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Peginterferon α-2a (40KD) Plus Ribavirin

A Review of its Use in the Management of Patients with Chronic Hepatitis C and Persistently 'Normal' ALT Levels

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Data Selection

Sources: Medical literature published in any language since 1980 on peginterferon alfa-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 Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.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 ('peginterferon alfa-2a' or ' peginterferon alpha-2a' or 'pegylated interferon alfa-2a') and 'ribavirin' and 'hepatitis C'. EMBASE search terms were ('peginterferon alfa-2a' or 'pegylated interferon alfa-2a') and 'ribavirin' and 'hepatitis C'. AdisBase search terms were ('peginterferon-alfa-2a' or 'peginterferon-alpha-2a' or 'pegylated interferon alpha-2a') and 'ribavirin' and 'hepatitis C'. Searches were last updated 24 January 2005.

Selection: Studies in patients with chronic hepatitis C and normal ALT levels 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

Combination therapy with subcutaneous peginterferon α-2a (40KD) [Pegasys®] plus oral ribavirin (Copegus®) has been evaluated previously in patients with chronic hepatitis C and elevated ALT levels. A recent randomised, nonblind, multicentre trial examined the efficacy of this combination therapy in the treatment of patients with persistently 'normal' ALT levels.

These trial results showed that combination therapy with peginterferon α-2a (40KD) plus ribavirin is effective in patients with chronic hepatitis C and persistently normal ALT levels. Overall, a sustained virological response occurred in over 50% of patients who received combination therapy for 48 weeks, albeit with a low daily dosage of ribavirin. The tolerability profile of combination therapy in patients with persistently normal ALT levels is similar to that seen in patients with elevated ALT levels. The decision as to whether or not treatment should be initiated in patients with chronic hepatitis C and persistently normal ALT levels should be made on an individual basis. If a decision is made to treat, combination therapy with peginterferon α-2a (40KD) plus ribavirin can be considered a first-line treatment option.

Pharmacological Properties

Early viral kinetics following the initiation of peginterferon α-2a (40KD) plus ribavirin therapy in patients with chronic hepatitis C and persistently normal ALT levels were similar to those in patients with elevated ALT levels. The addition of ribavirin to peginterferon α-2a (40KD) therapy reduces virological relapse during follow-up, thereby increasing the sustained virological response rate, in patients with chronic hepatitis C; however, the mechanism by which ribavirin achieves this effect is not completely understood. Both peginterferon α-2a (40KD) and ribavirin have shown beneficial immunomodulatory effects in patients with chronic hepatitis C.

Pegylation of interferon-α slows the absorption and reduces the renal clearance of the drug. Serum concentrations of peginterferon α-2a (40KD) were maintained throughout the dosing interval with once-weekly subcutaneous administration. Metabolism in the liver is the primary clearance mechanism for peginterferon α-2a (40KD).

At steady state, a maximum ribavirin plasma concentration of 2748 ng/mL was reached at 2 hours when administered in combination with peginterferon α-2a (40KD) in patients with chronic hepatitis C; the drug accumulates with repeated administration. Ribavirin metabolism occurs via two pathways; both the parent drug and its metabolites are primarily excreted renally. The drug has an elimination half-life of ≈120–170 hours.

Therapeutic Efficacy

Patients with chronic hepatitis C and persistently normal ALT levels were randomised to receive subcutaneous peginterferon α-2a (40KD) 180μg once weekly plus oral ribavirin 800 mg/day for 24 (n = 212) or 48 (n = 210) weeks or no treatment (n = 69) in a randomised, nonblind, multicentre trial; the sustained virological response rate was assessed 24 weeks after the end of treatment.

The sustained virological response rate was significantly ($p < 0.001$) higher in patients who received peginterferon α-2a (40KD) plus ribavirin for 48 compared with 24 weeks in the combined patient group (52% vs 30%) and in patients infected with hepatitis C virus (HCV) genotype 1 (40% vs 13%). In patients infected with HCV genotypes 2 or 3, there was no significant difference in sustained virological response rates between patients treated for 24 weeks and those treated for 48 weeks (72% and 78%). None of the patients in the control arm had a sustained virological response.

Patients who did not have an early virological response to peginterferon α-2a (40KD) plus ribavirin therapy were highly unlikely to attain a sustained virological response. For example, when patients receiving combination therapy for 48 weeks were considered, 97% of the patients without an early virological response did not achieve a sustained virological response. Similar results were seen in subgroups of patients infected with either HCV genotype 1 or non-1 genotypes.

Health-related quality of life benefits occurred in patients who received peginterferon α-2a (40KD) plus ribavirin and achieved a sustained virological response compared with treated patients who did not achieve a sustained virological response.

Tolerability

The adverse event profile reported in patients with chronic hepatitis C and persistently normal ALT levels who received peginterferon α-2a (40KD) plus ribavirin was typical of that expected with this combination therapy, with no new adverse events identified. The most commonly occurring clinical adverse events included headache, fatigue, myalgia, pyrexia, insomnia, nausea, arthralgia, depression, irritability, rigors, alopecia, asthenia, diarrhoea and pruritus.

At least one adverse event was reported in 99% of peginterferon α-2a (40KD) plus ribavirin recipients and in 77% of untreated controls. Treatment-related adverse events were reported in 96% and 98% of patients who received peginterferon α-2a (40KD) plus ribavirin for 24 or 48 weeks. Most of the reported adverse events were of mild severity. Among patients treated for 24 or 48 weeks, clinical adverse events resulted in dose modification of peginterferon α-2a (40KD) in 11% and 19% of patients and in dose modification of ribavirin in 20% and 30% of patients. Laboratory abnormalities resulted in dose modification of peginterferon α-2a (40KD) in 16% and 22% of patients and in dose modification of ribavirin in 9% and 21% of patients.

