

London New Drugs Group APC/DTC Guidance Document

August 2002

Pegylated Interferons for Hepatitis C (peginterferon alfa-2a, peginterferon alfa-2b)

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Summary

- This document is an update of the document produced in March 2001 in order to take into account the launch of ViraferonPeg[®] in 2001 and the recent launch of Pegasys[®] - two pegylated forms of interferon alfa for the treatment of chronic hepatitis C. This supersedes the previous document.
- Pegylated recombinant interferon alfa-2a (Pegasys[®]) and pegylated recombinant interferon alfa-2b (ViraferonPeg[®]) are licensed for the treatment of chronic hepatitis C in adults in combination with or without ribavirin. Pegasys[®] can be used in patients with compensated liver disease.
- The National Institute of Clinical Excellence (NICE) has recommended that the treatment of choice for chronic hepatitis C at present is a combination of standard interferon alfa and ribavirin. This appraisal will be reviewed in October 2003. Pegylated interferons are not covered by the NICE guidance.
- The evidence for the use of Pegasys[®] with ribavirin is available in abstract form only and it is not possible to fully assess the data. The trials are due to be published later this year.
- Pegylated recombinant interferons (peginterferons) are significantly more effective than standard interferon monotherapy. Peginterferon alfa-2a and 2b are indicated for use in both treatment-naïve patients and those who have relapsed after treatment with standard interferon alfa monotherapy.
- It has been suggested that if no response is seen after 3 months of monotherapy, that no response will be seen if therapy is continued.
- Pegylated interferons are licensed for use as either monotherapy or in combination with ribavirin. Monotherapy is indicated if the patient is intolerant of ribavirin or if the use of ribavirin is contraindicated.
- The initial results of the trials with pegylated interferons and ribavirin look promising but the data are not yet fully published.
- Pegylated interferons should only be initiated by a specialist experienced in the management of chronic hepatitis C. They may not be suitable for initiation in primary care.
- Pegylated interferons can be administered once weekly instead of three times a week, as is the case with standard interferon alfa. This may have service implications for patients who are not able to self-administer.
- PegIntron[®] is another pegylated interferon alfa-2b which is being actively marketed for oncology patients with chronic myelogenous leukaemia (CML) and malignant melanomas.

Recommendations

- The use of peginterferons is outside of NICE guidance, which will not be updated until October 2003, according to the current timetable.
- The evidence from the RCTs show that treatment with pegylated interferon monotherapy is more effective than treatment with standard interferon monotherapy.
- The initial results from the combination therapy trials indicate that treatment with pegylated interferons and ribavirin is superior to treatment with standard interferons and ribavirin. The information though is in abstract form and it is difficult to make a definite decision until the data are fully published, which should be by the end of 2002. However, based on these initial data, expert consensus opinion (US National Institute of Health as well as London hepatologists) favours the use of pegylated interferons with ribavirin for 48 weeks for patients with Hepatitis C genotype 1 and 24 weeks for those with genotypes 2 and 3.

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Background

Hepatitis C is a blood borne viral illness with significant morbidity and mortality. Estimated prevalence in England and Wales varies from 200,000 to 400,000¹. In industrial countries Hepatitis C virus (HCV) accounts for 20% of cases of acute hepatitis, 70% of cases of chronic hepatitis, 40% of cases of end-stage cirrhosis, 60% of cases of hepatocellular carcinoma and 30% of liver transplants². There are six genetic types of hepatitis C – the most common is genotype 1 (40%) with the remainder being mainly genotypes 2 and 3¹. Genotypes 4, 5 and 6 are relatively rare in Britain and are found predominantly in the Middle East and Egypt, South Africa and Hong Kong respectively. It is estimated that approximately 75% of patients with hepatitis C in London have genotype 1. The incidence of new infections is now declining due to screening of blood products and the use of universal precautions in medical settings. Intravenous drug misuse is the main mode of transmission as the commonest way of transmitting the virus is by sharing blood-contaminated injecting equipment. Needle and syringe exchange schemes and risk-modifying programmes effective for preventing HIV transmission may be useful in reducing hepatitis C transmission. Deaths from the complications of hepatitis C infection are likely to increase over the next two decades due to the very long latent period of infection/disease³.

The clinical course is variable. About 15% of HCV infected individuals recover spontaneously and a further 25% have a benign outcome². Sixty percent will have biochemical evidence of chronic hepatitis but the majority have only mild to moderate necro-inflammatory lesions and minimal fibrosis². About 20-30% of subjects with chronic hepatitis C develop liver cirrhosis within 20 years and may die from liver-related causes¹. The incidence of hepatocellular carcinoma is 1-4% per year in patients with cirrhosis but it is rare in subjects with chronic hepatitis C who do not have cirrhosis^{2,3}.

Defining Response to Treatment in Hepatitis C

Patients with hepatitis C often have no symptoms but might have non-specific complaints such as fatigue, loss of appetite, right upper quadrant pain and nausea. The average time of disease progression from infection is 30 years and symptoms of chronic liver disease may only occur later in the disease. The presence of symptoms is a poor marker of the severity of the disease.

