

## British Society for Gastroenterology

### Guidance on the Treatment of Hepatitis C incorporating the Use of Pegylated Interferons

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Clinical guidelines issued by the BSG in July 2001 (1) on the management of Hepatitis C recommended the use of Interferon alpha and Ribavirin in patients with moderate or severe chronic hepatitis C as determined by liver biopsy. This is consistent with NICE HTA Guidance No 14 published in October 2000. The recent licensing of two formulations of pegylated interferon with proven superior efficacy in treating chronic hepatitis C has necessitated review of these guidelines.

The current guidance does not address the issue of who should be treated, but issues recommendations on how to use pegylated interferons in patients eligible for treatment according to previously published guidelines. However it should be recognised that these guidelines apply to adults only and not to paediatric patients.

#### Recommendations:

- Pegylated interferon in combination with ribavirin should be the treatment of first choice for patients with chronic hepatitis C who fulfil treatment criteria as defined by both NICE in HTA Guidance No 14 and previous BSG guidelines. (New NICE Guidance is due to be published in October 2003).  
(Recommendation grade A, evidence level 1a)
- Present data suggests equivalence of both currently available pegylated interferons in terms of sustained viral response.  
(Recommendation grade A, evidence level 1a)
- For genotypes 2 and 3 infection, 24 weeks treatment with pegylated interferon and ribavirin is recommended.  
(Recommendation grade A, evidence level 1b)
- For genotype 1 infection, 48 weeks treatment with pegylated interferon and ribavirin is recommended. Treatment should be stopped after 24 weeks treatment if HCV RNA remains detectable as a sustained virological response will not be achieved by continuing.  
(Recommendation grade A, evidence level 1a)
- Early prediction of lack of sustained viral response can be obtained in genotype 1 infection if HCV RNA remains detectable with a less than 2 log fall in viral load after 12 weeks of treatment. HCV RNA quantitation must be determined by an accurate and reproducible methodology.  
(Recommendation grade A, evidence level 1a)

**Background:** Pegylated interferon alpha 2b (P2b) (Viraferon-PEG) and Pegylated interferon alpha 2a (P2a) (Pegasys) have recently been licensed for use in the treatment of Chronic Hepatitis C (CHC). When used in combination with Ribavirin (R) both drugs have been shown in randomised controlled trials (RCTs) to offer

improved clinical effectiveness compared to standard interferon alpha and ribavirin (2,3). Clinical effectiveness has been assessed in terms of sustained virological response (SVR) defined as undetectable viraemia 24 weeks after the end of therapy. In addition pegylated interferons are more acceptable to patients than standard interferon because they can be administered once per week rather than three times per week. In RCTs patients receiving pegylated interferon and ribavirin reported a better quality of life than those receiving standard interferon and ribavirin. Analyses have shown that viral response rates measured as changes in viraemia after 12 weeks of therapy compared to baseline are highly predictive of failure to achieve a SVR. Pegylated interferons are more expensive than standard interferons.

**Methodology:** A review of the literature was performed. The recommendations represent the conclusions of the authors and are ratified by the Liver Section of the BSG. The results of randomised clinical trials of treatment of CHC incorporating pegylated interferons were examined. Published literature, conference abstracts and pre-publication data were considered along with recent consensus statements issued by the National Institutes of Health (USA) (4) and Association Française pour l'Etude du Foie (5).

The following data were sought and analysed:

- Overall efficacy
- Efficacy in subgroups of patients
- Adverse events
- Acceptability including ease of use and quality of life
- Pharmaco-economic data

### **Results:**

One trial comparing P2b+R with I+R (2), two trials comparing P2a+R and I+R (3,6) and one comparing P2a monotherapy with I monotherapy in cirrhosis (7) were analysed.

**Overall Efficacy:** All studies were powered to determine significant differences between treatment groups. SVR with P2b+R and P2a+R are comparable (54% and 56%). These SVR represent significant improvements over SVR to I+R (47% and 45%) and come from the two large phase III studies (2,3). There have been no RCT in which the effectiveness of P2b and P2a, either as monotherapy or in combination with ribavirin, has been compared directly and the responses seen in the trials are unlikely to represent a significant difference (recommendation grade A).