1. Chronic Hepatitis C with 'Normal' ALT Levels: Epidemiology and Natural History

Hepatitis C virus (HCV) is an RNA virus that belongs to the Flaviviridae family; there are six major HCV genotypes.[1] HCV infection is a common condition, with chronic disease developing in ≈85% of infected patients.[2] Chronic hepatitis C has a global prevalence averaging 1–2%.[3] The majority of patients with chronic hepatitis C remain without symptoms or significant liver disease for at least 2

decades following infection, with ≈20% of patients progressing to cirrhosis during this time period.[4] Up to 46% of patients with chronic hepatitis C have persistently 'normal' ALT levels;[5] the prevalence of cirrhosis in this subgroup of patients is 0.5–6%.[4] While there is currently no universally accepted definition for persistently normal ALT levels, in most trials it is defined as two or three ALT levels within the normal range obtained at least 1 month apart over a 6-month period preceding antiviral therapy.[4]

Historically, patients with chronic hepatitis C and persistently normal ALT levels were not considered appropriate candidates for antiviral therapy.[6] Patients with chronic hepatitis C and persistently normal ALT levels, in general, have histologically milder liver disease (stage 0–1 fibrosis) than patients with elevated ALT levels, as shown by the results of a recent retrospective analysis (figure 1).[7] Fibrosis progression occurs in these patients although generally at a slower rate than in patients with elevated ALT levels.[8,9] Despite this, there are several reasons why restricting antiviral therapy to patients with elevated ALT levels is no longer a valid approach.[10] For example, there is in fact only a weak association between the degree of ALT elevation and the severity of findings on liver biopsy,[11] meaning that ALT levels should not be considered a reliable surrogate marker for the severity of liver disease.[12] As seen in figure 1, patients with persistently normal ALT levels exhibit a range of disease severities, with an important minority of patients demonstrating moderate (stage 2) or advanced (stage 3–4) liver fibrosis.[7] Moreover, some patients with histologically mild disease will progress and go on to develop advanced fibrosis or cirrhosis.[12] Eradicating HCV is the primary goal of treatment in chronic hepatitis C; however, patients with mild disease may have other indications for therapy (e.g. they may be symptomatic or there may be concerns regarding potential transmission of HCV).[12]

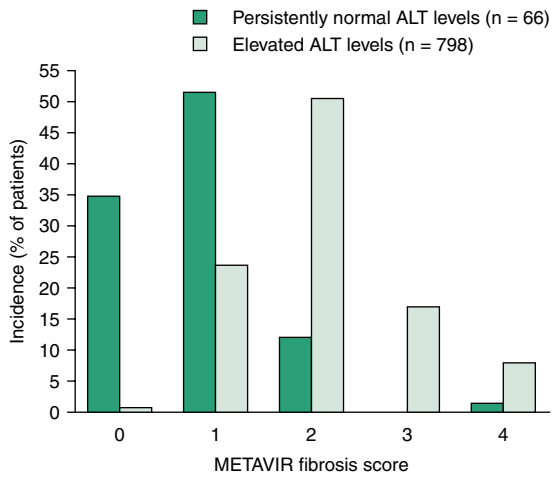

Fig. 1. Liver fibrosis stage in patients with chronic hepatitis C and normal or elevated ALT levels. Fibrosis was staged using the METAVIR system (a 5-point scale whereby 0 = no fibrosis, 1 = portal fibrosis without septa, 2 = portal fibrosis with few septa, 3 = septal fibrosis without cirrhosis and 4 = cirrhosis). Results of a retrospective European analysis.[7]

There has been concern that treating patients with normal ALT levels may result in some patients experiencing ALT 'flares' (i.e. increases in serum ALT levels to five or ten times the upper limit of normal). However, early reports[6] of ALT flares occurring in patients with normal ALT levels during treatment with conventional interferon-α have not been confirmed[13] (see also section 4).

Another historical reason for not treating patients with chronic hepatitis C and persistently normal ALT levels was the low rate of success associated with early antiviral therapies (e.g. monotherapy with conventional interferon was effective in only 10–15% of patients); these low success rates meant that patients with mild disease experienced only limited benefit from treatment.[10] Again, this argument for withholding treatment is no longer valid given the improved success rates achieved with new therapies.[10]

The current treatment of choice in patients with chronic hepatitis C is combination therapy with pegylated interferon-α plus ribavirin (Copegus®, Rebetol®)[1].[11,13] Pegylated interferons were developed to overcome the limitations of conventional interferon-α. Indeed, peginterferon α-2a (40KD) [Pegasys®], comprising recombinant interferon-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

α-2a conjugated to an inert 40KD polyethylene glycol (PEG) polymer, proved more effective than conventional interferon-α in terms of sustained virological response rates.[14] The PEG moiety protects interferon-α-2a from proteolytic degradation, as well as reducing its immunogenicity. Moreover, the large size of peginterferon α-2a (40KD) results in reduced renal clearance and prolonged systemic exposure, meaning that once-weekly administration is feasible. The addition of the synthetic guanosine analogue ribavirin to peginterferon α-2a (40KD) monotherapy leads to a further increase in sustained virological response rates in patients with chronic hepatitis C.[15]

The presence of elevated ALT levels was an inclusion criterion in the majority of studies examining the use of new therapies in patients with chronic hepatitis C.[12] This was carried over from the time before reliable HCV RNA assays were available and the diagnosis of non-A, non-B hepatitis (as hepatitis C was previously known) was dependent on clinical and histological features, including elevated ALT levels.[12] Also, normalisation of ALT levels was an endpoint in trials of interferon therapy. Consequently, the pivotal studies that established the efficacy of combination therapy with peginterferon α-2a (40KD) plus ribavirin in chronic hepatitis C were in patients with elevated serum ALT levels.[15,16] As such, uncertainty has surrounded the efficacy of this combination therapy in patients with persistently normal ALT levels; this article focuses on the use of peginterferon α-2a (40KD) plus ribavirin in this patient group.