Response to treatment can be assessed by measuring serum alanine transaminase (ALT) levels, by the presence of serum HCV-RNA and by liver biopsy. Biochemical response is normalisation of serum ALT concentrations (though about 50% of patients may have normal ALT levels). Virologic response is undetectable HCV-RNA. Biochemical and virologic responses may not be concordant. Sustained virologic response is believed to be the most important indicator of sustained efficacy in the treatment of hepatitis C and is associated with the greatest long term benefits⁴. Some patients respond initially but relapse either during therapy or within 6 months of treatment cessation. An end of treatment response (ETR) is determined at the end of a treatment course and a sustained response (SR) six months later⁵. Some patients without virologic responses may show improved histology on liver biopsy^{6,7}. This suggests that some patients benefit from standard interferon therapy even in the absence of virologic response. It has been suggested that such patients may benefit from maintenance therapy⁶ although there is at present insufficient evidence to recommend this.

There has been a recent report that treatment with standard interferon prevents worsening of compensated cirrhosis and inhibits development of hepatocellular carcinoma even in subjects who do not clear the virus⁸.

Current Treatments for Chronic Hepatitis C

In October 2000 the National Institute for Clinical Excellence endorsed standard interferon alfa plus ribavirin as the treatment of choice for chronic hepatitis C for defined patient groups. Standard interferon alfa plus ribavirin gives rates of sustained virologic response (SVR) of 41% after 48 weeks treatment¹.

Standard interferon alfa monotherapy is recommended where ribavirin is contraindicated or not tolerated¹ but SVR rates are lower than with combination therapy (16% SVR after 48 weeks therapy)^{1,9}.

Ribavirin is contraindicated in pregnancy (due to teratogenic effects); in breast feeding; in those with a history of severe pre-existing cardiac disease in the previous 6 months (due to the risk of haemolytic anaemia); in haemoglobinopathies including thalassaemia and sickle-cell anaemia; in those with chronic renal failure or creatinine clearance <50ml/min; in those with a history of severe psychiatric conditions; in severe hepatic dysfunction or decompensated cirrhosis of the liver; in those with autoimmune hepatitis or a history of autoimmune disease and in pre-existing thyroid disease unless controlled with conventional treatment¹⁰.

The exact mechanism of action of standard interferon is unknown, though it may alter host cell metabolism and inhibit viral replication. Ribavirin is a nucleoside analogue with a broad spectrum of antiviral activity against RNA viruses.

Recombinant interferons are licensed for other indications as well as for chronic hepatitis C.

- Roferon A[®] (Interferon alfa-2a):
Chronic hepatitis B and C; many oncology indications including hairy cell leukaemia; AIDS subjects with progressive, asymptomatic Kaposi's sarcoma; follicular non-Hodgkin's lymphoma and advanced renal cell carcinoma
- Pegasys[®] (Pegylated interferon alfa-2a):
Chronic hepatitis C
- Viraferon[®] (Interferon alfa-2b):
Chronic hepatitis B and C
- ViraferonPeg[®] (Pegylated Interferon alfa-2b):
Chronic hepatitis C

PegIntron[®] (standard interferon alfa-2b) is to be marketed for the treatment of CML and malignant melanomas. It is also being trialed for the treatment of leukaemia and solid tumours. This review does not deal with the use of PegIntron[®].

Pegylation is an attempt to increase the duration of action of standard interferons by increasing their absorption and half life. Peginterferons can be used as monotherapy or with ribavirin for the treatment of hepatitis C. Not all of the trials have been fully published but the evidence for the combination therapy is encouraging.

Pegylated Interferons

In pegylated interferon, the interferon moiety is conjugated with polyethylene glycol. Pegylation reduces the clearance of interferons thereby increasing exposure and enhancing efficacy. A practical advantage of pegylation is that it allows once weekly sub-cutaneous injections. In hepatitis C, standard interferon is given three times weekly.

The hepatitis C virus has a high rate of mutation, which may lead to the development of resistance. With pegylated interferons, therapeutic levels are maintained for much longer which may exert a greater pressure on viral replication (analogous to maintaining antibiotic levels over the minimum inhibitory concentration, MIC). This

should decrease the chance of mutation leading to resistance taking place and may account for the greater incidence of virus clearance in patients on pegylated interferons compared with non-pegylated interferons¹¹.

• Peginterferon alfa-2a (Pegasys[®])

Peginterferon alfa-2a consists of recombinant interferon alfa-2a conjugated with a 40 kDalton branched molecule of polyethylene glycol. Following a single subcutaneous injection of 180 micrograms of peginterferon alfa-2a in healthy subjects, serum concentrations of peginterferon alfa-2a are measurable within 3 to 6 hours¹². Within 24 hours, about 80% of the peak serum concentration is reached¹². Peak serum concentration is reached 72 to 96 hours after dosing and the terminal half life ranges from 50 to 130 hours¹². The absolute bioavailability of peginterferon alfa-2a is 84% and is similar to that seen with standard interferon alfa-2a¹². The half-life of peginterferon alfa-2a in patients with liver cirrhosis is about 70 to 90 hours, which is compatible with once weekly dosing¹³. Pegasys[®] is indicated for the treatment of histologically proven chronic hepatitis C in adult patients with elevated transaminases and who are positive for serum HCV-RNA, including patients with compensated cirrhosis.

