Drug review – Pegasys® (peginterferon alfa-2a [40 kDa])

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Summary

Chronic hepatitis C represents a public health time bomb. Hundreds of thousands of people are believed to be infected with the hepatitis C virus (HCV) in the UK, yet few have been screened and even fewer have been treated. Treatment regimens based on conventional interferon have been relatively successful, but are associated with only moderate efficacy in clearing HCV and the emergence of substantial adverse events. Recently, the use of pegylated interferon alfa, such as peginterferon alfa-2a (Pegasys®), has dramatically improved treatment efficacy for this patient population, and may also be associated with some improvements in the side-effect profile compared with non-pegylated (conventional) interferon. For example, a reduction in the incidence of flu-like symptoms has been reported with peginterferon alfa-2a. In summary, the use of peginterferon alfa provides an opportunity to tackle the growing problem of chronic hepatitis C in the UK and elsewhere.

Drugs in Context
DOI: http://dx.doi.org/10.7573/dic.212203

Citation: Clark, R. Drug Review – Hepatitis C. *Drugs in Context*: e212203. doi:10.7573/dic.212203

Date of last literature search: September 2006

NB: This article was originally published by CSF Medical Communications Ltd (CSF) in *Drugs in Context* 2007;3(2):65–83. *Drugs in Context* and all CSF copyrights were acquired by Just Medical Media Ltd in 2009.

Introduction

According to the latest figures, there are thought to be as many as 500,000 people in England and Wales who are infected with HCV, though only about 47,000 people have been diagnosed and 7,000 have been treated.[1] About 80% of individuals who are infected with HCV will go on to develop chronic hepatitis C, a condition which is often asymptomatic and develops slowly over 20–50 years after initial infection, but frequently results in serious clinical sequelae. About 30% of those who are infected will develop cirrhosis within 20–30 years, which can result in end-stage liver disease and the need for liver transplantation.[2,3] Thus, chronic hepatitis C represents a potential 'time bomb' of serious liver disease. Fortunately, recent developments in drug treatment mean that it is now a treatable infection in the majority of patients.

HCV is an RNA virus with six major genotypes (1–6) and multiple subtypes (a, b or c).[4] HCV genotype 1 predominates in European or North American patients, followed by genotypes 2 and 3. In general, genotype 1 is usually associated with lower response rates to antiviral treatments than genotypes 2 or 3. The primary goal of treatment for chronic hepatitis is the eradication of HCV and the absence of relapse during a subsequent treatment-free period (usually 24 weeks) essentially represents a cure . This is described as a sustained virological response.

Interferon alfa has been the main treatment for chronic hepatitis C for a number of years. When interferon alfa was administered in conjunction with ribavirin – a synthetic guanosine analogue with antiviral activity – enhanced sustained virological response rates were achieved.[4] However, the attachment of a polyethylene glycol (or PEG) moiety to interferon has further improved response rates, establishing peginterferon/ribavirin combination treatment as the current first-line intervention for chronic hepatitis C.[1,5]

Two peginterferons are currently licensed for use in the UK: peginterferon alfa-2a (Pegasys) and peginterferon alfa-2b (ViraferonPeg®). Here we will review the pharmacological, clinical and pharmacoeconomic evidence for peginterferon alfa-2a plus ribavirin (and peginterferon alfa-2a as monotherapy) in the treatment of chronic hepatitis C.

Pharmacology

Chemistry

Interferon alfa and related proteins have antiviral, antitumour and immunomodulatory activities.[6] Peginterferon alfa-2a consists of a branched 40 kDa PEG polymer attached to

recombinant interferon alfa-2a (approximately 20 kDa) via lysine residues and through a stable covalent amide bond.[6] Interferon alfa-2a is produced by recombinant DNA technology by inserting a human leukocyte interferon gene into *Escherichia coli*.

Development of peginterferon alfa-2a

Interferons bind to cell surface receptors and induce a complex cascade of protein–protein interactions and rapid activation of gene transcription.[7,8] This intracellular signalling process leads to the production of numerous effector proteins that, amongst other effects, results in the inhibition of viral replication and/or function in infected cells.[7,8]

As discussed previously, non-pegylated (conventional) interferons were initially used to treat hepatitis C, but their use as monotherapy was associated with low sustained virological response rates (<15% after 6 months of treatment).[9] Other limitations of conventional interferon therapy include:

- rapid absorption from the injection site
- large volume of distribution
- rapid renal clearance
- short serum half-life (~6 hours)
- significant acute and chronic side-effects (e.g. depression and flu-like symptoms).[6]

The recommended three-times weekly dosing schedule of conventional interferon for the treatment of chronic hepatitis C causes large peaks and troughs in plasma interferon levels, with peaks exacerbating side-effects and troughs resulting in viral breakthrough (interferon levels are undetectable within 24 hours of dosing).[6]

These limitations prompted researchers to investigate whether the attachment of PEG moieties to interferons would improve their pharmacological characteristics, thereby resulting in greater efficacy and improved tolerability. Pegylation of interferon alfa-2b with a linear 12 kDa PEG moiety increased the plasma half-life considerably, with a ten-fold decrease in clearance compared with the unpegylated parent interferon.[6] However, the 12 kDa PEG group was attached via an ester linkage, which was susceptible to hydrolysis.[6,9] The second generation of pegylated interferons for hepatitis C therapy involved combining interferon alfa-2a with a larger (40 kDa) branched PEG moiety attached via a stable covalent amide bond.[6] This led to further improvements in serum half-life, with detectable levels of peginterferon alfa-2a persisting over 168 hours (1 week).[6] Furthermore, the large (40 kDa) PEG moiety resulted in several distinct pharmacological characteristics including sustained absorption, restricted distribution and reduced clearance compared with the smaller, linear peginterferons as well as non-pegylated interferons.[6]

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Pharmacokinetics

The main pharmacokinetic characteristics of peginterferon alfa-2a are reported in Table 1, which also lists the same parameters for peginterferon alfa-2b. Peginterferon alfa-2a is given as a weekly 180 μg subcutaneous injection administered into the abdomen or thigh.[10] Peginterferon alfa-2a is well absorbed, with pegylation of interferon alfa resulting in a slower absorption rate; the mean time taken to reach peak plasma concentrations (t_{max}) was 78 hours for peginterferon alfa-2a and 10 hours for interferon alfa in healthy volunteers.[4,11] The time taken for half of the dose to be absorbed (mean absorption time) was 59 and 2.6 hours, for peginterferon alfa-2a and interferon alfa, respectively.[4,11]

The delayed t_{max} for peginterferon alfa-2a compared with standard interferon and the smaller, linear pegylated interferons (t_{max} of 15–44 hours for peginterferon alfa-2b) is a consequence of its sustained absorption characteristics.[6] This property contributes to an increased residence time of the molecule within the body, relatively constant serum concentrations with once-weekly dosing (peak-to-trough ratio of 1.5–2.0) and about 4–6 weeks to reach steady-state drug-plasma concentrations.[9,11,12] Peginterferon alfa-2a also has a low volume of distribution (6–14 litres compared with more than 40 litres for the smaller peginterferons and conventional interferons) and thus is restricted mainly to the vasculature and well-perfused organs such as the liver and kidneys.[6,9] This is an advantageous property as clearance of the virus from the blood and liver are believed to be critical for long-term antiviral efficacy.[6] Moreover, this property may explain why there is no need to adjust the dose of peginterferon alfa-2a according to weight as the volume of blood varies less than bodyweight between individuals.[6,9,13] This contrasts with peginterferon alfa-2b, which requires weight-related dose adjustment.

Table 1. Pharmacokinetic characteristics of the two pegylated interferons (peginterferon alfa-2a and peginterferon alfa-2b) following administration of a single dose.[9–11]

	Peginterferon alfa-2a	Peginterferon alfa-2b
Mean absorption time (hours)	59	2.6
t_{max} (hours)	~80	15–44
V_d	6–14 L	0.99 L/kg
Clearance	60–100 mL/h	22 mL/h/kg
$t_{1/2}$ (hours)	77	~40
Peak-to-trough ratio[a]	1.5–2.0	>10

[a]After multiple doses.
$t_{1/2}$, serum elimination half life; t_{max}, time to reach maximum serum concentration; V_d, volume of distribution.