2. Pharmacological Properties

This section provides a brief overview of the pharmacological properties of peginterferon α-2a (40KD) and ribavirin. Data concerning the pharmacological properties of these drugs in patients with chronic hepatitis C and persistently normal ALT levels are limited.[17] Thus, most of the data in this section were obtained from studies in patients with chronic hepatitis C and elevated ALT levels,[18-22] studies in patients with chronic hepatitis C in whom ALT status was not specified[23-26] and studies in healthy volunteers,[27-29] supplemented by data from the manufacturer's prescribing information.[30-33] Study participants generally received standard dosages of peginterferon α-2a (40KD) 180μg once weekly administered subcutaneously. Oral ribavirin was administered at a dosage of 800–1200 mg/day. Some studies are only available as abstracts and/or posters.[23,24,27-29,34]

Treatment with peginterferon α-2a (40KD) plus ribavirin has greater therapeutic efficacy than peginterferon α-2a (40KD) alone in patients with chronic hepatitis C and elevated ALT levels; the addition of ribavirin reduces virological relapse during follow-up, thereby increasing the sustained virological response rate.[35] However, the mechanism by which ribavirin achieves this effect is not completely understood.

2.1 Antiviral Activity

Given that the antiviral activity of peginterferon α-2a (40KD) and ribavirin in patients with chronic hepatitis C has been reviewed previously,[35] the main focus of this section is a recent analysis[17] of viral kinetics in patients with persistently normal ALT levels. The analysis included a subset of patients (n = 20) from the pivotal trial[36] discussed in section 3, and a subset of patients with elevated ALT levels (n = 19) from another trial[16] for comparative purposes.

Early viral kinetics following the initiation of peginterferon α-2a (40KD) plus ribavirin therapy in patients with chronic hepatitis C and persistently normal ALT levels were similar to those in patients with elevated ALT levels.[17] There were no statistically significant differences between these patient groups in terms of the first, second or third phases of viral decay. The first phase is rapid and reflects the inhibition of HCV replication and the degradation of free virus, the second phase is slower and reflects the degradation of infected cells and the third phase represents treatment-enhanced loss of infected cells. Most patients exhibited biphasic decay, with only nine patients with persistently normal ALT levels and seven patients with elevated ALT levels exhibiting triphasic decay. Virological response in chronic

hepatitis C may, in fact, be less associated with baseline ALT levels than with γ-glutamyltranspeptidase (γ-GT) levels, as inhibition of viral replication and the second and third phases of viral decay were significantly ($p \leq 0.02$) greater in patients with normal γ-GT levels than in patients with elevated γ-GT levels, when stratified for HCV genotype.[17]

Ribavirin has shown inhibitory effects against several viruses in *in vitro* and *in vivo* studies.[37,38] However, in clinical trials in patients with chronic hepatitis C, oral ribavirin monotherapy had negligible effects on serum HCV RNA levels.[18-20,22,25,26] Proposed mechanisms for the antiviral action of ribavirin include inhibition of HCV RNA-dependent RNA polymerase, depletion of intracellular guanosine pools or induction of lethal mutations in the virus.[25]

2.2 Immunomodulatory Effects

Peginterferon α-2a (40KD) has beneficial immunomodulatory effects in patients with chronic hepatitis C.[21] Administration of peginterferon α-2a (40KD) with or without ribavirin for 48 weeks induced a vigorous, sustained, HCV-specific, CD4+ T-helper 1 response in patients with chronic hepatitis C.[21] The response was multispecific in that it involved multiple core and nonstructural HCV antigens. These results were obtained from a subset of patients enrolled in two randomised studies who had a weak or no HCV-specific CD4+ T-cell response prior to therapy. In contrast, patients receiving interferon-α-2a had an HCV-specific CD4+ T-cell response that was of lower magnitude, more narrowly focused and, in most patients, short lived.

The limited antiviral activity of ribavirin (section 2.1) suggests that the beneficial effects of this agent when administered in combination with peginterferon α-2a (40KD) may be immune mediated. Indeed, ribavirin monotherapy has demonstrated positive immunomodulatory effects.[26,39,40] For example, according to the results of several *in vitro* and *in vivo* studies,[26,39,40] ribavirin may shift the helper T-cell response in favour of a type 1 response. Ribavirin also inhibited the production of proinflammatory cytokines, such as tumour necrosis factor-α and interleukin-1β, in mouse hepatitis virus strain 3-stimulated macrophages.[39] Adding ribavirin to phytohaemagglutinin-stimulated peripheral blood mononuclear cells isolated from patients with chronic hepatitis C reduced interferon-γ synthesis, decreased total DNA, RNA and protein synthesis, and increased the apoptosis rate of CD45+ and CD14+ cells.[41]

2.3 Pharmacokinetic Profile

2.3.1 Peginterferon α-2a (40KD)

This section mainly focuses on the pharmacokinetics of peginterferon α-2a (40KD) when administered as monotherapy, although data concerning the pharmacokinetics of peginterferon α-2a (40KD) when administered in combination with ribavirin are also discussed.[23] Results of a pivotal phase III trial showed no pharmacokinetic interaction between the two drugs.[30]

Pegylation of interferon-α slows the absorption and reduces the clearance of the drug.[24,27] The pharmacokinetics of subcutaneous peginterferon α-2a (40KD) 180μg administered once weekly for 48 weeks to patients with chronic hepatitis C are summarised in table I.[24] All patients (n = 14) receiving subcutaneous peginterferon α-2a (40KD) 180μg once weekly plus oral ribavirin 1000 or 1200 mg/day had serum trough concentrations of peginterferon α-2a (40KD) above the level of quantitation by week 4, indicating that serum concentrations of the drug are sustained throughout the dosing interval by this timepoint.[23]

Peginterferon α-2a (40KD) has an absolute bioavailability of 84%.[30] The drug has restricted

Table I. Pharmacokinetics of peginterferon α-2a (40KD) [PEG-IFN α-2a (40KD)] in patients with chronic hepatitis C (n = 16).[24] Subcutaneous PEG-IFN α-2a (40KD) 180μg was administered once weekly for 48 weeks

$C_{max,ss}$ (ng/mL)	25.6
t_{max} (h)	45
AUC_{168} (ng • h/mL)	3334
CL/F (mL/h)	60

AUC_{168} = area under the serum concentration-time curve from 0 to 168 hours; **CL/F** = apparent clearance; **$C_{max,ss}$** = maximum serum concentration at steady state; **t_{max}** = time to C_{max}.