• Peginterferon alfa-2b (ViraferonPeg[®])

Peginterferon alfa-2b consists of recombinant interferon alfa-2b conjugated with a 12 kDalton molecule of polyethylene glycol. Maximum concentrations are attained within 15 to 44 hours of subcutaneous administration with sustained maximal serum concentrations for 48 to 72 hours after administration and some accumulation over time. Rates of clearance from the body are about one tenth that for non-pegylated interferon alfa-2b with an elimination half life for peginterferon alfa 2b of about 40 hours¹⁴. ViraferonPeg[®] is indicated for the treatment of adult patients with histologically proven chronic hepatitis C who have elevated transaminases without liver decompensation and who are positive for serum HCV-RNA or anti-HCV.

Efficacy of Pegylated Interferon as monotherapy in Chronic Hepatitis C (also see appendices I & II)

- **Peginterferon alfa-2a (Pegasys®)**

Two fully published efficacy studies and one dose ranging study have been identified. The dose ranging study established 180 micrograms (mcg) weekly as the optimum dose based on SVR and side effect profile¹⁵.

One large open-label, parallel-dose, randomised efficacy trial involved 531 subjects with chronic hepatitis C¹¹. Subjects were randomly assigned to receive either 180mcg peginterferon alfa-2a or standard interferon alfa-2a for 48 weeks. The standard interferon alfa-2a dose was 6 mega units (MU) three times a week for 12 weeks then was reduced to 3MU three times a week for 36 weeks. After 48 weeks of treatment an SVR of 39% was seen with weekly peginterferon alfa-2a compared to 19% with standard interferon alfa-2a. This is clinically and statistically significant.

The second study was an open-label, randomised, parallel-dose study which enrolled 217 subjects with compensated cirrhosis⁷. Subjects were randomly assigned to either 90mcg or 180mcg peginterferon alfa-2a weekly or 3MU standard interferon alfa-2a three times a week for 48 weeks. After 48 weeks of treatment an SVR of 30% was seen with the higher dose of peginterferon alfa-2a compared to 7% with standard interferon alfa-2a. This difference was statistically significant. Subjects with cirrhosis are difficult to treat as there is a risk that neutropenia and thrombocytopenia may be exacerbated by standard interferon and/or ribavirin. Cirrhosis is also a marker for poor treatment response³. Subjects with decompensated cirrhosis and other complications were excluded. These increases in SVR are both clinically and statistically significant.

- **Peginterferon alfa-2b (ViraferonPeg®)**

One double-blind, randomised study of peginterferon alfa-2b in chronic hepatitis C has been identified⁴. Subjects were randomly assigned to receive either 0.5, 1.0 or 1.5mcg/kg per week of peginterferon alfa-2b or 3 MU of standard interferon alfa-2b three times a week for 48 weeks. The peginterferon doses were based on two previous dose ranging studies. Increasing the dose of peginterferon increased the SVR (33%, 41% and 49% respectively at week 48). These results were significantly

higher than the SVR rate seen with standard interferon treatment (24%). Sub-group analysis showed that subjects with genotypes 2 and 3 achieved the highest response rates in all treatment groups: 68% of those treated with 1.5mcg/kg peginterferon achieved SVR compared to 36% in the standard interferon group and 34% with genotype 1. This study showed that peginterferon alfa-2b, at all doses, is superior to and as safe as standard interferon alfa-2b for the treatment of hepatitis C.

Combination of pegylated interferons with ribavirin in Chronic Hepatitis C (also see appendices III & IV).

Both Schering and Roche have ongoing trials with this combination. As yet there is insufficient information to recommend the routine use of a combination of peginterferons with ribavirin. Adding ribavirin to standard interferon therapy reduces the risk of relapse, so the same would be expected if added to pegylated interferons.

- **Peginterferon alfa-2a (Pegasys®) plus ribavirin**

The combination of peginterferon alfa-2a with ribavirin in the treatment of chronic hepatitis C is now licensed and details of dosing can be found in the Summary of Product Characteristics for Pegasys®. Preliminary results of a number of studies using peginterferon alfa-2a and ribavirin for the treatment of chronic hepatitis C have been published in abstract form^{16, 17, 18}. A small phase 2 study (20 subjects) showed a virologic response of 70% at the end of treatment¹⁶. Sixteen subjects with HCV genotype 1 received 48 weeks treatment and four subjects with HCV genotype 2 received 24 weeks treatment. The abstract only reported the SVR rates for the subjects with HCV genotype 2, who all had achieved a SVR (rate 100%).

A randomised, double-blind phase III study of 1284 subjects was carried out for either 24 or 48 weeks with different dosing regimens of ribavirin (see Appendix III for doses and results)¹⁷. The peginterferon alfa-2a dose was the same for both groups, at 180mcg per week. The ribavirin dose ranged from 800mg to 1000-1200mg per day. After 24 weeks, 29% of subjects with genotype 1 and 78% of those with genotype 2 and 3 had undetectable hepatitis C virus RNA, after combination treatment with 800mg ribavirin. However, after 48 weeks 51% of subjects with genotype 1 had achieved an SVR with the higher dose of ribavirin whereas there was no significant change in the numbers of subjects with genotype 2 or 3 achieving SVR in either group (73% and 77%).

Another study in 1149 subjects compared peginterferon alfa-2a with ribavirin to peginterferon alfa-2a monotherapy and standard interferon alfa-2b plus ribavirin¹⁸. After 48 weeks of treatment SVR was achieved in 56% of subjects in the peginterferon alfa-2a/ribavirin group compared to 30% in the monotherapy group and 45% in the standard interferon alfa-2b/ribavirin group (see Appendix III).