Reduced clearance is a characteristic shared by all peginterferons compared with their parent proteins. However, peginterferon alfa-2a needs to be metabolised in order to be eliminated whereas peginterferon alfa-2b breaks down soon after injection to release free interferon alfa-2b, which is then excreted renally.[6,9] Peginterferon alfa-2a's requirement for non-specific protease activity for its metabolism, which mostly occurs in the liver, significantly reduces its clearance thereby contributing to its longer half-life compared with peginterferon alfa-2b.[6] Differences in the metabolism between these two peginterferons means that doses of peginterferon alfa-2b need to be modified in patients with renal impairment (creatine clearance <50 mL/minute), whereas peginterferon alfa-2a does not require major dose modifications until the glomerular filtration rate has fallen to below 20 mL/minute.[9] A starting dose of 135 μg of peginterferon alfa-2a should be used for patients with end-stage renal disease.[10] However, patients with any degree of renal impairment should be carefully monitored and appropriate reductions in dose made in the event of adverse reactions.[10] The pharmacokinetic profile of peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis or bridging fibrosis is similar to that in non-cirrhotic patients with chronic hepatitis C and also in healthy volunteers.[4,11] Adjustments in the recommended dosage of 180 μg once weekly are not usually necessary in elderly patients.[10] However, drug absorption is slightly slower in elderly (>60 years) than in young healthy male volunteers (t_{max} 116 *vs* 81 hours, respectively).[4] The elderly also have a greater (but clinically non-significant) systemic exposure to peginterferon alfa-2a than younger individuals (area under the serum-concentration time curve of 1.66 *vs* 1.30 mg.h/L, respectively).[4] Moreover, the elimination half-life is longer in healthy elderly than in healthy younger men (110 *vs* 61 hours, respectively).[4]

Peginterferon alfa-2a's requirement for non-specific protease activity significantly reduces its clearance, thereby contributing to its longer half life.

Drug–drug interactions

The number of recorded drug–drug interactions for peginterferon alfa-2a is small, possibly because it is not dependent on extensive oxidative metabolism and thus is not generally subject to inductive or inhibitory activity of other agents.[8] Multiple doses of peginterferon alfa-2a had no significant effects on drug metabolism mediated by cytochrome P450 (CYP) 2C9, 2C19, 2D6 or 3A4 isoenzymes in 15 healthy male adults.[11] However, multiple doses of peginterferon alfa-2a administered with theophylline resulted in decreased clearance of theophylline. This is believed to be due to interferon alfa-mediated inhibition of CYP1A2 *de novo* synthesis.[11]

Clinical efficacy

Peginterferon alfa-2a vs unpegylated interferon as monotherapy

Four large randomised, open-label trials have compared peginterferon alfa-2a with conventional interferon alfa-2a for the treatment of chronic hepatitis C in interferon-naïve patients.[14–17] In all of these studies, peginterferon alfa-2a was administered as a subcutaneous injection once weekly and the virological response and biochemical efficacy was assessed at 48 weeks (i.e. the end of scheduled treatment) and then again after a 24-week treatment-free follow-up period. A histological response was also assessed at the end of follow up. Definitions of virological,

biochemical and histological response used in these and other studies described throughout this review are given in Table 2.

The studies that have compared peginterferon alfa-2a with conventional interferon alfa-2a for the treatment of chronic hepatitis C are summarised in Table 3. A dose-ranging trial compared the efficacy of once-weekly subcutaneous injections of peginterferon alfa-2a (45, 90, 180 and 270 μg) with conventional interferon alfa-2a (3 million international units [MIU]) given three-times weekly.[14] A majority of patients who received the 180 and 270 μg doses of peginterferon alfa-2a had a significant end of treatment response (60 and 56%, respectively) compared with the conventional interferon group (12%), with biochemical responses reported in 38, 27 and 15% of patients, respectively. Sustained virological responses were significantly higher in the peginterferon alfa-2a 90, 180 and 270 μg groups than in the conventional interferon group. Moreover, most patients who achieved an end of treatment virological response did so within the first 16 weeks of treatment, particularly those in the peginterferon alfa-2a 180 and 270 μg groups (78 and 73%, respectively). However, the proportion of patients achieving a histological response (47–66%) was similar in all treatment groups. From the results of this study it was apparent that the 180 μg peginterferon alfa-2a dose was associated with optimal efficacy amongst the range of doses tested.

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A further study compared doses of 135 and 180 μg of peginterferon alfa-2a with conventional interferon alfa-2a therapy.[15] In this study, patients given peginterferon alfa-2a, 135 and 180 μg, were more than three-times (odds ratios 3.3 and 3.2, respectively) as likely to achieve a sustained virological response than patients in the conventional interferon group. Moreover, both doses of peginterferon alfa-2a were associated with significantly higher biochemical responses and sustained biochemical responses than conventional interferon therapy (Table 3). Sustained virological response also correlated highly with sustained biochemical response, whilst 70% of those who obtained either an end of treatment virological response or biochemical response also had a histological response in all three treatment arms.

In a study comparing two large groups of patients treated with an optimal dose of peginterferon alfa-2a (180 μg, once weekly) and conventional interferon alfa-2a, peginterferon treatment was associated with a higher end of treatment virological responses (69 *vs* 28%, respectively; p=0.001) and sustained virological responses (39 *vs* 19%, respectively; p=0.001).[16] In a traditionally difficult-to-treat subgroup of patients with HCV genotype 1 infection, treatment with peginterferon alfa-2a was associated with a 28% sustained virological response, compared with 39% for all genotypes in this study. The rate of sustained biochemical response was also greater in the peginterferon than in the conventional interferon group (45 *vs* 25%,

Table 2. Definitions of virological, biochemical and histological responses (as used throughout the review [unless otherwise stated]).

Response	Definition
End of treatment virological response	Percentage of patients with undetectable HCV RNA[a] at the end of treatment.
Sustained virological response	Percentage of patients with undetectable HCV RNA[a] 24 weeks after the end of treatment.
Biochemical response	Percentage of patients with previously elevated ALT levels with normal or below normal levels at the end of treatment.
Sustained biochemical response	Percentage of patients with previously elevated ALT levels with normal or below normal levels 24 weeks after the end of treatment.
Histological response	A decrease of at least 2 points in the Histological Activity Index[b] assessed from liver biopsies obtained 24 weeks after the end of treatment.

ALT, alanine aminotransferase; HCV, hepatitis C virus.
[a]Measured by polymerase chain reaction (PCR) assay with lower limit of detection of 100 copies/mL.
[b]Where a score of zero denotes no inflammatory changes and no fibrosis and a score of 22 indicates multinodular necrosis, marked intralobular degeneration and focal necrosis, marked portal inflammation and cirrhosis.

Table 3. Trials comparing the efficacy of subcutaneous peginterferon alfa-2a (Pegasys®) and conventional interferon alfa-2a (INF) in interferon-naïve patients.[14–17]

Study (total randomised)	Trial design	Study regimen (drug dose and duration)	Number (%) with end of treatment response	Number (%) with sustained virological response
Reddy *et al.*[14] (n=159)	Randomised, open-label	Pegasys®, 45 μg weekly, 48 weeks	6 (30)	2 (10)
		Pegasys®, 90 μg weekly, 48 weeks	9 (45)*	6 (30)*
		Pegasys®, 180 μg weekly, 48 weeks	27 (60)*	16 (36)*
		Pegasys®, 270 μg weekly, 48 weeks	23 (56)*	12 (29)*
		INF α-2a, 3 MIU, thrice weekly, 48 weeks	4 (12)	1 (3)
Pockros *et al.*[15] (n=639)	Randomised, open-label	Pegasys®, 135 μg weekly, 48 weeks	114 (53)*	61 (28)*
		Pegasys®, 180 μg weekly, 48 weeks	115 (55)*	58 (28)*
		INF α-2a, 3 MIU, thrice weekly, 48 weeks	47 (22)	23 (11)
Zeuzem *et al.*[16] (n=531)	Randomised, open-label	Pegasys®, 180 μg weekly, 48 weeks	185 (69)*	103 (39)*
		INF α-2a, 6 MIU, thrice weekly, 12 weeks, then 3 MIU, thrice weekly, 36 weeks	73 (28)	50 (19)
Heathcote *et al.*[17a] (n=271)	Randomised, open-label	Pegasys®, 90 μg weekly, 48 weeks	40 (42)*	14 (15)
		Pegasys®, 180 μg weekly, 48 weeks	38 (44)*	26 (30)*
		INF α-2a, 3 MIU, thrice weekly, 48 weeks	12 (14)	7 (8)

*$p \leq 0.05$ *vs* interferon α-2a group. INF, interferon; MIU, million international units; Pegasys®, peginterferon alfa-2a.
[a]All patients in this study had bridging fibrosis or cirrhosis

respectively; $p=0.001$). Furthermore, the proportion of patients with both a sustained virological and sustained biochemical response was higher in the peginterferon than the conventional interferon group (38 *vs* 17%, respectively; $p=0.001$). There was also a high degree of correlation between sustained virological and sustained biochemical responses: of the 153 patients from both groups with a sustained virological response, 147 (96%) also had a sustained biochemical response.

Finally, in a study conducted in patients with chronic hepatitis C and cirrhosis or bridging fibrosis, a greater proportion of those given peginterferon alfa-2a (180 μg) had an end of treatment virological or biochemical response or a sustained virological or biochemical response, than those who were given conventional interferon alfa-2a.[17]

In summary, patients with chronic hepatitis C, with or without cirrhosis or bridging fibrosis, are more likely to achieve a virological or biochemical response, or a sustained virological or biochemical response, with peginterferon alfa-2a treatment (particularly the 180 μg weekly dose), than when receiving conventional interferon therapy.

Patients with chronic hepatitis C, with or without cirrhosis or bridging fibrosis, are more likely to achieve a sustained virological response with peginterferon alfa-2a treatment than when receiving conventional interferon therapy.

