MEDICAL INFORMATION

OSU College of Pharmacy - Drug Use Research & Management
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Approved Prescribing Information on Toviaz, can be accessed via the following link http://labeling.pfizer.com/ShowLabeling.aspx?id=540. In the event this link should not work, please access the product's Approved Prescribing Information at www.pfizer.com.

August 22, 2013

Dear OSU College of Pharmacy:

Our colleague, Eunmee Lee, has referred your inquiry regarding TOVIAZ (fesoterodine fumarate) to Medical Information.

If you did not specifically request this information, please call 1-800-438-1985 to report this to us.

I hope the information enclosed proves to be of help and interest. Please do not hesitate to contact us at 1-800-438-1985, or via www.pfizermedinfo.com, should you require anything further.

Sincerely,

Sraddha Thapa, PharmD.
Pfizer Medical Information

US13-076705

Disclaimers

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Dear OSU College of Pharmacy:

I'm writing on behalf of the Toviaz Medical Affairs team at Pfizer.

Additional data have been published for Toviaz (fesoterodine fumarate) in the last couple of years and are not included in the Preliminary Scan Report #3 , dated April 2013 . We would suggest you include the following three Toviaz studies in your current Scan Report on drugs for overactive bladder:

1. Evaluation of cognitive function in healthy older subjects treated with fesoterodine

   Kay GG, Maruff P, Scholfield D, et al. Evaluation of cognitive function in healthy older subjects treated with fesoterodine. Postgrad Med. 2012;124(3):7-15.

2. Flexible-dose fesoterodine in elderly adults with overactive bladder: results of the randomized, double-blind, placebo-controlled study of fesoterodine in an aging population trial.

   Wagg A, Khullar V, Marschall-Kehrel D, et al. Flexible-dose fesoterodine in elderly adults with overactive bladder: results of the randomized, double-blind, placebo-controlled study of fesoterodine in an aging population trial. J Am Geriatr Soc. 2013;61(2):185-93.

3. Efficacy and safety of flexible dose fesoterodine in men and women with overactive bladder symptoms including nocturnal urinary urgency.

   Weiss JP, Jumadilova Z, Johnson TM 2nd, et al. Efficacy and safety of flexible dose fesoterodine in men and women with overactive bladder symptoms including nocturnal urinary urgency. J Urol. 2013;189(4):1396-401.

The abstracts for the studies are listed below.

1. Postgrad Med. 2012 May;124(3):7-15. doi: 10.3810/pgm.2012.05.2543.
Evaluation of cognitive function in healthy older subjects treated with fesoterodine.
Kay GG, Maruff P, Scholfield D, Malhotra B, Whelan L, Darekar A, Martire DL.
Source
Cognitive Research Corporation, Saint Petersburg, FL 33701 , USA. gkay@cogres.com
Abstract
OBJECTIVE:
To evaluate the cognitive effects of fesoterodine 4 and 8 mg versus placebo in healthy older adults.
METHODS:
This was an active- and placebo-controlled, double-blind, double-dummy crossover study conducted using healthy volunteers (aged 65-85 years) with baseline Mini-Mental State Examination score ≥ 26. The study comprised 4 treatment periods: fesoterodine 4 mg for 6 days; fesoterodine 4 mg for 3 days followed by fesoterodine 8 mg for 3 days; placebo for 6 days; and placebo for 6 days with alprazolam 1 mg on day 6. The treatment sequence was randomized, with a 3- to 6-day washout between periods. Subjects completed computer-based cognitive assessments and the Rey Auditory Verbal Learning Test on day 1 (before dosing) and day 6 (after dosing) of each period. The primary endpoint was the Detection task; secondary endpoints were the Identification task, 1-card learning task, Continuous Paired Associate Learning task, Groton Maze Learning Task, and the Rey Auditory Verbal Learning Test.

RESULTS:
Among 18 subjects in the per protocol set, changes from baseline to day 6 with fesoterodine 4 and 8 mg were not significantly different from placebo for any endpoint ($P > 0.05$); alprazolam produced significant impairment in all endpoints versus placebo ($P < 0.05$). No serious adverse events were reported; the most common adverse events were dry mouth for fesoterodine and sedation for alprazolam. No sedation was reported with fesoterodine.
CONCLUSION:
In healthy older adults, fesoterodine 4 and 8 mg once daily had no statistically significant effects versus placebo on any cognitive function assessed, including memory; alprazolam 1 mg produced statistically significant deterioration.

2. J Am Geriatr Soc. 2013 Feb;61(2):185-93. doi: 10.1111/jgs.12088.
Flexible-dose fesoterodine in elderly adults with overactive bladder: results of the randomized, double-blind, placebo-controlled study of fesoterodine in an aging population trial.
Wagg A, Khullar V, Marschall-Kehrel D, Michel MC, Oelke M, Darekar A, Bitoun CE, Weinstein D, Osterloh I.
Source
Division of Geriatric Medicine, University of Alberta, Edmonton, Alberta, Canada.
adrian.wagg@ualberta.ca
Abstract
OBJECTIVES:
To assess the efficacy and safety of flexible-dose fesoterodine in elderly adults with overactive bladder (OAB).
DESIGN:
Twelve-week, randomized, double-blind, placebo-controlled trial.
SETTING:
Sixty-one outpatient clinics in Europe, Israel, and Turkey.
PARTICIPANTS:
Seven hundred ninety-four individuals aged 65 and older (47% male) with OAB symptoms for 3 months or longer, mean of eight or more micturitions and three or more urgency episodes per 24 hours, at least some moderate problems on Patient Perception of Bladder Condition (PPBC), and Mini-Mental State Examination (MMSE) score of 20 or greater.
INTERVENTIONS:
Participants were randomized to fesoterodine or placebo for 12 weeks, with stratification according to age (>75 vs ≤ 75) and dosing time (morning vs evening). Participants receiving fesoterodine started on 4 mg and could increase to 8 mg at week 4 or 8 and de-escalate to 4 mg at week 8 (sham escalation for placebo).
MEASUREMENTS:
Changes from baseline in bladder-diary variables (primary endpoint, urgency episodes) and patient-reported outcomes including OAB Questionnaire, Treatment Benefit Scale (TBS), PPBC, Urgency Perception Scale (UPS), and OAB Satisfaction Questionnaire (OAB-S); all observed or reported adverse events.
RESULTS:
By week 8, 64% of fesoterodine-treated and 71% of placebo-treated participants opted for dose escalation. At week 12, the fesoterodine group had statistically significantly greater improvement than the placebo group in urgency episodes, micturitions, nocturnal micturitions, incontinence pad use, and OAB Questionnaire scores but not urgency urinary incontinence episodes. Responder rates on TBS, PPBC, UPS, and OAB-S were statistically significantly higher with fesoterodine. Improvements in most diary variables and participant-reported outcomes were greater with fesoterodine than placebo in participants in both age groups and when administered in the morning

and evening. Rates of dry mouth and constipation were 34% and 9% with fesoterodine and 5% and 3% with placebo, respectively. Rates of adverse events and discontinuations were generally similar in participants in both age groups. There was no change in MMSE score.

CONCLUSION:

Fesoterodine was associated with significantly greater improvements in most diary variables and participant-reported outcomes than placebo and was generally well tolerated in older people.

3. J Urol. 2013;189(4):1396-401. doi: 10.1016/j.juro.2012.11.067.

Efficacy and safety of flexible dose fesoterodine in men and women with overactive bladder symptoms including nocturnal urinary urgency.

Weiss JP, Jumadilova Z, Johnson TM 2nd, Fitzgerald MP, Carlsson M, Martire DL, Malhotra A.

Source

SUNY Downstate College of Medicine, Brooklyn, New York 11203, USA. urojock@aol.com

Abstract

PURPOSE:

Awakening from sleep to urinate is the hallmark of nocturia, a condition that impacts several facets of health related quality of life and for which current therapy is suboptimal. Given the paucity of prospective data on antimuscarinics for the management of nocturia, we investigated the efficacy and safety of flexible dose fesoterodine for the treatment of nocturnal urgency in subjects with nocturia and overactive bladder.

MATERIALS AND METHODS:

Subjects with 2 to 8 nocturnal urgency episodes per 24 hours began a 2-week, single-blind, placebo run-in followed by 1:1 randomization to 12 weeks of double-blind treatment with fesoterodine (4 mg daily for 4 weeks with an optional increase to 8 mg) or placebo using predefined criteria for nocturnal urgency episodes, nocturnal urine volume voided and total 24-hour urine volume voided. The primary end point was change from baseline to week 12 in the mean number of micturition related nocturnal urgency episodes per 24 hours.

RESULTS:

Overall 963 subjects were randomized from 2,990 screened, and 82% of subjects treated with fesoterodine and 84% of those treated with placebo completed the study. Significant improvements in the primary end point (-1.28 vs -1.07), in nocturnal micturitions per 24 hours (-1.02 vs -0.85) and in nocturnal frequency urgency sum (-4.01 vs -3.42) were observed with fesoterodine vs placebo (all $p \leq 0.01$). Health related quality of life measures (overactive bladder questionnaire Symptom Bother -20.1 vs -16.5, sleep 22.3 vs 19.9 and other domains; all $p < 0.05$) were improved with fesoterodine.

CONCLUSIONS:

To our knowledge this is the first prospective study to assess antimuscarinic efficacy for reducing nocturnal urgency. Flexible dose fesoterodine significantly reduced nocturnal urgency episodes vs placebo in subjects with overactive bladder.

This letter is in response to your request for information on APRICOT, the pivotal Phase III clinical trial for Pegasys® (peginterferon alfa-2a) plus Copegus® (ribavirin, RBV) for the treatment of HIV/HCV coinfection. This document includes retrospective analyses of this study.

APRICOT Trial

In Brief

- HIV/HCV coinfected patients treated with Pegasys/Copegus had higher sustained virologic response (SVR) rate (40%) than coinfected patients treated with Pegasys alone (20%) or IFN alfa-2a/RBV (12%).

- In patients coinfected with HIV and HCV genotype 1, SVR was higher with Pegasys/Copegus treatment (29%) compared with Pegasys alone (14%) or IFN alfa-2a/RBV (7%). In patients with HIV and HCV genotypes 2 or 3, SVR was 62% in the Pegasys/Copegus group, 36% with Pegasys alone, and 20% with IFN alfa-2a/RBV.

- The adverse event profile and incidence of events in this trial were similar to that reported with Pegasys/Copegus in HCV-monoinfected patients.

APRICOT: Study Design and Results

The AIDS Pegasys Ribavirin International Coinfection Trial (APRICOT) is a multinational, randomized, placebo-controlled, Roche-sponsored registration trial. A total of 860 HIV/HCV coinfected patients received study medication in APRICOT.[1] Patients were randomized to 1 of 3 treatment arms for 48 weeks of therapy followed by a 24-week, treatment-free follow-up: A) interferon alfa-2a 3 MIU 3 times weekly plus ribavirin 800 mg daily (n=285), B) Pegasys 180 mcg/week plus placebo daily (n=286), or C) Pegasys 180 mcg/week plus Copegus 800 mg daily (n=288).

Patients treated with Pegasys/Copegus had higher rates of end-of-treatment (EOT) virologic response (47%) and SVR (40%, $p<0.001$ vs IFN/RBV) than patients treated with Pegasys alone or IFN alfa-2a/RBV.[1] The rate of SVR in patients treated with Pegasys alone (20%) was significantly higher than that in patients treated with IFN/RBV (12%, $p=0.008$) suggesting that Pegasys alone is a suitable alternative to patients who cannot tolerate ribavirin in a combination regimen. Pegasys/Copegus also yielded higher SVRs than the other regimens when patients were grouped by genotype. In the Pegasys/Copegus group, HCV genotype 1 patients had SVR of 29% and those with HCV genotypes 2 or 3 had SVR of 62%. In Pegasys/Copegus patients, the EOT response rate was 38% for patients infected with HCV genotype 1 and 64% for patients infected with HCV genotypes 2 or 3. The adverse event profile and incidence of events in this trial were similar to that reported with the use of Pegasys/Copegus in HCV-monoinfected patients.

APRICOT Sub-Analyses

Several sub-analyses have been conducted using the APRICOT data. Sub-analyses of interest include:

- SVR and Use of Highly Active Antiretroviral Therapy (HAART)[2]
- Effect of Protease Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors on Liver Histology[3]
- Quality of Life[4]

Additional sub-analyses provide information on the predictability of SVR at Week 4[5-8], effect of cumulative drug exposure[9,10], SVRs according to baseline HCV RNA[11,12], bridging fibrosis/cirrhosis[13], steatosis[14], patients with persistently normal ALT[15], and patients with HCV genotype 4 infection[16]. SVRs were also analyzed as a function of safety[17] and according to the use of growth factors[18] and baseline HIV-related factors[19-22]. Other sub-analyses include an evaluation of histologic response[23,24] and hepatic decompensation during therapy[25].

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Please see the reference list and contact Genentech Medical Communications if additional information on a specific sub-analysis is desired.

APRICOT Trial References

For abstracts from the American Association for the Study of Liver Diseases (AASLD) Annual Scientific Meetings, Conference on Retroviruses and Opportunistic Infections (CROI), European Association for the Study of the Liver (EASL) Congress Meetings, or Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), please access online at www.aasld.org, www.retroconference.org, www.icaac.org, or www.easl.eu, respectively.

1. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med 2004;351:438-450.

2. Torriani FJ, Katlama C, Sulkowski M, et al. Sustained virological response to peginterferon alfa-2a (40KD) (Pegasys®) plus ribavirin (Copegus®) in HIV-HCV co-infected patients according to antiretroviral therapy in the AIDS Pegasys ribavirin international co-infection trial (APRICOT). Presented at the 10th European AIDS Conference in Dublin, Ireland; November 17-20, 2005. PE13.2/14 Poster.

3. Sterling RK, Lissen E, Clumeck N, et al. Effect of protease inhibitors and non-nucleoside reverse transcriptase inhibitors on liver histology in HIV-HCV co-infection: analysis of patients enrolled in the AIDS Pegasys ribavirin international co-infection trial (APRICOT). Presented at the 12th Conference on Retroviruses and Opportunistic Infections in Boston, Massachusetts; February 22-25, 2005. CROI Poster #951.

4. Dieterich DT. HIV-HIV co-infected patients achieving a sustained virological response (SVR) with peginterferon alfa-2a (40KD) (Pegasys®) plus ribavirin (Copegus®) have improved health-related quality of life (HRQL). Presented at the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy in Washington, DC; October 30-November 2, 2004. ICAAC Abstract #H1750.

5. Barreiro P, Vispo E, Nuñez M, et al. HCV relapses upon completion of peg-interferon plus ribavirin in HIV-infected patients: rate, timing, and predictors. Presented at the 43rd Annual Meeting of the European Association for the Study of the Liver in Milan, Italy; April 23-27, 2008. EASL Abstract #770.

6. Dieterich DT, Duff F, Sulkowski M, et al. Sustained virological response in HIV-HCV co-infected patients with HCV genotype 1 infection who have a rapid virological response at week 4 of treatment with peginterferon alfa-2a (40KD) (Pegasys®) plus ribavirin (Copegus®): AIDS Pegasys ribavirin international co-infection trial (APRICOT). Presented at the 13th Conference on Retroviruses and Opportunistic Infections in Denver, Colorado; February 5 - 9, 2006. CROI Poster #856.

7. Torriani FJ. Predictability of virologic response at week 4 and week 12 of peginterferon alfa-2a (40KD) (Pegasys®) plus ribavirin (Copegus®) therapy in HIV-HCV co-infected genotype 1 patients in APRICOT. Presented at the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy in Washington, DC; December 16-19, 2005. ICAAC Oral presentation #V-1178.

8. Rodriguez-Torres M, Rockstroh J, DePamphilis J, et al. Prediction of SVR in HCV genotype 1 patients co-infected with HIV based on virologic responses at week 4 and 12 of treatment with peginterferon alfa-2a (40KD) (Pegasys®) plus ribavirin (Copegus®): retrospective analysis of APRICOT. Presented at the 59th Annual Meeting of the American Association for the Study of Liver Diseases in San Francisco, California; October 31-November 4, 2008. AASLD Poster #1855.

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9. Opravil M, Torriani F, Sasadeusz J, et al. Treatment exposure and sustained virological response in genotype 1 patients treated with peginterferon alfa-2a (40KD) (Pegasys®) plus ribavirin (Copegus®) therapy in APRICOT. Presented at the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy in Washington, DC; December 16-19, 2005. ICAAC Oral presentation #V-1179.

10. Opravil M, Torriani F, Sasadeusz J, et al. Treatment exposure and sustained virologic response (SVR) in genotype 1 patients treated with peginterferon alfa-2a (40KD) (PEG IFNα-2a) + ribavirin (RBV) in APRICOT (AIDS Pegasys ribavirin international co-infection trial). Presented at the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy in Washington, DC; December 16-19, 2005. ICAAC Abstract #V-1179.

11. Rodriguez-Torres M, Torriani FJ, Lissen E, et al. Baseline viral load as a predictor of SVR rate with peginterferon alfa-2a (40KD) (Pegasys®) plus ribavirin (Copegus®) in APRICOT. Presented at the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy in San Francisco, California; September 27-30, 2006. ICAAC Abstract.

12. Rodriguez-Torres M, Torriani FJ, Lissen E, et al. Baseline viral load as a predictor of SVR rate with peginterferon alfa-2a (40KD) (Pegasys®) plus ribavirin (Copegus®). Presented at the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy in San Francisco, California; September 27-30, 2006. ICAAC Poster.

13. Sasadeusz J, Godofsky E, Sterling R, et al. Safety and efficacy of peginterferon alfa-2a (Pegasys®) plus ribavirin (Copegus®) in HIV-HCV co-infected patients with cirrhosis/bridging fibrosis: results of the AIDS Pegasys ribavirin international co-infection trial (APRICOT). Presented at the 55th Annual Meeting of the American Association for the Study of Liver Diseases in Boston, Massachusetts; October 29-November 2, 2004. AASLD Abstract #372.

14. Rodriguez-Torres M, Govindarajan S, Sola R, et al. Hepatic steatosis in patients with HIV-HCV co-infection enrolled in the AIDS Pegasys ribavirin international co-infection trial (APRICOT): clinical characteristics and response to treatment. Presented at the 56th Annual Meeting of the American Association for the Study of Liver Diseases in San Francisco, California; November 11-15, 2005. AASLD Poster #1197.

15. Gonzalez J, Moreno S, Von Wichmann MA, et al. Association between sustained virological response and ALT levels in HIV-HCV co-infected patients who received peginterferon alfa-2a (Pegasys®) plus ribavirin (Copegus®) in the AIDS Pegasys ribavirin international co-infection trial (APRICOT). Presented at the 56th Annual Meeting of the American Association for the Study of Liver Diseases in San Francisco, California; November 11-15, 2005. AASLD Poster #1167.

16. Soriano V, Mendes-Correa MC, Goncales Jr FL, et al. Efficacy of peginterferon alfa-2a (40KD) (Pegasys®) plus ribavirin (Copegus®) in patients with HCV genotype 4 infection in the AIDS Pegasys ribavirin international co-infection trial (APRICOT). Presented at the 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment in Rio de Janeiro, Brazil; July 24-27, 2005. IAS Poster #TuPe1.1C23.

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18. Dieterich DT. Impact of growth factors on treatment outcomes in patients with HIV-HCV co-infection in the AIDS Pegasys® ribavirin international co-infection trial (APRICOT). Presented at the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy in Washington, DC; December 16-19, 2005. ICAAC Oral presentation #V-1176.

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19. Cooper D, Dore G, Torriani FJ, et al. HCV- but not HIV-related factors at baseline predict the response to treatment with peginterferon alfa-2a (40KD) (Pegasys®) plus ribavirin (Copegus®) in patients with HIV-HCV co-infection: predictor analysis from the AIDS Pegasys ribavirin co-infection trial (APRICOT). Presented at the XV International AIDS Conference in Bangkok, Thailand; July 11-16, 2004. IAC Poster #MoPeB3329.

20. Opravil M, Sasadeusz J, Cooper DA, et al. Effect of baseline CD4 cell count on the efficacy and safety of peginterferon alfa-2a (40KD) plus ribavirin in patients with HIV/hepatitis C virus coinfection. J Acquir Immune Defic Syndr 2008;47:36-49.

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ANDROGEL® (testosterone gel) 1% and 1.62%
MEDICAID CLINICAL SUMMARY
Updated March 18, 2013

INDICATIONS AND DOSAGE
ANDROGEL (testosterone gel) 1% and 1.62% are FDA-approved for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone due to primary or secondary hypogonadism (congenital or acquired). In primary hypogonadism, men usually have low serum testosterone levels and gonadotropins (FSH, LH) above the normal range. In secondary (hypogonadotropic) hypogonadism, men have low testosterone serum levels but have gonadotropins in the normal or low range.[1,2] The limitations of use for AndroGel are: (1) safety and efficacy of ANDROGEL in males less than 18 years old have not been established and (2) topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure. ANDROGEL is a Federally-controlled substance (Schedule III). Androgel 1.62% carries similar box warnings as other topical testosterone therapies in its class. These are: (1) virilization in children who were secondarily exposed to testosterone gel, (2) children should avoid contact with unwashed or unclothed application sites in men using testosterone gel, and (3) healthcare providers should advise patients to strictly adhere to recommended instructions for use.

Dosage and administration for ANDROGEL 1.62% differs from ANDROGEL 1% and the two are not interchangeable. ANDROGEL 1% is supplied as either a 75 g (60 metered-dose) pump that delivers 1.25 g of product that contains 12.5 mg of testosterone when the pump mechanism is fully depressed once or in individual packets that contain 25mg or 50mg of testosterone (2.5 g or 5 g packets). ANDROGEL 1.62% is supplied in a metered-dose pump that delivers 20.25 mg of testosterone per complete pump actuation or in individual packets that contain 20.25mg or 40.5mg of testosterone (1.25 g or 2.5 g). The metered-dose pump is capable of dispensing 60 metered pump actuations (1 pump actuation delivers 1.25 g of gel). ANDROGEL should be applied once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and upper arms. This area will be covered by the patient's shirt to avoid unintentional exposure to women and children to areas where AndroGel has been applied. Do not apply Androgel 1.62% to any other parts of the body including abdomen and genitals. ANDROGEL 1% may also be applied to the abdomen. After applying the gel, the application site should be allowed to dry for a few minutes prior to dressing and hands should be washed with soap and water. Virilization has been reported in children who were secondarily exposed to testosterone gel; children should avoid contact with unwashed or unclothed application sites. Signs of virilization in children and women and the possibility of secondary exposure to testosterone gel should be brought to the attention of the healthcare provider. Testosterone gel should be promptly discontinued until cause of the virilization is found.

ANDROGEL 1.62% is contraindicated in men with breast cancer or known or suspected prostate cancer, and in women who are or may become pregnant, or are breastfeeding, as testosterone may cause fetal harm, and in men with known hypersensitivity to any of the ingredients in ANDROGEL, including alcohol and soy products. ANDROGEL is a Federally controlled substance (Schedule III).

Dose adjustment and monitoring. Dose should be titrated based on pre-dose morning serum testosterone concentrations approximately 14 days and 28 days after dosage initiation or titration. Initial dosage of ANDROGEL 1% is 50mg. Initial dosage of ANDROGEL 1.62% is 40.5 mg. Dosage should be adjusted if needed based on serum testosterone levels and as instructed by the physician. If the serum testosterone concentration exceeds the normal range, the daily ANDROGEL dose may be decreased. If the serum testosterone concentration consistently exceeds the normal range therapy should be discontinued. Periodic assessment of serum testosterone, prostate-specific antigen, signs and symptoms of benign prostatic hyperplasia (BPH), hemoglobin, hematocrit, liver function test and lipid levels is recommended in patients taking ANDROGEL.

Please review the full ANDROGEL PI for comprehensive safety & efficacy data, which can be found at www.rxabbvie.com.

ANDROGEL 1% CLINICAL EFFICACY AND SAFETY: A pivotal multi-center, randomized, parallel-group, active-controlled, 180-day 2-phase study evaluated the efficacy and safety of ANDROGEL1% in 227 hypogonadal men.[1,3] During the Initial Treatment Period (days 1-90), 73 patients were randomized to ANDROGEL1% 50mg daily, 78 patients to ANDROGEL 1% 100 mg daily, and 76 patients to a non-scrotal testosterone transdermal system. Patients who were originally randomized to ANDROGEL 1% 50 mg daily who had single-sample serum testosterone levels below the normal range on Day 60 were titrated to 75 mg daily on Day 91. Patients who were originally randomized to ANDROGEL 1% 100 mg daily who had single-sample serum testosterone levels above the normal range on Day 60 were titrated to 75 mg daily on Day 91. During the Extended Treatment Period (days 91-180), 51 patients continued on ANDROGEL 1% 50mg daily, 52 patients continued on ANDROGEL 1% 100 mg daily, 41 patients continued on a non-scrotal testosterone transdermal system (5 mg daily), and 40 patients received ANDROGEL 1% 75 mg daily. Mean peak, trough and average serum testosterone concentrations within the normal range were achieved on the first day of treatment with doses of 50 mg and 100 mg. In patients continuing on ANDROGEL 1% 50mg and 100mg, these mean testosterone levels were maintained within the normal range for the 180-day duration of the study. Testosterone concentrations were maintained as long as the patient continued to properly apply the prescribed ANDROGEL 1% treatment. Of 129 hypogonadal men who were appropriately titrated with ANDROGEL 1% and who had sufficient data for analysis, 87% achieved an average serum testosterone level within the normal range on Treatment Day 180. In patients treated with ANDROGEL 1%, there were no observed differences in the average daily serum testosterone concentrations at steady-state based on age, cause of hypogonadism, or body mass index.[1] ANDROGEL 1% 50 mg/day and 100 mg/day resulted in significant increases over time in total body mass and total body lean mass, while total body fat mass and the percent body fat decreased significantly. These changes were maintained for 180 days of treatment during the original study. Changes in the 75 mg dose group were similar. Bone mineral density in both hip and spine increased significantly from baseline to day 180 with 100 mg ANDROGEL 1%. ANDROGEL 1% treatment at 50 mg/day and 100 mg/day for 90 days produced significant improvement in libido (measured by sexual motivation, sexual activity and enjoyment of sexual activity as assessed by patient responses to a questionnaire). ANDROGEL 1% treatment at 50 mg/day and 100 mg/day produced positive effects on mood and fatigue. Similar changes were seen after 180 days of treatment and in the group treated with the 75 mg dose.[1]

The safety of ANDROGEL 1% was evaluated in the previously described 180-day Phase 3 study in 227 hypogonadal men[1,3] and in a 3-year open-label extension study of 162 hypogonadal men.[1] During the initial 6-month study, the mean change in PSA values had a statistically significant increase of 0.26 ng/mL. Serum PSA was measured every 6 months thereafter in the 3-year extension study. There was no additional statistically significant increase observed in mean PSA from 6 months through 36 months. However, there were increases in serum PSA observed in approximately 18% of individual patients. The overall mean change from baseline in serum PSA values for the entire group from month 6 to 36 was 0.11 ng/mL. Patients with BPH treated with androgens are at increased risk for worsening signs and symptoms of BPH. Patients treated with androgens may be at increased risk for prostate cancer. Treatment with androgens may lead to: azoospermia, edema in patients with preexisting

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cardiac, renal or hepatic disease, gynecomastia, sleep apnea in those with risk factors, changes in insulin sensitivity or glycemic control, and changes in anticoagulant activity. The most common adverse reactions (incidence ≥ 5%) reported included acne, application site reactions, abnormal lab tests, and prostatic disorders.

ANDROGEL 1.62% CLINICAL EFFICACY AND SAFETY: The efficacy and safety of ANDROGEL 1.62% in hypogonadal men (aged 18 to 80 years) was evaluated in 53 US centers. The study was comprised of two periods, a randomized, double-blind, parallel-group, placebo-controlled period from Day 1 through Day 182 and an open-label period from Day 182 to Day 364. At Day 112, ≥75% of subjects on active treatment were required to fall within the normal serum testosterone concentration range of 300-1000 ng/dL. In addition, the lower bound of the 95% CI was to be not less than 65%. For the open-label period of the study, ≥75% of subjects who enrolled in the open-label portion of the study and who were continuing active treatment, were to have C_{avg} within normal range of 300-1000 ng/dL on Day 364, and lower bound of the 95% CI could not be <65%. A total of 274 hypogonadal men with an average serum testosterone concentration <300 ng/dL were enrolled. Study participants were randomized to 40.5 mg of ANDROGEL 1.62% or matching placebo gel in a 6:1 ratio (234 active; 40 placebo). Predose serum total testosterone and other secondary assessments were obtained on Days 14, 28, and 42 for the purpose of making dose adjustments. No dose was titrated below 20.25 mg or above 81 mg. Results indicated that 82% of patients demonstrated restoration of testosterone levels and achieved an average serum testosterone level (561 ng/dL) within the normal range on Day 112 vs. 37% of study participants who were treated with placebo (P<0.0001).[2,5,6] During the open-label period 163 subjects, aged 26 to 77 years, continued on active 1.62% testosterone gel. In 28 subjects who had previously received placebo, the dose was titrated to normal levels of serum total testosterone. Dose adjustments for both groups were allowed at specific visits to maintain serum testosterone within a normal range. On day 364, 77.9% of the continuing active subjects and 87.0% of the formerly placebo subjects had C_{av} values within the eugonadal range.

