ADIS DRUG EVALUATION

Drugs 2003; 63 (7): 701-730
0012-6667/03/0007-0701/$33.00/0

Peginterferon-α-2a (40kD) Plus Ribavirin

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

Gillian M. Keating and *Monique P. Curran*

Adis International Limited, Auckland, New Zealand

Various sections of the manuscript reviewed by:

F. Bonino, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy; ***W. Cassidy***, Louisiana State University, Health Science Center, Baton Rouge, Louisiana, USA; ***P. Ferenci***, Department of Internal Medicine IV, University of Vienna, Vienna, Austria; ***S.K. Herrine***, Division of Gastroenterology and Hepatology, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, USA; ***G.V. Papatheodoridis***, Second Department of Internal Medicine, University of Athens School of Medicine, Athens, Greece; ***G. Ramadori***, Department of Internal Medicine, Georg-August University Gottingen, Gottingen, Germany.

Data Selection

Sources: Medical literature published in any language since 1980 on peg-interferon-alpha-2a plus ribavirin, identified using Medline and EMBASE, 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 Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.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: Medline search terms were 'interferon alpha 2a' and ('peg$' or 'polyethylene glycols') and 'ribavirin'. EMBASE search terms were 'alpha 2a interferon' and 'peg$' and 'ribavirin'. AdisBase search terms were ('peg-interferon-alpha-2a' or 'RO-253036') and 'ribavirin'. Searches were last updated 21 Feb 2003.

Selection: Studies in patients with chronic hepatitis C who received peginterferon-α-2a plus ribavirin. 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, ribavirin, chronic hepatitis C, pharmacodynamics, pharmacokinetics, therapeutic use.

Contents

Summary

Abstract

Pegylation of interferon-α-2a is associated with improved sustained virological response rates in patients with chronic hepatitis C. Subsequently, combination therapy with peginterferon-α-2a (40kD) [Pegasys®[1]] and ribavirin (Copegus™, Rebetol®) was investigated to establish if the efficacy of peginterferon-α-2a (40kD) monotherapy could be further enhanced. Subcutaneous peginterferon-α-2a (40kD) was administered at a dosage of 180μg once weekly and oral ribavirin was usually administered at a dosage of 1000 or 1200 mg/day.

In treatment-naive patients with chronic hepatitis C, the sustained virological response rate (assessed 24 weeks after the end of a 48-week treatment period) was significantly higher in peginterferon-α-2a (40kD) plus ribavirin recipients than in peginterferon-α-2a (40kD) plus placebo recipients or interferon-α-2b plus ribavirin recipients (56% vs 29% and 44%). Retrospective analysis revealed that peginterferon-α-2a (40kD) plus ribavirin recipients who did not achieve an early virological response were unlikely to achieve a sustained response.

Treatment with peginterferon-α-2a (40kD) plus another antiviral agent (ribavirin, mycophenolate mofetil, amantadine, or ribavirin and amantadine) was beneficial in patients with chronic hepatitis C who had relapsed during or after, or had not responded to, treatment with interferon-α-2b plus ribavirin. In the relapse study, sustained virological response rates in recipients of peginterferon-α-2a (40kD) plus ribavirin were 45% with and 38% without amantadine.

Peginterferon-α-2a (40kD) plus ribavirin appears beneficial in patients with chronic hepatitis C considered difficult to treat (e.g. patients infected with

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

hepatitis C virus genotype 4, African-American patients, patients with advanced fibrosis or cirrhosis and patients co-infected with HIV).

Flu-like symptoms and depression occurred significantly less frequently with peginterferon-α-2a (40kD) plus ribavirin than with interferon-α-2b plus ribavirin. Similar proportions of patients receiving peginterferon-α-2a (40kD) plus ribavirin, peginterferon-α-2a (40kD) plus placebo and interferon-α-2b plus ribavirin withdrew from treatment because of laboratory abnormalities or other adverse events.

In conclusion, combination therapy comprising subcutaneous peginterferon-α-2a (40kD) and oral ribavirin is an important new treatment option for chronic hepatitis C. Peginterferon-α-2a (40kD) plus oral ribavirin is significantly more effective than peginterferon-α-2a (40kD) monotherapy or interferon-α-2b plus ribavirin at inducing a sustained virological response in treatment-naive patients with chronic hepatitis C. Preliminary data suggest that peginterferon-α-2a (40kD) plus ribavirin is also beneficial in treatment-experienced patients and in patients who have traditionally been considered difficult to treat. Combination therapy with peginterferon-α-2a (40kD) and oral ribavirin is poised to become a valuable first-line treatment option in chronic hepatitis C.

Pharmacodynamic Properties

The antiviral activity of interferon-α-2a (determined according to serum 2′, 5′-oligoadenylate synthetase activity) is augmented by pegylation. The first phase of the decline in hepatitis C virus (HCV) RNA levels in patients with chronic hepatitis C treated with once-weekly peginterferon-α-2a (40kD) 180μg occurs within the first 48 hours and is probably due to inhibition of HCV replication and degradation of the free virus; the second phase is characterised by a stable exponential decay possibly related to the rate of degradation of the infected cells. The first and second phases of viral decline were significantly larger in patients infected with HCV non-1 genotypes than in those infected with HCV genotype 1 (patients received peginterferon-α-2a [40kD] or interferon-α-2a).

Viral decline was also HCV genotype-dependent in recipients of peginterferon-α-2a (40kD) plus ribavirin: a biphasic viral decline was observed in 92% of 60 patients infected with HCV genotypes 2 or 3, but in only 44% of 104 patients infected with HCV genotype 1. In addition, early viral kinetics in patients infected with HCV genotype 4 who received peginterferon-α-2a (40kD) in combination with ribavirin were similar to those of patients infected with HCV genotype 1. In patients with chronic hepatitis C infected with HCV genotype 1, viral decay after 28 days' treatment was significantly more rapid in patients treated with peginterferon-α-2a (40kD) in combination with ribavirin than that in patients treated with peginterferon-α-2a (40kD) alone. In addition, mean viral load after 12 weeks' therapy was significantly lower in patients with chronic hepatitis C who received peginterferon-α-2a (40kD) 180μg once weekly plus ribavirin 1000 or 1200 mg/day than in patients who received peginterferon-α-2b (12kD) 1 μg/kg once weekly plus ribavirin 1000 or 1200 mg/day (2.8 vs 3.9 $\log_{10}$ IU/mL).

Ribavirin inhibits several viruses *in vitro* and *in vivo*. *In vitro* studies suggest that several mechanisms may account for the antiviral action of ribavirin (e.g. the depletion of intracellular guanosine pools and inhibition of viral RNA polymerase). However, in clinical trials in patients with chronic hepatitis C, oral ribavirin monotherapy had a negligible effect on serum HCV RNA levels. Ribavirin may

alter the helper T-cell response in favour of a type 1 response. The addition of ribavirin to phytohaemagglutinin-stimulated peripheral blood mononuclear cells isolated from patients with chronic hepatitis C resulted in a decrease in the synthesis of interferon-γ, inhibition of total DNA, RNA and protein synthesis, and apoptosis of CD45+ and CD14+ cells.

Treatment with peginterferon-α-2a (40kD) alone or with ribavirin for 48 weeks induced a vigorous, multispecific, sustained, HCV-specific, CD4+ T-helper 1 response in therapy-naive patients with chronic hepatitis C (patients had weak or no HCV-specific CD4+ T-cell responses before treatment); a multispecific response is characterised by a response to multiple (core and nonstructural) HCV antigens. In comparison, the HCV-specific, CD4+ T-cell response in interferon-α-2a recipients was of lower magnitude, more narrowly focused and, in the majority of patients, short lived. In patients who achieved a sustained virological response, the frequency, vigour and breadth of the HCV-specific, CD4+ T-cell response was significantly greater than in patients who relapsed or had a partial or no response to treatment. Patients who achieved a sustained response had high interferon-γ and low interleukin (IL)-4 and IL-10 production.

Pharmacokinetic Properties

Data regarding the pharmacokinetics of peginterferon-α-2a (40kD) and ribavirin when administered as combination therapy are lacking (although no pharmacokinetic interaction between these two drugs was observed in a substudy of a large clinical trial).

Peginterferon-α-2a (40kD)

Pegylation slows the absorption rate of interferon-α; in healthy volunteers, the mean time (t_{max}) taken to reach the maximum serum concentration (C_{max}) was 78 hours for peginterferon-α-2a (40kD) and 10 hours for interferon-α. In patients with chronic hepatitis C, C_{max} values of 15.4 and 25.6 μg/L were reached after single and multiple (once weekly) doses of peginterferon-α-2a (40kD) 180μg; t_{max} values were 80 and 45 hours. Steady-state serum concentrations were reached 5–8 weeks after the initiation of a once-weekly regimen.

In healthy volunteers, the clearance of peginterferon-α-2a (40kD) after a single 180μg dose was >100-fold lower than that of interferon-α (dose not stated) [0.08 vs 11.8 L/h] and the terminal elimination half-life ($t_{1/2}$) of peginterferon-α-2a (40kD) was almost 9-fold longer than that of interferon-α (77 vs 9 hours). Total body clearance values for patients with chronic hepatitis C after single and multiple (once weekly for 48 weeks) doses of peginterferon-α-2a (40kD) 180μg were 0.08 and 0.06 L/h.

The absorption of a single dose of subcutaneous peginterferon-α-2a (40kD) 180μg was slower in healthy elderly men than in healthy younger men (t_{max} 116 vs 81 hours). Although the elderly men had a greater systemic exposure to the drug than the younger men (area under the serum concentration-time curve [AUC] of 1.66 vs 1.30 mg • h/L), this was not considered clinically significant. The $t_{1/2}$ of peginterferon-α-2a (40kD) was longer in the elderly than in the younger men (110 vs 61 hours).

The pharmacokinetics of peginterferon-α-2a (40kD) in patients with various degrees of renal impairment were not appreciably different from those in patients with normal renal function, although clearance of the drug was reduced by

25–45% in patients with end-stage renal disease undergoing haemodialysis. The pharmacokinetics of peginterferon-α-2a (40kD) were similar in patients with chronic hepatitis C who did and did not have cirrhosis.

The clearance of theophylline was reduced in healthy volunteers receiving multiple doses of peginterferon-α-2a (40kD).

Ribavirin

Ribavirin is rapidly and extensively absorbed following oral administration. However, because of first-pass metabolism, the mean absolute bioavailability was 64% in patients with chronic hepatitis C. There was a linear relationship between ribavirin dose (200–1200mg) and AUC from time zero to the final timepoint (AUC_{tf}) and a curvilinear relationship between ribavirin dose and C_{max}. In patients with chronic hepatitis C, mean C_{max} values after single or multiple (twice daily) doses of ribavirin 600mg were 782 and 3680 μg/L (reached after 1.7 and 3 hours) and AUC_{tf} values were 13.4 and 228.0 mg • h/L. Steady-state plasma concentrations were attained in about 4 weeks (oral ribavirin 600mg twice daily). Oral ribavirin has a large volume of distribution (2825L) and shows no detectable binding to plasma proteins.

Metabolism of ribavirin occurs via a reversible phosphorylation pathway in nucleated cells and a degradative pathway which yields a triazole carboxylic acid metabolite. The principal route of elimination for both ribavirin and its triazole metabolites is renal. The $t_{1/2}$ of ribavirin after a single oral dose of 600mg was 43.6 hours. The mean $t_{1/2}$ value of 298 hours obtained after discontinuation of multiple doses of ribavirin 600mg most likely reflects the high tissue affinity of the drug and its slow elimination from nonplasma compartments.

In individuals without chronic hepatitis C administered a single oral dose of ribavirin 400mg, the ribavirin AUC_{tf} was 3-fold higher in patients with a creatinine clearance of 0.6–1.8 L/h (10–30 mL/min) than in healthy volunteers. Ribavirin was not effectively removed by haemodialysis.

In patients with varying degrees of hepatic dysfunction, the pharmacokinetics of oral ribavirin 600mg administered as a single dose were not significantly different from those in healthy volunteers, apart from mean C_{max} values which were significantly lower in healthy volunteers than in patients with mild, moderate or severe hepatic impairment.

Therapeutic Efficacy

A number of studies have examined the efficacy of combination therapy with peginterferon-α-2a (40kD) and ribavirin in patients with chronic hepatitis C. Most of these studies are currently only available as abstracts or posters. In most studies, patients received subcutaneous peginterferon-α-2a (40kD) 180μg once weekly in combination with oral ribavirin 1000 or 1200 mg/day (depending on bodyweight) for 48 weeks. The primary endpoint in most studies was the sustained virological response rate (assessed 24 weeks after the cessation of therapy and defined as an undetectable HCV RNA level).

Forty-eight weeks' treatment with peginterferon-α-2a (40kD) plus ribavirin induced a significantly ($p < 0.001$) higher sustained virological response rate (56%) than peginterferon-α-2a (40kD) plus placebo (29%) or interferon-α-2b plus ribavirin (44%) in treatment-naive patients with chronic hepatitis C ($n = 1121$) in a randomised, multicentre, fully published study. Retrospective analysis of this study suggested that peginterferon-α-2a (40kD) plus ribavirin recipients

who do not achieve an early virological response at 12 weeks are unlikely to achieve a sustained virological response. Another analysis of this study found that peginterferon-α-2a (40kD) plus ribavirin recipients had better health-related quality of life than interferon-α-2b plus ribavirin recipients, as assessed by the Short Form-36 Health Survey and the Fatigue Severity Scale.

Preliminary results from a randomised, multicentre study indicate that in patients infected with HCV non-1 genotypes, 24 weeks' therapy with peginterferon-α-2a (40kD) in combination with ribavirin is as effective as 48 weeks' therapy, and a lower dosage of ribavirin (800 mg/day) is as effective as the standard dosage (1000 or 1200 mg/day) with regards to sustained virological response. However, in patients infected with HCV genotype 1, the sustained virological response rate was highest in patients who received treatment with peginterferon-α-2a (40kD) and the higher dosage of ribavirin for 48 weeks.

The addition of amantadine to peginterferon-α-2a (40kD) plus ribavirin was examined in treatment-naive patients with chronic hepatitis C in two studies. After 24 weeks' treatment, patients had biochemical response rates of 63% and 76% and virological response rates of 76% and 65%.

Combination therapy with peginterferon-α-2a (40kD) and another antiviral agent (ribavirin 800–1000 mg/day, mycophenolate mofetil 1g twice daily, amantadine 100mg twice daily, or ribavirin plus amantadine) was beneficial in patients with chronic hepatitis C who had relapsed during or after, or had not responded to, treatment with interferon-α-2b in combination with ribavirin. In the relapse study, sustained virological response rates of 45% and 38% were seen in recipients of peginterferon-α-2a (40kD) plus ribavirin with or without amantadine, respectively; a sustained biochemical response rate was observed in 16–55% of patients across all treatment groups. In the nonresponse study, the end-of-treatment virological response rate at 48 weeks was 11–40%.