Peginterferon alfa-2a in combination with ribavirin

All HCV genotypes

Two large-scale clinical trials have investigated the effectiveness of combination treatment with peginterferon alfa-2a plus ribavirin for the treatment of chronic hepatitis C.[18,19] Several other trials have also specifically evaluated the effectiveness of peginterferon alfa-2a plus ribavirin treatment in smaller subgroups of patients according to the nature of the infecting HCV genotype.[20–22]

Following the demonstration of greater efficacy for pegylated compared with conventional interferon (see preceding section) and the observation that the addition of ribavirin to conventional interferon yields additional clinical benefit, the utility of combining peginterferon alfa-2a and ribavirin was investigated. A randomised trial determined whether peginterferon

Significantly more patients in the peginterferon alfa-2a plus ribavirin group experienced a sustained virological response compared with patients given peginterferon alfa-2a monotherapy or conventional interferon alfa-2b plus ribavirin.

alfa-2a plus ribavirin was more effective than peginterferon alfa-2a monotherapy or conventional interferon alfa-2b plus ribavirin.[18] A total of 1,121 patients were randomised to 48 weeks' treatment with either: peginterferon alfa-2a, 180 μg once weekly, plus ribavirin, 1,000 or 1,200 mg (depending on patient's body weight) once daily; peginterferon alfa-2a, 180 μg once weekly, plus placebo once daily; or conventional interferon alfa-2b, 3 MIU three-times weekly, plus ribavirin, 1,000 or 1,200 mg (dosed according to patients' weight). Clinical efficacy was determined by virological response at the end of treatment and after 24 weeks of treatment-free follow up (i.e. sustained virological response).

Significantly more patients in the peginterferon alfa-2a plus ribavirin group experienced a sustained virological response compared with patients given peginterferon alfa-2a monotherapy or conventional interferon alfa-2b plus ribavirin (Figure 1). Data from this study were further analysed according to the nature of the infecting HCV genotype (Table 4). Forty-six percent of patients with HCV genotype 1 who received peginterferon alfa-2a plus ribavirin had a

Figure 1. Sustained virological response after 48 weeks' treatment with (1) peginterferon, 180 μg once weekly, plus ribavirin, 1,000 or 1,200 mg once daily; (2) peginterferon alfa-2a, 180 μg once weekly, plus placebo once daily; or (3) interferon alfa-2b, 3 MIU three-times weekly, plus ribavirin, 1,000 or 1,200 mg.[18]

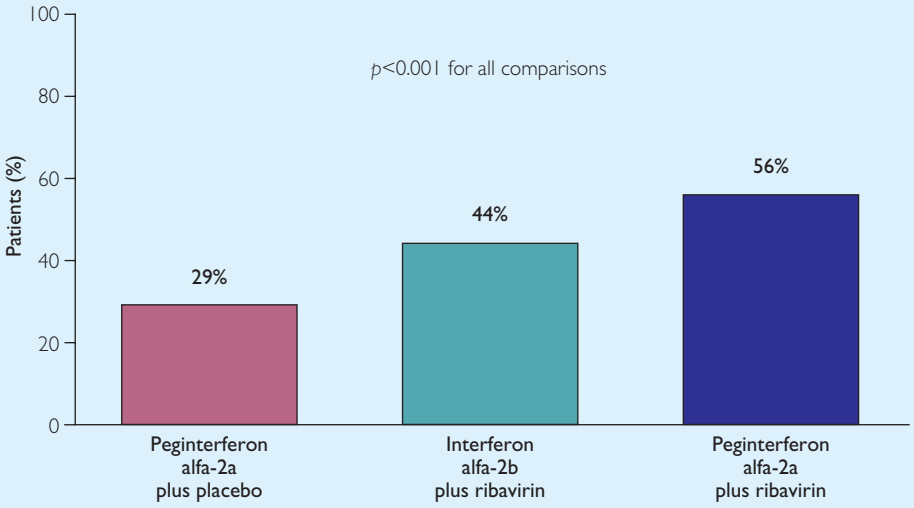

Table 4. The number (%) of patients with a sustained virological response according to genotype and baseline hepatitis C virus (HCV) RNA values after 48 weeks' treatment with: peginterferon alfa-2a, 180 μg once weekly, plus ribavirin, 1,000 or 1,200 mg once daily; peginterferon alfa-2a, 180 μg once weekly, plus placebo once daily; or conventional interferon alfa-2b, 3 MIU three-times weekly, plus ribavirin, 1,000 or 1,200 mg once daily.[18]

	Peginterferon alfa-2a plus ribavirin	Conventional interferon alfa-2b plus ribavirin	Peginterferon alfa-2a
HCV genotype			
All patients	255/453 (56)*	197/444 (44)	66/224 (29)
Genotype 1	138/298 (46)†	103/285 (36)	30/145 (21)
Genotype 2 or 3	106/140 (76)‡	88/145 (61)	31/69 (45)
Genotype 4	10/13 (77)§	4/11 (36)	4/9 (44)
Baseline HCV RNA			
≤2x10^6 copies/mL	99/159 (62)**	78/150 (52)	32/69 (46)
>2x10^6 copies/mL	156/293 (53)††	119/292 (41)	34/155 (22)

*p<0.001 *vs* conventional interferon alfa-2b plus ribavirin; †p<0.01 *vs* conventional interferon alfa-2b plus ribavirin; ‡p<0.005 *vs* conventional interferon alfa-2b plus ribavirin. §no p-value calculated due to small sample size; **p<0.04 *vs* conventional interferon alfa-2b plus ribavirin; ††p<0.003 *vs* conventional interferon α-2b plus ribavirin.

sustained virological response compared with 36% in the conventional interferon alfa-2b plus ribavirin group and 21% of those who received peginterferon alfa-2a monotherapy ($p<0.001$ for both comparisons). Significantly superior responses were also observed in patients infected with HCV genotypes 2 or 3, with a sustained virological response rate of 76% reported in the peginterferon alfa-2a plus ribavirin group, and also in patients with higher or lower baseline HCV RNA levels (Table 4).

Peginterferon alfa-2a plus ribavirin was tolerated at least as well as peginterferon alfa-2a monotherapy or conventional interferon alfa-2b plus ribavirin. Higher rates of pyrexia (56 *vs* 43%; $p<0.001$), myalgia (50 *vs* 42%; $p=0.02$), rigors (35 *vs* 24%; $p<0.001$) and depression (30 *vs* 22%; $p=0.01$) occurred in the conventional interferon alfa-2b plus ribavirin group compared with the peginterferon alfa-2a plus ribavirin group.

A randomised, double-blind trial assessed the efficacy and safety of 24 or 48 weeks of treatment with peginterferon alfa-2a plus either a low or a standard dose of ribavirin.[19] A total of 1,311 patients with chronic hepatitis C were randomised to peginterferon alfa-2a, 180 μg once weekly, for 24 or 48 weeks, plus a low dose (800 mg/day) or a standard weight-adjusted dose (1,000 or 1,200 mg/day) of ribavirin. Patients were categorised as either 48-LD (48 weeks, low ribavirin dose), 48-SD (48 weeks, standard ribavirin dose), 24-LD (24 weeks, low ribavirin dose) or 24-SD (24 weeks, standard ribavirin dose). Sustained virological response was defined as an undetectable serum HCV RNA level at the end of treatment and during the 12–24-week follow-up period.

Patients treated for 48 weeks were more likely to achieve a sustained virological response than those who were treated for 24 weeks (48-LD or 48-SD *vs* 24-LD or 24-SD, odds ratio [OR] 1.53 [95% CI 1.17–2.01]; $p=0.002$). Moreover, the likelihood of achieving a sustained virological response was greater amongst patients who were given a standard weight-based dose of ribavirin than amongst those given a low dose of ribavirin (24-SD or 48-SD *vs* 24-LD or 48-LD, OR 1.41 [95% CI 1.10–1.81]; $p=0.01$). The optimal treatment regimen of peginterferon alfa-2a plus standard-dose ribavirin for 48 weeks produced an overall sustained virological response rate of 63%.