Adverse reactions reported in >2% of patients and more frequently than placebo in the 182-day, double-blind period of the ANDROGEL 1.62% clinical study included an increase in prostate-specific androgen (PSA; 11.1% vs. 0%) with a mean increase in PSA of 0.14 ng/mL, emotional lability (2.6% vs. 0%), hypertension (2.1% vs. 0%), increase in hematocrit or hemoglobin (2.1% vs. 0), and contact dermatitis (includes 4 patients with contact dermatitis at non-application sites) (2.1% vs. 0%). In the open-label period of the study (N=191), the most commonly reported adverse reaction (experienced by greater than 2% of patients) was increased PSA (n=13; 6.2%) and sinusitis.[1] Severe treatment emergent adverse events (TEAEs), events that interrupted the subject's usual daily activity, were reported for 11/234 (4.7%) in the testosterone group vs. none in the placebo group.[4] The severe TEAEs included: back pain, myocardial infarction, tachycardia, diarrhea, dyspepsia, gastroenteritis, pneumonia, fall, diabetes mellitus, pituitary tumor, radicular pain, libido increased, sleep disorder, and erection increased. Some subjects experienced more than one TEAE. All events considered severe were single occurrences with the exception of back pain (2/234, 0.9%).

SUMMARY

The Endocrine society's guideline recommends making a diagnosis of hypogonadism in men with symptoms and signs consistent with low serum testosterone levels. Testosterone treatment should be initiated for symptomatic men with androgen deficiency aiming at achieving levels in the mid-normal range and should be monitored using a standardized treatment plan.[4] Patient's preference, pharmacokinetics, and treatment burden should be taken into account when initiating therapy. ANDROGEL 1% and ANDROGEL 1.62% are FDA-approved for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: Primary Hypogonadism or Hypogonadotropic Hypogonadism.[1,2]

REFERENCES

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A wealth of clinical data supports the Pegasys label, including nine pivotal clinical trials with more than 3,500 patients. In addition to the information detailed below, please refer to the enclosed medical response documents and copyright-paid reprints for recent scientific literature on the use of Pegasys.

Summary of New Clinical Information

Prescribing information updates for Pegasys® (peginterferon alfa-2a)

07/02/2013 (new indication): Pegasys in combination with Copegus and an approved Hepatitis C Virus (HCV) NS3/4A protease inhibitor is indicated in adult patients (18 years of age and older) with HCV genotype 1 infection (see the Package Insert of the specific HCV NS3/4A protease inhibitor for further information).[1.1]

1. Pegasys® [package insert]. July 2013. §1.1 INDICATIONS AND USAGE, Chronic Hepatitis C.

Comparative studies between PegIFN-2a and 2b in patients with CHC

The following data are provided in response to the conclusion on page 1 of Oregon State's HCV class review regarding the AHRQ meta-analysis of Pegasys in comparison to PegIFN-2b.

Overall

The conclusion states: There continues to be low strength evidence of a slightly lower chance of achieving an SVR with dual therapy with pegylated interferon alfa-2b compared to dual therapy with pegylated interferon alfa- 2a (pooled RR 0.87, 95% CI 0.80 to 0.95; I2=27.4%), while dual therapy with interferon alfa-2b is associated with a lower risk of serious adverse events than dual therapy with interferon alfa-2a (pooled RR 0.76, 95% CI 0.71 to 0.88; I2=0.0%).

According to the original AHRQ report, the strength of evidence is moderate and they do not use the adjective "slightly" when they describe the lower likelihood of achieving SVR with dual therapy with PegIFN-2b as compared to Pegasys.[1]

Safety

The conclusion describes the rate of serious adverse events (SAEs) for Pegasys as compared to PegIFN-2b. While the rate of SAEs is an important factor in assessing a drug's safety profile, the following safety measurements may also be considered:

- Additional Data from AHRQ:[1]
  - There was no difference between dual therapy with PegIFN-2b and dual therapy with Pegasys in risk of withdrawal due to AEs (six trials, pooled RR 1.1, 95% CI 0.73 to 1.7, I^2=42%).
  - In addition to the AHRQ report finding that *treatment*-related SAEs are nearly identical for the three arms studied (4.4%. 3.9%, and 4.4%), the IDEAL trial showed that Pegasys had a lower rate of treatment discontinuation of than the two PegIFN-2b arms (51.5%, 47.0%, and 40.0%). [1,3]
  - Studies cited by AHRQ but not described:
    - Currently there is one trial evaluating PegIFN-2b and Pegasys in the context of triple therapy, which is the standard of care for genotype 1 HCV patients. This trial showed similar AE profiles across all triple therapy treatment arms.[2] A greater number of patients using Pegasys had HCV RNA negative at week 4 and thus were eligible for a shortened course of therapy of 24 weeks vs 48 weeks. Shorter courses of therapy may have a positive impact on tolerability and medication adherence.
    - The PEAK trial was a prospective, randomized, open-label trial that compared Pegasys plus ribavirin therapy with PegIFN-2b ribavirin therapy in treatment-naïve patients with HCV genotype 1 and high viral load. [4] A similar AE profile was found between the two treatment groups.
    - A prospective, randomized trial conducted by Ascione et al. compared the safety and efficacy of Pegasys plus ribavirin with PegIFN-2b ribavirin therapy in 320 treatment-naive, Italian patients.[5] The AE profiles were similar between groups. Discontinuation rates for the Pegasys arm was 3.2% and 1.5% in genotype 1/4 and 2/3, respectively; whereas, rates for PegIFN-2b treated patients were reported as 14% and 13.4%.
- Additional Data from Supplemental References (*copyright-paid reprints enclosed for your review*):
  - A Cochrane Hepato-Biliary Group meta-analysis of 11 randomized controlled trials compared Pegasys plus ribavirin versus PegIFN-2b plus ribavirin. It showed no significant difference in AEs leading to discontinuation (RR of 0.79, 95% CI 0.51 to 1.23, p=0.42).[6]

- Yang et al. conducted a meta-analysis of seven randomized controlled trials (over 1820 patients) comparing Pegasys and PegIFN-2b in combination with ribavirin for chronic HCV. Pegasys had a significantly lower discontinuation rate than PegIFN-2b (27.9% versus 33.9%, p<0.0001) in naïve patients.[7]

- Singal et al. conducted a meta-analysis of nine studies comparing Pegasys and PegIF-2b in treatment-naïve HCV patients. Treatment discontinuation rates due to SAE reported in six studies were similar (OR of 0.66, 95% CI 0.37 to 1.16, p = 0.15).[8]

Efficacy

- Studies cited by AHRQ but not described:
  - The PEAK trial, conducted in 385 treatment-naive, HCV genotype 1 patients with high viral load, showed that viral load decline over 12 weeks was similar between patients treated with Pegasys or PegIFN-2b 1.5 mg/kg/wk, however, patients treated with Pegasys had higher mean interferon trough concentrations at Weeks 4, 8, and 12.[4]

  - Ascione et al reported that the rate of SVR in Pegasys-treated patients was significantly higher (68.8%) than in PegIFN-2b treated patients (54.4%, p=0.008).[5] Pegasys patients also had significantly higher rates of SVR when analyzed by genotype and high baseline viral load (>500,000 IU/mL). The rate of SVR was similar between groups in cirrhotic patients. Multivariate analysis showed that male sex, absence of cirrhosis, genotype 2/3, and treatment with Pegasys were independent predictors of SVR with statistically significant Odds Ratio values of 1.93, 2.36, 4.83, and 2.32, respectively.

- Additional Data from Supplemental References (*copyright-paid reprints enclosed for your review*):
  - The Cochrane Hepato-Biliary Group meta-analysis of SVR included eight trials (4,335 patients), and showed that treatment with Pegasys significantly increased SVR rate compared with PegIFN-2b (47% vs 41%; Risk Ratio=1.11, 95% CI: 1.04-1.19; p=0.004).[6]
    - A subgroup analysis evaluating data from 6 trials for genotypes 1/4 yielded a risk ratio (RR) in favor of Pegasys (RR=1.21, 95% CI: 1.03-1.42). A subgroup analysis evaluating data from 5 trials for genotypes 2/3 yielded a RR in favor of Pegasys (RR=1.11, 95% CI: 1.02-1.22).

  - Yang et al. reported a significantly higher SVR rate with Pegasys when compared PegIFN-2b (46.7% versus 42.4%, p=0.01).[7]
    - The same trend was observed for naïve, genotype 1/4, and genotype 2/3 patients. The early virologic response (EVR) and end-of-treatment response (ETR) rates were also significantly higher in the Pegasys group than in the PegIFN-2b group (56.1% versus 49.8%, p<0.0001; 67.9% versus 56.6%, p<0.00001, respectively).

  - Singal et al. in a meta-analysis of nine studies showed a higher SVR in treatment-naïve HCV patients with Pegasys as compared to PegIFN-2b (RR=1.36, 95% CI: 1.07–1.73, p= 0.01).[8]

  - A recent Cochrane meta-analysis was published that compared the rapid virologic response (RVR) and early virologic response (EVR) of Pegasys vs PegIFN-2b.[9] These endpoints were studied to help support and guide clinical decision making in the present scenario of triple combination therapy. It was found that Pegasys treatment may be associated with a higher complete EVR and RVR when compared to PegIFN-2b. Moreover, this study took Cochrane Hepato-Biliary Group's SVR results into account and found that the overall efficacy of Pegasys was 11% or higher than that of PegIFN-2b when all genotypes were considered, and 20% higher when only data on genotypes 1 and 4 were included.[6,9]

Additional Populations

Compared to PegIFN-2b, Pegasys is additionally indicated in adult patients with HIV and HCV coinfection and CD4 count greater than 100 cells/mm^3 and for adults with HBV.[10,11] Pegasys is indicated for the treatment of pediatric patients aged 5-17 years; PegIFN-2b is indicated for pediatric patients aged 3-17 years. Finally, there are dosing recommendations for Pegasys and ribavirin in patients with varying degrees of renal impairment, including those on dialysis; whereas PegIFN-2b in combination with ribavirin are contraindicated in patients with a creatinine clearance of less than 50 ml/min.

Looking to the future of HCV therapies and in recognition of new drugs in the pipeline, please note that Pegasys is the most commonly included pegylated interferon backbone of the HCV drug regimens in development.[12]

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This letter is in response to your request for information on the use of telaprevir (dosed every 8 hours or every 12 hours) in combination with Pegasys® (peginterferon alfa-2a) or peginterferon alfa-2b for the treatment of chronic hepatitis C (CHC) genotype 1.

Pegasys and Peginterferon alfa-2b with Telaprevir

In Brief

- A Phase II study evaluated the use of telaprevir dosed every 8 hours or every 12 hours in combination with Pegasys or peginterferon alfa-2b in treatment naïve CHC genotype 1 patients.

Phase II Study

The C208 study (n=161) was a prospective, multicenter, randomized, open-label trial which evaluated the use of telaprevir 750 mg every 8 hours or telaprevir 1,125 mg every 12 hours in combination with Pegasys or peginterferon alfa-2b with ribavirin in treatment naïve CHC genotype 1 patients.[1] Treatment duration was 24 or 48 weeks based on viral-guided therapy.

A logistic regression model showed no significant differences in sustained virologic response (SVR) between all treatment groups ($p \geq 0.787$), between the pooled telaprevir groups (p=0.997), or between the pooled peginterferon alfa groups (p= 0.906).[1] Refer to Table 1 for study details.

Table 1: C208 Study Details[1]

Study	Treatment Arms	SVR	Relapse	Safety
Telaprevir 750 mg every 8 hours or 1,125 mg every 12 hours with Pegasys or PegIFN-2b/ribavirin				
C208[1]	Telaprevir 750 mg every 8h, Pegasys 180 mcg/wk, ribavirin 1,000/1,200 mg/d x 12 wks followed by Pegasys plus ribavirin (n=40)	85%	n=3	Adverse events were comparable across all treatment groups. The most common adverse events reported across telaprevir regimens included rash, pruritis, anemia, nausea, influenza-like illness, asthenia and headache.
	Telaprevir 750 mg every 8h, PegIFN-2b, ribavirin x 12 wks followed by PegIFN-2b plus ribavirin (n=42)	81%	n=4	
	Telaprevir 1,125 mg every 12h, Pegasys 180 mcg/wk, ribavirin 1,000/1,200 mg/d x 12 wks followed by Pegasys plus ribavirin (n=40)	83%	n=3	
	Telaprevir 1,125 mg every 12h, PegIFN-2b, ribavirin x 12 wks followed by PegIFN-2b plus ribavirin (n=39) Treatment duration (24 wk vs 48 wk) for all groups was based on viral-guided therapy. Patients with HCV RNA undetectable at Weeks 4- 20 received 24 wks.	82%	n=1	

Pegasys and Peginterferon alfa-2b with Telaprevir

1. Marcellin P, Forns X, Goeser T, et al. Telaprevir is effective given every 8 or 12 hours with ribavirin and peginterferon alfa-2a or -2b to patients with chronic hepatitis C. Gastroenterology 2011;140:459-468.

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This letter is in response to your request for information on Pegasys® (peginterferon alfa-2a) and peginterferon alfa-2b (Peg-IFN alfa-2b). This document includes prospective, randomized studies comparing the two combination regimens for the treatment of chronic hepatitis C (CHC).

This response was developed according to the principles of evidence-based medicine and is limited to prospective, randomized studies in >250 patients and meta-analysis of randomized, clinical trials.

Pegasys and Peginterferon alfa-2b

In Brief

- There are 5 recent, prospective, randomized studies each with >250 patients that compare the safety and efficacy of Pegasys plus Copegus® (ribavirin, RBV) therapy with Peg-IFN alfa-2b plus ribavirin.
    - The IDEAL study, a Phase IIIb study sponsored by Schering-Plough and conducted in 3,070 treatment-naive hepatitis-C virus (HCV) genotype 1-infected patients, showed that sustained virologic response (SVR) rates were similar between patients receiving Pegasys 180 mcg/wk, Peg-IFN alfa-2b 1.0 mcg/kg/wk, or Peg-IFN alfa-2b 1.5 mcg/kg/wk, all with RBV.
    - The PEAK trial, conducted in 385 treatment-naive, HCV genotype 1 patients with high viral load, showed that viral load decline over 12 weeks was similar between patients treated with Pegasys or Peg-IFN alfa-2b 1.5 mg/kg/wk, however, patients treated with Pegasys had higher mean interferon trough concentrations at Weeks 4, 8, and 12.
- A meta-analysis of randomized clinical trials comparing Pegasys with Peg-IFN alfa-2b showed higher SVR with Pegasys, but no difference in adverse events leading to discontinuation.

Clinical Experience

Prospective, Randomized Studies in HCV Genotype 1 Patients

The IDEAL Study

The IDEAL study was a Phase IIIb study designed to compare the safety and efficacy of PegIntron 1 mcg/kg/wk with 1.5 mcg/kg/wk in combination with weight-based RBV in treatment-naive patients infected with genotype 1 CHC. A third study arm with Pegasys 180 mcg/week plus RBV 1,000/1,200 mg daily was added by the sponsor.[1]

The study was an open-label, parallel-group, multicenter US study where 3,070 patients were randomized in a 1:1:1 ratio to 1 of the following 3 treatment arms for 48 weeks[2]:

Table 2: Treatment Arms in the IDEAL Study[2]

Arm	N	Treatment Regimen	
1	1019	Peg-IFN alfa-2b 1.5 mcg/kg/wk +	Ribavirin 800 mg/d for pts. 40-65 kg
			Ribavirin 1,000 mg/d for pts. 65-85 kg
2	1016	Peg-IFN alfa-2b 1.0 mcg/kg/wk +	Ribavirin 1,200 mg/d for pts. 85-105 kg
			Ribavirin 1,400 mg/d for pts. 105-125 kg
3*	1035	Pegasys 180 mcg/wk +	Ribavirin 1,000 mg/d for pts. < 75 kg
			Ribavirin 1,200 mg/d for pts. ≥75 kg

Note: * Pegasys/ribavirin arm was open-label, Peg-IFN alfa-2b arms 1 & 2 were double-blinded.
Abbreviations: Peg-IFN=peginterferon; pts=patients.

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Initial RBV dose reductions for the management of anemia (hemoglobin <10 g/dL) are shown below (Table 3).[1]

Table 3: Initial RBV Dose Reductions across Arms[1]

	Peg-IFN alfa-2b + Ribavirin				Pegasys + Ribavirin	
Weight (kg)	40-65	>65-85	>85-105	>105-125	<75	≥75
Starting dose (mg/d)	800	1,000	1,200	1,400	1,000	1,200
Initial dose reduction	-200	-200	-200	-400	-400	-600

Note: * RBV dose could be decreased by an additional 200 mg/day as necessary.
Abbreviation: Peg-IFN=peginterferon.

All patients had compensated liver disease and weighed between 40 – 125 kg.[2] Patients were stratified according to baseline viral load and whether they were African-American or non-African American. The primary endpoint of the study was the proportion of patients with SVR, defined as HCV RNA <27 IU/mL at the end of follow-up (Week 24 or, if missing, Week 12).[2] Co-primary comparisons were SVR rates in Arm 1 (Peg-IFN alfa-2b 1.5 mcg/kg/wk + RBV 800-1,400 mg/d) vs Arm 2 (Peg-IFN alfa-2b 1.0 mcg/kg/week + RBV 800-1400 mg/day) and arm 1 (Peg-IFN alfa-2b 1.5 mcg/kg/wk + RBV 800-1,400 mg/d) vs Arm 3 (Pegasys 180 mcg/wk + RBV 1,000/1,200 mg/d).[1]

Baseline characteristics and demographics were similar between groups: 60% male, 71% Caucasian, 82% with HCV RNA >600,000 IU/mL at baseline, 59% with steatosis >0%, 84% with METAVIR fibrosis score 0/1/2, and 11% with METAVIR score 3/4.[2] The mean weight of Pegasys-treated patients was 83 ± 17 kg, 84 ± 17 kg in the Peg-IFN alfa-2b 1.5 arm and 83 ± 16 kg in the Peg-IFN alfa-2b 1.0 arm.[2]

A significantly greater proportion of patients in the Pegasys arm achieved undetectable HCV RNA at weeks 12, 24, and end-of-treatment compared with the Peg-IFN alfa-2b 1.5 mcg/kg/wk arm (Table 4).[2] Overall SVR rates were similar between groups, with 41% of Pegasys/RBV patients attaining SVR. The overall SVR rates in the Peg-IFN alfa-2b arms were 40% in the 1.5 mcg/kg/wk arm and 38% in the 1.0 mcg/kg/wk arm. Relapse rates were 32% in the Pegasys/RBV arm, 24% and 20% in the higher- and lower-dose Peg-IFN alfa-2b arms, respectively (Table 4). Relapse was defined as undetectable HCV RNA at end of treatment, but detectable levels during the follow-up period.[2] Specifics on how these rates were calculated, including accounting for patients lost to follow-up, were not presented.[2,3]

Table 4: Virologic Response and Relapse Rates (ITT Analysis)[2]

	Pegasys / RBV (n=1035)	Peg-IFN alfa-2b 1.5 / RBV (n=1019)	Peg-IFN alfa-2b 1.0 / RBV (n=1016)	p-value**
Week 4 Undetectable HCV RNA (RVR)	12%	11%	8%	0.73
Week 12 Undetectable HCV RNA (cEVR)	45%	40%	36%	0.01
Week 24 Undetectable HCV RNA	62%	51%	48%	<0.001
End-of-Treatment Response Rates (EoTR)	64%	53%	49%	<0.001
SVR Rates	41%	40%	38%[c]	0.57
Relapse Rates*	32%[a]	24%	20%[b]	-

Notes: ** p-value for Peg-IFN alfa-2b 1.5 mcg/kg/wk vs Pegasys 180 mcg/wk; [c] Peg-IFN alfa-2b 1.5 vs 1.0 mcg/kg/wk (p=0.20); * p-value calculations not provided; [a] Peg-IFN alfa-2b 1.5 mcg/kg/wk vs Pegasys 180 mcg/wk: 8% difference; statistically significant; 95% CI,-13.2%,-2.8%; [b] Peg-IFN alfa-2b 1.5 vs 1.0 mcg/kg/wk: 4% difference; not significant; 95% CI, -1.6%, 8.6%.
Abbreviations: cEVR=complete early virologic response; HCV=hepatitis C virus; ITT=intention to treat; Peg-IFN=peginterferon; RBV=ribavirin; RVR=rapid virologic response; SVR=sustained virologic response.

SVR rates according to weight are shown in Table 5 and analysis of SVR by other factors are shown in Table 6.[2] Multivariate logistic regression model showed that the following factors were predictive of SVR: baseline HCV RNA <600,000 IU/mL (p<0.001), non-Black/African American race (p<0.001), fibrosis 0/1/2 (p<0.001), steatosis 0% (p<0.001), fasting glucose <5.6 mmol/L (p<0.001), and elevated ALT (p=0.005).[2,3]

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Table 5: SVR Rates (%) according to Body Weight[2]						
Weight	**Pegasys/RBV**		**Peg-IFN alfa-2b 1.5/RBV**		**Peg-IFN alfa-2b 1.0/RBV**	
kg	**RBV mg/d**	**SVR**	**RBV mg/d**	**SVR**	**RBV mg/d**	**SVR**
40-65	1000	43% (69/160)	800	46% (65/142)	800	37% (52/140)
>65-<75	1000	41% (72/175)	1,000	37% (55/150)	1,000	40% (66/165)
≥75-85	1200	46% (123/270)	1,000	36% (99/272)	1,000	37% (93/250)
>85-105	1200	36% (117/322)	1,200	41% (142/348)	1,200	37% (140/383)
>105	1200	39% (42/108)	1,400	42% (45/107)	1,400	45% (35/78)
Abbreviations: Peg-IFN=peginterferon; RBV=ribavirin; SVR=sustained virologic response.						

Table 6: SVR Rates (%) in Subgroups of Interest[2,3]			
	Pegasys/RBV (n=1,035)	**Peg-IFN alfa-2b 1.5/ RBV (n=1,019)**	**Peg-IFN alfa-2b 1.0/ RBV (n=1,016)**
Female	42	44	36
Male	40	37	39
African American/Black	26	23	17
Caucasian	44	44	44
Steatosis, 0%	49	48	46
Steatosis, >0%	36	35	33
Baseline HCV RNA ≤600,000 IU/mL	66	61	59
Baseline HCV RNA >600,000 IU/mL	36	35	33
METAVIR Fibrosis 0/1/2	44	42	39
METAVIR Fibrosis 3/4	24	21	30
Actual RBV received Wks 0-12			
≤13 mg/kg/d	38	38	36
>13 mg/kg/d	43	44	42
Erythropoietin Use			
Yes	45	51	51
No	40	38	36
Abbreviations: HCV=hepatitis C virus; Peg-IFN=peginterferon; RBV=ribavirin; SVR=sustained virologic response.			

The median actual RBV doses received by Pegasys patients who were nonresponders, relapsers or attained SVR were 13.2 mg/kg/d, 13.0 mg/kg/d, and 13.4 mg/kg/d.[2] In the Peg-IFN alfa-2b 1.5 mcg/kg/wk arm, the respective median doses were 12.5 mg/kg/d, 12.1 mg/kg/d, and 12.4 mg/kg/d ($p<0.001$ for RBV dose received vs Pegasys arm) and in the Peg-IFN alfa-2b 1.0 mcg/kg/wk arm they were 12.5 mg/kg/d, 12.5 mg/kg/d, and 12.6 mg/kg/d ($p<0.001$ for RBV dose received vs Pegasys arm). Median and interquartile ranges 25% and 75% were presented for the 3 groups. The distribution beyond the 25% (lowest RBV received) was not shown.[2]

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Adverse events (AEs) were similar between the 3 groups, with a range of flu-like symptoms being the most common adverse events.[2] Serious AEs occurred in 12% (4% treatment-related) of patients receiving Pegasys and in 9% (4% in each group were treatment-related) of patients in both Peg-IFN alfa-2b arms. Discontinuation rates were similar between the Pegasys and Peg-IFN alfa-2b 1.5 mcg/kg/wk arms with 13% of patients in each group withdrawing from the study due to serious AEs. The discontinuation rate in the lower Peg-IFN alfa-2b arm was 10%. Serious psychiatric AEs occurred in 1% in both the Pegasys arm and lower-dose Peg-IFN alfa-2b arm compared with 2% of patients in the higher-dose Peg-IFN alfa-2b arm. These AEs led to discontinuation in 3%, 2%, and 2% of patients in Arms 1, 2, and 3, respectively.[3] Anemia (hemoglobin < 10 g/dL) occurred in 30% of patients receiving Pegasys compared with 31% and 25% of patients in the higher- and lower-dose Peg-IFN alfa-2b arms, respectively. The rates of neutropenia (<750/mm3) were 27%, 22%, and 15% in the Pegasys, Peg-IFN alfa-2b 1.5 mcg/kg/wk and 1.0 mcg/kg/wk arms, respectively. The percentage of patients using epoetin was similar between arms at 14% to 17%. There were 6 (1 treatment-related) deaths in the Pegasys arm, 5 (1 treatment-related) in the Peg-IFN alfa-2b 1.5 arm and 1 in the lower dose Peg-IFN alfa-2b arm.[2]

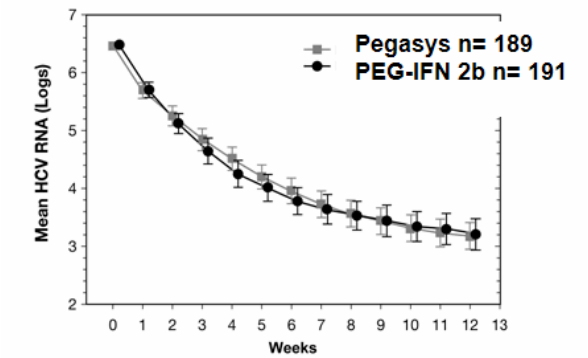
The PEAK Study

The PEAK trial was a prospective, randomized, open-label trial that compared the changes in HCV RNA concentrations after 12 weeks of Pegasys plus RBV therapy with Peg-IFN alfa-2b and Rebetol (ribavirin, RBV) therapy in treatment-naïve patients with HCV genotype 1 and high viral load (> 800,000 IU/mL).[4] The study showed that viral load decline over 12 weeks was similar between the 2 therapies, however, patients treated with Pegasys had markedly higher mean trough concentrations of interferon at Weeks 4, 8, and 12 compared with patients treated with Peg-IFN alfa-2b.

A total of 385 patients were randomized to receive Pegasys 180 mcg/wk plus RBV 1,000/1,200 mg/d or Peg-IFN alfa-2b 1.5 mcg/kg/wk plus RBV 1,000/1,200 mg/d for 12 weeks.[4] After Week 12, all patients were given the opportunity to complete the remaining 48 weeks with Pegasys/RBV, therefore, SVR data does not exist between the 2 original study arms. Baseline characteristics in the 2 treatment groups were similar: 67% male, 70% Caucasian, 85% >40 years old, 71% >75 kg, 35% with BMI >30 kg/m^2, 15% cirrhotic, 69% with abnormal ALT, and a mean HCV RNA 6.5 ± 0.03 $\log_{10}$ IU/mL.

HCV RNA viral load throughout the 12-week study period was comparable between both treatment groups with no significant difference at any time point (Figure 1).[4] The percentage of Pegasys- and Peg-IFN alfa-2b-treated patients with a ≥2-$\log_{10}$ drop or undetectable HCV RNA at Week 4 was 41.8% vs 49.2% and at Week 12 was 66.1% vs 63.4%. The percentage of Pegasys- and Peg-IFN alfa-2b-treated patients that achieved RVR was 7.4% vs 11.5% and those with undetectable HCV RNA at Week 12 was 39.2% vs 44.0%, respectively. At Week 4, a similar proportion of patients in the Pegasys and Peg-IFN alfa-2b treatment groups were null responders, defined as a <1-$\log_{10}$ reduction in HCV RNA (37.6% vs 37.7%). By Week 12, 21.7% of patients in the Pegasys group and 30.9% of patients in the Peg-IFN alfa-2b group were null responders.

Figure 1. Mean Viral Load over Time in Pegasys and Peg-IFN alfa-2b Patients[4]



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Patients treated with Pegasys had higher mean trough concentrations of interferon at Weeks 4, 8, and 12. At all 3 time points, 1%-2% of patients in the Pegasys group had undetectable interferon trough levels below the level of quantitation compared with 58%-68% of patients in the Peg-IFN alfa-2b (Table 7).[4]

Table 7: Trough Concentration of Pegylated Interferon over Time [4]

	Pegasys + Ribavirin (n=189)			Peg-IFN alfa-2b and ribavirin (n=191)		
Week	**n**	**Concentration, pg/ml (mean ±SE)**	**% BLQ**	**n**	**Concentration, pg/ml (mean ±SE)**	**% BLQ**
4	152	12,089 ±439	0.7	178	150 ±17	68.0
8	146	12,781 ±448	2.1	174	147 ±10	62.6
12	144	12,846 ±451	0.7	168	154 ±11	58.3

Abbreviations: BLQ=below limit quantitation (250 pg/ml for Pegasys, 150 pg/ml for Peg-IFN alfa-2b); Peg-IFN=peginterferon; pg=picograms.