biodistribution[24] and is predominantly found in the bloodstream and extracellular fluid (volume of distribution at steady state of 6–14L).[30] Metabolism in the liver by nonspecific proteases is the primary clearance mechanism for peginterferon α-2a (40KD).[42]

The pharmacokinetics of peginterferon α-2a (40KD) were not altered to a clinically significant extent in men versus women,[31] in healthy elderly men (aged >60 years) versus healthy younger men (aged 18–25 years),[28] in patients with chronic hepatitis C versus healthy volunteers,[30] in patients with with mild cirrhosis (Child-Pugh class A) versus those without cirrhosis,[30] or in patients with various degrees of renal impairment versus patients with normal renal function.[34] The reduced renal clearance of peginterferon α-2a (40KD) compared with conventional interferon-α means that it can be administered in patients with end-stage renal disease undergoing haemodialysis; peginterferon α-2a (40KD) should be initiated at a lower dosage in such patients.[30,31]

Repeated administration of peginterferon α-2a (40KD) did not significantly affect drug metabolism mediated by the cytochrome P450 (CYP) isozymes CYP2C9, CYP2C19, CYP2D6 or CYP3A4.[29] However, peginterferon α-2a (40KD) inhibited CYP1A2, meaning that the clearance of theophylline (a CYP1A2 substrate) was reduced.[29]

2.3.2 Ribavirin

Ribavirin is rapidly absorbed following oral administration.[33] In patients with chronic hepatitis C, the pharmacokinetics of oral ribavirin 1200 mg/day following 12 weeks' administration in combination with peginterferon α-2a (40KD) are shown in table II.[33]

The bioavailability of ribavirin increased when administered with a high-fat meal.[33] Ribavirin accumulates with repeated administration, such that the steady-state maximum plasma concentration (C_{max}) is 4-fold higher than the C_{max} following a single dose.[33]

Ribavirin metabolism occurs via a degradative pathway in which deribosylation and amide hydrolysis yields a triazole carboxylic metabolite, and a reversible phosphorylation pathway in nucleated cells.[32] Both the parent drug and its metabolites are primarily excreted renally.[32] Following oral administration of radiolabelled ribavirin, 61% of the radioactivity was excreted in the urine and 12% was excreted in the faeces, with unchanged ribavirin accounting for 17% of the administered dose.[32] Ribavirin is neither a substrate for, nor an inhibitor of, CYP isozymes.[33] The drug had a long elimination half-life and a total apparent clearance of ≈26 L/h following a single oral dose (table II).[33]

Table II. Pharmacokinetics (mean values) of ribavirin (RBV) in patients with chronic hepatitis C.[33] Oral RBV 1200 mg/day was administered in combination with subcutaneous peginterferon α-2a (40KD) for 12 weeks. Patients (n = 39) weighed >75kg

C_{max} (ng/mL)	2748
t_{max} (h)	2
AUC_{12} (ng • h/mL)	25 361
$t_{½}$ (h)	≈120–170[a]
CL (L/h)	≈26[a]

a These data were obtained following a single dose of RBV (dose not specified).

AUC_{12} = area under the plasma concentration-time curve from 0 to 12 hours; **CL** = clearance; **C_{max}** = maximum plasma concentration; **$t_{½}$** = elimination half-life; **t_{max}** = time to C_{max}.

In patients without chronic hepatitis C who received a single dose of ribavirin 400mg, the area under the plasma concentration-time curve from time zero to the final timepoint was 3-fold greater in patients with creatinine clearance (CL_{CR}) of 0.6–1.8 L/h (10–30 mL/min) than in patients with normal renal function, and 2-fold greater in patients with CL_{CR} of 1.8–3.6 L/h (30–60 mL/min) than in patients with normal renal function.[32] Patients with CL_{CR} <3 L/h (<50 mL/min) should not receive ribavirin.[33]

The ribavirin dosage does not need to be adjusted in patients with hepatic dysfunction, according to the results of a study in patients with mild-to-severe hepatic impairment (Child-Pugh class A–C).[43]

3. Therapeutic Efficacy

The efficacy of peginterferon α-2a (40KD) plus ribavirin in patients with chronic hepatitis C and persistently normal ALT levels has been examined in a randomised, nonblind, multicentre trial.[36] Pa-

tients were randomised to receive subcutaneous peginterferon α-2a (40KD) 180μg once weekly plus oral ribavirin 800 mg/day for 24 (n = 212) or 48 (n = 210) weeks or no treatment (n = 69).[36] Patients were considered to have persistently normal ALT levels if they had ALT activity less than or equal to the upper limit of normal on at least three occasions that were at least 4 weeks apart; at least one value was obtained during screening and at least one value was obtained 6–18 months prior to screening. The mean maximum ALT level at baseline was 23.7–24.5 IU/L across the three treatment arms (maximum of three measurements).

Across the three treatment arms, 67–68% of patients were infected with HCV genotype 1 at baseline.[36] Infection with HCV genotypes 2, 3 and 4 was present in 18–20%, 9% and 3–4% of patients, respectively; ≤1% of patients were infected with HCV genotypes 5 or 6. Patients with no histological evidence of liver disease were excluded from the study, as were patients with evidence of cirrhosis or transition to cirrhosis. Across the three treatment groups, 66–77% of patients were liver fibrosis stage 0–1 at baseline, 14–21% were stage 2, 7–12% were stage 3–4 and <1% were greater than stage 4. In addition, 74–80% of patients had a necroinflammatory activity score of <5, 19–25% had a score of 5–10 and <1% had a score of >10 (liver histology was scored using the Ishak histological activity index scoring system). Women made up 60% of the study population.[36]

The primary endpoint was the sustained virological response rate (section 3.1), defined as an undetectable serum HCV RNA level (assessed using a qualitative polymerase chain reaction [PCR] assay [limit of detection 50 IU/mL]) 24 weeks after the end of therapy.[36]

An additional analysis[44] of this study[36] examined the effect of peginterferon α-2a (40KD) plus ribavirin on health-related quality of life (HR-QOL) [section 3.2]. HR-QOL was assessed using the Short Form 36 (SF-36) Health Survey and the Fatigue Severity Scale (FSS).[44] Domain scores on the SF-36 are scored from 0 (worst) to 100 (best) and the FSS comprises a total fatigue score and a 100mm visual analogue scale (VAS) score (with lower scores indicating better HR-QOL).