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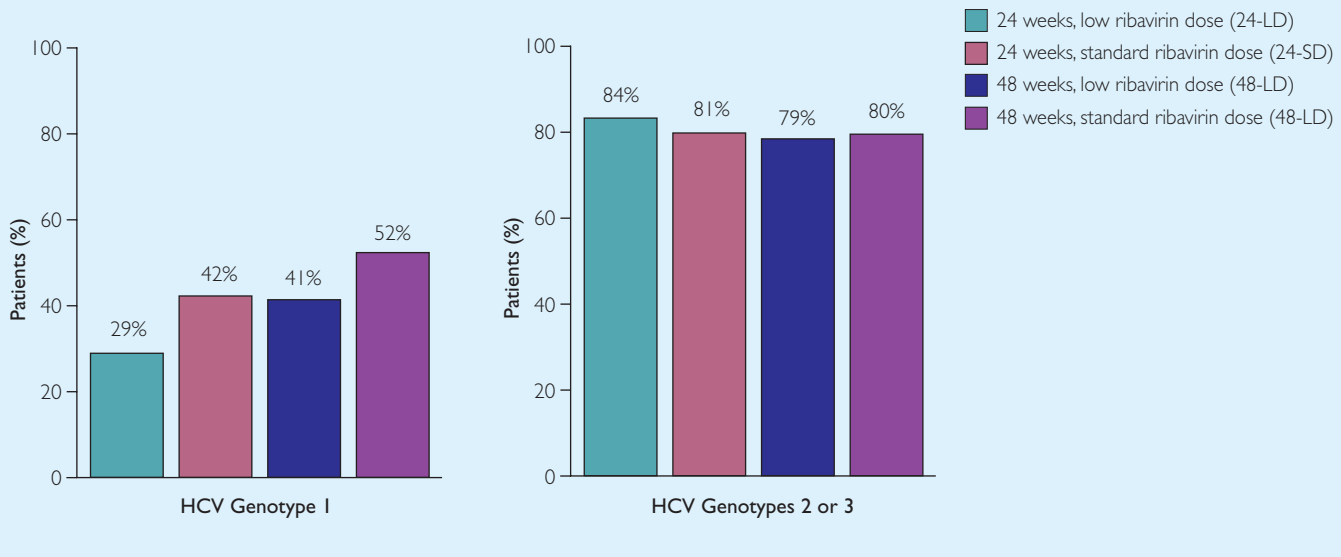
Data from this study were stratified according to HCV genotype as this is a major predictor of treatment response (Figure 2). According to sustained virological responses, amongst those with HCV genotype 1, treatment for 48 weeks was more effective than for 24 weeks (OR 2.19 [95% CI 1.52–3.16]; $p<0.001$) whilst standard-dose ribavirin was more effective than low-dose ribavirin (OR 1.55 [95% CI 1.14–2.10]; $p<0.005$) The 48-SD group had the highest sustained virological response rate (52%) for patients with HCV genotype 1. Sustained virological response rates were far more consistent across treatment groups for

Figure 2. Sustained virological response rates according to hepatitis C virus genotype in patients randomised to 24 or 48 weeks of treatment with peginterferon alfa-2a, 180 μg once weekly, and either a low dose (800 mg/day) or a standard weight-based dose of ribavirin (1,000 or 1,200 mg/day).[19]



patients with HCV genotypes 2 or 3, varying from 79–84%, with no significant influence from either treatment duration or ribavirin dose regimen (Figure 2).

All treatment regimens were generally well tolerated with the majority of side-effects being mild or moderate in severity. However, severe and serious adverse events were slightly less frequently reported in patients who were treated for 24 weeks than in those who underwent 48 weeks of treatment (*p*-values not reported).

HCV genotype 1

Genotype 1 is the most prevalent HCV genotype and accounts for about 50–60% of HCV infections in the UK.[20] Patients infected with this subtype also tend to respond poorly compared with infections by HCV genotypes 2 and 3. A number of studies have evaluated whether treatment with peginterferon alfa-2a plus ribavirin allows for a shorter duration of treatment in specific subgroups of patients infected with genotype 1 HCV.[20,21]

For example, one recent study has investigated the possibility of customising the treatment regimens of patients infected with HCV genotype 1 (and genotype 4) according to their virological response (as determined by HCV RNA levels) after 4 and 12 weeks.[23] All patients enrolled into this study (n=371) were treatment naïve and were initially randomised to treatment with peginterferon alfa-2a, 180 μg once weekly, plus weight-adjusted ribavirin (1,000 or 1,200 mg/day). After 4 weeks of treatment, HCV RNA levels were evaluated in all patients and those with a rapid virological response (defined as an undetectable HCV RNA level) were assigned to a shortened duration of treatment of 24 weeks (group D). These patients were described as 'super-responders'. Patients without a rapid virological response continued treatment and were re-evaluated at 12 weeks. At this stage, patients with an early virological response (unquantifiable HCV RNA or ≥2 $\log_{10}$ decrease in HCV RNA) were randomised to either 48 (group A) or 72 weeks of treatment (group B). Patients who showed no response at this stage were treated for 72 weeks (group C).

Interim data from this study have been reported.[23] Patients with genotype 1 (or genotype 4) who experienced a rapid virological response after 4 weeks (group D) were successfully treated with a shortened duration of treatment as evidenced by a sustained virological response rate of 87% after 24 weeks. For genotype 1 specifically, the sustained virological response rate was 84%. In addition, those patients who had the greatest viral suppression at week 4 had a lower chance of relapse than those with higher HCV RNA levels. Thus, this analysis indicates that 24 weeks' treatment is effective in patients with genotypes 1/4 who achieve a rapid virological response. Further studies are desirable to more fully evaluate the possibility of using a shorter treatment regimens in rapid responders with genotype 1 HCV.

24 weeks' treatment is effective in patients with genotypes 1/4 who achieve a rapid virologic response.

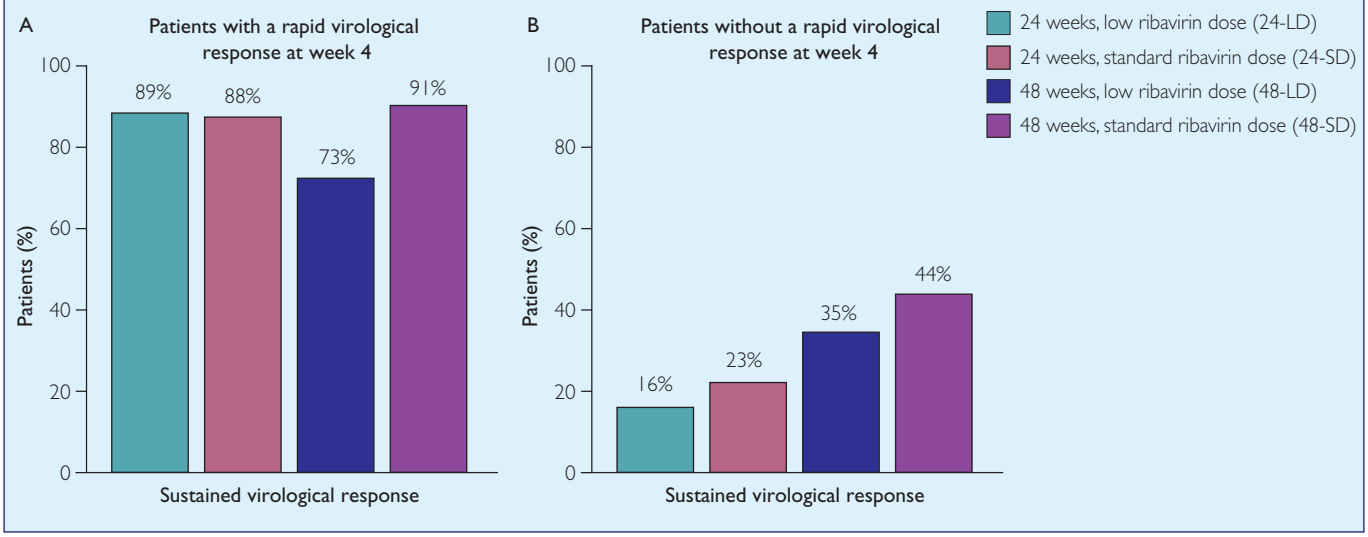
A *post hoc* analysis of a subgroup of patients infected with genotype 1 HCV from a trial previously described in this review evaluated the factors associated with a rapid virological response (at week 4) and a sustained virological response (HCV RNA <50 IU/mL) at the end of the follow-up period.[19,21] A total of 740 genotype 1 patients with chronic hepatitis C were randomised to peginterferon alfa-2a, 180 μg once weekly, for 24 or 48 weeks, plus low dose (800 mg/day) or standard weight-based dose (1,000 or 1,200 mg/day) of ribavirin. As discussed previously, patients were categorised as either 48-LD (48 weeks, low ribavirin dose), 48-SD (48 weeks, standard ribavirin dose), 24-LD (24 weeks, low ribavirin dose) or 24-SD (24 weeks, standard ribavirin dose).

Sustained virological response rates for patients with and without a rapid virological response are shown in Figure 3. This clearly illustrates that patients with a rapid virological response in each of the four treatment groups had consistently higher sustained virological response rates than those without a rapid virological response. Fifty one patients out of a total of 216 (24%) had a rapid virological response in the 24-week treatment groups. Sustained virological response rates were considerably higher in patients with a rapid virological response than those without a rapid virological response (89 *vs* 16%, respectively).

A rapid virological response was the best predictor of either end of treatment or sustained virological response for patients receiving 24 weeks' treatment.

