

Peginterferon- α -2a (40kD)

A Review of its Use in the Management of Chronic Hepatitis C

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Data Selection

Sources: Medical literature published in any language since 1980 on peg-interferon-alpha-2A, identified using Medline, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase search terms were 'peg-interferon-alpha-2A' or 'RO-253036' or 'RO-25-8310'. Medline search terms were 'peg interferon alpha-2A' or 'peg-modified interferon alfa-2a'. Searches were last updated 5 Nov 2001.

Selection: Studies in patients with chronic hepatitis C who received peginterferon- α -2a (40kD). Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Peginterferon- α -2a, pharmacodynamics, pharmacokinetics, therapeutic use.

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Summary

Abstract

Peginterferon- α -2a (40kD) is a new 'pegylated' subcutaneous formulation of interferon- α -2a that has been developed to improve on the pharmacokinetic profile and therapeutic efficacy of interferon- α -2a. Peginterferon- α -2a (40kD) is produced by the covalent attachment of recombinant interferon- α -2a to a branched mobile 40kD polyethylene glycol moiety, which shields the interferon- α -2a molecule from enzymatic degradation, reduces systemic clearance and enables once-weekly administration.

Peginterferon- α -2a (40kD) was significantly more effective than interferon- α -2a in interferon- α therapy-naïve adults with chronic hepatitis C in three non-blind, randomised, multicentre trials. Virological responses (intention-to-treat results) were achieved in 44 to 69% of patients with or without cirrhosis after 48 weeks of treatment with peginterferon- α -2a (40kD) 180 μ g/week; sustained virological responses 24 weeks after the end of treatment occurred in 30 to 39% of patients. Virological responses at the end of treatment and at long-term follow-up were significantly higher than those achieved with interferon- α -2a. Peginterferon- α -2a (40kD) was significantly more effective than interferon- α in patients with or without cirrhosis infected with HCV genotype 1.

Sustained biochemical responses achieved with peginterferon- α -2a (40kD) 180 μ g/week ranged from 34 to 45% and were significantly higher than with interferon- α -2a. Recipients of peginterferon- α -2a (40kD) also experienced histological improvements; 24 weeks after discontinuation of treatment with peginterferon- α -2a (40kD) 180 μ g/week, 54 to 63% of patients had a \geq 2-point improvement in histological activity index score. Peginterferon- α -2a (40kD) produced histological responses in patients (with or without cirrhosis) with or without a sustained virological response.

Peginterferon- α -2a (40kD) produced better results than interferon- α -2a alone or interferon- α -2b plus oral ribavirin on various measures of quality of life in patients with chronic hepatitis C.

The tolerability profile of peginterferon- α -2a (40kD) is broadly similar to that of interferon- α -2a in patients with chronic hepatitis C with or without cirrhosis. Headache, fatigue and myalgia are among the most common adverse events.

Conclusion: Peginterferon- α -2a (40kD) administered once weekly produces significantly higher sustained responses, without compromising tolerability, than interferon- α -2a administered thrice weekly in noncirrhotic or cirrhotic patients with chronic hepatitis C, including those infected with HCV genotype 1 – a group in whom interferon- α treatment has usually been unsuccessful. Peginterferon- α -2a (40kD) is a valuable new treatment option and appears poised to play an important role in the first-line treatment of patients with chronic hepatitis C,

**Overview of
Pharmacodynamic
Properties**

including difficult-to-treat patients such as those with compensated cirrhosis and/or those infected with HCV genotype 1.

The interferons are naturally occurring proteins with nonspecific regulatory activity. These cytokines are secreted by many mammalian cells and influence cell growth and differentiation, modulate the immune response and inhibit the replication of a number of viruses including hepatitis B and C. The antiviral activity of interferon- α is achieved by its ability to alter interactions between the host and virus in a complex manner.

When administered as a drug, interferon- α -2a induces a nonspecific antiviral state in the virus-infected cell which results in the inhibition of HCV replication. The drug also has immunomodulatory effects that intensify specific host immune responses against the virus. These effects include activation of macrophages, natural killer cells and cytotoxic T lymphocytes and stimulation of the production of type 1 T-helper cells. The anti-inflammatory properties of interferon- α -2a are achieved via inhibition of the production of tumour necrosis factor α , interleukin (IL)-1 and IL-8 and stimulation of the production of IL-10.

The pharmacological activity of interferon- α -2a is augmented by pegylation. The activity of 2',5'-oligoadenylate synthetase (OAS), a key effector protein synthesised in response to interferon- α stimulation, increased with dose in volunteers who received single 45, 135 or 270 μ g subcutaneous doses of peginterferon- α -2a (40kD), or single 3 or 18MU subcutaneous doses of interferon- α -2a. Maximum serum OAS activity occurred approximately 48 hours after administration and remained at about this level for up to 168 hours (1 week) in the peginterferon- α -2a (40kD) [\geq 135 μ g] treatment groups.

Preliminary results of a small randomised comparative trial indicate that peginterferon- α -2a (40kD) treatment (180 μ g/week for 48 weeks; n = 14) produces more robust HCV-specific CD4+ T helper 1 immune responses than interferon- α -2a (6MU three times a week for 12 weeks then 3MU three times a week for 36 weeks) in therapy-naive patients with chronic hepatitis C (with weak or no HCV-specific CD4+ responses before treatment).

The rate of viral decline was HCV genotype-dependent in patients treated with peginterferon- α -2a (40kD) or interferon- α -2a. The first and second phases of viral decline were significantly faster in patients infected with HCV non-1 genotypes than in those infected with HCV genotype 1 receiving treatment with peginterferon- α -2a (40kD) 180 μ g weekly.

**Overview of
Pharmacokinetic
Properties**

Peginterferon- α -2a (40kD) is well absorbed after single subcutaneous doses in healthy volunteers or multiple subcutaneous doses in patients with chronic hepatitis C.

Three to 8 hours after a single 180 μ g dose of the drug, 'substantial' concentrations (values not reported) of peginterferon- α -2a (40kD) were detected in the serum of 10 healthy volunteers. Peginterferon- α -2a (40kD) was delivered to the systemic circulation at a sustained rate; the mean maximum serum concentration (C_{max}) of peginterferon- α -2a (40kD) was 14.2 μ g/L and was reached in mean time (t_{max}) of 78 hours. After single 180 μ g doses of peginterferon- α -2a (40kD), serum peginterferon- α -2a (40kD) concentrations were sustained for longer than concentrations of interferon- α -2a in healthy volunteers.

In 16 patients with chronic hepatitis C who received multiple doses of peginterferon- α -2a (40kD) 180 μ g/week, the peginterferon- α -2a C_{max} was 25.6

$\mu\text{g/L}$ and the t_{max} was 45 hours. After single 180 μg doses ($n = 14$), C_{max} and t_{max} values were 15.4 $\mu\text{g/L}$ and 80 hours, respectively; steady-state concentrations of the drug were attained 5 to 8 weeks after initiation of the once-weekly regimen in these patients.

Peginterferon- α -2a (40kD) is cleared by both the liver and kidney and the liver plays an important role in the metabolism of the drug. Because of its large size and branched nature, peginterferon- α -2a (40kD) undergoes reduced renal clearance compared with that of standard interferon- α , thus prolonging hepatic exposure to the pegylated interferon. Pegylation resulted in a >100-fold reduction in the renal clearance of interferon- α -2a in 10 volunteers who received a single 180 μg dose of peginterferon- α -2a (40kD). Metabolic products of peginterferon- α -2a (40kD) are eliminated via the kidneys. However, clearance via the kidneys does not appear to be extensive as the pharmacokinetics of the drug in patients with chronic renal impairment (creatinine clearance values ≥ 20 ml/min; ≥ 1.2 L/h) are not appreciably different from those in patients with normal renal function. In patients with chronic hepatitis C and cirrhosis, the terminal half-life of peginterferon- α -2a (40kD) was 70 to 90 hours.

Peginterferon- α -2a (40kD) showed no significant effects on drug metabolism mediated by CYP2C9, 2C19, 2D6 and 3A4 isoenzymes in healthy nonsmoking male volunteers. However, as documented with interferon- α , the clearance of theophylline (metabolised by CYP1A2) was significantly reduced (compared with baseline) in volunteers receiving multiple doses of peginterferon- α -2a (40kD).

Therapeutic Efficacy

The therapeutic efficacy of peginterferon- α -2a (40kD) has been investigated in 3 nonblind, randomised, multicentre, comparative trials that enrolled a total of 961 patients with chronic hepatitis C with or without cirrhosis who had not been previously treated with interferon- α . One of these trials was a dose-finding trial and the other two were large multinational comparative trials enrolling patients with or without cirrhosis (typical of a general population of patients with hepatitis C) or patients with cirrhosis or bridging fibrosis. Peginterferon- α -2a (40kD) was administered as a subcutaneous injection once weekly for 48 weeks in all three trials. The virological and biochemical efficacy of study medication was assessed at the end of treatment and after a 24-week treatment-free follow-up period, to establish the durability of responses. The efficacy of various dosages of peginterferon- α -2a (40kD) was compared with interferon- α -2a, administered at a dosage of either 6MU three times a week for 12 weeks, then 3MU three times a week (6/3MU three times a week), or 3MU three times a week.

Overall, virological responses (undetectable HCV RNA in the plasma) [intention-to-treat results] were achieved in 44 to 69% of patients with or without cirrhosis after 48 weeks of treatment with peginterferon- α -2a (40kD) 180 $\mu\text{g/week}$. At the 24-week follow-up evaluation, sustained virological responses in the peginterferon- α -2a (40kD) 180 μg groups ranged from 30 to 39%. Virological responses both at the end of treatment and at long-term follow-up were significantly higher than those achieved with interferon- α (6/3MU or 3MU three times a week) at the end of treatment (12 to 28%) and at the 24-week follow-up evaluation (3 to 19%).

Peginterferon- α -2a (40kD) was significantly more effective than interferon- α in patients with or without cirrhosis infected with HCV genotype 1, achieving

sustained virological responses in 28% of patients compared with 7% of interferon- α -2a recipients. As in patients with less advanced disease, sustained virological responses in patients with cirrhosis infected with HCV genotype 1 tended to be higher in patients treated with peginterferon- α -2a (40kD) 90 (5%) and 180 μ g/week (13%) than in recipients of interferon- α -2a (2%). In patients with a histological diagnosis of cirrhosis at baseline, virological responses were about 4-fold higher in the patients treated with peginterferon- α -2a (40kD) 180 μ g/week (32%) than in the interferon- α -2a treatment group (7%).

Across the three trials, end-of-treatment biochemical responses (defined as the reduction of previously elevated ALT levels to levels at or below the normal level) were achieved in 38 to 46% of patients in the peginterferon- α -2a (40kD) 180 μ g/week treatment groups and in 15 to 39% of patients in the interferon- α -2a groups (intention-to-treat results); sustained biochemical responses in the peginterferon- α -2a (40kD) 180 μ g/week groups ranged from 34 to 45% and were significantly higher than sustained responses in the interferon- α -2a treatment groups (9 to 25%).

