-IFNα-2a and high-dose RBV, respectively). These differences were mainly due to the higher relapse rate in the groups with the standard dose of pegylated interferon, more than to a higher risk of primary failure.

As the authors state, the higher SVR rates in the Peg-IFN α-2a high-dose groups resulted from improved viral kinetics observed during the first 72 hours of therapy. This finding suggests that high-dose interferon induction therapy may obtain similar results, but current data are controversial and this strategy needs to be studied further.[11-13] It is expected that the results of other studies, currently under way, will shed some light on this question.

The second strategy, i.e., to extend duration therapy up to 72 weeks, has demonstrated some efficacy only in the subgroup of patients with partial early viral response (EVR), those with a reduction ≥ 2 $\log_{10}$ at week 12 of therapy but with HCV-RNA still detectable in blood. The probability of reaching SVR by these patients is much lower than that for complete EVR,[14,15] due to a high incidence of relapse after viral response at the end of therapy. Two studies have demonstrated that 72 weeks of combined therapy significantly increase the rate of SVR, from 17% to 29%[14] and from 18% to 38%,[16] respectively. Other authors have experienced the «accordion regime» consisting of a progressive increase of the duration therapy in relation with the time elapsed from the start of therapy until HCV-RNA is non-detectable in blood.[17] However, the indiscriminate use of this strategy does not improve the SVR rate[18] and it increases the costs and the frequency and severity of side effects. Two authorised and recent reviews may help to take the best decission in individual patients,[19,20] but it should be stated that the prolongation of therapy is not contemplated in current guidelines for therapy of chronic hepatitis C.[21,22] On the light of current knowledge, however, it seems that these documents should be actualized in forthcoming consensus conferences.

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