**Ribavirin dosing:** Further analysis of the trial using P2b + ribavirin at a daily dose of 800mg daily (2), suggests that ribavirin dose should be tailored according to weight (recommendation grade B), with patients receiving ribavirin >10.6mg /kg/day achieving an overall SVR of 61%. This equates to daily doses of over 800mg for those weighing 65kg or more. In a second study of P2a+R (6), patients were randomised to receive either 800mg or 1-1.2g ribavirin daily for 24-48 weeks. The benefits of higher dose ribavirin in this study were observed only in patients infected with genotype1 HCV (recommendation grade A).

### **Efficacy in Subgroups:**

*Genotype 1:* In patients with genotype 1(G1) both P2a+R and P2b+R are more effective than IR (SVR 46%:36% and 42%:33% respectively). Patients receiving P2b and ribavirin >10.6mg/kg/day had a SVR of 48%. In a further study looking at the effect of dose and duration, 48 weeks treatment with P2a and ribavirin 1-1.2g/day proved most effective (6). P2a + R 1-1.2g/day resulted in an SVR of 51% which was

significantly better than results achieved with lower doses of ribavirin and / or shorter duration of treatment (recommendation grade A).

*Genotype 2/3:* In patients with genotype 2 or 3 (G2/3) P2a+R was more effective than I+R (76%:61%) but P2b+R was equivalent to I+R (82%:79%). In a RCT investigating P2a+R, treatment of patients with non-genotype 1 infection (predominantly G2/3) for 24 weeks with reduced dose R (800mg/day) was as effective as treatment for 48 weeks with full dose R (1-1.2g/day) (6) (recommendation grade A).

*Cirrhosis:* Low rates of SVR have previously discouraged the use of anti-viral treatment in patients with cirrhosis. Recent results now show pegylated interferon to be effective in individuals with advanced fibrosis (recommendation grade A). In patients with established Childs A grade cirrhosis pegylated interferon monotherapy with P2a has been shown to be more effective than I monotherapy (30%:8%) (7). In patients with bridging fibrosis or cirrhosis P2a+R and P2b+R were more effective than I+R (43%:33% (3) and 44%:41% (2) respectively). In a further trial of P2a+R a SVR of 50% was achieved in cirrhotic patients with 48 weeks treatment using ribavirin at a dose of 1-1.2g (6).

There is little data on the safety of treating patients with either varices or advanced cirrhosis (Childs grade B or C severity) with some reports of significant toxicity, and for now these patients should only be treated as part of a clinical trial (recommendation grade C).

**Adverse events:** The discontinuation rates for adverse events were similar for the pegylated interferon/ribavirin and standard interferon/ribavirin combinations. Dose adjustments for toxicity are very frequently needed reinforcing the need for close clinical monitoring of patients undergoing treatment. Quality of life: Patients using pegylated interferons report less impairment of quality of life during therapy than patients using standard interferons. This may in part relate to the lower frequency of injections with the long acting therapies.

**International Guidelines:** The NIH Management of Hepatitis C Consensus Statement (4) recognises that pegylated interferons are more effective than standard interferons. The Association Française pour l'Etude du Foie Consensus Conference recommended the use of pegylated interferons in the treatment of CHC (5).

**Pharmaco economics:** At the time of writing there are no published data on the cost-effectiveness of regimens that include the use of pegylated interferons. However data presented in abstract form suggest that pegylated interferon/ribavirin regimens will be cost effective. Cost effectiveness will be improved further when therapy is stopped for patients in whom there is reliable evidence of a failure of response at 12 weeks.

**Doses and Duration of therapy:** A consensus view accommodating presented data, the International guidelines and pharmaceutical data sheets is:

**Dosing:**

**P2a+R.** The dose of P2a is 180mcg in all patients. In genotype 2/3 patients RCT evidence supports the use of P2a at 180mcg and Ribavirin at a dose of 800mg per day in patients irrespective of weight. In G1 patients P2a + R 1-1.2g should be used (recommendation grade A).