- **Peginterferon alfa-2b (ViraferonPeg[®]) plus ribavirin**

The combination of peginterferon alfa-2b with ribavirin in the treatment of chronic hepatitis C is now licensed and details of dosing can be found in the Summary of Product Characteristics for ViraferonPeg[®]. A randomised, open-label, dose-ranging 24 week study comparing peginterferon alfa-2b plus ribavirin with peginterferon alfa-2b alone has been published¹⁹. The peginterferon alfa-2b doses ranged from 0.35mcg/kg/week up to 1.4mcg/kg/week. Ribavirin doses ranged from 600 to 1200mg per day. The authors concluded that safety and tolerability of combined peginterferon alfa-2b and ribavirin and peginterferon alfa-2b alone are comparable. This study, however, used small patient numbers (see Appendix IV).

A second, 48 week open label, randomised study has been conducted²⁰. Subjects received peginterferon alfa-2b 1.5mcg/kg/week plus 800mg ribavirin per day (high dose peginterferon); peginterferon alfa-2b 1.5mcg/kg/week for 4 weeks then 0.5mcg/kg/week plus 1000-1200mg ribavirin per day (low dose peginterferon) or standard interferon alfa-2b 3MU three times a week plus ribavirin 1000-1200mg per day. At follow-up (24 weeks after completing therapy), SVR was achieved in 54% of subjects in the high dose peginterferon group, compared to 47% in both the low dose peginterferon group and the standard interferon alfa group. This benefit was greatest in subjects with HCV genotype 1, the most common type and the most difficult to treat. 42% of subjects with HCV genotype 1 responded to high dose peginterferon alfa-2b plus ribavirin compared to 33% with standard interferon alfa-2b plus ribavirin. Subgroup analysis suggests that titrating doses of both peginterferon alfa-2b and ribavirin to body weight may lead to higher response rates as the likelihood of SVR occurring increases as the doses of ribavirin and peginterferon alfa-2b increase. No new or unusual adverse reactions were seen, though an increase in influenza-like reactions were seen in the high dose peginterferon alfa-2b group (see Appendix IV).

Adverse Effects

- **Peginterferon alfa-2a (Pegasys[®])**

Adverse effects of pegylated interferon alfa-2a appear to be similar in character and incidence to those encountered with standard interferons. The most frequently reported adverse events with peginterferon alfa-2a were fatigue, headache, myalgia, rigors and pyrexia⁷. The most serious adverse events were psychiatric disorders, although in one study depression was less common in subjects treated with the pegylated product (16% vs 23%)¹¹. The pegylated form is larger and unable to penetrate the blood-brain barrier as well as standard interferon.

1.7% of subjects treated with peginterferon alfa-2a and less than 1% treated with peginterferon alfa-2a plus ribavirin needed dose modification or discontinuation due to increased ALT levels¹².

Moderate neutropenia affected 22% of subjects treated with pegylated interferon alfa-2a in combination with ribavirin and severe neutropenia affected 4.7% of subjects¹².

There was an increased incidence of injection site reactions with peginterferon alfa-2a compared to the conventional product (25 vs 15%)¹².

In patients with cirrhosis, who are more likely to suffer adverse effects, dose modification due to thrombocytopenia was necessary in a greater proportion of subjects treated with the pegylated product (6% with standard interferon alfa-2a, 18% and 19% with 90mcg and 180mcg of peginterferon alfa-2a respectively)¹². In this at-risk group, discontinuation due to adverse effects was necessary in 8% of subjects assigned to standard interferon and in 7% and 13% of subjects assigned to peginterferon alfa-2a at 90 and 180 micrograms respectively¹².

- **Peginterferon alfa-2b (ViraferonPeg[®])**

Adverse effects of peginterferon alfa-2b are similar to those encountered with non-pegylated interferon alfa-2b. With the lower dose of peginterferon alfa-2b the incidence of most side effects was similar to standard interferon, while flu-like symptoms, weight loss, anorexia, dizziness and alopecia occurred more frequently with the higher dose.

Injection site reactions occurred more commonly with peginterferon alfa-2b than standard interferon alfa-2b (42 to 44% vs 16%).

Most adverse events were mild to moderate and manageable by appropriate additional therapy and dose adjustment. Rates of dose reduction due to

neutropenia and thrombocytopenia increased with increasing dose of peginterferon alfa-2b but there was no consistent pattern for discontinuation^{4,12}.

Special Patient Populations

• Renal Impairment

Clearance of peginterferon alfa-2b (ViraferonPeg[®]) is reduced in those with significant renal impairment. It is recommended that subjects are monitored closely and the dose reduced if necessary¹⁴. There is evidence that clearance of peginterferon alfa-2a (Pegasys[®]) is primarily hepatic and is unaffected by renal impairment^{21,22}, however a starting dose of 135mcg is recommended¹⁴. There are no data on the value of these drugs in those with severe renal failure or on dialysis.

