Pegasys
Hoffmann-La Roche
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Hoffmann-La Roche has developed a PEGylated interferon α-2a, Pegasys, for the potential treatment of chronic hepatitis C and hepatitis B virus infection. It was first approved in Switzerland in August 2001 [418280] and was expected to be launched in September/October 2001 [419333]. In May 2000, Roche submitted a BLA to the US FDA, for approval to market Pegasys for the treatment of chronic HCV infection in non-cirrhotic and cirrhotic patients with compensated liver disease [329723], [343688], [367781]. Approval was still pending in December 2000 [387363], [392848]. Roche expects the US launch to take place in the second half of 2001 [400857]. In April 2001, Roche received a complete response letter from the FDA for Pegasys and was working with the FDA to address the questions raised in the letter [407550], [418310]. In August 2001, Roche expected approval for HCV in the US in 2002 and for HBV in 2004 [419333]. At this time, Roche planned to file an sNDA for combination with ribavirin [421285]. By March 2001, EU and Canadian filings had been made [401793]. Roche also planned to launch the product for chronic HBV infection and various malignancies in 2004 and 2005, respectively [409857]. Pegasys was filed for registration in Brazil in the first part of 2000 [418310]. As of December 1999, the drug was in phase II for HCV infection in Japan. It is being developed by Nippon Roche, which intended to extrapolate foreign phase III data for use in an NDA application in Japan [351804]. As a result of a meeting of Japan’s PMSB in March 2001, Pegasys may be given priority in the review of its NDA, if submitted [403782].

In August 2001, Schering-Plough entered into a licensing agreement with F-Hoffman-La Roche Ltd and Hoffmann-La Roche Inc that settles all patent disputes between the two companies’ peginterferon products. Under the terms of the agreement, Schering-Plough and Roche will cross license to each other all patents applicable to Peg-Intron and Pegasys. The settlement agreement also includes a Schering-Plough sublicense of Enzon’s branched PEG patents to Roche [418935], [418856]. Roche is collaborating with Maximm Pharmaceuticals to develop PEG-IFN α-2a in conjunction with Maximm’s Maxavine [378609]. In July 1998, Hoffmann-La Roche and Weston Medical signed a global agreement to license INTRAJECT, (Weston’s single-use, disposable, prefilled, needle-free injector for subcutaneous delivery of injectable liquid pharmaceuticals), for delivery of Pegasys [292119]. In April 1999, ABN Amro predicted annual sales of SFr 25 million in 2000, rising to SFr 75 million in 2002 [328676]. In September 2000, Merrill Lynch predicted sales of SFr 70 million in 2001, rising to SFr 700 million in 2004 [383742]. In March 2001, Deutsche Bank estimated that the product has sales potential of SFr 1600 million [421009].

Introduction
One of the more promising treatments soon to be licensed is PEGylated interferon. The polyethylene glycol (PEG) moiety of this drug is a water-soluble polymer that is covalently linked to the cytokine, interferon α-2a. Two versions of this combination have been developed, one with interferon α-2a hooked to a branched PEG moiety with an average molecular weight of 40 kDa called PEGinterferon α-2a (Pegasys, Hoffman-La Roche), the subject of this evaluation: [423774], and the other a linear PEG with an average molecular weight of 12 kDa hooked to interferon α-2b (PEG-Intron, Schering Plough) [423909].

Synthesis and SAR
PEGinterferon α-2a is made by covalently attaching a 40 kDa branched form of PEG to interferon α-2a by a process known as PEGylation [304385]. The branched nature of the PEG structure results in a very large molecular volume, not unlike branches of a tree, and such a structure allows covalent attachment of PEG at only a few points on the interferon molecule. The mono-PEGylated interferon α-2a is comprised of four major positional isomers that interact with the amino acid lysine found on the interferon protein at positions 31, 123, 131 and 134 [411522]. The conjugation of PEG to interferon is thought to significantly alter the ability of interferon to bind to its cellular receptor but does confer certain advantages [387363], such as shielding the interferon protein from degradative proteolytic enzymes allowing greater half-life for the drug in the blood, which contains many naturally-occurring proteinases [395947]. The covalent coating of the interferon molecule may also make it less immunogenic, which would also enhance its concentration in the blood by protecting it from immune clearance [411522]. Another benefit is that the interferon becomes more water-soluble [346773] and thus more bioavailable than unconjugated interferon, again resulting in higher blood concentrations.