The adverse event profile was similar between the 2 treatment groups.[4] However the relative frequency of chills, fever, influenza-like illness, decreased appetite, rash, vomiting, and injection-site erythema was at least 25% higher in the Peg-IFN alfa-2b group than the Pegasys group. The frequency of dyspnea was at least 25% higher in the Pegasys plus RBV group. Two of 189 (1%) patients prematurely discontinued Pegasys/RBV treatment and 11 of 191 (5.7%) prematurely discontinued Peg-IFN alfa-2b for safety reasons. Sixteen additional patients in each group discontinued due to non-safety reasons.

No differences in neutrophil counts, platelet counts and hemoglobin concentrations were seen in the Pegasys and Peg-IFN alfa-2b groups at baseline or Weeks 4, 8, and 12.[4] Grade 3 or greater neutropenia, thrombocytopenia, and anemia were seen in 43.4% and 34.8%, 1.1% and 0%, and 15.5% and 17.5% of Pegasys and Peg-IFN alfa-2b patients, respectively.

Prospective, Randomized Studies in Patients with Genotypes 1-4

Milan Safety Tolerability (MIST) Study

The MIST study compared the safety, tolerability, and SVR rates of Pegasys 180 mcg/wk plus RBV 800 – 1,200 mg/d with Peg-IFN alfa-2b 1.5 mcg/kg/week plus RBV 800 – 1,400 mg/day in 431 treatment-naïve patients.[5] The study showed that the 2 peginterferons had similar safety and tolerability. In the overall population and the genotype 1/4 group, complete early virologic response (cEVR), end of treatment response (EoTR), and SVR rates were higher in patients receiving Pegasys compared with those receiving Peg-IFN alfa-2b. Additionally, treatment with Pegasys was an independent predictor of SVR.

Patients were randomized in a 1:1 ratio, and stratified by genotype, to receive Pegasys (n=212) or Peg-IFN alfa-2b (n=219) for 48 weeks in genotypes 1/4 and 24 weeks in genotypes 2/3.[5] HCV genotypes 1 and 4 patients in the Pegasys arm received RBV 1,000 mg or 1,200 mg/d and genotypes 2 and 3 received RBV 800 mg/d. All Peg-IFN alfa-2b patients received weight-based RBV. The authors planned for 210 patients in each arm to detect a non-inferiority margin difference of 10% with more than 80% power.

Baseline characteristics were similar between groups.[5] Over 50% of patients had genotypes 1 or 4 in the Pegasys and Peg-IFN alfa-2b groups (51% vs 52%, respectively). A similar proportion of patients in the Pegasys and Peg-IFN alfa-2b arms (20.3% vs 17.8%, respectively) had cirrhosis (Ishak score S5,6).

In the overall population and in patients with HCV genotype 1 or 2, more patients receiving Pegasys had a cEVR, EoTR, and SVR compared with patients receiving Peg-IFN alfa-2b; RVR rates were similar between groups.[5] The rates of virologic response was similar in patient with HCV G3 between arms. Relapse rates were similar between the Pegasys and Peg-IFN alfa-2b arms (16% vs 18%, p0.6). Relapse rate in the HCV G3 patients were higher in the Peg-IFN alfa-2b arm (11% vs 0%).

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In the overall population, independent predictors of SVR by multivariate logistic regression analysis were infection with genotype 2/3 (Odd's Ratio=7.97), age <40 yrs (OR=3.2), HCV RNA <600,000 IU/mL (OR=1.49), and treatment with Pegasys (OR=1.88).[5]

Table 8: Virologic Response Rates (%)[5]

	Pegasys + RBV (n=212)	Peg-IFN alfa-2b 1.5 + RBV (n=219)	p-value
RVR, %			
Overall	62%	57%	0.31
Genotype 1	37%	30%	0.4
Genotype 2	94%	91%	0.6
Genotype 3	79%	72%	0.7
cEVR, %			
Overall	80%	69%	0.01
Genotype 1	66%	46%	0.01
Genotype 2	97%	95%	0.7
Genotype 3	97%	91%	0.6
EoTR, %			
Overall	78%	67%	0.009
Genotype 1	65%	44%	0.007
Genotype 2	96%	93%	0.9
Genotype 3	94%	91%	0.9
SVR, %			
Overall	66%	54%	0.02
Genotype 1	48%	32%	0.04
Genotype 2	96%	82%	0.01
Genotype 3	65%	69%	0.9
Genotype 4	44%	31%	0.5

Abbreviations: cEVR=complete virologic response, EoTR=End-of-treatment response; Peg-IFN=peginterferon; RBV=ribavirin; RVR=rapid virologic response; SVR=sustained virologic response.

A subgroup analysis of the MIST study evaluated SVR outcomes according to the extent of liver fibrosis.[6] Patients were stratified according to Ishak fibrosis scores: mild fibrosis (S0-S2), moderate fibrosis (S3-S4), and cirrhosis (S5-S6). SVR rates by genotype and fibrosis scores are shown in Table 9. Logistic regression analysis showed moderate to severe fibrosis (S3-S6) to be an independent predictor of treatment failure to Peg-IFN alfa-2b but not Pegasys combination therapy (OR=2.4, 95% CI: 1.30-4.50).

Table 9: SVR Rates by Fibrosis Score[6]

Genotype	Ishak fibrosis score	Pegasys + RBV (n=212)	Peg-IFN alfa-2b + RBV (n=219)
G 1/4	Mild fibrosis (S0-S2)	47%	44%
	Moderate fibrosis (S3-S4)	51%	21%*
	Cirrhosis (S5-S6)	44%	24%
G 2/3	Mild fibrosis (S0-S2)	89%	83%
	Moderate fibrosis (S3-S4)	88%	76%
	Cirrhosis (S5-S6)	69%	64%

Note: * p=0.05 compared with S0-S2.
Abbreviations: G=genotype; Peg-IFN=peginterferon; RBV=ribavirin; SVR=sustained virologic response.

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Table 10 shows the similar rate of adverse events and treatment discontinuations between arms.

Table 10: Adverse Events & Treatment Discontinuations[5]

Safety Outcomes, n (%)	Pegasys + RBV (n=212)	Peg-IFN alfa-2b 1.5 + RBV (n=219)	p-value
Serious ADE	2 (1%)	1 (1%)	0.2
Treatment discontinuation			
For safety reasons	16 (7%)*	17 (8%)**	0.8
For non-safety reasons	2 (1%)	6 (3%)	0.2
Dose reductions			
PEG-IFN dose reduction	22 (10%)	14 (6%)	0.2
RBV dose reduction	119 (56%)	123 (56%)	1.0
Anemia			
Grade 2	35 (16%)	50 (23%)	0.1
Grade 3	2 (1%)	2 (1%)	0.6
Neutropenia (grade 3)	46 (22%)	34 (16%)	0.1
Thrombocytopenia (grade 2-3)	5 (2%)	3 (1%)	0.5
GCSF use	21 (10%)	15 (7%)	0.3
EPO use	30 (14%)	27 (12%)	0.6
Depression	19 (9%)	15 (7%)	0.4
Other Adverse Events			
Influenza-like syndrome	134 (63%)	136 (62%)	0.8
Gastrointestinal symptoms	8 (4%)	12 (5%)	0.5
Psychiatric symptoms	79 (37%)	70 (32%)	0.3
Coughing and dyspnea	22 (10%)	25 (11%)	0.8
Dermatological symptoms	99 (47%)	91 (42%)	0.3

Notes: * Reasons: SAE (n=2); anemia and neutropenia (n=7); depression (n=2); non protocol (n=5); ** Reasons: SAE (n=1); anemia and neutropenia (n=5); depression (n=2); non protocol (n=9).
Abbreviations: ADE=adverse drug event; EPO=epoetin; GCSF=granulocyte colony-stimulating factor; Peg-IFN=peginterferon; RBV=ribavirin.

Ascione et al.

A prospective, randomized trial conducted in 320 treatment-naive, Italian patients compared the safety and efficacy of Pegasys 180 mcg once weekly plus RBV 1,000/1,200 mg daily with Peg-IFN alfa-2b 1.5 mcg/kg/week plus RBV 1,000/1,200 mg daily.[7] The study showed that patients receiving Pegasys had a higher rates of SVR overall in addition to greater SVR rates in all genotypes, in patients with chronic hepatitis and in patients with high viral load (HVL=HCV RNA >500,000 IU/mL at baseline). Multivariate analysis also showed that Pegasys was a significant predictor of SVR.

All patients were > 18 years of age, had ALT >1.5 x ULN in the last 6 months, recent liver biopsy (within 6 months), negative pregnancy test and abstained from alcohol for past 6 months.[7] Patients were stratified based on HCV genotype. Baseline characteristics were similar between both groups. Overall baseline characteristics included 55% male, 57% HCV genotype 1, 31% HCV genotype 2, mean age 50 years, mean BMI 25 kg/m^2, 55% with HVL, and 18.4% with cirrhosis.

Patients with HCV genotypes 1 and 4 received 48 weeks of treatment and HCV genotype 2 and 3 patients received 24 weeks.[7] RBV was dose reduced in 200 mg decrements, as necessary, due to anemia, severe cough, or intolerable itching. Overall, 197 patients (61.6%) attained SVR after treatment. The rate of SVR in Pegasys-treated patients was significantly higher (68.8%) than in Peg-IFN alfa-2b-treated patients (54.4%, p=0.008). Patients receiving Pegasys also had significantly higher rates of SVR when analyzed by genotype and high baseline viral load (>500,000 IU/mL). The rate of SVR was similar between groups in cirrhotic patients. Multivariate analysis showed that male sex, absence of cirrhosis, genotype 2/3, and treatment with Pegasys were independent predictors of SVR with statistically significant Odds Ratio values of 1.93, 2.36, 4.83, and 2.32, respectively.

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Table 11: Virologic Response by HCV Genotype (%) [7]				
	Overall	**Pegasys + RBV (n=160)**	**Peg-IFN alfa-2b 1.5 + RBV (n=160)**	**p-value**
EVR, %	79.1%	85%	73.1%	0.009
cEVR	69.7%	75.6%	65%	0.037
pEVR	8.8%	9.4%	8.1%	0.692
EoTR, %	74.1%	83.8%	64.4%	<0.0001
SVR, %	61.6%	68.8%	54.4%	0.008
G1/4	47.3%	54.8%	39.8%	0.04
G2	83.8%	91.8%	76.0%	0.062
G3	74.3%*	77.8%	70.6%	0.92
SVR by diagnosis, %				
CHC	65.5%	75.6%	55.9%	0.005
Cirrhosis	44.1%	42.4%	46.1%	0.774
SVR by baseline HCV RNA, %				
≤500,000 IU/mL	67.1%	68.4%	65.7%	0.727
>500,000 IU/mL	57.1%	69.0%	46.2%	0.002
Relapse rate	12.5%	15%	10%	0.176

Note: * p=0.21 for comparison between SVR in G2 vs. G3.
Abbreviations: cEVR=complete early virologic response; CHC=chronic hepatitis C; EoTR=End-of-treatment response, EVR=early virologic response; G=genotype; HCV=hepatitis C virus; Peg-IFN=peginterferon; pEVR=partial early virologic response; RBV=ribavirin; SVR=sustained virologic response.

The adverse event profiles and dose modifications were similar between groups, with fatigue and arthralgia being the most common adverse events.[7] Discontinuation rates for the Pegasys arm were 3.2% and 1.5% in genotype 1/4 and 2/3, respectively; whereas, rates for Peg-IFN alfa-2b-treated patients were reported as 14% and 13.4%.

Prospective, Randomized Study in HCV Genotype 4 Patients

Comparison of Peginterferons Using Viral Guided Therapy

A prospective, randomized double-blind trial conducted in 268 treatment-naive, genotype 4 CHC patients compared the safety and efficacy of Pegasys 180 mcg once weekly or Peg-IFN alfa-2b 1.5 mcg/kg/week, each with RBV 1000/1200 mg/day.[8] Patients with RVR and cEVR were treated for 24 and 36 weeks, respectively. Patients with pEVR and slow responders (undetectable HCV RNA at 24 weeks) were treated for 48 and 72 weeks, respectively.

Table 13 shows virologic response rates between arms.[8] SVR was higher in patients receiving Pegasys, and a greater proportion of patients in the Peg-IFN alfa-2b arm had pEVR or slow response. Normalization of ALT occurred earlier in patients treated with Pegasys (median 28 days vs 36 days Peg-IFN alfa-2b). Patients with SVR in both arms had stabilization of steatosis and fibrosis. Younger age, RVR, cEVR, >2log decline at Week 2, and fibrosis scores <4 were predictive of SVR by multiple logistic regression analysis.

Table 13: Virologic Response in Genotype 4 Patients[8]			
Virologic Response, %	**Pegasys + RBV**	**Peg-IFN alfa-2b + RBV**	**p-value**
RVR	45%	26%	0.01
SVR	74%	59%	.047

Abbreviations: Peg-IFN=peginterferon; RBV=ribavirin; RVR=rapid virologic response; SVR=sustained virologic response.

Dose modifications for neutropenia and depression were more frequent in patients treated with Peg-IFN alfa-2b.[8] Compliance and quality of life score were higher in patients treated with Peg-IFN alfa-2b.

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Meta-analysis of Randomized Clinical Trials

The Cochrane Hepato-Biliary Group identified 12 randomized clinical trials (total of 5,008 patients) and conducted a meta-analysis to evaluate SVR rates and adverse events (AEs) leading to discontinuation in patients treated with Pegasys or Peg-IFN alfa-2b, each with weight-based RBV.[9]

The meta-analysis of SVR included eight trials (4,335 patients), and showed that treatment with Pegasys significantly increased SVR rate compared with Peg-IFN alfa-2b (47% vs 41%; Risk Ratio=1.11, 95% CI: 1.04-1.19; p=0.004).[9] Table 14 shows the Risk Ratio for each study.

A subgroup analysis evaluating data from 6 trials for genotypes 1/4 yielded a risk ratio (RR) in favor of Pegasys (RR=1.21, 95% CI: 1.03-1.42).[9] A subgroup analysis evaluating data from 5 trials for genotypes 2/3 yielded a RR in favor of Pegasys (RR=1.11, 95% CI: 1.02-1.22).

Table 14: Meta-analysis Comparing SVR Rates of Pegasys vs Peg-IFN alfa-2b[9]

Study (year)	Pegasys, n/N	Peg-IFN alfa-2b, n/N	Weight	Risk Ratio (M-H, Fixed, 95% CI)
Sinha, 2004	14/24	10/18	1.5%	1.05 (0.62,1.79)
Yenice, 2006	18/40	13/40	1.4%	1.38 (0.79,2.43)
Scotto, 2008	14/71	13/72	0.9%	1.09 (0.55,2.16)
Kolakowska, 2008	28/33	27/34	8.6%	1.07 (0.85,1.34)
Laguno, 2009	44/96	36/86	3.9%	1.09 (0.79,1.52)
McHutchison, 2009	423/1,035	792/2,035	51.8%	1.05 (0.96,1.15)
Rumi, 2008	140/212	119/219	17.9%	1.22 (1.04,1.42)
Ascione, 2008	110/160	87/160	13.9%	1.26 (1.06,1.51)
Total (95% CI)	791/1,671	1,097/2,664	100%	1.11 (1.04,1.19)

Notes: Heterogeneity: Tau^2=0.00; Chi^2=5.65, df=7(p=0.58); I^2=0%; Test for overall effect Z=3.23 (p=0.001).
Abbreviations: M-H=Mantel-Haenszel; Peg-IFN=peginterferon; SVR=sustained virologic response.

The meta-analysis for AEs leading to discontinuation included 11 studies and showed no significant difference between the two peginterferons (RR=0.79, 95% CI: 0.51-1.23; p=0.42).[9]

Table 15: Meta-analysis Comparing Adverse Events Leading to Treatment Discontinuation for Pegasys vs Peg-IFN alfa-2b[9]

Study (year)	Pegasys		Peg-IFN alfa-2b		Weight	Risk Ratio (M-H, Fixed, 95% CI)
	Events	Total	Events	Total		
Bruno (2004)	0	10	0	10	-	Not estimable
Sinha (2004)	0	24	1	18	1.8%	0.25 (0.01, 5.88)
Berak (2005)	3	116	3	121	5.9%	1.04 (0.21, 5.06)
Yenice (2006)	3	40	3	40	6.2%	1.00 (0.21, 4.66)
Silva (2006)	2	18	4	18	6.0%	0.50 (0.10, 2.40)
Di Bisceglie (2007)	2	189	11	191	6.4%	0.18 (0.04, 0.82)
Scotto (2008)	10	71	8	72	12.5%	1.27 (0.53, 3.03)
McHutchison (2009)	135	1,035	227	2,035	22.9%	1.17 (0.96, 1.43)
Rumi (2009)	16	212	17	219	15.7%	0.97 (0.50, 1.87)
Laguno (2009)	12	96	7	86	12.3%	1.54 (0.63, 3.72)
Ascione (2009)	4	160	22	160	10.3%	0.18 (0.06, 0.52)
Total (95% CI)	187/1,971		303/2,970		100%	0.79 (0.51, 1.23)

Notes: Heterogeneity: Tau^2=0.21; Chi^2=19.79, df=9 (p=0.02); I^2=55%; Test for overall effect Z=1.04 (p=0.30).
Abbreviations: M-H=Mantel-Haenszel; Peg-IFN=peginterferon.

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Pegasys and Peginterferon alfa-2b References

For abstracts from the American Association for the Study of Liver Diseases (AASLD) Annual Scientific Meetings, or the European Association for the Study of the Liver (EASL) Congress Meetings, please access online at www.aasld.org, or www.easl.eu, respectively.

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This letter is in response to your request for information on the combination use of Pegasys® (peginterferon alfa-2a) with boceprevir.

Pegasys with Boceprevir

In Brief

- **Prescribing Information**
  - Pegasys in combination with Copegus and an approved Hepatitis C Virus (HCV) NS3/4A protease inhibitor is indicated in adult patients (18 years of age and older) with HCV genotype 1 infection (see the Package Insert of the specific HCV NS3/4A protease inhibitor for further information).
  - Pegasys in combination with Copegus is indicated in patients with HCV genotypes other than 1, pediatric patients (5-17 years of age), or in patients with HCV genotype 1 infection where use of an HCV NS3/4A protease inhibitor is not warranted based on tolerability, contraindications or other clinical factors.
  - See the Package Insert of the specific HCV NS3/4A protease inhibitor for information regarding dosing regimen, duration and administration of the protease inhibitor in combination with Pegasys and ribavirin for treatment of genotype 1 infection.
- **Published Literature**
  - The safety and efficacy of boceprevir in combination with Pegasys and ribavirin (P/R) was examined in a placebo controlled study of adult patients with chronic hepatitis C genotype 1 infection who failed prior treatment with P/R. The overall sustained virologic response (SVR) rate of subjects treated with boceprevir in combination with Pegasys and ribavirin was 64% (86/134) and 21% (14/67) in subjects treated with placebo plus Pegasys and ribavirin. Adverse events reported more frequently in the boceprevir-containing arm compared with the control arm included anemia, neutropenia, dysgeusia, diarrhea, rash, myalgia, leucopenia, and vomiting.

Clinical Experience

Flamm et al. reported the results of a multi-center, double-blind (with respect to placebo or boceprevir), placebo-controlled trial of 201 adult patients with chronic hepatitis C genotype 1 infection who demonstrated responsiveness to previous treatment with peginterferon alfa and ribavirin, but failed to achieve an SVR.[1] Demonstrated responsiveness was defined as nonresponse (a decrease in the HCV-RNA level of at least 2 log10 IU/mL by Week 12 but with a detectable HCV RNA level during the therapy period) or relapse (an undetectable HCV RNA level at the end of treatment, without subsequent attainment of SVR). Patients were assigned in a 1:2 ratio to a 4-week lead-in phase of peginterferon alfa 2a and ribavirin (P/R), dosed 180 mcg/wk and 1000-1200 mg/day in 2 divided doses, respectively, followed by placebo plus P/R for 44 weeks (Pegasys/R) or boceprevir (800 mg three times daily) plus P/R for 44 weeks (BOC/Pegasys/R). Patients who did not achieve undetectable HCV-RNA at Treatment Week 12 discontinued all treatments.

The primary efficacy endpoint was SVR, defined as undetectable plasma HCV-RNA at follow-up week 24, in all patients who received at least one dose of any study medication (primary analysis).[1] The key secondary objective was to compare SVR in patients who received at least one dose of placebo or boceprevir. Patients were stratified by response to therapy (nonresponder or relapser) and HCV genotype (1a or 1b). IL28B polymorphism was also recorded and evaluated as a predictor of SVR.

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A total of 201 patients were randomized and treated.[1] No significant difference between treatment groups in baseline demographic characteristics was observed. Most patients were male (70%), non-black (90%), had HCV genotype 1a (56%), a baseline viral load of >800,000 IU/mL (77%), an IL28b CT genotype (64%), and were previous relapsers (72%).

Both the primary efficacy endpoint and the secondary analysis were found to be statistically significant between the Pegasys/R and BOC/Pegasys/R groups.[1] In the pre-specified primary analysis, 21% (14/67) if patients in the Pegasys/R arm who received one dose of any study medication achieved an SVR compared to 64% (86/134) of patients in the BOC/Pegasys/R arm ($p<0.0001$). Of those patients who received at least one dose of placebo or boceprevir, the SVR rates were 21% (14/67) and 66% (86/130), respectively. Response rates based on on-treatment response and select baseline characteristics are shown in Table 1 below.

Table 1: SVR Rates[1]

	Pegasys/R % (n/N)	BOC/Pegasys/R % (n/N)
Overall Response		
Primary analysis - all patients who received at least one dose of any study medication	21 (14/67)	64 (86/134)
End of Treatment Response	42 (28/67)	74 (99/134)
Relapse Rate	33 (7/21)	12 (11/95)
Secondary analysis - patients who received at least one dose of placebo or boceprevir	21 (14/67)	66 (86/130)
Treatment Response (historical and current)		
Prior Relapse	28 (13/47)	70 (69/98)
Prior Nonresponse	5 (1/20)	47 (17/36)
Poor Response to Interferon (<1 log10 IU/mL decline in HCV RNA at week 4)	0 (0/7)	39 (7/18)
Interferon Responsive (≥1 log10 IU/mL decline in HCV RNA at week 4)	25 (14/57)	71 (79/112)
Week 8 HCV-RNA Detectable	16 (9/56)	42 (21/50)
Week 8 HCV RNA Undetectable	44 (4/9)	89 (64/72)
IL28b Genotype		
CC	50 (5/10)	63 (12/19)
CT	15 (5/34)	64 (38/59)
TT	14 (1/7)	82 (14/17)

Abbreviations: BOC=boceprevir; R=ribavirin; SVR=sustained virological response.

Resistance-associated variants (RAVs) were evaluated by population sequencing of plasma samples in patients assigned to the BOC/Pegasys/R arm.[1] There were 125 patients who had baseline DNA sequencing and received at least one dose of boceprevir. Of these 125 patients, 8 patients had baseline RAVs, with 3 of these patients achieving SVR (38%). Samples for sequencing were available for 33/44 patients who did not attain a SVR. RAVs detected in G1a subjects include V36M, R155K/T, and T54S and the following in G1b subjects, T54A, V55A, and V170A. The numbers of patients with post-baseline RAVs categorized by the reason for virologic failure are presented Table 2.

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Table 2: Response Type in Patients Who Did Not Achieve SVR in the BOC/Pegasys/R Arm[1]	
Patient Category	**Patients with RAVs detected/Patients with resistance data available (n/N, %)**
Non-SVR	8/33 (24)
Incomplete virological response	3/4 (75)
Viral breakthrough	1/1 (100)
Relapse	2/9 (22)
Nonresponder	2/19 (11)
Abbreviations: BOC=boceprevir; R=ribavirin; RAV=resistance-associated variants; SVR=sustained virological response.	

Post-baseline RAVs were detected in 5/10 (50%) of poor interferon responders (<1 $\log_{10}$ IU/mL decline in HCV RNA at week 4) compared with 2/22 (9%) of interferon responders (≥1 $\log_{10}$ IU/mL decline in HCV RNA at week4).[1]

A multivariate logistic regression analysis was performed to identify predictors of SVR.[1] Factors significantly associated with achievement of SVR included response at Treatment Week 4 (≥1 $\log_{10}$ IU/mL decline in HCV-RNA), assignment to boceprevir treatment, and historical classification as a relapser. IL28b was not identified as a predictor of SVR.

Patients enrolled in the BOC/Pegasys/R arm received a 3.2-fold longer duration of treatment than patients enrolled in the Pegasys/R arm, as more patients in the control arm discontinued therapy due to the Treatment Week 12 futility rule.[1] Significantly more patients enrolled in the BOC/Pegasys/R arm discontinued treatment or had a dose modification due to an adverse event (AE) ($p<0.05$ for BOC/Pegasys/R vs. Pegasys/R). Two deaths were reported in the BOC/Pegasys/R arm, one occurred 2 days after completion of therapy due to heart failure and the second death was reported 15 days after completion due to *Staphylococcus aureus* bronchopneumonia.

The most common AEs reported (occurring in ≥10% in any group) and occurring in significantly more BOC/Pegasys/R treated patients compared with Pegasys/R include anemia, neutropenia, dysgeusia, diarrhea, rash, myalgia, leucopenia, and vomiting.[1] Neutropenia was reported in 31% of BOC/Pegasys/R treated patients and 18% of Pegasys/R. In both treatment arms, patients were effectively managed by using guidelines for dose modification (17% vs. 13%, respectively) or granulocyte colony-stimulating factor treatment (14% vs. 12%). Serious AEs caused by infection were reported in 7 patients (5%) treated with BOC/Pegasys/R with risk factors of cirrhosis (3 patients) and diabetes (2 patients). None of these patients had grade 3/4 neutropenia before the event. Anemia (defined as hemoglobin <10 g/dL) was reported in 27% of patients treated with Pegasys/R and 50% in patients treated with BOC/Pegasys/R. Anemia was effectively managed in these patients with ribavirin dose reduction (0% vs. 8%, respectively) and erythropoietin use alone (28% vs. 29%), or both (56% vs. 57%). No serious AEs were reported due to anemia, but one patient discontinued treatment due to anemia.

Pegasys with Boceprevir References

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This letter is in response to your request for information on the use of telaprevir in combination with Pegasys® (peginterferon alfa-2a) and ribavirin for the treatment of chronic hepatitis C (CHC) genotype 1.

This response was developed according to the principles of evidenced-based medicine and is limited to prospective and retrospective Phase III data from published studies. Some of the data presented here may differ from that presented in the telaprevir prescribing information.

Pegasys with Telaprevir in CHC Genotype 1

In Brief

- The most common adverse drug reactions to telaprevir combination therapy (incidence at least 5% higher with telaprevir than in controls) were rash, pruritus, anemia, nausea, hemorrhoids, diarrhea, anorectal discomfort, dysgeusia, fatigue, vomiting, and anal pruritus.
- Treatment-Naïve
    - In the Phase III ADVANCE study, CHC genotype 1 treatment-naïve patients treated with telaprevir plus Pegasys and ribavirin had significantly higher sustained virologic response (SVR) rates compared with patients treated with Pegasys and ribavirin alone.
    - Results of the Phase III ILLUMINATE study showed that in treatment-naïve genotype 1 patients attaining an extended rapid virologic response (eRVR; undetectable hepatitis C virus [HCV] RNA at Weeks 4 and 12), SVR rates with a 24-week telaprevir-based regimen were noninferior to the same 48-week telaprevir-based regimen.
- Previously Treated
    - Telaprevir combined with Pegasys and ribavirin significantly improved SVR rates in previously treated CHC genotype 1 patients compared with Pegasys and ribavirin alone, regardless of whether patients received a lead-in phase.

Telaprevir Prescribing Information

Indications and Usage

Telaprevir, in combination with peginterferon alfa and ribavirin, is indicated for the treatment of genotype 1 CHC in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon-based treatment, including prior null responders, partial responders, and relapsers.

Telaprevir must not be used as monotherapy and must only be used in combination with peginterferon alfa and ribavirin. A high proportion of previous null responders (particularly those with cirrhosis) did not achieve SVR and had telaprevir resistance-associated substitutions emerge on treatment with telaprevir combination treatment.

Telaprevir efficacy has not been established for patients who have previously failed therapy with a treatment regimen that includes telaprevir or other HCV NS3/4A protease inhibitors.

The most common adverse drug reactions to telaprevir combination therapy (incidence at least 5% higher with telaprevir than in controls) were rash, pruritus, anemia, nausea, hemorrhoids, diarrhea, anorectal discomfort, dysgeusia, fatigue, vomiting, and anal pruritus.