Peginterferon- α -2a (40kD) also produced beneficial effects on liver histology. At the end of the follow-up period, between 54 and 63% of patients (with paired liver biopsies) treated with peginterferon- α -2a (40kD) 180 μ g/week had a ≥ 2 -point improvement in histological activity index scores in the three trials.

In patients with cirrhosis, a significantly larger proportion of patients treated with peginterferon- α -2a (40kD) 180 μ g/week than with interferon- α -2a had histological improvements (≥ 2 -point improvement in histological activity index scores) at 72 weeks (54 vs 31%). A histological response correlated with both sustained virological and biochemical responses. In addition to the beneficial histological effects produced by peginterferon- α -2a (40kD) in patients with or without cirrhosis with sustained virological responses, peginterferon- α -2a (40kD) also produced histological improvements in patients (with or without cirrhosis) without a sustained virological response. In patients with cirrhosis or bridging fibrosis without a sustained virological response, histological improvements were achieved in 35, 33 and 26% of patients in the peginterferon- α -2a (40kD) 180 μ g, peginterferon- α -2a (40kD) 90 μ g and interferon- α -2a groups, respectively.

Quality of Life

Peginterferon- α -2a (40kD) achieves superior results, during and after treatment, on various measures of quality of life in patients with chronic hepatitis C (including patients with cirrhosis) compared with interferon- α -2a alone or interferon- α -2b plus oral ribavirin, according to preliminary data reported in abstracts.

Peginterferon- α -2a (40kD) was associated with a more marked increase in self-assessed health improvement [as measured by the standardised 36-question short form (SF-36) Health Survey] than interferon- α -2a in patients with chronic hepatitis C and cirrhosis.

A pooled analysis of data from 1441 patients who participated in 3 randomised multinational comparative trials showed significant improvements in measurements of fatigue (using the Fatigue Severity Scale) and SF-36 scores among patients with a sustained virological response.

Peginterferon- α -2a (40kD) 180 μ g/week produced significantly less impairment in quality of life and less fatigue than interferon- α -2a 6/3MU three times

weekly during the first 12 weeks of treatment (evaluated patients were participants in a large multinational comparative trial).

Within the first 12 weeks of treatment, therapy-naïve recipients of peginterferon- α -2a experienced significantly better quality of life than recipients of interferon- α -2b plus oral ribavirin in a large comparative multicentre trial. Assessments were made using the Hepatitis Quality of Life Questionnaire.

Tolerability

The tolerability profile of subcutaneous peginterferon- α -2a (40kD) is broadly similar to that of subcutaneous interferon- α -2a in patients with chronic hepatitis C. Types of adverse events were similar in patients in the peginterferon- α -2a (40kD) and interferon- α -2a treatment groups in the 2 large multinational comparative trials. Adverse events in recipients of peginterferon- α -2a (40kD) were not dose-related in noncirrhotic patients (with the exception of rigors) or in patients with more advanced liver disease.

In the largest comparative trial conducted in patients with chronic hepatitis (most of whom showed no histological evidence of cirrhosis or bridging fibrosis at baseline), headache, fatigue, pyrexia, myalgia, rigors and alopecia were the most common adverse events reported in patients receiving peginterferon- α -2a (40kD) 180 μ g/week.

In patients with chronic hepatitis C and cirrhosis, the most common adverse events in recipients of peginterferon- α -2a (40kD) 180 μ g/week were fatigue, headache, myalgia, rigors, pyrexia and nausea. Incidences of these adverse events were generally similar in recipients of peginterferon- α -2a (40kD) 180 μ g or 90 μ g/week or interferon- α -2a 3MU three times a week.

Interferon- α may produce undesirable adverse effects on bone marrow, thus limiting the use of the drug in some patients. In the trial that enrolled patients with cirrhosis or bridging fibrosis, marked decreases in both neutrophil and platelet counts often occurred in recipients of peginterferon- α -2a (40kD) or interferon- α -2a. Nevertheless, these effects were effectively managed by a reduction in dose.

The relative tolerability of peginterferon- α -2a (40kD) or interferon- α -2b plus ribavirin treatment in therapy-naïve patients with chronic hepatitis C was assessed using the Work Productivity and Activity Impairment (WPAI) Instrument in a large (n = 412) comparative trial. During the first 4 to 12 weeks of treatment, patients receiving interferon- α -2b plus ribavirin had missed 8.7 hours of work per week due to health versus 0.2 hours per week missed by recipients of peginterferon- α -2a (40kD). Overall, lost productivity per week was \$US117.20 vs \$US34.70 (1999 values) for the interferon- α -2b/ribavirin and peginterferon- α -2a (40kD) groups, respectively.

Dosage and Administration

Dosages of subcutaneously administered peginterferon- α -2a (40kD) evaluated in adult patients with chronic hepatitis C (with or without cirrhosis) in clinical trials ranged from 45 to 270 μ g/week. The optimal dosage of the drug was found to be 180 μ g once weekly. Data are limited on the efficacy and tolerability of peginterferon- α -2a (40kD) in patients with chronic hepatitis C aged <18 years or >60 years.

1. Scope of the Review

Hepatitis C virus (HCV) infection is the most common chronic bloodborne infection in the US and the leading cause of chronic liver disease worldwide. An estimated 170 million people throughout the world are infected with HCV and the infection has been reported to account for 70% of cases of chronic hepatitis and 40% of cases of cirrhosis in industrialised countries.^[1,2] About 2.7 million people in the US are estimated to have active HCV infection.^[2] In 1999, the global prevalence of chronic hepatitis C ranged from 0.1 to 5%.^[3-5]

Transmission of HCV usually occurs through direct percutaneous exposure to infected blood from various sources. Although intravenous drug users are at greatest risk of acquiring HCV infection and represent about 50% of annual infections, 'sporadic' cases of infection acquired via unknown routes may also occur. HCV, an RNA virus belonging to the Flaviviridae, is classified into 6 predominant genotypes based on differences in a highly conserved region of the HCV genome. At present, there is no effective vaccine available for the protection of healthy individuals against this genetically diverse virus.^[6,7]

Approximately 15% of individuals infected with HCV spontaneously recover, while a further 25% are asymptomatic, have normal ALT levels and histological lesions that are usually benign. Most HCV-infected individuals with mild non-specific symptoms (e.g. malaise and mild fatigue) have elevated ALT levels, minimal fibrosis and mild or moderate necroinflammatory lesions, and may not develop advanced liver disease. However, about 10 to 20% of infected patients have progressive liver disease and develop cirrhosis 10 to 20 years after acquiring the infection. These individuals may die of cirrhosis-related complications, including hepatocellular carcinoma.^[3,8] The incidence of hepatocellular carcinoma in patients with cirrhosis shows marked geographical variation and has been estimated to range from 1 to 4% per year.^[3]

Although interferon- α has been the standard treatment for chronic hepatitis C for more than a decade, it produces sustained responses in only 15 to 25% of patients. Limitations in the effectiveness of interferon- α have been attributed in part to its rapid systemic clearance and short plasma elimination half-life of about 8 hours. Plasma concentrations of the drug decrease to low trough levels between each administration. In addition, the frequently used 3-times weekly administration schedule of interferon- α produces peak drug concentration/trough concentration cycles which compromise the tolerability of the drug because of the high incidence of peak concentration-related adverse effects. Although daily administration or increased dosages of interferon- α may achieve clearance of HCV RNA, daily regimens of the drug are inconvenient, costly and may not be well tolerated.^[9-12]

To overcome the limitations of standard treatment with interferon- α in patients with chronic hepatitis C, new treatment approaches are being investigated in this rapidly changing area of clinical practice. This review focuses on a new 'pegylated' formulation of interferon- α -2a called peginterferon- α -2a (40kD) [peg-interferon- α -2a; Pegasys®]. The pegylation process involves attaching an inert polyethylene glycol (PEG) moiety to another 'base' molecule. Using this process, recombinant interferon- α -2a (figure 1) has been increased in size by the covalent binding of a 40kD branched mobile PEG moiety to produce a large PEG-interferon- α -2a complex with a protective barrier that shields the interferon- α -2a molecule from enzymatic degradation by the human metabolic system while maintaining its pharmacological effects and reducing its immunogenicity.^[13,14] The large size of the peginterferon- α -2a (40kD) molecule reduces renal clearance, thereby prolonging systemic exposure of the drug. Because of the changes in metabolism of peginterferon- α -2a (40kD), the drug is given in an easily administered once-weekly regimen rather three times weekly, the standard administration schedule for interferon- α -2a. Peginterferon- α -2b is the only other pegylated interferon- α currently available for the treatment of patients with chronic hepatitis C; however,

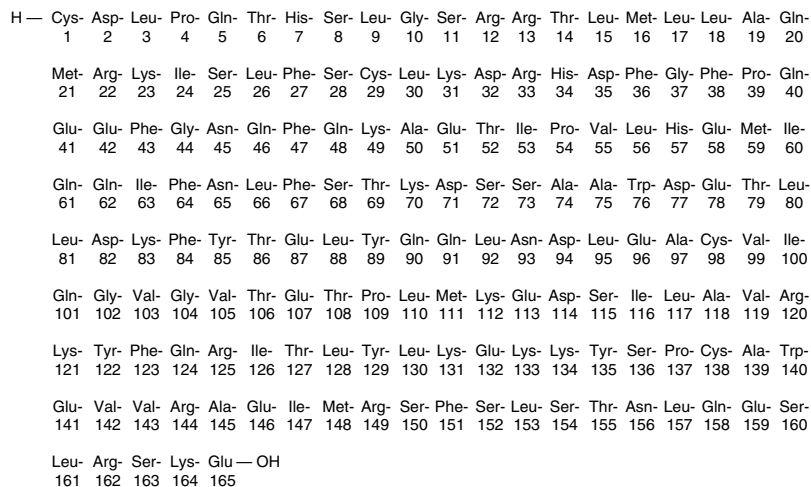


Fig. 1. Structure of interferon- α -2a.

discussion of this agent is beyond the scope of this review.

Clinical trials evaluating combination therapy with peginterferon- α -2a (40kD) and ribavirin are underway^[15-18] or completed,^[19] but are not discussed in detail in this review, which focuses on the efficacy of peginterferon- α -2a (40kD) monotherapy.

2. Overview of Pharmacodynamic Properties

2.1 General Effects

The interferons are a family of naturally occurring proteins with nonspecific regulatory activity. These cytokines are secreted by many mammalian cells and influence cell growth and differentiation, modulate the immune response and inhibit the replication of a number of viruses including hepatitis B and C. Although the antiviral, immunomodulatory and anti-inflammatory properties of interferon- α are thought to contribute towards its beneficial effects in patients with chronic hepatitis C, the exact mechanism of action of this cytokine in hepatitis C has yet to be established.^[20] The mechanisms of action of interferon- α have been reviewed in detail elsewhere;^[21-23] this section therefore provides a

brief overview of its putative antiviral activity in patients with chronic hepatitis C.