In addition to the development of the drug, a less painful, needle-free delivery system has been engineered by Weston Medical [292119]. Hoffman-La Roche has partnered with Weston Medical in response to the likelihood that patients suffering from chronic hepatitis will probably need medication for prolonged periods of time. The device is a needle-free injector to be used for the delivery of the Hoffman La Roche PEGylated Interferon α-2a. Intreject is a single-use, disposable, pre-filled, needle-free subcutaneous drug delivery system for injectable pharmaceuticals.

Originator Hoffmann-La Roche Inc
Status Registered
Indication Hepatitis B virus infection, hepatitis C virus infection, Myeloid leukemia, Renal tumor, Solid tumor
Action Antiviral
Biotechnology Protein (conjugated)
Synonyms PEGinterferon alpha-2a, Roche, PEGylated IFN alpha-2a, Roche, interferon (PEGylated, alpha-2a), Roche, PEG-IFN-alpha-2a, Roche, R-420, Ro-25-8310, polyethylene glycol interferon alpha-2a, Roche
Pharmacology
A number of studies have been made that verify the advantages described above in using PEGylated interferon α-2a. In one pharmacokinetic study, sustained delivery of PEGylated interferon α-2a was achieved, with maximum concentrations 80 h post-delivery, and substantial concentrations seen even at 3 to 8 h after dosing [346775], thus suggesting that a once-a-week dosing regimen might be adequate to achieve active levels of drug sustainable for one week. Half-life increased from the typical 4 to 6 h for interferon α-2a [325063], Preliminary preclinical and human volunteer studies suggested that this formulation given once a week leads to sustained interferon levels in the blood at clinically relevant concentrations for a week [408979]. The same was also demonstrated in cirrhotic patients, and this was comparable to data obtained from a study of non-cirrhotic patients dosed once a week [157051], [324866]. These studies suggested a first-order adsorption model for the pharmacokinetics/pharmacodynamics of the compound [377014].

The mechanism of how exogenous interferon mediates the immune system in hepatitis-infected patients has not been known. Some have suggested that interferon α enhances T helper cell responses [423911]. One clinical study demonstrated that patients treated with PEGylated interferon had a significant increase in the potency and frequency of CD4+ responses to hepatitis C infection when compared to patients receiving standard interferon [408861]. Patients receiving PEGylated interferon also had significantly higher levels of γ-interferon and lower post-treatment levels of interleukin-10 (IL-10) in response to hepatitis C antigens. Significantly, patients from this study who achieved a sustained virological response had a similar immune profile to the one described above. Thus, in some manner PEGylated interferon enhances T helper cell responses.

Metabolism
Clearance of Pegasys is via the liver [399565] and blood levels are unaffected by renal impairment [399567].

Toxicity
Adverse events in phase II clinical trials with Pegasys have been similar to those observed for standard interferon therapies [367783] and have included such symptoms as fatigue, headache, myalgia/arthritis, flu-like symptoms, nausea and vomiting, fever, chills, partial alopecia, diarrhea, abdominal pain, depression, irritability, insomnia, and anorexia. In addition, dose-dependent reduction of thrombocytes and neutrophils was more frequent with Pegassys treatment than with currently available interferons [324866]. In another trial in which the drug was given once a week to patients with chronic hepatitis C infections and bridging fibrosis and cirrhosis for 48 weeks (with a 24 week follow-up period), the adverse events were no different than those seen in patients receiving standard interferon therapy for the same period of time [399550].

Clinical Development
Phase I
A phase I trial investigated the effects of Pegassys in patients with advanced renal carcinoma [407119]. The compound was administered once a week by subcutaneous injection and an escalating dosing regimen, starting at 180 μg/week and rising to 450 μg/week in 90 μg/week increments, was used. The object of this trial was to assess the pharmacokinetics, toxicity and immunomodulatory properties of the compound. A steady-state serum concentration was achieved after around 5 weeks. Most patients had mild-to-moderate adverse reactions of the type typically associated with interferon treatments. The 450 μg/week dose was determined to be optimal to achieve good serum levels of drug without having unacceptable toxicity for the patient. As expected, this dose also had some immunomodulatory activity. After one year, 78% of patients were still alive.