• Hepatic Impairment

Peginterferon alfa-2b (ViraferonPeg[®]) has not been evaluated in severe hepatic impairment. Haematological tests should be carried out prior to and during treatment. Treatment should be discontinued in patients who develop prolongation of coagulation markers, which might indicate liver decompensation¹⁴. Peginterferon alfa-2a (Pegasys[®]) has been used successfully in patients with compensated liver cirrhosis but there is no information in those with decompensated liver disease.^{7,14}

• The elderly

The manufacturers of peginterferon alfa-2a (Pegasys[®]) and peginterferon alfa-2b (ViraferonPeg[®]) do not recommend any dose modification in the elderly. Absorption of peginterferon alfa-2a (Pegasys[®]) is delayed and half-life is prolonged but there is evidence that the effects are comparable to those seen in younger subjects²³.

• Children

There are no published data on the use of pegylated interferons in children.

• Women of childbearing potential

The manufacturers of peginterferon alfa-2a (Pegasys[®]) and peginterferon alfa-2b (ViraferonPeg[®]) recommend that women of childbearing potential should use effective contraception during treatment and that

peginterferons should not be used in pregnancy. Both have been shown to be abortifacient in primates therefore they are likely to have this effect. These issues should be discussed with women prior to the initiation of treatment. Hepatitis C may be transmitted from mother to infant although the rate of transmission is only about 5%³.

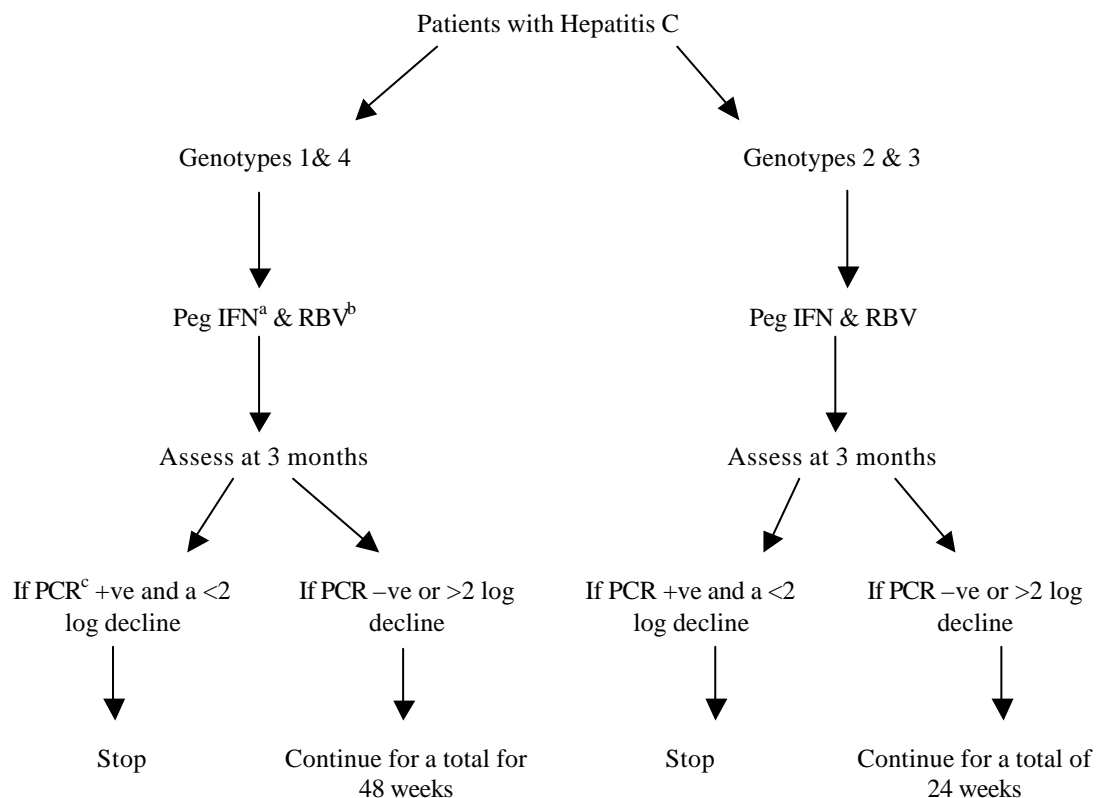
Algorithm for treatment of Hepatitis C

The following algorithm has been devised by Dr Kevin Moore, Senior Lecturer, Centre for Hepatology, Royal Free Hospital in collaboration with six London Consultants in Hepatology*. It refers to the treatment of hepatitis C with pegylated interferons only. (* Dr Suzanne Norris, Kings College Hospital.; Dr Geoff Dusheiko, Royal Free Hospital; Dr Elspeth Allstead, Royal London Hospital; Professor Howard Thomas and Dr Graham Foster, St Marys Hospital and Dr Nickolai Naomov, University College Hospital).

Contraindications to ribavirin include pregnancy, women or men not taking adequate contraceptive precautions, severe cardiac disease, advanced cirrhosis, marked anaemia and renal failure. Patients for whom combination therapy is contra-indicated should be treated with a pegylated interferon monotherapy for 1 year. For patients with significant renal impairment, there is some data to suggest that pegylated interferon alfa-2a is preferred since this pegylated interferon is also cleared by the liver.