In this analysis a rapid virological response was the best predictor of either end of treatment or sustained virological response for patients receiving 24 weeks' treatment (OR 23.7, 95% CI 9.1–61.7). Low baseline HCV RNA levels and the presence of subtype 1b infection were independently associated with a rapid virological response. These observations raise the possibility that performing an HCV RNA assay after 4 weeks of treatment with peginterferon alfa-2a plus ribavirin may help to determine the appropriate treatment duration for patients infected with genotype 1 HCV. Based on these data, the licence for peginterferon alfa-2a in Europe has recently been revised to allow for a shorter 24-week course of treatment in patients

Figure 3. Sustained virological response rates with (A) and without a rapid virological response (<50 IU/mL at week 4 of treatment) (B) in patients infected with HCV genotype 1 and randomised to 24 or 48 weeks of treatment with peginterferon alfa-2a, 180 μg once weekly, and either a low dose (800 mg/day) or a standard weight-based dose of ribavirin (1,000 or 1,200 mg/day).[21]



infected with genotype 1 HCV and with a low pre-treatment viral load (<800,000 IU/mL) and an undetectable load at weeks 4 and 24.[10]

HCV genotype 2 or 3

Sustained virological response rates in patients infected with HCV genotypes 2 and 3 are generally much higher than those achieved in patients with genotype 1.[22] Moreover, treatment duration with peginterferon alfa-2a in combination with ribavirin (800 mg/day) can be reduced from 48 to 24 weeks without compromising sustained virological response rates.[19,22] As a consequence, peginterferon alfa-2a plus ribavirin treatment is now licensed for 24 weeks' duration regardless of the initial viral load in patients with these genotypes.[10] A number of studies have investigated whether an even shorter duration of treatment (16 weeks) would be as effective as the standard 24-week treatment regimen for patients with an HCV genotype of 2 or 3.[22–24]

In one study, patients were treated for 4 weeks with peginterferon alfa-2a, 180 μg once weekly, plus ribavirin, 800–1,200 mg/day (dosed according to bodyweight; ≤65 kg: 800 mg; 65–85 kg: 1,000 mg; >85 kg: 1,200 mg).[22] Patients with a rapid virological response by week 4 (defined as an HCV RNA <600 IU/mL) were randomised at week 8 to a total treatment duration of 16 weeks (group A) or 24 weeks (group B). Those without a rapid virological response were treated for a total of 24 weeks (group C). All patients were followed up for 24 weeks after the end of the treatment phase. The primary end point was sustained virological response, defined as non-detectable HCV RNA (<600 IU/mL) at week 24 after completion of 16 or 24 weeks of treatment. After 4 weeks' treatment, a virological response was reported in 93% of patients. End of treatment and sustained virological responses varied minimally according to the duration of treatment: 94 and 82%, respectively in group A (n=71); 85 and 80% in group B (n=71); and 73 and 36% for group C (n=11), respectively. Sustained biochemical response rates were 89, 87 and 67% in groups A, B and C, respectively. Thus, 16 weeks of combination treatment with peginterferon alfa-2a plus ribavirin may be sufficient for some patients infected with HCV genotypes 2 or 3, at least in those who achieved a rapid virological response at week 4. There was also a trend towards a lower rate of adverse events in the 16-week treatment group compared with the 24-week treatment group. High pre-treatment HCV RNA levels (>800,000 IU/mL) significantly reduced the sustained virological response in individuals infected with HCV genotype 3 compared with those with a lower pre-treatment viral load (≤800,000 IU/mL) (59 *vs* 85%, respectively; p=0.003), though this observation was not apparent in patients infected with HCV genotype 2. The sustained virological response in patients with HCV genotype 3 was not compromised by a 16-week

treatment duration (group A) compared with a 24-week duration (group B) for those with a lower (<800,000 IU/mL) pre-treatment viraemia (93 and 84%, respectively; *p*-value not reported). However, in genotype 3 patients with a higher baseline viraemia (>800,000 IU/mL), the sustained virological response was markedly higher for 24- than for 16-weeks of treatment (67 *vs* 55%, respectively; $p>0.2$), though this did not reach statistical significance. Thus, shortening the duration of therapy from 24 to 16 weeks should be viewed with caution for patients with HCV genotype 3, as baseline HCV load is a complicating factor.

A much larger randomised, open-label multinational study (ACCELERATE) further evaluated whether a 16-week treatment course was as effective as the currently licensed 24-week schedule in patients infected with HCV genotype 2 or 3. Data from the ACCELERATE study were presented at the European Association for the Study of the Liver (EASL) in April 2006.[24] ACCELERATE enrolled 1,469 treatment-naïve patients infected with HCV genotypes 2 or 3 to treatment with peginterferon alfa-2a, 180 µg once weekly, plus ribavirin, 800 mg/day, for 16 or 24 weeks, followed by 24 weeks of treatment-free follow-up. In contrast to the previously described study by von Wagner *et al.*,[22] this larger controlled study consistently reported significantly higher sustained viral response rates with 24 weeks compared with 16 weeks of treatment (76 *vs* 65%; $p<0.0001$). In addition, the superiority of the 24-week treatment regimen was apparent regardless of the nature of the infecting HCV genotype (i.e. genotype 2 or 3), baseline HCV RNA levels or the presence or absence of a rapid virological response. Furthermore, the provision of an additional 8 weeks of therapy also decreased the rate of relapse during the treatment-free period, with a near doubling in the number of relapsers in the 16-week treatment group compared with the 24-week group (relapse rates: 16 *vs* 29%, for the 24- and 16-week treatment groups, respectively). The incidence of adverse events was similar in the two treatment groups though more patients in the 24-week group required their dose of peginterferon alfa-2a or ribavirin to be modified or discontinued. In summary, this larger study suggests that 16 weeks' treatment is inferior to the current standard of care, which is 24 weeks' treatment with peginterferon and ribavirin.

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HCV genotype 4

Compared with genotypes 1, 2 and 3, HCV genotype 4 infects comparatively few patients with chronic hepatitis C (<5% of patients are infected with genotypes 4, 5, 6 or mixed genotypes in European or North American populations).[25] Consequently, clinical efficacy data in this population are limited. Therefore, current guidance recommends treating these cases in the same manner as genotype 1 infections.[1,5]

A combined analysis of data from patients infected with HCV genotype 4 enrolled in two large trials discussed previously,[18,19] revealed that sustained virological response rates were obtained in 19 of 24 patients (79%) treated with peginterferon alfa-2a, 180 µg once weekly, plus ribavirin, 1,000 or 1,200 mg/day, for 48 weeks.[26] However, none of the five patients treated with a lower dose of ribavirin (800 mg/day) for 24 weeks achieved a sustained virological response, suggesting that combination therapy with full-dose ribavirin (1,200 mg/day) for 48 weeks is required in this group.[26]

A meta-analysis of randomised controlled trials comparing peginterferon alfa-2a or alfa-2b plus ribavirin with conventional interferon plus ribavirin in patients with HCV genotype 4 (n=424) also reached a similar conclusion.[25] Sustained virological response was higher in those genotype 4 patients treated with peginterferon plus ribavirin than conventional interferon plus ribavirin (55 *vs* 30%, respectively; relative risk 1.71 [95% CI 1.15–2.56]; $p=0.0088$). Sustained virological response was greater in those given standard- (1,000 or 1,200 mg/day) than low-dose (800 mg/day) ribavirin (72 *vs* 45.8%, respectively; $p=0.01$).[25]

Sustained virological response was higher in those genotype 4 patients treated with peginterferon plus ribavirin than conventional interferon plus ribavirin.

In summary, combination therapy with peginterferon alfa-2a and ribavirin offers a more effective and an equally well-tolerated treatment option compared with peginterferon monotherapy or conventional interferon combination treatment with ribavirin for all HCV genotypes. As HCV genotypes 2 and 3 are easier to treat than genotypes 1 or 4, the duration of treatment can be reduced from 48 to 24 weeks without affecting efficacy. However, based on data presented earlier in this review,[21] the licence for peginterferon alfa-2a in Europe has recently been revised.[10] Thus, a shorter, 24-week course is now also an option for patients with genotype 1 HCV with a low pre-treatment viral load (<800,000 IU/mL) and an undetectable viral load at weeks 4 and 24 and for patients with genotype 4 HCV regardless of pre-treatment viral load and an undetectable viral load at weeks 4 and 24.

Predictors of response

Several factors are known to be predictors of response, and these have been investigated in a number of *post hoc* analyses[21,27] of the large combination peginterferon alfa-2a plus ribavirin clinical trials described in the previous section.[18,19] As we have seen throughout this review, HCV genotype and viral load are the strongest predictors of treatment response, with genotypes 1 and 4 generally requiring a longer duration of treatment than genotypes 2 and 3. *Post hoc* analyses also evaluated the importance of an early virological response as a key predictor of a sustained virological response. Emerging data suggests that a week 4 rapid virological response is a very strong predictive factor of sustained virological response.[27] In addition, a further analysis suggested that it may be possible to terminate the treatment of non-responders (defined as <2 $\log_{10}$ decrease in HCV RNA) after 12 weeks of treatment as a negative predictive value of 97% could be obtained at this point.[27] Insulin resistance, fibrosis and HCV genotype have also found to be independent variables related to sustained virological response rates in patients (n=159) with chronic hepatitis C (excluding those with diabetes or fasting glucose levels >7 mmol/L).[28]

HCV genotype and viral load are the strongest predictors of response, with genotypes 1 and 4 requiring longer treatment than genotypes 2 and 3.