In a phase I study in 18 evaluable patients with chronic myelogenous leukemia (CML), Pegassys seemed to be of some benefit, determined histologically and cytogenetically [356535], even though in these patients, the maximum tolerated dose had not been reached. In addition, serum concentrations of drug in these patients were maintained at peak levels for up to 168 h after dosing, again demonstrating the benefit of PEGylating interferon to increase the half-life of the cytokine. In a similar study, the efficacy of Pegassys was evaluated alone or in combination with a standard antitumor agent, cytarabine, in patients with relapsed or chronic phase CML [393583].

Another application for Pegassys was examined in a preliminary study initiated to investigate the safety and efficacy of the drug in patients with recurrent HCV infection 6 to 60 months after liver transplantation [408240]. Half of the treatment-naive patients were given Pegassys (180 μg once-weekly) and the others were not treated. After 24 weeks of treatment, almost half of the treated patients demonstrated a 2 log10 drop in viral RNA in the blood, and 25% of those had undetectable levels of viral RNA. The study is scheduled to be completed by January 2002.

Phase II
The pharmacokinetics of various doses of Pegassys were studied in a controlled, randomized, multicenter trial. Hepatitis C patients with cirrhosis received either 90 or 180 μg of the drug once weekly for 48 weeks with a 24 week follow-up observation period [324866]. Drug levels in the blood were similar for both diseased patients and healthy volunteers with similar adverse events to those reported by patients experienced with traditional interferon therapy.

A randomized, controlled, ascending dose-ranging study evaluated the efficacy of Pegassys treatment, assessing its safety and tolerance, and ascertained the optimal dose [325063], [325907], [402025]. Patients who were hepatitis C-negative, determined by detecting viral RNA in the serum, and with near normal serum liver enzyme profiles were enrolled. The patients received either standard interferon treatment or one of four doses of Pegassys once-weekly. Adverse effects were similar for both treatments and dose-dependent for Pegassys. The optimal dose for sustained reduction of virus and minimal side effects was determined to be 180 μg [325870].

In one of the largest prospective trials, involving patients with hepatitis C infection with advanced liver disease, data confirmed that a weekly dose of 180 μg of Pegassys achieved a sustained virological response 4-fold higher than the standard therapy of 3 million IU of interferon three times
per week [367781], [367783], [392474]. This outcome was in agreement with an earlier small-scale study [346775], [324886] in which Pegasis (180 µg once-weekly) substantially reduced the virus load to undetectable levels in the blood. In another study, again examining hepatitis C patients with cirrhosis, over half of the patients showed a favorable response to a weekly dose of 180 µg of Pegasis as measured by histology (an indicator of disease progression), whereas only 31% of patients receiving standard interferon therapy showed similar histological responses [367793], [367783], [399583].

In a study of hepatitis C patients without cirrhosis using the same dosing regimen described above, 63% showed improved histology compared to 57% treated with ribavirin (ICI Pharmaceuticals Inc./Schering-Plough Ltd) [367783]. In a different study of hepatitis C without cirrhosis using the dosing regimen described above, over a third of patients treated with Pegasis sustained a virological response leading to undetectable levels of hepatitis C with no unusual adverse events [346775]. In a follow-up study, where Pegasis was given once-weekly, patients with cirrhosis had improved histology similar to that seen with patients who were treated with interferon α-2a (Roferon-A; Hoffman-La Roche Inc) [367393], [399587]. Another study demonstrated that Pegasis lowered viral RNA levels to the undetectable threshold in about 76% of the patients receiving drug and viral RNA remained undetectable for 24 weeks after completion of therapy [505483], [399574].

Perhaps of greater importance from the patient's perspective was a quality-of-life study in chronically infected hepatitis C patients who received Pegasis monotherapy once a week or standard interferon α-2a three times per week [367785]. Patients receiving Pegasis reported a marked increase in general quality of life when compared to those patients evaluated who received standard interferon. This finding bodes well for adherence to long-term dosing regimens. Several studies endeavored to determine whether the effects of Pegasis were dependent on the age and race of the patient population. One study revealed that black patients have enhanced responses to Pegasis treatment compared to interferon α-2a [402049] and another trial in elderly patients demonstrated comparable pharmacodynamics compared to other age groups treated with Pegasis [402055].