The use of combination therapy with peginterferon-α-2a (40kD) and ribavirin has been examined in a number of patient groups that have traditionally been considered difficult to treat. In patients infected with HCV genotype 4, peginterferon-α-2a (40kD) in combination with ribavirin was associated with numerically higher end-of-treatment (week 48) virological response rates than interferon-α-2a plus ribavirin, interferon-α-2b plus ribavirin or peginterferon-α-2a (40kD) plus placebo, in two analyses. In one of these analyses, the sustained virological response rate was 77% in peginterferon-α-2a (40kD) plus ribavirin recipients, 44% in peginterferon-α-2a (40kD) plus placebo recipients and 42% in interferon-α-2b plus ribavirin recipients.

An end-of-treatment (week 48) virological response was reported in 33% of non-Hispanic African-American patients and 54% of Caucasian patients (intent-to-treat analysis) who received peginterferon-α-2a (40kD) in combination with ribavirin (patients were infected with difficult-to-treat HCV genotype 1). A biochemical response occurred in 51% and 50% of patients, respectively.

In treatment-naive patients with chronic hepatitis C and advanced fibrosis or cirrhosis, combination therapy with peginterferon-α-2a (40kD) and ribavirin 600–1200 mg/day was associated with a virological response rate of 89% after 24 weeks' treatment. A sustained virological response occurred in 43% of peginterferon-α-2a (40kD) plus ribavirin recipients, 21% of peginterferon-α-2a

(40kD) plus placebo recipients and in 33% of interferon-α-2b plus ribavirin recipients in a subgroup analysis of the fully published trial that included treatment-naive patients with cirrhosis. In treatment-experienced patients with chronic hepatitis C and advanced cirrhosis/fibrosis, 18% of patients who had not responded to previous treatment with interferon or interferon plus ribavirin achieved a sustained virological response after 48 weeks' combination therapy with peginterferon-α-2a (40kD) and ribavirin.

Combination therapy with peginterferon-α-2a (40kD) and ribavirin was associated with a significantly ($p = 0.0003$) higher virological response rate after 24 weeks' treatment than interferon-α-2a plus ribavirin (44% vs 15%) in patients with chronic hepatitis C who were co-infected with HIV. In another trial in patients who were co-infected with HCV and HIV and who had not responded to prior treatment with interferon-α, 5 of 13 (38%) peginterferon-α-2a (40kD) monotherapy recipients and 4 of 17 (24%) peginterferon-α-2a (40kD) plus ribavirin 800 mg/day recipients achieved a virological response after a mean 24 weeks' therapy.

Tolerability

Flu-like symptoms (e.g. pyrexia, myalgia and rigor) and depression occurred significantly ($p \leq 0.02$) less frequently in peginterferon-α-2a (40kD) plus ribavirin recipients than in interferon-α-2b plus ribavirin recipients in a fully published study (incidence of 22–43% vs 30–56%). Clinical adverse events such as fatigue, headache, insomnia, nausea, dermatitis, alopecia and irritability occurred with similar frequency in the two treatment groups (21–54% vs 18–55%).

Similar proportions of patients receiving peginterferon-α-2a (40kD) plus ribavirin, peginterferon-α-2a (40kD) plus placebo and interferon-α-2b plus ribavirin withdrew from treatment because of laboratory abnormalities (1–3%) or other adverse events (6–10%). Occurrence of a laboratory abnormality such as anaemia, neutropenia or thrombocytopenia resulted in modification of the dosage of peginterferon-α-2a (40kD) in 25% of patients and ribavirin in 24% of patients who received this combination, of peginterferon-α-2a (40kD) in 24% of patients and placebo in 4% of patients who received this combination and of interferon-α-2b in 8% of patients and ribavirin in 19% of patients who received this combination.

In clinical studies, <1% of peginterferon-α-2a (40kD) plus ribavirin recipients required dosage modification or discontinued therapy because of an increase in alanine aminotransferase (ALT) levels. Abnormalities in thyroid function tests that required clinical intervention occurred in 4.9% of combination therapy recipients.

Dosage and Administration

Combination therapy with peginterferon-α-2a (40kD) and ribavirin is approved in the EU for use in the treatment of adults with histologically proven chronic hepatitis C who have elevated serum transaminase levels and who are serum HCV RNA-positive, including patients with compensated cirrhosis; treatment is indicated both in treatment-naive patients and in patients relapsing after an initial response with interferon-α. In the US, combination therapy with peginterferon-α-2a (40kD) and ribavirin is approved for use in adults with chronic hepatitis C who have compensated liver disease and who have not previously received interferon-α.

The recommended dosage of peginterferon-α-2a (40kD) is 180μg administered once weekly by subcutaneous injection. It is recommended that ribavirin be administered orally (with food) at a dosage of 1000 or 1200 mg/day according to bodyweight (US prescribing information recommends that patients infected with HCV genotypes 2 or 3 receive ribavirin 800 mg/day). The recommended duration of the combination treatment is 48 weeks in patients infected with HCV genotypes 1 or 4, although patients infected with HCV genotypes 2 or 3 may be treated for only 24 weeks. Treatment discontinuation may be considered at 12 weeks in patients who fail to achieve an early virological response, particularly if they do not have cirrhotic disease.

A reduction in the dosage of peginterferon-α-2a (40kD) or ribavirin, or treatment discontinuation, may be needed in certain patient populations (e.g. patients with end-stage renal disease) or in patients who experience certain adverse events (e.g. neutropenia, thrombocytopenia, anaemia or increased ALT levels). Dosage reduction is not necessary when starting treatment with peginterferon-α-2a (40kD) in elderly patients. The use of peginterferon-α-2a (40kD) in patients with decompensated cirrhosis (i.e. patients with Child-Pugh class B or C disease or bleeding oesophageal varices) has not been evaluated.

In the EU and the US, contraindications to the use of peginterferon-α-2a (40kD) plus ribavirin include autoimmune hepatitis and hepatic decompensation; combination therapy is also contraindicated in neonates and infants and in women who are pregnant and men whose partners are pregnant (because ribavirin has been shown to have teratogenic and/or embryocidal effects). At least two forms of effective contraception should be used during combination therapy and for 6 months after discontinuing ribavirin treatment. Additional contraindications in the EU include a history of severe pre-existing cardiac disease, severe hepatic dysfunction, some psychiatric conditions and lactation. Combination therapy is also contraindicated in the US in patients with haemoglobinopathies. US prescribing information recommends that peginterferon-α-2a (40kD) be used with caution in patients with pre-existing cardiac disease, autoimmune disorders or a history of depression and that ribavirin should not be administered to patients with severe renal impairment (creatinine clearance <3 L/h [<50 mL/min]).

Standard haematological, biochemical and thyroid function tests should be performed before starting combination therapy and should be repeated periodically during treatment (women of childbearing potential should also be screened for pregnancy). Patients with pre-existing cardiac disorders should have an ECG performed before starting treatment.

Patients with chronic hepatitis C who are co-infected with HIV should be closely monitored and treatment should be discontinued in patients who progress to a Child-Pugh score of ≥7. Combination therapy should not be commenced in patients with a Child-Pugh score of ≥6 at baseline.

Serum theophylline levels should be monitored, and the dosage of theophylline adjusted as required, in patients receiving theophylline in addition to combination therapy with peginterferon-α-2a (40kD) and ribavirin. Combination therapy with ribavirin and didanosine is not recommended, and the use of ribavirin in combination with stavudine or zidovudine should be avoided.

1. Introduction

Chronic hepatitis C is a common condition, with a global prevalence averaging 1–2%.[1] It is estimated that approximately 170 million people worldwide are infected with hepatitis C virus (HCV).[2,3] Approximately 85% of patients with HCV infection go on to develop chronic disease and, of these patients, up to 20% will eventually develop cirrhosis, which may lead to liver failure and hepatocellular carcinoma.[4-6] Indeed, deaths due to cirrhosis and the incidence of hepatocellular carcinoma are increasing in both the US and the UK.[1] Moreover, chronic hepatitis C is the leading cause of liver transplantation in the US and Western Europe.[1-3]

HCV is an RNA virus belonging to the Flaviviridae family.[2] Six major HCV genotypes (1–6) along with multiple subtypes (a, b, c) have been identified.[2,7] Patients in the US and Western Europe are most likely to have genotype 1a or 1b HCV infection, followed by genotypes 2 and 3.[2,6] Genotype 1 is generally associated with lower response rates to antiviral treatment than genotypes 2 or 3.[2,7]

The established goal of treatment in patients with chronic hepatitis C is sustained virological response. Patients who achieve a sustained virological response have a low likelihood of late virological relapse. Moreover, it appears that the absence of detectable virus may translate into benefits such as resolution of liver injury and a reduction in hepatic fibrosis as well as a reduced risk of developing hepatocellular carcinoma.[8]

Although interferon-α has been a mainstay of treatment in chronic hepatitis C for a number of years, monotherapy is associated with low response rates in the long term, with <20% of patients achieving a sustained virological response.[4] Pegylated interferons such as peginterferon-α-2a (40kD) [Pegasys®] were developed in order to overcome the limitations of conventional interferon-α. Peginterferon-α-2a (40kD) comprises recombinant interferon-α-2a, synthesised in *Escherichia coli*, conjugated to an inert 40kD polyethylene glycol (PEG) polymer.[9] The PEG moiety protects the interferon-α-2a molecule from proteolytic degradation and reduces its immunogenicity.[10,11] Because of its large size, peginterferon-α-2a (40kD) has reduced renal clearance (section 3.1.2) which results in prolonged systemic exposure, allowing once-weekly administration.[3,10] In chronic hepatitis C, peginterferon-α-2a (40kD) monotherapy is associated with higher sustained virological response rates than interferon-α-2a monotherapy, as recently reviewed in *Drugs*.[12]

Ribavirin (Copegus™, Rebetol®) is a synthetic guanosine analogue that has shown antiviral activity against a variety of DNA and RNA viruses, including viruses of the Flaviviridae family.[13] Adding ribavirin to interferon-α monotherapy has been shown to improve sustained virological response rates, and combination therapy with conventional interferon-α and ribavirin was the standard of care for the treatment of chronic hepatitis C in the late 1990s.[13] Subsequently, combination therapy comprising pegylated interferons and ribavirin has become a focus of attention. This review examines the role of peginterferon-α-2a (40kD) plus ribavirin in the treatment of chronic hepatitis C.

2. Pharmacodynamic Properties

This section summarises data from previous reviews of peginterferon-α-2a (40kD)[12] (administered alone) and ribavirin (administered with or without interferon-α-2b)[13] published in *Drugs*. In addition, the antiviral (section 2.1) and immunomodulatory (section 2.2) properties of peginterferon-α-2a (40kD) and ribavirin administered in combination are outlined. The mechanism of action responsible for the enhanced therapeutic efficacy observed with peginterferon-α-2a (40kD) plus ribavirin combination therapy compared with peginterferon-α-2a (40kD) monotherapy (section 4.1.1) has not been firmly established.

Several of these studies are only available as abstracts or posters.[14-21]

2.1 Antiviral Activity

2.1.1 Peginterferon-α-2a (40kD)

Interferon-α binds to the cell surface receptors of virus-infected cells, inducing the release of more than 20 effector proteins (e.g. 2′, 5′-oligoadenylate synthetase [OAS], double-stranded RNA-dependent protein kinase and Mx proteins).[12,22,23] These proteins inhibit viral replication and/or function at various stages.[12,23-25]

The antiviral activity of interferon-α-2a (determined according to serum OAS activity) is augmented by pegylation. Following administration of a single subcutaneous dose of peginterferon-α-2a (45, 135 or 270μg) or conventional interferon-α-2a (3 or 18MU), the activity of OAS increased with dose in healthy volunteers (number not stated).[15] Peak serum OAS activity was reached approximately 48 hours after administration of peginterferon-α-2a, and remained near to the peak level for up to 1 week. In contrast, serum OAS levels declined rapidly after reaching a mean peak level 24 hours after administration of interferon-α-2a.[15]

Maximum OAS activity was lower in healthy elderly volunteers (aged >60 years; n = 12) than in younger volunteers (aged 18–25 years; n = 12) who received peginterferon-α-2a (40kD),[16] indicating that elderly individuals are less sensitive to the induction of OAS by this agent. Moreover, the level and duration of peginterferon-α-2a (40kD)-induced OAS activity was less in patients with severe renal impairment (creatinine clearance 1.2–2.4 L/h [20–40 mL/min]) [n = 6] than in patients with milder renal impairment (creatinine clearance >2.4 L/h [>40 mL/min]) or without renal impairment (n = 24).[17]

The decline in HCV RNA levels in patients with chronic hepatitis C treated with once-weekly peginterferon-α-2a (40kD) 180μg (n = 17) has been characterised by two phases.[26] The first phase of decline (probably representing treatment-induced inhibition of HCV replication and degradation of the free virus) occurs within the first 48 hours. The second phase is characterised by a relatively stable exponential decay that is thought to be related to the rate of degradation of the infected cells.[26] Moreover, the rate of viral decline was HCV-genotype dependent in recipients of peginterferon-α-2a (40kD) or interferon-α-2a (combined analysis), with the first ($p = 0.045$) and second ($p < 0.001$) phases of viral decline being significantly larger in patients infected with HCV non-1 (mostly 2 or 3) genotypes than in those infected with HCV genotype 1.[26]

2.1.2 Ribavirin

Ribavirin inhibits several viruses *in vitro* and *in vivo*.[27,28] Moreover, ribavirin directly inhibits replication of an HCV replicon in Huh7 hepatoma cells; a ribavirin concentration of 15 μmol/L inhibited replication by 50%.[18] Inhibition was not reversible.[18]

The mechanisms by which ribavirin exerts its antiviral effects are not clearly understood. *In vitro* studies suggest that several mechanisms may account for the antiviral action of the drug, including the depletion of intracellular guanosine pools and inhibition of viral RNA polymerase.[27]

However, in clinical trials in patients with chronic hepatitis C, oral ribavirin monotherapy had a negligible effect on serum HCV RNA levels and/or transient effects on serum alanine aminotransferase (ALT) levels.[29-34] Almost all patients relapsed following completion of therapy.