Special populations

Human Immunodeficiency Virus (HIV)-coinfected patients

In Europe and the USA about 15–30% of people infected with HIV are also infected with HCV.[8] HCV/HIV coinfection appears to result in a more rapid progression of liver disease and is also more difficult to treat than infection with HCV alone.[4,7,29] As HCV-associated liver disease is a leading cause of morbidity and premature mortality in people infected with HIV (particularly since the advent of effective antiretroviral therapy for HIV infections) all patients with HIV should be screened for HCV.[29,30]

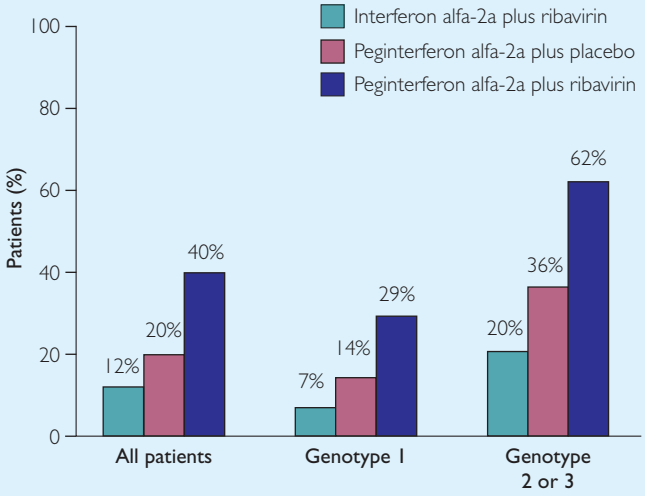
A number of trials have investigated the use of peginterferon alfa-2a plus ribavirin for the treatment of HCV/HIV coinfected patients.[31,32] In the AIDS Pegasys Ribavirin International Coinfection Trial (APRICOT), 868 interferon-naïve patients who had chronic hepatitis C and were coinfected with HIV were randomised to one of the following treatments: peginterferon alfa-2a, 180 μg once weekly, plus ribavirin, 800 mg/day; peginterferon alfa-2a, 180 μg once weekly, plus placebo; or conventional interferon alfa-2a, 3 MIU three-times weekly, plus ribavirin (dose not reported).[31] All treatments were administered for 48 weeks with a 24-week, treatment-free follow-up period thereafter. The primary efficacy variable was sustained virological response (defined as serum HCV RNA <50 IU/mL at the end of follow-up [i.e. 72 weeks]).

Sustained virological response rates were higher amongst patients given peginterferon alfa-2a plus ribavirin than those who received either conventional interferon plus ribavirin (40 *vs* 12%, respectively; $p<0.001$) or peginterferon alfa-2a monotherapy (40 *vs* 20%, respectively; $p<0.001$). In addition, peginterferon alfa-2a monotherapy was more effective than conventional interferon combination therapy (20 *vs* 12%, respectively; $p=0.008$). This latter observation suggests that peginterferon alfa-2a monotherapy is a suitable treatment option for coinfected individuals who cannot tolerate, or who are contraindicated for ribavirin treatment. HCV genotype was an important determinant of sustained response rates in this study. In patients infected with genotype 1, sustained virological response rates were 29, 14 and 7% in the peginterferon/ribavirin combination treatment, peginterferon monotherapy and conventional interferon/ribavirin combination therapy groups, respectively. For genotypes 2/3, the corresponding values were 62, 36 and 20% (Figure 4). All treatments were equally well tolerated, with withdrawals due to adverse events or laboratory abnormalities in 15–16% of patients in these groups.[8,31]

Data from a large open-label study of HIV/HCV coinfected patients have recently been reported.[32]The Pegasys Plus Ribavirin for HCV Treatment in HIV/HCV Coinfection (PRESCO) study randomised 389 patients to peginterferon alfa-2a (180 μg/day) plus ribavirin dosed according to body weight (1,000 or 1,200 mg/day). Patients infected with genotypes 2/3 received 24 weeks' treatment whilst those with genotypes 1/4 were randomised to 48 weeks therapy. Furthermore, in the light of findings from the APRICOT study which demonstrated lower relapse rates with a longer duration of treatment, the PRESCO study was amended during patient recruitment to include an arm that allowed for an extension in the duration of therapy to 72 weeks for patients infected with genotype 1/4 and to 48 weeks for those with genotypes 2/3.

The study reported a sustained virological response rate of 49.6% for the entire patient population, which represented a higher rate than other studies that have evaluated the effects of this treatment strategy in this patient population. This may relate to the fact that PRESCO

Figure 4. Sustained virological response rates for patients with chronic hepatitis C coinfected with HIV.[31]



used standard weight-adjusted doses of ribavirin in contrast to other studies which used ribavirin at a fixed dose (800 mg/day). When the data were evaluated according to the identity of the infecting HCV genotype, the following sustained virological response rates were reported: 35.6% for HCV genotype 1; 32.6% for genotype 4; and 72.4% for genotypes 2 and 3. In addition, extending the duration of treatment increased the sustained virological responses for the genotype 1/4 group to 53% compared with 31% in the 48-week group (p=0.004). However, a 44% discontinuation rate was reported amongst patients with HCV genotype 1 who received prolonged treatment. For the genotype 2/3 group, 48 weeks of treatment resulted in an 82% sustained virological response rate compared with a 67% response in the group that was treated for 24 weeks (p=0.04).

Clinical trial results from patients with chronic hepatitis coinfected with HIV show that peginterferon alfa-2a plus ribavirin is more effective than other regimens.

In conclusion, clinical trial results from patients with chronic hepatitis coinfected with HIV show that peginterferon alfa-2a plus ribavirin is more effective than other regimens such as conventional interferon with ribavirin or peginterferon alfa-2a without ribavirin. The current licence for peginterferon alfa-2a in this population is based upon the outcomes in APRICOT; 48 weeks of peginterferon alfa-2a plus 800 mg/day of ribavirin, irrespective of genotype.

Patients with normal liver transaminases

About 25% of patients with chronic hepatitis C have persistently normal or near normal alanine aminotransferase (ALT) levels.[8,33] Liver inflammation and fibrosis progression rates appear to be slower in this subpopulation compared with patients with persistently elevated ALT levels, although quality of life is similarly impaired in both groups.[8,33] Unfortunately, most clinical trials of peginterferon alfa-2a have specifically excluded patients with normal ALT levels. One open-label trial has investigated the utility of peginterferon alfa-2a plus ribavirin for this population.[33] Patients with at least three normal ALT values over an 18-month period were randomised to one of three treatment groups: peginterferon alfa-2a, 180 µg once weekly, plus ribavirin, 800 mg/day, for 24 weeks (n=212); the same combination for 48 weeks (n=210); or no treatment (n=69).[33] All patients were monitored over 72 weeks. The primary efficacy variable was sustained virological response, defined as undetectable serum HCV RNA at the end of 24 weeks of untreated follow-up.

About 25% of patients with chronic hepatitis C have persistently normal or near normal ALT levels.

Patients with normal ALT levels respond to treatment with peginterferon alfa-2a plus ribavirin similarly to those with raised ALT levels, with efficacy strongly influenced by treatment duration and HCV genotype.

None of the patients in the untreated control group cleared HCV RNA. However, sustained virological response rates of 30 and 52% were obtained in the 24- and 48-week treatment groups, respectively. For HCV genotype 1 specifically the corresponding rates were 13 and 40%, respectively (p<0.0001), and for genotype 2 or 3 these values were 72 and 78%, respectively (p=0.452). For genotype 4, sustained virological response rates were similar to those with genotype 1 infection (13% in patients treated for 24 weeks and 56% in those treated for 48 weeks). Adverse events were generally mild in severity, with 7 and 14% of patients in the 24- and 48-week treatment groups withdrawing due to adverse events or laboratory abnormalities.

In summary, patients with normal ALT levels respond to treatment with peginterferon alfa-2a plus ribavirin similarly to those with raised ALT levels, with efficacy strongly influenced by treatment duration and HCV genotype. This suggests that the treatment algorithms for patients with chronic hepatitis C and raised ALT levels should be extended to those who have normal ALT levels. Peginterferon alfa-2a is the only interferon specifically licensed for the treatment of patients with normal ALT levels. Mild chronic hepatitis C is often associated with normal ALT levels. Recent guidelines from the National Institute for Health and Clinical Excellence (NICE) now recommend peginterferon treatment of patients with mild disease.[1]

Non-responding or relapsing patients

Non-responders to interferon or peginterferon or patients who responded but relapsed during the treatment-free follow-up period, have been re-treated with peginterferon alfa-2a plus ribavirin in several studies in an effort to determine whether re-treatment is worthwhile.[34–37] Data from these trials are summarised in Table 5.

Sustained virological response rates were particularly low (18%) for patients with cirrhosis or bridging fibrosis who were non-responders to previous standard interferon therapy, with or without ribavirin.[37] However, it seems particularly worthwhile to re-treat patients who relapse following 24 weeks of peginterferon alfa-2a plus ribavirin treatment (from the trial by Hadziyannis *et al.*,[19] mentioned earlier), with sustained virological response rates of 55% being obtained.[36] Likewise, peginterferon plus ribavirin for 48 weeks was moderately effective in

Peginterferon plus ribavirin for 48 weeks was moderately effective in treating patients who failed to respond to standard interferon therapy, with or without ribavirin.