The combination of ribavirin and interferon α-2a had previously shown efficacy in hepatitis C-infected patients with chronic liver disease [423930]. However, some patients discontinued therapy because of a number of adverse events [411022]. Thus, several phase II trials were undertaken to test the efficacy of ribavirin therapy in combination with Pegasis [346775], [399578], [399585], [409437]. In a small pilot study, Pegasis was administered once weekly at 180 µg in combination with 1000 to 2000 mg oral ribavirin twice-daily for up to 48 weeks, with a 24 week post-treatment follow-up [346775]. At 48 weeks, 70% of the patients with chronic hepatitis C infection had undetectable levels (< 100 copies/ml of hepatitis C RNA) of virus in the blood. Adverse events were scored from mild to moderate in severity for most patients, although 4 of 20 patients were more severely affected.

In an open-label, non-randomized, multicenter phase II study, patients with renal cell carcinoma were administered weekly doses of 450 µg Pegasis for 24 weeks. The drug was well tolerated and appeared to be as safe as unmodified interferon. The median survival time was 14.8 months and compared favorably with standard interferon therapy [410429]. In April 2001, phase II trials for treatment of solid and hematological tumors with PEGylated interferon α-2a had started [406292].

Phase III
One of the first large phase III clinical trials from which results were released was a study involving 531 patients with chronic hepatitis C infection [365179], [392481], [399577], [423936]. The purpose of the study was to verify, using a phase III protocol, the data accumulated from the many phase I and II trials comparing safety and efficacy of both treatments. The patients were treated with Pegasis (180 µg once-weekly for 48 weeks) or interferon α-2a (6 million IU, three times per week for 12 weeks, followed by 3 million IU, three times per week for 36 weeks). Of the patients receiving Pegasis, 30% sustained viral clearance, while only 19% of those receiving regular interferon sustained viral clearance. In a randomized, controlled phase II/III trial with intent-to-treat analysis involving patients who had cirrhosis, 29% of cirrhotic patients treated with 180 µg doses of Pegasis had no detectable levels of viral RNA after 48 weeks, compared to 6% treated with currently marketed interferon and using the standard interferon dosing regimen [346775].

A multicenter phase III trial evaluated the efficacy of treatment of hepatitis C-infected patients with Pegasis (180 µg once-weekly) in combination with oral ribavirin (1000 to 1200 mg) or interferon α-2a (Rebetron; ICI Pharmaceuticals Inc./Schering-Plough Corp) (6 million IU three times weekly) and ribavirin [410119], [411546]. Of the patients enrolled, 65% were infected with biopsy-proven genotype 1 hepatitis C virus and 14% had cirrhosis. Patients treated with the Pegasis/ribavirin combination achieved a 56% sustained response rate, while those receiving standard interferon/ribavirin had a 45% rate of clearance of virus with normal liver enzyme profiles after 6 months. More importantly, 40% of those patients with genotype 1 virus infections, which has in the past appeared to be refractory to other treatments, seemed to have cleared the virus (to undetectable levels), whereas only 37% in the standard interferon treatment group did so [412150]. Several investigators have reported clinical trials using a drug other than ribavirin in combination with Pegasis to treat patients with chronic hepatitis C infections. Those drugs included mycophenolate mofetil (Roche Holding AG) and amantadine [409428], [409430]. In one multicenter study, patients not responding to standard combination therapy with interferon α-2a and ribavirin were treated with several different drugs in combination with Pegasis [409430]. In another trial, patients who had relapsed on traditional interferon therapy were treated [409426]. Patients who received Pegasis plus ribavirin had sustained virus response rates of 68%; patients receiving amantadine plus Pegasis a response rate of 32.2%; and those receiving mycophenolate mofetil had a 72.4% response rate. Even more patients (80.6%) registered undetectable hepatitis C RNA when treated with a combination of Pegasis, ribavirin and amantadine.
There are several ongoing phase III clinical trials still enrolling patients. Among those are ‘The Hep C Antiviral Long-Term TX Against Cirrhosis’ (HALT-C) trials [423944], [423950], involving Pegasys monotherapy and combination studies with ribavirin. In addition, another approved proposal will include a protocol for treating chronic delta hepatitis entitled ‘Treatment of Chronic Delta Hepatitis with PEGylated Interferon’ [423958]. It will be a small trial with 10 to 20 patients positive for HDV RNA and HBsAg for up to five years being treated with Pegasys. There are also two trials that will involve patients with concurrent HIV and hepatitis C infections, and children with HIV infections. The first is a randomized, partially-blind, multicenter, three-arm study designed to treat adults with Pegasys alone or in combination with ribavirin or with interferon plus ribavirin [423959]. The other study will evaluate the safety, tolerability and anti-HIV activity of Pegasys in HIV-positive children, aged 3 to 16 months [423960]. In addition, as of April 2001, Pegasys was in phase III clinical trials for hepatitis B infections [400857].