2.1.3 Peginterferon-α-2a (40kD) Plus Ribavirin

Ribavirin did not appear to affect early viral kinetics in patients infected with HCV genotype 1 who were also treated with peginterferon-α-2a (40kD).[19] In a viral kinetics study, patients were treated for 48 weeks with peginterferon-α-2a (40kD) 180μg once weekly without (n = 17) or with ribavirin 1000 or 1200 mg/day (n = 10). The median degradation rate of free virus was 1.73 and 2.74/day during the first phase of viral decay, and 0.05 and 0.16/day during the second phase of viral decay, respectively. After 28 days, viral decay was significantly more rapid in patients treated with peginterferon-α-2a (40kD) plus ribavirin than in patients treated with peginterferon α-2a (40kD) alone ($p < 0.001$), suggesting that ribavirin has a weak and/or a delayed antiviral effect.[19]

Mean viral load after 12 weeks' therapy was significantly lower in patients with chronic hepatitis C who received peginterferon-α-2a (40kD) 180μg once weekly in combination with ribavirin 1000 or 1200 mg/day (n = 10) than in patients who received peginterferon-α-2b (12kD) 1 μg/kg once weekly plus ribavirin 1000 or 1200 mg/day (n = 12) [2.8 vs 3.9 $\log_{10}$ IU/mL; $p < 0.01$].[14] No significant between-group difference in viral load was seen at 1 or 4 weeks. It has been suggested that the difference in viral kinetics between the two pegylated interferons may reflect the differing pharmacokinetic properties of the two drugs[14,35] (it should also be noted that the recommended dosage of peginterferon-α-2b [12kD] for use in combination with ribavirin is 1.5 μg/kg/week).[36]

As in patients treated with peginterferon-α-2a (40kD) alone (see section 2.1.1), the viral decline was HCV genotype-dependent in recipients of combination therapy with peginterferon-α-2a (40kD) and ribavirin.[20] In recipients of peginterferon-α-2a (40kD) plus ribavirin (dosages not stated), a biphasic viral decline was observed in 92% of 60 patients infected with HCV genotype 2 or 3, but in only 44% of 104 patients infected with HCV genotype 1. Moreover, 38% of patients infected with HCV genotype 1, but only 3% of patients infected with HCV genotype 2 or 3, had a triphasic pattern of viral decline.[20] In addition, early viral kinetics in patients infected with HCV genotype 4 who received peginterferon-α-2a (40kD) 180μg once weekly in combination with ribavirin 1000–1200 mg/day were similar to those in patients infected with HCV genotype 1.[21]

2.2 Immunomodulatory Effects

2.2.1 Ribavirin

Oral ribavirin 1000–1200 mg/day had no effect on serum interleukin (IL)-12, IL-4 or interferon-γ levels in patients with chronic hepatitis C in a retrospective analysis[34] of a 24-week randomised, double-blind, placebo-controlled study.[30] On the other hand, several *in vivo* and *in vitro* studies indicate that ribavirin may alter the helper T-cell response in favour of a type 1 response.[34,37,38]

The addition of ribavirin to phytohaemagglutinin-stimulated peripheral blood mononuclear cells isolated from patients with chronic hepatitis C resulted in a decrease in the synthesis of interferon-γ, inhibition of total DNA, RNA and protein synthesis, and apoptosis of CD45+ and CD14+ cells.[39]

2.2.2 Peginterferon-α-2a (40kD) ± Ribavirin

Results obtained from a subset of therapy-naive patients with chronic hepatitis C who were enrolled in two randomised studies (and who had a weak or no HCV-specific CD4+ T-cell response before treatment) indicate that 48 weeks' treatment with peginterferon-α-2a (40kD) alone or in combination with ribavirin induced a vigorous, multispecific, sustained, HCV-specific, CD4+ T-helper 1 response (a multispecific response is characterised by a response to multiple [core and nonstructural] HCV antigens).[40] In comparison, the HCV-specific CD4+ T-cell response in interferon-α-2a recipients was of lower magnitude, more narrowly focused and, in the majority of patients, short lived. Patients received interferon-α-2a 6MU three times a week for 12 weeks then 3MU three times a week for 36 weeks (n = 14), peginterferon-α-2a (40kD) 180 μg/week for 48 weeks (n = 14) or peginterferon-α-2a (40kD) 180 μg/week in combination with ribavirin 800–1200 mg/day for 48 weeks (n = 14).

A sustained virological response (defined as undetectable HCV RNA levels 24 weeks after the end of therapy) occurred in 14% of interferon-α-2a recipients, 42% of peginterferon-α-2a (40kD) recipients and 57% of peginterferon-α-2a (40kD) plus ribavirin recipients.[40] In these patients, the frequency, vigour and breadth of the HCV-specific, CD4+ T-cell response was significantly greater than in patients who relapsed or had a partial response ($p < 0.01$) or in patients who did not respond ($p < 0.001$). Patients who achieved a sustained response had high interferon-γ and low IL-4 and IL-10 production.

3. Pharmacokinetic Profile

This section outlines the pharmacokinetic properties of peginterferon-α-2a (40kD) and ribavirin administered as monotherapy; data regarding the pharmacokinetics of these drugs when adminis-

Table I. Summary of mean pharmacokinetic parameters of peginterferon-α-2a (40kD) and ribavirin in adult patients with chronic hepatitis C; each drug was administered as monotherapy

Parameter	Peginterferon-α-2a (40kD)[42]a		Ribavirin[45]b	
	single dose (n = 14)	multiple doses (n = 16)	single dose (n = 12)	multiple doses (n = 12)
t_{max} (h)	80	45	1.7[c]	3
C_{max} (μg/L)	15.4[d]	25.6[d,e]	782[f]	3680[f]
AUC (mg • h/L)	1.82[d,g]	3.33[d,g]	13.4[f,h]	228.0[f,h]
$t_{½}$ (h)			43.6	298
F (%)			64[i]	
Vd (L)			2825[i]	
CL (L/h)	0.08	0.06	38.2	

a Peginterferon-α-2a (40kD) 180μg was administered subcutaneously as single or multiple (once weekly for 48 weeks) doses.

b Ribavirin 600mg was administered orally as single or multiple (twice daily; duration not stated) doses.

c Evaluated in 11 patients.

d Serum.

e At steady state.

f Plasma.

g Assessed from 0–168 hours.

h Assessed from 0 hours to the last measurable ribavirin concentration.

i Data obtained from a single-dose pharmacokinetic study using ^{14}C-labelled ribavirin 600mg in five patients.

AUC = area under the serum/plasma concentration-time curve; **C_{max}** = maximum serum/plasma drug concentration; **CL** = total clearance; **F** = oral bioavailability; **$t_{½}$** = terminal elimination half-life; **t_{max}** = time to reach C_{max}; **Vd** = volume of distribution.

tered as combination therapy are lacking (although no pharmacokinetic interaction between peginterferon-α-2a [40kD] and ribavirin was observed in a substudy of a large clinical trial).[9] Most of the studies reported in this section are available as abstracts.[16,17,41-44]

3.1 Peginterferon-α-2a (40kD)

This section summarises data from a previous review of peginterferon-α-2a (40kD) published in *Drugs*,[12] and includes data from more recently published studies.

3.1.1 Absorption and Distribution

Peginterferon-α-2a (40kD) is well absorbed after single subcutaneous doses in healthy volunteers,[46] or single or multiple subcutaneous doses in patients with chronic hepatitis C.[42]

In healthy volunteers, the mean maximum serum concentration (C_{max}) after a single subcutaneous dose of peginterferon-α-2a (40kD) 180μg (n = 10) or interferon-α (dose not stated; n = 34) was 14.2 μg/L versus 13.4 IU/mL.[41] Pegylation of interferon-α results in a slower absorption rate; the mean time taken to reach C_{max} (t_{max}) was 78 hours for peginterferon-α-2a (40kD) and 10 hours for interferon-α. The mean absorption time (time required for 50% of the dose to be absorbed) was 59 and 2.6 hours in the corresponding treatment groups.[41] Sixty-one percent of the peginterferon-α-2a (40kD) dose was absorbed compared with 80% of the interferon-α dose.[41]

In patients with chronic hepatitis C, C_{max} values of 15.4 and 25.6 μg/L were reached after single and multiple doses of peginterferon-α-2a (40kD); t_{max} values were 80 and 45 hours[42] (see table I for drug dosage and study design details). Steady-state serum concentrations were reached 5–8 weeks after the initiation of a once-weekly regimen. Peginterferon-α-2a (40kD) displays restricted biodistribution in patients with chronic hepatitis C.[42]

3.1.2 Metabolism and Elimination

Data concerning the metabolism of peginterferon-α-2a (40kD) are lacking, although in rats the majority of radiolabelled peginterferon-α-2a (40kD) was excreted via the kidney.[9]

Because of its large size and branched nature, peginterferon-α-2a (40kD) undergoes reduced renal clearance compared with that of interferon-α-2a,

thus prolonging exposure to the pegylated interferon.[12]

In healthy volunteers, the clearance of peginterferon-α-2a (40kD) after a single 180μg dose was >100-fold less than that of interferon-α (dose not stated) [0.08 vs 11.8 L/h] and the terminal elimination half-life ($t_{1/2}$) of peginterferon-α-2a (40kD) was almost 9-fold longer than that of interferon-α (77 vs 9 hours).[41]

Total body clearance values for patients with chronic hepatitis C after single and multiple doses of peginterferon-α-2a (40kD) were 0.08 and 0.06 L/h, respectively (table I).[42]

3.1.3 Special Patient Populations

The absorption of a single dose of subcutaneous peginterferon-α-2a (40kD) 180μg was slower in healthy elderly men aged >60 years (n = 12; t_{max} 116 hours) than in healthy younger men aged 18–25 years (n = 12; t_{max} 81 hours).[16] C_{max} values were similar in elderly and young men. The elderly had a greater systemic exposure to the drug than younger men (the area under the serum concentration-time curve [AUC] was 1.66 vs 1.30 mg • h/L); however, this was not considered clinically significant. The $t_{1/2}$ of peginterferon-α-2a (40kD) was longer in healthy elderly men than in healthy younger men (110 vs 61 hours).

The absorption and distribution of peginterferon-α-2a (40kD) was not altered in patients with various degrees of renal impairment (patients with the most severe renal impairment had creatinine clearance values of 1.2–2.4 L/h [20–40 mL/min]), compared with patients with normal renal function.[17] Total body clearance ranged from 0.08–0.118 L/h and $t_{1/2}$ ranged from 76–117 hours. However, the clearance of peginterferon-α-2a (40kD) was reduced by 25–45% in patients with end-stage renal disease undergoing haemodialysis and the starting dosage of the drug should be reduced in patients with end-stage renal disease (section 6).[9]

The pharmacokinetics of peginterferon-α-2a (40kD) appear similar in patients with chronic hepatitis C who do or do not have cirrhosis (Child-Pugh grade A).[9] In patients with chronic hepatitis C and cirrhosis, the $t_{1/2}$ after administration of multiple weekly doses of peginterferon-α-2a (40kD) 90 or 180μg was 70–90 hours.[43]

Data are lacking concerning the pharmacokinetics of peginterferon-α-2a (40kD) in paediatric patients.[47]

3.1.4 Potential Drug Interactions

Peginterferon-α-2a (40kD) showed no significant effects on drug metabolism mediated by cytochrome P450 (CYP) 2C9, 2C19, 2D6 and 3A4 isoenzymes in healthy volunteers. However, in a manner similar to that of interferon-α-2a, the clearance of theophylline (metabolised by CYP1A2) was reduced in volunteers receiving multiple doses of peginterferon-α-2a (40kD)[44] [section 6].

3.2 Ribavirin

This section summarises the pharmacokinetics of ribavirin when administered as monotherapy, as previously reviewed in *Drugs*.[13] The majority of data have been obtained from prescribing information[45] and a review article.[48]

3.2.1 Absorption and Distribution

Ribavirin is rapidly and extensively absorbed following oral administration (table I). However, because of first-pass metabolism, the mean absolute bioavailability was 64% in patients with chronic hepatitis C who received a single dose of oral ribavirin 600mg.[45]

There was a linear relationship between ribavirin dose (200–1200mg) and AUC from time zero to the final timepoint (AUC_{tf}) [the final timepoint is defined as the last measurable ribavirin concentration].[45] The relationship between ribavirin dose and C_{max} was curvilinear. In patients with chronic hepatitis C, mean C_{max} values after single or multiple (twice daily) ribavirin 600mg doses were 782 and 3680 μg/L and were reached after 1.7 and 3 hours. Respective values for AUC_{tf} were 13.4 and 228.0 mg • h/L (table I). The mean steady-state plasma concentration of oral ribavirin (600mg twice daily) was attained in about 4 weeks (2200 μg/L).[45,48]

The AUC_{tf} and C_{max} of ribavirin increased by 70% when a single oral dose of ribavirin was admin-

istered with a high-fat meal. Thus, ribavirin should be administered with food (section 6).[45]

The volume of distribution (Vd) of ribavirin following oral administration was large (2825L), confirming the high tissue affinity of this drug (table I).[45] It has been suggested that the high Vd in nonplasma compartments is a reflection of the mechanism of uptake of the drug into cells by membrane transporters, which are present on most types of cells. Ribavirin shows no detectable binding to plasma proteins.[45,48]

3.2.2 Metabolism and Elimination

Metabolism of ribavirin occurs via two pathways: a reversible phosphorylation pathway in nucleated cells and a degradative pathway which yields a triazole carboxylic acid metabolite.[45] The principal route of elimination for both ribavirin and its triazole metabolites is renal.[48] After oral administration of a single dose of ^{14}C-labelled ribavirin 600mg, about 61% of the radioactivity was excreted in the urine and 12% in the faeces during a 336-hour period; 17% of the administered dose is excreted unchanged in the urine.[45]

The $t_{1/2}$ of ribavirin after a single oral dose of 600mg was 43.6 hours. The lengthy mean $t_{1/2}$ value for ribavirin (298 hours) obtained after discontinuation of administration of multiple doses of ribavirin 600mg is likely to reflect the high tissue affinity of the drug and its slow elimination from nonplasma compartments.[45,48]

Following a single oral dose of ribavirin 600mg, the mean total clearance was 38.2 L/h in patients with chronic hepatitis C (see table I).[45]

3.2.3 Special Patient Populations

In individuals without chronic hepatitis C administered a single oral dose of ribavirin 400mg, the ribavirin AUC_{tf} was 3-fold higher in patients with a creatinine clearance of 0.6–1.8 L/h (10–30 mL/min) than in healthy volunteers (creatinine clearance >5.4 L/h [>90 mL/min]).[45] Ribavirin was not effectively removed by haemodialysis and its use is not recommended in patients with severe renal impairment (creatinine clearance <3 L/h [<50 mL/min]) [section 6].

Pharmacokinetic values (apart from C_{max} values) of oral ribavirin 600mg administered as a single dose in patients with varying degrees of hepatic dysfunction were not significantly different from those in healthy volunteers.[49] Mean C_{max} values were significantly lower in healthy volunteers (643 μg/L; $p = 0.029$) than in patients with mild (886 μg/L), moderate (1048 μg/L) or severe (1273 μg/L) hepatic dysfunction.[49]

The pharmacokinetics of ribavirin have not been examined in paediatric or elderly patients.[45]

3.2.4 Potential Drug Interactions

Ribavirin does not induce or inhibit any CYP isoenzymes.[48] No pharmacokinetic interactions have been observed between ribavirin and theophylline.[48]

The ribavirin AUC_{tf} was reduced by 14% when ribavirin was coadministered with an antacid containing magnesium, aluminium and simethicone. Although this reduction is unlikely to be clinically relevant, this has yet to be confirmed in further studies.[45,48]

4. Therapeutic Efficacy

A number of trials have examined the efficacy of combination therapy with subcutaneous peginterferon-α-2a (40kD) and oral ribavirin in patients with chronic hepatitis C. Most of these trials were of randomised, controlled, multicentre design.[50-61] In one randomised controlled trial, the ribavirin dosage was blinded throughout the study and the duration of treatment was blinded until week 24;[51] in another randomised controlled trial, the administration of ribavirin was blinded although peginterferon-α-2a (40kD) and interferon-α-2b were administered in a nonblind manner.[50] Several other studies were of nonblind design[55-61] and the degree of blinding was not stated in the remaining randomised, controlled trials.