Table 5. Trials investigating the efficacy of open-label peginterferon alfa-2a plus ribavirin for the re-treatment of patients with chronic hepatitis C who previously failed to achieve a response or a sustained response (relapsed).[34–37]

Reference	Patients	Regimen (drug, dose and duration)	Sustained virological response rate (number of patients [%])	
			Non-responders	Relapsers
Sherman *et al.*[34]	312 patients[a] (212 non-responders, 100 relapsers) following conventional interferon therapy, with or without ribavirin	Peginterferon alfa-2a, 180 μg weekly, plus ribavirin, 1,000 or 1,200 mg/day, for 24 or 48 weeks	48/212 (23)	41/100 (41)
Herrine *et al.*[35]	Patients (n=124)[a] treated with conventional interferon who either failed to respond or who had viral breakthrough during this treatment	48 weeks' treatment with peginterferon alfa-2a, 180 μg weekly, plus: – ribavirin, 1,000 or 1,200 mg/day – mycophenolate mofetil, 2 g/day – amantadine, 200 mg/day – ribavirin + amantidine	 12/32 (38) 5/29 (17) 3/31 (10) 14/31 (45)	
Berg *et al.*[36]	Patients (n=64) who relapsed during 24 weeks' untreated follow-up after having an end-of-treatment virological response to 24 weeks of peginterferon alfa-2a/ribavirin combination treatment	Peginterferon alfa-2a, 180 μg weekly, plus ribavirin, 1,000 or 1,200 mg/day, for 48 weeks	–	35/64 (55)
Shiffman *et al.*[37]	Patients (n=604) with cirrhosis or bridging fibrosis who were non-responders to previous standard interferon therapy, with or without ribavirin	Peginterferon alfa-2a, 180 μg weekly, plus ribavirin, 1,000 or 1,200 mg/day, for 48 weeks[b]	109 (18)	–

[a]Sustained virological response defined as undetectable HCV RNA (<50 IU/mL) after a 24-week untreated follow-up period.
[b]Only 210/604 (35%) of patients had a response (undetectable HCV RNA) at 20 weeks and this group went on to receive a full 48-week treatment regimen. Data presented here are for this group.

treating patients who failed to respond to standard interferon therapy, with or without ribavirin, or who relapsed following these treatment regimens (Table 5).[35]

The black population

The prevalence of HCV infection in black Americans is approximately double that amongst Caucasian Americans.[8,38] Furthermore, in general, black patients with chronic hepatitis generally respond less favourably to treatment with interferon and are more likely to be infected with HCV genotype 1 (~90% of cases are genotype 1) compared with other ethnic groups.[26,39]

One clinical trial has specifically investigated the efficacy, safety and tolerability of peginterferon alfa-2a plus ribavirin in this group of patients.[38,39] A prospective, non-comparative, open-label trial involved 78 non-Hispanic black (HCV genotype 1) and 28 Caucasian American interferon-naïve patients with chronic hepatitis C.[38,39] All patients received peginterferon alfa-2a, 180 μg once weekly, plus weight-adjusted ribavirin, 1,000 or 1,200 mg/day, for 48 weeks, and were followed up for an additional 24 weeks. The primary efficacy evaluation was the proportion of patients with a sustained virological response, defined as an undetectable (<50 IU/mL) level of serum HCV RNA. A sustained virological response was obtained in 26% of black and 39% of Caucasian patients, supporting the trend towards a poorer response to treatment amongst black patients. Treatment was associated with a good safety and tolerability profile in both groups. Although the sustained virological response rate appears to be low for black patients, the study authors stated that it is higher than has been reported previously in smaller retrospective studies.

Quality of life

Chronic hepatitis C as well as the adverse effects and dosing schedule of conventional interferon regimens can significantly impair patients' health-related quality of life.[11] Patients with chronic hepatitis C have lower (worse) scores on all scales of the Short-Form (SF)-36, whilst those patients who achieved a sustained virological response scored higher across all scales, particularly on the physical health domains.[40]

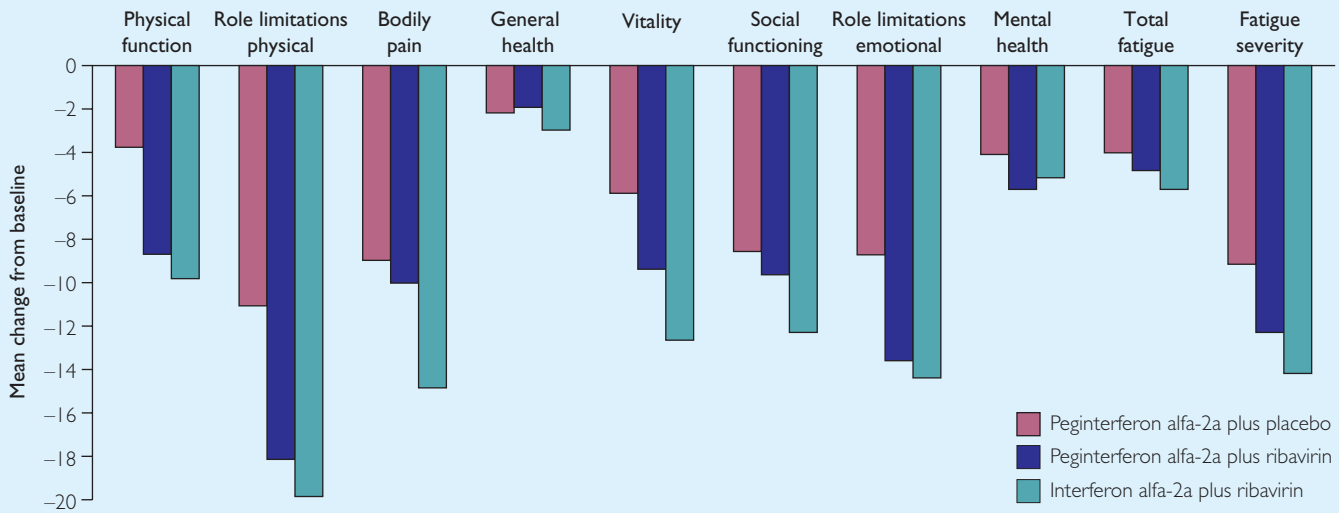
A pooled analysis of data derived from three open-label, randomised studies, which enrolled 1,441 patients with chronic hepatitis C and investigated the health-related quality of life of patients given peginterferon alfa-2a monotherapy or conventional interferon alfa-2a monotherapy.[41] Interferon-naïve patients were randomised to one of two treatment groups: peginterferon alfa-2a, 90, 135 or 180 μg, once weekly; or interferon alfa-2a, 6 MIU three-times weekly for 12 weeks, followed by 3 MIU three-times weekly for 36 weeks or 3 MIU three-times weekly for 48 weeks. All patients were monitored after a follow-up period of 24 weeks after treatment was completed, and sustained virological response was defined as undetectable HCV RNA (<100 copies/mL) at the end of the follow-up period. The SF-36 and Fatigue Severity Scale (FSS) were used to evaluate patients' health-related quality of life. During treatment, patients who were given peginterferon alfa-2a reported better quality of life and less fatigue than those taking conventional interferon as demonstrated by improvements in seven out of eight of the SF-36 domains, SF-36 summary scores and the FSS total and FSS visual analogue scale scores (all $p<0.05$). Thus, treatment with peginterferon alfa-2a is associated with greater improvements in quality of life than conventional interferon alfa-2a monotherapy.

Treatment with peginterferon alfa-2a is associated with greater improvements in quality of life than conventional interferon alfa-2a monotherapy.

A prospective, open-label trial compared the effects of 48 weeks' treatment with either peginterferon alfa-2a, 180 μg once weekly, or conventional interferon alfa-2b, 3 MIU three-times weekly, plus ribavirin, 1,000 or 1,200 mg, on the quality of life of patients with chronic hepatitis C (n=412).[42] The peginterferon alfa-2a group experienced less impairment in quality of life than those who received conventional interferon/ribavirin as demonstrated by the SF-36 summary score and the Hepatitis Quality of Life Questionnaire (HQLQ)-specific scale. This difference was particularly apparent in the first 24 weeks of treatment. Furthermore, the peginterferon alfa-2a group also had less impairment of work functioning and productivity across all measures and at all visits.

