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PEGINTERFERON ALFA AND RIBAVIRIN FOR THE TREATMENT OF CHRONIC HEPATITIS C

(PART-REVIEW OF TA75 AND TA106)

This review is to appraise the NICE current guidance on clinical and cost effectiveness of PEG IFN and ribavirin. Since TA075 and TA106 were published there have been changes to the Summary of Product Characteristics for the peginterferons, including extensions to the licences as follows:

Peginterferon alfa-2a

- *– Extension of the therapeutic indication to include treatment in patients who previously did not respond to interferon (pegylated or non-pegylated) in combination therapy with ribavirin. This includes patients that achieved an early virological response but then did not achieve an end of treatment sustained virological response (relapsers) and patients that were treated but did not achieve a virological response (non-responders).*
- *– Option to shorten the treatment duration in patients with genotype 2 or 3 with low viral load at the start of the treatment and a rapid viral response (defined as HCV RNA undetectable by week 4) from 24 weeks to 16 weeks.*
- *– Option to shorten the treatment duration in patients with genotype 1 with a low viral load and rapid viral response (defined as HCV RNA*

Peginterferon alfa-2b

– Extension of the therapeutic indication of peginterferon alfa-2b in combination with ribavirin to include treatment in patients who previously did not respond to interferon (pegylated or non-pegylated) in combination therapy with ribavirin or interferon monotherapy.

– Extension of the therapeutic indication in combination with ribavirin to include treatment in patients co-infected with HIV

Retreatment

A number of factors should be considered with analysing the role of retreatment with PEG IFN and ribavirin for prior non responders. There is a growing unmet medical need for treatment options for previous treatment failures to Interferon (IFN) alpha and ribavirin (RBV) combination therapy; non responders and relapsers make up a substantial proportion of patients seen in specialist clinics in the UK. They however form a heterogeneous group of patients who have received a variety of prior treatment regimens. By definition any patient who completes a course of treatment that did not result in a sustained virological response (SVR) can be described as failing treatment. However, there are different patterns of response in these patients. The prior patterns of response may significantly differentiate patients and their likelihood of achieving an SVR if re-treated with PEG IFN and ribavirin. Definitions of prior non response are increasingly important in the assessment of new antiviral therapies for hepatitis C, but have not been standardised. Broadly speaking these groups can be considered as follows:

Non responder: No significant virological response occurred during treatment and the patient never became HCV RNA negative at any point during treatment. Some investigators have differentiated between null responses showing little decline in HCV RNA (< 1 log

decline) and non responders who show a decline in HCV RNA but did not become HCV RNA negative.
Slow responder: HCV RNA shows a decline, but does not become negative until after 12 weeks of response
Partial responder or "breakthrough". Virological response occurred, (before 24 weeks) but is not maintained at the end of treatment, i.e. the patient "broke through"
Relapser: Virological response occurred; the patient became HCV RNA negative and remained negative through the end of treatment, but relapse occured before 6 months post-treatment.

The patterns of prior response are important as they are likely to determine the likelihood of response to retreatment. These parameters are also clearly sensitive to the sensitivity of testing for HCV RNA.

Prior treatment could involve any of the following hepatitis C antiviral regimens: standard interferon (IFN) monotherapy, standard IFN combination treatment with ribavirin (RBV) pegylated IFN alfa-2a monotherapy, pegylated IFN alfa monotherapy, pegylated IFN alfa combination therapy with RBV. The data for retreatment show variability in regimens used, patients studied, and outcomes observed.

These data will require careful analysis; However among patients with a prior non response to standard IFN with or without RBV, retreatment with pegylated IFN alpha plus RBV for 48 weeks can be expected to result in SVR in approximately 20% of patients. Other data suggest somewhat lower response rates.

Among patients with a prior relapse to standard IFN + RBV, retreatment with pegylated IFN alpha + RBV for 48 weeks resulted in SVR in a higher proportion: approximately 40%.

Several favourable and unfavourable factors for retreatment of hepatitis C exist and are tabulated below (From Darling JM, Fried MW. Optimizing treatment regimens in hepatitis C. Clin Liver Dis. 2006 Nov;10(4):835-50.

Favorable and unfavorable Factors for Re-treatment of Hepatitis C

Factor	Favourable	Unfavourable
Previous treatment regimen	IFN monotherapy	IFN + RBV
Previous response to therapy	Relapse, partial response	Null response
Genotype	2 or 3	1
Serum HCV RNA	Low	High
Race	Caucasian, Hispanic, Asian	African American
Stage of fibrosis	Minimal	Advanced or cirrhosis
Prior treatment adherence	Poor (if reversible factors)	Complete
Patient motivation	High	Low
Darling JM, Fried MW. Optimizing treatment regimens in hepatitis C. Clin Liver Dis. 2006 Nov;10(4):835-50.		

These considerations have hitherto influenced physicians when weighing up retreatment for chronic hepatitis C, where funding for such attempts was available. There are marginal potential benefits to retreatment of patients who were non responders to standard IFN plus RBV using pegylated IFN alpha plus RBV. There is apparently very little likelihood of benefit to retreatment of patients who were non responders or relapsers to a prior course of pegylated IFN + RBV.

A number of retreatment trials include EPIC and HALT C have provided some evidence of the likelihood of retreatment of patients with advanced fibrosis or cirrhosis treated with PEG IFN alpha or beta and RBV. The overall SVR rates are in the region of 20%. Again these data show greater benefit in patients who relapsed after a prior course of IFN and RBV. In these studies week 12 HCV RNA was a good predictor of SVR: in EPIC for example, 56% of those with undetectable HCV RNA at treatment week 12 attained an SVR. Genotype, fibrosis stage and baseline viral load remain significant predictors of SVR. The likelihood of achieving SVR was greatly influenced by the patients' baseline characteristics. Generally, prior relapsers responded better than non responders in these studies. However, genotype, degree of fibrosis, and prior treatment received were also important factors predictive of SVR; G2/3 subjects responded better than G1 subjects regardless of prior response. Undetectable HCV-RNA at treatment week 12 remained the pivotal predictor of SVR: Approximately 50% of subjects with undetectable HCV-RNA at week 12 achieved SVR vs 5% with less than 2 log decline

These factors will need to be weighed by NICE in considering the extension. It is noteworthy that two new protease inhibitors namely telaprevir and boceprevir are in advanced phase 3 trials. These new agents may, on the basis of preliminary data, prove to have greater efficacy in prior non responders than retreatment with PEG IFN and RBV alone. However the efficacy of these protease inhibitors against non – 1 genotypes is either restricted or undetermined.

<u>Shortening of treatment duration: naïve patients</u>

There is considerable appeal in considering shortening of treatment in patients with favourable parameters that allow shorter duration. Shortening of treatment improves tolerability and cost. However, HCV RNA kinetics on therapy is critical to assess the likelihood of achieving a SVR in patients receiving shorter duration of therapy. The standard treatment duration in HCV genotype 1 patients is 48 weeks, and for genotype 2 and 3, 24 weeks. However several studies have suggested that a shorter duration could be as efficient as the standard duration in HCV 1, 2 and 3 patients with a rapid virus response (RVR) ie. those who become HCV RNA negative by sensitive PCR after 4 weeks of treatment. The exact baseline virus load to predict shortened duration remains debated. Recent randomized controlled trials suggest that patients receiving 24 weeks of therapy could have slightly lower SVR rates than those receiving 48 weeks of treatment. These data will require careful analysis.

Again the combination of treatment with telaprevir may lead to shortened treatment for naïve genotype 1 patients. The efficacy of telaprevir against other genotypes of HCV is restricted however.