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Dosing Recommendations

Treatment Naïve and Prior Relapse Patients			
HCV-RNA	**Triple Therapy Telaprevir, PEG-IFN, RBV**	**Dual Therapy PEG-IFN, RBV**	**Total Treatment Duration**
Undetectable (Target Not Detected) at Weeks 4 and 12	First 12 weeks	Additional 12 weeks	24 weeks
Detectable (1,000 IU/mL or less) at Weeks 4 and/or 12	First 12 weeks	Additional 36 weeks	48 weeks
Prior Partial and Null Responder Patients			
	Triple Therapy Telaprevir, PEG-IFN, RBV	**Dual Therapy PEG-IFN, RBV**	**Total Treatment Duration**
All Patients	First 12 weeks	Additional 36 weeks	48 weeks
Abbreviations: RBV= ribavirin; PEG-IFN= peginterferon alpha			

Treatment-naïve patients with cirrhosis who have undetectable HCV-RNA (Target Not Detected) at weeks 4 and 12 of telaprevir combination treatment may benefit from an additional 36 weeks of peginterferon and ribavirin (48 weeks total).

Dose Reduction and Discontinuation of Dosing

To prevent treatment failure, the dose of telaprevir must not be reduced or interrupted. Refer to the respective prescribing information for dose modification of Pegasys and ribavirin.

Patients with inadequate viral response are unlikely to achieve SVR, and may develop treatment-emergent resistance substitutions. Discontinuation of all therapy is recommended in patients with (1) HCV-RNA levels ≥1,000 IU/mL at Treatment Week 4 or 12; or (2) confirmed detectable HCV-RNA levels at Treatment Week 24. If peginterferon alfa or ribavirin is discontinued for any reason, telaprevir must also be discontinued.

Contraindications

Telaprevir in combination with peginterferon alfa and ribavirin is contraindicated: in women who are or may become pregnant and in men whose female partners are pregnant.

Telaprevir is contraindicated:

- When combined with drugs that are highly dependent on cytochrome P450 (CYP3A) for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.
- When combined with drugs that strongly induce CYP3A and thus may lead to lower exposure and loss of efficacy of telaprevir.
- In combination with: alfuzosin, rifampin, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, St. John's wort (*Hypericum perforatum*), lovastatin, simvastatin, pimozide, sildenafil or tadalafil (for treatment of pulmonary arterial hypertension), orally administered midazolam, and triazolam.

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Clinical Experience

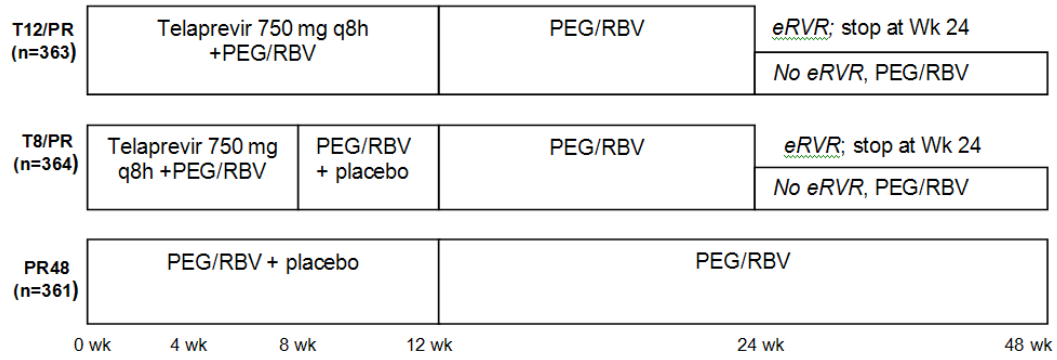
Use in Treatment-Naïve Patients

ADVANCE: Triple Therapy in Treatment-Naïve CHC Genotype 1 Patients

The ADVANCE trial (n=1,088) was a double-blind, randomized, placebo-controlled Phase III study that evaluated the efficacy and safety of telaprevir, Pegasys and ribavirin in treatment-naïve, genotype 1 CHC patients.[1] Patients received 8 or 12 weeks of telaprevir 750 mg every 8 hours plus Pegasys 180 mcg/week and ribavirin 1,000/1,200 mg/day (for 24 or 48 weeks), or Pegasys and ribavirin for 48 weeks. Telaprevir-treated patients with undetectable HCV RNA at Weeks 4 and 12 of treatment (eRVR; extended rapid virologic response) received a total of 24 weeks of therapy; whereas patients who became undetectable at Week 24 received a total of 48 weeks of therapy. See Figure 1 for study design details. The primary endpoint was SVR (undetectable HCV RNA 24 weeks posttreatment).

Patients were discontinued from telaprevir if HCV RNA was >1,000 IU/mL at Week 4 (Pegasys and ribavirin therapy were continued).[1] All patients with <2 $\log_{10}$ HCV RNA decline at Week 12 or who were HCV RNA detectable from Weeks 24-40 were withdrawn from all treatment.

Figure 1. ADVANCE Study Design[1]



Abbreviations: eRVR= extended rapid virologic response; PEG/RBV (PR): Pegasys/Ribavirin; T=telaprevir; Wk=weeks

Across treatment cohorts at baseline, the majority of patients had HCV RNA ≥800,000 IU/mL (77%) and were infected with HCV genotype 1a subtype (58%-59%).[1] A total of 58% of patients were male, 21% had bridging fibrosis or cirrhosis, 11% were Hispanic, and 9% were Black.

A significantly greater proportion of patients achieved SVR with 12-week and 8-week telaprevir-based regimens (75% and 69%, respectively) compared with the Pegasys/ribavirin control arm (44%, p<0.001).[1] Refer to Table 1 for additional results.

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Table 1: Treatment Outcomes in ADVANCE[1]			
	T12/PR (n=363)	**T8/PR (n=364)**	**PR48 (n=361)**
RVR, n (%)	246 (68)	242 (66)	34 (9)
eRVR, n (%)	212 (58)	207 (57)	29 (8)
EOTR, n (%)	314 (87)	295 (81)	229 (63)
Overall SVR, n (%)	271 (75)*	250 (69)*	158 (44)
SVR in patients with RVR, n/N (%)	206/246 (84)	188/242 (78)	32/34 (94)
SVR in patients with eRVR, n/N (%)	189/212 (89)	171/207 (83)	28/29 (97)
SVR in patients with detectable HCV RNA at Weeks 4 or 12, n/N % (%)	82/151 (54)	79/157 (50)	130/332 (39)
Relapse, n/N (%)	27/314 (9)	28/295 (9)	64/229 (28)

*p<0.001 vs PR48
Abbreviations: eRVR= extended rapid virologic response (undetectable HCV RNA at Weeks 4 and 12); EOTR= end of treatment response (undetectable HCV RNA at end of treatment); P=Pegasys; R=ribavirin; RVR=rapid virologic response (undetectable HCV RNA at Week 4); SVR=sustained virologic response; T=telaprevir

Similarly, subanalyses revealed higher rates of SVR in patients receiving either telaprevir-based regimen compared with Pegasys and ribavirin alone, in the following groups: genotype 1a and 1b patients, Black/African Americans, patients with HCV RNA ≥800,000 IU/mL at baseline, and patients with bridging fibrosis or cirrhosis (see Table 2).[1]

Table 2: SVR in Subgroups in ADVANCE[1]			
	T12/PR (n=363)	**T8/PR (n=364)**	**PR48 (n=361)**
Genotype 1a	71%	66%	41%
Genotype 1b	79%	74%	48%
Black or African Americans	62%	58%	25%
Baseline HCV RNA levels ≥800,000 IU/mL	74%	66%	36%
Bridging fibrosis or cirrhosis	62%	53%	33%

Abbreviations: HCV=hepatitis C virus; IU=international units; P=Pegasys; R=ribavirin; RVR=rapid virologic response; SVR=sustained virologic response; T=telaprevir.

Virologic failure during the treatment period was defined as meeting the criteria for a stopping rule, HCV RNA >1,000 IU per milliliter at Week 12 even if the HCV RNA decline was >2 $\log_{10}$, or detectable HCV RNA at the end of treatment (Week 24 or 48).[1] There were similar rates of virologic failure (3%) in both telaprevir groups during the first 12 weeks of therapy. After 12 weeks, the rate of virologic failure was higher in the T8/PR (10.2%) group compared with the T12/PR (5.0%) group and was associated with wild-type and lower-level telaprevir-resistant variants.[2] There were 91 patients with sequencing data available with telaprevir-resistant variants after not achieving SVR; 55 (60%) patients no longer had detectable resistant variants after study conclusion. The median time to loss of detectability of resistant variants for T54, A156, V36, and R155 variants was 13, 24, 36 and 44 weeks, respectively.

Refer to Table 3 for information on adverse events and rates of treatment-related withdrawals. Rash and anemia were the most frequently reported adverse events that led to withdrawal from telaprevir-based therapy.

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Table 3: Serious Adverse Events, Most Common Adverse Events (≥ 25%), and Discontinuation Rates (%)[1]			
	T12/PR (n=363)	**T8/PR (n=364)**	**PR48 (n=361)**
Serious Adverse Event	9	9	7
Any Adverse Event	99	99	98
Fatigue	57	58	57
Pruritis	50	45	36
Headache	41	43	39
Nausea	43	40	31
Rash	37	35	24
Anemia	37	39	19
Insomnia	32	32	31
Diarrhea	28	32	22
Pyrexia	26	30	24
Musculoskeletal disorders	39	41	50
Infections and infestations	28	37	38
Metabolic and nutrition disorders	31	30	24
Discontinuations Due to Adverse Events			
Telaprevir/placebo discontinued	11	7	1
All drugs discontinued (during telaprevir/placebo phase)	7	8	4
All drugs discontinued (during overall study period)	10	10	7
Abbreviations: P=Pegasys; R=ribavirin; T=telaprevir.			

Four deaths occurred during the study (n=2 for T12PR; suicide, HCV infection and liver disease; n=1 for T8PR; unknown cause; n=1, PR48 suicide).[1] One death, in the PR48 group, occurred during therapy.

Skin Reactions

Rash was primarily eczematous and resolved upon cessation of therapy.[1] Moderate and severe rash were managed by sequentially discontinuing telaprevir, followed by ribavirin after 7 days and, if indicated, Pegasys for continued progression. During the telaprevir/placebo phase, there were 7% of patients in the T12PR group and 5% in the T8PR group who discontinued telaprevir due to rash, and 1.4% and 0.5% in the two groups, respectively, discontinued all treatment due to rash. There was 1 case of Stevens-Johnson Syndrome which occurred approximately 11 weeks after the last dose of telaprevir.

Anemia

During the telaprevir/placebo phase, discontinuations of telaprevir or placebo due to anemia occurred in 4%, 2%, and 0% of patients in the T12/PR, T8/PR and PR48 groups, respectively and 1%, 3%, and <1% of the patients in the three groups, respectively, discontinued all treatments.[1]

Anemia was primarily managed with ribavirin dose modifications; the use of erythropoietin-stimulating agents was not permitted per protocol. There were 17 patients in each of the telaprevir groups and 6 patients in the PR48 group that received blood transfusions during the study.

There were greater decreases in hemoglobin with telaprevir combination therapy compared with Pegasys and ribavirin alone; hemoglobin levels increased after discontinuation of telaprevir.[1] The largest difference in mean hemoglobin levels between the T12PR group and the PR48 group (1.04 g/dL lower in the T12PR group) and between the T8PR group and the PR48 group (1.11 g/dL lower in the T8PR group) occurred at Week 8.

Fatigue

Worsening of fatigue (measured by Fatigue Severity Scale [FSS] total score) was observed in all treatment groups from baseline to Week 12.[3] Improvements in FSS scores after Week 12 occurred in all

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groups, with the strongest improvements observed in T/PR patients treated for 24 weeks. At Week 72, mean fatigue scores were improved from baseline and were similar among all groups.

IL28B Genotype Testing

IL28B genotype testing (rs 12979860) was conducted in 454/1,088 (42%) Caucasian patients enrolled in the ADVANCE study.[4] There were 33%, 49% and 18% of patients that had a CC, CT and TT genotype, respectively. Telaprevir-based therapy improved eRVR and SVR rates across all IL28B genotypes compared with Pegasys/ribavirin alone. Patients with the CC genotype treated with T12PR experienced higher rates of SVR compared with PR48 (90% vs 64%). The greatest improvements of SVR with T12PR vs PR48 were observed in non-CC patients (CT: 71% vs 25%; TT: 73% vs 23%). In telaprevir-treated patients, 72%, 54% and 48% of CC, CT and TT patients achieved eRVR, respectively, compared with 16%, 3% and 0% of Pegasys/ribavirin patients, respectively. In telaprevir-treated patients who achieved eRVR, 91% attained SVR (97% of CC, 88% of CT/TT) with 24 weeks of therapy and 45% of non-eRVR telaprevir-treated patients achieved SVR (67% of CC, 38% CT/TT) with 48 weeks of therapy.

ILLUMINATE: Optimal Duration of Therapy in Treatment -Naïve HCV Genotype 1 Patients

The ILLUMINATE trial was an open-label, randomized, noninferiority Phase III study that evaluated the optimal duration of telaprevir-based therapy (24 weeks vs 48 weeks) in HCV genotype 1 treatment-naïve patients achieving an eRVR (undetectable HCV RNA at Weeks 4 and 12).[5]

Patients (n=540) were treated with telaprevir 750 mg every 8 hours, Pegasys 180 mcg/wk plus ribavirin 1,000/1,200 mg/daily until Week 12.[5] Patients who achieved eRVR were randomized at Week 20 to continue receiving Pegasys plus ribavirin for 24 or 48 weeks of total treatment. Patients not achieving eRVR were assigned 48 weeks of treatment.

Patient characteristics included: 60% male, 79% Caucasian, 14% Black, and 28% bridging fibrosis or cirrhosis.[5]

There were 65% (n=352) of patients that achieved eRVR.[5] The percentage of patients achieving eRVR, SVR in the 24-week group was noninferior to the 48-week group (92% vs 88%, respectively; 95% CI: -2-11). Overall SVR was 72%.

The most common adverse events, in order of frequency, were fatigue (68%), pruritis (51%), nausea (47%), anemia (39%), rash (37%), insomnia (32%), diarrhea (28%), and influenza-like illness (26%).[5] In patients attaining eRVR, there were more serious adverse events in the 48-week group compared with the 24-week group (10% vs 2%, p=0.005).

Retrospective, Pooled Analyses of ADVANCE and ILLUMINATE

Several retrospective, pooled analyses of the ADVANCE and ILLUMINATE studies were conducted to evaluate factors affecting treatment outcomes.[6-8] Patients included in these analyses received 12 weeks of telaprevir with either 24 or 48 weeks of Pegasys and ribavirin (T12PR; n=903, from ADVANCE and ILLUMINATE studies) and were compared with patients who received Pegasys plus ribavirin alone (PR) in the ADVANCE study (n=361).

Anemia and SVR

More patients in the T12PR group (n=361/885; 41%) experienced anemia (hemoglobin<10 g/dL) compared with the PR group (n=92/354; 26%).[9] SVR rates were similar in patients with or without anemia receiving T12PR (refer to Table 4). In the T12PR and PR groups, 72% (260/361) and 58% (53/92) of patients with anemia, respectively, had ribavirin dose reductions due to adverse events compared with 11% (60/524) and 6% (16/262) of T12PR and PR patients without anemia, respectively.

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Table 4: SVR Rates in Patients With and Without Anemia, n/N (%)[9]		
	Patients with Anemia	**Patients without Anemia**
T12PR	267/361 (74%)	384/524 (73%)
PR	46/92 (50%)	108/262 (41%)
Notes: T12/PR: Telaprevir 750 mg Q8h, Pegasys 180 mcg/wk plus ribavirin 1,000/1,200 mg/d x 12 wks followed by Pegasys plus ribavirin for 12 or 36 weeks; PR48: Pegasys 180 mcg/wk plus ribavirin 1,000/1,200 mg/d x 48 wks		

Race/Ethnicity and SVR

SVR rates in Black/African American and Hispanic/Latino patient populations were higher in patients receiving T12PR compared with patients treated with PR alone (Table 5).[10]

Table 5: Treatment Outcomes by Race or Ethnicity, %[10]					
	RVR	**eRVR**	**SVR**	**Relapse**	**On-Treatment Virologic Failure**
Black/African American					
T12PR (n=99)	61	46	61	13	9
PR (n=28)	7	7	25	36	46
Hispanic/Latino					
T12PR (n=89)	64	58	70	7	7
PR (n=38)	8	8	39	26	32
Notes: T12/PR: Telaprevir 750 mg Q8h, Pegasys 180 mcg/wk plus ribavirin 1,000/1,200 mg/d x 12 wks followed by Pegasys plus ribavirin for 12 or 36 weeks; PR48: Pegasys 180 mcg/wk plus ribavirin 1,000/1,200 mg/d x 48 wks Abbreviations: eRVR= extended rapid virologic response; RVR= rapid virologic response ; SVR= sustained virologic response					

Early HCV Clearance and SVR

At Weeks 1, 2 and 4, 6%, 22% and 20% of T12PR patients had undetectable HCV RNA, respectively, vs 2%, 3% and 3% of patients treated with Pegasys plus ribavirin, respectively.[8] In both treatment groups, early undetectable HCV RNA was associated with SVR. In T12PR patients with undetectable HCV RNA at Weeks 1, 2 and 4, SVR rates were 90%, 83% and 77%, respectively.

Use in Previously Treated Patients

<u>REALIZE: Retreatment in Genotype 1 Relapsers and Nonresponders</u>

REALIZE was a Phase III, randomized, double-blind, placebo-controlled study (n=663) that evaluated the efficacy and safety of telaprevir-based regimens in genotype 1 CHC patients who were relapsers or nonresponders to prior treatment with pegylated interferon and ribavirin.[11] Relapsers were defined as patients who had undetectable HCV RNA at the completion of a prior course of therapy but became HCV RNA detectable during the 24-week follow-up. Nonresponders were categorized as no/null responders (<2 $\log_{10}$ reduction in HCV RNA at Week 12 with prior course of therapy) or partial responders (achieved ≥ 2 $\log_{10}$ reduction at Week 12, but were HCV RNA detectable at end of previous treatment).

Patients received 12 weeks of telaprevir in combination with Pegasys and ribavirin, with or without a 4-week lead-in with Pegasys and ribavirin, compared with a control arm of Pegasys and ribavirin.[11] All patients received therapy for a total of 48 weeks. Dosing included: Telaprevir 750 mg every 8 hours, Pegasys 180 mcg once weekly, and ribavirin 1,000/1,200 mg/day. See Figure 2 for study design.

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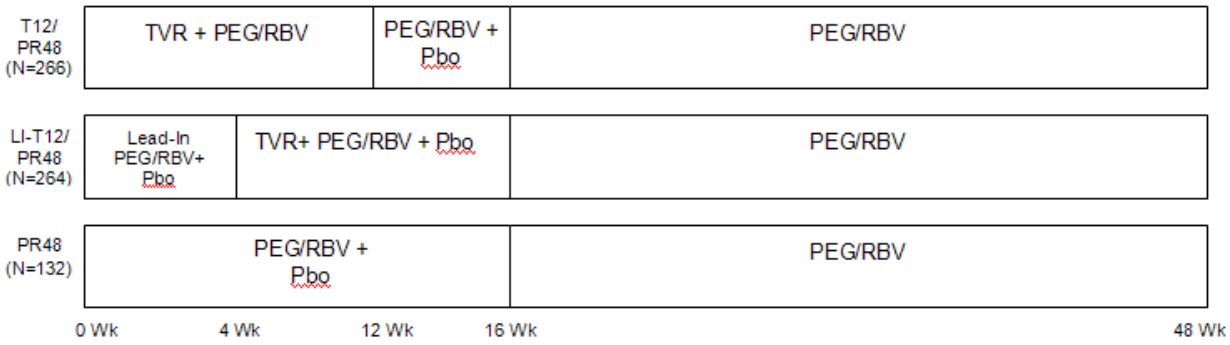
Figure 2. REALIZE Study Design (2:2:1)[11]



Abbreviations: LI= Lead-in; Pbo= placebo; PEG/RBV (PR)= Pegasys/Ribavirin; TVR (T)= telaprevir; Wk= Week

Telaprevir was stopped if HCV RNA levels were >100 IU/mL at Weeks 4, 6 and 8.[11] All treatment was discontinued in patients with <2 $\log_{10}$ HCV RNA decline at Week 12 in the T12/PR48 or PR48 group or Week 16 in the lead-in T12/PR48 or in any patients who were HCV RNA detectable at Weeks 24 or 36.

Baseline characteristics across treatment cohorts included: 67%-72% male, 89%-95% White, 3%-8% Black, 9%-15% Hispanic, 23%-27% cirrhotic, 22-23%% had bridging fibrosis, and 86%-89% of patients had baseline HCV RNA ≥800,000 IU/mL.[11] There were 53% of patients who had a prior relapse, 18% who had a prior partial response, and 28% who had a prior no/null response.

Overall SVR rates were 64% in the T12PR48 group, 66% in the lead-in T12PR48 group, and 17% in the PR48 group.[11] The lead-in group had comparable rates of SVR compared with the no lead-in telaprevir group. Refer to Table 6 for treatment outcomes in the relapser and nonresponder populations.

There were 97/530 (18%) patients receiving telaprevir who experienced virologic failure (defined as discontinuation due to virologic stopping rule and/or viral breakthrough).[12] There was no significant difference in virologic failure rates with (45/264; 17%) or without lead-in (52/266; 20%). The majority of patients who experienced virologic failure were prior null-responders (78%) and were infected with HCV genotype 1a (71%). Resistant variants were no longer detectable during the median follow-up of 11 months in 58% (n=60/104) of patients who had failed treatment and had telaprevir-resistant variants at the time of failure.

Table 6: Treatment Outcomes in REALIZE, n/N (%)[11]

	T12/PR48	Lead-In T12/PR48	PR48
Prior Relapsers			
SVR	121/145 (83%)*	124/141 (88%)*	16/68 (24%)
Relapse	10/135 (7%)	9/138 (7%)	30/46 (65%)
Virologic Failure	2/145 (1%)	1/141 (<1%)	18/68 (26%)
Prior Nonresponders (Overall)			
SVR	50/121 (41%)*	51/123 (41%)*	6/64 (9%)
Prior Partial Responders			
SVR	29/49 (59%)*	26/48 (54%)*	4/27 (15%)
Relapse	8/39 (21%)	9/36 (25%)	0
Virologic Failure	9/49 (18%)	9/48 (19%)	19/27 (70%)
Prior No/Null Responder			
SVR	21/72 (29%)*	25/75 (33%)*	2/37 (5%)
Relapse	8/30 (27%)	9/36 (25%)	3/5 (60%)
Virologic Failure	41/72 (57%)	35/75 (47%)	31/37% (84%)

*p<0.001 vs PR48
Abbreviations: SVR=sustained virologic response

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The telaprevir arms were pooled to assess SVR by baseline fibrosis stage and prior response (Table 7).[13]

Table 7: SVR in REALIZE by Baseline Fibrosis Stage and Prior Response[13]

	Pooled T12/PR48	PR48
Prior Relapsers		
Bridging Fibrosis	53/62 (85%)	2/15 (13%)
Cirrhosis	48/57 (84%)	2/15 (13%)
Prior Partial Responders		
Bridging Fibrosis	10/18 (56%)	0/5 (0%)
Cirrhosis	11/32 (34%)	1/5 (20%)
Prior Null Responders		
Bridging Fibrosis	15/38 (39%)	0/9 (0%)
Cirrhosis	7/50 (14%)	1/10 (10%)

Refer to Table 8 for adverse events and treatment-related withdrawal rates.[11] Moderate and severe rash were managed by sequentially discontinuing telaprevir, followed by ribavirin after 7 days and, if indicated, Pegasys for continued progression.

Grade 3 adverse events (mainly anemia, neutropenia, and leukopenia) were reported more frequently in the two telaprevir groups than in the control group during the overall study period (37% vs 22%).[11] Anemia was primarily managed with ribavirin dose modifications (25% [133/532] in the pooled T12/PR48 group vs 12% [16/132] in the PR48 group); the use of erythropoietin-stimulating agents was not permitted per protocol.[14] Transfusions were received by 7% (38/532) of patients in the T12/PR48 group vs <1% (1/132) in the PR48 group. Anemia was a predictor of SVR in the PR48 group (p=0.031) but not in the pooled T12/PR48 group (p=0.18).

Table 8: Adverse Events and Treatment-Related Discontinuation Rates, %[11]

	T12/PR48 (n=266)	Lead-In T12/PR48 (n=264)	PR48 (n=132)
Serious Adverse Events	12	12	5
Adverse Events (>25%) During any Treatment Phase			
Fatigue	55	50	40
Pruritis	52	50	27
Headache	42	41	37
Rash	37	36	19
Infections	37	38	36
Nausea	35	33	23
Influenza-like Illness	32	36	25
Anemia	30	36	15
Insomnia	26	32	26
Diarrhea	25	26	14
Pyrexia	23	27	27
Asthenia	19	23	29
Discontinuations During Telaprevir/Placebo Phase			
Telaprevir or Placebo discontinued	15	11	3
Discontinuations During any Treatment Phase			
Pegasys Discontinued	8	7	6
Ribavirin Discontinued	9	8	6
All drugs discontinued (simultaneously)	6	4	3

Subanalysis of Telaprevir Lead-In Arm

A subanalysis of the REALIZE study was conducted to evaluate the relationship of virologic response at the end of the 4-week lead-in phase and SVR.[15] SVR rates in patients receiving telaprevir were higher compared with the control group, regardless of response (< or ≥1 $\log_{10}$ decline in HCV RNA) at the end of the lead-in phase. Prior treatment categorization was a better predictor of SVR with telaprevir than Week 4 response after a lead-in. In the lead-in T12/PR48, 10% of prior relapsers, 40% of partial responders

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and 59% of null responders experienced <1 log_{10} decline in HCV RNA at Week 4. In these patients receiving lead-in T12/PR48, SVR in the prior relapsers and partial responders were higher (62% and 56%, respectively) compared with prior null responders (15%). In the lead-in T12/PR48 and PR48 groups, 90% of prior relapsers, 60% of partial responders and 41% of null responders experienced ≥1 log_{10} decline in HCV RNA at Week 4. In these patients, SVR in the prior relapsers and partial responders were higher (94% and 59%, respectively) compared with prior null responders (54%).

IL28B Genotype Testing: Exploratory Analysis

A retrospective, genome-wide association study in 527 patients in the REALIZE study evaluated the effect of IL28B rs 12979860 polymorphism on SVR.[16] The presence of CC, CT and TT IL28B genotype occurred in 18%, 61% and 21% of patients, respectively. Within prior response categories (relapsers, partial responders, and null responders) SVR rates with telaprevir were similar across IL28B genotypes.

Patients receiving a telaprevir-based regimen achieved higher SVR rates across IL28B genotypes compared with patients receiving Pegasys and ribavirin alone. In telaprevir-treated patients, 79%, 60% and 61% of CC, CT and TT patients achieved SVR, respectively, compared with 29%, 16% and 13% of Pegasys/ribavirin patients, respectively.

Predictors of SVR

A posthoc analysis of the REALIZE study evaluated predictors of response with telaprevir combination therapy.[17] Previous response to peginterferon/ribavirin (Odds ratio [OR] 2.81, p<0.0001), baseline LDL (OR 2.13, p<0.0001) and fibrosis stage (OR 0.74, p=0.0022) were significant predictors of SVR. On-treatment response, eRVR (OR 7.8), was the strongest predictor of SVR when added to the model. Age, race, ALT/AST, gender, BMI, HOMA-IR (homeostasis model for assessment-insulin resistance), HDL, triglycerides, GGT (gamma-glutamyl transpeptidase) were not independently predictive of SVR (p>0.05 for each) in the overall population.

Phase IIIB C219 Rollover Study

A single-arm, open-label, rollover study examined the efficacy and safety of telaprevir-based therapy in patients who did not achieve SVR after treatment with Pegasys and ribavirin alone in the REALIZE study.[18] Of the 81 patients who did not attain SVR in the Pegasys and ribavirin arm, 32 (40%) were null responders, 27 (33%) were relapsers, and 22 (27%) were partial responders. Tables 9 and 10 describe the outcomes and safety from this study.

Table 9: C219 Treatment Outcomes Based on Prior Response*[18]

Outcome (n/%)	Relapser (n=27)	Partial Responder (n=22)	Null Responder (n=32)	All Patients (n=81)
SVR	22 (81)	16 (73)	11 (34)	49 (60)
Virologic failure† on treatment	1 (4)	3 (14)	18 (56)	22 (27)
Relapse‡	1/25 (4)	1/19 (5)	3/14 (21)	5/58 (9)
Other§	3 (11)	2 (9)	0	5 (6)

*Based on entry to C219 study; † Defined as meeting a virologic stopping rule or experiencing viral breakthrough; ‡ Determined using denominator equal to the number of patients with HCV RNA < 25 IU/mL, "target not detected" at the end of treatment; § Defined as patients with detectable HCV RNA at the end of treatment with no viral breakthrough or patients with undetectable HCV RNA at the end of treatment but who discontinued the study prior to SVR assessment.
Abbreviation: SVR=sustained virologic response.

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Table 10: C219 Safety Outcomes[18] (n=81)	
Parameter	**%**
Most frequently reported adverse events* (≥30%)	
Pruritis	42
Fatigue	41
Rash	36
Anemia	32
Serious adverse events	
Anemia	4
Biliary colic	1
Pyelonephritis	1
Treatment discontinued due to adverse events	5
*During telaprevir treatment phase, most adverse events (not specified) were classified as grade 1/2.	

