Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C – part review of existing guidance no. 75.

Comments on behalf of the Royal College of Physicians and the British Association for the Study of the Liver

Introduction

Existing NICE guidance (no. 75) recommends peg-IFN and ribavirin treatment for patients aged 18 and older who have moderate/severe hepatitis C (defined by histology). Patients with symptoms of extrahepatic infection that impair quality of life (QOL) may be treated on clinical grounds without histology. Thus asymptomatic patients require liver biopsy to assess eligibility for treatment, and treatment is not made available for patients with histologically mild infection (defined as a fibrosis score < 3/6 and necroinflammatory score < 4/18 using the Ishak system). The purpose of this *part review* is to consider extension of the existing guidance to patients with mild hepatitis C infection. An important implication of the expansion of the existing guidance is that histological severity will no longer determine eligibility for treatment and a liver biopsy will not be required prior to commencing therapy.

Recent published evidence

The study of Zeuzem [1] specifically targeted HCV-infected patients with persistently normal ALT. Consistent with the known association of normal ALT with hsitologically mild disease, 90% of patients had a fibrosis score less than 3/6. Treated patients received 24 or 48 weeks of combination peg-IFN and ribavirin. Compared with patients who were included in earlier published studies of peg-IFN/ribavirin [2-4], patients included in the Zeuzem trial were much more likely to female, and the median weight of the cohort was 10 kg less than those included in those studies. Zeuzem examined the safety and efficacy of treatment for such patients and Kronenberger [5] examined viral kinetics in this cohort. These studies demonstrated comparable efficacy for patients with predominantly mild disease and confirmed the importance of baseline genotype, viral titre and treatment duration as determinants of response to treatment. The predictive capacity of EVR (early virological response) assessment at 12 weeks of treatment was confirmed. Thus, for normal ALT patients with histologically mild disease, virological response to treatment and the ability of treatment to establish a sustained virological response was confirmed. Safety issues were not different from studies involving patients with elevated ALT (predominantly moderate/severe disease). Viewed in the context of previously published studies of peg-IFN/ribavirin, these observations suggest that normal ALT patients with mild histological damage should not be viewed as a distinct subset of HCV patients, but are simply at the less damaged end of the spectrum of HCV-associated disease. The principal determinants of response to treatment are shared by the entire spectrum of patients and are virological i.e. genotype and viral titre.

Wright et al [6] examined the safety and efficacy of conventional (non-peg) IFN and ribavirin for treatment of patients with histologically mild infection (fibrosis score < 3/6 and necroinflammatory score < 4) and normal or elevated ALT. The study included an untreated control group and a QOL assessment. Response rates

appear slightly inferior to those published for the registration studies of conventional IFN/ribavirin, with SVR's for genotypes 1 and non-1 of 18% and 49% respectively. No new safety/tolerability issues were identified. Specific assessment suggested that treatment was associated with some improvement of health related QOL (measured by the SF36 scoring system) in comparison with the untreated comparison cohort, and improvement was irrespective of treatment outcome.

Viewed together, these studies confirm that antiviral treatment with IFN and ribavirin based treatment regimes is safe and effective for patients with mild HCV infection. Thus, asymptomatic patients with mild disease can be cured of HCV infection with acceptable treatment-associated morbidity.

Opinion

The current approach to patients with mild hepatitis C involves deferring therapy in those who have mild disease. This is based on the argument that the demonstration of mild histological damage identifies the patient with slow fibrosis progression and with a predicted long interval to achievement of cirrhosis. Deferral of treatment may permit such patients to benefit from improvements of antiviral therapy (which may be inevitable) before eventually undergoing treatment

There is an emerging consensus that some of these arguments may be unsafe. Triage of patients according to risk is based on a single histological assessment which is prone to sampling error and to observer error. In many patients with chronic HCV infection the progress of liver fibrosis is not predictable, [7] and some patients with mild HCV will later develop accelerated disease. In a few patients the disease progression may be very rapid [8]. Many clinicians report that a proportion of patients with mild hepatitis C do not attend for regular follow up, and therefore disease progression in these patients may go undetected. The current requirement for pre-treatment liver biopsy almost certainly dissuades a substantial proportion of patients from submitting themselves for investigation and treatment. Many of these will have moderate/severe disease. Hence biopsy based treatment algorithms for chronic HCV infection may lead to lost opportunities for effective therapeutic intervention.

In the USA the NIH consensus statement suggests that the decision to treat patients with mild disease should be individualised and based on patient preference and on the patient's willingness (or not) to undergo repeat biopsies to assess disease progression. It acknowledges that many patients are not interested in the wait and see approach. The patient with mild disease can generally be reassured of a favourable short-term and intermediate term prognosis, but long term outcome cannot be predicted with confidence. Successful treatment removes uncertainty and obviates the need for repeated histological assessment.

The decision to treat an infected patient is a complex one, and includes an individualised assessment of prognosis, an assessment of likelihood of response to treatment, as well as the social and domestic context of each patient. Though histological assessment may inform the discussion, a patient's desire to be treated must follow an informed discussion with his/her physician and might be made without recourse to liver biopsy. In our view the decision to perform a liver biopsy should follow an informed patient/doctor discussion about the merits and risks, with a clear

agreement and understanding of how the results of biopsy will influence the management plan for the specific patient.

Conclusion

We believe that emerging clinical evidence supports an expansion of the guidance no.75 to recommend peg-IFN/ribavirin treatment for patients with mild HCV infection. The expansion of the guidance to recommend treatment for patients with any degree of histological severity invites a reappraisal of the need for liver biopsy before treatment. That decision should be made by the patient following an informed discussion with the physician of the pros and cons of liver biopsy, and requires prospective agreement about the role for histology in determining the specific management plan for the patient.

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