In the June 2002 US National Institute of Health Consensus Development Conference on the Management of Hepatitis C²⁴, several important therapeutic advances were discussed, including the introduction of PEG-interferon with ribavirin therapy. In their draft guidelines they state the following:

“Overall, PEG-interferon plus ribavirin is more effective than standard interferon-ribavirin combination or PEG-interferon alone. SVRs were similar with both forms of PEG-interferon (alpha 2a and 2b) when used in combination with ribavirin. Factors associated with successful therapy include genotypes other than 1, lower baseline viral load, and less fibrosis or inflammation on liver biopsy. It appears that 24 weeks of treatment and a lower dose of ribavirin is adequate for genotypes 2 and 3. Early viral response (EVR), defined as a minimum 2 log decrease in viral load during the first 12 to 24 weeks of treatment, has been identified as predictive of SVR. Those who fail to achieve an EVR have only a small chance of achieving a SVR even if therapy is continued for a full year.”



a) PegIFN: Pegylated interferon; b) RBV: Ribavirin; c) PCR: polymerase chain reaction test

Issues for Consideration

- The evidence for the use of peginterferon alfa-2a with ribavirin looks promising but is available in abstract form only. The trials are due to be published later this year.
- Peginterferons as monotherapy are significantly more effective than standard interferons as monotherapy in the treatment of chronic hepatitis C.
- NICE guidance¹ states that approximately 28% of subjects with genotype 1 have a SVR after 48 weeks of combination treatment – this response is increased greatly with peginterferon/ribavirin treatment. It appears that subjects with genotype 1 may benefit from 48 weeks of treatment with peginterferon plus ribavirin, compared to 24 weeks for those with other genotypes.
- Patients on monotherapy who have not responded virologically after three months are unlikely to respond with further treatment.
- Patients on combination therapy who have not responded virologically after six months are unlikely to respond to further treatment.
- Due to the complexity of patient selection and monitoring, treatment with peginterferons should be initiated and monitored by a clinician experienced in the management of hepatitis C.
- It is unclear whether treatment with peginterferons and ribavirin should be based on standard dosing or dosing according to weight. ViraferonPeg[®] dosing is weight based compared to a standard dose with Pegasys[®]. Choice may ultimately depend on physician preference.
- A standard dose pre-filled syringe may be more convenient for the patient than drawing up the correct dose from vials. This would influence which product will be used.
- It is important to have adequate support services with Hepatitis Nurse Specialists as an essential part of them.
- If subjects receive treatment in a clinic or require nursing help at home, once weekly treatment with peginterferons will have service implications but costs should be less than with standard interferons.

Acquisition Costs

Drug	Dose and Frequency	Basic NHS Cost (based on 24 weeks treatment for a 70kg adult)
Interferon alfa-2a (Roferon-A [®]) (prefilled syringes)	3 to 6 mega units three times weekly (3MU = £16.20)	£1166.40 to £2332
Interferon alfa-2a (Roferon-A [®]) multidose cartridge	3 to 6 mega units three times weekly (18MU = £97.19)	£1166.40 to £2332
Interferon alfa-2b (Viraferon [®]) multidose cartridges plus injection pen	3 mega units three times weekly (15MU = £97.20)	£1400
Peginterferon alfa-2a (Pegasys [®]) pre-filled syringe	180mcg once weekly (180mcg = £142)	£3408
Peginterferon alfa-2b (ViraferonPeg [®]) vials	1.5 microgram/kg once weekly (combination therapy) (120mcg = £162)	£3888
Ribavirin (Rebetol [®]) (only in combination with interferon alfa)	400mg in the morning and 600mg in the evening (patient under 75kg) (84 x 200mg = £296.40)	£2964

Basic NHS price.

Below are estimated costs per patient population of 100,000. It is estimated that 1000 patients would carry hepatitis C virus. Of those, 15-20% will have been identified (150-200 patients) and about 20% of these will have cirrhosis and need to be prioritised for treatment (approximately 40 patients). Costs have been calculated if 75% are infected with genotypes 1 and 4 and 25% with genotypes 2 and 3, based on NICE guidance with standard interferon (3MU three times a week) and ribavirin, and according to the algorithm with peginterferon and ribavirin. Doses of ribavirin and peginterferon alfa-2b are based on a 70kg person.

Standard interferon and ribavirin:

(24 weeks treatment for G2&3 and 48 weeks for G1&4)

Genotypes 1 & 4: £247,824

Genotypes 2 & 3: £41,304

Peginterferon and ribavirin:

(According to algorithm and based on 80% of patients with genotypes 1&4 continuing for a full 48 weeks and 80% of those with genotype 2 & 3 continuing for a full 24 weeks).

Genotypes 1 & 4: £324,972 (peginterferon alfa-2a) – £349,452 (peginterferon alfa-2b).

Genotypes 2 & 3: £57,348 (peginterferon alfa-2a) – £61,668 (peginterferon alfa-2b).

The estimated increased costs for using pegylated interferons and ribavirin based on a patient population of 100,000 would be up to £121,992.

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This document reflects the views of the LNDG and may not reflect those of the reviewers.