Only one trial has been fully published;[50] the rest are available as abstracts or posters.[51-64] Most of the studies available as abstracts or posters did not state p values when reporting results.

Across the different trials, patients had a mean age of approximately 41–50 years.[50-57,60-63] Inclu-

sion criteria included chronic hepatitis C[50-64] that was biopsy proven,[50-52,57-61,63] detectable HCV RNA levels[51,52,58,59,61,63] and elevated ALT levels.[50-52,54-56,59-63] In these studies, 45–100% of patients were infected with HCV genotype 1,[50-56,59-64] although one study assessed the efficacy of peginterferon-α-2a (40kD) in combination with ribavirin in patients infected with HCV genotype 4[57] (section 4.3.1). Exclusion criteria included neutropenia,[50] thrombocytopenia,[50,63] anaemia,[50,51,63] HIV co-infection,[50,51,60] hepatitis B,[51,60] decompensated liver disease,[50,51,60] psychiatric disease that was not well controlled,[50] an elevated serum creatinine level (>1.5 times the upper limit of normal),[50] Child-Pugh score ≥7 points,[63] a previous complication of cirrhosis (e.g. variceal haemorrhage, ascites or hepatic encephalopathy),[63] alcohol or drug dependence[50,63] and substantial coexisting medical conditions.[50,51,63] In individual trials, patients generally appeared well matched across treatment groups with regards to baseline disease characteristics (e.g. age, ALT levels, baseline viral load, HCV genotype and histological diagnosis); in one trial examining the effect of treatment duration and ribavirin dosage on virological response rate, more patients infected with HCV genotype 1 who had high viral titres were deliberately randomised to receive 48, rather than 24, weeks' therapy.[51]

Unless stated otherwise, the dosage of subcutaneous peginterferon-α-2a (40kD) administered in these trials was 180μg once weekly, and ribavirin was administered orally at a dosage of 1000 mg/day to patients weighing ≤75kg and 1200 mg/day to patients weighing ≥75kg (treatment arms in several studies included patients receiving ribavirin 600–800 mg/day,[59] 800 mg/day[51,57,60,64] or 800–1000 mg/day[55,56]). In most studies, patients received treatment for 48 weeks and were then followed for another 24 weeks.[50,52-57,59,62]

The primary endpoint in most studies was the sustained virological response rate, assessed 24 weeks after the cessation of therapy and defined as an undetectable HCV RNA level.[50-57,59,60] However, this endpoint has not yet been reported in a number of studies; these studies are ongoing and only preliminary data are available. Thus, reported endpoints include virological response rates after 12, 24 or 48 weeks' therapy (virological response was defined as an undetectable HCV RNA level unless specified otherwise).[52-55,57,59,60,62,64] In one study, the primary endpoint was the virological response rate after 24 weeks' therapy.[58] Biochemical response (defined as the normalisation of serum ALT levels) was also reported in some studies.[53,54,56,57,62] Histological response was generally not assessed/reported in these trials.

Additional analyses of two of the previously-mentioned trials[50,51] have also been conducted and are available as abstracts or posters.[65-69]

4.1 In Treatment-Naive Patients

4.1.1 Virological Responses

Combination therapy with peginterferon-α-2a (40kD) and ribavirin was significantly more effective than peginterferon-α-2a (40kD) plus placebo ($p < 0.001$) or subcutaneous interferon-α-2b 3MU three times weekly plus ribavirin ($p < 0.001$) at inducing a sustained virological response (primary endpoint; response rates 56%, 29% and 44%, respectively) in treatment-naive patients with chronic hepatitis C (table II), according to the results of a fully published study in 1121 patients.[50] Similarly, the end-of-treatment virological response rate at 48 weeks was significantly higher in peginterferon-α-2a (40kD) plus ribavirin recipients than in peginterferon-α-2a (40kD) plus placebo recipients ($p = 0.01$) or interferon-α-2b plus ribavirin recipients ($p < 0.001$) [table II].

As expected, virological response rates were higher in patients infected with HCV genotypes 2 or 3 than in patients infected with HCV genotype 1. A sustained virological response occurred in significantly more peginterferon-α-2a (40kD) plus ribavirin recipients than interferon-α-2b plus ribavirin recipients in patients infected with either HCV genotype 1 ($p = 0.01$) or HCV genotypes 2 or 3 ($p = 0.005$) [figure 1].[50]

Additional analyses found that sustained virological response rates were lower in patients enrolled in centres in the US than in patients enrolled

Table II. Virological response rates in treatment-naive patients with chronic hepatitis C. Results of two randomised, controlled trials in which patients were treated for 48wk and were followed up for a subsequent 24wk

Reference	Treatment regimen[a]	No. of patients randomised (mean plasma HCV RNA level at baseline [copies/mL])	Virological response rate[b] (% of patients)		Sustained virological response rate[c] (% of patients)
			after 12wk treatment	after 48wk treatment	
Fried et al.[50]	PEGIFNα2a 180μg qw + RIB 1000 or 1200 mg/day	453 (6.0×10^6)	86	69*†	56**†
	PEGIFNα2a 180μg qw + PL	224 (5.9×10^6)		59	29
	IFNα2b 3MU tiw + RIB 1000 or 1200 mg/day	444 (6.0×10^6)		52	44
Ideo et al.[52]d	PEGIFNα2a 180μg qw + RIB 1000 or 1200 mg/day	93 (765 $\log_{10}$)	67		
	PEGIFNα2a 180μg qw + AMA 200 mg/day	88 (772 $\log_{10}$)	55		

a All interferons were administered subcutaneously; other treatments were administered orally.

b Defined as an undetectable HCV RNA level, except for the 12wk assessment in Fried et al.[50] when a virological response was defined as an undetectable HCV RNA level or a ≥2-$\log_{10}$ decrease from baseline in HCV RNA level.

c Assessed 24wk after the cessation of therapy and defined as an undetectable HCV RNA level.

d Poster.

AMA = amantadine; **HCV** = hepatitis C virus; **IFNα2b** = interferon-α-2b; **PEGIFNα2a** = peginterferon-α-2a (40kD); **PL** = placebo; **qw** = once weekly; **RIB** = ribavirin; **tiw** = three times weekly; * p = 0.01, ** p < 0.001 vs PEGIFNα2a + PL; † p < 0.001 vs IFNα2b + RIB.

in centres outside of the US.[70] For example, among patients infected with HCV genotype 1, the sustained virological response rates in peginterferon-α-2a (40kD) plus ribavirin recipients, peginterferon-α-2a (40kD) plus placebo recipients and interferon-α-2b plus ribavirin recipients were 31%, 11% and 29% in US centres and 54%, 28% and 42% in non-US centres. This was attributed to patients in the US being more likely to have poor prognostic variables such as higher bodyweight, older age or cirrhosis. Exploratory analyses found that geographic region did not in itself significantly contribute to treatment response.

Another study has examined the effect of duration of treatment and ribavirin dosage on the sustained virological response rate.[51] In this study, treatment-naive patients with chronic hepatitis C were randomised to receive peginterferon-α-2a (40kD) plus ribavirin 800 mg/day for 24 (n = 207) or 48 weeks (n = 361) or peginterferon-α-2a (40kD) plus ribavirin 1000 or 1200 mg/day for 24 (n = 280) or 48 weeks (n = 436). Results indicate that in patients infected with HCV non-1 genotypes, sustained virological response rates were similar regardless of the ribavirin dosage or the duration of treatment.[51] In patients with HCV genotype 1 infection, the sustained virological response rate was highest in patients who received combination therapy with peginterferon-α-2a (40kD) and the higher dosage of ribavirin for 48 weeks.

The finding that 48 weeks' therapy with peginterferon-α-2a (40kD) plus ribavirin 1000 or 1200 mg/day is the optimal regimen in patients infected with HCV genotype 1[51] is supported by preliminary data from another trial.[60] In this study, patients with undetectable HCV RNA levels after 24 weeks' treatment with peginterferon-α-2a (40kD) plus ribavirin 800 mg/day were randomised at week 26 to a further 22 weeks' treatment with peginterferon-α-2a (40kD) plus ribavirin (n = 180) or peginterferon-α-2a (40kD) monotherapy (n = 180). The rate of virological breakthrough was 2.7% and 11.4% in combination therapy and monotherapy recipients at the end of treatment and 14.3% and 34.3% 12 weeks after the end of treatment.[60]

Retrospective analysis[65] of the fully published study[50] revealed that peginterferon-α-2a (40kD) plus ribavirin recipients who did not achieve an early virological response (defined as an undetectable HCV RNA level or a ≥2-$\log_{10}$ decrease from baseline in the HCV RNA level after 12 weeks' treatment; table II) appeared unlikely to achieve a

sustained virological response. Sixty-three of the 453 peginterferon-α-2a (40kD) plus ribavirin recipients did not achieve an early virological response and 61 of these patients (97%) did not achieve a sustained virological response. Moreover, the sustained virological response rate was higher among patients who achieved an early virological response and who adhered to study treatment (>80% adherence) than among patients who achieved an early virological response but did not adhere to study treatment (<80% adherence) [75% vs 48%].[65] The ability of early (week 12) virological response to predict the sustained virological response rate in recipients of peginterferon-α-2a (40kD) plus ribavirin (n = 194) is being examined in another ongoing trial.[61] Results to date indicate that 53% and 90.3% of patients infected with HCV genotype 1 or HCV genotypes 2 or 3 had undetectable HCV RNA levels after 12 weeks' therapy and 64.5% and 91.3% had undetectable HCV RNA levels after 24 weeks' therapy.

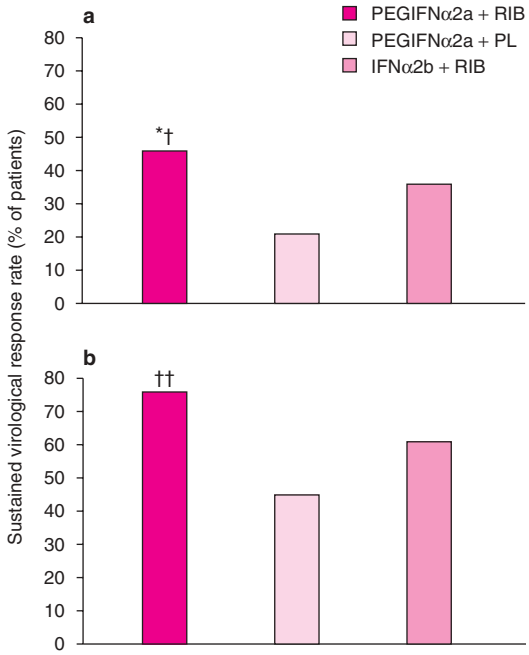

Fig. 1. Sustained virological response rates in patients with chronic hepatitis C infected with HCV genotype 1 (**a**) or HCV genotypes 2 or 3 (b).[50] Patients were randomised to receive SC peginterferon-α-2a (40kD) [PEGIFNα2a] 180μg once weekly plus oral ribavirin (RIB) 1000 or 1200mg once daily (according to bodyweight), PEGIFNα2a + placebo (PL), or SC interferon-α-2b (IFNα2b) 3MU three times weekly + RIB, for 48 weeks; 298, 145 and 285 patients, respectively, had genotype 1 HCV infection and 140, 69 and 145 patients, respectively, had genotype 2 or 3 HCV infection at baseline. Sustained response was assessed 24 weeks after stopping therapy. In (**b**), it was not stated if the difference between PEGIFNα2a plus RIB and PEGIFNα2a plus PL recipients was statistically significant. **HCV** = hepatitis C virus; **SC** = subcutaneous; * $p < 0.001$ vs PEGIFNα2a + PL; † $p = 0.01$, †† $p = 0.005$ vs IFNα2b + RIB.

The early (week 12) virological response rate was 67% in peginterferon-α-2a (40kD) plus ribavirin recipients and 55% in peginterferon-α-2a (40kD) plus amantadine 200 mg/day recipients in an ongoing trial in treatment-naive patients with chronic hepatitis C (table II).[52] Approximately 58% of patients were infected with HCV genotypes 1 or 4. Among these patients, the early virological response rate was 51% in peginterferon-α-2a (40kD) plus ribavirin recipients and 40% in peginterferon-α-2a (40kD) plus amantadine recipients.[52]

4.1.2 Health-Related Quality-of-Life Considerations

Further analysis of the fully published study[50] discussed in section 4.1.1 revealed that peginterferon-α-2a (40kD) plus ribavirin recipients had better health-related quality of life than interferon-α-2b plus ribavirin recipients.[68] Peginterferon-α-2a (40kD) plus ribavirin recipients had significantly higher scores than interferon-α-2b plus ribavirin recipients on several domains of the Short Form-36 Health Survey (SF-36) after just 2 weeks of therapy (role physical [$p < 0.01$], bodily pain [$p = 0.01$], vitality [$p < 0.0001$] and social functioning [$p = 0.04$]). Bodily pain, vitality and social functioning scores remained significantly higher in peginterferon-α-2a (40kD) plus ribavirin recipients than in interferon-α-2b plus ribavirin recipients after 24 weeks' therapy.

Moreover, recipients of peginterferon-α-2a (40kD) in combination with ribavirin had experienced significantly less fatigue than interferon-α-2b plus ribavirin recipients after 2 weeks' therapy ($p < 0.01$), as assessed by the Fatigue Severity Scale.[68] During treatment, the degree and impact of fatigue was significantly lower in peginterferon-α-2a (40kD) plus ribavirin recipients than in interferon-α-2b plus ribavirin recipients ($p = 0.02$).

Table III. Biochemical and virological response rates after 24 weeks' therapy in patients with chronic hepatitis C. Results of two randomised, multicentre trials[a]

Reference	Treatment regimen[b]	No. of randomised patients (% of patients with baseline viral load >2 × 10^6 copies/mL)	Biochemical response rate[c] (% of patients)	Virological response rate[d] (% of patients)
Di Bisceglie et al.[53]e,f	PEGIFNα2a + RIB + AMA[g]	19	76	65
	PEGIFNα2a + AMA[g]	21	53	76
	PEGIFNα2a + MYC[g]	58	53	56
	IFNα2b + RIB[g]	55	78	60
Mangia et al.[54]h	PEGIFNα2a 180μg qw + RIB 1000 or 1200 mg/day + AMA 200mg od	119 (53)	63	76
	IFNα2a 3MU tiw + RIB 1000 or 1200 mg/day + AMA 200mg od	120 (31)	49	43
	IFNα2a 3MU tiw + RIB 1000 or 1200 mg/day	120 (55)	53	45

a The degree of blinding was not stated in either trial.

b All interferons were administered subcutaneously; other treatments were administered orally.

c Defined as normalisation of ALT levels.

d Defined as undetectable HCV RNA levels.

e Abstract.

f Overall, the mean ALT level was 109 U/L and 67% of patients had a high viral load at baseline.

g Dosage not stated for any of the drugs administered in the combination regimen.

h Poster.