Unlike many anti-HIV drugs, which target the functions of HIV proteins, the antiviral activity of interferon- α is achieved by its ability to alter interactions between the host and virus in a complex manner.^[22] After administration, interferon- α binds to high-affinity receptors on the target cell surface which activates a cascade of reactions in the cell and triggers the activation of many genes. The numerous cellular activities of interferon- α are mediated by the products of these interferon- α -inducible genes.^[21,22] The antiviral activity of interferon- α is achieved via two different but complementary mechanisms. Firstly, interferon- α induces a nonspecific antiviral state in the virus-infected cell [e.g. by stimulating the 2',5'-oligoadenylate synthetase (OAS) system and Mx proteins] which leads to the inhibition of HCV replication. Secondly, the drug induces immunomodulatory effects that intensify specific host immune responses against the virus.^[22] The immunomodulatory effects of interferon- α are triggered by its binding to the surface receptors of immune cells. Activation of macrophages, natural killer cells and cytotoxic T lymphocytes, and stimulation of the production of

type 1 T-helper cells are among the many immunomodulatory effects produced by the drug. Interferon- α also has anti-inflammatory properties, which are achieved via inhibition of the production of tumour necrosis factor α , interleukin (IL)-1 and IL-8 and stimulation of the production of IL-10, a cytokine that produces a down-regulation of the pro-inflammatory response and modulation of hepatic fibrogenesis.^[22]

Data on the pharmacodynamic properties of peginterferon- α -2a (40kD) in humans are limited at present. However, preliminary results of one investigation showed that the pharmacological activity of interferon- α -2a is augmented by pegylation.^[24] The activity of OAS, a key effector protein synthesised in response to interferon- α stimulation and involved in interferon-mediated inhibition of viral function,^[21,22] increased with dose in volunteers (number not reported) after single 45, 135 or 270 μ g subcutaneous doses of peginterferon- α -2a (40kD), or single 3 or 18MU subcutaneous doses of interferon- α -2a.^[24] Notably, maximum serum OAS activity occurred approximately 48 hours after administration of the dose and remained at about this level for up to 168 hours (1 week) before declining in the peginterferon- α -2a (40kD) [$\geq 135\mu$ g] treatment groups,^[24] reaching baseline after the second week following administration. Interferon- α -2a 3MU produced less OAS activity than the 18MU dose and, as with the higher dose, OAS activity declined 24 hours after administration.^[24]

In another investigation (see section 3.1.3),^[25] maximum concentrations of OAS were lower in healthy elderly volunteers than in younger volunteers (1509 vs 2130 pmol/hour) after single 180 μ g subcutaneous doses of peginterferon- α -2a (40kD), indicating that elderly individuals are less sensitive to the induction of OAS by this agent.

Preliminary results of a small randomised comparative trial indicate that peginterferon- α -2a (40kD) treatment (180 μ g/week for 48 weeks; n = 14) produces more robust HCV-specific CD4+ T helper 1 immune responses than interferon- α -2a (6MU three times a week for 12 weeks then 3MU three times a week for 36 weeks) in therapy-naïve

patients with chronic hepatitis C (with weak or no HCV-specific CD4+ responses before treatment).^[26] Patients with a sustained virological response [8 of 14 peginterferon- α -2a (40kD) recipients and 3 of 14 interferon- α -2a recipients] had multispecific vigorous HCV-specific CD4+ responses with high interferon- γ and low IL-10 production. This finding may explain why patients who have received treatment with peginterferon- α -2a (40kD) have higher sustained virological responses than interferon- α -2a-treated patients (see section 4.1).^[26]

2.2 Effects on Viral Kinetics

The effect of interferon- α treatment on HCV has previously been characterised as having two phases: an initial decline in viral load during the first 24 to 48 hours that may reflect treatment-induced inhibition of HCV replication and the degradation of free virus, and a secondary decline that is a stable exponential decay and thought to be related to the rate of degradation of infected cells.^[27] In a viral kinetic study, patients treated with either peginterferon- α -2a (40kD) 180 μ g once weekly for 48 weeks (n = 17) or interferon- α -2a 6MU three times weekly for 12 weeks and then 3MU three times weekly for 36 weeks (n = 16) showed an initial phase of viral decline (during the first 24 hours of treatment) that was rapid and similar in both groups, and considered to be a reflection of degradation of free HCV RNA.^[27]

The rate of viral elimination was HCV genotype-dependent in patients treated with peginterferon- α -2a (40kD) or interferon- α -2a, with the first and second phases of viral decline significantly ($p < 0.05$) steeper in patients infected with HCV non-1 genotypes than in those infected with HCV-1. This may explain why patients infected with HCV genotypes 2 and 3 benefit from shorter treatment periods.^[27] In patients infected with HCV genotype 1 exhibiting first-phase viral decay, the rate of degradation of free virus was $2.86 \pm 1.89 \text{ day}^{-1}$ and $2.12 \pm 1.56 \text{ day}^{-1}$ in the peginterferon- α -2a (40kD) and interferon- α -2a groups, respectively; corresponding values for patients infected with HCV non-1 genotypes were $3.90 \pm 2.21 \text{ day}^{-1}$ and

$3.71 \pm 1.47 \text{ day}^{-1}$. The rate of viral decline decreased during the subsequent 24 hours and led to a second phase during which time the exponential decay was relatively stable and may have been related to the rate of degradation of HCV-infected cells.

During this second phase, viral decline was also HCV genotype-dependent. In patients infected with HCV genotype 1 who had a virological response to treatment, the second phase decline of HCV RNA was $0.06 \pm 0.08 \text{ day}^{-1}$ and $0.02 \pm 0.03 \text{ day}^{-1}$ in the peginterferon- α -2a (40kD) and interferon- α -2a treatment groups, respectively; corresponding values in patients infected with HCV non-1 genotype were $0.44 \pm 0.33 \text{ day}^{-1}$ and $0.88 \pm 0.64 \text{ day}^{-1}$. The second phase decline was predictive of both an end of treatment ($p = 0.06$) and a sustained ($p = 0.003$) virological response. Indeed, the second phase of HCV RNA decline was low ($<0.05 \text{ day}^{-1}$) in the majority of patients who did not have a virological response at the end of treatment and, conversely, was high ($>0.25 \text{ day}^{-1}$) in those patients who had a sustained virological response.

3. Overview of Pharmacokinetic Properties

Pharmacokinetic investigations of peginterferon- α -2a (40kD) have been conducted in small numbers of healthy young adult and elderly volunteers (single-dose studies) and adult patients with hepatitis C (multiple-dose studies). Peginterferon- α -2a (40kD) and interferon- α -2a were administered subcutaneously, once and thrice weekly, respectively, in most of the studies discussed in this section; pharmacokinetic parameters of peginterferon- α -2a (40kD) are summarised in table I.

The pharmacokinetic characteristics of peginterferon- α -2a (40kD) in patients with chronic hepatitis C are similar after single and multiple doses of the drug.^[31] Preliminary data from a single-dose investigation indicate that the pharmacokinetic profile of peginterferon- α -2a (40kD) in patients with varying degrees of stable chronic renal impairment [creatinine clearance (CL_{CR}) values

$\geq 20 \text{ ml/min}$; $\geq 1.2 \text{ L/h}$] is similar to that in patients with normal renal function.^[32]

3.1 Absorption

Peginterferon- α -2a (40kD) is well absorbed after single subcutaneous doses in healthy volunteers or multiple subcutaneous doses in patients with chronic hepatitis C.

3.1.1 Healthy Volunteers

Three to 8 hours after a single 180 μg dose of the drug, 'substantial' concentrations (values not reported) of peginterferon- α -2a (40kD) were detected in the serum of 10 healthy volunteers. Peginterferon- α -2a (40kD) was delivered to the systemic circulation at a sustained rate; the mean maximum serum concentration (C_{max}) of peginterferon- α -2a (40kD) was 14.2 $\mu\text{g/L}$ (compared with 13.4 IU/ml for interferon- α -2a; previously published result) and was reached in a mean time (t_{max}) of 78 hours (compared with 10 hours for interferon- α -2a)^[30] [table I]. In a recent review, Kozlowski et al.^[33] reported that almost constant blood concentrations of peginterferon- α -2a (40kD) are achieved with once weekly administration of the drug (figure 2).

Serum peginterferon- α -2a (40kD) concentrations in 10 volunteers who received single 180 μg doses of the drug were sustained for longer than the

Table I. Summary of pharmacokinetic parameters of peginterferon- α -2a (40kD) [after single subcutaneous doses of 180 μg] in healthy adult volunteers aged <65 years; for comparison, values for standard interferon- α from previous investigations are also shown^[9,14,28-30]

Parameter	Value	
	peginterferon- α -2a (40kD)	'standard' interferon- α
C_{max}	14.2 $\mu\text{g/L}$	13.4 IU/ml
t_{max} (h)	78	10
% Absorbed	61	80
MAT (h)	59	2.6
CL (L/h)	0.08	11.8
Vd (L)	8-12 ^a	31-73 ^b
$t_{1/2}$ (h)	77	8

a After single subcutaneous doses of 45 to 270 μg .

b After a single intravenous dose.

CL = clearance; C_{max} = maximum serum concentration; MAT = mean absorption time; t_{max} = time to reach maximum serum concentration; $t_{1/2}$ = serum elimination half-life; Vd = volume of distribution.

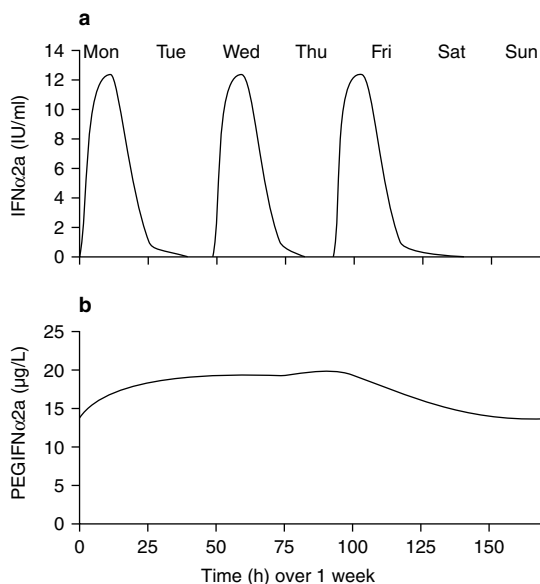


Fig. 2. Blood concentrations of (a) interferon- α -2a and (b) peginterferon- α -2a (40kD), as reported by Kozłowski et al.^[33] IFN α 2a = interferon- α -2a; PEGIFN α 2a = peginterferon- α -2a (40kD).

concentrations of interferon- α -2a reported in an earlier study.^[30] Serial blood samples were collected for up to 168 hours for determination of serum peginterferon- α -2a (40kD) concentrations and data were compared with published results for interferon- α -2a. Proportions absorbed via the subcutaneous route were 61% for peginterferon- α -2a (40kD) compared with 80% for interferon- α -2a.^[30] Given that sampling in this study was limited to up to 168 hours, these data indicate that the absolute bioavailability of peginterferon- α -2a is at least 60%.

