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Peginterferon and ribavirin in HCV: Improvement of sustained viral response

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Peginterferon alfa in combination with ribavirin is and will remain for the next years the current standard for treatment of chronic hepatitis C. The new antivirals currently investigated in phase II of III trials may augment the overall response rates but require peginterferon/ribavirin as backbone. The cure rate of peginterferon/ribavirin treatment can be improved by better education of treating physicians to identify and treat conditions which negatively influence the final outcome of therapy. Specific focus is the prevention and/or early treatment of common side effects of therapy including anaemia, cytopenia and depression. In selected patients increasing the dose of peginterferon and/or ribavirin may augment response rates. Measuring the viral response at various time points during treatment allows individualization of treatment duration. Treatment duration may be shortened in patients with undetectable HCV-RNA after 4 weeks of therapy, on the other hand slow virologic responders may benefit from prolonged treatment.

Key words: Chronic hepatitis C; Treatment; Peginterferon; Ribavirin.

The current treatment of choice for chronic hepatitis C is the combination of pegylated interferon plus ribavirin.[1,2] With this combination, more than 50% of patients achieve a sustained virologic response (SVR),[3–5] although the probability of successful viral eradication in an individual depends on a range of viral and patient-related prognostic factors. The most important prognostic factor in a patient with chronic hepatitis C is the viral genotype. Genotype 1 is the most prevalent among the six hepatitis C virus (HCV) genotypes, and SVR rates are significantly lower in patients infected with genotype 1 than genotype 2 or 3.[3–5] Much progress has been made in optimizing treatment regimens. This involves customizing the initial dose of ribavirin and the planned duration of combination therapy to the infecting genotype, and then modifying the duration of treatment based on the virologic response during the first 4–12 weeks

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of therapy. Development of new therapies targeted against the hepatitis C virus (HCV) is ongoing at a rapid pace but not a single of the new drugs has been licenced yet, most studies are in still phase 1 or 2. Further evaluation of many new compounds was halted because of emerging new safety concerns. The most advanced drug is the protease inhibitor telaprevir, but this drug requires combination with peginterferon and ribavirin.[6] Thus, the current standard of care treatments, peginterferon and ribavirin, will continue to play a critical role in HCV-infected patients, serving as the backbone of future therapies to prevent the emergence of resistance and facilitate the eradication of the infection. Accordingly, strategies to maximize the effectiveness of peginterferon plus ribavirin therapy are currently critically relevant to the treatment of hepatitis C. These strategies include treatment of modifiable pretreatment factors associated with poor response, improvement of adherence to peginterferon and ribavirin, and individualization of treatment according to specific response predictors.

Determinants of viral responsiveness to peginterferon/ribavirin therapy are not fully understood but likely include a multitude of baseline and on-treatment factors that can be categorized as patient factors, virus factors, treatment factors, and clinician factors. Although many patient and disease-specific characteristics, such as age, sex, race, and HCV genotype, cannot be modified, other factors such as obesity, insulin resistance, and cytopenia can be controlled before or on treatment to maximize the effectiveness of peginterferon/ribavirin therapy by improving patient tolerability and/or the management of treatment. Clinicians and patients should develop strategies to address these modifiable factors in a systematic fashion before initiating HCV treatment. Further efforts are needed to educate and train physicians and mid-level providers regarding HCV disease and its management to identify candidates for therapy and to improve their chances of treatment success.

OPTIMIZATION OF RESPONSE PRETREATMENT

Obesity, insulin resistance, and steatosis

In all studies, increased body weight is an important negative predictor of response to interferon-based therapy in chronic hepatitis C.[7] Independent of steatosis,[8,9] obese patients (BMI $>$ 30) have an 80% lower probability of achieving an SVR during HCV therapy when compared with those who are not obese.[10] The biologic basis for impaired interferon responsiveness seems to be most related to obesity. In addition, insulin resistance may be associated with increased viral replication,[11] can enhance development of hepatic steatosis and fibrosis[12] and the occurrence of hepatocellular carcinoma.[13] Thus, one possible explanation for impaired response to interferon-based therapy is that obese patients may have higher rates of advanced liver disease, which is known to respond less well. Interventions that improve and reduce BMI and/or improve insulin resistance may result in better HCV treatment outcomes. Weight loss has been associated with histologic and biochemical improvement in patients with HCV infection and nonalcoholic fatty liver disease.[14] A systematic review of studies examining the effectiveness of lifestyle modification by reduced caloric intake and increased physical activity in HCV-infected patients with NAFLD highlighted the need for a multidisciplinary approach involving individualized counselling and guidance from dietitians, psychologists, and physical therapists.[15] Unfortunately, to date, no randomized, controlled trial has been conducted to test if weight loss before HCV therapy will improve virologic outcomes. At present, the role of pharmacologic