Retrospective Pooled Analyses of ADVANCE, ILLUMINATE, and REALIZE

A retrospective analysis of patients from the ADVANCE, ILLUMINATE, and REALIZE studies evaluated the on-treatment HCV-RNA levels and SVR in relation to HCV-RNA thresholds (HCV-RNA >1000 IU/mL for treatment-naïve and or >100 IU/mL for treatment-experienced) and timepoints (Week 4 and 12 for treatment-naïve and Weeks 4, 6, 8, and 12 for treatment-experienced) that were applied in these studies to identify patients unlikely to achieve SVR.[19] Included in this analysis were treatment naïve (n=903 [n=844 evaluated]) patients who received 12 weeks of telaprevir (T) with Pegasys (P) and ribavirin (R) with either 12 or 36 additional weeks of PR and treatment-experienced (n=266 [n=254 evaluated]) patients who received 12 weeks of T with PR followed by 36 weeks of PR. Viral dynamic modeling based on data from Phase III studies was used to simulate achievement of SVR with different futility rules. At week 4, 1.7% (14/844) treatment-naïve, 0.7% (1/138) prior relapsers, 0% (0/46) prior partial responders, and 14% (10/70) prior null responders had HCV-RNA >1000 IU/mL, and none of these patients achieved SVR with continued PR treatment. In addition, 23/25 patients reached HCV-RNA nadir at or prior to Week 4 with an increase in HCV-RNA levels by Week 4. Of the 16/844 treatment-naïve patients and 7/254 treatment-experienced patients with HCV-RNA levels between 100-1000 IU/mL at week 4, 22% (5/23) achieved SVR with continued treatment. Modeling data confirmed that patients with HCV-RNA levels between 100-1000 IU/mL at week 4 would benefit from continued treatment with T and PR, but patients with HCV-RNA >1000 IU/mL at week 4 would not.

Luo et al. performed a retrospective analysis of patients receiving telaprevir plus Pegasys and ribavirin in phase III trials (ADVANCE, ILLUMINATE and REALIZE) to evaluate whether SVR12 (undetectable HCV-RNA at follow-up week 12) was comparable with SVR24 (undetectable HCV-RNA at follow-up week 24).[20] Across the three studies, a similar proportion of patients on telaprevir-based regimens achieved SVR12 and SVR24. Concordance between SVR12 and SVR 24 was similar in both treatment-naïve (98% in ADVANCE, 98% in ILLUMINATE) and treatment-experienced patients (99% in REALIZE). Concordance was also similar in cirrhotic (99%) and non-cirrhotic patients (98%). There were 10/1579 (0.6%) of telaprevir-treated patients who relapsed between SVR12 and SVR24, and 13/1579 (0.8%) were lost to follow-up or missing data.

Roberts et al. assessed efficacy outcomes based on ribavirin dose reductions in the phase III trials (ADVANCE, ILLUMINIATE, and REALIZE).[21] Ribavirin dose reductions to ≤600 mg daily had no substantial effect on SVR rates in treatment-naïve and previously treated patients who received telaprevir-based combination therapy.

Resistance Testing in Phase III Trials

Viral resistance was studied in a pooled analysis of the ADVANCE, ILLUMINATE, and REALIZE studies.[22,23] There were 255 patients who did not attain SVR, with detectable resistant variants, included in the analysis (ADVANCE, n=82; ILLUMINATE, n=69; REALIZE, n=104). After the follow-up period (range, 2 weeks-16 months), population sequencing revealed that 60% of patients no longer had

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telaprevir-resistant variants. Loss of resistant variants occurred more rapidly in patients infected with HCV genotype 1b compared with 1a (0.8 months vs 10 months). Refer to Table 9 for additional information.

Table 11: Viral Resistance in Phase III Studies[22]

	Patients with no detectable variants at the end of study, % (n/N)	Median time to loss of detectable variant, months (95% confidence interval)*
V36A/M	68 (115/169)	10 (8,11)
T54A/S	84 (27/32)	4 (2, 5)
R155I/K/M/T	59 (100/170)	11 (10,13)
A156S/T/V	86 (19/22)	4 (3, 6)
V36M + R155K†	52 (65/124)	14 (12,14)

*Based on Kaplan-Meier estimates
†Patients included in estimates of loss of detectable V36M+R155K double variant are also included in the summaries of loss of detectable V36A/M and R155I/K/M/T variants

Durability of response

A 3-year virology follow-up study, EXTEND, is being conducted to assess the durability of SVR in patients previously enrolled in Phase II or Phase III telaprevir studies.[24] Results of an interim analysis showed that after a median of 21 months follow-up, 99% (220/221) subjects maintained HCV undetectable after telaprevir-based therapy. In patients who did not achieve SVR after telaprevir-based therapy (n=162), variants (ie, NS3) associated with decreased sensitivity to telaprevir were no longer detectable in 83% (134/162) of patients (median follow-up time 29 months).

Pegasys with Telaprevir in CHC Genotype 1 References

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Peginterferon alpha-2a Is Associated with Higher Sustained Virological Response than Peginterferon alfa-2b in Chronic Hepatitis C: Systematic Review of Randomized Trials

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A combination of weekly pegylated interferon (peginterferon) alpha and daily ribavirin represents the standard of care for the treatment of chronic hepatitis C according to current guidelines. It is not established which of the two licensed products (peginterferon alpha-2a or peginterferon alfa-2b) is most effective. We performed a systematic review of head-to-head randomized trials to assess the benefits and harms of the two treatments. We searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and LILACS through July 2009. Using standardized forms, two reviewers independently extracted data from each eligible trial report. We statistically combined data using a random effects meta-analysis according to the intention-to-treat principle. We identified 12 randomized clinical trials, including 5,008 patients, that compared peginterferon alpha-2a plus ribavirin versus peginterferon alfa-2b plus ribavirin. Overall, peginterferon alpha-2a significantly increased the number of patients who achieved a sustained virological response (SVR) versus peginterferon alfa-2b (47% versus 41%; risk ratio 1.11, 95% confidence interval 1.04-1.19; $P = 0.004$ [eight trials]). Subgroup analyses of risk of bias, viral genotype, and treatment history yielded similar results. The meta-analysis of adverse events leading to treatment discontinuation included 11 trials and revealed no significant differences between the two peginterferons. *Conclusion:* Current evidence suggests that peginterferon alpha-2a is associated with higher SVR than peginterferon alfa-2b. However, the paucity of evidence on adverse events curbs the decision to definitively recommend one peginterferon over the other, because any potential benefit must outweigh the risk of harm. (HEPATOLOGY 2010;51:1176-1184.)

Globally, an estimated 170 million people are chronically infected with hepatitis C virus, and 3 to 4 million persons are infected each year.[1] Analysts estimate the United States prescription market for hepatitis C to be approximately $3 billion annually. A combination of weekly subcutaneous injections of long-acting pegylated interferon (peginterferon) and oral ribavirin represents the current standard of care according to the American Association for the Study of Liver Diseases practice guideline.[2] Currently, there are two licensed products: peginterferon alpha-2a (Pegasys, Hoffmann-La Roche) and peginterferon alfa-2b (PegIntron, Schering-Plough Corporation). Lately, there has been considerable controversy over which treatment options are the most

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; OIS, optimum information size; peginterferon, pegylated interferon; RCT, randomized clinical trial; RR, risk ratio; SVR, sustained virological response.

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effective. A recent randomized clinical trial (RCT) published in the *New England Journal of Medicine* concluded that the two treatments are comparable in both benefits and harms.[3] However, findings from a single RCT, even a very large one, are rarely definitive, and caution should be taken to ensure reproducibility of its findings.[4-9] Systematic reviews and meta-analysis including all available trials are considered the highest level of evidence, and provide valuable information on the quality and strength of the available evidence.[10] We therefore conducted a Cochrane systematic review to identify, assess, and collectively analyze all RCTs that would add to the body of evidence and strengthen inferences about which form of peginterferon may work best.

Materials and Methods

The present systematic review is based on our peer-reviewed published Cochrane Hepato-Biliary Group protocol.[11]

Eligibility Criteria. This review includes RCTs, irrespective of language or publication status, comparing peginterferon alpha-2a with peginterferon alfa-2b given with or without cointerventions (such as ribavirin) in patients with chronic hepatitis C. We excluded RCTs if they included patients that had undergone liver transplantation.

Outcomes. The prespecified primary outcomes were sustained virological response (SVR), liver-related morbidity plus all-cause mortality, and adverse events leading to treatment discontinuation. SVR was defined as the number of patients with undetectable hepatitis C virus RNA in serum by sensitive test 6 months after the end of treatment.

Data Sources and Searches. We searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and LILACS through July 2009. We identified further trials by searching conference abstracts, journals, and gray literature. We used the key words *hepatitis C*, *peginterferon*, *pegylated interferon*, *viraferonpeg*, *pegintron*, and *pegasys* either as MeSH terms or as free-text words.

Study Selection and Data Collection. Two authors independently screened titles and abstracts for potential eligibility and the full texts for final eligibility. We extracted the data using a standardized data collection form to record study design and methodological characteristics, patient characteristics, interventions, outcomes, and missing outcome data. Authors of included trials were contacted for additional information not described in the published reports.

Methodological Quality Assessment. Methodological quality and hence risk of bias was defined as the confidence that the design and the report of the RCT would restrict bias in the comparison of the intervention.[12] The assessment was based on published reports and information provided by the authors of included trials. Following the implications of empirical evidence,[12-14] the methodological quality of the trials was assessed based on sequence generation allocation concealment, blinding of outcome assessors, incomplete outcome data (lost to follow-up and adherence to intention-to-treat analysis), and early stopping for benefit.

Data Synthesis and Analysis. The analyses were performed using Review Manager 5.0 and Trial Sequential Analysis version 0.8. Dichotomous data were expressed as the risk ratio (RR) with 95% confidence interval (CI). Furthermore, the number needed to treat was derived from the RR in meta-analyses where the 95% CI (or the RR) did not include zero. Heterogeneity was explored using a chi-square test, and the quantity of heterogeneity was measured using the I^2 statistic.[15] Sources of heterogeneity were assessed with subgroup analysis and meta-regression whenever possible. Subgroup analyses were performed only when data from at least two trials were available for each subgroup. Meta-regression was performed only for meta-analyses including more than 10 trials. Suitable sensitivity analysis was identified during the review process. When patients were lost to follow-up, data were analyzed according to the intention-to-treat principle. Intention-to-treat analysis was performed assuming poor outcome in both groups, where dropouts were considered failures and the total number of patients was used as the denominator. We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach[16] to present the summary of findings for the patient important outcomes.

Assessment of Reliability and Meta-analysis Sample Size Requirements. To assess the reliability of pooled inferences from our meta-analysis on SVR, we calculated the optimum information size (OIS)—that is, the required meta-analysis sample size—to detect a 10% relative risk reduction in SVR, assuming an average event rate of 50% in the two treatment arms, assuming that 30% of the variation in the meta-analysis would be explained by variation across trials, and using statistical error levels of alpha = 5% and beta = 10% (90% power). Meta-analyses conducted before surpassing their OIS are analogous to interim analyses in single RCTs, and thus necessitate adjustment of the threshold for statistical significance to maintain the predetermined maximum risk of obtaining a false positive results (set to alpha 5% in our analysis). We therefore substituted the conventional 5% threshold for statistical significance with those of Lan-DeMets alpha-spending monitoring boundaries.[8,17-19]

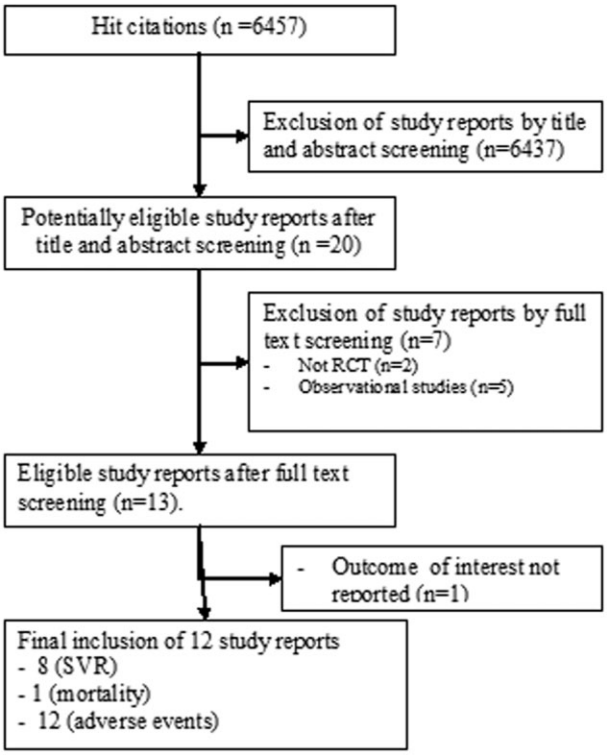

Fig. 1. Study screening flow chart.

Results

Study Characteristics. Figure 1 shows the results of the study screening. Twelve trials, including a total number of 5,008 participants,[3,20-30] that met our inclusion criteria[31] were retrieved. All trials compared peginterferon alpha-2a (180 μg/week) versus peginterferon alfa-2b (1-1.5 μg/kg/week). All trials administered ribavirin as a cointervention to both peginterferon arms. The dose of ribavirin was weight-based, ranging from 800 to 1,400 mg. The hepatitis C genotype of the included patients varied among trials. One trial included patients with history of previous hepatitis C treatment.[26] One trial included patients with human immunodeficiency virus patients.[24] Table 1 presents the patient and intervention characteristics. Table 2 presents the methodological quality of eligible randomized trial.

Effects of Interventions. The meta-analysis using intention-to-treat analysis for SVR included eight trials (4,335 participants).[3,23-26,28-30] Overall, peginterferon alpha-2a significantly increased the number of patients who achieved an SVR (47%) versus peginterferon alfa-2b (41%) (RR 1.11, 95% CI 1.04-1.19; $P = 0.004$). The number needed to treat was 25 patients (95% CI 14-100). Using RR as the measure of effect, the Cochran homogeneity test statistic yielded a P value of 0.58, and the heterogeneity was $I^2 = 0\%$ (Fig. 2).

Most subgroup analyses revealed no significant interactions. Data from six trials[3,24-26,29,30] for genotype 1 and 4 yielded an RR in favor of peginterferon alpha-2a (RR 1.21, 95% CI 1.03-1.42). Using relative risk as the measure of effect, the Cochran homogeneity test statistic yielded a P value of 0.21, and the heterogeneity was $I^2 = 30\%$. Data from five trials[23-26,30] for genotype 2 and 3 yielded an RR in favor of peginterferon alpha-2a (RR 1.11, 95% CI 1.02-1.22). Using RR as the measure of effect, the Cochran homogeneity test statistic yielded a P value of 0.89, and the heterogeneity was $I^2 = 0\%$.

Sensitivity analyses revealed no change in the significance of effects, and there was no significant change of magnitude of treatment effects. A sensitivity analysis including only trials with adequate randomization and allocation concealment did not change the pooled estimate. Additionally, excluding the trial that included patients with human immunodeficiency virus and the trial with nonresponder patients did not change the pooled estimate.

To assess the reliability of pooled inferences from our meta-analysis on SVR, we calculated the OIS required to detect a 10% relative risk reduction in SVR to be 5,990 patients. Statistical significance assessed with Lan-DeMets alpha-spending monitoring boundaries are presented in Fig. 3. Based on the adjusted threshold for statistical significance the meta-analysis on SVR was still significant in favor to peginterferon alpha-2a.

Adverse events leading to treatment discontinuation were reported in 11 trials.[3,20-22,24-30] Data from these trials yielded an RR of 0.79 (95% CI 0.51-1.23). Using RR as the measure of effect, the Cochran homogeneity test statistic yielded a P value of 0.42, and the heterogeneity was $I^2 = 2\%$ (Fig. 4). Furthermore, the included trials reported on numerous adverse events that did not lead to treatment discontinuation. Adverse events included hematological changes (neutropenia, thrombocytopenia, and anemia), psychological changes (depression), and other systemic events (fatigue, headache, insomnia, fever, nausea, and dyspnea). None of the included trials reported on any patients with liver-related morbidity.

Only one trial reported on all-cause mortality.[3] Seven patients died during the treatment period, and five died during or after the follow-up period. Two of these deaths were due to a suicide 6 months after the end of treatment with peginterferon alfa-2b and a myocardial infarction during treatment with peginterferon alfa-2a.

Table 3 presents the GRADE evidence profile regarding SVR and adverse events leading to treatment discontinuation.

Discussion

In this systematic review, we have summarized the available evidence from RCTs comparing peginterferon

Table 1. Characteristics of the Included Trials

Study	Peginterferon	Ribavirin	Ribavirin Dose Modification	Baseline Treatment History	HCV Genotype	Outcome Reported
Ascione (2008)	alpha-2a, 180 μg/week alfa-2b, 1.5 μg/kg/ week for 24-48 weeks*	1,000-1,200 mg/day†	200 mg‡	Treatment-naïve	1, 2, 3, 4	SVR, adverse events
Berak (2005)	alpha-2a, 180 μg/week alfa-2b, 1.0 μg/kg/ week for 12 weeks	Weight-based	NR	NR	Non 2/3	Adverse events
Bruno (2004)	alpha-2a, 180 μg/week alfa-2b, 1.0 μg/kg/ week for 12 weeks	1,000-1,200 mg/day†	NR	Treatment-naïve	1, 2, 3	Adverse events
DiBisceglie (2007)	alpha-2a, 180 μg/week alfa-2b, 1.5 μg/kg/ week for 12 weeks	1,000-1,200 mg/day†	NR§	Treatment-naïve	1	Adverse events
Kolakowska (2008)	alpha-2a, 180 μg/week alfa-2b, 1.5 μg/kg/ week for 24 weeks	Weight-based	NR	Treatment-naïve	3	SVR, adverse events
Laguno (2009)	alpha-2a, 180 μg/week alfa-2b, 1.5 μg/kg/ week for 48 weeks	800-1,200 mg/day¶	NR	Treatment-naïve	1, 2, 3, 4	SVR, adverse events
McHutchison (2009)	alpha-2a, 180 μg/week alfa-2b, 1-1.5 μg/kg/ week for 24-48 weeks*	800-1,400 mg/day$	200-600 mg**	Treatment-naïve	1	SVR, adverse events
Rumi (2008)	alpha-2a, 180 μg/week alfa-2b, 1.5 μg/kg/ week for 24-48 weeks*	800-1,200 mg/day††	200 mg#	Treatment-naïve	1, 2, 3, 4	SVR, adverse events
Scotto (2008)	alpha-2a, 180 μg/week alfa-2b 1.5 μg/kg/ week for 24-48 weeks*	15 mg/kg/day	4.6 mg/kg/day	Nonresponders	1, 2, 3, 4	SVR, adverse events
Silva (2006)	alpha-2a, 180 μg/week alfa-2b, 1.5 μg/kg/ week for 8 weeks	13 mg/kg/day	None allowed	Treatment-naïve	1	Adverse events
Sinha (2004)	alpha-2a, 180 μg/week alfa-2b, 1.5 μg/kg/ week for 24-48 weeks*	1,000-1,200 mg/day	NR	Treatment-naïve	1, 2, 3, 4	SVR, adverse events
Yenice (2006)	alpha-2a, 180 μg/week alfa-2b, 1.5 μg/kg/ week for 24-48 weeks*	800-1,200 mg/day§§	200-600 mg¶¶	Treatment-naïve	1	SVR, adverse events

*Patients affected by genotypes 1 or 4 received 48 weeks of treatment, while those affected by genotypes 2 or 3 were treated for 24 weeks.

$Peginterferon alfa-2b arm: 40-65 kg, 800 mg/day; >65-85 kg, 1,000 mg/day; >85-105 kg, 1,200 mg/day; and >105-125 kg, 1,400 mg/day. Peginterferon alpha-2a arm: <75 kg, 1,000 mg/day; ≥75 kg, 1,200 mg/day.

†1,000 mg/day in patients <75 kg, 1,200 mg/day in patients ≥75 kg.

‡Reduced in 200-mg decrements if the hemoglobin level decreased to <100 g/L or ≥30 g/L, or in the event of a severe cough or intolerable itching. Ribavirin was discontinued if the hemoglobin level decreased to <85 g/L.

§The reduction dose was not stated; however, the same dose reduction was applied for both arms.

¶800 mg for body weight <60 kg; 1,000 mg for 60-75 kg; 1,200 mg for >75 kg.

**For the peginterferon alfa-2b arm, the dose reduction occurred in two steps. The first step was a reduction of either 200 mg (in patients receiving 800-1,200 mg/day ribavirin) or 400 mg (in patients receiving 1,400 mg/day). The second step was reduction by another 200 mg, if required for resolution of the adverse event. For the peginterferon alpha-2a arm, the dose reduction consisted of a reduction to 600 mg/day. For all patients, ribavirin dose reduction was required if the hemoglobin level was <10 g/dL. Treatment with both drugs was permanently discontinued if the level was <8.5 g/dL.

††For the peginterferon alpha-2a arm, genotypes 1 and 4 were given 1,000 mg/day for <75 kg and 1,200 mg/day for ≥75 kg; genotypes 2 and 3 were given 800 mg/day. For the peginterferon alfa-2b arm, the doses were 800 mg/day for <65 kg, 1,000 mg for 65-85 kg, and 1,200 mg for ≥85 kg.

‡‡Ribavirin dose was reduced by 200 mg/day in patients with a hemoglobin level <10 g/dL, whereas it was discontinued in patients with <8.5 g/dL hemoglobin.
Abbreviation: HCV, hepatitis C virus; NR, not reported; SVR, sustained viral response.

§§40-64 kg, 800 mg; 65-85 kg, 1,000 mg; >85 kg, 1,200 mg.

¶¶Ribavirin dose was reduced to 600 mg in patients with a hemoglobin level <10 g/dL who had no cardiac problems. The same dose was maintained until the end of treatment. Ribavirin treatment was discontinued when the hemoglobin level was <8.5 mg/dL.

alpha-2a with peginterferon alfa-2b, both given in combination with weight-based ribavirin. Our results suggest that the combination of peginterferon alpha-2a and weight-based ribavirin may achieve significantly higher SVR than the combination of peginterferon alfa-2b and weight-based ribavirin. Only one trial reported mortality.[3] None of the included trials reported on liver-related morbidity. Our results also suggest that the two peginter-

Table 2. Methodological Quality of Eligible Trials

Trial	Concealment of Allocation	Outcome Assessors Blinded	Loss to Follow-up	Adherence to Intention-to-Treat Principle	Stopping Early for Benefits
Ascione (2008)	Yes	Yes	0	Yes	No
Berak (2005)	Unclear	Unclear	6	Yes	No
Bruno (2004)	Yes	Unclear	0	Yes	No
DiBisceglie (2007)	Yes	Unclear	45	Yes	No
Kolakowska (2008)	Unclear	Unclear	0	Unclear	No
Laguno (2009)	Yes	Unclear	34	Yes	No
McHutchison (2009)	Yes	Unclear	653	Yes	No
Rumi (2008)	Yes	Unclear	119	Yes	No
Scotto (2008)	Yes	Unclear	18	Yes	No
Silva (2006)	Yes	Yes	6	No	No
Sinha (2004)	Yes	Unclear	1	Yes	No
Yenice (2006)	Unclear	Unclear	6	Unclear	No

ferons may be comparable with regard to adverse events leading to treatment discontinuation. However, evidence on liver-related morbidity or mortality and adverse events is sparse, and the meta-analysis on adverse events is likely to be underpowered to detect any difference.

The GRADE findings in Table 3 show that in general, we can have high confidence in the current evidence on treatment benefits (measured as SVR), whereas we can only have low confidence in the current evidence on harms (measured as adverse events leading to discontinuation). For both outcomes, there were no serious limitations in the study design of the included trials. Information on the methodological quality was incomplete in a few small-sized trials. However, our sensitivity analyses did not reveal any important change of intervention effects. In our study, the trials that adequately reported methodological quality items are large trials, and dominate the pooled estimates of effect. Therefore, it is unlikely that pooled estimates are biased. In the meta-analyses for SVR, there were no serious inconsistencies across trials and the meta-analyses had adequate precision adjudicated by crossing of the adjusted threshold for statistical significance (the Lan-DeMets monitoring boundaries). Only a comparison of the largest trial[3] with the second and third largest trials[25,30] yielded moderate discrepancy. The latter two were both sufficiently statistically powered to detect a difference between the two peginterferons, and unlike the largest trial, which was funded by the manufacturer of peginterferon alfa-2b, these two trials were not funded by either of the two manufacturers. Because the meta-analysis for SVR only included eight trials, we did not perform a funnel plot to explore publication bias; however, because this meta-analysis included a seemingly reasonable mix of small and large trials yielding fairly consistent results, publication bias presented little concern. Nonetheless, we have some concerns with regard to indirectness. In the identified trials, virological response was the predominant measure of benefit. Many of the trials measured SVR, which is currently the commonly used surrogate outcome measure of benefit. Recent large cohort studies show correlation between the presence of viremia and mortality.[31,32] However, it is important to remember that SVR (and early virological response and end-of-treatment virological re-

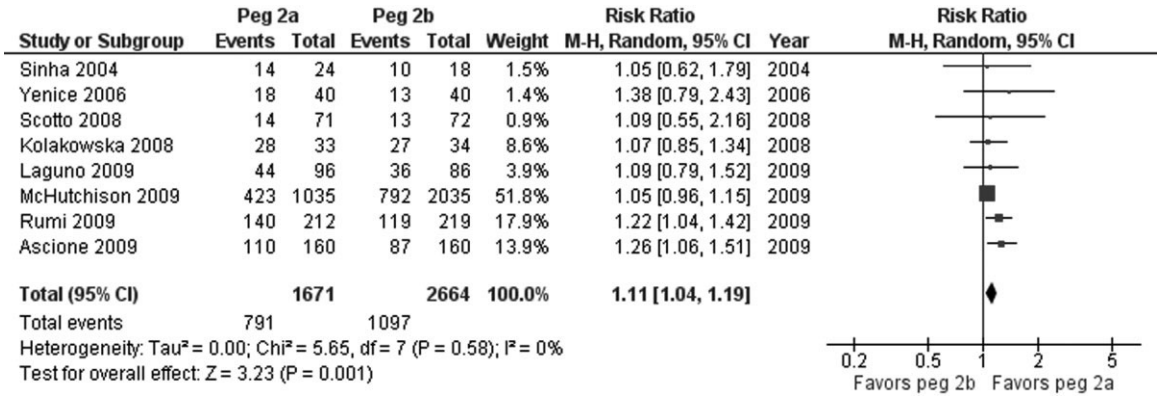

Fig. 2. Forest plot of comparison: Peginterferon alpha-2a versus peginterferon alfa-2b, outcome: Sustained virological response.

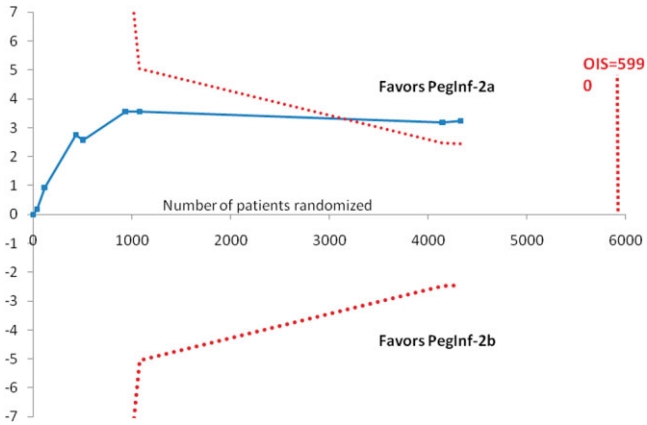

Fig. 3. Lan-DeMets statistical monitoring boundaries for assessing statistical significance. The solid blue curve presents the cumulative meta-analysis test-score and the inward sloping red dotted curves present the adjusted threshold for statistical significance—the two-sided LanDeMets monitoring boundaries. Test scores above the upper monitoring boundaries are statistically significant in favor of peginterferon alpha-2a (at an alpha = 5% level).

sponse) is still only a putative (that is, nonvalidated) surrogate outcome.[33] Because RCTs need to inform clinical practice, clinical outcomes such as the risk of liver failure, hepatocellular carcinoma, and mortality would be of greater interest to patients and clinicians. Such measures nevertheless require a follow-up of at least 5 years. Currently, no RCTs comparing the two peginterferons are of such longevity. In the meta-analysis on adverse events, there were serious discrepancies across trials. The proportions of observed adverse events differed greatly across the trials, and the direction of effect was also heterogeneous. It is noteworthy that the IDEAL trial[3] included three intervention arms: one for peginterferon alpha-2a and two for peginterferon alfa-2b. The two peginterferon alfa-2b arms consisted of a regular 1.5 μg/kg/week dosage and a low 1.0 μg/kg/week dosage. The regular dosage arm yielded a similar proportion of adverse events as the peginterferon alpha-2a arm, whereas the low-dose peginterferon alfa-2b group yielded a lower proportion of adverse events. Including or excluding the low-dose peginterferon alfa-2b arm from the meta-analysis had no visible impact on the estimated effect. Furthermore, the meta-analysis on adverse events had low precision. A post hoc OIS calculation that was geared to detect a minimally important difference of 10% relative risk reduction, based on the assumption of average population risk rate of 10%, and employed a 5% maximum type I error and 80% power, suggested that a minimum of 27,000 patients would need to be randomized for a conclusive adverse events meta-analysis. The current number of patients in the adverse events meta-analysis is approximately 5,000 (less than 20% of what is required).

There are some concerns regarding the nonstandardization of the ribavirin dose given across trials. The weight-based dose of ribavirin ranged from 800 to 1,400 mg. However, the weight cutoff varied among trials as well as within the same trial. In the largest included trial,[3] patients weiging 40-65 kg received a lower dose of ribavirin (800 mg) in the peginterferon alfa-2b arm compared with a higher dose of ribavirin (1,000 mg) in the peginterferon alpha-2a arm. However, patients in the peginterferon alfa-2b arm achieved higher SVR compared with patients in the peginterferon alpha-2a arm (46% versus 43%). Also, patients weighing more than 105 kg received a higher dose of ribavirin in the peginterferon alfa-2b arm (1,400 mg) compared with a lower dose of ribavirin (1,200 mg) in the peginterferon alpha 2a arm. Regardless, patients in the peginterferon alfa-2b arm achieved higher

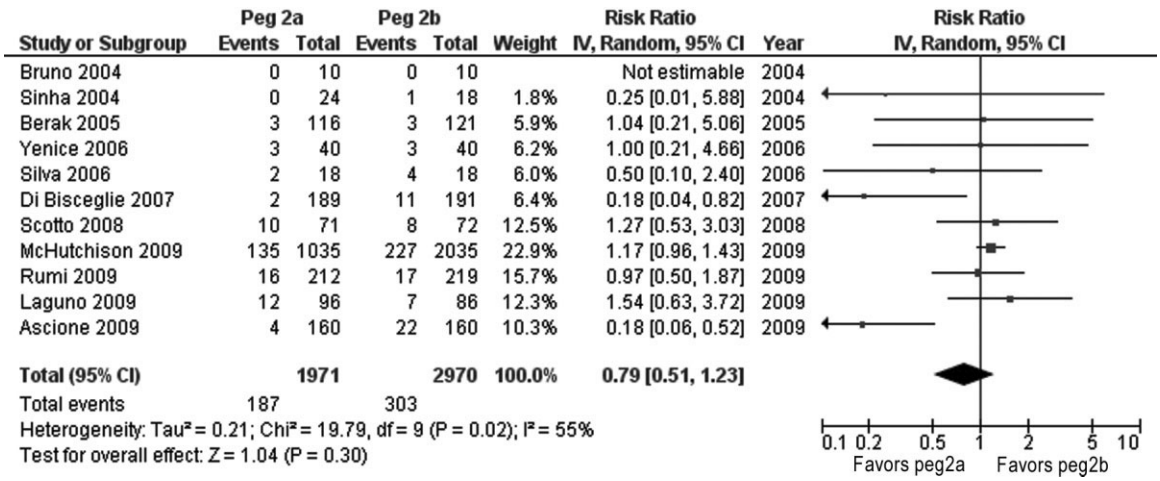

Fig. 4. Forest plot of comparison: Peginterferon alfa-2a versus peginterferon alfa-2b, outcome: Adverse events leading to treatment discontinuation.

Table 3. Summary of Findings: Peginterferon alpha-2a versus Peginterferon alfa-2b for Chronic Hepatitis C

Outcomes	Illustrative Comparative Risks* (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)†	Comments
	Assumed Risk: Peginterferon alfa-2b	Corresponding Risk: Peginterferon alpha-2a				
SVR	Medium risk population		RR1.1 (1.03-1.18)	4,335 (8)	⊕⊕⊕⊕	
	481 per 1,000	529 per 1,000 (495-568)			High‡	
Adverse events	Medium risk population		RR0.8 (0.51-1.26)	4,621 (10)	⊕⊕⊖⊖	
leading to treatment discontinuation	75 per 1,000	60 per 1,000 (38-94)			Low§,¶,#	

Patient or population: chronic hepatitis C. Intervention: peginterferon alpha-2a. Comparison: **p**eginterferon alfa-2b.

*The basis for the assumed risk (the median control group risk across studies) is provided in the other footnotes in this table. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

†GRADE Working Group grades of evidence: High: Further research is very unlikely to change our confidence in the estimate of effect. Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low: We are very uncertain about the estimate.

‡Many of the trials measured SVR, which is currently recognized as the best patient surrogate outcome measure of benefit. However, it is important to remember that SVRs are still only invalidated surrogate outcomes and thus do not necessarily predict patient important outcomes such as liver failure and hepatocellular carcinoma.

§The proportions of observed adverse events differ substantially across the trials, and the direction of effect is heterogeneous. However, because the event rate is still relatively low across all trials, all of the included trials may be subject to considerable random error, thus explaining the apparent heterogeneity in direction of estimates.

¶The Ideal trial includes three groups: one for peginterferon alpha-2a and two for peginterferon alfa-2b. The two peginterferon alfa-2b arms consist of a regular 1.5 dose and a low 1.0 dose. The regular-dose group yields similar proportion of adverse as the peginterferon alpha-2a group, whereas the low-dose peginterferon alfa-2b group yields a lower proportion of adverse events. Including/excluding the low-dose group from the meta-analysis had no visible impact on the pooled effect.

#Post hoc optimal information size calculations based on 5% type I error, 80% power, a minimally important difference of 10%, and an average risk rate of 10% suggest that a minimum of 27,000 patients need to be randomized for a conclusive adverse events meta-analysis. The current number of patients is approximately 5,000.

SVR compared with patients in the peginterferon alpha-2a arm (42% versus 39%). It is also interesting that in the same trial, patients who developed anemia and thus required ribavirin dose reduction achieved a higher SVR than patients who did not require the ribavirin dose to be reduced. Accordingly, we do not think that the varying doses of ribavirin have major confounding influence on our observations regarding type of peginterferon. More research needs to be performed to explore the optimal ribavirin dose. Ribavirin dose reduction due to adverse events was only reported in five trials.[3,25,26,29,30] Four of these trials applied the same dose reduction in both arms.[25,26,29,30] Only one trial applied different ribavirin dose reduction for two arms.[3] Excluding this trial from our meta-analysis for SVR did not change our estimate.

The strengths of this Cochrane Hepato-Biliary Group systematic review are that it is built on a peer-reviewed published protocol, used extensive searches until recently, considers risks of systematic errors (bias), and considers risks of random errors (chance) by adjusting the threshold for statistical significance according to the information and strength of evidence in the cumulative meta-analysis. A possible limitation is the unavailability of full reports of all included trials. Two of the eight included trials in the meta-analysis for SVR are only available as abstracts. However, we were able to successfully retrieve the necessary data for one of the two abstracts via e-mail correspondence with the authors,[28] and thus, the bias risk assessment of the included trial was performed to a satisfactory extent. Our sensitivity analysis did not show any important changes. In our study, the trials that were published as a full paper are large, and dominated the pooled estimates of effects. Moreover, empirical evidence suggests that trials that fail to refute the null hypothesis have lower odds of being published, especially those not funded by the industry.[34-40] Thus, many of the included abstracts may have a low probability of being published. In fact, including these abstracts in our systematic review may likely be a strength rather than a limitation. By including abstracts, we are looking at the complete available body of evidence. By excluding abstracts, we would only be looking at a subset defined through the biased publication mechanisms of the present day, which would increase the likelihood of publication bias considerably. Selective outcome reporting was difficult to assess in this review. Most of the included trials were not adequately registered or had their protocols publicly available prior to trial completion. Hopefully, the initiation of the World Health Organization International Clinical Trials Registry Platform will facilitate such assessments for future trials.[41,42] Another limitation in this review was insufficient reporting. Investigators of future trials are therefore well advised to adhere to the Consolidated Standards for Reporting of Trials in order to improve the quality of trial reports.[43]

These potential limitations and concerns may lower our confidence in the estimates of intervention effect. However, in our meta-analysis for SVR there is no apparent heterogeneity ($I^2 = 0\%$), and the direction of the treatment effect is the same across all included trials. Fur-

ther research is unlikely to change our confidence in the estimate of the effect. It is a common misconception that large RCTs are generally more reliable than meta-analyses. The reason this misconception has prevailed is due to a number of highly cited papers that compared high-quality large trials with collections of low-quality small trials (an unfair comparison). In empirical studies where high-quality large trials are compared with a collection of high-quality small trials, the results from the two are typically nondiscrepant. In the case of the IDEAL trial,[3] the results still show an effect—albeit small—in favor of peginterferon alpha-2a. There are many examples of large trials that underestimate the treatment effect simply by chance.

Current evidence suggests that peginterferon alpha-2a is significantly superior to peginterferon alfa-2b regarding benefits (SVR, which is clearance of the virus from the blood). However, there is insufficient evidence to detect any differences regarding harms (mortality and adverse events). Future trials must further the correlation between achieving SVR and clinically relevant outcomes such as risk of cirrhosis, hepatocellular carcinoma, and mortality.

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Review Article

Efficacy and Tolerability of Peginterferon α-2a and Peginterferon α-2b, Both plus Ribavirin, for Chronic Hepatitis C: A Meta-Analysis of Randomized Controlled Trials

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Background. The efficacy and tolerability of peginterferon α-2a and peginterferon α-2b in chronic hepatitis C (CHC) patients remain controversial. *Methods*. PubMed, Ovid, and Cochrane libraries were electronically searched until August 30, 2012. Studies that met the inclusion criteria were systematically evaluated by two reviewers independently. *Results*. The overall sustained virologic response (SVR) rate of the peginterferon α-2a group was significantly higher than that of the peginterferon α-2b group (46.7% versus 42.4%, P value = 0.01). The same tendency was observed for naïve, genotype 1/4, and genotype 2/3 patients. The early virologic response (EVR) and end-of-treatment response (ETR) rates were significantly higher in the peginterferon α-2a group than in the peginterferon α-2b group (56.1% versus 49.8%, $P < 0.0001$; 67.9% versus 56.6%, $P < 0.00001$, resp.). Peginterferon α-2a had a significantly lower discontinuation rate than peginterferon α-2b (27.9% versus 33.9%, $P < 0.0001$) in naïve patients. In both naïve CHC and hepatitis C virus genotype 1 patients, peginterferon α-2a had a higher relapse rate than peginterferon α-2b. *Conclusions*. Peginterferon α-2a has superior efficacy with higher EVR, ETR, and SVR than peginterferon α-2b for CHC patients, both plus ribavirin. Peginterferon α-2a might obtain a similar or even lower discontinuation rate than peginterferon α-2b. However, peginterferon α-2a had a higher relapse rate than peginterferon α-2b.

1. Introduction

The World Health Organization has estimated that up to 170 million people (approximately 3% of the world population) worldwide might be infected with hepatitis C virus (HCV). This virus is responsible for approximately 350,000 deaths every year. HCV is cleared spontaneously in only approximately 20% of individuals. Chronic infection frequently progresses to cirrhosis, end-stage liver disease, hepatocellular carcinoma, and death [1–4].

Currently, in many countries, the recommended therapy for chronic hepatitis C (CHC) is still the combination of peginterferon α and ribavirin [1, 2]. Two licensed products of peginterferon α are available: peginterferon α-2a (Pegasys, Hoffmann-La Roche, Nutley, NJ, USA) and peginterferon α-2b (Peg-Intron, Schering Plough Corp., Kenilworth, NJ, USA). However, differences in structural modifications and dosing (weight-adjusted versus fixed) between the two peginterferons may lead to various clinical outcomes. In addition, a recommendation about the two regimens has not been proposed in the current guidelines [5–11]. Although recent studies have compared the response rates obtained using the two peginterferons in CHC, they have failed to reach a consensus as to which treatment options are the most effective.

Some systematic reviews [12–15], which include meeting abstracts or HCV/HIV coinfected patients, concluded that peginterferon α-2a has higher sustained virologic response (SVR) than peginterferon α-2b in CHC but revealed that

both have similar safety. The virologic responses and tolerability of peginterferon plus ribavirin in HCV/HIV coinfected patients are substantially different from those in chronic HCV monoinfected patient. In addition, some reported meeting abstracts were found to be inadequate. Thus, we performed a meta-analysis of randomized controlled trials (RCTs) with critical inclusion and exclusion criteria to evaluate the efficacy and tolerability of the two regimens.

2. Materials and Methods

2.1. Search Strategy. We searched PubMed, Ovid, and Cochrane libraries until August 30, 2012. The following medical subject headings were used: "Hepatitis C, Chronic," "interferons," "peginterferon alfa/alpha/α-2a," "peginterferon alfa/alpha/α-2b," and "ribavirin." Electronic searches were supplemented with manual searches of reference lists of all retrieved review articles, primary studies, and abstracts from meetings to identify other studies not found in the electronic searches. The literature was searched by two authors (Z. Yang and L. Zhuang) independently.

2.2. Study Selection. Two authors independently selected trials and discussed them with each other when inconsistencies were found. Articles that meet the following criteria were included: (1) study types, randomized controlled trials; (2) participants, chronic HCV virus monoinfection patients either naïve or retreatment were randomly divided into two groups; (3) interventions, peginterferon α-2a and peginterferon α-2b, both plus ribavirin; (4) outcome measures, studies that used one or more of the following measurements were eligible: rapid virologic response (RVR), early virologic response (EVR), end-of-treatment virologic response (ETR), SVR, relapse rate, and discontinuation rate; and (5) full texts available.

Studies with the following situations were excluded: (1) followup period less than 6 months and (2) studies that included patients with other liver diseases (e.g., HBV infection, human immunodeficiency virus infection, and hepatocellular carcinoma) aside from HCV.

2.3. Quality Assessment. The methodological qualities of the included RCTs were assessed according to Cochrane Collaboration's tool described in Handbook version 5.1.0 [16]. Two authors (Z. G. Yang and L. Yang) assessed the quality independently, and inconsistency was discussed with a third review author (X. R. Chen) who acted as an arbiter.

2.4. Data Extraction. Two researchers read the full texts independently and extracted the following contents: publication data (first author's name, year of publication, and country of population studied), study design, sample size, patient characteristics (age, gender, body weight, distribution of genotype, and liver histology), treatment protocol (peginterferon type and dose, ribavirin dose), outcome measures (RVR, EVR, ETR, SVR, relapse rate, and discontinuation rate), and reasons for discontinuing combination therapy. Authors were contacted by e-mail for additional information if data were unavailable.

2.5. Definitions. Chronic hepatitis C is defined by anti-HCV positive, HCV RNA positive as determined by a qualitative polymerase chain reaction (PCR) assay for more than 6 months. The primary outcome measure of efficacy of SVR was defined by a sensitive PCR assay as the absence of HCV RNA from serum at 24 weeks after completion of therapy. Secondary outcome measures of tolerability, including discontinuation rate, RVR, EVR, and ETR, were also determined. RVR was defined using a sensitive PCR assay as undetectable HCV RNA at 4 weeks after treatment. EVR was defined as ≥2 log reduction or complete absence of HCV RNA at 12 weeks after therapy compared with the baseline level. Undetectable virus at the end of either a 24-week or 48-week course of therapy was referred to as ETR. Virologic relapse refers to the reappearance of HCV RNA in serum after treatment was discontinued and ETR was documented.

2.6. Statistical Methods. Data were processed in accordance with the Cochrane Handbook [16]. Intervention effects were expressed with odds ratios (ORs) and associated 95% confidence intervals (CIs) for dichotomous data. By contrast, the effects were expressed with mean differences and 95% CIs for continuous data. Heterogeneity among studies was informally assessed by visual inspection of forest plots and formally estimated using χ^2 and I^2 tests (both $P > 0.05$; $I^2 < 50\%$ indicates no evidence of heterogeneity between the pooled studies) [17]. The fixed-effects model was first used for meta-analyses. The random-effects model was used in the presence of heterogeneity. Description analysis was performed when the quantitative data could not be pooled. Intention-to-treat (ITT) principle was used. Review Manage (v. 5.1; The Cochrane Collaboration) was used for data analysis.

3. Results

3.1. Study and Patient Characteristics. A total of 1166 abstracts of clinical trials were found and reviewed. Of these 1166 abstracts, 45 were retrieved, 6 [18–23] were excluded because they were published as abstract proceedings, 1 [24] was excluded because patients received monotherapy of peginterferon α-2a/2b at the first 4 weeks, 1 [25] was excluded because it was not designed randomly, 1 [26] was excluded because patients received 1.0 μg/kg peginterferon α-2b, 1 [27] was excluded because it included patients with HCV/HIV coinfection, and 1 [28] was excluded because duplicate data from the same medical center were published. Finally, 7 trials [5–11] met our inclusion criteria (Table 1).

Totally 1845 and 1823 patients were randomly treated with peginterferon α-2a and peginterferon α-2b, respectively, both plus ribavirin. The baseline characteristics of each study included in this meta-analysis are described in Table 2.

3.2. Methodological Quality Assessment. All studies included in this meta-analysis were described as randomized. Three

Table 1: Baseline characteristics of the included trials in this meta-analysis.

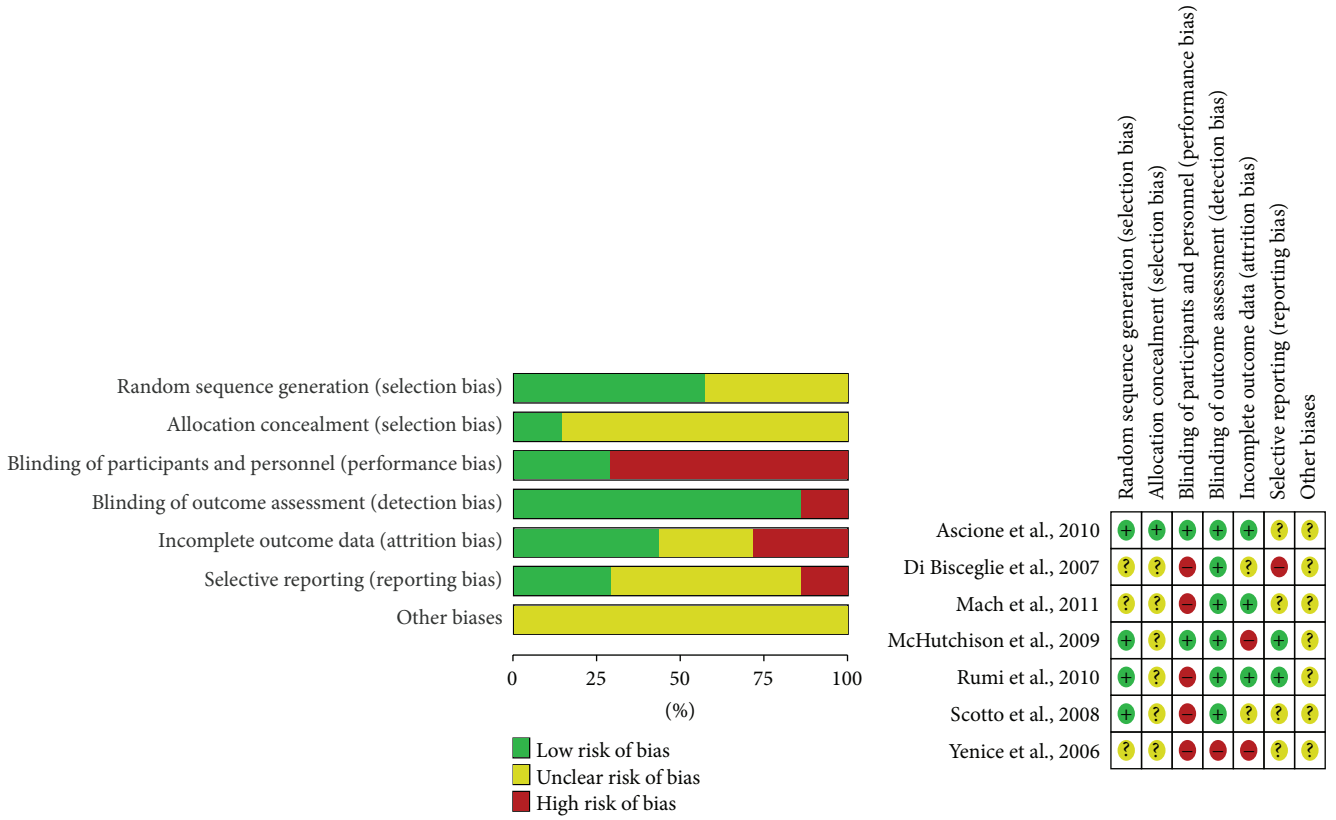
Study	Peginterferon	Ribavirin	Baseline treatment history	HCV genotype	Treatment in weeks	Country	Publication year	Study type
Yenice et al. [5]	α-2a 180 ug/week; α-2b 1.5 ug/kg/week	800–1200 mg/day	Naïve	1	24 or 48	Turkey	2006	RCT
Di Bisceglie et al. [6]	α-2a 180 ug/week; α-2b 1.5 ug/kg/week	1000–1200 mg/day	Naïve	1	12	USA	2007	RCT
Scotto et al. [7]	α-2a 180 ug/week; α-2b 1.5 ug/kg/week	15 mg/kg/day	Nonresponders	1,2,3,4	48	Italy	2008	RCT
McHutchison et al. [8]	α-2a 180 ug/week; α-2b 1.5 ug/kg/week	800–1400 mg/day	Naïve	1	24 or 48	IDEAL study team	2009	RCT
Rumi et al. [9]	α-2a 180 ug/week; α-2b 1.5 ug/kg/week	800–1200 mg/day	Naïve	1,2,3,4	24 or 48	Italy	2010	RCT
Ascione et al. [10]	α-2a 180 ug/week; α-2b 1.5 ug/kg/week	1000–1200 mg/day	Naïve	1,2,3,4	24 or 48	Italy	2010	RCT
Mach et al. [11]	α-2a 180 ug/week; α-2b 1.5 ug/kg/week	1000–1200 mg/day	Naïve	1b	48	Poland	2011	RCT

Table 2: Baseline characteristics in the two groups of peginterferon α-2a and peginterferon α-2b in this meta-analysis.

Study	Peginterferon group	Total patients	Mean age (years)	Gender (male/female)	HCV genotype (1/2/3/4)	F3-4 OR cirrhosis, N (%)	Body weight (kg)	BMI (kg/m^2)
Yenice et al. [5]	α-2a	37	49.95	13/24	37/0/0/0	NA	NA	NA
	α-2b	37	50.84	10/27	37/0/0/0	NA	NA	NA
Di Bisceglie et al. [6]	α-2a	189	46.9 ± 0.52	121/68	189/0/0/0	28 (14.8)	86.5 ± 1.34	29.2 ± 0.44
	α-2b	191	48.4 ± 0.56	136/55	191/0/0/0	29 (15.2)	85.4 ± 1.32	28.5 ± 0.42
Scotto et al. [7]	α-2a	71	45.86 ± 9.33	42/29	45/6/8/12	13 (18.3)	80.7	18.5–24.9 (n = 32), 25–29.9 (n = 34), ≥30 (n = 5)
	α-2b	72	47.82 ± 9.61	40/32	47/5/9/11	13 (18.1)	78.9	18.5–24.9 (n = 35), 25–29.9 (n = 30), ≥30 (n = 7)
McHutchison et al. [8]	α-2a	1035	47.6 ± 8.2	613/422	1035/0/0/0	110 (10.6)	82.8 ± 16.6	NA
	α-2b	1019	47.5 ± 7.8	613/406	1019/0/0/0	111 (10.9)	84.0 ± 16.5	NA
Rumi et al. [9]	α-2a	212	51.6 ± 12.0	128/84	91/69/34/18	43 (20.3)†	72.2 ± 14.6	25.5 ± 4.4
	α-2b	219	52.8 ± 12.0	120/99	87/74/32/26	39 (17.8)†	68.9 ± 12.0	24.8 ± 3.7
Ascione et al. [10]	α-2a	160	51.3 ± 10.3	81/79	89/49/18/4	33 (20.6)	70.4 ± 10.6	25.5 ± 3.1
	α-2b	160	48.9 ± 11.3	94/66	92/50/17/1	26 (16.3)	69.9 ± 10.7	25.3 ± 3.0
Mach et al. [11]	α-2a	138	45.2 ± 10.5	80/58	138/0/0/0	13 (9.4)	NA	24.5 ± 0.9
	α-2b	122	44.2 ± 13.6	73/49	122/0/0/0	12 (9.8)	NA	25.1 ± 1.3

NA: not available; BMI: Body mass index; †Ishak score S5, 6.
F0–4 (F0: no fibrosis; F1: portal fibrosis without septa; F2: portal fibrosis with few septa; F3: numerous septa without cirrhosis; F4: cirrhosis).
All baseline characteristics were comparative between the two groups.

studies [5, 6, 11] did not report the method of randomization, but randomization was adequate in other studies [7–10]. Among these studies, two were randomized by a computer-generated randomization list [9, 10], one was randomized by an interactive voice system [8], and the study by Scotto et al. was randomized by a table of random numbers [7]. One study revealed that the randomization list was not available to the treating physicians. Double blinding was described in one trial by McHutchison et al. [8]. And, Ascione et al. [10] designed a study where the physician received the report on the allocation of each patient from an independent researcher who knew nothing about the patient except for the genotype. The statistical analyses in one study by Yenice et al. [5] were not based on ITT, and more than 20% of the participants in the study by McHutchison et al. were lost to followup, both of which were considered as high risk in the item of



(a) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

(b) Risk of bias summary: review authors' judgements about each risk of bias item for each included study

Figure 1: Risk of bias assessment.

incomplete outcome data. No descriptions of lost to followup were found in the two studies by Di Bisceglie et al. [6] and Scotto et al. [7], thus accounting for the ambiguity in the item of incomplete outcome. No patient was lost to followup in the study by Ascione et al., and the other studies described the lost to followup participants, which were balanced between the two groups and considered low risk. Selective reporting was found in the study by Di Bisceglie et al. because it failed to include the expected results (e.g., SVR rate) for such a study. The other potential biases were unclear in these trials (Figure 1).

3.3. Virologic Responses. The overall SVR rates for CHC patients treated with peginterferon α-2a plus ribavirin and CHC patients treated with peginterferon α-2b plus ribavirin were 46.7% (773/1656), and 42.4% (692/1632), respectively (OR = 1.20, 95% CI = 1.04–1.38, and $P = 0.01$; Figure 2(a)). For naïve patients with no interferon experience, subgroup analysis found that the SVR rate was significantly higher in the peginterferon α-2a group than in the peginterferon α-2b group (47.9% versus 43.5%, OR = 1.20, 95% CI = 1.04–1.39, $P = 0.01$, Figure 2(b)). For genotype 1/4 patients, peginterferon α-2a could obtain a higher SVR than peginterferon α-2b (42.2% versus 38.3%, OR = 1.17, 95% CI = 1.01–1.36, $P = 0.03$, Figure 2(c)). For CHC patients with genotype 2/3, peginterferon α-2a might achieve a higher SVR rate than peginterferon α-2b (82.6% versus 74.3%, OR = 1.71, 95% CI = 1.01–2.89, and $P = 0.04$; Figure 2(d)).

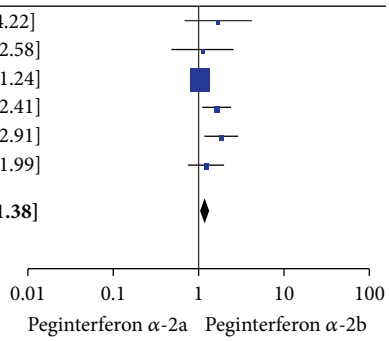
Only three studies [6, 8, 9] reported the RVR rate in patients who received peginterferons plus ribavirin. No difference in RVR rate was found between the two regimens (23.2% versus 23.4%, OR = 1.01, 95% CI = 0.83–1.23, and $P = 0.91$; Figure 3(a)). However, patients treated with peginterferon α-2a could achieve significantly higher EVR rates than those treated with peginterferon α-2b (56.1% versus 49.8%, OR = 1.32, 95% CI = 1.15–1.52, and $P < 0.0001$; Figure 3(b)). Meta-analysis of RCTs [5, 7–11] by a fixed-effects model ($P = 0.17$, $I^2 = 36\%$) revealed that, compared with peginterferon α-2b, peginterferon α-2a increased the ETR rate significantly in patients with chronic hepatitis C (67.9% versus 56.6%, OR = 1.66, 95% CI = 1.43–1.92, and $P < 0.00001$; Figure 3(c)).