Data from additional analyses of the pivotal trial[36] are available as abstracts and/or posters.[44-47]

3.1 Sustained Virological Response Rate

Combination therapy with peginterferon α-2a (40KD) plus ribavirin induced sustained virological responses in patients with chronic hepatitis C and persistently normal ALT levels.[36] In contrast, none of the patients in the control arm had a sustained virological response;[36] HCV RNA levels remained stable in these patients throughout the study, with no patient spontaneously clearing HCV.[46]

The sustained virological response rate was significantly higher in patients who received peginterferon α-2a (40KD) plus ribavirin for 48 weeks compared with 24 weeks in the combined patient group (relative risk [RR] 1.7; 95% CI 1.4, 2.2) and in patients infected with HCV genotype 1 (RR 3.1; 95% CI 1.9, 4.9) [table III].[36] Sustained virological response rates were also numerically higher among patients infected with HCV genotype 4 who were treated for 48 rather than 24 weeks (table III) [statistical analysis not reported]. In patients infected with HCV genotypes 2 or 3, there was no significant difference in sustained virological response rates between patients treated for 24 weeks and those treated for 48 weeks (table III).

Among patients infected with HCV genotype 1, sustained virological response rates were numerically higher in patients with a low versus high viral load at baseline (47% vs 27% in patients treated for 48 weeks and 16% vs 9% in patients treated for 24 weeks) [statistical analysis not reported].[36] Similar results were obtained in patients infected with HCV genotype 4, with four of six (67%) and one of three (33%) patients with low or high baseline viral loads achieving a sustained virological response after 48 weeks' treatment, and one of six (17%) and zero of two (0%) patients with low or high baseline viral loads achieving a sustained virological response after 24 weeks' treatment (statistical analysis not reported). Baseline viral load did not appear to influence the sustained virological response rate in pa-

Table III. Sustained virological response (SVR) rates in patients with chronic hepatitis C and persistently normal ALT levels who received subcutaneous peginterferon α-2a (40KD) [PEG-IFN α-2a (40KD)] plus oral ribavirin (RBV).[36][a] Patients received treatment for 24wk (n = 212) or 48wk (n = 210); SVR was assessed 24wk after the end of therapy and was defined as an undetectable serum hepatitis C virus (HCV) RNA level

Dosage × duration (wk)	SVR rate (%) [no. of patients]			
	all patients[b]	patients infected with HCV genotype 1	patients infected with HCV genotypes 2 or 3	patients infected with HCV genotype 4[c]
PEG-IFN α-2a (40KD) 180μg qw + RBV 800 mg/day × 24	30 [63/212]	13 [19/144]	72 [42/58]	13 [1/8]
PEG-IFN α-2a (40KD) 180μg qw + RBV 800 mg/day × 48	52* [109/210]	40* [57/141]	78 [46/59]	56 [5/9]

a No patients in the control arm (in which patients received no treatment) achieved an SVR. Thus, results for this treatment arm (n = 69) are not presented.

b Three PEG-IFN α-2a (40KD) plus RBV recipients (two treated for 24wk and one treated for 48wk) were infected with HCV genotypes 5 or 6.

c Statistical analysis was not reported for patients infected with HCV genotype 4.

qw = once weekly; * $p < 0.001$ vs comparator.

tients infected with genotypes 2 or 3; in patients treated for 24 or 48 weeks, sustained virological response rates were 80% in those with low viral loads at baseline and 70% in those with high viral loads at baseline. Low and high viral loads were defined as HCV RNA levels of ≤800 000 IU/mL and >800 000 IU/mL, respectively.

Further analysis revealed that treatment duration and baseline viral load were significant and independent predictors of sustained virological response in patients infected with HCV genotype 1, whereas patient age was significantly and independently associated with sustained virological response in patients infected with HCV non-1 genotypes.[36]

Patients with chronic hepatitis C and persistently normal ALT levels who did not have an early virological response to peginterferon α-2a (40KD) plus ribavirin therapy were highly unlikely to attain a sustained virological response.[45] An early virological response was defined as an undetectable HCV RNA level (assessed using a qualitative PCR assay [limit of detection 50 IU/mL]) or a ≥2-$\log_{10}$ decrease in the HCV RNA level (assessed using a quantitative PCR assay [limit of quantitation 600 IU/mL]) after 12 weeks of treatment. Among patients who received peginterferon α-2a (40KD) plus ribavirin for 48 weeks (n = 210), 84% had an early virological response and 16% did not.[45] Of those patients who did not achieve an early virological response, 97% did not achieve a sustained virological response and 3% did. Among patients who experienced an early virological response, 62% achieved a sustained virological response and 38% did not.

Similar results were seen in subgroups of patients infected with either HCV genotype 1 or non-1 genotypes.[45] For example, in patients infected with HCV genotype 1 who were treated for 48 weeks (n = 141), 81% had an early virological response and 19% did not. Of those patients who did not achieve an early virological response, 96% did not achieve a sustained virological response and 4% did. Among patients who did experience an early virological response, 49% achieved a sustained virological response and 51% did not. Finally, in patients infected with HCV non-1 genotypes who were treated for 24 or 48 weeks (n = 137), 91% had an early virological response and 9% did not. None of the patients who failed to achieve an early virological response went on to experience a sustained virological response. Among patients who did experience an early virological response, 77% achieved a sustained virological response and 23% did not. Thus, overall, not achieving an early virological response had a negative predictive value of 96–100% for achieving a sustained virological response.