3.1.2 Patients with Chronic Hepatitis C

After multiple doses of peginterferon- α -2a (40kD) [180 μ g/week; n = 16] C_{max} was 25.6 μ g/L and t_{max} was 45 hours in patients with chronic hepatitis C who were participating in a phase III trial.^[31] After single 180 μ g doses (n = 14), C_{max} and t_{max} values were 15.4 μ g/L and 80 hours, respectively. Steady-state concentrations of the drug were attained 5 to 8 weeks after initiation of the

once-weekly regimen in these patients. At steady-state, the ratio of serum peak to trough concentrations of peginterferon- α -2a (40kD) was about 1.5 to 2.0, indicating that serum concentrations of the drug were sustained during the 1-week dosage interval. It is anticipated that peginterferon- α -2a (40kD) will be undetectable in the serum (i.e. serum concentration $\leq 0.1 \mu$ g/L) 4 to 6 weeks after the discontinuation of 48 weeks' treatment with a dosage of 180 μ g/week.^[31]

The pharmacokinetic profile of peginterferon- α -2a (40kD) in patients with chronic hepatitis C and cirrhosis or bridging fibrosis is similar to that in both noncirrhotic patients with chronic hepatitis C and healthy volunteers.^[34] 40 cirrhotic patients with chronic hepatitis C received subcutaneous peginterferon- α -2a (40kD) 90 or 180 μ g/week for 48 weeks followed by a 24-week observation period. Almost dose-proportional C_{max} values were reported at about 80 hours after the first dose of peginterferon- α -2a (40kD) in cirrhotic patients with chronic hepatitis C: values for the 90 and 180 μ g doses were 4.9 and 7.8 μ g/L, respectively, and steady-state trough concentrations were 6.1 and 12.3 μ g/L.

3.1.3 Elderly Volunteers

The absorption of peginterferon- α -2a (40kD) after a single 180 μ g dose is slower in healthy elderly men aged >60 years (n = 12; t_{max} 116 hours) than in healthy young men aged 18 to 25 years (n = 12; t_{max} 81 hours).^[25] Peginterferon- α -2a (40kD) C_{max} values were similar in elderly and young men (9.1 and 10.3 μ g/L), but the elderly group had greater systemic exposure to the drug (area under the serum concentration-time curve values were 1663 and 1295 μ g \cdot h/L, respectively) suggesting that the drug should be used with caution in elderly patients with chronic hepatitis C. However, this was not considered by the investigators to result in an increase in the biological activity of the drug (section 2.1).

3.2 Distribution

Peginterferon- α -2a (40kD) displays restricted biodistribution in patients with chronic hepatitis

C^[31] and in animals,^[29] with highest concentrations occurring in the liver where the drug can be most effective.^[29] The drug was recovered from injection site tissue, blood, liver, kidneys and spleen in rats after a single intravenous or subcutaneous dose of radiolabelled peginterferon- α -2a (40kD). Amounts of radioactive peginterferon- α -2a (40kD) were highest in the liver and kidney (6.9 and 1.4%, respectively) 14 days after the single intravenous dose; similar results were obtained after a single subcutaneous dose of the drug.^[29] Concentrations of peginterferon- α -2a (40kD) were $\leq 1\%$ in all other organs examined.

3.3 Metabolism and Elimination

Peginterferon- α -2a (40kD) is cleared by both the liver and the kidney and the liver plays an important role in the metabolism of the drug.^[29] Because of its large size and branched nature, peginterferon- α -2a (40kD) undergoes reduced renal clearance compared with that of standard interferon- α , thus prolonging hepatic exposure to the pegylated interferon.

Pegylation resulted in a >100 -fold reduction in the renal clearance of interferon- α -2a in 10 volunteers who received a single 180 μ g dose of peginterferon- α -2a (40kD); clearance values for peginterferon- α -2a (40kD) and standard interferon- α were 0.08 and 11.8 L/h (data from previous investigations), respectively.^[30] Peginterferon- α -2a (40kD) had a mean clearance of 0.060 L/h in 16 patients with chronic hepatitis C who received peginterferon- α -2a (40kD) 180 μ g/week for 48 weeks.^[31]

Peginterferon- α -2a (40kD) was shown to be cleared mainly by hepatic metabolism in rats [after an initial period of ≥ 24 hours when ¹⁴C-labelled peginterferon- α -2a (40kD) remained unmetabolised in the liver].^[29] The liver : blood ratio of radiolabelled peginterferon- α -2a (4kD) concentrations was greater than that of interferon- α , suggesting that peginterferon- α -2a (40kD) provides the liver with greater exposure to interferon- α than standard interferon- α .^[30]

Metabolic products of peginterferon- α -2a (40kD) are eliminated via the kidneys. However, clearance

via the kidneys does not appear to be extensive as the pharmacokinetics of the drug in patients with varying degrees of chronic renal impairment (CL_{CR} values ≥ 20 ml/min; ≥ 1.2 L/h) are not appreciably different from those in patients with normal renal function.^[32] Elimination occurred at a consistent rate during the 14-day period after administration of a single intravenous or subcutaneous dose in rats.^[29] During this time, proportions of the total radioactive dose eliminated in the urine and faeces were 51 and 9.6%, respectively.

In patients with chronic hepatitis C and cirrhosis, the terminal half-life ($t_{1/2}$) of peginterferon- α -2a (40kD) [70 to 90 hours] was similar to that in healthy volunteers (77 hours).^[34] The $t_{1/2}$ of peginterferon- α -2a (40kD) was longer in elderly than in young men (110 vs 61 hours).^[25]

3.4 Drug Interactions

Peginterferon- α -2a (40kD) appears to have a favourable drug interaction profile. Indeed, multiple doses of peginterferon- α -2a (40kD) showed no significant effects on drug metabolism mediated by cytochrome P450 (CYP) 2C9, 2C19, 2D6 or 3A4 isoenzymes in 15 nonsmoking healthy male adults.^[35] However, multiple-dose administration of peginterferon- α -2a (40kD) with theophylline resulted in a decrease in the clearance of theophylline (metabolised by CYP1A2) compared with baseline. The interaction between interferon- α and theophylline is well documented and is due to interferon- α -mediated inhibition of CYP1A2 *de novo* synthesis.^[35]

4. Therapeutic Efficacy

The therapeutic efficacy of peginterferon- α -2a (40kD) in adults with chronic hepatitis C has been investigated in three nonblind, randomised, multicentre, comparative trials that enrolled a total of 961 patients who had not been previously treated with interferon- α (table II).^[36-38]

One of these trials was a dose-finding trial^[36] and the other two were large multinational phase II/III^[38] and phase III^[37] trials.

Table II. Efficacy of peginterferon- α -2a (40kD) [PEGIFN α 2a] in the treatment of adults^a with chronic hepatitis C; summary of results of nonblind, randomised, multicentre trials comparing PEGIFN α 2a with interferon- α -2a (IFN α 2a)

Reference	Mean age (y)	No. of pts enrolled (plasma HCV RNA level $\times 10^6$ copies/ml at baseline)	Treatment regimen ^b (duration of follow-up in wks)	% (no.) of pts with responses at the end of treatment		% (no.) of pts with sustained responses at 24-week follow-up		
				virological ^{c,d}	biochemical ^{d,e}	virological ^d	biochemical ^d	histological ^f
Patients without cirrhosis^g								
Reddy et al. ^[36]	41.9	20 (1.7)	PEGIFN α 2a 45 μ g/wk \times 48wk (24)	30 (6)	20 (4)	10 (2)	10 (2)	47 (7)
	43.1	20 (1.2)	PEGIFN α 2a 90 μ g/wk \times 48wk (24)	45 (9)*	20 (4)	30 (6)**	25 (5)	59 (10)
	42	45 (2.3)	PEGIFN α 2a 180 μ g/wk \times 48wk (24)	60 (27)***	38 (17)*	36 (16)**	38 (17)**	63 (19)
	41.6	41 (2.8)	PEGIFN α 2a 270 μ g/wk \times 48wk (24)	56 (23)***	27 (11)	29 (12)**	27 (11)	66 (19)
	41.8	33 (3.1)	IFN α 2a 3MU 3 \times /wk \times 48wk (24)	12 (4)	15 (5)	3 (1)	9 (3)	57 (13)
Patients with or without cirrhosis^h								
Zeuzem et al. ^[37]	40.6	267 (7.4)	PEGIFN α 2a 180 μ g/wk \times 48 wk (24)	69 (185)**	46 (123)	39 (103)**	45 (120)**	63
	41	264 (8.2)	IFN α 2a 6MU 3 \times /wk for 12wk then 3MU 3 \times /wk for 36wk (24)	28 (73)	39 (104)	19 (50)	25 (65)	55
Patients with cirrhosis								
Heathcote et al. ^[38]	47.2	96 (6.3) ⁱ	PEGIFN α 2a 90 μ g/wk for 48wk (24)	42 (40)**	35 (34)*	15 (14)	20 (19)	44 (27/61)
	47.1	87 (5.7) ^j	PEGIFN α 2a 180 μ g/wk for 48wk (24)	44 (38)**	39 (34)*	30 (26)**	34 (30)**	54 (37/68)*
	46.9	88 (6.3) ^k	IFN α 2a 3MU 3 \times /wk for 48wk (24)	14 (12)	22 (19)	8 (7)	15 (13)	31 (17/55)

a Patients had not been previously treated with interferon- α .

b PEGIFN α 2a and IFN α 2a were administered as subcutaneous injections.

c A virological response was defined as undetectable plasma levels of HCV RNA (lower limit of detection 100^[37,38] or 2000^[36] copies/ml at 24 weeks; 100 copies/ml at 72 weeks).^[36-38]

d Intention-to-treat data.

e A biochemical response was defined as the normalisation of previously elevated serum ALT levels.

f A histological response was defined as a ≥ 2 -point improvement in the histological activity index score.

g At baseline, bridging fibrosis was reported in 15, 5, 9 and 2% of patients in the PEGIFN α 2a 45, 90, 180 and 270 μ g groups, respectively, and in 18% of those in the IFN α 2a group.

h At baseline, bridging fibrosis was reported in 7 and 5% of patients in the PEGIFN α 2a and IFN α 2a groups, respectively; cirrhosis was reported in 4 and 10% of patients in the PEGIFN α 2a and IFN α 2a groups, respectively.

i 79% of patients had cirrhosis and 20% had bridging fibrosis.

j 79% of patients had cirrhosis and 21% had bridging fibrosis.

k 76% of patients had cirrhosis and 24% had bridging fibrosis.