A secondary analysis of data from a large open-label study (n=1,121) described previously in this review,[18] investigated health-related quality of life during treatment with peginterferon alfa-2a, with or without ribavirin, or conventional interferon alfa-2b plus ribavirin.[43] Patients given peginterferon alfa-2a in combination with ribavirin had better health-related quality of life than those who received conventional interferon plus ribavirin, with significant differences reported on three SF-36 domains and both FSS scores ($p<0.05$). The group given peginterferon alfa-2a as monotherapy had the least impairment (Figure 5). These results show that

Figure 5. Difference from baseline in chronic hepatitis C patients' quality-of-life scores during treatment weeks 2–48.[43]



reductions in health-related quality of life that typically occur during the early weeks of conventional interferon therapy were less marked with peginterferon treatment. This difference may lead to better treatment compliance and thus superior clinical outcomes from peginterferon- than conventional interferon-based treatments.[43] Encouraging results have also been obtained in a secondary analysis of data from a peginterferon alfa-2a/ribavirin regimen conducted in patients with normal ALT levels, and illustrated that eradication of HCV is associated with a better quality of life and less fatigue.[44]

Safety and tolerability

The adverse event profile reported for peginterferon alfa-2a is similar to that for conventional interferon alfa, but some side-effects such as flu-like symptoms and depression appear to be less frequently reported.[4]

Figure 6 illustrates the adverse events experienced by patients (n=1,121) in a large, open-label trial of peginterferon alfa-2a, with or without ribavirin, and conventional interferon alfa-2b.[4,18] Flu-like symptoms (pyrexia, myalgia and rigors) and depression are significantly less common in patients receiving peginterferon alfa-2a plus ribavirin than in those given conventional interferon plus ribavirin. The occurrence of laboratory abnormalities such as anaemia, neutropenia or thrombocytopenia resulting in dosage adjustment of the peginterferon (24%) and/or ribavirin combination (25%) was, however, more common than in those given combination treatment with conventional interferon alfa-2b (8%) and/or ribavirin (19%).[4,18]

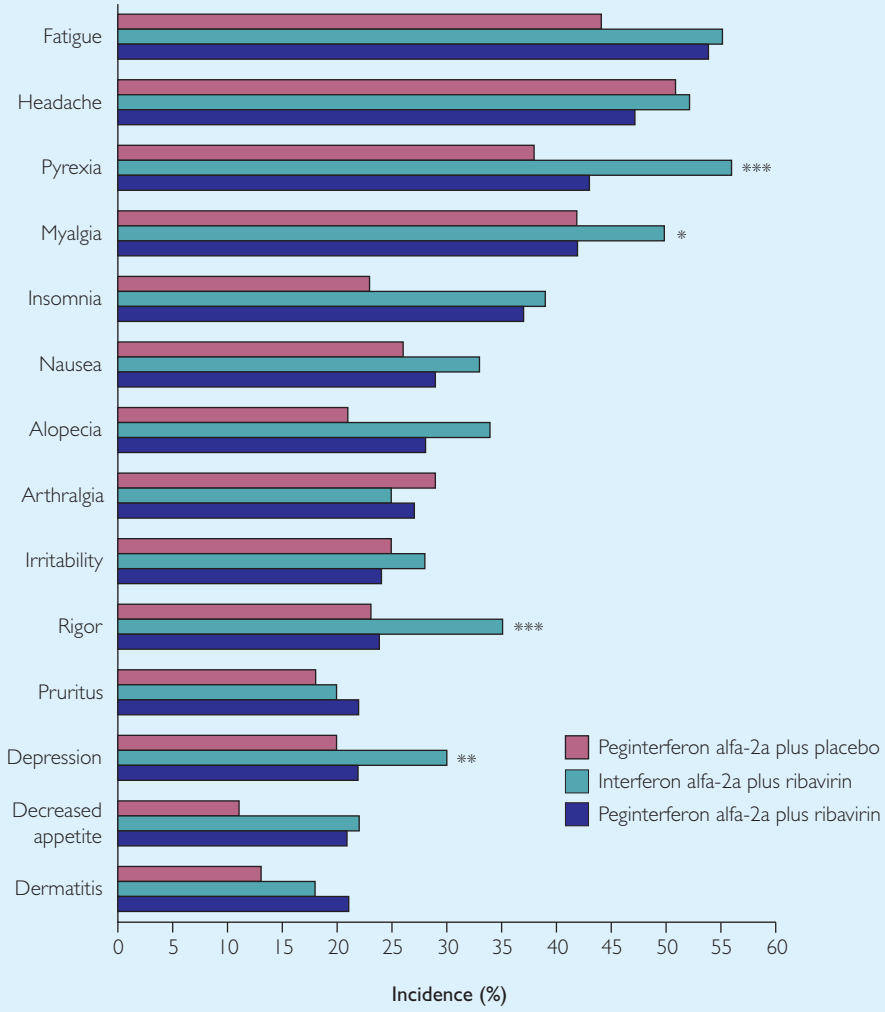
The adverse event profile for peginterferon alfa-2a is similar to that for conventional interferon-α, but some side-effects such as flu-like symptoms and depression appear to be less frequently reported.

Pharmacoeconomics

The cost-effectiveness of pegylated interferon (alfa-2a and alfa-2b), both given in combination with ribavirin, has been assessed from a UK perspective, using data from two large randomised, controlled trials.[3,18,45] A Markov model was used to follow a theoretical cohort of 1,000 patients over a 30-year period. The incremental cost saving per quality-adjusted life year (QALY) for pegylated dual treatment compared with conventional interferon combination therapy was £12,123. Other studies have looked specifically at the costs for peginterferon alfa-2a with ribavirin, comparing these with standard interferon combination therapy, though not from the UK perspective. For example, in the USA, peginterferon alfa-2a plus ribavirin was associated with an increase in QALYs of 0.70 and 1.05 for genotypes 1 and 2/3, respectively.[46] Moreover, sensitivity analyses revealed that treatment with peginterferon alfa-2a plus ribavirin remained cost-effective (i.e. below US$16,500 per QALY) after adjustment for a variety of key clinical and cost parameters. A similar study from the perspective of the Italian health service, where the costs of treatment with peginterferon alfa-2a and ribavirin were compared with those of standard interferon combination therapy, estimated that the weighted average incremental cost-effectiveness ratio for all HCV genotypes was €6,811 per life-year gained and €7,865 per

Treatment with peginterferon alfa-2a plus ribavirin appears to be a more cost-effective first-line treatment option than conventional interferon plus ribavirin.

Figure 6. Incidence of adverse events in treatment-naïve patients with chronic hepatitis C (n=1,121) given peginterferon alf-2a, 180 μg once weekly, with or without ribavirin, or conventional interferon alfa-2b, 3 MIU three-times weekly, plus ribavirin.[4,18] *p=0.02; **p=0.01; ***p<0.001 *vs* peginterferon/ribavirin.



QALY gained.[47] Finally, peginterferon alfa-2a plus ribavirin treatment has also been shown to be cost-effective for patients with persistently normal ALT levels and in patients coinfected with HIV.[48,49]

In summary, treatment with peginterferon alfa-2a plus ribavirin appears to be a more cost-effective first-line treatment option than conventional interferon plus ribavirin, regardless of HCV genotype, patients' ALT levels or coinfection with HIV.

Key points

- Historically, non-pegylated interferons were used to treat chronic hepatitis C, but were associated with low sustained virological response rates, even when used in combination with ribavirin.
- Attachment of PEG moieties to conventional interferons conferred more favourable pharmacological characteristics, such as a longer half-life resulting in less frequent dosing, less fluctuation in plasma drug levels and improvements in the safety profile.
- Use of a large (40 kDa) PEG moiety (as found in peginterferon alfa-2a) has resulted in distinct pharmacological advantages such as sustained absorption, restricted distribution and reduced clearance when compared with smaller, linear peginterferons (e.g. peginterferon alfa-2b).
- Monotherapy with peginterferon alfa-2a is more effective than conventional interferon monotherapy or combination therapy with ribavirin in patients with chronic hepatitis C, with or without cirrhosis or fibrosis.
- Significantly more patients given peginterferon alfa-2a plus ribavirin had a sustained virological response than those who received either peginterferon alfa-2a monotherapy or conventional interferon alfa-2b plus ribavirin combination therapy for all HCV genotypes.
- HCV genotypes 1 and 4 require longer courses of treatment than genotypes 2 and 3. However, the licence for peginterferon alfa-2a now allows for a shorter course of treatment in patients with genotype 1 HCV with a low viral load who exhibit a rapid virological response.
- Other patient subgroups that are difficult to treat, but which still have better outcomes with peginterferon alfa-2a plus ribavirin compared with conventional interferon-based treatments, include those coinfected with HIV and those who relapse after previous treatment with conventional interferon.
- Many patients with chronic hepatitis C have normal ALT levels, and these patients can also be treated effectively with peginterferon alfa-2a plus ribavirin.
- Peginterferon alfa-2a treatment, with or without ribavirin, is associated with superior quality of life scores than conventional interferon-based therapy, and is also more cost-effective.
- Peginterferon alfa-2a plus ribavirin exhibits fewer flu-like symptoms and less depression than conventional interferon-based therapy. However, laboratory anomalies such as neutropenia are more frequently observed.

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Acknowledgements

Figure 1 is adapted from Fried *et al.*, 2002.[18]
Figure 2 is adapted from Hadziyannis *et al.*, 2004.[19]
Figure 3 is adapted from Jensen *et al.*, 2006.[21]
Figure 4 is adapted from Torriani *et al.*, 2004.[31]
Figure 5 is adapted from Hassanein *et al.*, 2004.[43]
Figure 6 is adapted from Keating and Curran, 2003.[4]