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Appendix I: Clinical Trials of PegInterferon alfa-2a

Reference	Study Design	Subjects	Outcome Measures and Results		Comments
Zuezem et al. NEJM 2000; 343: 1666-72.	Phase 3, open label, parallel group, randomised, multicentre trial. Subjects received either interferon alfa 2a 6 million units three times weekly for 12 weeks and then 3 million units 3 times weekly for 36 weeks or pegylated interferon alfa 2a weekly for 48 weeks.	531 treatment-naïve subjects with chronic hepatitis C raised ALT.	Sustained virologic response at week 72 (ITT population)		
			Interferon alfa-2a 6MU reducing to 3MU (3/wk)	19%	
			Peginterferon alfa-2a 180mcg weekly	39%	
			Histologic response at week 72 (only subjects with paired specimens)		
			Interferon alfa-2a	55%	
			Peginterferon alfa-2a	63%	
Heathcote et al NEJM 2000; 343: 1673-80.	Open label, randomised, parallel group multicentre study. Subjects were randomised to either interferon alfa-2a 3million units 3 times weekly, PegInterferon alfa-2a 90 micrograms weekly or PegInterferon alfa-2a 180 micrograms weekly for 48 weeks.	271 treatment-naïve subjects with chronic hepatitis C, biopsy proven cirrhosis or bridging fibrosis, raised ALT	Sustained virologic response at week 72		This is a difficult to treat population and as expected response rates were lower, however the difference between conventional and pegylated interferons was statistically significant. Even in subjects who did not show a sustained virologic response more than a third showed histologic improvement.
			Interferon alfa-2a 3MU 3/week	8%	
			Peginterferon alfa-2a 90 mcg/week	15%	
			Peginterferon alfa-2a 180 mcg/week	30%	
			Histologic response at week 72 (only subjects with paired specimens)		
			Interferon alfa-2a	31%	
			Peginterferon alfa-2a 90 mcg	44%	
			Peginterferon alfa-2a 180 mcg	54%	

Appendix II: Clinical Trials of PegInterferon alfa-2b

Reference	Study Design	Subjects	Outcome Measures and Results		Comments
Lindsay et al. Hepatology 2001; 34: 395-403	Double blind, active control, randomised study	1219 treatment naïve, adult subjects with chronic hepatitis C confirmed by positive HCV-RNA, chronic hepatitis and abnormal ALT. Subjects with decompensated liver disease were excluded. Subjects were treated for 48 weeks and were followed up 6 months later.	End of treatment response (ETR) (virologic)		Almost all subjects with a sustained virologic response also normalised ALT (only 4% had an ALT above the upper limit of normal). Differences between conventional interferon and pegylated interferon were statistically significant There was a dose response for pegylated interferon alfa 2b but results for 1.0 and 1.5micrograms/kg groups were similar. The authors conclude that PEG interferon alfa 2b is superior to and as safe as interferon alfa 2b
			0.5 mcg/kg PegInterferon weekly	33%	
			1.0 mcg/kg PegInterferon weekly	41%	
			1.5 mcg/kg PegInterferon weekly	49%	
			Interferon alfa-2a 3million IU thrice weekly	24%	
			Sustained virological response (SVR)		
			0.5 mcg/kg PegInterferon weekly	18%	
			1.0 mcg/kg PegInterferon weekly	25%	
			1.5 mcg/kg PegInterferon weekly	23%	
			Interferon alfa-2a 3million IU thrice weekly	12%	

Appendix III: Clinical Trials of PegInterferon alfa-2a with Ribavirin (RBV)

Reference	Study Design	Subjects	Outcome Measures and Results			Comments
			Sustained virological response (SVR)	24 weeks	48 weeks	
Sulkowski MS, Reindollar R, Yu J. [Abstract] DDW 2000, San Diego, USA 2000;	Phase II open label study. Treatment was given for 48 weeks to subjects with genotype 1 and 24 weeks for all others.	20 subjects with chronic hepatitis C.	Sustained virological response (SVR)			The information is only available in abstract form. Small study with only 20 subjects and four of those had genotype 2.
			Peginterferon alfa-2a 180mcg/week plus RBV 1000-1200mg/day.	Genotype 2: 100%	Genotype 1: 63%	
Hadziyannis SJ, Cheinquer H, Morgan T, Diago M, et al. [Abstract] European Study for the Association of Liver, Madrid, Spain, 2002.	Phase III, randomised, double blind, multicentre study. Therapy was given for either 24 or 48 weeks.	1284 treatment-naïve subjects	Sustained virological response (SVR)	24 weeks	48 weeks	The information is only available in abstract form with the accompanying presentation. Results show that peginterferon alfa-2a with ribavirin is more effective at achieving SVR than standard interferon and ribavirin.
			Peginterferon alfa-2a 180mcg/week plus RBV 800 mg/day	Genotype 1: 29% Others: 78%	Genotype 1: 40% Others: 73%	
			Peginterferon alfa-2a 180mcg/week plus RBV 1000-1200 mg/day	Genotype 1: 41% Others: 78%	Genotype 1: 51% Others: 77%	
Fried MW, Shiffman ML, Reddy RK, Smith C, Marino G, Goncales F. [Abstract] DDW, Atlanta, USA 2001.	Phase III, randomised, actively controlled, multicentre study. Therapy was given for 48 weeks and follow up was 24 weeks later.	1149 treatment-naïve subjects with serologically and biopsy proven chronic hepatitis C, persistently increased ALT and quantifiable plasma viral RNA.	Sustained virological response (SVR)			The information is only available in abstract form with the accompanying presentation. Results show that peginterferon alfa-2a with ribavirin is more effective at achieving SVR than standard interferon and ribavirin.
			Peginterferon alfa-2a 180mcg/week plus RBV 1000-1200mg/day.		56% (46% genotype 1; 76% genotypes 2&3)	
			Peginterferon alfa-2a 180mcg/week		30%	
			Interferon alfa-2a 3MU 3/week plus RBV 1000-1200mg/day.		45% (37% genotype 1; 60% genotype 2&3)	