HCV = hepatitis C virus; **MU** = mega units; **pts** = patients; **3 \times /wk** = three times a week. * $p \leq 0.05$; ** $p \leq 0.009$; *** $p \leq 0.00009$ vs IFN α 2a.

Peginterferon- α -2a (40kD) was administered as a subcutaneous injection once weekly for 48 weeks in all three trials. The virological and biochemical efficacy of study medication was assessed at the end of treatment and after a 24-week treatment-free follow-up period, to establish the durability of responses. The efficacy of various dosages of peginterferon- α -2a (40kD) was compared with interferon- α -2a, administered at a dosage of either 6MU three times a week for 12 weeks then 3MU (6/3MU) three times a week, or 3MU three times a week.

Criteria for inclusion in these trials included a positive test for anti-HCV antibody, an HCV RNA level of >2000 copies/ml [by polymerase chain reaction (PCR) assay] and a serum ALT level above the upper limit of normal on 2 occasions during the previous 2 months. A diagnosis of chronic hepatitis C was confirmed by liver biopsy during the year preceding enrolment into the trial.^[36-38] All or most patients had no histological evidence of cirrhosis or bridging fibrosis in two of the trials,^[36,37] and the other trial enrolled patients with a histological diagnosis of compensated cirrhosis or bridging fibrosis without clinical evidence of progressive disease.^[38] Exclusion criteria included neutropenia (neutrophil count $<1.5 \times 10^9/L$) and thrombocytopenia (platelet count $<90 \times 10^9/L$), a serum creatinine level >1.5 times the upper limit of normal, and alcohol/drug dependence during the preceding year.

The efficacy of peginterferon- α -2a (40kD) and interferon- α treatment was based on *virological*, *biochemical* and *histological* responses in all three studies. A virological response was defined as the percentage of patients with undetectable levels of HCV RNA at the end of treatment (week 48) measured by a sensitive PCR assay method (lower limit of detection 100 copies/ml^[37,38]) and after a further 24 week treatment-free follow-up period (i.e. week 72). In all three trials, the primary endpoint was the proportion of patients with a virological response (HCV RNA levels <100 copies/ml) at the 72-week evaluation; this was termed a 'sustained virological response'.

A biochemical response was defined as the normalisation of previously elevated ALT levels to

levels at or below the normal level at the end of the treatment period. A sustained biochemical response was defined as the normalisation of ALT levels at the 72-week assessment. A sustained biochemical response was a primary efficacy parameter in the two large comparative trials^[37,38] and was a secondary efficacy parameter in the dose-finding trial reported by Reddy et al.^[36]

Liver biopsies were performed to assess the histological response at week 72. This was a secondary endpoint in all three trials and was defined as a decrease of ≥ 2 points in the total score of the (Knodell^[39]) Histological Activity Index (HAI), where 0 = no inflammatory changes and no fibrosis and 22 = multilobular necrosis, marked intralobular degeneration and focal necrosis, marked portal inflammation and cirrhosis.^[37]

4.1 Virological Responses

A small dose-finding phase II trial was conducted by Reddy et al.^[36] (table II) to determine the most appropriate dosage of peginterferon- α -2a (40kD) for evaluation in subsequent larger comparative clinical trials. The optimal dosage, on the basis of sustained virological responses and adverse events (see section 6), appeared to be 180 $\mu\text{g}/\text{week}$.

In this trial, end-of-treatment and sustained virological responses were significantly ($p \leq 0.05$) higher in patients (most of whom did not have bridging fibrosis) treated with peginterferon- α -2a (40kD) 90, 180 or 270 $\mu\text{g}/\text{week}$ than in those treated with interferon- α -2a 3MU three times a week (table II).

Virological responses (intention-to-treat data) were 30, 45, 60 and 56% after 48 weeks of treatment with peginterferon- α -2a (40kD) 45, 90, 180 and 270 $\mu\text{g}/\text{week}$, compared with 12% in the interferon-treated patients (table II). At the 24-week follow-up evaluation, sustained virological responses were 10, 30, 36 and 29% in the 45, 90, 180 and 270 $\mu\text{g}/\text{week}$ peginterferon- α -2a (40kD) groups and 3% in the interferon- α -2a group.

End-of-treatment and sustained virological responses to peginterferon- α -2a (40kD) increased in a dose-dependent manner over the 45, 90 and 180

$\mu\text{g}/\text{week}$ dose range; no further improvement in response was observed in the recipients of the highest (270 $\mu\text{g}/\text{week}$) dose of peginterferon- α -2a (40kD). Patients with HCV genotypes other than type 1 at baseline had higher sustained virological responses than those with the HCV genotype 1 (statistical significance not reported) across all arms of the trial. In the 37 evaluable patients with HCV non-1 genotypes, sustained virological responses in the peginterferon- α -2a (40kD) 45, 90, 180 and 270 $\mu\text{g}/\text{week}$ groups were 20, 67, 50 and 67%, respectively; corresponding responses in the 97 evaluable patients with the HCV genotype 1 at baseline were 7, 14, 31 and 12%. None of the four patients with HCV non-1 genotypes and 1 of 25 patients with HCV genotype 1 treated with interferon- α -2a had a sustained virological response.

In the two large multinational trials reported by Zeuzem et al.^[37] and Heathcote et al.^[38] summarised in table II, virological responses (intention-to-treat results) were achieved in 69%^[37] of patients typical of a general population with chronic hepatitis C and 44%^[38] of patients with cirrhosis or bridging fibrosis at the end of treatment (week 48) with peginterferon- α -2a (40kD) 180 $\mu\text{g}/\text{week}$.^[37,38] At the 24-week follow-up evaluation, sustained virological responses in the peginterferon- α -2a (40kD) 180 μg groups were 39%^[37] and 30%.^[38] Virological responses both at the end of treatment and at long-term follow-up were significantly higher than those achieved with interferon- α 6/3MU or 3MU three times a week at the end of treatment (28%^[37] and 14%^[38]) and at the 24-week follow-up evaluation (19%^[37] and 8%^[38]). In a subsequent investigation that used transcription-mediated amplification (TMA),^[40] a different method for measuring HCV RNA in serum or plasma (limit of detection 50 copies/ml; 10 IU/ml) than PCR-based assay, residual HCV RNA was detected in 7 and 33% of end-of-treatment plasma samples from patients who had relapsed after treatment with peginterferon- α -2a (40kD) or interferon- α -2a, respectively, in the trial reported by Zeuzem et al.^[37] In patients with a sustained virological response, HCV RNA was detected (using TMA) in 3 of 78 end-of-treatment plasma samples and in none of

the end-of-treatment follow-up plasma samples from recipients of peginterferon- α -2a (40kD). Complete concordance between the TMA and PCR-based assay results for virological non-responders both at the end of treatment and at the end of follow-up was reported.^[40]

Peginterferon- α -2a (40kD) produced significantly higher end-of-treatment and sustained virological responses than interferon- α -2a in patients with chronic hepatitis C in the largest trial (number enrolled = 531; 360 completed the trial) conducted by Zeuzem et al. (table II).^[37] At baseline, most of the enrolled patients showed no histological evidence of cirrhosis; bridging fibrosis was reported in 7 and 5% of patients in the peginterferon- α -2a (40kD) and interferon- α -2a groups, respectively, and cirrhosis was present in 4 and 10% of patients in the two groups.

After 48 weeks of treatment with peginterferon- α -2a (40kD) 180 $\mu\text{g}/\text{week}$ or interferon- α -2a 6/3MU three times a week, end-of-treatment virological responses (intention-to-treat results) were 69 and 28% ($p = 0.001$); at the 24-week follow-up assessment, sustained virological responses were 39 and 19% ($p = 0.001$) [table II; figure 3].

All 103 patients in the peginterferon- α -2a (40kD) group with a sustained virological response had baseline plasma HCV RNA levels >10 000 copies/ml; 101 of these patients had either undetectable levels of HCV RNA or had a 100-fold decrease in HCV RNA levels after 12 weeks of therapy. Similarly, at the same timepoint, viral load had decreased by >2 log in 98% of patients in the interferon- α -2a group who had a sustained response.^[37] Sustained virological responses according to pretreatment HCV genotype are shown in table III.

In patients infected with HCV genotype 1 at baseline, sustained virological responses were achieved in significantly more patients in the peginterferon- α -2a (40kD) group than in the interferon- α -2a group (28 vs 7%; $p < 0.01$).^[41] Virological responses achieved in patients with compensated cirrhosis or bridging fibrosis treated with peginterferon- α -2a (40kD) 90 or 180 $\mu\text{g}/\text{week}$ were significantly higher than with interferon- α -2a 3MU three times

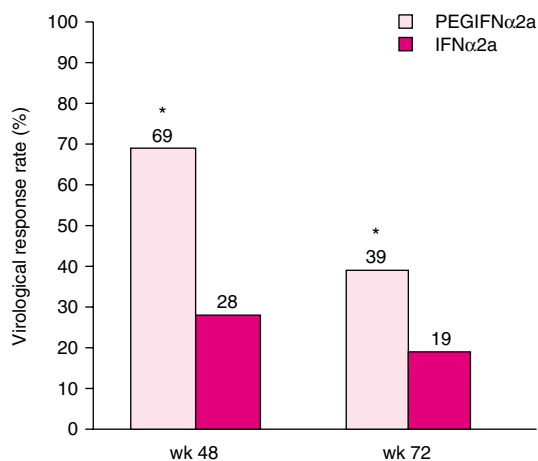


Fig. 3. Virological responses^a in patients with chronic hepatitis C^b after treatment with peginterferon- α -2a (40kD) [PEGIFN α 2a] or interferon- α -2a (IFN α 2a) [intention-to-treat data] in a nonblind, randomised, multicentre, comparative trial.^[37] Patients received either PEGIFN α 2a 180 μ g/week (n = 267) or IFN α 2a 6MU three times a week for 12 weeks then 3MU three times a week (n = 264); responses shown are those reported at the end of treatment (week 48) and at the follow-up evaluation (week 72).^[37] a Defined as undetectable plasma levels of HCV RNA (lower limit of detection 100 copies/ml).

b At baseline, bridging fibrosis was reported in 7 and 5% of patients in the PEGIFN α 2a and IFN α 2a groups, respectively; cirrhosis was reported in 4 and 10% of patients in the PEGIFN α 2a and IFN α 2a groups, respectively.

* p = 0.001 vs IFN α 2a.

a week in the trial reported by Heathcote et al. (table II).^[38] At week 48 (the end of treatment), 42 and 44% of recipients of peginterferon- α -2a (40kD) 90 and 180 μ g/week, respectively, and 14% of interferon- α -2a recipients had undetectable levels of HCV RNA in the plasma [p = 0.001 for both doses of peginterferon- α -2a (40kD) vs interferon- α -2a]. Although the two doses of peginterferon- α -2a (40kD) produced similar end-of-treatment responses, virological suppression was more durable in the recipients of the 180 μ g/week regimen; at the 72-week follow-up assessment, sustained virological responses in the peginterferon- α -2a (40kD) 90 and 180 μ g/week groups were, respectively, 15 (not statistically significant vs interferon- α -2a) and 30% (p = 0.001 vs interferon- α -2a) and 8% in the

interferon- α -2a group.^[38] Virological responses were similar among patients with cirrhosis and those with bridging fibrosis.