Side effects and Contraindications
The adverse reactions to Pegasys include all the side effects typically seen with currently-approved interferon therapies, including fatigue, headache, myalgia/arthritis, flu-like symptoms, nausea and vomiting, fever, chills, partial alopecia, diarrhea, abdominal pain, depression, irritability, insomnia and anorexia [324866]. There also appears to be a dose-dependent reduction of white blood cells, albeit clinically acceptable. The only contraindication is the use of Pegasys in combination with ribavirin in pregnant women or perhaps in young children whose mothers are pregnant, since ribavirin may have teratogenic potential [423961], [423962].

Patent Commentary
Until recently, the patent for Pegasys was disputed in litigation. Both Hoffman-La Roche and Schering-Plough had disputed each company’s patents for PEGylated interferon in the US and Europe. However, in September 2001 that dispute was apparently resolved. Schering-Plough and Roche will cross-license to each other all patents applicable to their PEGylated interferon products, PEG-Intron and Pegasys, respectively. The settlement also includes a Schering-Plough sublicense of any branched PEG product made by Enzon (a collaborator with Schering-Plough) when it is used as part of an interferon therapeutic agent. In addition, Schering-Plough will cooperate to obtain the right to acquire a license from ICN Pharmaceuticals Inc to use oral ribavirin in combination with Roche’s PEGylated interferon [418935]. Roche also filed for a patent in Brazil in September 2001 [418936].

Current Opinion
PEGylated interferon α-2a (Pegasys) represents a major step forwards for our ability to treat chronic hepatitis C infections. It is as safe as traditional interferon therapy, but appeared to be much more efficacious in every clinical trial in which it was evaluated. PEGylation dramatically increases the half life of the drug in serum, which may contribute to the reduction of viral RNA to undetectable levels, the prolonged sustained responses observed even after discontinuation of therapy and the apparent histological improvements frequently seen in the recent clinical trials. It also seems to be effective in a number of difficult-to-treat groups, including those with HCV virus genotypes 1 and 4, cirrhotics, patients with renal impairment, the elderly and blacks. It will be interesting to see if patients with hepatitis will have to be treated continually with the drug or whether it could possibly cure the disease, i.e., no detectable levels of virus RNA for a year following treatment and permanent histological improvement. That may be possible, even likely, in non-cirrhotic patients. In addition, not only is PEGylated interferon α-2a effective against hepatitis C infections but it seems to also have certain oncological indications as well. Thus, PEGylated interferon-2a is a relatively safe and useful drug, which should dramatically facilitate the treatment of hepatitis and certain types of cancers.

Licensing
Maxim Pharmaceuticals Inc
Roche is collaborating with Maxim Pharmaceuticals to develop Pegasys in conjunction with Maxim’s Maxamine (qv) [378609].

Schering-Plough Corp
In August 2001, Schering-Plough entered into a licensing agreement with Hoffman-La Roche Ltd that settles all patent disputes regarding the two companies’ PEGinterferon products. Under the terms of the agreement, Schering-Plough and Roche will cross-license to each other all patents applicable to PEG-Intron and Pegasys. The settlement agreement also includes a Schering-Plough sublicense of Enzon’s branched PEG patents to Roche [418935], [418936].

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### Literature classifications

#### Chemistry

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<td>Synthesis of PEGylated interferon.</td>
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#### Clinical