3.4. Discontinuation Rate and Dose Modification. All the patients that did not complete the treatment duration were considered as discontinuing therapy, either for adverse events or nonsafety reasons. Of the studies included in this meta-analysis, two [6, 7] reported the number of patients who withdrew from therapy for nonsafety reasons, whereas one

Study or subgroup	Peginterferon α-2a Events	Total	Peginterferon α-2b Events	Total	Weight	Odds ratio M-H, fixed, 95% CI
Yenice et al., 2006	18	40	13	40	2%	1.7 [0.68, 4.22]
Scotto et al., 2008	14	71	13	72	2.9%	1.11 [0.48, 2.58]
McHutchison et al., 2009	423	1035	406	1019	68.1%	1.04 [0.87, 1.24]
Rumi et al., 2010	140	212	119	219	11.2%	1.63 [1.11, 2.41]
Ascione et al., 2010	110	160	87	160	7.6%	1.85 [1.17, 2.91]
Mach et al., 2011	68	138	54	122	8.2%	1.22 [0.75, 1.99]
Total (95% CI)		**1656**		**1632**	**100%**	**1.2 [1.04, 1.38]**
Total events	773		692			

Heterogeneity: $\chi^2 = 8.84$, df = 5 ($P = 0.12$); $I^2 = 43\%$

Test for overall effect: $Z = 2.56$ ($P = 0.01$)

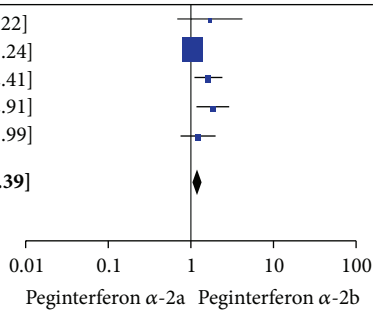


(a) The overall SVR rate of CHC patients treated with the two types of peginterferons

Study or subgroup	Peginterferon α-2a Events	Total	Peginterferon α-2b Events	Total	Weight	Odds ratio M-H, fixed, 95% CI
Yenice et al., 2006	18	40	13	40	2.1%	1.7 [0.68, 4.22]
McHutchison et al., 2009	423	1035	406	1019	70.1%	1.04 [0.87, 1.24]
Rumi et al., 2010	140	212	119	219	11.5%	1.63 [1.11, 2.41]
Ascione et al., 2010	110	160	87	160	7.9%	1.85 [1.17, 2.91]
Mach et al., 2011	68	138	54	122	8.4%	1.22 [0.75, 1.99]
Total (95% CI)		**1585**		**1560**	**100%**	**1.2 [1.04, 1.39]**
Total events	759		679			

Heterogeneity: $\chi^2 = 8.81$, df = 4 ($P = 0.07$); $I^2 = 55\%$

Test for overall effect: $Z = 2.55$ ($P = 0.01$)

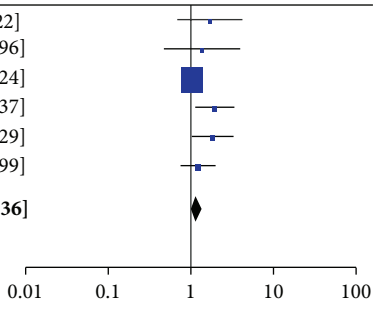


(b) The SVR rate of naïve CHC patients

Study or subgroup	Peginterferon α-2a Events	Total	Peginterferon α-2b Events	Total	Weight	Odds ratio M-H, fixed, 95% CI
Yenice et al., 2006	18	40	13	40	2.2%	1.7 [0.68, 4.22]
Scotto et al., 2008	9	57	7	58	1.8%	1.37 [0.47, 3.96]
McHutchison et al., 2009	423	1035	406	1019	75.8%	1.04 [0.87, 1.24]
Rumi et al., 2010	52	109	36	113	5.8%	1.95 [1.13, 3.37]
Ascione et al., 2010	51	93	37	93	5.2%	1.84 [1.03, 3.29]
Mach et al., 2011	68	138	54	122	9.1%	1.22 [0.75, 1.99]
Total (95% CI)		**1472**		**1445**	**100%**	**1.17 [1.01, 1.36]**
Total events	621		553			

Heterogeneity: $\chi^2 = 8.06$, df = 5 ($P = 0.15$); $I^2 = 38\%$

Test for overall effect: $Z = 2.12$ ($P = 0.03$)

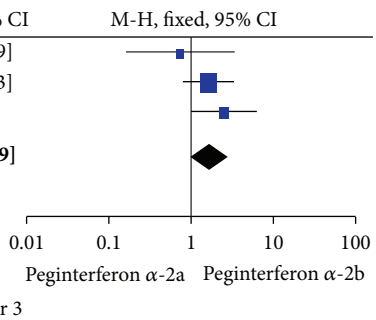


(c) The SVR rate of CHC patients with HCV genotype 1 or 4

Study or subgroup	Peginterferon α-2a Events	Total	Peginterferon α-2b Events	Total	Weight	Odds ratio M-H, fixed, 95% CI
Scotto et al., 2008	5	14	6	14	17.7%	0.74 [0.16, 3.39]
Rumi et al., 2010	88	103	83	106	54.8%	1.63 [0.79, 3.33]
Ascione et al., 2010	59	67	50	67	27.5%	2.51 [1, 6.3]
Total (95% CI)		**184**		**187**	**100%**	**1.71 [1.01, 2.89]**
Total events	152		139			

Heterogeneity: $\chi^2 = 1.84$, df = 2 ($P = 0.4$); $I^2 = 0\%$

Test for overall effect: $Z = 2.01$ ($P = 0.04$)

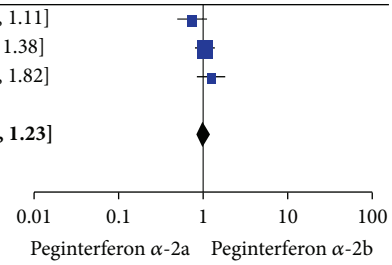


(d) The SVR rate of CHC patients with HCV genotype 2 or 3

Figure 2: SVR rates of chronic hepatitis C patients who received the two regimens of peginterferon α-2a and peginterferon α-2b, both plus ribavirin.

Study or subgroup	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight	Odds ratio M-H, fixed, 95% CI
Di Bisceglie et al., 2007	79	189	94	191	26.7%	0.74 [0.49, 1.11]
McHutchison et al., 2009	123	1035	116	1019	50.5%	1.05 [0.8, 1.38]
Rumi et al., 2010	132	212	125	219	22.8%	1.24 [0.84, 1.82]
Total (95% CI)		**1436**		**1429**	**100%**	**1.01 [0.83, 1.23]**
Total events	334		335			

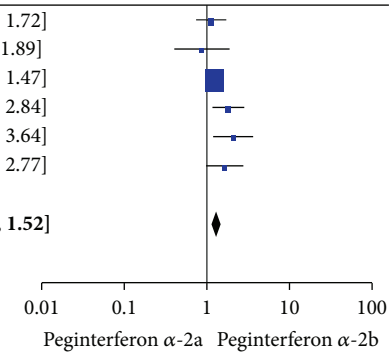
Heterogeneity: $\chi^2 = 3.42$, df = 2 ($P = 0.18$); $I^2 = 41\%$
Test for overall effect: $Z = 0.11$ ($P = 0.91$)



(a) RVR rate comparison

Study or subgroup	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight	Odds ratio M-H, fixed, 95% CI
Di Bisceglie et al., 2007	125	189	121	191	11.7%	1.13 [0.74, 1.72]
Scotto et al., 2008	16	71	18	72	4%	0.87 [0.4, 1.89]
McHutchison et al., 2009	466	1035	407	1019	64.6%	1.23 [1.03, 1.47]
Rumi et al., 2010	170	212	151	219	8.4%	1.82 [1.17, 2.84]
Ascione et al., 2010	136	160	117	160	5%	2.08 [1.19, 3.64]
Mach et al., 2011	99	138	74	122	6.4%	1.65 [0.98, 2.77]
Total (95% CI)		**1805**		**1783**	**100%**	**1.32 [1.15, 1.52]**
Total events	1012		888			

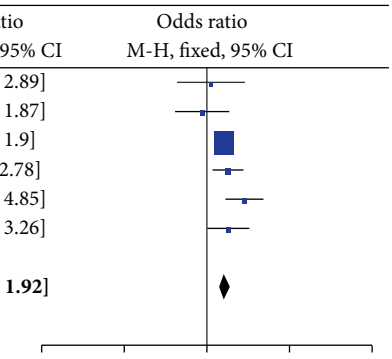
Heterogeneity: $\chi^2 = 7.54$, df = 5 ($P = 0.18$); $I^2 = 34\%$
Test for overall effect: $Z = 3.98$ ($P < 0.0001$)



(b) EVR rate comparison

Study or subgroup	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight	Odds ratio M-H, fixed, 95% CI
Yenice et al., 2006	28	40	27	40	2.9%	1.12 [0.44, 2.89]
Scotto et al., 2008	17	71	19	72	5.1%	0.88 [0.41, 1.87]
McHutchison et al., 2009	667	1035	542	1019	69%	1.6 [1.34, 1.9]
Rumi et al., 2010	166	212	146	219	11.1%	1.8 [1.17, 2.78]
Ascione et al., 2010	134	160	103	160	6%	2.85 [1.68, 4.85]
Mach et al., 2011	113	138	87	122	5.9%	1.82 [1.01, 3.26]
Total (95% CI)		**1656**		**1632**	**100%**	**1.66 [1.43, 1.92]**
Total events	1125		924			

Heterogeneity: $\chi^2 = 7.81$, df = 5 ($P = 0.17$); $I^2 = 36\%$
Test for overall effect: $Z = 6.78$ ($P < 0.00001$)



(c) ETR rate comparison

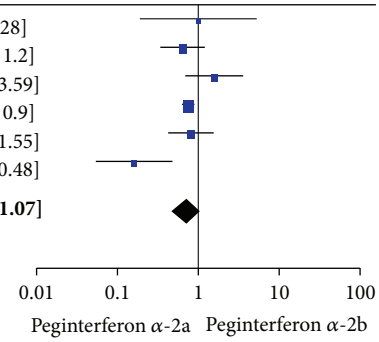
Figure 3: The RVR, EVR, and ETR rates of CHC patients treated with the two regimens.

[11] did not provide the exact discontinuation number of patients. Meta-analysis of RCTs [5–10] by a random-effects model ($P = 0.05$, $I^2 = 55\%$) revealed that peginterferon α-2a and peginterferon α-2b had a similar discontinuation rate for CHC patients, including naïve and retreatment ones with any HCV genotype ($P = 0.11$, Figure 4(a)). By contrast, meta-analysis of RCTs [5, 6, 8–10] by a fixed-effects model ($P = 0.09$, $I^2 = 50\%$) revealed that peginterferon α-2a had a significantly lower discontinuation rate than peginterferon α-2b for naïve CHC patients (27.9% versus 33.9%, OR = 0.71, 95% CI = 0.61–0.84, and $P < 0.0001$; Figure 4(b)).

No adequate data of peginterferon α or ribavirin dose reduction were reported in the studies by Yenice et al. [5], Di Bisceglie et al. [6], Ascione et al. [10], and Mach et al. [11]. However, the same dose reduction was applied for both arms in two studies [6, 10]. For the modification of peginterferon dose, meta-analysis of RCTs [7–9] by a fixed-effects model ($P = 0.26$, $I^2 = 25\%$) indicated no difference in the two types of peginterferons (22.2% versus 20.7%, OR = 1.09, 95% CI = 0.90–1.31, and $P = 0.40$; Figure 4(c)). For the reduction of ribavirin dose, meta-analysis of RCTs [5, 7–9] by a fixed-effects model ($P = 0.76$, $I^2 = 0\%$) revealed no statistical

Study or subgroup	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight	Odds ratio M-H, random, 95% CI
Yenice et al., 2006	3	40	3	40	5.1%	1 [0.19, 5.28]
Di Bisceglie et al., 2007	18	189	27	191	19%	0.64 [0.34, 1.2]
Scotto et al., 2008	17	71	12	72	14.3%	1.57 [0.69, 3.59]
McHutchison et al., 2009	414	1035	479	1019	33.1%	0.75 [0.63, 0.9]
Ascione et al., 2010	18	212	23	224	18.6%	0.81 [0.42, 1.55]
Rumi et al., 2010	4	160	22	160	9.9%	0.16 [0.05, 0.48]
Total (95% CI)		**1707**		**1706**	**100%**	**0.72 [0.48, 1.07]**
Total events	474		566			

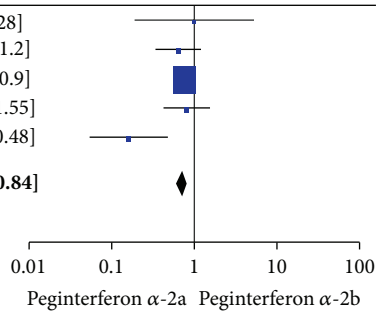
Heterogeneity: $\tau^2 = 0.12$; $\chi^2 = 11.21$, df = 5 ($P = 0.05$); $I^2 = 55\%$
Test for overall effect: $Z = 1.62$ ($P = 0.11$)



(a) The overall discontinuation rate

Study or subgroup	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight	Odds ratio M-H, fixed, 95% CI
Yenice et al., 2006	3	40	3	40	0.8%	1 [0.19, 5.28]
Di Bisceglie et al., 2007	18	189	27	191	6.8%	0.64 [0.34, 1.2]
McHutchison et al., 2009	414	1035	479	1019	80.8%	0.75 [0.63, 0.9]
Rumi et al., 2010	18	212	23	224	5.7%	0.81 [0.42, 1.55]
Ascione et al., 2010	4	160	22	160	6%	0.16 [0.05, 0.48]
Total (95% CI)		**1636**		**1634**	**100%**	**0.71 [0.61, 0.84]**
Total events	457		554			

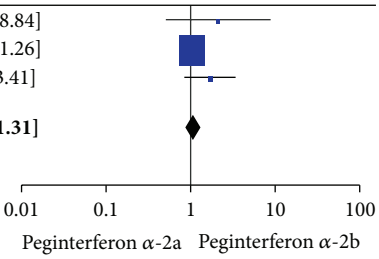
Heterogeneity: $\chi^2 = 7.94$, df = 4 ($P = 0.09$); $I^2 = 50\%$
Test for overall effect: $Z = 4.14$ ($P < 0.0001$)



(b) The discontinuation rate of naïve CHC patients treated with the two types of peginterferons

Study or subgroup	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight	Odds ratio M-H, fixed, 95% CI
Scotto et al., 2008	6	71	3	72	1.3%	2.12 [0.51, 8.84]
McHutchison et al., 2009	264	1035	254	1019	92.7%	1.03 [0.85, 1.26]
Rumi et al., 2010	22	212	14	219	6%	1.7 [0.84, 3.41]
Total (95% CI)		**1318**		**1310**	**100%**	**1.09 [0.9, 1.31]**
Total events	292		271			

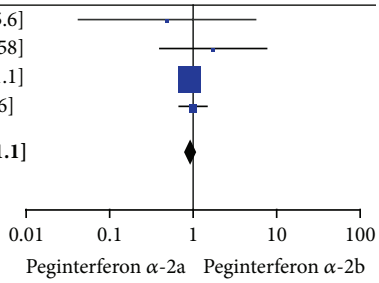
Heterogeneity: $\chi^2 = 2.67$, df = 2 ($P = 0.26$); $I^2 = 25\%$
Test for overall effect: $Z = 0.85$ ($P = 0.4$)



(c) Peginterferon dose modification of CHC patients treated with the two types of peginterferons

Study or subgroup	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight	Odds ratio M-H, fixed, 95% CI
Yenice et al., 2006	1	40	2	40	0.7%	0.49 [0.04, 5.6]
Scotto et al., 2008	5	71	3	72	0.9%	1.74 [0.4, 7.58]
McHutchison et al., 2009	322	1035	338	1019	80.2%	0.91 [0.76, 1.1]
Rumi et al., 2010	119	212	123	219	18.1%	1[0.68, 1.46]
Total (95% CI)		**1358**		**1350**	**100%**	**0.93 [0.79, 1.1]**
Total events	447		466			

Heterogeneity: $\chi^2 = 1.16$, df = 3 ($P = 0.76$); $I^2 = 0\%$
Test for overall effect: $Z = 0.85$ ($P = 0.4$)

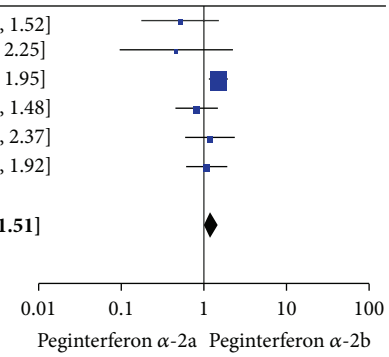


(d) Ribavirin dose modification of CHC patients treated with the two types of peginterferons

Figure 4: The discontinuation rates and drugs modification of CHC patients who received the two regimens.

Study or subgroup	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight	Odds ratio M-H, fixed, 95% CI
Yenice et al., 2006	10	28	14	27	5.5%	0.52 [0.18, 1.52]
Scotto et al., 2008	3	17	6	19	2.8%	0.46 [0.1, 2.25]
McHutchison et al., 2009	193	612	123	523	54.7%	1.5 [1.15, 1.95]
Rumi et al., 2010	26	166	27	146	14.6%	0.82 [0.45, 1.48]
Ascione et al., 2010	24	134	16	103	8.9%	1.19 [0.59, 2.37]
Mach et al., 2011	45	113	33	87	13.5%	1.08 [0.61, 1.92]
Total (95% CI)		**1070**		**905**	**100%**	**1.23 [1, 1.51]**
Total events	301		219			

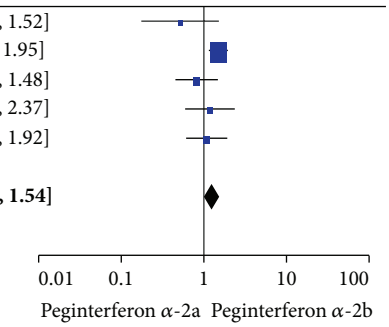
Heterogeneity: $\chi^2 = 8.1$, df = 5 ($P = 0.15$); $I^2 = 38\%$
Test for overall effect: $Z = 2$ ($P = 0.05$)



(a) The overall relapse comparison

Study or subgroup	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight	Odds ratio M-H, fixed, 95% CI
Yenice et al., 2006	10	28	14	27	5.7%	0.52 [0.18, 1.52]
McHutchison et al., 2009	193	612	123	523	56.2%	1.5 [1.15, 1.95]
Rumi et al., 2010	26	166	27	146	15%	0.82 [0.45, 1.48]
Ascione et al., 2010	24	134	16	103	9.2%	1.19 [0.59, 2.37]
Mach et al., 2011	45	113	33	87	13.9%	1.08 [0.61, 1.92]
Total (95% CI)		**1053**		**886**	**100%**	**1.25 [1.02, 1.54]**
Total events	298		213			

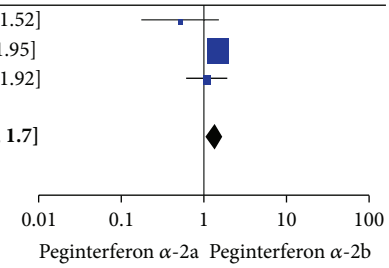
Heterogeneity: $\chi^2 = 6.61$, df = 4 ($P = 0.16$); $I^2 = 39\%$
Test for overall effect: $Z = 2.15$ ($P = 0.03$)



(b) The relapse rate of naïve CHC patients treated with the two types of peginterferons

Study or subgroup	Peginterferon α-2a Events	Peginterferon α-2a Total	Peginterferon α-2b Events	Peginterferon α-2b Total	Weight	Odds ratio M-H, fixed, 95% CI
Yenice et al., 2006	10	28	14	27	7.5%	0.52 [0.18, 1.52]
McHutchison et al., 2009	193	612	123	523	74.2%	1.5 [1.15, 1.95]
Mach et al., 2011	45	113	33	87	18.3%	1.08 [0.61, 1.92]
Total (95% CI)		**753**		**637**	**100%**	**1.35 [1.07, 1.7]**
Total events	248		170			

Heterogeneity: $\chi^2 = 4.21$, df = 2 ($P = 0.12$); $I^2 = 52\%$
Test for overall effect: $Z = 2.51$ ($P = 0.01$)



(c) The relapse rate of CHC patients with HCV genotype 1 or 4 treated with the two types of peginterferons

Figure 5: The relapse rate of CHC patients who received the two regimens.

difference between the two groups (32.9% versus 34.5%, OR = 0.93, 95% CI = 0.79–1.10, and $P = 0.40$; Figure 4(d)).

3.5. Relapse Rate. No difference in relapse rate for CHC patients treated with the two regimens was noted in the meta-analysis of RCTs [5, 7–11] by a fixed-effects model (28.1% versus 24.2%, OR = 1.23, 95% CI = 1.00–1.51, and $P = 0.05$; Figure 5(a)). However, subgroup analysis showed that, for naïve CHC patients, peginterferon α-2a obtained a higher relapse rate than peginterferon α-2b (28.3% versus 24.0%, OR = 1.25, 95% CI = 1.02–1.54, and $P = 0.03$; Figure 5(b)). For HCV genotype 1 patients, peginterferon α-2a had a higher relapse rate than peginterferon α-2b (32.9% versus 26.7%, OR = 1.35, 95% CI = 1.07–1.70, and $P = 0.01$; Figure 5(c)).

4. Discussion

Most previous meta-analyses concluded that peginterferon α-2a has higher SVR rate than peginterferon α-2b in CHC patients, but no difference in the safety profile was noted [12–15]. However, a recent meta-analysis has revealed that these two types of peginterferons have similar effects on RVR, SVR, and tolerability [29]. Moreover, the above analyses included either meeting abstracts or coinfected patients of HIV/HCV,

which may have an impact on the conclusions. In the present meta-analysis, we included more RCTs and restricted our trial analyses to full papers. We excluded abstracts because they did not contain adequate details of patients and outcomes.

Interferon-based therapy could lower the risk of cirrhosis and hepatocellular carcinoma and improve the survival of CHC patients who have an SVR with a large possibility through eradicating HCV and cutting liver fibrosis procession. Our analysis showed that peginterferon α-2a might achieve a higher SVR rate than peginterferon α-2b, including nonresponders. Subgroup analysis revealed that peginterferon α-2a was also more effective than peginterferon α-2b for HCV genotype 1 or 4 patients or treatment-naïve patients. However, these two types of peginterferons had similar SVR effects on HCV genotype 2 or 3 patients. These analyses indicated a difference in antiviral activity between the two therapeutic regimens. A previous study [30] proved that combination therapy with peginterferon α-2a is an independent pretreatment predictor of SVR (OR = 1.88, 95% CI = 1.20–2.96). Peginterferon α-2a achieves higher SVR rates than peginterferon α-2b in patients infected with HCV-1 and HCV-2; however, the two therapeutic regimens obtain similar SVR rates in patients infected with HCV-3 and HCV-4 [9]. Our results indicated that patients with genotype 2 or 3 had similar SVR rates in both groups. Given that the patients included in this meta-analysis mostly had HCV genotype 1 or 4, only less than 200 patients in each group were infected with HCV genotype 2 or 3; high-quality trials with a large sample size are needed to estimate the efficacy of the two regimens for genotype 2 or 3 CHC patients, especially for the comparison of the therapeutic efficacy in each genotype stratum.

Further analysis showed that no significant difference in RVR rate was found in the patients treated with the two peginterferon-α-based regimens. However, peginterferon α-2a could achieve higher EVR and ETR rates in CHC patients than peginterferon α-2b. Early eradication of HCV is important to the therapeutic resolution of CHC, and RVR remains the most notable on-treatment response predictor of SVR. Moreover, the present guidelines concluded that the absence of EVR is the most robust means of identifying nonresponders. Approximately 97%–100% of the treatment-naïve patients with HCV genotype 1 infection who did not reach EVR failed to elicit SVR. Thus, patients without EVR can discontinue therapy early without compromising their chance to elicit SVR [1, 2]. This finding might be associated with the potentially higher SVR rate of patients treated with peginterferon α-2a. ETR does not accurately predict the occurrence of SVR; however, ETR is necessary for SVR to take place [1, 2, 31].

Our meta-analysis of RCTs [5–10] suggests that the two peginterferons may be comparable with regard to any reasons leading to treatment discontinuation, including naïve and retreatment patients with any HCV genotype. However, for naïve CHC patients, peginterferon α-2a had a significantly lower discontinuation rate than peginterferon α-2b. Previous meta-analyses [12–15] concluded that peginterferon α-2a has a similar safety profile as peginterferon α-2b. Given that our results were based on ITT analysis, all patients who withdrew therapy were considered as treatment discontinuation, either for adverse events or nonsafety reasons. The reason above may explain why our analysis of discontinuation rate in naïve CHC patients conflicted with those of the previous studies.

Although peginterferon α-2a should achieve higher virologic responses and gain lower discontinuation rate, peginterferon α-2a had a higher relapse rate than peginterferon α-2b. The high relapse rate with peginterferon α-2a was a novelty, as in previous studies. Relapse rates ranged from 17% to 25% for peginterferon α-2a in patients with HCV genotype 1 [32, 33], which is significantly lower than the 31.5% reported in the IDEAL study [8]. These findings were not supported by two randomized studies that reported no difference in relapse rate between the two regimens [9, 10]. Many factors might have contributed to the difference in the findings above. Some of these factors include differences in epidemiological and genetic characteristics, mean body weight, distribution of genotype CC in the IL28B polymorphism, and ribavirin dose reduction schemes applied to the two regimens [34]. Maintaining a high ribavirin dose (≥12 mg/kg/day) during the full treatment period can lead to suppression of relapse in HCV-1 patients responding to peginterferon α-2b plus ribavirin. Ribavirin dosing seems to be instrumental in preventing posttreatment relapse [35], and ribavirin concentration in the later stages of treatment is an important marker for discriminating relapse [34, 36]. In the present meta-analysis, no significant difference in peginterferon and/or ribavirin dose reduction was found between the two groups. However, in the IDEAL study by McHutchison et al. [8], the dose reduction for the peginterferon α-2b arm occurred in two steps. The first step was a reduction of either 200 mg (in patients receiving 800 mg/day–1,200 mg/day of ribavirin) or 400 mg (in patients receiving 1,400 mg/day). The second step was reduction by another 200 mg, if required for resolution of the adverse event. For the peginterferon α-2a arm, the dose was reduced to 600 mg/day. The abrupt reduction of ribavirin dose to 600 mg/day might have played a crucial role in the high relapse rates observed in patients receiving the peginterferon α-2a regimen [8–10, 34].

Therefore, the peginterferon α-2a regimen holds a slight advantage in terms of virologic responses and discontinuation rates compared with the peginterferon α-2b regimen. This advantage may be considered as a direct consequence of the better pharmacokinetic profile of peginterferon α-2a than peginterferon α-2b. The pharmacodynamic properties of peginterferon α-2a allow slower absorption and elimination than peginterferon α-2b. Therefore, maximum concentrations occur later with peginterferon α-2a than with peginterferon α-2b. Peginterferon α-2b is associated with fluctuating blood levels and rapid rise and fall in the blood level because of the relatively rapid release of interferon α-2b molecule [37–39]. Previous studies [38, 40] showed that the concentration of peginterferon α-2b did not remain stable over the week as a whole. At the end of the week, serum interferon could not be detected in most patients treated with peginterferon α-2b. When interferon was no longer detectable in the serum, the viral load increased until the next interferon injection. This phenomenon increases the potential for more side effects and reduces the efficacy of the

drug. Peginterferon α-2b is distributed widely in the body fluids and tissues [14, 39]. By contrast, peginterferon α-2a is distributed predominantly to the blood and interstitial fluid, resulting in high drug concentrations in the liver. The reduced clearance of peginterferon α-2a, as a consequence of metabolism via nonspecific proteases, provides significant, consistent, and measurable therapeutic plasma levels even at the end of the weekly dosing period [41]. These differences between the two types of peginterferons should lead to better compliance and superior safety of peginterferon α-2a [14].

In conclusion, current evidence suggests that peginterferon α-2a has superior efficacy with higher EVR, ETR, and SVR than peginterferon α-2b for CHC patients, both plus ribavirin. Peginterferon α-2a might obtain similar or even lower discontinuation rate than peginterferon α-2b. However, peginterferon α-2a had a higher relapse rate than peginterferon α-2b. Further trials must focus on the comparison of the two types of peginterferons in terms of achieving SVR and clinically relevant outcomes, such as liver-related cirrhosis, hepatocellular carcinoma, mortality, and morbidity.

Abbreviations

CHC: Chronic hepatitis C
HCV: Hepatitis C virus
RVR: Rapid virologic response
EVR: Early virologic response
ETR: End-of-treatment virologic response
SVR: Sustained virologic response
CI: Confidence interval.

Conflict of Interests

The authors declare that they have no conflict of interests.

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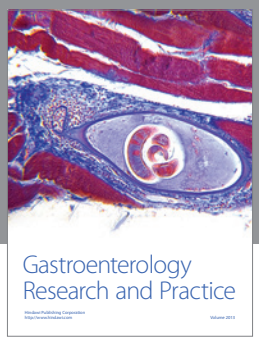

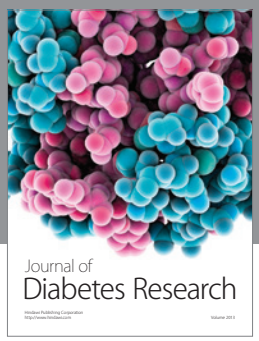

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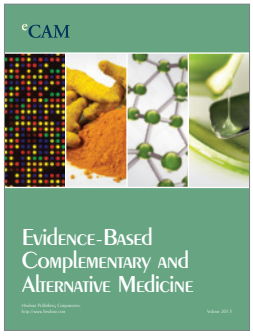

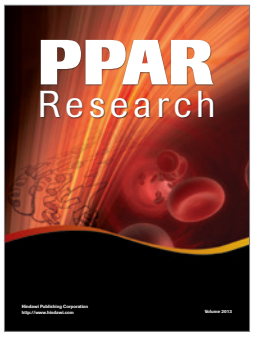

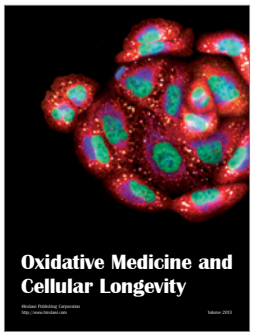

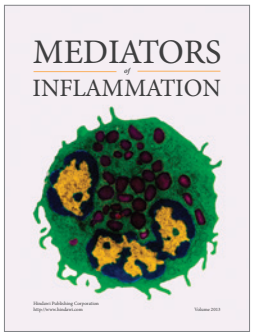

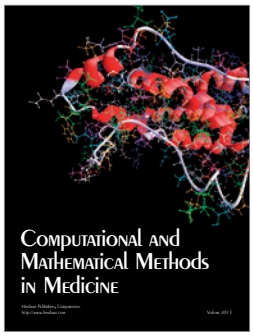

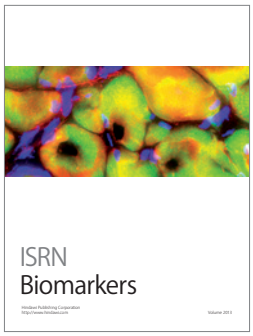

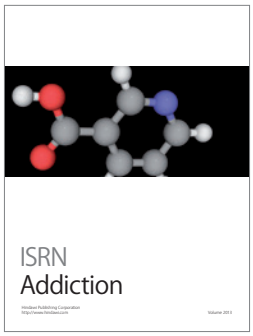

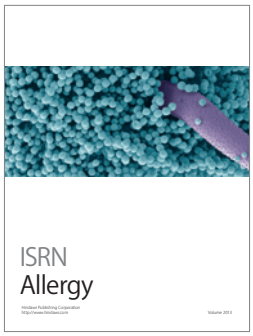

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REVIEW

Peginterferon Alfa-2a Is Superior to Peginterferon Alfa-2b in the Treatment of Naïve Patients with Hepatitis C Virus Infection: Meta-Analysis of Randomized Controlled Trials

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Abstract
Background Pegylated interferon (PEGIFN) and ribavirin combination is the standard of care for the treatment of chronic hepatitis C virus (HCV) infection. Studies comparing the efficacy and safety of PEGIFN alfa-2a and PEGIFN alfa-2b in treatment-naïve HCV-infected patients have shown conflicting results.
Aim We performed a systematic review and meta-analysis of studies comparing the efficacy and safety of PEGIFN alfa-2a and PEGIFN alfa-2b in HCV-infected patients naïve to treatment.
Methods Nine studies (five abstracts) with 3,546 patients (1,771 treated with PEGIFN alfa-2a) comparing PEGIFN alfa-2a and PEGIFN alfa-2b in treatment-naïve HCV patients were analyzed. Efficacy outcomes were sustained virologic response (SVR) and treatment discontinuation rates due to serious adverse effects (SAE).
Results Pooled data on outcomes (reported as odds ratios [ORs] with 95% confidence intervals [CIs]: [OR (95% CI)]) showed higher SVR in patients treated with PEGIFN alfa-2a as compared to treatment with PEGIFN alfa-2b [1.36 (1.07–1.73); $P = 0.01$]. Subgroup analysis of good quality studies on SVR in genotypes 2 and 3 also favored PEGIFN alfa-2a over PEGIFN alfa-2b (1.91 [1.09–3.37]; $P = 0.02$). SVR results obtained with the two types of IFN showed no impact of viral load and the presence or absence of cirrhosis. Treatment discontinuation rates due to SAE, reported in six studies (two abstracts) on 3,211 patients (1,604 treated with PEGIFN alfa-2a), were similar in the two types of PEGIFN [0.66 (0.37–1.16); $P = 0.15$].
Conclusions PEGIFN alfa-2a has superior efficacy with higher SVR as compared to PEGIFN alfa-2b in treatment-naïve HCV-infected patients. The safety profile of the two types of PEGIFN was similar.

Keywords Hepatitis C virus · HCV · Pegylated interferon alfa-2a · Pegylated interferon alfa-2b · Antiviral therapy · Meta-analysis

Introduction

Hepatitis C virus (HCV) infection is seen in nearly 4 million people in the United States and about 180 million people worldwide [1]. About 80% of the infected people are viremic and have chronic HCV infection [1, 2]. Currently, the standard of care for the treatment of chronic HCV infection is a combination of weekly subcutaneous pegylated interferon (PEGIFN) injections and daily oral ribavirin weight-based therapy for genotypes 1 and 4, and fixed 800 mg ribavirin dose for genotypes 2 and 3 [3]. The goal of treatment is to achieve sustained virologic response (SVR), defined as negative HCV RNA 24 weeks after completion of the treatment. Patients with genotypes 1 and 4 are treated for 48 weeks, with 40–50% SVR rates, while genotypes 2 and 3 infections are treated for 24 weeks, with 70–80% SVR rates [4–6].

Two types of PEGIFN are currently available for the treatment of chronic HCV infection: PEGIFN alfa-2a or

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PEGIFN-2a (Pegasys, Hoffman-La Roche, Nutley, NJ) and PEGIFN alfa-2b or PEGIFN-2b (PegIntron, Merck/Schering Plough Corp., Whitehouse Station, NJ) [7]. Several studies have compared the response rates obtained with the two PEGIFNs in chronic HCV infection. However, these studies have produced conflicting results. We decided to conduct a systematic review and meta-analysis of studies with the aim of assessing whether one pegylated interferon is superior to the other in the treatment of chronic HCV infection. Since randomized controlled trials (RCTs) provide the strongest and most robust evidence, we included only RCTs in our analysis. Because the response rate in patients who are previous non-responders to HCV treatment and those with human immunodeficiency virus (HIV) co-infection are substantially different compared to treatment-naïve patients, we restricted our analysis to studies that included only patients who were naïve to HCV treatment.

Methods

Identification and Selection of Studies

Literature Search

Two investigators (A.K.S. and S.C.J.) independently searched the electronic literature database (PubMed, OVID, Cochrane Reviews, EMBASE, and ISI Web of Science). Any conflict between the reviewers was resolved by consensus. The MeSH search terms included: HCV, pegylated interferon alfa-2a, pegylated interferon alfa-2b, ribavirin, and antiviral therapy. Boolean logic was used to combine the words.

Study Selection and Outcome Measures

The studies were selected for analysis based on the following criteria: (1) study design: RCT; (2) study population: patients with treatment-naïve chronic HCV infection; (3) treatment: PEGIFN alfa-2a versus PEGIFN alfa-2b; (4) treatment outcome reported: documentation of SVR, defined as negative HCV RNA 24 weeks after completing the treatment schedule; and discontinuation or interruption of treatment due to adverse effects. Patients with any previous treatment for HCV, non-responders to previous HCV treatment, and patients with HIV and hepatitis B virus (HBV) co-infections were excluded. Studies not reporting at least one of the outcomes of interest were also excluded.

Assessment of Study Quality

Two reviewers (A.K.S. and S.C.J.) independently assessed the study quality using the Jadad criteria for RCTs [8]. Any conflict between the reviewers was resolved by consensus. Studies were graded using the following five parameters: (1) randomization methodology well described or not; (2) randomization appropriate or not; (3) blinding well described or not; (4) blinding appropriate or not; (5) drop-outs or withdrawals well detailed or not. Each parameter was given a numeric score of 0 or 1, with the total minimum score of 0 and maximum score of 5. Studies with a score of 2 or less were rated as poor quality, and those with a score of 3 or more points were classified as good-quality studies.

Data Collection

All of the selected studies were reviewed independently by two reviewers (A.K.S. and S.C.J). The information collected from each study included the following: publication details (year, author, country, abstract or full paper); patient demographics (mean age in years, % males vs. females, mean body mass index [BMI], % genotypes 1 or 4, and % with cirrhosis); sample size (total and for each group); duration of treatment; and number (%) of patients achieving SVR; and proportion of patients requiring treatment discontinuation due to serious adverse effects (SAE). Data were collected in a predefined Microsoft Excel spreadsheet.

Data Analysis and Statistical Methods

The data were entered into the Comprehensive Meta-Analysis Version 2.0 software. The data were then pooled separately for the various outcomes of interest. Odds ratio (OR) with 95% confidence interval (CI) was used as the effect measure using a random effects model. Publication bias was assessed looking at the funnel plot and by Egger's test. Heterogeneity was assessed by Chi^2 statistics. The results were considered to be significant at $P < 0.05$. Sensitivity analyses were performed after removing the highest and lowest ORs. Subgroup analyses were performed for SVR outcome for the following variables: genotype (2 or 3 and 1 or 4); baseline viral load (high and low with a cut-off at 600,000 IU/mL in two studies and 500,000 IU/mL in one study); and the presence or absence of cirrhosis.

Results

Selection of Studies

After the initial screening, nine studies (five reported as abstracts) were selected. All studies compared the response to PEGIFN alfa-2a and PEGIFN alfa-2b with respect to the

SVR and treatment discontinuation rates. The study selection and attrition process which resulted in the 14 selected studies is shown in Fig. 1.

Characteristics of the Included Studies

Nine RCTs involving 3,546 patients (1,771 treated with PEGIFN alfa-2a; sample size 42–2,054; mean age 40–52 years; 31–63% males) were analyzed. The majority of the studies were carried out in the West, mostly in Europe and the United States, except for one study which was conducted in Asia. Most studies were of good quality, except for those reported as abstracts. Some of the studies did not report all of the outcomes of interest (Table 1).

Quantitative Analysis

Pooled analysis of the data showed that the odds of achieving SVR were higher by 36% with PEGIFN alfa-2a as compared to PEGIFN alfa-2b (Fig. 2). However, the odds of treatment discontinuation due to SAE were similar with PEGIFN alfa-2a and PEGIFN alfa-2b (Fig. 3). The data were homogeneous for both outcomes. No evidence was detected to suggest any publication bias for any of the analyses. After excluding studies that were reported as abstracts and poor-quality studies, the results remained in favor of PEGIFN alfa-2a with respect to SVR (1.43 [1.01–2.02]; $P = 0.044$). Similarly, sensitivity analyses obtained after excluding studies with the highest and lowest ORs favored PEGIFN alfa-2a (1.30 [1.02–1.67; $P = 0.035$].

The SVR rates were 53% and 48% with PEGIFN alfa-2a and PEGIFN alfa-2b, respectively. Subgroup analyses of SVR outcome were performed for the following: type of publication (abstracts vs. full papers); genotype status (genotypes 2 or 3 and genotypes 1 or 4); viral load (high viral load and low viral load with cut-off at 600,000 IU/mL in two studies [9, 10] and 500,000 IU/mL in one study [11]); and cirrhosis (presence or absence). A trend for improved SVR was seen with PEGIFN alfa-2a as compared to PEGIFN alfa-2b on subgroup analysis for genotype status. After excluding poor-quality studies, the SVR was higher with PEGIFN alfa-2a as compared to PEGIFN alfa-2b for patients with genotypes 2 or 3 infection (1.91 [1.09–3.37]; $P = 0.02$), with no heterogeneity (Chi^2 $P = 0.53$). However, there was no significant difference between the two types of PEGIFN on the SVR rate based on viral load and the presence or absence of cirrhosis (Table 2). The data were homogeneous for all of the analyses except for subgroup analyses on patients with high viral load ($P = 0.015$).

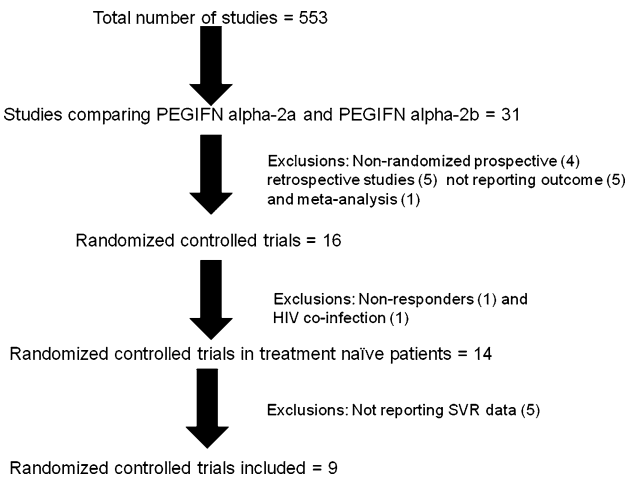

Fig. 1 Literature search and study selection process

Discussion

The current standard of care for the treatment of chronic HCV infection is a combination of pegylated interferon and ribavirin [3]. Two types of PEGIFN approved for the treatment of HCV infection are PEGIFN-2a and PEGIFN-2b [7]. Studies comparing the response rates obtained with the two PEGIFNs have produced conflicting results. A previous meta-analysis on this subject found PEGIFN alfa-2a to be superior to PEGIFN alfa-2b in terms of SVR rates, but there was no difference in the safety profile [12]. However, this study included patients who were previous non-responders to interferon therapy and those with HIV co-infection. In the present meta-analysis, we have included more randomized control trials and have restricted our analysis to treatment-naïve HCV patients. Further, we also included all reports published as abstracts. This is important, since including abstracts reduces the risk of any publication bias [13].

Our analysis showed that PEGIFN alfa-2a has superior therapeutic efficacy as compared to PEGIFN alfa-2b in achieving SVR. Sensitivity analyses after excluding studies with the highest and lowest ORs and subgroup analyses after excluding studies reported as abstracts (rated as poor-quality studies) did not significantly alter the findings of this analysis. Whether the superior therapeutic efficacy results in lower morbidity and mortality in patients treated with PEGIFN alfa-2a cannot be answered by this analysis, since only one study provided morbidity and mortality data [10]. However, based on the findings of other studies, it is tempting to conclude that superior SVR rates are associated with improvement in morbidity and mortality [14–16].

The treatment of HCV infection has evolved greatly over the last two decades [3]. Initial studies using standard interferon-alfa provided disappointing SVR results of less than 20% [17]. However, with the introduction of ribavirin

Table 1 Baseline features of the studies included in the analysis

Study (year)	Country	Total sample (PEGIFN-2a)	% males	Mean age in years	% GT 1 or 4	% cirrhotics	Treatment in weeks	Study quality score
Sinha et al. (2004) [20]*	USA	42 (24)	NA	NA	67	NA	24	3
Yenice et al. (2006) [21]	Turkey	74 (37)	31	50	100	NA	48	3
Khan et al. (2007) [22]*	Pakistan	66 (33)	NA	NA	100	NA	24	2
Kolakowska-Rzadzka et al. (2008) [23]*	Poland	67 (33)	54	40	100	51	24	1
Kamal et al. (2009) [24]*	Egypt	291 (134)	NA	NA	100	NA	NA	2
Magni et al. (2009) [25]*	Italy	218 (100)	66	44	52	NA	48	2
McHutchison et al. (2009) [10]	USA	2,054 (1,035)	60	48	100	11	48	5
Ascione et al. (2010) [11]	Italy	320 (160)	55	50	58	18	48	5
Rumi et al. (2010) [9]	Italy	431 (212)	58	52	51	18	48	3

OR odds ratio, *PEGIFN* pegylated interferon, *GT* genotype, *NA* not available

* Abstract publication

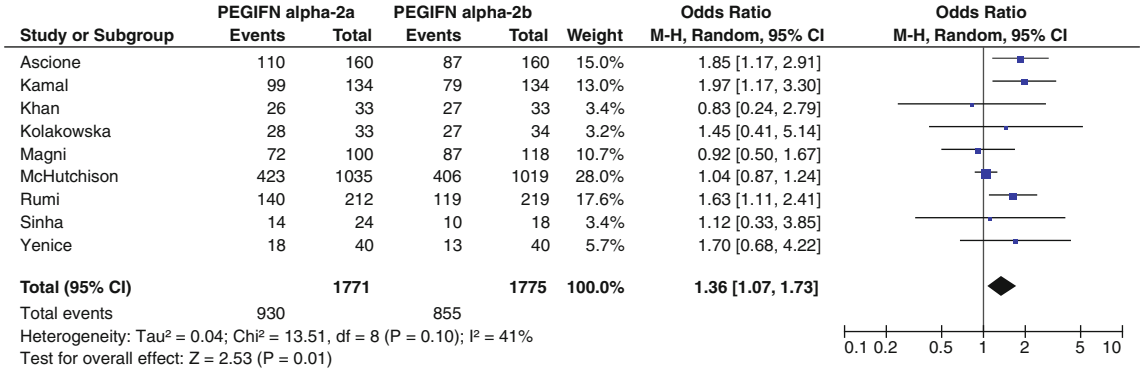

Fig. 2 Pooled data comparing pegylated interferon (PEGIFN) alfa-2a and PEGIFN alfa-2b for achieving sustained virologic response (SVR) in treatment-naïve patients with chronic hepatitis C virus (HCV) infection. The results show that PEGIFN alfa-2a achieved better SVR compared to PEGIFN alfa-2b

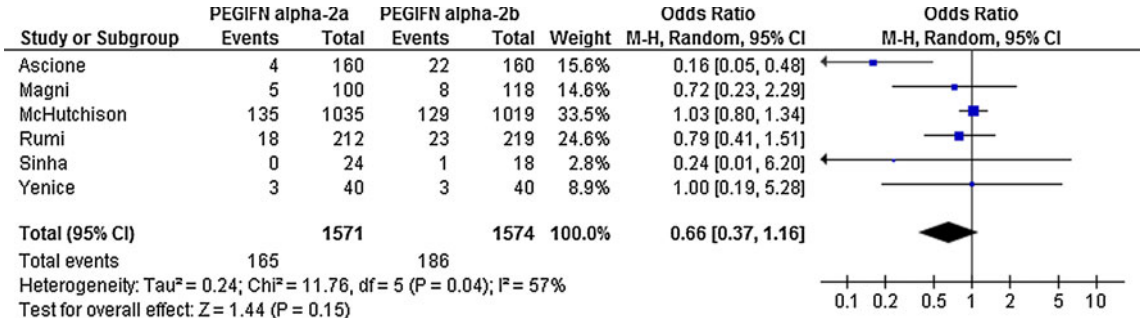

Fig. 3 Pooled data comparing PEGIFN alfa-2a and PEGIFN alfa-2b on treatment discontinuation rates due to serious adverse effects (SAE) in treatment-naïve patients with chronic HCV infection. The results show that treatment discontinuation rates due to SAE were similar with PEGIFN alfa-2a and PEGIFN alfa-2b

and, subsequently, PEGIFN in 2001–2002, the treatment of HCV infection has improved markedly, with SVR rates of nearly 50% for genotypes 1 or 4 infections and 80% for genotypes 2 or 3 infections [4–6]. Pegylated interferon is synthesized by attaching a polyethylene glycol (PEG) moiety to interferon [7]. This results in altered pharmacokinetic and pharmacodynamic properties of the interferon molecule, ensuing a longer duration of action [7]. The change in the pharmacological properties allows weekly dosing instead of three times a week with standard IFN [7]. PEGIFN alfa-2b has an unstable urethane bond between PEG and IFN molecules, making it sensitive to

Table 2 Pooled subgroup analysis for sustained virologic response (SVR)

Subgroup	No. of studies (abstracts)	No. of patients (PEGIFN-2a treated)	OR [95% CI] *P*-value	Heterogeneity Chi^2; *P*-value	Egger's test *P*-value
Cirrhosis	3 (0)	364 (188)	1.05 [0.65–1.71] 0.84	2.18; 0.34	0.8
Viral load					
High	3 (0)	2,098 (1,048)	1.41 [0.84–2.37] 0.19	8.40; 0.015	0.31
Low	3 (0)	707 (359)	1.43 [0.98–2.10] 0.06	2.80; 0.25	0.85
Genotype					
1/4	5 (1)	2,655 (1,320)	1.37 [0.99–1.91] 0.06	8.07; 0.089	0.16
2/3	5 (3)	565 (273)	1.52 [0.98–2.37] 0.06	2.59; 0.63	0.16

OR odds ratio, *PEGIFN* pegylated interferon

hydrolysis after subcutaneous injection, causing the rapid release of the IFN alfa-2b molecule [18]. By contrast, PEGIFN alfa-2a has a more stable amide bond between PEG and IFN molecules [18]. This ensures a longer half life of the PEGIFN alfa-2a molecule. The stability of the PEGIFN alfa-2a molecule results in slower absorption and elimination of the compound compared to PEGIFN alfa-2b, with a resultant more prolonged therapeutic effect [18]. Pharmacodynamic studies have shown that PEGIFN alfa-2a is available at a maximum concentration for up to 168 h or 7 days as compared to only 72 h or 3 days for PEGIFN alfa-2b [19].

Two large RCTs have been published recently and both have found PEGIFN alfa-2a to be more effective compared to PEGIFN alfa-2b [9, 11]. However, the largest comparative trial (IDEAL study) published previously showed that, although the ETR was better with PEGIFN alfa-2a compared to PEGIFN alfa-2b (64% vs. 53%), the SVR rates were similar (41% vs. 40%), mostly due to higher relapse rates with PEGIFN alfa-2a (28% vs. 20%) [10]. It should be noted that all patients in the IDEAL study were of genotype 1 HCV infection [10]. By contrast, nearly one-half of patients included in the recently reported studies were of genotypes 2 and 3 HCV infections [9, 11].

Our subgroup analysis based on HCV genotypes showed a trend towards better SVR rates with PEGIFN alfa-2a as compared to PEGIFN alfa-2b for both genotypes 1 and 4 (43% vs. 40%; $P = 0.06$), as well as for genotypes 2 and 3 infections (85% vs. 79%; $P = 0.06$). The lack of significance may be related to the relatively small number of patients ($n = 565$; 273 treated with PEGIFN-2a for genotypes 2 or 3, and $n = 2{,}655$; 1,320 treated with PEGIFN-2a for genotypes 1 or 4) included in the analysis. However, after excluding poor-quality studies, a higher SVR was seen with PEGIFN alfa-2a as compared to PEGIFN alfa-2b for patients with genotypes 2 or 3 infection. Similarly, subgroup analyses based on the presence or absence of cirrhosis (32% vs. 30%; $P = 0.8$) and on the baseline viral load did not show any difference between the two treatment groups. A limitation of the viral load analyses was the varying definition of high viral load; two studies used >600,000 IU/mL [9, 10] and one study used >500,000 IU/mL as the cut-off value [11].

The pharmacodynamic properties of PEGIFN alfa-2a which allows slow absorption and elimination of the drug results in sustained and stable blood levels [7, 18, 19]. By contrast, because of the relatively rapid release of the IFN alfa-2b molecule, PEGIFN alfa-2b is associated with fluctuating blood levels, with rapid rise and fall in the blood levels [18, 19]. This increases the potential for more side effects as well as reduces the efficacy of the drug. Furthermore, PEGIFN alfa-2b is distributed widely in the body fluids and tissues, which makes it mandatory to employ weight-based doses. On the other hand, PEGIFN alfa-2a is used at a fixed dose of 180 mcg weekly [7, 18]. These differences between the two types of PEGIFN should lead to better compliance and superior safety of PEGIFN alfa-2a. In this pooled analysis, although the treatment discontinuation rates due to SAE were lower with PEGIFN alfa-2a as compared to PEGIFN alfa-2b, the difference was not significant (10.4% vs. 11.8%; $P = 0.15$). Future prospective studies with a larger sample size are proposed in order to compare the safety of PEGIFN alfa-2a and PEGIFN alfa-2b.

In conclusion, PEGIFN alfa-2a has superior therapeutic efficacy and similar safety profile as compared to PEGIFN alfa-2b. The superiority of PEGIFN alfa-2a needs to be assessed in non-responders to previous HCV treatment and

in patients with concomitant HIV infection. Furthermore, studies are needed with a longer follow-up comparing the impact of the two PEGIFNs on liver-related morbidity and mortality outcomes.

Conflict of interest No financial or any other kind of assistance was received for this study. None of the authors have any disclosures.

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To whom it may concern,

We find the conclusions of the review to be reasonable based on the evidence presented. However, by concentrating on only the most high-profile systematic reviews, the current analysis may have understated some recent findings, especially in the area of sulfonylurea safety. A recent high-quality systematic review and meta-analysis found that sulfonylureas are associated with increased mortality and higher risk of stroke. When compared to DPP4 inhibitors, sulfonylureas were associated with an overall increase in the risk of major cardiovascular events. We suggest that the Oregon Health Authority examine this evidence and consider whether it influences their recommendations.

Monami et al. (2013) Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials. Diabetes Obesity and Metabolism; Article first published online: 13 MAY 2013 DOI: 10.1111/dom.12116

Sincerely,

Richard Chapell
Assoc. Dir.:HTA/CER
US Outcomes Research
Merck & Co., Inc.

The AstraZeneca/Bristol-Myers Squibb Alliance would like to provide you the website address for the online publication of the SAVOR trial prior to the availability of a printed copy. Please visit the Cardiology section of the New England Journal of Medicine website by typing the following URL address into your browser:

http://www.nejm.org/

The article was published following the sessions at the European Society of Cardiology's Annual Congress held in Amsterdam, Netherlands August 31 through September 4, 2013 and it is located in the Cardiology section.

Article Title: *"Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus"*

Author: Scirica BM, Bhatt DL, Braunwald E, et al.

The study was funded by AstraZeneca and Bristol-Myers Squibb. Some of the authors are employees of AstraZeneca or Bristol-Myers Squibb, and some of the authors have received compensation from AstraZeneca or Bristol-Myers Squibb in connection with the study and/or during the previous 12 months in connection with other engagements.

Indication and Limitations of Use for ONGLYZA® (saxagliptin)

ONGLYZA® (saxagliptin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings.

ONGLYZA should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

ONGLYZA has not been studied in patients with a history of pancreatitis.

ONGLYZA is not indicated to reduce the risk of macrovascular or microvascular complications associated with diabetes.

Important Safety Information for ONGLYZA

Contraindications

- **History of a serious hypersensitivity reaction to ONGLYZA (eg, anaphylaxis, angioedema, or exfoliative skin conditions)**

Warnings and Precautions

- **Pancreatitis:** There have been postmarketing reports of acute pancreatitis in patients taking ONGLYZA. After initiating ONGLYZA, observe patients carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue ONGLYZA and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk of developing pancreatitis while using ONGLYZA.

- **Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin:** When ONGLYZA® was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of confirmed hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. Therefore, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia when used in combination with ONGLYZA.

- **Hypersensitivity Reactions:** There have been postmarketing reports of serious hypersensitivity reactions in patients treated with ONGLYZA, including anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with ONGLYZA, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue ONGLYZA, assess for other potential causes for the event, and institute alternative treatment for diabetes. Use caution in patients with a history of angioedema to another DPP-4 inhibitor as it is unknown whether they will be predisposed to angioedema with ONGLYZA.

- **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA or any other antidiabetic drug.

Most Common Adverse Reactions

- Most common adverse reactions reported in ≥5% of patients treated with ONGLYZA and more commonly than in patients treated with control were upper respiratory tract infection (7.7%, 7.6%), headache (7.5%, 5.2%), nasopharyngitis (6.9%, 4.0%) and urinary tract infection (6.8%, 6.1%).

- When used as add-on combination therapy with a thiazolidinedione, the incidence of peripheral edema for ONGLYZA 2.5 mg, 5 mg, and placebo was 3.1%, 8.1% and 4.3%, respectively.

- Confirmed hypoglycemia was reported more commonly in patients treated with ONGLYZA 2.5 mg and ONGLYZA 5 mg compared to placebo in the add-on to glyburide trial (2.4%, 0.8% and 0.7%, respectively), with ONGLYZA 5 mg compared to placebo in the add-on to insulin (with or without metformin) trial (5.3% and 3.3%, respectively),with ONGLYZA 2.5 mg compared to placebo in the renal impairment trial (4.7% and 3.5%, respectively), and with ONGLYZA 5 mg compared to placebo in the add-on to metformin plus sulfonylurea trial (1.6% and 0.0%, respectively).

Drug Interactions
Because ketoconazole, a strong CYP3A4/5 inhibitor, increased saxagliptin exposure, the dose of ONGLYZA should be limited to 2.5 mg when coadministered with a strong CYP3A4/5 inhibitor (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin).
Use in Specific Populations

- **Patients with Renal Impairment**: The dose of ONGLYZA is 2.5 mg once daily for patients with moderate or severe renal impairment, or with end-stage renal disease requiring hemodialysis (creatinine clearance [CrCl] ≤ 50 mL/min). ONGLYZA should be administered following hemodialysis. ONGLYZA has not been studied in patients undergoing peritoneal dialysis. Assessment of renal function is recommended prior to initiation of ONGLYZA and periodically thereafter.

- **Pregnant and Nursing Women**: There are no adequate and well-controlled studies in pregnant women. ONGLYZA, like other antidiabetic medications, should be used during pregnancy only if clearly needed. It is not known whether saxagliptin is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when ONGLYZA is administered to a nursing woman.

- **Pediatric Patients**: Safety and effectiveness of ONGLYZA in pediatric patients have not been established.

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On behalf of myself and my AZ Alliance Medical Counterpart, Scott Larson

Linda McClurg Craig
Senior Account Director