In the patients with a histological diagnosis of cirrhosis at baseline, virological responses were about 4-fold higher in the patients treated with peginterferon- α -2a (40kD) 180 μ g/week (32%) than in the interferon- α -2a treatment group (7%) [statistical significance not reported].^[38] As in patients with less advanced disease,^[37] sustained virological responses in the patients infected with HCV genotype 1 were higher (statistical significance not reported) in the patients treated with peginterferon- α -2a (40kD) 90 (5%) and 180 μ g/week (13%) than in the interferon- α -2a group (2%) [table III]. In patients with a combination of poor prognostic factors at baseline (i.e. infection with HCV genotype 1, viral load >2 000 000 copies/ml), the sustained virological response was higher in the peginterferon- α -2a (40kD) 180 μ g/week group than in the peginterferon- α -2a (40kD) 90 μ g/week group (10 vs 0%).^[38]

4.2 Biochemical Responses

As with virological responses, biochemical responses in the peginterferon- α -2a (40kD) treatment groups increased in a dose-dependent manner over the 45 to 180 μ g dose range in the dose-finding trial. The end-of-treatment and sustained response achieved with the 180 μ g/week dosage of peginterferon- α -2a (40kD) [38% at both evaluations] was significantly higher (p \leq 0.05) than responses obtained with interferon- α -2a treatment (15 and 9%; table II).^[36]

In the two larger trials, end-of-treatment biochemical responses were 46^[37] and 39%^[38] in the peginterferon- α -2a (40kD) 180 μ g/week treatment groups compared with 39 and 22% in the interferon- α -2a groups (intention-to-treat results) [table II]; sustained biochemical responses in the patients treated with peginterferon- α -2a (40kD) 180 μ g/week were significantly higher (p \leq 0.05) than sustained responses in the interferon- α treatment groups (table II).

After 48 weeks of treatment, end-of-treatment biochemical responses were reported in 46% of pa-

Table III. Sustained virological responses according to pretreatment HCV genotype in adults^a with chronic hepatitis C with or without cirrhosis who were treated with peginterferon- α -2a (40kD) [PEGIFN α 2a] or interferon- α -2a (IFN α 2a) in two nonblind randomised multicentre trials^[37,38,41] (see table II for overall sustained virological response rates)

Treatment regimen ^b (duration of follow-up)	Sustained virological response ^c (%)			
	HCV-1 ^d	HCV non-1 ^d	HCV-2 ^d	HCV-3 ^d
Patients with or without cirrhosis^{[41]e,f}				
PEGIFN α 2a 180 μ g/wk \times 48 wk (24)	28**		64	54*
IFN α 2a 6MU 3 \times /wk for 12wk then 3MU 3 \times /wk for 36wk (24)	7		50	32
Patients with cirrhosis or bridging fibrosis^{[38]e}				
PEGIFN α 2a 90 μ g/wk for 48wk (24)	5	29		
PEGIFN α 2a 180 μ g/wk for 48wk (24)	13 ^g	51		
IFN α 2a 3MU 3 \times /wk for 48wk (24)	2	15		

a Patients had not been previously treated with interferon- α .

b Study drugs were administered as subcutaneous injections.

c Defined as the percentage of patients with undetectable plasma levels of HCV RNA (<100 copies/ml) at wk 72 (i.e. 24 weeks after the end of treatment).

d Pretreatment HCV genotype. In the trial reported by Heathcote et al.,^[38] sustained virological responses (according to pretreatment genotype) were reported for patients with HCV-1 genotype and for patients with HCV genotypes other than 1 (or with no genotype data).

e See table II for further study details.

f Data were reported in an oral presentation of the trial reported by Zeuzem et al.^[37]

g The sustained virological response in this treatment group was higher in patients with HCV genotype 1b infection than in those with HCV genotype type 1a infection (20 vs 9%).

HCV = hepatitis C virus; * $p = 0.01$; ** $p < 0.01$ vs IFN α 2a.

tients treated with peginterferon- α -2a (40kD) 180 μ g/week and in 39% of recipients of interferon- α -2a 6/3MU three times a week in the trial reported by Zeuzem.^[37] At week 72, sustained biochemical responses were achieved in a significantly larger proportion of peginterferon- α -2a (40kD) than interferon- α -2a recipients (45 vs 25%; $p = 0.001$). In addition, a significantly greater proportion of patients in the peginterferon- α -2a (40kD) than in the interferon- α -2a group had both a sustained virological and biochemical response at the follow-up evaluation. Notably, in the peginterferon- α -2a (40kD) treatment group, sustained virological and biochemical responses were higher (64 and 67%, respectively) in patients with a virological but not a biochemical response at the end of treatment than in patients with both a virological and biochemical response at the end of treatment (50 and 60%, respectively).^[37]

In the trial reported by Heathcote et al.^[38] serum ALT levels had normalised in 35 and 39% of peginterferon- α -2a (40kD) 90 and 180 μ g/week recipients, respectively, by the end of treatment

and in 22% of patients treated with interferon- α -2a.^[38] Sustained biochemical responses were documented in 20% of patients who had been treated with peginterferon- α -2a (40kD) 90 μ g/week (non-significant vs interferon- α -2a), in 34% of patients in the peginterferon- α -2a (40kD) 180 μ g treatment group ($p = 0.004$ vs interferon- α -2a) and in 15% of patients in the interferon- α -2a arm. Percentages of patients with both a sustained biochemical and sustained virological response were the same as the percentages of patients with a sustained virological response.^[38]

4.3 Histological Responses

In the dose-finding trial, median total HAI scores had decreased from baseline (indicating improvements in liver histology) by 1, 2, 3 and 2 points in the peginterferon- α -2a (40kD) 45, 90, 180 and 270 μ g/week groups, respectively, at week 72; in the interferon- α -2a group, the HAI score had decreased by two points (statistical analyses not reported).^[36]

At the end of the follow-up period, 54 and 63% of patients (with paired liver biopsies) treated with peginterferon- α -2a (40kD) 180 μ g/week had a ≥ 2 -point improvement in HAI score in the two larger trials reported by Zeuzem et al.^[37] and Heathcote et al.^[38] (table II).

Almost half the patients (44 to 47%) without virological or biochemical responses (irrespective of treatment group) had histological responses at the 72-week assessment in the trial reported by Zeuzem et al.^[37] A larger proportion of patients with a virological response (but not a biochemical response) had a histological response than patients with both a virological and biochemical response at week 48 (79 vs 64%).

Histological responses with peginterferon- α -2a (40kD) or interferon- α -2a in patients with chronic hepatitis C and compensated cirrhosis or bridging fibrosis^[38] are shown in table II and figure 4.

A significantly larger proportion of patients treated with peginterferon- α -2a (40kD) 180 μ g/week than with interferon- α -2a had a histological response at 72 weeks (54 vs 31%; $p = 0.02$). A histological response was found to correlate with both sustained virological and biochemical responses.^[38]

Importantly, in addition to the beneficial histological effects produced by peginterferon- α -2a (40kD) in patients with or without cirrhosis who had a sustained virological response, peginterferon- α -2a (40kD) also produced histological responses in patients without a sustained virological response.^[38,42,43] Preliminary results reported in an abstract showed that the proportion of patients with a histological response (reported in 430 patients without a sustained virological response) in the two large multinational trials was higher in those who had received peginterferon- α -2a (40kD) 180 μ g [47% (21 of 45 patients)] than in the interferon- α -2a-treated patients [30% (28 of 94 patients)]; the between-group difference was not statistically significant ($p = 0.06$).^[42] In patients with cirrhosis (at baseline) who did not have a virological response, histological responses were 35, 33 and 26% in the peginterferon- α -2a (40kD) 180 μ g, peginterferon-

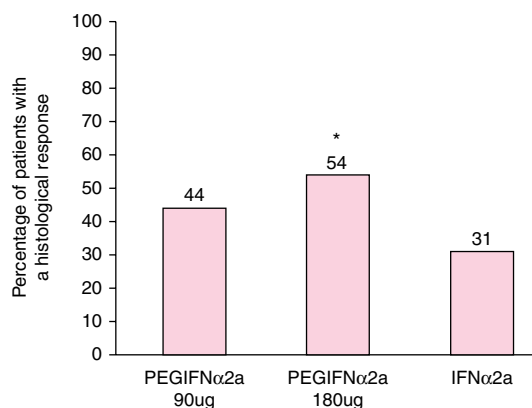


Fig. 4. Histological responses with peginterferon- α -2a (40kD) [PEGIFN α 2a] or interferon- α -2a (IFN α 2a) in patients with chronic hepatitis C and compensated cirrhosis in a nonblind, multicentre, comparative trial.^[38] Patients were randomised to receive PEGIFN α 2a 90 μ g ($n = 96$; n evaluable = 61) or 180 μ g ($n = 87$; n evaluable = 68) weekly, or IFN α 2a 3MU three times weekly ($n = 88$; $n = 55$) for 48 weeks. Histological response was defined as a ≥ 2 -point improvement in Histological Activity Index score 28 weeks after the end of treatment. * $p = 0.02$ vs IFN α 2a.

α -2a (40kD) 90 μ g and interferon- α -2a recipients, respectively, in the trial reported by Heathcote et al.^[38]

5. Quality of Life

The debilitating effects of chronic hepatitis C disease, as well as the adverse effects and frequent administration schedule of standard interferon- α therapy, can significantly impair health-related quality of life. Preliminary data reported in several abstracts indicate that peginterferon- α -2a (40kD) achieves superior results, during and after treatment, on various measures of quality of life in patients with chronic hepatitis C (including patients with cirrhosis) compared with interferon- α -2a alone^[44-46] or interferon- α -2b plus oral ribavirin.^[47,48]

Peginterferon- α -2a (40kD) was associated with a more marked increase in self-assessed health improvement [as measured by the standardised 36-question short form (SF-36) Health Survey] than interferon- α -2a in patients with chronic hepatitis C and cirrhosis.^[45] After 48 weeks of treatment with peginterferon- α -2a (40kD) or interferon- α -2a

and a 24-week post-treatment follow-up period, 48 and 26% of patients, respectively, reported feeling better or much better when asked to rate their general health at the time of questioning compared with one year before.^[45]

A pooled analysis of data from 1441 patients who participated in three randomised multinational comparative trials showed significant improvements in measurements of fatigue (using the Fatigue Severity Scale) [$p < 0.0001$ vs baseline] and SF-36 scores ($p = 0.0003$ to $p < 0.0001$ vs baseline) among patients with a sustained virological response. Among the subset of patients with cirrhosis who had a sustained virological response, significant improvements were reported in fatigue scores, in five of eight domains of the SF-36 scores and in SF-36 physical and mental component summary scores.