Appendix IV: Clinical Trials of PegInterferon alfa-2b (PEG) with Ribavirin (RBV)

Reference	Study Design	Subjects	Outcome Measures and Results	
Glue P, Rouzier-Panis R, Raffanel C, Sabo R, Gupta SK, Salfi M, Jacobs S, Clement RP. <i>Hepatology</i> 2000;32:647-53.	Rising, multiple-dose, active controlled, parallel group, open label study. Therapy was given for 24 weeks followed by 24 week follow-up period.	72 treatment-naïve subjects with compensated liver disease due to chronic hepatitis C and increased ALT levels. Subjects with other liver disease or HIV were excluded.	Sustained virological response (SVR) at 24 weeks – Combination therapy	
			Peginterferon alfa-2b 0.35mcg/kg/week with/without RBV 600 or 800mg/day (see comments).	58%
			Peginterferon alfa-2b 0.7mcg/kg/week with/without RBV 600 or 800 or 1000-1200mg/day (see comments).	69%
			Peginterferon alfa-2b 1.4mcg/kg/week with/without RBV 600 or 800 or 1000-1200mg/day (see comments).	81%
			Sustained virological response (SVR) at 48 weeks – Combination therapy	
			PEG 0.35mcg/kg/week with RBV.	17%
			PEG 0.7mcg/kg/week with RBV.	53%
			PEG 1.4mcg/kg/week with RBV.	60%
<p>Comments</p> <ul style="list-style-type: none"> • Study numbers are too small to be conclusive – each treatment group consisted of nine subjects, three of whom received monotherapy with peginterferon alfa-2b and six who received combination therapy. • Results were not shown according to the genotypes. • Ribavirin doses were increased as safety and tolerability were evaluated with lower doses. • The most common side effect seen was influenza-like symptoms which increased as the peginterferon alfa-2b dose increased: 17% with 0.35mcg/kg compared to 44% with 1.4mcg/kg. • Comparison of adverse effects with peginterferon alfa-2b monotherapy and combination therapy showed similar tolerability profiles. The addition of ribavirin had no obvious effects on the adverse events reported. • A greater decrease in haemoglobin concentration was seen in subjects treated with combination therapy compared to monotherapy but no patient had a haemoglobin level of less than 10g/dl. Greatest reductions were seen in all groups around week four. Haemoglobin normalised within four weeks of completing therapy. 				

Reference	Study Design and Subjects	Outcome Measures and Results	
Manns MP, McHutchison JG, Gordon SC, Ristgi VK, Shiffman M, Reindollar R et al. <i>Lancet</i> 2001; 358: 958-965.	Randomised, open label, multi-centre study. Therapy given for 48 weeks with follow-up 24 weeks later. 1530 treatment-naïve subjects with chronic hepatitis confirmed by liver biopsy and with raised ALT. Subjects with decompensated cirrhosis were excluded.	Sustained virological response (SVR) at 48 weeks	
		Peginterferon alfa-2b 1.5mcg/kg/week (higher dose) plus RBV 800mg/day.	65% overall; 42% genotype 1
		Peginterferon alfa-2b 1.5mcg/kg/week for 4 weeks then 0.5mcg/kg/week for 44 weeks (lower dose) plus RBV 1000-1200mg/day for 48 weeks.	56% overall; 34% genotype 1
		Interferon alfa-2b 3MU three times a week plus RBV 1000-1200mg/day.	54% overall; 33% genotype 1
		Sustained virological response (SR) at follow-up	
		PEG higher dose plus RBV 800mg/day.	54% overall (42% genotype 1; 82% genotypes 2&3)
		PEG lower dose plus RBV 1000-1200mg/day for 48 weeks.	47% overall (34% genotype 1; 80% genotypes 2&3)
		Interferon alfa-2b 3MU three times a week plus RBV 1000-1200mg/day.	47% overall (33% genotype 1; 79% genotypes 2&3)
<p>Comments:</p> <ul style="list-style-type: none"> • The SVR rate of higher dose Peginterferon alfa-2b and ribavirin was significantly higher than with lower dose peginterferon alfa-2b / standard interferon alfa-2b and ribavirin. • The greatest benefits were seen in subjects with genotype 1(42% compared to an average response rate of 29-32% with standard interferon alfa-2b.) • The side effect profile of peginterferon alfa-2b and ribavirin was similar to that of standard interferon and ribavirin. Influenza-like symptoms were more common in the peginterferon alfa-2b group, possibly due to the increased dose of interferon in the pegylated product. • Discontinuation of therapy due to anaemia was rare and dose modifications occurred in 9% of subjects treated with high dose peginterferon compared to 13% treated with standard interferon due to haemoglobin levels below 10g/dl. Maximal reductions in haemoglobin occurred between weeks 4 to 8 in all groups. • Less than 1% of all subjects discontinued therapy due to neutropenia. 18% in the higher dose peginterferon alfa-2b group and 8% in the standard interferon group required dose reductions though. • Nearly all the subjects with SVR at the end of treatment also had normal ALT levels. No significant increase in ALT levels (5x baseline) were seen and in each group 3%, 2% and 1% respectively of subjects had an increase of 2x baseline values. 			