Reductions from baseline in serum ALT levels occurred in peginterferon α-2a (40KD) plus ribavirin recipients who achieved a sustained virological response, according to a *post hoc* analysis[47]

of the pivotal trial.[36] Median ALT levels were 10.1 and 9.2 IU/L at the end of follow-up in patients who received treatment for 24 or 48 weeks and achieved a sustained virological response.[47] The reduction suggests that baseline ALT activity in these patients may have been exceeding their true 'healthy' ALT activity (despite being within the 'normal' range). When peginterferon α-2a (40KD) plus ribavirin recipients were grouped according to whether they had 'low normal' or 'high normal' ALT levels (using a cut-off point of ≈20 IU/L), there was no significant between-group difference in the sustained virological response rate.

3.2 Health-Related Quality of Life

Patients with chronic hepatitis C and persistently normal ALT levels who received peginterferon α-2a (40KD) plus ribavirin and achieved a sustained virological response experienced HR-QOL benefits compared with treated patients who did not achieve a sustained virological response.[44]

Compared with peginterferon α-2a (40KD) plus ribavirin recipients who did not achieve a sustained virological response, treated patients who achieved a sustained virological response had significantly better adjusted SF-36 domain scores for general health (61.1 vs 71.2; $p < 0.0001$), pain index (65.4 vs 76.9; $p < 0.0001$), role physical (64.6 vs 77.1; $p < 0.01$), social functioning (74.2 vs 80.0; $p < 0.05$) and vitality (54.7 vs 64.4; $p < 0.0001$) at the end of follow-up.[44] Moreover, the adjusted SF-36 physical component score was significantly better in treated patients who achieved a sustained virological response versus those who did not (49.9 vs 45.0; $p < 0.0001$). Adjusted FSS total scores (31.5 vs 36.3; $p < 0.01$) and VAS (28.0 vs 39.0; $p < 0.001$) were also significantly better in peginterferon α-2a (40KD) plus ribavirin recipients who achieved a sustained virological response than in those who did not. These between-group differences were mainly attributed to worsening of SF-36 and FSS scores among nonresponders.[44]

Compared with untreated controls, recipients of peginterferon α-2a (40KD) plus ribavirin who achieved a sustained virological response had significantly better adjusted SF-36 domain scores for general health (63.9 vs 71.6; $p < 0.0001$) and vitality (56.5 vs 63.9; $p < 0.01$).[44]

4. Tolerability

The adverse event profile reported in patients with chronic hepatitis C and persistently normal ALT levels who received peginterferon α-2a (40KD) plus ribavirin[36] (see section 3 for study details) was typical of that expected with this combination therapy,[35] with no new adverse events identified. The most commonly occurring clinical adverse events in these patients (occurring in ≥20% of patients in at least one treatment arm) included headache, fatigue, myalgia, pyrexia, insomnia, nausea, arthralgia, depression, irritability, rigors, alopecia, asthenia, diarrhoea and pruritus (figure 2).[36] Adverse events such as headache, fatigue, myalgia, insomnia and asthenia were reported in 7–17% of untreated controls, suggesting that some adverse events that are often considered related to interferon therapy may, in fact, be manifestations of chronic hepatitis C.[36] Severe depression occurred in 2% of patients receiving peginterferon α-2a (40KD) plus ribavirin for 24 weeks and in 3% of patients receiving combination therapy for 48 weeks; depression (all severities) occurred in 6% of untreated controls (figure 2).

Almost all patients (99%) receiving peginterferon α-2a (40KD) plus ribavirin reported at least one clinical adverse event, compared with 77% of untreated controls.[36] Treatment-related adverse events were reported in 96% of patients who received peginterferon α-2a (40KD) plus ribavirin for 24 weeks and in 98% of patients who were treated for 48 weeks. Most of the reported adverse events were of mild severity, with severe adverse events occurring in 26% of patients who were treated for 24 weeks, in 33% of patients who were treated for 48 weeks and in 14% of untreated controls. Serious adverse events occurred in 8%, 16% and 6% of patients in the corresponding treatment groups. Among patients treated for 24 or 48 weeks, clinical adverse events resulted in dose modification of peginterferon α-2a (40KD) in 11% and 19% of

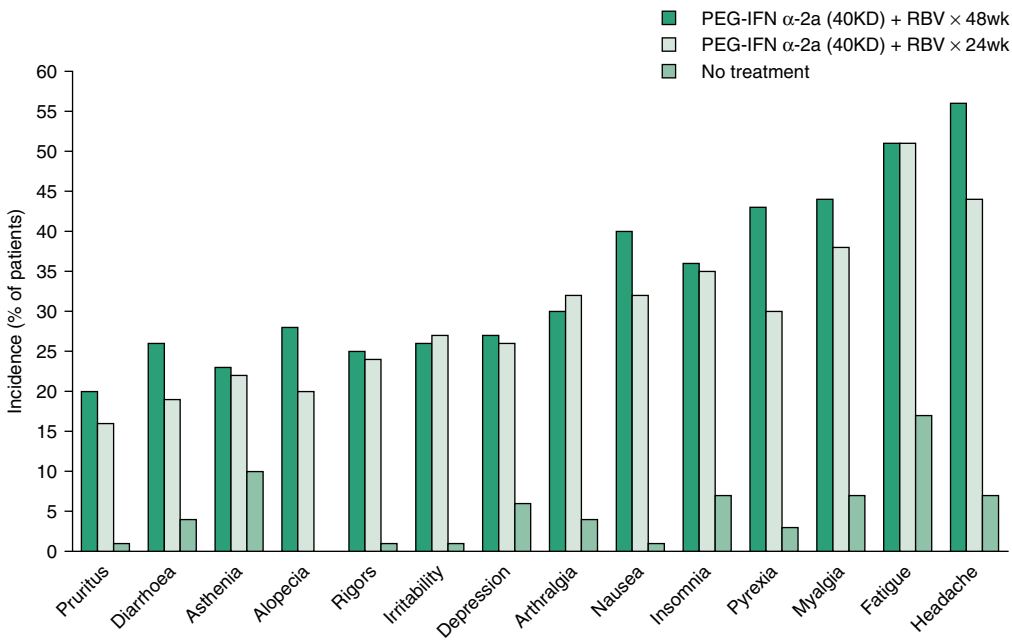

Fig. 2. Incidence of clinical adverse events (≥20% in at least one treatment arm) in patients with chronic hepatitis C and persistently normal ALT levels who received peginterferon α-2a (40KD) [PEG-IFN α-2a (40KD)] plus ribavirin (RBV).[36] In this randomised, open-label, multicentre study, patients received subcutaneous PEG-IFN α-2a (40KD) 180μg once weekly plus oral RBV 800 mg/day for 24 (n = 212) or 48 (n = 210) weeks or no treatment (n = 69). Statistical analyses were not reported.

patients and in dose modification of ribavirin in 20% and 30% of patients.