Notably, an analysis of quality of life during treatment found that peginterferon- α -2a (40kD) 180 μ g/week produced significantly less impairment in quality of life and less fatigue than interferon- α -2a 6/3MU three times weekly during the first 12 weeks of treatment.^[44] The assessments were made using the SF-36 and Fatigue Severity Scale at weeks 2 and 12 (evaluated patients were from the trial reported by Zeuzem et al.^[37]). Patients treated with peginterferon- α -2a (40kD) experienced more vitality, less disabling fatigue and fewer problems with work or other daily activities as a result of physical health and emotional problems than patients treated with standard interferon- α -2a during the initial 12 weeks of therapy.

Within the first 12 weeks of treatment, therapy-naive recipients of peginterferon- α -2a (40kD) experienced significantly better quality of life than recipients of interferon- α -2b plus oral ribavirin in a large ($n = 412$) comparative multicentre trial.^[47,48] Assessments using the Hepatitis Quality of Life Questionnaire indicated that patients treated with peginterferon- α -2a (40kD) had quality of life scores that were clinically and statistically superior to those in the interferon- α -2b/ribavirin group in eight of eight SF-36 domains, mental and physical summary scores and four chronic hepatitis C-specific domains.^[48]

6. Tolerability

The tolerability profile of subcutaneous peginterferon- α -2a (40kD) is broadly similar to that of subcutaneous interferon- α -2a in patients with chronic hepatitis C with adverse events and laboratory abnormalities typical of those documented with unmodified interferon- α .^[36-38,49]

6.1 General Adverse Events

Adverse events reported in patients receiving peginterferon- α -2a (40kD) monotherapy (at dosages of 45 to 270 μ g/week) in randomised, non-blind, comparative trials (table II) were typical of those produced by interferon- α in previous trials. Types of adverse events were similar in patients in the peginterferon- α -2a (40kD) and interferon- α -2a treatment groups. Adverse events in recipients of peginterferon- α -2a (40kD) were not dose-related in noncirrhotic patients^[36,37] (with the exception of rigors^[36]) or in patients with more advanced liver disease.^[38]

In the largest comparative trial conducted in patients with chronic hepatitis [most of whom showed no histological evidence of cirrhosis or bridging fibrosis at baseline (table II)], headache, fatigue, pyrexia, myalgia, rigors and alopecia were among the most common adverse events reported in patients receiving peginterferon- α -2a (40kD) 180 μ g/week. Adverse events reported in >10% of patients treated with either peginterferon- α -2a (40kD) or interferon- α -2a are shown in figure 5.^[37]

Although the tolerability profile of peginterferon- α -2a (40kD) was broadly similar to that of interferon- α -2a, incidences of most adverse events were generally lower with peginterferon- α -2a (40kD) than with interferon- α -2a.^[37] Psychiatric events were the most frequent serious adverse events and were noted in six patients treated with peginterferon- α -2a (40kD) [severe depression in four patients, personality disturbance in one patient and psychosis in one patient].^[37]

In patients with chronic hepatitis C and cirrhosis,^[38] the most common adverse events documented in recipients of peginterferon- α -2a (40kD) 180 μ g/week were fatigue (incidence 62%), headache (50%),

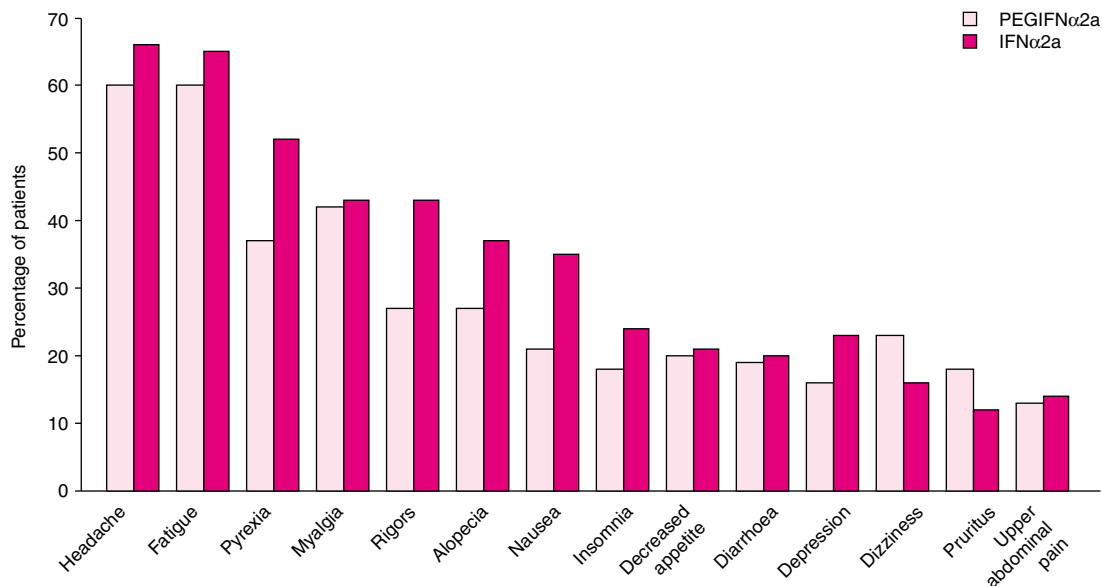


Fig. 5. Adverse events reported in patients with chronic hepatitis C (with or without cirrhosis) receiving treatment with peginterferon- α -2a (40kD) [PEGIFN α 2a] or interferon- α -2a (IFN α 2a) in a nonblind, multicentre, comparative trial.^[37] Patients were randomised to receive treatment with either PEGIFN α 2a 180 μ g/week (n = 267) or IFN α 2a 6MU three times a week for 12 weeks then 3MU three times a week (n = 264) for 48 weeks.

myalgia (51%), rigors (43%), pyrexia (38%) and nausea (34%). Incidences of these adverse events were generally similar in recipients of peginterferon- α -2a (40kD) 180 or 90 μ g/week or interferon- α -2a 3MU three times a week, although myalgia occurred in a larger proportion of patients treated with peginterferon- α -2a (40kD) 180 μ g/week (51%) than with peginterferon- α -2a (40kD) 90 μ g (36%) or interferon- α -2a (38%).^[38] Treatment was discontinued because of adverse events in 13, 7 and 8% of patients in the peginterferon- α -2a (40kD) 180 μ g, peginterferon- α -2a (40kD) 90 μ g and interferon- α -2a groups, respectively. One recipient of peginterferon- α -2a (40kD) 90 μ g and two recipients of peginterferon- α -2a (40kD) 180 μ g died after the end of treatment: two patients died of hepatic failure (179 and 420 days after the end of treatment) and the other died of a hepatic neoplasm 219 days after the end of treatment. A fourth patient died of a cerebral haemorrhage (after a suspected methadone overdose) 24 hours after the end

of treatment with peginterferon- α -2a (40kD) 180 μ g/week.

The relative tolerability of peginterferon- α -2a (40kD) or interferon- α -2b plus ribavirin treatment in therapy-naïve patients with chronic hepatitis C was assessed using the Work Productivity and Activity Impairment (WPAI) Instrument in a large (n = 412) comparative trial (see section 5).^[47,48] During the first 4 to 12 weeks of treatment, patients receiving interferon- α -2b plus ribavirin reported that they had missed 8.7 hours of work per week due to health versus 0.2 hours per week missed by recipients of peginterferon- α -2a (40kD) [results reported in an abstract]. In addition to lost hours, patients receiving interferon- α -2b plus ribavirin reported impaired productivity at work during 22.3% of working hours compared with 8.5% for those receiving peginterferon- α -2a (40kD). Overall, lost productivity per week was \$US117.20 vs \$US34.70 (1999 values) for the interferon- α -2b/ribavirin and peginterferon- α -2a (40kD) groups, respectively.^[47]

6.2 Laboratory Abnormalities

Interferon- α may produce undesirable adverse effects on bone marrow, thus limiting the use of the drug in some patients.^[38] Of particular note, exacerbation of cirrhosis-related neutropenia and thrombocytopenia has been observed in some patients with chronic hepatitis C receiving interferon- α .^[38] In the trial reported by Heathcote et al.,^[38] marked decreases in both neutrophil and platelet counts often occurred in recipients of peginterferon- α -2a (40kD) [180 or 90 μ g/week] or interferon- α -2a. Nevertheless, these effects were effectively managed by a reduction in dose. Mean neutrophil counts decreased in the three groups shortly after the start of treatment, but stabilised and then returned to baseline levels after the discontinuation of treatment. None of the patients in any of the three treatment arms discontinued treatment because of neutropenia; two patients only [in the peginterferon- α -2a (40kD) 180 μ g/week group] discontinued treatment because of thrombocytopenia. No patient developed hepatic decompensation or had a systemic infection or a serious haemorrhage.

In noncirrhotic patients with chronic hepatitis C,^[37] the neutrophil count decreased to $<0.5 \times 10^9/L$ in 12 patients receiving treatment with peginterferon- α -2a (40kD) and in four recipients of interferon- α -2a; none of these patients developed serious infections. The dose of study medication was modified because of the development of neutropenia in 11 and 7% of peginterferon- α -2a (40kD) and interferon- α -2a recipients, respectively. Anaemia was documented in three patients receiving peginterferon- α -2a (40kD) [one patient discontinued treatment because of this] and in none of the interferon- α -2a-treated patients. Thrombocytopenia was reported rarely in both treatment groups.

Dose-dependent decreases in median values of haemoglobin levels, platelet counts and neutrophil counts occurred across all treatment arms in the ascending-dose trial in noncirrhotic patients.^[36] Haemoglobin levels decreased to <120 g/L in the three peginterferon- α -2a (40kD) treatment groups,

but remained within the normal range throughout the trial. None of the trial participants discontinued treatment because of anaemia. Median platelet counts had stabilised 8 to 12 weeks after the start of treatment and had returned to normal values 4 weeks after the end of treatment (week 52).^[36] Neutrophil counts remained within the normal range in all treatment groups with the exception of the peginterferon- α -2a (40kD) 270 μ g/week group.

7. Dosage and Administration

The optimal dosage of subcutaneously administered peginterferon- α -2a (40kD) for the treatment of patients with chronic hepatitis C with or without cirrhosis was 180 μ g once weekly in the dose-finding trial reported by Reddy et al.^[36] Data are limited on the efficacy and tolerability of peginterferon- α -2a (40kD) in patients with chronic hepatitis C aged <18 years or >60 years. All of the interferons- α are contraindicated in patients with a history of major depressive illness, autoimmune disorders, thrombocytopenia or solid organ transplantation because of the risk of serious adverse events.^[4,50] Interferon- α is not recommended for the treatment of pregnant women with chronic hepatitis C.