**P2b+R.** The dose of P2b is weight based at 1.5mcg/kg and patients should receive >10.6mg/kg of Ribavirin. This equates to 800mg / day for patients weighing <65kg; 1g / day for those 65-85kg; 1.2g / day for those >85kg (recommendation grade B).

**Duration:**

**Genotype 2/3:** RCT evidence supports the use of 24 weeks of therapy with P2a at 180mcg and Ribavirin at a dose of 800mg per day (recommendation grade A). It is likely that the shorter duration of therapy in genotype 2/3 cases can be extrapolated to P2b from P2a, but current manufacturer's recommendations would advocate weight based dosing of Ribavirin with P2b (recommendation grade B).

**Genotype 1:** 48 weeks treatment with full dose ribavirin is needed for genotype 1 infection (recommendation grade A).

**Genotypes 4/5:** Whilst RCT data divided cases into genotype 1 and non-1, nearly all non-1 cases were genotype 2 or 3 and data on genotypes other than 1, 2 or 3 is limited. For now they should be treated as for genotype 1 infection for 48 weeks (recommendation grade C).

***Early prediction of response:***

Pooled data from 2 large clinical studies of P2a and P2b show that accurate prediction of lack of SVR is possible after 12 weeks of treatment (recommendation grade A). Just 1.6% of patients who remained PCR positive after 12 weeks with a less than 2 log drop in viral load achieved a SVR despite going on to receive 48 weeks of treatment (8). Using these criteria, up to 20% of genotype 1 infected cases could have treatment stopped at 12 weeks. In contrast failure to reach these criteria will result in stopping treatment in as few as 3% of genotype 2/3 patients. For genotype 1, but not genotype 2/3, the cost savings of stopping treatment early clearly outweigh the cost of additional virological testing (8). It is important to recognise that errors do occur in HCV RNA quantitation even when measured with a reliable test in a quality assured laboratory. Furthermore, for patients with extensive fibrosis or cirrhosis there may be additional benefit in terms of reduced histological activity or cancer risk by continuing with treatment even if a SVR is not achievable (recommendation grade C). In these cases qualitative HCV RNA testing at 24 weeks may be more appropriate.

### **Acute Hepatitis C virus infection**

Recently published data support the use of early anti-viral therapy for acute HCV infection with very high sustained viral clearance rates (9). The regimen studied used high doses (5MU) of interferon monotherapy daily for 4 weeks and then three times weekly for another 20 weeks. The average delay from infection to starting treatment (when known) was 89 days.

There is currently no data on the efficacy of pegylated interferon used alone or in combination with ribavirin in the treatment of acute HCV infection. It is likely, although not proven, that the most effective treatment for chronic HCV infection will also be effective in treating acute HCV.