ALT = alanine aminotransferase; **AMA** = amantadine; **IFNα2a** = interferon-α-2a; **IFNα2b** = interferon-α-2b; **MYC** = mycophenolate mofetil; **od** = once daily; **PEGIFNα2a** = peginterferon-α-2a (40kD); **qw** = once weekly; **RIB** = ribavirin; **tiw** = three times weekly.

4.1.3 In Combination with Amantadine

Two studies compared the use of triple therapy comprising peginterferon-α-2a (40kD), ribavirin and amantadine with various other treatment regimens in treatment-naive patients with chronic hepatitis C.[53,54] After 24 weeks' treatment, biochemical response rates of 63% and 76% and virological response rates of 76% and 65% were seen in recipients of triple therapy (table III).

4.2 In Treatment-Experienced Patients

4.2.1 Virological and Biochemical Responses

Combination therapy with peginterferon-α-2a (40kD) and another antiviral agent was beneficial in patients with chronic hepatitis C who had relapsed during or after treatment with interferon-α-2b plus ribavirin, or who had not responded to treatment with interferon-α-2b plus ribavirin. Two studies examined the use of peginterferon-α-2a (40kD) in combination with ribavirin 800–1000 mg/day, mycophenolate mofetil 1g twice daily, amantadine 100mg twice daily, or ribavirin plus amantadine in treatment-experienced patients with chronic hepatitis C.[55,56] Patients who had not responded had received ≥12 weeks' therapy with interferon-α-2b in combination with ribavirin,[55] and patients who had relapsed had developed positive HCV RNA levels during or after completing ≥6 months' therapy with interferon-α-2b plus ribavirin.[56]

In the relapse study,[56] the highest sustained virological response rates were seen in recipients of peginterferon-α-2a [40kD] plus ribavirin with (45%) or without (38%) amantadine (although no statistical analysis is reported). Sustained virological response rates are not yet available for the nonresponse study,[55] although virological response rates during treatment were lower than those observed in the relapse study (table IV). In the nonresponse study, the end-of-treatment (week 48) virological response rate was 11–40%.[55] The viral load at 12 weeks was predictive of the end-of-treatment response rate only in patients receiving peginterferon-α-2a (40kD) in combination with ribavirin.[55] In both studies, virological response rates were lowest

Table IV. Virological response rates in treatment-experienced patients with chronic hepatitis C. In two randomised, nonblind, multicentre studies, patients had not responded to,[55] or had relapsed during or after,[56] previous treatment with interferon-α-2b plus ribavirin (RIB)

Reference	Treatment regimen[a]	No. of patients randomised (% of patients with viral load >1 × 10^6 IU/mL at baseline)	Virological response rate[b] (% of patients)			Sustained virological response rate[c] (% of patients)
			after 12wk treatment	after 24wk treatment	after 48wk treatment	
Afdhal et al.[55][d]	PEGIFNα2a + RIB	30 (63)	33	30	25	
	PEGIFNα2a + MYC	29 (69)	14	31	28	
	PEGIFNα2a + AMA	28 (64)	0	18	11	
	PEGIFNα2a + RIB + AMA	31 (71)	19	39	40	
Herrine et al.[56][e]	PEGIFNα2a + RIB	32 (56)	66	69	60	38
	PEGIFNα2a + MYC	29 (65)	59	72	72	17
	PEGIFNα2a + AMA	31 (48)	32	32	42	10
	PEGIFNα2a + RIB + AMA	31 (61)	77	81	71	45

a PEGIFNα2a was administered subcutaneously at a dosage of 180μg qw and all other treatments were administered orally (RIB 800–1000 mg/day, MYC 1g bid and AMA 100mg bid).

b Virological response was defined as an undetectable HCV RNA level.

c Sustained virological response was defined as an undetectable HCV RNA level 24 weeks after discontinuing therapy.

d Abstract.

e Poster.

AMA = amantadine; **bid** = twice daily; **HCV** = hepatitis C virus; **MYC** = mycophenolate mofetil; **PEGIFNα2a** = peginterferon-α-2a (40kD); **qw** = once weekly.

in recipients of peginterferon-α-2a (40kD) plus amantadine (table IV).[55,56]

Biochemical response rates are only available for the relapse study (figure 2); a sustained biochemical response (assessed 24 weeks after the discontinuation of therapy) was observed in 16–55% of patients.[56]

It may be possible to successfully re-treat patients with chronic hepatitis C who relapse following treatment with peginterferon-α-2a (40kD) in combination with ribavirin, according to the results of a subgroup analysis[67] of a study[51] discussed in section 4.1.1. This analysis included patients who had undetectable HCV RNA levels after treatment discontinuation (24 weeks' treatment) with peginterferon-α-2a (40kD) plus ribavirin (800 or 1000/1200 mg/day) but had developed detectable HCV RNA levels after a further 24 weeks' follow-up (n = 64). After an additional 48 weeks' combination therapy, 84% of patients had a virological response. Moreover, the sustained virological response rate was 53%.[67]

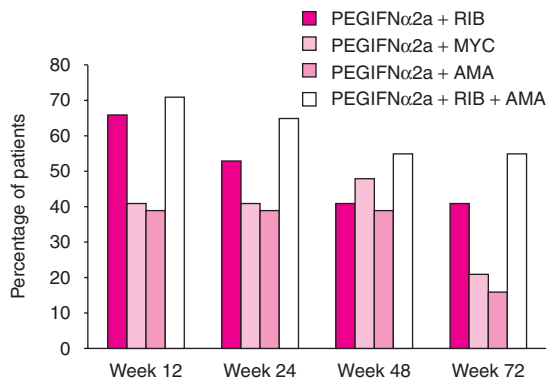

Fig. 2. Biochemical response rates in treatment-experienced patients with chronic hepatitis C.[56] In this randomised, nonblind, multicentre study, patients had relapsed during or after treatment with interferon-α-2b plus ribavirin (RIB) and received 48 weeks' treatment with subcutaneous peginterferon-α-2a (40kD) [PEGIFNα2a] 180μg once weekly in combination with oral RIB 800–1000 mg/day (n = 32), oral mycophenolate mofetil (MYC) 1g twice daily (n = 29), oral amantadine (AMA) 100mg twice daily (n = 31) or AMA plus RIB (n = 31). Biochemical response was defined as normalisation of alanine aminotransferase levels and was assessed after 12, 24 and 48 weeks' treatment and 24 weeks after stopping treatment (week 72; sustained biochemical response).

4.3 In Special Patient Groups

The use of combination therapy with peginterferon-α-2a (40kD) and ribavirin has been examined in a number of special patient groups, including patients infected with HCV genotype 4[57,66,69] (section 4.3.1), African-American patients[62] (section 4.3.2), patients with advanced fibrosis/cirrhosis[50,59,63] (section 4.3.3) and patients with HIV coinfection[58,64] (section 4.3.4). Chronic hepatitis C in these patient groups has traditionally been considered difficult to treat.

4.3.1 In Genotype 4 Hepatitis C Virus Infection

Genotype 4 is the predominant HCV genotype in the Middle East and in parts of North and Central Africa (e.g. a prevalence of genotype 4 HCV infection of up to ≈70% has been reported in Saudi Arabia[71,72] and of ≈90% in Egypt[72]). In a nonblind trial conducted in Saudi Arabia[57] and a subgroup analysis[69] of the fully published study[50] discussed in section 4.1.1, treatment with peginterferon-α-2a (40kD) in combination with ribavirin was associated with numerically higher 12-week,[57] 48-week[57,69] and sustained[69] virological response rates than interferon-α-2a plus ribavirin, interferon-α-2b plus ribavirin or peginterferon-α-2a (40kD) monotherapy in patients infected with HCV genotype 4 (table V; no statistical analyses reported). In the nonblind study (in which patients received oral ribavirin at a dosage of 400mg twice daily), peginterferon-α-2a (40kD) plus ribavirin recipients had an end-of-treatment (week 48) biochemical response rate of 80% (table V).[57]

Forty-eight weeks appears to be the optimal duration of treatment with peginterferon-α-2a (40kD) plus ribavirin, with 1000–1200 mg/day being the optimal ribavirin dosage, in patients infected with HCV genotype 4, according to the results of a retrospective analysis[66] of two studies[50,51] discussed in section 4.1.1. In this analysis, end-of-treatment and sustained virological response rates were highest (both 79%) in patients who received peginterferon-α-2a (40kD) in combination with ribavirin 1000 or 1200 mg/day for 48 weeks compared with patients who received a lower dosage of ribavirin (800 mg/day) and/or 24 weeks' treatment.[66]

Table V. Virological and biochemical response rates in patients infected with HCV genotype 4. Results of a nonblind, randomised, multicentre study[57] and a subgroup analysis[69] of a randomised, multicentre study[50]

Reference	Treatment regimen[a]	No. of patients (mean HCV RNA level × 10^6 IU/mL at baseline)	Virological response rate[b] (% of patients)		Sustained virological response rate[c] (% of patients)	Biochemical response rate[d] (% of patients)	
			after 12wk treatment	after 48wk treatment		after 12wk treatment	after 48wk treatment
Rodes et al.[69]e	PEGIFNα2a 180μg qw + RIB 1000 or 1200 mg/day	13		77	77		
	PEGIFNα2a 180μg qw + PL	9		56	44		
	IFNα2b 3MU tiw + RIB 1000 or 1200 mg/day	12		58	42		
Shobokshi et al.[57]f	PEGIFNα2a 180μg qw + RIB 400mg bid	60 (0.46)	77	67		57	80
	PEGIFNα2a 180μg qw	60 (0.39)	60	59		53	42
	IFNα2a 4.5MU tiw + RIB 400mg bid	60 (0.41)	43	37		44	37

a All interferons were administered subcutaneously; other treatments were administered orally.

b Defined at 48wk as an undetectable HCV RNA level[57,69] and at 12wk as either an undetectable HCV RNA level or a drop in HCV RNA level of ≥2 $\log_{10}$.[57]

c Assessed 24wk after the cessation of therapy and defined as an undetectable HCV RNA level.

d Defined as normalisation of alanine aminotransferase levels.

e Abstract (viral load at baseline range 0.04–14.2 × 10^6 copies/mL; 61% had a viral load >2 × 10^6 copies/mL).

f Poster.

bid = twice daily; **HCV** = hepatitis C virus; **IFNα2a** = interferon-α-2a; **IFNα2b** = interferon-α-2b; **PEGIFNα2a** = peginterferon-α-2a (40kD); **PL** = placebo; **qw** = once weekly; **RIB** = ribavirin; **tiw** = three times weekly.

4.3.2 In African-American Patients

African-American patients with chronic hepatitis C have been shown to have 6-fold lower sustained virological response rates to interferon monotherapy than Caucasian patients (2% vs 12%).[73] Sustained virological response rates were improved in African-American patients who received 48 weeks' combination therapy with interferon and ribavirin, although they were still lower than those achieved in Caucasians (23% vs 42%).[74] One possible explanation for the lower response rate in African-American patients is that they have a higher prevalence of HCV genotype 1 than Caucasians.[75]

The efficacy of peginterferon-α-2a (40kD) plus ribavirin has been examined in non-Hispanic African-American (n = 78) and Caucasian (n = 28) patients with chronic hepatitis C (patients were infected with HCV genotype 1 and were treatment naive).[62] After 48 weeks' therapy, a virological response was reported in 33% of African-American patients and 54% of Caucasian patients (intent-to-treat analysis) and a biochemical response in 51% and 50%. In this nonblind, multicentre study, more African-American than Caucasian patients had high HCV RNA levels ($\geq 1 \times 10^6$ IU/mL) at baseline (58% vs 43%).

4.3.3 In Advanced Fibrosis/Cirrhosis

Response rates to interferon-α therapy are halved in patients with cirrhosis, compared with unaffected patients.[76] The use of combination therapy with peginterferon-α-2a (40kD) and ribavirin in treatment-naive patients with chronic hepatitis C and advanced fibrosis or cirrhosis has been examined in a nonblind trial[59] and a subgroup analysis of the fully published study discussed in section 4.1.1.[50] Peginterferon-α-2a (40kD) plus ribavirin was associated with a high virological response rate (89%) after 24 weeks' treatment in the nonblind trial.[59] Forty-five patients received lower-dose ribavirin (600 mg/day in patients weighing ≤75kg and 800 mg/day in patients weighing >75kg) and 43 received higher-dose ribavirin (1000 mg/day in patients weighing ≤75kg and 1200 mg/day in patients weighing >75kg). There was no significant difference between treatment arms in the virological response rate.

In the subgroup analysis (n = 144), a sustained virological response occurred in 43% of peginterferon-α-2a (40kD) plus ribavirin recipients, 21% of peginterferon-α-2a (40kD) plus placebo recipients and in 33% of interferon-α-2b plus ribavirin recipients.[50]

A lower sustained virological response rate occurred in a noncomparative study (the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis [HALT-C] study) that enrolled treatment-experienced patients with chronic hepatitis C and advanced cirrhosis/fibrosis (n = 293).[63] In the lead-in phase of the HALT-C study, 18% of patients who had not responded to previous treatment with interferon or interferon in combination with ribavirin achieved a sustained virological response after 48 weeks' combination therapy with peginterferon-α-2a (40kD) and ribavirin. The sustained virological response rate was significantly higher among patients who had previously received interferon than among those who had previously received interferon plus ribavirin (30% vs 11%; $p < 0.0001$), among patients infected with HCV genotypes 2 or 3 compared with HCV genotype 1 (52% vs 14%; $p < 0.0001$) and in Caucasian or Hispanic patients compared with African-American patients (20% and 17% vs 6%; $p = 0.043$).

4.3.4 In HIV Co-Infection

Patients with chronic hepatitis C who are co-infected with HIV experience more rapid progression of their liver disease.[77,78] In such patients, peginterferon-α-2a (40kD) in combination with ribavirin was associated with a significantly higher virological response rate after 24 weeks' treatment than interferon-α-2a (6MU three times weekly for 12 weeks followed by 3MU three times weekly) plus ribavirin (both treatment groups received an initial ribavirin dosage of 600 mg/day titrated to a maximum of 1000 mg/day) [44% vs 15%; $p = 0.0003$].[58] 133 patients were included in this study.

