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9th February 2010

Dear Dr Longson

Re: Hepatitis C - peginterferon alfa and ribavirin – Part review of TA75 and TA106: Assessment report

The Royal College of Physicians is grateful for the opportunity to respond to the above. We would like to make the following comments which have been coordinated by our clinical expert nominee [redacted]

Hepatitis C remains a numerically important disease in the United Kingdom. Only a proportion of patients have responded to treatment with pegylated interferon (PEG-IFN) and ribavirin (RBV). There is a growing unmet medical need for treatment options for previous treatment failures to Interferon (IFN) alpha and ribavirin (RBV) 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: During treatment, the 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 undetectable, and remained negative through the end of treatment, but relapse occurred before 6 months post-treatment.

Rapid Viral Response: (RVR) HCV RNA becomes undectable by 4 weeks of treatment.

Early Viral Response: (EVR) HCV RNA levels decline by 2 logs within by 12 weeks of treatment.

Complete Early Viral Response (cEVR) HCV RNA becomes undetectable after 4 weeks of treatment but before 12 weeks of treatment.

Sustained Virological response: (SVR) HCV RNA is undetectable at the end of 24 or 48 weeks of treatment (in patients treated appropriately depending on genotype) and remains undetectable 24 weeks after completion of treatment.

Thus some patients prove more sensitive to re-treatment. In general response rates for naive patients infected with genotype 2 or 3 are higher than those observed for patients infected with genotype 1 and 4, but several factors determine the response to treatment (see earlier report and below). HIV – HCV coinfected patients may also benefit from treatment with PEG-IFN and RBV.
A number of retreatment trials include EPIC and HALT C have provided some evidence of the likelihood of response to 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 (cEVR) 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.

The current assessment report focuses on three extensions to the licence of PEG-IFN: retreatment, shortened courses and HIV-HCV co-infected patients. In particular the licence extensions permit genotype 1 patients with a low virus load (LVL) variously defined in past clinical trials but (< 600,000 IU/m in the licencel) and a rapid viral response (RVR) (defined as HCV RNA undetectable by week 4) and undetectable HCV RNA at week 24 to receive 24 rather than 48 weeks treatment. Several studies have indicated similar efficacy in those with an RVR for shorter courses of treatment for genotype 2 or 3. The current NICE guidance does not as yet make provision for patients who have not responded to, or failed, a previous course of, PEG-IFN and RBV combination therapy.

The objective of this assessment was to assess the cost effectiveness of abbreviated treatment courses and retreatment of hepatitis B. The reviewer is somewhat constrained by the fact that the current Southampton Health Assessment technology document is not in the public domain, and the results and methodology cannot be described in detail. However it is pertinent to point out that a critique of the sponsors' methodology and results is provided as well as an independent assessment.

Methodology: scope

The relevant comparator for studies evaluating the efficacy of shortened treatment courses is standard treatment duration (e.g. 48 weeks for genotype 1 patients; 24 weeks for genotype 2 or 3 patients). For patients with genotype 2 or 3 with LVL at the start of treatment and an RVR - shortened courses of 16 weeks are assessed. For patients with genotype 1 with LVL and an RVR (defined as HCV RNA undetectable by week 4 and at week 24) - shortened course of 24 weeks are assessed. For patients with genotype 4 with an RVR (defined as HCV RNA undetectable by week 4 and at week 24) - shortened course of 24 weeks are assessed.

For patients who have been previously treated with combination therapy, and for HCV/HIV co-infected patients, the comparator is best supportive care (BST): in effect monitoring and treatment without any form of interferon therapy

Assessment of clinical effectiveness is made for abbreviated courses of treatment. These data can be summarised within the constraints of the report, and are well covered in the report.

In patients with LVL (≤800,000 IU/ml) who attained an RVR, SVR rates were comparable between groups who received the standard duration of treatment and those who received shortened courses, for both genotype 1 and genotype 2 or 3. These data infer that this patient group can receive shortened courses of peginterferon combination therapy without compromising SVR rates.

A detailed clinical effectiveness analysis is not provided for re-treatment, or for 48 vs 72 weeks of retreatment, and induction doses unfortunately.

An economic analysis has been undertaken in patients eligible for a shortened course of treatment compared with standard length of treatment; and for patients eligible for re-treatment following previous non-response or relapse to treatment, compared with best standard of care (BSC). An economic analysis has been undertaken in patients who are co-infected with HIV, compared to BSC

Sponsor review

ICER data are presented for abbreviated treatment. The Roche submission included assessment of abbreviated treatment in patients with LVL; retreatment for non responders; and HIV –HCV co-infected patients. The ICERs are reported. It appears that amongst the non responder groups retreatment with PEG-IFN and RBV is dominant for relapsers. The value of shortened treatment of genotype 2 and 3 is more favourable than shortened treatment for genotype 1 and 4.

PEG IFN and RBV treatment for HIV co-infected patients is dominant.

Several rules including a dual positive rule may have been breached when considering net benefit so that this is greatest for genotype 2 and 3. Concerns are expressed in the report regarding the age of patients and age of disease specific utilities on cost effectiveness.

The Schering plough dossier is similarly reviewed for retreatment and coinfected patients.

Independent review

The independent review suggests that shorted treatment results in higher ICERS for genotype 1 given the differences in SVR; PEG-IFN RBV shorter treatment dominated standard duration of treatment for genotype 2 or 3 patients for patients achieving an RVR. PEG IFN and RBV dominated for shortened treatment in genotype 1 patients with LVL at baseline and achieving an RVR.

There are some differences between the sponsors' analysis and the independent scrutiny. This reviewer however would accept the conclusion that that shortened treatment duration may be a highly cost-effective option, in a situation there is no difference (or a very small difference) in SVR between shortened and standard treatment duration.

For re-treatment, Genotype 2 and 3 retreatment dominated BSC. Less value can be placed on the retreatment costs of genotype 1 and 4.

Conclusions

Whatever scenario is applied the re-treatment of relapsers with PEG-IFN and RBV dominates. The adoption of early stopping rules (in these analysis no EVR at 12 weeks) improves the value costs of re-treatment. These in fact could be made more stringent if a rule necessitating a negative or undetectable HCV RNA at 12 weeks (complete EVR (cEVR) is applied.

The distribution of patients with regard to disease status and age is important. It is important to note that patients requiring re-treatment for a prior failed treatment are older and may have more advanced disease. Treatment of coinfected patients is possible; more favourable results and less costs are associated with the treatment of genotype 2 and 3 than genotype 1.

Generally, prior relapsers respond better than non responders in these studies. However, genotype, degree of fibrosis, and prior treatment received were also important factors predictive of SVR; genotype 2 or 3 subjects respond better than genotype 1 subjects regardless of prior response.

A single nucleotide polymorphism at the IL28b locus has recently been shown to be associated with response to therapy in naive genotype 1 patients. The role of this polymorphism and its positive and negative predictive value in both naive and retreated patients, and indeed in patients treated with shorter duration of therapy is currently being actively explored. If the current data are confirmed it is likely that this polymorphism will prove to be an important clinical utility in determining the duration of treatment with PEG RBV in patients with genotype 1 infection, and in patients for whom retreatment is

contemplated. However its role in determining response in naive and exposed non-1 genotypes is unknown.

It is noteworthy that two new protease inhibitors namely telaprevir and perhaps boceprevir are in advanced phase 3 trials in naive and non responsive patients. Preliminary data suggests greater efficacy of telaprevir in prior non responders. These new agents may 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. They are not been developed further for genotype 3.

These factors as well as the economic arguments should influence the judgement required on value cost of retreatment.

Yours sincerely

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Registrar