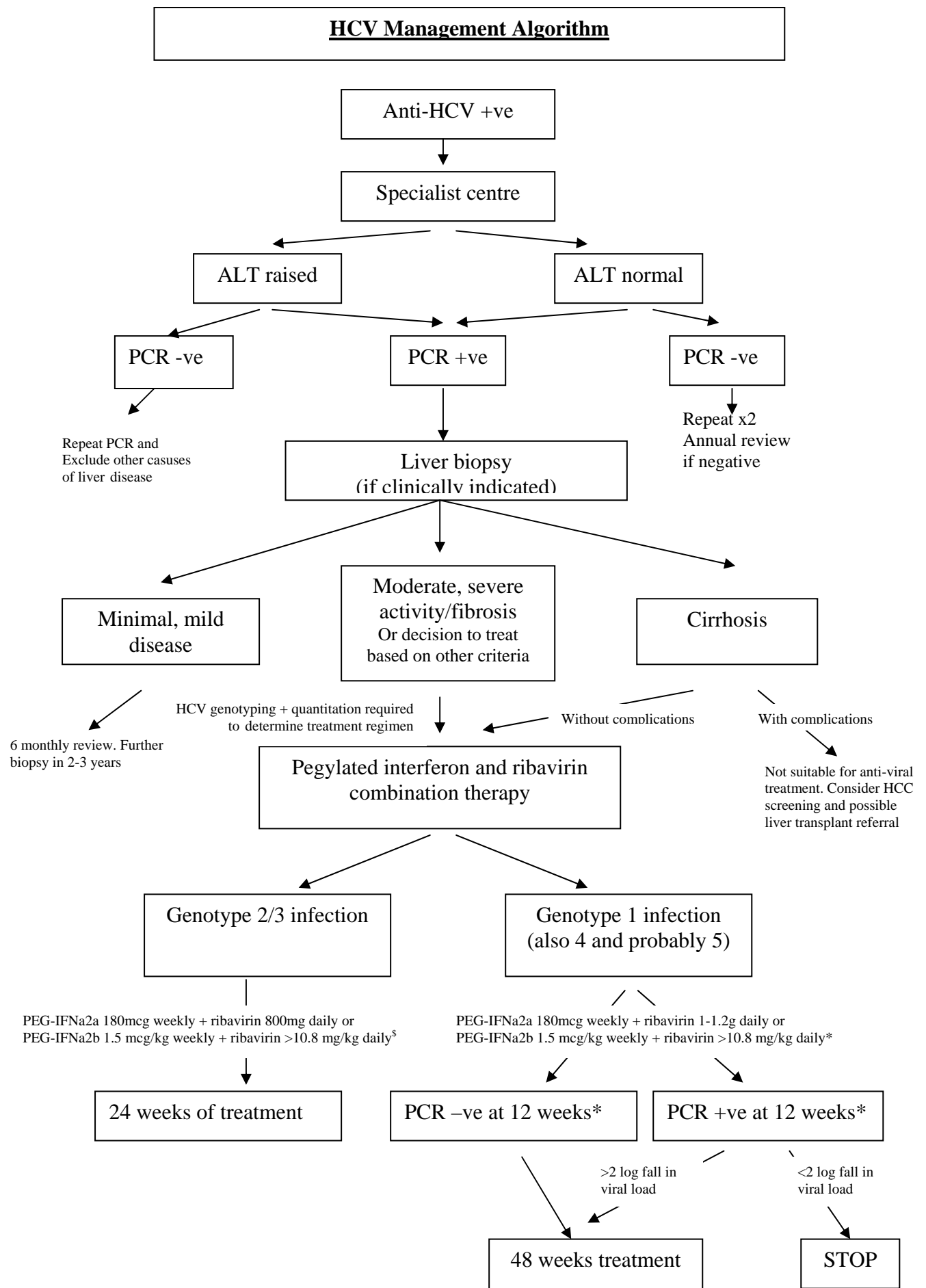
#### ***Recommendations for acute HCV:***

- Early anti-viral therapy is indicated in cases identified with acute infection.  
(recommendation grade B, evidence level 2b)
- The choice of anti-viral treatment regimen is between high dose daily standard interferon and pegylated interferon in combination with ribavirin at standard dosing.

(Recommendation level D)

#### ***References:***

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3. Fried MW, Schiffman ML, Reddy R et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. NEJM 2002;347:975-982.
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5. Treatment of hepatitis C. Consensus Conference, Association Francaise pour l'Etude du Foie. Meeting held in Paris 27<sup>th</sup>-28<sup>th</sup> Feb 2002.
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7. Heathcote EJ, Shiffman ML, Cooksley WG et al. Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. NEJM 2000;343:1673-1680.
8. Davis GL. Monitoring of Viral Levels During Therapy of Hepatitis C. Hepatology 2002;36 (5), Suppl. 1:S145-S151.
9. Jaekel E, Cornberg M, Wedemeyer H et al. Treatment of acute hepatitis C with interferon alfa-2b. NEJM 2001;345:1452-1457.



- \* if viral quantitation not available / appropriate, stopping treatment is determined by positive qualitative PCR at 24 weeks
- <sup>§</sup>Based on extrapolation of evidence from P2a+R