In patients with chronic hepatitis C who were co-infected with HIV and who had not responded to prior treatment with interferon-α, 5 of 13 (38%)

peginterferon-α-2a (40kD) monotherapy recipients and 4 of 17 (24%) peginterferon-α-2a (40kD) plus ribavirin 800 mg/day recipients achieved a virological response after a mean 24 weeks' therapy in an interim analysis of a randomised trial.[64]

5. Tolerability

Most of the data in this section concerning the tolerability of peginterferon-α-2a (40kD) plus ribavirin combination therapy in patients with chronic hepatitis C are obtained from the fully published study[50] discussed in section 4.1.1, supplemented by data from the prescribing information.[9,47] Clinical adverse events occurring significantly less frequently ($p \leq 0.02$) in peginterferon-α-2a (40kD) plus ribavirin recipients than in interferon-α-2b plus ribavirin recipients (incidence of 22–43% vs 30–56%) included flu-like symptoms (e.g. pyrexia, myalgia and rigor) and depression (figure 3).[50] Other clinical adverse events (e.g. fatigue, headache, insomnia, nausea, dermatitis, alopecia and irritability) occurred with similar frequency (21–54% vs 18–55%) in the two treatment groups (figure 3). In this study, injection site reactions occurred in 23% of peginterferon-α-2a (40kD) plus ribavirin recipients and in 16% of interferon-α-2b plus ribavirin recipients (statistical analysis not reported).[47]

Similar proportions of patients receiving peginterferon-α-2a (40kD) plus ribavirin, peginterferon-α-2a (40kD) plus placebo and interferon-α-2b plus ribavirin withdrew from treatment because of laboratory abnormalities (3%, 1% and 1%, respectively) or other adverse events (7%, 6% and 10%).[50] Peginterferon-α-2a (40kD) has been shown to suppress bone marrow function and ribavirin has been associated with haemolytic anaemia.[47] Occurrence of a laboratory abnormality such as anaemia, neutropenia or thrombocytopenia resulted in modification of the dosage of peginterferon-α-2a (40kD) in 25% of patients and ribavirin in 24% of patients who received this combination, of peginterferon-α-2a (40kD) in 24% of patients and placebo in 4% of patients who received this combination and of interferon-α-2b in 8% of patients and ribavirin in 19% of patients who received this combination.[50]

During treatment, maximal reductions in median haemoglobin values of 3.7, 3.6 and 2.2 g/dL oc-

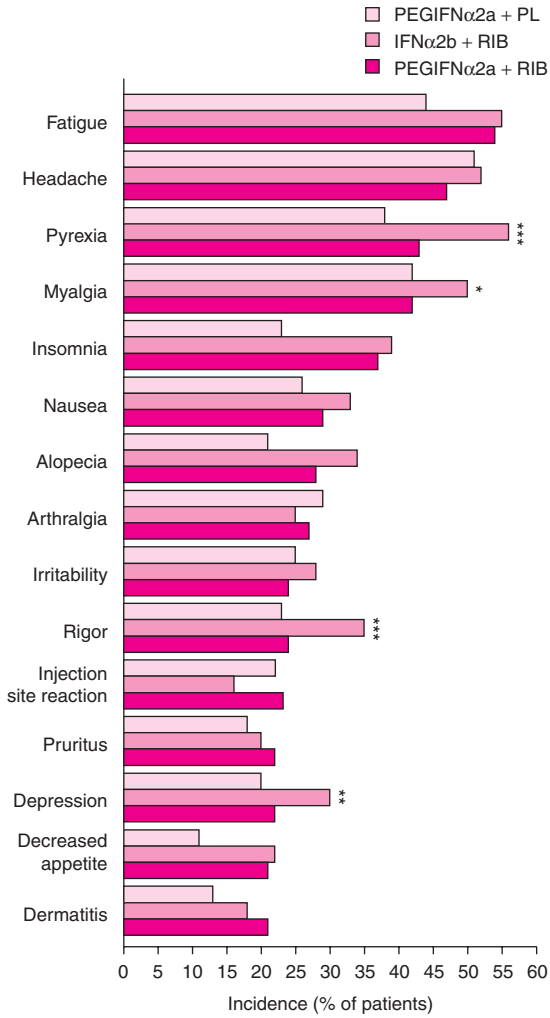

Fig. 3. Incidence of clinical adverse events in treatment-naive patients with chronic hepatitis C. In this randomised, multicentre study, patients received SC peginterferon-α-2a (40kD) [PEGIFNα2a] 180μg qw plus oral ribavirin (RIB) 1000 or 1200 mg/day (n = 451), SC interferon-α-2b (IFNα2b) 3MU tiw plus RIB (n = 443) or PEGIFNα2a plus placebo (PL) [n = 223].[50] The incidence of injection site reactions in PEGIFNα2a plus PL recipients is derived from a pooled analysis of three clinical studies (statistical analysis was not reported for this endpoint).[47] **qw** = once weekly; **SC** = subcutaneous; **tiw** = three times weekly; * p = 0.02, ** p = 0.01, *** p < 0.001 vs PEGIFNα2a + RIB.

curred in patients receiving peginterferon-α-2a (40kD) plus ribavirin, interferon-α-2b plus ribavirin and peginterferon-α-2a (40kD) plus placebo, respectively.[50] Haemoglobin levels decreased in all treatment groups between weeks 1 and 8 before stabilising and returning to near baseline values after treatment ended. Similarly, neutrophil levels decreased in all treatment groups in the first two weeks before stabilising and returning to baseline values when treatment was completed. Patients who received peginterferon-α-2a (40kD) in combination with either ribavirin or placebo experienced progressive reductions in platelet counts in the first 8 weeks of treatment; platelet counts subsequently stabilised and returned to normal within 4 weeks of completing treatment. No such reduction in platelet counts was seen in interferon-α-2b plus ribavirin recipients.

Fewer than 1% of peginterferon-α-2a (40kD) plus ribavirin recipients required dosage modification or discontinued therapy because of an increase in ALT levels.[9] Abnormalities in thyroid function tests that required clinical intervention occurred in 4.9% of combination therapy recipients.[9]

6. Dosage and Administration

Combination therapy with peginterferon-α-2a (40kD) and ribavirin is approved in the EU for use in the treatment of adults with histologically proven chronic hepatitis C who have elevated serum transaminase levels and who are serum HCV RNA-positive, including patients with compensated cirrhosis; combination therapy is indicated both in treatment-naive patients and in patients who responded to prior therapy with interferon-α but relapsed after treatment was discontinued.[9] In the US, combination therapy with peginterferon-α-2a (40kD) and ribavirin is approved for use in adults with chronic hepatitis C who have compensated liver disease and who have not previously received interferon-α.[47] It is considered optimal to administer peginterferon-α-2a (40kD) in combination with ribavirin; monotherapy with peginterferon-α-2a (40kD) should generally be reserved for patients who do not tolerate ribavirin or have a contraindication to ribavirin therapy.[9]

The recommended dosage of peginterferon-α-2a (40kD) is 180μg administered once weekly by subcutaneous injection.[9,47] Ribavirin should be administered orally (with food; section 3.2.1) in two divided doses.[9,47] In the EU, the recommended ribavirin dosage is 1000 mg/day in patients weighing <75kg and 1200 mg/day in patients weighing ≥75kg.[9] US prescribing information recommends that patients infected with HCV genotypes 1 or 4 receive ribavirin 1000 or 1200 mg/day (according to bodyweight) and those infected with HCV genotypes 2 or 3 receive 800 mg/day.[47]

The recommended duration of treatment with peginterferon-α-2a (40kD) in combination with ribavirin is 48 weeks in patients infected with HCV genotypes 1 or 4; however, patients infected with HCV genotypes 2 or 3 may be treated for 24 weeks.[47] It appears that patients who fail to achieve an early virological response to peginterferon-α-2a (40kD) therapy (i.e. after 12 weeks' treatment) are unlikely to achieve a sustained virological response (section 4.1.1) and it has been suggested that treatment discontinuation be considered in such patients, particularly if they do not have cirrhotic disease.[9]

A reduction in the dosage of peginterferon-α-2a (40kD) or ribavirin, or treatment discontinuation, may be needed in certain patient populations (e.g. patients with end-stage renal disease) or in patients who experience certain adverse events (e.g. neutropenia, thrombocytopenia, anaemia or increased ALT levels) [table VI].[9] Dosage reduction is not necessary when starting treatment with peginterferon-α-2a (40kD) in elderly patients. The use of peginterferon-α-2a (40kD) in patients with decompensated cirrhosis (i.e. patients with Child-Pugh grade B or C disease or bleeding oesophageal varices) has not been evaluated.

In the EU and the US, contraindications to the use of peginterferon-α-2a (40kD) in combination with ribavirin include autoimmune hepatitis and hepatic decompensation; combination therapy is also contraindicated in neonates and infants (because peginterferon-α-2a [40kD] contains benzyl alcohol

Table VI. Recommendations for dosage adjustment of peginterferon-α-2a (40kD) [PEGIFNα2a] or ribavirin (RIB) in patients with chronic hepatitis C experiencing certain laboratory adverse events and/or a certain comorbidity[9,47]

Adverse event/co-morbidity	Action
ANC ≤750/mm3	↓ PEGIFNα2a dosage[a]
ANC ≤500/mm3	Temporarily withhold PEGIFNα2a until ANC ≥1000/mm3. Restart treatment at a dosage of 90μg once weekly
Platelet count ≤50 000/mm3	↓ PEGIFNα2a dosage to 90μg once weekly
Platelet count ≤25 000/mm3	Discontinue combination therapy
Stable cardiac disease and Hb ↓ by ≥2 g/dL during any 4wk of treatment	↓ RIB dosage to 600 mg/day[b]
Stable cardiac disease and Hb <12 g/dL despite 4wk on a ↓ RIB dosage	Discontinue RIB therapy[c]
No significant cardiac disease and Hb <10 g/dL and ≥8.5 g/dL	↓ RIB dosage to 600mg (200mg in the morning and 400mg in the evening)[b]
No significant cardiac disease and Hb <8.5 g/dL	Discontinue RIB therapy[c]
Progressive/persistent ↑ in ALT levels	↓ PEGIFNα2a dosage to 135μg once weekly
Progressive ↑ in ALT levels despite dose reduction, progressive ↑ in ALT levels with ↑ bilirubin levels, or hepatic decompensation	Discontinue combination therapy
End-stage renal disease	Commence PEGIFNα2a at a dosage of 135μg once weekly

a A reduction to 135μg once weekly is usually sufficient, although reduction to 90 or 45μg once weekly may be needed.

b A return to the original RIB dosage is not recommended.

c If the abnormality is reversed RIB may be recommenced at a dosage of 600 mg/day and ↑ to 800 mg/day at the discretion of the physician; a return to the original RIB dosage is not recommended.

ALT = alanine aminotransferase; **ANC** = absolute neutrophil count; **Hb** = haemoglobin; ↓ = decrease/d; ↑ = increase/d.

as an excipient) and in women who are pregnant and men whose partners are pregnant (because ribavirin has been shown to have teratogenic and/or embryocidal effects).[9,47,79] It is essential that at least two forms of effective contraception are used during combination therapy and for 6 months after discontinuing ribavirin treatment.[47,79] Additional contraindications in the EU include a history of severe pre-existing cardiac disease (including cardiac disease that has been unstable or uncontrolled in the previous 6 months), severe hepatic dysfunction, a pre-existing severe psychiatric condition or a history of a severe psychiatric disorder (e.g. depression) and lactation.[9] Combination therapy is also contraindicated in the US in patients with haemoglobinopathies.[47] US prescribing information recommends that peginterferon-α-2a (40kD) be used with caution in patients with pre-existing cardiac disease, autoimmune disorders or a history of depression,[47] and that ribavirin should not be administered to patients with severe renal impairment (creatinine clearance <3 L/h [<50 mL/min]) [section 3.2.3].[79]

Standard haematological, biochemical and thyroid function tests should be performed before starting combination therapy and women of childbearing potential should be screened for pregnancy.[9,47] Haematological tests should be repeated after 2 and 4 weeks of therapy and biochemical tests should be repeated after 4 weeks of therapy; tests should be repeated periodically during treatment.[47] Pregnancy testing should be performed during treatment and for 6 months after treatment has finished.[47] Patients with pre-existing cardiac disorders should have an ECG performed before starting treatment with peginterferon-α-2a (40kD) plus ribavirin.[9]

Patients with chronic hepatitis C and HIV co-infection should be closely monitored during peginterferon-α-2a (40kD) plus ribavirin therapy and treatment should be discontinued in patients who progress to a Child-Pugh score of ≥7. Combination therapy should not be commenced in patients with a Child-Pugh score of ≥6 at baseline.[9]

Serum theophylline levels may increase in patients receiving theophylline in addition to peginterferon-α-2a (40kD) plus ribavirin. Thus, serum

theophylline levels should be monitored in such patients and the dosage of theophylline should be adjusted downwards if necessary (section 3.1.4).[9] Combination therapy with ribavirin and didanosine is not recommended as this regimen has been associated with adverse effects such as fatal hepatic failure, pancreatitis and lactic acidosis in clinical trials.[79] In addition, the use of ribavirin in combination with stavudine or zidovudine should be avoided as ribavirin has been shown to antagonise the anti-HIV effects of these antiretroviral agents *in vitro*.[79]

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

Chronic hepatitis C is associated with considerable patient morbidity and mortality as well as high healthcare costs.[4,80] A recent consensus statement from the US National Institutes of Health (NIH) states that treatment is recommended in patients with chronic hepatitis C who have an increased risk of developing cirrhosis.[81] Such patients characteristically have HCV RNA levels >50 IU/mL, portal or bridging fibrosis and inflammation and necrosis of at least moderate severity on liver biopsy, and persistently elevated ALT levels.[81] In certain patient groups, the risks and benefits of treatment should be assessed on an individual basis (e.g. patients with normal ALT levels, patients with mild liver disease, patients co-infected with HIV and active injection drug users), and in other patient groups more data are needed before firm recommendations for treatment can be made (e.g. patients with advanced liver disease and children with chronic hepatitis C).[81]

Interferon-α has played a pivotal role in the management of chronic hepatitis C since the mid-1980s.[1] The recent development of the pegylated interferons represents an important advance. Pegylation prevents the rapid elimination of interferon-α from the body,[10] as demonstrated by peginterferon-α-2a (40kD) which has a clearance that is over 100-fold lower and a $t_{1/2}$ that is almost 9-fold longer than that of interferon-α (section 3.1.2). This has the benefit of allowing once-weekly administration. Moreover, the extended drug activity avoids the intermittent increases in viral load seen on treatment-free days in patients receiving conventional interferon-α three times weekly.[3,82]

The management of chronic hepatitis C is a rapidly evolving field and older treatment guidelines do not reflect the availability of combination therapy with peginterferon-α plus ribavirin.[83-85] More recent treatment guidelines recommend the use of combination therapy with peginterferon-α and ribavirin in treatment-naive patients with chronic hepatitis C.[81] Much of the data regarding combination therapy with peginterferon-α-2a (40kD) and ribavirin are of a preliminary nature (i.e. most of it is currently only available in abstract or poster form and statistical analyses are lacking). Moreover, many of the studies are ongoing and have not yet reached their primary endpoint (sustained virological response rate). However, the results of the one fully published study[50] in treatment-naive patients with chronic hepatitis C demonstrate the superior efficacy (i.e. significantly higher sustained virological response rate) of peginterferon-α-2a (40kD) plus ribavirin over peginterferon-α-2a (40kD) monotherapy or interferon-α-2b plus ribavirin (section 4.1.1). Thus, combination therapy comprising peginterferon-α-2a (40kD) and ribavirin can be considered a first-line treatment option for treatment-naive patients with chronic hepatitis C; such treatment is approved in both the US and the EU (section 6). Treatment guidelines issued by the US NIH state that conventional interferon-α plus ribavirin is also a first-line option in patients infected with HCV genotypes 2 or 3,[81] although a subgroup analysis of the fully published study demonstrated that in such patients the sustained virological response rate was significantly higher in peginterferon-α-2a (40kD) plus ribavirin recipients than interferon-α-2b plus ribavirin recipients (76% vs 61%) [figure 1].[50] In earlier studies examining the use of combination therapy with conventional interferon-α and ribavirin, sustained virological response rates of 66%[86] and 79%[87] were reported in patients infected with HCV non-1 genotypes or HCV genotypes 2 or 3 who received interferon-α-2b plus ribavirin.