8. Place of Peginterferon- α -2a (40kD) in the Management of Chronic Hepatitis C

Chronic hepatitis C is a major healthcare problem worldwide and has an estimated average global prevalence of 3%. The WHO estimates that 170 million people worldwide are infected with HCV, of whom up to 90% may progress to chronic liver disease.^[1] The disease typically progresses slowly, with about 15% of patients spontaneously recovering; 25% of patients remain asymptomatic, have normal serum ALT levels and histological lesions that are generally benign.^[3] Although most individuals with biochemical evidence of chronic hepatitis C have minimal fibrosis and mild or moderate necroinflammatory lesions, and will probably not develop liver disease, about 20% of patients develop advanced disease and may die of liver-related illnesses (e.g. cirrhosis, hepatocellu-

lar carcinoma) in 10 to 20 years.^[3] HCV accounts for a 70% prevalence of chronic hepatitis, 40% prevalence of end-stage cirrhosis, 60% prevalence of hepatocellular carcinoma and for 30% of liver transplants in industrialised countries.^[3] Combined direct and indirect costs of HCV infection in the US in 1997 were estimated to be \$US5.46 billion in a recent study.^[51]

Guidelines from the US Department of Human and Health Services recommend antiviral therapy for those patients with chronic hepatitis C who are at highest risk of developing cirrhosis, i.e. patients who are anti-HCV positive and have persistently increased serum ALT levels, detectable levels of HCV RNA and histological evidence of portal or bridging fibrosis, or inflammation and necrosis.^[4] Careful clinical monitoring is suggested as an alternative to antiviral therapy for patients with less severe histological changes in whom cirrhosis may not develop, and is also an option for patients with compensated cirrhosis (in the absence of ascites, jaundice, variceal haemorrhage or encephalopathy).

Since the mid 1980s, interferon- α monotherapy has been extensively evaluated in adults with chronic hepatitis C and has played an essential role in the management of the disease. During successful interferon- α therapy, elevated ALT levels decrease to normal and HCV RNA becomes undetectable in the plasma. The drug also has beneficial effects on liver histology, reducing necroinflammation and possibly controlling fibrosis. However, virological and biochemical responses achieved with interferon- α are less than ideal, with only about one-third of patients having a loss of detectable plasma HCV RNA after treatment with an optimal subcutaneous regimen of 3MU three times a week for 12 months. In addition, disease relapse is common and sustained virological responses of only 15 to 25% (often less than 20%) have been reported within 12 months (usually within 6 months) after the end of treatment.^[2-4,52]

The limited therapeutic efficacy of interferon- α in patients with chronic hepatitis C has been largely attributed to its pharmacokinetic characteristics. Interferon- α has a short plasma elimination half-life ($t_{1/2}$) [about 8 hours]. Although the drug can

be administered daily, it is usually given three times a week because of the inconvenience and high cost of daily administration. Thus, between each administration, plasma concentrations of the drug can decrease to low trough levels. Tolerability problems are also encountered with three-times-weekly administration of the drug, as this dosage schedule produces peak drug concentration/trough concentration cycles and a high incidence of peak concentration-related adverse effects.^[9-12]

The management of patients with chronic hepatitis C is generally based on recent consensus guidelines.^[1,3,6] Recent British clinical guidelines reported by Booth et al.^[1] and EASL guidelines (published in 1999)^[3] recommend that patients who have not previously received interferon- α therapy should be considered for combination therapy with interferon- α plus ribavirin. In addition, studies have shown that combination therapy with interferon- α plus ribavirin may be beneficial in patients relapsing on interferon- α monotherapy.^[53] and this treatment approach is also reflected in the British guidelines.^[1] Ribavirin is a synthetic guanosine analogue with a broad spectrum of activity against numerous DNA and RNA viruses. Although ribavirin shows only modest activity against HCV, it markedly increases the activity of interferon- α against HCV when the two agents are used in combination. Combination therapy with interferon- α and ribavirin for 6 to 12 months typically produces 2-fold higher sustained virological responses than interferon- α monotherapy in comparative clinical trials and is therefore currently the standard treatment for patients with chronic hepatitis C who have not received previous interferon- α therapy.^[4,50,54-56] This combination has been shown to produce sustained virological responses in about 40 to 50% of patients compared with 15 to 25% with interferon- α alone. However, as with interferon- α monotherapy, fewer than 30% of patients infected with HCV genotype 1 have a sustained virological response.^[4] Moreover, the combination is often not well tolerated. For example, anaemia, usually attributed to the ribavirin component of the regimen, occurs commonly. Combination therapy with interferon- α plus ribavirin is contraindicated

in patients with renal failure and in those who have received organ (other than liver) transplants.^[55]

Recently, research efforts have focused on the development and evaluation of well-tolerated treatment strategies that produce potent and sustained inhibition of HCV in patients at risk of disease progression and in those with a poor prognosis.

Peginterferon- α -2a (40kD), a new agent for the treatment of chronic hepatitis C, has a favourable pharmacokinetic profile, which is characterised by the rapid attainment of therapeutic plasma concentrations, a >100-fold reduction in clearance compared with that of interferon- α -2a and a $t_{1/2}$ that is almost 10-fold longer than that of interferon- α (section 3). The antiviral activity of the drug (as determined by OAS activity) is sustained for at least 168 hours in healthy adult volunteers (section 2).

Peginterferon- α -2a (40kD) demonstrated good efficacy in several randomised multicentre trials conducted in a total of 961 patients with chronic hepatitis C who had not received previous treatment with interferon- α . Of note, at baseline, a proportion of these patients had related compensated cirrhosis or bridging fibrosis,^[36-38] a population in whom treatment with interferon- α generally produces low response rates and a high incidence of adverse events (usually toxic effects on bone marrow).^[38] In these trials, virological responses were reported in 44 to 69% of patients with or without cirrhosis after 48 weeks of treatment with peginterferon- α -2a (40kD) 180 μ g weekly; sustained virological responses 24 weeks after the discontinuation of treatment ranged from 30 to 39%. Virological responses both at 48 weeks and at long-term follow-up were significantly higher in the peginterferon- α -2a (40kD) groups than in the recipients of interferon- α -2a 6/3MU or 3MU three times a week (12 to 28% at the end of treatment; 3 to 19% at follow-up 24 weeks after the discontinuation of treatment).

Virological responses produced after treatment with peginterferon- α -2a (40kD) 90 or 180 μ g/week were significantly higher than with interferon- α -2a 3MU three times a week in patients with compensated cirrhosis or bridging fibrosis in one of the trials (see section 4.1). At week 48, 42 and 44% of

recipients of peginterferon- α -2a (40kD) 90 and 180 μ g/week, respectively, and 14% of interferon- α -2a recipients had undetectable levels of HCV RNA in the plasma. Virological suppression was significantly more durable in patients who had been treated with the 180 μ g/week regimen than in recipients of interferon- α -2a; at the 72-week follow-up assessment, sustained virological responses were, respectively, 30% and 8%.^[38] Virological responses were similar among patients with cirrhosis and those with bridging fibrosis. Virological responses achieved in patients treated with peginterferon- α -2a (40kD) were similar to those previously reported in trials of 48 weeks of treatment with interferon- α plus ribavirin in patients with chronic hepatitis C.^[57-59] However, direct comparisons are required before definitive conclusions can be drawn regarding the relative efficacy of these two treatments.^[37] Nevertheless, these findings suggest that peginterferon- α -2a (40kD) monotherapy is a useful alternative to combination therapy with interferon- α plus ribavirin for patients unable to tolerate ribavirin.

Of note, a sustained virological response of 28% was reported in peginterferon- α -2a (40kD)-treated patients (with or without cirrhosis) infected with HCV genotype 1, a group in whom interferon- α generally produces virological response rates of <10%.^[37] There were no marked differences in sustained virological responses between patients infected with HCV subtype 1a and those infected with HCV subtype 1b.

Biochemical responses were also significantly higher in recipients of peginterferon- α -2a (40kD) 180 μ g weekly (including those with bridging fibrosis or cirrhosis) than in patients treated with the interferon- α -2a regimen (see section 4.2). At the end of treatment, previously elevated serum ALT levels had normalised in 38 to 46% in patients in the peginterferon- α -2a (40kD) 180 μ g once-weekly groups compared with 15 to 39% of patients treated with interferon- α -2a; biochemical responses at long-term follow-up ranged from 34 to 45% for peginterferon- α -2a (40kD) 180 μ g and from 9 to 25% for interferon- α -2a.^[36-38] Treatment with peginterferon- α -2a (40kD) also produced im-

provements in liver histology in patients with chronic hepatitis C with or without cirrhosis (see section 4.3). 54 and 63% of patients treated with peginterferon- α -2a (40kD) 180 μ g/week had a \geq 2-point improvement in HAI scores;^[37,38] the histological response tended to be higher in the trial that enrolled noncirrhotic patients plus a small proportion of patients with cirrhosis or bridging fibrosis than in patients with more advanced disease (63 vs 54%). Importantly, in addition to the beneficial histological effects produced by peginterferon- α -2a (40kD) in patients with or without cirrhosis who had a sustained virological response, peginterferon- α -2a (40kD) also produced histological responses (\geq 2-point improvement in the HAI score) in patients without a sustained virological response. In the trial that enrolled patients with cirrhosis or bridging fibrosis,^[38] peginterferon- α -2a (40kD) produced higher virological, biochemical or histological responses than interferon- α -2a; sustained responses were broadly similar to those reported in a study group that consisted largely of noncirrhotic patients.^[37]

Although only a few therapies are currently available for the treatment of patients with chronic hepatitis C, including peginterferon- α -2b alone or in combination with ribavirin, a number of new treatment strategies are undergoing evaluation. Triple therapy with interferon- α , amantadine plus ribavirin, dual therapy with pegylated interferon- α -2a (40kD) plus ribavirin, triple therapy regimens including peginterferon- α -2a (40kD), interferon- α plus thymalfasin (thymosin- α 1), and DNA vaccine strategies are among the treatments currently being investigated.^[3,60-63] However, none of these treatments have been directly compared with peginterferon- α -2a (40kD) monotherapy in phase III trials.

The tolerability profile of subcutaneous peginterferon- α -2a (40kD) is broadly similar to that of subcutaneous interferon- α -2a in patients with chronic hepatitis C with or without cirrhosis. Adverse events and laboratory abnormalities in recipients of peginterferon- α -2a (40kD) 180 μ g/week were typical of those documented with unmodified interferon- α (section 6). Headache, fatigue, py-

rexia, myalgia, rigors and alopecia were among the most common adverse events in patients with or without cirrhosis.

In conclusion, peginterferon- α -2a (40kD) administered once weekly produces significantly higher sustained responses, without compromising tolerability, than interferon- α -2a administered three times weekly in noncirrhotic or cirrhotic patients with chronic hepatitis C, including those infected with HCV genotype 1 – a group in whom interferon- α treatment has usually been unsuccessful. Peginterferon- α -2a (40kD) is a valuable new treatment option that appears poised to play an important role in the first-line treatment of patients with chronic hepatitis C, including difficult-to-treat patients, such as those with compensated cirrhosis and/or those infected with HCV genotype 1.

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