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<td>Adverse events were very similar to those observed for standard interferon treatment.</td>
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<td>Phase I trial in liver transplant patients with recurrent hepatitis C infection. Patients received Pegasys 180 µg/week monotherapy.</td>
<td>After 24 weeks, ~ 50% of the treated patients had a &gt; log₂ drop in viral RNA in the blood and 25% had undetectable levels of viral RNA.</td>
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<td>Phase I clinical trial in patients with advanced renal carcinoma receiving Pegasys (180 µg/week sc, rising to 450 µg/week, in 90 µg/week increments).</td>
<td>Adverse events were mild-to-moderate. The optimal dose proved to be 450 µg/week, with 78% of patients surviving after one year.</td>
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<td>Serum concentrations in these patients were maintained at peak levels for up to 168 h after dosing.</td>
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<td>Pharmacokinetics</td>
<td>Phase II trials in healthy human volunteers, and cirrhotic and non-cirrhotic patients infected with hepatitis C virus.</td>
<td>Sustained interferon levels in the blood could be achieved at clinically relevant concentrations for a week. Half-life in serum determined to be ~ 90 h.</td>
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<td>Phase II trial in patients with chronic hepatitis C infection receiving Pegasys (180 µg once-weekly), in combination with oral ribavirin (1000 to 2000 mg twice daily), for up to 48 weeks, with a 24-week post-treatment follow-up period.</td>
<td>Adverse events were scored from mild to moderate in severity for most patients, although 4 of 20 patients had severe adverse events.</td>
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<td>Randomized, controlled phase II trial in hepatitis C patients treated with Pegasys (90 or 180 µg once-weekly for 46 weeks, with a 24-week follow-up observation period).</td>
<td>Drug levels in the blood were similar for both diseased patients and healthy volunteers. Similar adverse events to those experienced with traditional interferon therapy were seen. A dose-dependent reduction of thrombocytopenia and neutropenia was observed.</td>
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<td>Randomized, controlled, multicenter phase II/III intent-to-treat trial in cirrhotic patients treated with Pegasys (180 µg once-weekly).</td>
<td>Sustained delivery of Pegasys was achieved with maximum concentrations occurring 60 h post-delivery, although substantial concentrations were seen at 3 to 8 h after dosing.</td>
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<td>Optimizing dose, safety, efficacy and end-treatment response</td>
<td>Randomized, controlled, phase II/III, ascending, dose-ranging study. Pegasys (45, 90, 180 or 270 µg, once weekly) and interferon α-2a (3 million IU, three times weekly) were administered for 24 weeks in intent-to-treat hepatitis C positive (viral RNA) patients with normal serum levels.</td>
<td>Adverse effects were similar for both treatments and dose-dependent with Pegasys. The optimal dose for sustained reduction of virus and minimal side effects was determined to be 180 µg.</td>
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<td>Randomized, controlled, multicenter phase II/III intent-to-treat trial in cirrhotic patients treated with Pegasys (180 µg once-weekly).</td>
<td>Sustained delivery of Pegasys was achieved with maximum concentrations occurring 60 h post-delivery, although substantial concentrations were seen at 3 to 8 h after dosing.</td>
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Clinical (continued)

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<tr>
<th>Effect Studied</th>
<th>Experimental Model</th>
<th>Results</th>
<th>Reference</th>
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<td><strong>Efficacy and quality of life.</strong></td>
<td>Randomized, controlled, multicenter phase III/IIIb trial, in patients with advanced liver disease receiving Pegasys (180 μg weekly).</td>
<td>Pegasys achieved a sustained virological response 4-fold higher than standard interferon. Histological improvement was seen even though virus was still detectable; 65% of patients receiving Pegasys showed histological improvement, compared to 31% of patients receiving standard interferon. Patients receiving Pegasys reported a marked increase in general quality of life when compared to those patients evaluated receiving standard interferon treatment.</td>
<td>367781 357683 392474 397393 399983 357468 397885</td>
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<td><strong>Efficacy of combination therapy.</strong></td>
<td>Multicenter phase III trial in patients with biopsy-proven genotype 1 hepatitis C virus infection (n = 655), 14% of whom also had cirrhosis. Patients were treated with Pegasys (180 μg once-weekly) in combination with oral ribavirin (1000 to 1200 mg daily) for 48 weeks, or with interferon α-2a (Ribavirin 3 million IU three times a week).</td>
<td>Patients treated with the Pegasys/ribavirin combination sustained a 56% response rate, while those receiving standard interferon/ribavirin attained a 45% rate of clearance with normal liver enzyme profiles after six months. Of the patients with genotype 1 virus infections, 46% cleared the virus to undetectable levels, compared to only 37% in the standard interferon treatment group.</td>
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<td><strong>Efficacy combination therapy.</strong></td>
<td>Phase III trial in patients who relapsed on unmodified interferon therapy.</td>
<td>Patients who received Pegasys plus ribavirin had sustained virus response rates of 68%; patients receiving amantadine plus Pegasys had a response rate of 32.2%, and those receiving mycophenolate mofetil had a 72.4% response rate. Of the patients in the treatment group receiving a combination of Pegasys, ribavirin and amantadine, 86% responded with undetectable viral RNA levels.</td>
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