Two studies have examined the addition of amantadine to combination therapy comprising peginterferon-α-2a (40kD) and ribavirin in treatment-naive patients with chronic hepatitis C (section 4.1.3),[53,54] although it should be noted that triple therapy was not compared with dual therapy comprising peginterferon-α-2a (40kD) and ribavirin in either study. However, peginterferon-α-2a (40kD) plus ribavirin with or without amantadine was investigated in treatment-experienced patients with chronic hepatitis C who had experienced disease relapse during or after treatment with interferon-α-2b plus ribavirin (section 4.2).[56] Triple therapy was associated with a sustained virological response rate of 45%, compared with 38% in dual therapy recipients. Similarly, end-of-treatment (week 48) virological response rates were 40% in peginterferon-α-2a (40kD) and ribavirin plus amantadine recipients and 25% in peginterferon-α-2a (40kD) plus ribavirin recipients in patients with chronic hepatitis C who had not responded to treatment with interferon-α-2b plus ribavirin (section 4.2).[55] Although these results are of interest, the fact that statistical analyses are not yet available makes it difficult to draw conclusions on any additional benefits of amantadine.

Several factors have to be taken into consideration when deciding whether to retreat patients with chronic hepatitis C who have intermediate degrees of fibrosis and who have relapsed after, or not responded to, antiviral treatment.[81] Such factors include the previous type of response (i.e. relapse or nonresponse), previous treatment, the difference in efficacy between the previous and the repeat treatment regimen, severity of disease, HCV genotype and other factors predictive of response (e.g. baseline viral load, baseline ALT quotient, liver biopsy findings, age),[8] and tolerance of and adherence to previous therapy.[81] Combination therapy with peginterferon-α-2a (40kD) and ribavirin is currently approved in the EU for use in patients who initially respond to interferon-α therapy but subsequently relapse (section 6).[9] More data are needed concerning the retreatment of patients who relapse after, or do not respond to, treatment with peginterferon-α plus ribavirin.[81] A subgroup analysis[67] revealed a sustained virological response rate of 53% in patients with chronic hepatitis C who relapsed following treatment with peginterferon-α-2a (40kD) plus ribavirin and who were then retreated with peginterferon-α-2a (40kD) plus ribavirin (section 4.2).

Patients with advanced fibrosis or cirrhosis are considered more difficult to treat than patients with less advanced disease and are at particular risk of experiencing hepatic decompensation. Thus, such patients should be considered for retreatment if they relapse after, or do not respond to, antiviral treatment.[81] In the lead-in phase of the ongoing HALT-C trial, the sustained virological response rate after 48 weeks' combination therapy with peginterferon-α-2a (40kD) and ribavirin was 18% in patients with chronic hepatitis C and advanced cirrhosis/fibrosis who had not responded to previous treatment with interferon or interferon plus ribavirin (section 4.3.3).[63] The ultimate goal of HALT-C is to establish if maintenance therapy with low-dose peginterferon-α-2a (40kD) can prevent the progression of fibrosis and the development of hepatic decompensation in patients who do not achieve a sustained virological response after peginterferon-α-2a (40kD) plus ribavirin therapy.[63]

Combination therapy with peginterferon-α-2a (40kD) and ribavirin also appears to have potential in the treatment of other patient groups with chronic hepatitis C considered difficult to treat (e.g. patients infected with HCV genotype 4, African-American patients and patients co-infected with HIV) [section 4.3].

Data from studies directly comparing peginterferon-α-2a (40kD) plus ribavirin with peginterferon-α-2b (12kD) plus ribavirin are currently lacking, although the results of a viral kinetics study[14] indicate that peginterferon-α-2a (40kD) plus ribavirin therapy was associated with a greater reduction in viral load at 12 weeks than peginterferon-α-2b (12kD) plus ribavirin (it should be noted that in this study peginterferon-α-2b [12kD] was administered at two-thirds of its recommended dosage[36]) [section 2.1.3]. Whether this will trans-

late into a difference in clinical outcome in the longer term is not yet clear.

Some of the study results discussed in section 4 have contributed to recent changes in treatment recommendations. Previously, it was recommended that patients should be assessed after 24 weeks' antiviral treatment and that, in general, treatment should be discontinued in those with detectable HCV RNA levels.[88] However, retrospective analysis[65] of the fully published study[50] discussed in section 4.1.1 revealed that peginterferon-α-2a (40kD) plus ribavirin recipients who did not achieve an early virological response after 12 weeks' treatment appeared unlikely to achieve a sustained virological response. Thus, it may be possible to discontinue treatment as early as 12 weeks in nonresponders. This strategy would limit the exposure of patients to treatment that is not proving successful, thereby avoiding potential toxicity and reducing costs, and is supported by guidelines recently issued by the US NIH.[81]

In the past, treatment guidelines recommended that the duration of peginterferon-α plus ribavirin treatment in patients with chronic hepatitis C should be 48 weeks, regardless of HCV genotype.[88] However, the preliminary results of a study[51] discussed in section 4.1.1 suggest that 24 weeks of therapy may be of similar efficacy to 48 weeks in patients infected with HCV non-1 genotypes. Moreover, in this study,[51] patients infected with HCV non-1 genotypes who received a lower dosage of ribavirin (800 mg/day) had a similar outcome to those who received the standard ribavirin dosage (1000 or 1200 mg/day). Reducing the duration of treatment to 24 weeks in patients infected with HCV non-1 genotypes would have cost benefits. Moreover, administering a lower dosage of ribavirin may result in improved tolerability. This strategy of administering peginterferon-α plus ribavirin 800 mg/day for only 24 weeks to patients infected with HCV genotypes 2 or 3 is supported by recent US NIH treatment guidelines.[81]

With regards to clinical adverse events, combination therapy with peginterferon-α-2a (40kD) and ribavirin was better tolerated than interferon-α-2b plus ribavirin, with flu-like symptoms and depression occurring significantly more frequently in the latter group of patients (section 5).[50] Similar proportions of patients receiving peginterferon-α-2a (40kD) plus ribavirin and interferon-α-2b plus ribavirin withdrew from treatment because of laboratory abnormalities, although dosage modification because of a laboratory abnormality was required more frequently in recipients of peginterferon-α-2a (40kD) than in recipients of interferon-α-2b.[50] Whether the need for dosage modification in some patients means that reported sustained virological response rates will be harder to achieve in clinical practice remains to be seen. In the fully published study, among peginterferon-α-2a (40kD) plus ribavirin recipients with an early virological response, sustained virological response rates in patients who required substantial dosage reduction were similar to those in patients who maintained the full dosing schedule (67% vs 75%).[50] Haematopoietic growth factors (e.g. epoetin alfa) appear to be of benefit in patients who develop anaemia during combination therapy; additional studies are needed to establish exactly how these agents can be best employed.[89] Similarly, cytokines (e.g. granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor) may have potential in the management of neutropenia associated with peginterferon-α-2a (40kD) plus ribavirin, although more data are needed to determine if these agents are suitable for routine use in this indication.[89]

In conclusion, combination therapy comprising subcutaneous peginterferon-α-2a (40kD) and oral ribavirin is an important new treatment option for chronic hepatitis C. Peginterferon-α-2a (40kD) plus oral ribavirin is significantly more effective than peginterferon-α-2a (40kD) monotherapy or interferon-α-2b plus ribavirin at inducing a sustained virological response in treatment-naive patients with chronic hepatitis C. Preliminary data suggest that peginterferon-α-2a (40kD) plus ribavirin is also beneficial in treatment-experienced patients and in patients who have traditionally been considered difficult to treat. Combination therapy with peginterferon-α-2a (40kD) and oral ribavirin is poised

to become a valuable first-line treatment option in patients with chronic hepatitis C.

References

1. Davis GL. Treatment of chronic hepatitis C: combination therapy permanently eradicates the virus in at least 40% of patients. BMJ 2001 Nov 17; 323: 1141-2
2. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med 2001 Jul 5; 345 (I): 41-52
3. Luxon BA, Grace M, Brassard D, et al. Pegylated interferons for the treatment of chronic hepatitis C infection. Clin Ther 2002; 24 (9): 1363-83
4. Koff RS. Disease management program for hepatitis C: a team approach to setting goals. Dis Manage Health Outcomes 2001; 9 (8): 431-9
5. Powell DW, Abramson BZ, Balint JA, et al. National Institutes of Health Consensus Development Conference Panel statement: management of hepatitis C. Hepatology 1997 Sep; 26 (3 Suppl. 1): 2S-10S
6. Ahmed A, Keeffe EB. Treatment strategies for chronic hepatitis C: update since the 1997 National Institutes of Health Consensus Development Conference. J Gastroenterol Hepatol 1999 May; 14 Suppl.: S12-8
7. Hoofnagle JH. Course and outcome of hepatitis C. Hepatology 2002 Nov; 36 (5 Suppl. 1): S21-9
8. Lindsay KL. Introduction to therapy of hepatitis C. Hepatology 2002 Nov; 36 (5 Suppl. 1): S114-20
9. European Agency for the Evaluation of Medicinal Products. Summary of product characteristics: Pegasys [online]. Available from URL: http://www.eudra.org [Accessed 2002 Oct 31]
10. Shiffman ML. PEGylated interferons: what role will they play in the treatment of chronic hepatitis C? Curr Gastroenterol Rep 2001; 3: 30-7
11. Kozlowski A, Charles SA, Harris JM. Development of pegylated interferons for the treatment of chronic hepatitis C. Biodrugs 2001; 15 (7): 419-29
12. Perry CM, Jarvis B. Peginterferon-α-2a (40kD): a review of its use in the management of chronic hepatitis C. Drugs 2001; 61 (15): 2263-88
13. Scott LJ, Perry CM. Interferon-α-2b plus ribavirin: a review of its use in the management of chronic hepatitis C. Drugs 2002; 62 (3): 507-56
14. Bruno R, Debiaggi M, Ciappina V, et al. Hepatitis C virus (HCV) dynamics during therapy with peginterferon alfa-2a (40kD) (Pegasys®) compared with peginterferon alfa-2b (12kD) (Peg-Intron®) in naive patients with chronic hepatitis C (CHC) [poster]. 53rd Annual Meeting of the American Association for the Study of Liver Diseases; 2002 Nov 1-5; Boston (MA)
15. Xu Z-X, Hoffman J, Patel I, et al. Single-dose safety/tolerability and pharmacokinetic/ pharmacodynamics (PK/PD) following administration of ascending subcutaneous doses of pegylated-interferon (PEG-IFN) and interferon α-2a (IFN α-2a) to healthy subjects [abstract no. 2157]. Hepatology 1998 Oct; 28 (4 Pt. 2): 702A
16. Martin NE, Modi MW, Reddy R. Characterization of pegylated interferon alfa-2a (Pegasys™) in the elderly [abstract no. 755]. Hepatology 2000 Oct; 32 (4 Pt. 2): 348A
17. Martin P, Mitra S, Farrington K, et al. Pegylated (40kDa) interferon alfa-2a (Pegasys™) is unaffected by renal impairment [abstract no. 842]. Hepatology 2000 Oct; 32 (4 Pt. 2): 370A
18. Wilkinson TCI, Laxton C, Hobbs E, et al. Characterisation of interferon alfa-2A and pegylated interferon alfa-2A in combination with ribavirin, mycophenolic acid or VX-497 as inhibitors of HCV replicon replication. J Hepatol 2001 Apr; 34 Suppl. 1: 117-8
19. Zeuzem S, Herrmann E, Lee J-H, et al. Effect of ribavirin on viral kinetics in hepatitis C virus genotype 1 infected patients treated with pegylated interferon α2a [abstract no. 1544]. Hepatology 2001; 34 (4 Pt. 2): 558
20. Neumann AU, Zeuzem S, Ferrari C, et al. Ditto-HCV early viral kinetic report - novel decline patterns in gen 1 but not gen 2-3 patients treated with peg-interferon-alfa-2a and ribavirin [abstract no. 430]. J Hepatol 2002 Apr; 36 Suppl.1: 121
21. Pawlotsky J-M, Hezode C, Pellegrin B, et al. Early HCV genotype 4 replication kinetics during treatment with peginterferon alfa-2a (Pegasys)-ribavirin combination: a comparaison with HCV genoptypes 1 and 3 kinetics [abstract no. 511]. Hepatology 2002 Oct; 36 (4 Pt. 2): 291A
22. Baron S, Tyring SK, Fleischmann Jr WR, et al. The interferons: mechanisms of action and clinical applications. JAMA 1991 Sep 11; 266 (10): 1375-83
23. Cirelli R, Tyring SK. Major therapeutic uses of interferons. Clin Immumother 1995; 3: 27-87
24. Perry CM, Wagstaff AJ. Interferon-α-n1: a review of its pharmacological properties and therapeutic efficacy in the management of chronic viral hepatitis. Biodrugs 1998 Feb; 9: 125-54
25. Perry CM, Wilde MI. Interferon-α-2a: a review of its use in chronic hepatitis C. Biodrugs 1998 Jul; 10: 65-89
26. Zeuzem S, Herrmann E, Lee J-H, et al. Viral kinetics in patients with chronic hepatitis C treated with standard or peginterferon α2a. Gastroenterology 2001; 120: 1438-47
27. Patterson JL, Fernandez-Larsson R. Molecular mechanisms of action of ribavirin. Rev Infect Dis 1990; 12 (6): 1139-46
28. Sidwell RW, Robins RK, Hillyard IW. Ribavirin: an antiviral agent. Pharmacol Ther 1979; 6 (1): 123-46
29. Reichard O, Andersson J, Schvarcz R, et al. Ribavirin treatment for chronic hepatitis C. Lancet 1991 May 4; 337 (8749): 1058-61
30. Dusheiko G, Main J, Thomas H, et al. Ribavirin treatment for patients with chronic hepatitis C: results of a placebo-controlled study. J Hepatol 1996 Nov; 25 (5): 591-8
31. Di Bisceglie AM, Shindo M, Fong T-L, et al. A pilot study of ribavirin therapy for chronic hepatitis C. Hepatology 1992 Sep; 16 (3): 649-54
32. Reichard O, Yun Z-B, Sönnerborg A, et al. Hepatitis C viral RNA titers in serum prior to, during, and after oral treatment with ribavirin for chronic hepatitis C. J Med Virol 1993 Oct; 41 (2): 99-102
33. Bodenheimer Jr HC, Lindsay KL, Davis GL, et al. Tolerance and efficacy of oral ribavirin treatment of chronic hepatitis C: a multicenter trial. Hepatology 1997 Aug; 26 (2): 473-7
34. Hultgren C, Milich DR, Weiland O, et al. The antiviral compound ribavirin modulates the T helper (Th) 1/Th2 subset balance in hepatitis B and C virus-specific immune responses. J Gen Virol 1998 Oct; 79 (10): 2381-91
35. Formann E, Jessner W, Bennett L, et al. Twice-weekly administration of peginterferon alfa-2b PEG-Intron™ (12kD) improves viral kinetics in patients with HCV genotype 1 [poster]. 53rd Annual Meeting of the Association for the Study of Liver Diseases; 2002 Nov 1-5; Boston (MA)
36. Schering Corporation. PEG-Intron (peginterferon alfa-2b) powder for injection product information [online]. Available from