Transient increases in ALT levels to >30 but <60 IU/L occurred in 40% and 38% of patients receiving peginterferon α-2a (40KD) plus ribavirin for 24 or 48 weeks and in 45% of untreated controls.[36] Increases in ALT levels to >60 but <150 IU/L occurred in 14%, 11% and 6% of patients in the corresponding patient groups, with increases to >150 IU/L occurring in ≤2% of patients across treatment arms. Most moderate elevations in ALT levels occurred at the time of virological relapse in patients receiving peginterferon α-2a (40KD) plus ribavirin. No severe ALT flares occurred in peginterferon α-2a (40KD) plus ribavirin recipients.

A reduction in haemoglobin levels to <10.0 but >8.5 g/dL occurred in 5% of patients receiving peginterferon α-2a (40KD) plus ribavirin for 24 weeks and in 11% of patients receiving combination therapy for 48 weeks.[36] Reductions in haemoglobin levels to <8.5 g/dL, neutrophil counts to $<0.5 \times 10^9$/L and platelet counts to $<50 \times 10^9$/L occurred in ≤5% of peginterferon α-2a (40KD) plus ribavirin recipients. Hypothyroidism or hyperthyroidism occurred in ≤2% of patients receiving combination therapy. Among patients treated for 24 or 48 weeks, laboratory abnormalities resulted in dose modification of peginterferon α-2a (40KD) in 16% and 22% of patients and in dose modification of ribavirin in 9% and 21% of patients.

5. Dosage and Administration

In the US, combination therapy with peginterferon α-2a (40KD) plus ribavirin is approved for use in adults with chronic hepatitis C who have compensated liver disease and have not received prior treatment with interferon-α.[31] In the EU, the combination is approved for use in adults with chronic hepatitis C who are positive for serum HCV RNA, including patients with compensated cirrhosis.[30,48] Combination therapy is approved for use in the EU in both previously untreated patients and in patients

who have had a prior response to interferon-α and subsequently relapsed.[30]

The recommended dosage of peginterferon α-2a (40KD) is 180μg administered once weekly by subcutaneous injection.[30,31] Ribavirin should be administered orally in two divided doses.[30,31] A ribavirin dosage of 1000 mg/day is recommended in patients infected with HCV genotype 1 (or HCV genotype 4 in the US[31]) who weigh <75kg and a ribavirin dosage of 1200 mg/day is recommended in patients infected with HCV genotype 1 (or HCV genotype 4 in the US[31]) who weigh ≥75kg.[30,31] Patients infected with HCV genotypes 2 or 3 should receive ribavirin 800 mg/day, regardless of bodyweight.[30,31]

The duration of combination therapy varies according to the HCV genotype.[30,31] A treatment duration of 48 weeks is recommended in patients infected with HCV genotype 1 (or HCV genotype 4 in the US[31]) compared with 24 weeks in patients infected with HCV genotypes 2 or 3.[30,31]

Local prescribing information should be consulted for contraindications, precautions and warnings associated with peginterferon α-2a (40KD) plus ribavirin combination therapy, as well as for recommended dosage adjustments in patients experiencing certain adverse events (e.g. neutropenia, anaemia, thrombocytopenia, depression, hepatic impairment).

6. Place of Peginterferon α-2a (40KD) Plus Ribavirin in the Management of Patients with Chronic Hepatitis C and Persistently 'Normal' ALT Levels

Chronic hepatitis C has a global prevalence averaging 1–2%.[3] Patients with chronic hepatitis C who develop cirrhosis are at risk of progressing to liver failure and hepatocellular carcinoma. Indeed, chronic hepatitis C is now the most common reason for liver transplantation in both Western Europe and the US.[3]

The management of patients with chronic hepatitis C is a rapidly changing field. Current guidelines from the US National Institutes of Health (NIH)[11] and the American Association for the Study of Liver Diseases (AASLD)[13] recommend that patients with chronic hepatitis C and an increased risk of cirrhosis receive treatment. Combination therapy with peginterferon-α plus ribavirin is the preferred treatment option.[11,13] Treatment with peginterferon-α plus ribavirin 800 mg/day for 24 weeks is deemed sufficient in patients infected with HCV genotypes 2 or 3.[11,13] In contrast, patients infected with HCV genotype 1 should receive peginterferon-α plus ribavirin 1000 or 1200 mg/day (depending on bodyweight) for 48 weeks, given that HCV genotype 1 is less amenable to treatment than HCV genotypes 2 or 3.[11,13] Moreover, NIH guidelines state that treatment need not be extended past 12 weeks in nonresponders,[11] and AASLD guidelines state that treatment may be discontinued at 12 weeks in nonresponders,[13] given that these patients are unlikely to subsequently go on to achieve a sustained virological response.

Results of the pivotal trial in patients with persistently normal ALT levels concur with NIH and AASLD recommendations.[36] The sustained virological response rate was similar in patients infected with HCV genotypes 2 or 3 who received combination therapy for 24 or 48 weeks (>70%; section 3.1).[36] However, sustained virological response rates were significantly higher in patients infected with HCV genotype 1 who were treated for 48 versus 24 weeks (section 3.1).[36] The optimal ribavirin dosage in patients infected with HCV genotype 1 (1000 or 1200 mg/day depending on bodyweight) was not employed in the pivotal trial,[36] as data supporting this regimen were not yet available at the time that the trial was planned. Possibly, the sustained virological response rate may have been further improved if this optimal regimen had been used.[36] Current prescribing information does not differentiate between patients with persistently normal or elevated ALT levels in terms of recommending ribavirin 1000 or 1200 mg/day in HCV genotype 1 (section 5). However, further data confirming the optimal ribavirin dosage in patients with persistently normal ALT levels would be of interest, as would be data confirming the findings of this initial trial. In line with NIH and

AASLD recommendations, patients with persistently normal ALT levels who did not have an early virological response to peginterferon α-2a (40KD) plus ribavirin therapy were highly unlikely to attain a sustained virological response[45] (section 3.1).

Although cross-study comparisons should be made with caution, the sustained virological response rate of 52% achieved in patients with persistently normal ALT levels who received peginterferon α-2a (40KD) plus ribavirin 800 mg/day for 48 weeks[36] (section 3.1) is the same as the sustained virological response rate achieved in a pivotal trial including patients with elevated ALT levels who received the same regimen (52%).[16] Furthermore, findings concerning the optimum duration of therapy in patients with persistently normal ALT levels infected with different HCV genotypes (section 3.1) are similar to those in patients with elevated ALT levels.[16] One difference between the trial in patients with persistently normal ALT levels who received peginterferon α-2a (40KD) plus ribavirin[36] and pivotal trials of this combination therapy in those with elevated ALT levels[15,16] that may have affected outcome is that patients with cirrhosis or transition to cirrhosis were excluded from the former trial,[36] whereas 25%[16] and 13%[15] of patients had bridging fibrosis or cirrhosis in the latter trials.

Combination therapy with peginterferon α-2a (40KD) plus ribavirin had a similar tolerability profile in patients with persistently normal ALT levels[36] (section 4) to that seen in patients with elevated ALT levels.[15,16] In addition, dose modification of peginterferon α-2a (40KD) or ribavirin because of adverse events or laboratory abnormalities occurred in similar proportions of patients with persistently normal[36] (section 4) or elevated[15] ALT levels. No severe ALT flares occurred in combination therapy recipients (section 4).[36]

Thus, the results of the trial in patients with chronic hepatitis C and persistently normal ALT levels[36] show the efficacy of peginterferon α-2a (40KD) plus ribavirin combination therapy in this patient group. The question that remains to be answered is whether or not routine treatment is warranted in all patients with persistently normal ALT levels.

As discussed in section 1, the historical approach of never offering treatment to patients with chronic hepatitis C and normal ALT levels is no longer valid. However, it is currently unclear whether patients with chronic hepatitis C and persistently normal ALT levels and/or histologically mild liver disease should routinely receive antiviral therapy.[4] Arguments in favour of treatment include the potential to interrupt the progression of liver disease (especially given that it is not yet possible to predict which individual patients are going to progress faster than others) and prevent future HCV-related complications, and the potential to achieve high sustained virological response rates, given that a large proportion of patients with persistently normal ALT levels have mild fibrosis (which is easier to treat than more advanced disease).[4] Arguments against treatment are that patients with persistently normal ALT levels generally have a favourable natural history without treatment, that the definition of what constitutes a normal ALT level is not clear, and that current antiviral therapy is associated with adverse effects.

As such, the best approach for now is to manage patients on an individual basis, a stance supported by the NIH and AASLD guidelines.[11,13] Issues to consider when deciding whether or not to treat include factors linked to treatment outcome (e.g. HCV genotype, viral load, histological stage of disease, patient age), patient motivation and preference, HR-QOL, the presence of symptoms or complications of HCV infection, the presence of comorbid illness and the duration of disease.[4]

There is also controversy among experts over whether or not patients with chronic hepatitis C and persistently normal ALT levels should routinely undergo liver biopsy.[4] As noted previously, some patients with persistently normal ALT levels will have extensive hepatic fibrosis, and AASLD guidelines state that liver biopsy is currently the only way to obtain the information needed to guide treatment decisions in such patients.[13]

More data are needed concerning the natural history of chronic hepatitis C in patients with persistently normal ALT levels. Given that the presence of abnormal ALT levels often serves as the trigger leading to the diagnosis of HCV infection, a problem facing researchers is the difficulty of diagnosing patients with HCV infection if they are without apparent symptoms and have normal ALT levels.[4] Another hindrance is that liver biopsy is currently the only way to accurately assess liver histology in these patients. The development of a noninvasive test for evaluating liver fibrosis would be a major advance. Although patients with persistently normal ALT levels generally have less extensive histological disease than those with elevated ALT levels (section 1), a considerable proportion of patients with persistently normal ALT levels in the pivotal trial had moderate-to-advanced necroinflammation and fibrosis of a clinically significant stage (section 3).[36] Also, as mentioned in section 1, there is currently no universally accepted definition for what constitutes a persistently 'normal' ALT level. Recent studies suggest that the upper limit of the normal ALT range should be shifted downwards;[49,50] an additional analysis[47] of the pivotal trial[36] in patients with persistently normal ALT levels provides support for this view (section 3.1).

Besides peginterferon α-2a (40KD), the other pegylated interferon-α recommended for use in combination with ribavirin in patients with chronic hepatitis C is peginterferon-α-2b (12KD). Twelve-week results from a small (n = 21) trial in patients with persistently normal ALT levels suggest that the combination of peginterferon-α-2b (12KD) plus ribavirin is also effective in this patient group.[51] However, these data have not yet been fully published and sustained virological response rates have not yet been reported. To date, there are a lack of data from large, well designed, head-to-head trials comparing the effect of the two pegylated interferons (plus ribavirin) on sustained virological response rates in patients with chronic hepatitis C.

In conclusion, combination therapy with peginterferon α-2a (40KD) plus ribavirin is effective in patients with chronic hepatitis C and persistently normal ALT levels. Overall, a sustained virological response occurred in over 50% of patients who received combination therapy for 48 weeks, albeit with a low daily dosage of ribavirin. The tolerability profile of combination therapy in patients with persistently normal ALT levels is similar to that seen in patients with elevated ALT levels. The decision as to whether or not treatment should be initiated in patients with chronic hepatitis C and persistently normal ALT levels should be made on an individual basis. If a decision is made to treat, combination therapy with peginterferon α-2a (40KD) plus ribavirin can be considered a first-line treatment option.

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