URL: http://www.schering-plough.com [Accessed 2003 Jan 16]
37. Ning Q, Brown D, Parodo J, et al. Ribavirin inhibits viral-induced macrophage production of TNF, IL-1, the procoagulant fgl2 prothrombinase and preserves Th1 cytokine production but inhibits Th2 cytokine response. J Immunol 1998 Apr 1; 160 (7): 3487-93
38. Tam RC, Pai B, Bard J, et al. Ribavirin polarizes human T cell responses towards a Type 1 cytokine profile. J Hepatol 1999 Mar; 30 (3): 376-82
39. Meier V, Bürger E, Mihm S, et al. Ribavirin inhibits DNA, RNA, and protein synthesis in PHA-stimulated human peripheral blood mononuclear cells: possible explanation for therapeutic efficacy in patients with chronic HCV infection. J Med Virol 2003; 69: 50-8
40. Kamal SM, Fehr J, Roesler B, et al. Peginterferon alone or with ribavirin enhances HCV-specific CD4+ T-helper 1 responses in patients with chronic hepatitis C. Gastroenterology 2002 Oct; 123 (4): 1070-83
41. Martin NE, Sy S, Modi M. The enhanced efficacy of PEG(40K)-IFNα-2a (PEGASYS™) in chronic hepatitis C (CHC) may be explained by the optimization of the pharmacokinetics (PK) of interferon (IFN) by a branched methoxy 40 kDa polyethylene glycol (PEG) moiety [abstract]. 9th International Congress on Infectious Diseases; 2000 Apr 10-13; Buenos Aires
42. Modi MW, Fried M, Reindollar RW, et al. The pharmacokinetic behavior of pegylated (40kDa) interferon alfa-2a (Pegasys™) in chronic hepatitis C patients after multiple dosing [abstract no. 939]. Hepatology 2000 Oct; 32 (4 Pt. 2): 394A
43. Heathcote EJ, Pockros PJ, Fried MW, et al. The pharmacokinetics of pegylated-40K interferon alfa-2A (PEG-IFN) in chronic hepatitis C (CHC) paients with cirrhosis [abstract no. G3190]. Gastroenterology 1999 Apr; 116 (4 Pt. 2): A735
44. Sy S, Martin NE, Patel IH, et al. Drug interactions between PEG(40K)-IFNα-2a (PEGASYS™) and cytochrome P450 (CYP450)-metabolized drugs are unlikely except for those metabolized by CYP1A2 [abstract]. 9th International Congress on Infectious Diseases; 2000 Apr 10-13; Buenos Aires
45. Ribavirin (Rebetol): Mosby's Drug Consult Update 4 [online]. Available from URL: http://www.mosbysdrugconsult.com [Accessed 2002 Oct 17]
46. Algranati NE, Sy S, Modi M, et al. A branched methoxy 40 kDa polyethylene glycol (PEG) moiety optimizes the pharmacokinetics (PK) of peginterferon α-2A (PEG-IFN) and may explain its enhanced efficacy in chronic hepatitis C (CHC) [abstract no. 120]. Hepatology 1999 Oct; 30 (4 Pt. 2): 190A
47. Hoffmann-La Roche Inc. Pegasys® (peginterferon alfa-2a): complete product information [online]. Available from URL: http://www.rocheusa.com/products/pegasys/pi/pdf [Accessed 2002 Dec 10]
48. Glue P. The clinical pharmacology of ribavirin. Semin Liver Dis 1999; 19 Suppl. 1: 17-24
49. Glue P, Schenker S, Gupta S, et al. The single dose pharmacokinetics of ribavirin in subjects with chronic liver disease. Br J Clin Pharmacol 2000 May; 49: 417-21
50. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002 Sep 26; 347 (13): 975-82
51. Hadziyannis SJ, Cheinquer H, Morgan T, et al. Peginterferon alfa-2a (40 kD) (Pegasys) in combination with ribavirin (RBV): efficacy and safety results from a phase III, randomized, double-blind, multicentre study examining effect of duration of treatment and RBV dose [abstract no. 1 plus oral presentation]. J Hepatol 2002 Apr; 36 Suppl. 1: 3
52. Ideo G, Angelico M, Chirianni A, et al. Pegylated 40 kDa IFN α-2a plus amantadine (AMA) or ribavirin (RBV) in naives with chronic hepatitis C (CHC) [poster]. 37th Annual Meeting of the European Association for the Study of the Liver; 2002 Apr 15-21; Madrid
53. Di Bisceglie AM, Bernstein DE, Rustgi VR, et al. Pegylated interferon alfa-2A (PEGASYS®) in new combination therapies: a report of a randomized, multicenter efficacy and safety study [abstract no. 408]. J Hepatol 2001 Apr; 34 Suppl. 1: 143
54. Mangia A, Ricci GL, Minerva N, et al. Pegylated (40 kD) interferon alfa-2a (Pegasys®) or recombinant 3 MIU tiw in combination with ribavirin and amantadine versus standard Tx in naive patients with chronic hepatitis HCV: a randomized controlled trial [poster]. 37th Annual Meeting of the European Association for the Study of the Liver; 2002 Apr 15-21; Madrid
55. Afdhal N, Flamm S, Imperial JC, et al. Analyses of 40 KDA peginterferon alfa-2A (PEGASYS®) in combination with ribavirin, mycophenolate mofetil, amantadine, or amantadine plus ribavirin in patients that relapsed or did not respond to Rebetron™ therapy: a report of two randomized, multicenter, efficacy and safety studies [abstract no. 277 plus oral presentation]. Hepatology 2001 Oct; 34 (4 Pt. 2): 243A
56. Herrine SK, Brown R, Esposito S, et al. Efficacy and safety of peginterferon alfa-2a (Pegasys®) combination therapies in patients with chronic hepatitis C (CHC) who relapsed on interferon alfa-2b plus ribavirin (Rebetron™) therapy [poster]. 53rd Annual Meeting of the American Association for the Study of Liver Diseases; 2002 Nov 1-5; Boston (MA)
57. Shobokshi OA, Serebour FE, Skakni L. Peginterferon alfa-2a (40kD) as monotherapy or in combination with ribavirin significantly improves end-of-treatment response rate in HCV genotype 4 chronic active hepatitis patients [poster]. 53rd Annual Meeting of the American Association for the Study of Liver Diseases; 2002 Nov 1-5; Boston (MA)
58. Chung R, Andersen J, Alston B, et al. A randomized, controlled trial of pegylated interferon alpha-2a with ribavirin vs. interferon alpha-2a with ribavirin for the treatment of chronic HCV in HIV co-infection: ACTTG A5071 [abstract]. 9th Conference of Retroviruses and Opportunistic Infections; 2002 24-28 Feb; Seattle (WA)
59. Helbling B, Stamenic I, Cerny A, et al. Pegylated (40 kDa, Branched) interferon alfa-2a (PEG-IFN) and ribaviring (RIBA) in IFN-naive patients with hepatitis C and advanced fibrosis/cirrhosis: interim results of a randomized, controlled trial [abstract no. 84]. Gastroenterology 2002 Apr; 122 (4 Suppl. 1): A-627
60. Bronowicki JP, Ouzan D, Asselah T. Efficacy and safety of 22 weeks of maintenance therapy with peginterferon alfa-2a (40kD) (Pegasys®) alone versus peginterferon alfa-2a (40kD) plus ribavirin in naive patients infected with chronic hepatitis C and hepatitis C virus genotype 1 who responded to a 24-week course of peginterferon alfa-2a (40kD) plus ribavirin: preliminary analysis of an open, multicenter, randomized trial [poster]. 53rd Annual Meeting of the American Association for the Study of Liver Diseases; 2002 Nov 1-5; Boston (MA)
61. Brandao CE, Perez-Gomez R, Pessoa MG, et al. Prospective evaluation of early virologic response associated with peginterferon alfa-2a (40kD) (Pegasys®) and ribavirin from a phase IV, randomized study examining the effects of treatment duration in hepatitis C patients infected with HCV genotype 1 [poster]. 53rd Annual Meeting of the American Association for the Study of Liver Diseases; 2002 Nov 1-5; Boston (MA)

62. Jeffers LJ, Cassidy W, Howell C, et al. Peginterferon alfa-2a (40kD) (Pegasys®) in combination with ribavirin in African American and Caucasian patients with HCV genotype 1: a preliminary report of a comparative, multicenter, efficacy and safety study [poster]. 53rd Annual Meeting of the American Association for the Study of Liver Diseases; 2002 Nov 1-5; Boston (MA)

63. Shiffman M, HALT-C Trial Investigators. Retreatment of HCV non-responders with peginterferon and ribavirin: results from the lead-in phase of the hepatitis C antiviral long-term treatment against cirrhosis (HALT-C) trial [abstract no. 527 plus oral presentation]. Hepatology 2002 Oct; 36 (4 Pt. 2): 295A

64. Rodriguez-Torres M, Rodríguez-Orengo J. Efficacy of Peg-IFN-alfa 2a (PEGASYS) vs Peg-IFN alfa 2a and RBV for HIV/HCV coninfected patients that are nonresponders to previous IFN therapy [abstract no. V-686]. 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy; 2002 Sep 27-30; San Diego (CA)

65. Ferenci P, Shiffman ML, Fried MW, et al. Early prediction of response to 40 kDa peginterferon alfa-2a (Pegasys®) plus ribavirin in patients with chronic hepatitis C [abstract no. 716]. Hepatology 2001 Oct; 34 (4 Pt. 2): 351A

66. Diago M, Hadziyannis SJ, Bodenheimer H, et al. Optimized virological response in patients with genotype 4 chronic hepatitis C treated with peginterferon alfa-2a (40kD) (Pegasys®) in combination with ribavirin (RBV) [poster]. 53rd Annual Meeting of the American Association for the Study of Liver Diseases; 2002 Nov 1-5; Boston (MA)

67. Goncales F, Bernstein DE, Berg C, et al. Peginterferon alfa-2a (40kD) (Pegasys®) plus ribavirin in chronic hepatitis C: retreatment of patients who relapsed virologically after 24 weeks of therapy [poster]. 53rd Annual Meeting of the American Association for the Study of Liver Diseases; 2002 Nov 1-5; Boston (MA)

68. Hassanien TI, Cooksley WGE, Sulkowski M, et al. QOL benefits observed as early as week 2 with peginterferon alfa-2a (40kD) (Pegasys®) in combination with ribavirin (RBV) versus interferon alfa-2b plus RBV [poster]. 37th Annual Meeting of the European Association for the Study of the Liver; 2002 Apr 15-21; Madrid

69. Rodes J, Desmond P, Horsmans Y, et al. Enhanced virological response in genotype 4 chronic hepatitis C patients treated with 40 kDa peginterferon alfa-2a (PEGASYS) in combination with ribavirin (RBV) compared with treatment with interferon alfa-2b plus RBV or 40 kDa peginterferon alfa-2a alone [abstract]. 8th International Symposium on Hepatitis C and Related Viruses; 2001 Sep 2-5; Paris

70. Hoffmann-La Roche. Briefing materials updating information on the safety and efficacy of Pegasys® in combination with Copegus™ for the treatment of adult patients with chronic hepatitis C infection [online]. Available from URL: http://www.fda.gov/ohrms/dockets/ac/02/briefing/3909b1 [Accessed 2003 Jan 17]

71. Shobokshi O, Serebour FE, Skakni L, et al. Hepatitis C genotype and subtypes in Saudi Arabia. J Med Virol 1999; 58: 44-8

72. Fakeeh M, Zaki AM. Hepatitis C: prevalence and common genotypes among ethnic groups in Jeddah, Saudi Arabia. Am J Trop Med Hyg 1999; 61 (6): 889-92

73. Reddy KR, Hoofnagle JH, Tong MJ, et al. Racial differences in responses to therapy with interferon in chronic hepatitis C. Hepatology 1999 Sep; 30 (3): 787-93

74. McHutchison JG, Poynard T, Pianko S, et al. The impact of interferon plus ribavirin on response to therapy in black patients with chronic hepatitis C. Gastroenterology 2000; 119 (5): 1317-23

75. Howell C, Jeffers L, Hoffnagle JH. Hepatitis C in African Americans: summary of a workshop. Gastroenterology 2000; 119 (5): 1385-96

76. Collier J, Chapman R. Combination therapy with interferon-α and ribavirin for hepatitis C: practical treatment issues. Biodrugs 2001; 15 (4): 225-38

77. Sánchez-Quijano A, Andreu J, Gavilán F, et al. Influence of human immunodeficiency virus type 1 infection on the natural course of chronic parenterally acquired hepatitis C. Eur J Clin Microbiol Infect Dis 1995; 14: 949-53

78. Thomas DL. Hepatitis C and human immunodeficiency virus infection. Hepatology 2002 Nov; 36 (5 Suppl. 1): S201-9

79. Roche Laboratories Inc. Copegus™ (ribavirin, USP) tablets: complete product information [online]. Available from URL: http://www.rocheusa.com/products/copegus/pi.pdf [Accessed 2002 Dec 10]

80. Kim WR. The burden of hepatitis C in the United States. Hepatology 2002 Nov; 36 (5 Suppl. 1): S30-4

81. National Institutes of Health. National Institutes of Health Consensus Development Conference Statement: Management of Hepatitis C: 2002 - June 10-12, 2002. Hepatology 2002 Nov; 36 (5 Suppl. 1): S3-S20

82. Zeuzem S. Clinical implications of hepatitis C viral kinetics. J Hepatol 1999; 31 Suppl. 1: 61-4

83. Canadian Consensus Conference Rapporteur Group. Canadian Consensus Conference on the management of viral hepatitis. Can J Gastroenterol 2000; 14 Suppl. B: 5-20B

84. Consensus Panel. EASL International Consensus Conference on hepatitis C. J Hepatol 1999 May; 30: 956-61

85. Booth JCL, O'Grady J, Neuberger J, et al. Clinical guidelines on the management of hepatitis C. Gut 2001 Jul; 49 Suppl. I: 1-21

86. McHutchison JG, Gordon SC, Schiff ER, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. N Engl J Med 1998 Nov 19; 339 (21): 1485-92

87. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001 Sep 22; 358: 958-65

88. US Department of Veterans Affairs. Treatment recommendations for patients with chronic hepatitis C [online]. Available from URL: http://www.va.gov/hepatitisc/pved/treatmntgdlnes_00.htm [Accessed 2002 Nov 11]

89. Fried MW. Side effects of therapy of hepatitis C and their management. Hepatology 2002 Nov; 36 (5 Suppl. 1): S237-44

Correspondence: *Gillian M. Keating*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz