BlueCross BlueShield of Kansas City

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Pegylated Interferons

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Policy

BCBSKC will provide coverage for pegylated interferons indicated for the treatment of chronic hepatitis C (CHC) virus infection in adults and children.

Prior authorization is recommended for prescription benefit coverage of Pegasys and PegIntron (collectively referred to as "peginterferons" in these criteria) for HCV infection. The intent of this policy is to provide recommendations for use in hepatitis C *only*. The approval duration differs; refer to the recommended authorization criteria.

When Policy Topic is covered

FDA-Approved Indications

1. **Genotype 1, 4, 5, or 6 CHC - Treatment-naïve patients.** Approve peginterferon for 48 weeks in patients who meet all of the following criteria a, b, c, d, and e. Hepatitis C genotype must be obtained before starting therapy. Note: Baseline and TW 12 HCV RNA titers are necessary to determine the duration of therapy beyond 48 weeks (i.e., patients eligible for extended therapy to 72 weeks [*see* *Criteria 5*]).
   a) The patient is ≥ 2 years of age; AND
   b) Peginterferon is prescribed by or in consultation with a gastroenterologist, hepatologist, or infectious diseases physician; AND
   c) Peginterferon is prescribed in combination with ribavirin unless there is a contraindication or intolerance to ribavirin according to the prescribing physician; AND
   d) The patient is not on a waiting list for liver transplantation (see *Criteria 7*); AND
   e) The patient does not have recurrent hepatitis C after liver transplantation (see *Criteria 6*).

2. **Genotype 2 or 3 CHC - Treatment-naïve patients.** Approve peginterferon for the specified duration in patients who meet one of the following conditions a, b, c, or d.[8] Hepatitis C genotype must be obtained before starting therapy.
   a) **Patients with genotype 2 or 3 CHC without hepatitis B or HIV co-infection** (for patients with hepatitis B or HIV co-infection see *Condition 2b*)**.** Approve peginterferon for 24 weeks in patients who meet the following criteria i through vii.[8]
      i. Patient is ≥ 2 years of age; AND
      ii. Peginterferon is prescribed by or in consultation with a gastroenterologist, hepatologist, or infectious diseases physician; AND
      iii. Peginterferon is prescribed in combination with ribavirin unless there is a contraindication or intolerance to ribavirin according to the prescribing physician; AND
      iv. The patient does not have genotype 3 CHC and high viral titer (as determined by the prescribing physician) or advanced fibrosis (see *Condition 2c*); AND
      v. The patient is not 2 through 17 years of age with a high iron load at baseline (as determined by the prescribing physician) see (*Condition 2d*); AND
      vi. The patient is not on a waiting list for liver transplantation (see *Criteria 7*); AND

vii. The patient does not have recurrent hepatitis C after liver transplantation (see *Criteria 6*).

b) **Patient with genotype 2 or 3 CHC and HIV or hepatitis B co-infection**. Approve peginterferon for 48 weeks in patients who meet the following criteria i through v.
   i. Patient is ≥ 2 years of age; AND
   ii. Peginterferon is prescribed by or in consultation with a gastroenterologist, hepatologist, or infectious diseases physician; AND
   iii. Peginterferon is prescribed in combination with ribavirin unless there is a contraindication or intolerance to ribavirin according to the prescribing physician; AND
   iv. The patient is not on a waiting list for liver transplantation (see *Criteria 7*); AND
   v. The patient does not have recurrent hepatitis C after liver transplantation (see *Criteria 6*).

c) **Patient with CHC viral genotype 3 and high level of HCV RNA (as determined by the prescribing physician) or advanced fibrosis.** Approve peginterferon for 48 weeks in patients who meet the following criteria i through v. Note: High viral load usually is considered to be > 600,000 or 800,000 IU/mL.[56]
   i. Patient is ≥ 2 years of age; AND
   ii. Peginterferon is prescribed by or in consultation with a gastroenterologist, hepatologist, or infectious diseases physician; AND
   iii. Peginterferon is prescribed in combination with ribavirin unless there is a contraindication or intolerance to ribavirin according to the prescribing physician; AND
   iv. The patient is not on a waiting list for liver transplantation (see *Criteria 7*); AND
   v. The patient does not have recurrent hepatitis C after liver transplantation (see *Criteria 6*).

d) **Pediatric patient (2 through 17 years of age) with genotype 2 or 3 CHC and with high iron load at baseline (as determined by the prescribing physician).** Approve peginterferon for 48 weeks in patients who meet the following criteria i through iv.
   i. Peginterferon is prescribed by or in consultation with a gastroenterologist, hepatologist, or infectious diseases physician; AND
   ii. Peginterferon is prescribed in combination with ribavirin unless there is a contraindication or intolerance to ribavirin according to the prescribing physician; AND
   iii. The patient is not on a waiting list for liver transplantation (see *Criteria 7*); AND
   iv. The patient does not have recurrent hepatitis C after liver transplantation (see *Criteria 6*).

3. **CHC (any viral genotype) – Retreatment patients.**[15,21,27,40-42,63-67] Approve peginterferon for 48 weeks in patients who meet the following criteria a through g.
   a) Patient is ≥ 2 years of age; AND
   b) Peginterferon is prescribed by or in consultation with a gastroenterologist, hepatologist, or infectious diseases physician; AND
   c) Peginterferon is prescribed in combination with ribavirin unless there is a contraindication or intolerance to ribavirin according to the prescribing physician; AND
   d) The patient has previously received treatment with interferon or peginterferon with or without ribavirin (e.g., Intron A, Roferon A [interferon alfa-2a injection], Pegasys, PegIntron) for the treatment of hepatitis C; AND
   e) It has been ≥ 3 months since completion of the prior interferon/peginterferon treatment course; AND
   f) The patient is not on a waiting list for liver transplantation (see *Criteria 7*); AND
   g) The patient does not have recurrent hepatitis C after liver transplantation (see *Criteria 6*).

Other Uses with Supportive Evidence (in the Treatment of Hepatitis C)

4. **Patients with acute hepatitis C (i.e., infection within 6 months of exposure).** Approve peginterferon for 24 weeks in patients who meet the following criteria a, b, and c.
   a) Patient is ≥ 2 years of age; AND
   b) Peginterferon is prescribed by or in consultation with a gastroenterologist, hepatologist, or infectious diseases physician; AND
   c) It had been at least 8 weeks after acute onset (to allow for spontaneous resolution).[5]

5. **Extending therapy to 72 weeks in "slow responders"- Treatment-naïve patients (genotype 1, 4, 5 or 6).** Approve peginterferon for 24 weeks in patients who meet all of the following criteria (a through h). The total duration of treatment will be 72 weeks (48 weeks [approved in *Criteria 1*] plus an additional 24 weeks) for patients with delayed virologic response.
   a) Patient is ≥ 2 years of age; AND
   b) Peginterferon is prescribed by or in consultation with a gastroenterologist, hepatologist, or infectious diseases physician; AND
   c) Peginterferon is prescribed in combination with ribavirin unless there is a contraindication or intolerance to ribavirin according to the prescribing physician; AND
   d) The patient does not have HIV co-infection; AND
   e) The patient is not on a waiting list for liver transplantation (see *Criteria 7*); AND
   f) The patient does not have recurrent hepatitis C after liver transplantation (see *Criteria 6*); AND
   g) The viral titer has decreased by ≥ 2 $\log_{10}$, but the virus was still detectable at Week 12; AND
   h) The virus was undetectable at Week 24.

6. **Patients with recurrent hepatitis C after liver transplantation.** Approve peginterferon for 48 weeks in patients who meet the following criteria a, b, c and d.
   a) Patient is ≥ 2 years of age; AND
   b) Peginterferon is prescribed by a gastroenterologist, hepatologist, infectious diseases physician, or liver transplant physician affiliated with a liver transplant program; AND
   c) Peginterferon is prescribed in combination with ribavirin unless there is a contraindication or intolerance to ribavirin according to the prescribing physician; AND
   d) The patient has grade 2 fibrosis or greater.[30]

7. **Patients with CHC who are on the waiting list for liver transplantation.** Approve peginterferon for 12 months in patients who meet the following criteria a, b, and c.
   a) The patient is ≥ 2 years of age; AND
   b) Peginterferon is prescribed by a gastroenterologist, hepatologist, infectious diseases physician, or liver transplant physician affiliated with a liver transplant program; AND
   c) Peginterferon is prescribed in combination with ribavirin unless there is a contraindication or intolerance to ribavirin according to the prescribing physician.

8. **Patient has been started on Pegasys.** Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications or Other Uses with Supportive Evidence). Authorization duration will vary based on the indication but should not exceed a total duration of 72 weeks.

9. **Patient has been started on PegIntron.** Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications or Other Uses with Supportive Evidence). Authorization duration will vary based on the indication but should not exceed a total duration of 72 weeks.

10. **Indications other than hepatitis C.** Approve for 12 months. Pegasys and PegIntron have been used for many off-label indications in adults and for few indications in children.

When Policy Topic is not covered

Maintenance therapy in hepatitis C is considered **investigational.** The available evidence does not support use. Major published trials have failed to demonstrate a consistent benefit of maintenance therapy in the prevention of HCC.[17,24-25,44,60]

Considerations

This Blue Cross and Blue Shield of Kansas City policy Statement was developed using available resources such as, but not limited to: Hayes Medical Technology Directory, Food and Drug

Administration (FDA) approvals, Facts and Comparisons, National specialty guidelines, Local medical policies of other health plans, Medicare (CMS), Local providers.

Description of Procedure or Service

Pegasys and PegIntron are pegylated interferons (peginterferons) indicated for the treatment of chronic hepatitis C (CHC) virus infection in adults and children given as weekly subcutaneous injections.

Rationale

There are six HCV genotypes which affect both the dose and duration of therapy for hepatitis C. Most persons with CHC in the US are infected with genotypes 1, 2, or 3; genotype 1 accounts for 70% to 75% of infections.[6] The standard of care for patients with CHC has been the use of a peginterferon and ribavirin (PR).[18] These drugs are administered for either 48 weeks (HCV genotypes 1, 4, 5, and 6) or for 24 weeks (HCV genotypes 2 and 3). Historically, genotype 1 has been associated with a lower response to treatment than genotypes 2 or 3, SVR is estimated to occur in 40% to 50% of patient with genotype 1 infection and in 80% or more in patients with genotypes 2 or 3 infection treated with PR therapy. Advances in the treatment of CHC have changed the optimal treatment regimen for genotype 1 infection to include addition of an NS3/4A protease inhibitor (Victrelis and Incivek) to PR.[18] The approval of the NS3/4A protease inhibitors for HCV (Victrelis and Incivek) has lead to a substantially greater proportion of patients who are able to attain SVR and has also provided an option for shortened therapy in many patients with genotype 1 CHC. Attaining SVR is associated with long-term clearance of HCV infection and is regarded as "virologic cure".[5] In addition, SVR is associated with improved morbidity and mortality in individuals infected with HCV.

With chronic infection, HCV RNA levels (or viral load) are very high (ranging from 10^5 to 10^7 international units [IU]/mL) and can fluctuate widely among patients. There is little correlation between the severity of disease or disease progression and the absolute level of HCV RNA; however, HCV RNA levels give information on the likelihood of response to treatment in patients receiving antiviral therapy.

Treatment Response Definitions

The goal of treatment is to prevent complications and death from HCV infection.[5] Treatment responses are defined by surrogate virological parameters rather than a clinical endpoint. With the approval of the NS3/4A protease inhibitors for HCV, some new virological parameters have been developed. Several types of virological responses may occur and are labeled according to their timing relative to treatment:

- ***Rapid virologic response (RVR):*** HCV RNA < 50 IU/mL at TW 4.
- ***Early virologic response (EVR):*** ≥ 2 $\log_{10}$ reduction or complete absence of serum HCV RNA at TW 12 (compared to the baseline level).
- ***End-of-treatment response (ETR):*** Undetectable HCV RNA at the completion of treatment.
- ***SVR:*** Undetectable HCV RNA at the end of treatment and 24 weeks after completion of treatment.

SVR is often regarded as "virological cure", although hepatocellular carcinoma (HCC) can occur years later, especially when SVR occurs in the setting of cirrhosis. Historically SVR for genotype 1 patients has been assessed at Week 72 (following a 48 week course of therapy with PR). With approval of Victrelis and Incivek some patients with genotype 1 CHC may be eligible for a shorter duration of therapy based on prior treatment status and on-treatment virologic responses. Therefore, SVR is assessed 24 weeks after completion of therapy regardless of when that occurs.

An additional virologic response unique to Incivek guides treatment duration in some genotype 1 patients treated with Incivek:[4]

- ***Extended RVR (eRVR)*****:** Undetectable HCV RNA at TW 4 *and* TW 12.

eRVR has been used to predict patients that may benefit from a shorter duration of therapy. For purposes of assessing eRVR, an "undetectable" HCV RNA result is required; a confirmed "detectable but below limit of quantification" HCV RNA result should not be considered equivalent to "undetectable".

Futility Stopping Rules

According to guidelines from the American Association for the Study of Liver Diseases (AASLD), the success or failure of therapy for CHC is best assessed using HCV RNA testing using assays sensitive to a level of at least 100 IU/mL.[5] Guidelines for HCV as well as prescribing information for the peginterferon products (and protease inhibitors for HCV) are consistent in their recommendation that that patients being treated with PR discontinue therapy if HCV RNA is detectable at TW 24.[1-5,18] Additionally, with Victrelis, triple-drug therapy (Victrelis/PR) should be discontinued in patients with HCV RNA > 100 IU/ML at TW 12.[18] Discontinuation of triple-therapy with Incivek at TW 4 or TW 12 in patients with HCV RNA > 1,000 IU/mL is recommended.[18] With Victrelis and Incivek, "detectable" HCV RNA at TW 24 is defined as HCV RNA ≥ 10 to 15 IU/mL. Guideline recommendations (AASLD 2009) for PR are based on clinical trials that used qualitative HCV RNA assays with lower limits of detection of about 50 to 100 IU/mL (e.g., polymerase chain reaction [PCR]-based). Several assays have become available that have a limit of ≥ 5 to 10 IU/mL.

Interluekin-28B (*IL28B*) Polymorphism

In patients with genotype 1 CHC, host polymorphisms located upstream of the *IL28B* gene are associated with SVR to treatment with PR.[22] One single-nucleotide polymorphism that is highly predictive is the detection of the C or T allele at position *rs12979860*.[18] The CC genotype is found more than twice as frequently in persons who have spontaneously cleared HCV than in those who have progressed to CHC. Among persons with genotype 1 CHC who are treated with PR, SVR is achieved in 69%, 33%, and 27% of Caucasians who have the CC, CT, and TT genotypes, respectively; among Black patients corresponding SVR rates were 48%, 15%, and 13%, respectively. The predictive value of *IL28B* genotype testing for SVR is superior to that of the pretreatment HCV RNA level, fibrosis stage, age and sex, and is higher for HCV genotype 1 than for genotypes 2 and 3.

Although *IL28B* genotype provides information regarding the probability of SVR and abbreviated therapy that may be important to the healthcare provider and patient, there are insufficient data to support withholding therapy with peginterferon in patients less likely to respond based on test results. Additionally, there are insufficient data to determine whether *IL28B* testing can be used to recommend selection of PR alone over a protease inhibitor-based treatment in patients with a favorable genotype (CC) or in deciding upon the duration of therapy with either regimen; this is an evolving area research.

Clinical Efficacy Data

The clinical efficacy of peginterferon has been demonstrated in a variety of clinical settings: treatment-naïve patients, patients previously treated with peginterferon or interferon for hepatitis C, pediatric patients with hepatitis C, and in other special populations including patients with HIV co-infection, cirrhosis/fibrosis, and in patients slow to respond to therapy. In addition, the peginterferons have also been studied in combination with Incivek and Victrelis in adults with genotype 1 CHC who were treatment-naïve or had previously been treated with interferon or peginterferon for hepatitis C. Some clinical studies are discussed below.

Treatment-naïve

Without a protease inhibitor for HCV

Both peginterferon alfa products appear to produce similar rates of SVR when assessing comparable populations.[1-2,9-11] The duration of therapy that produces the greatest rate of SVR is 48 weeks in patients with genotype 1 or 4 CHC and 24 weeks in patients with genotype 2 or 3 CHC[1-2,12-13-14,16] although the number of patients with genotype 4 was small in some studies.[12-13,14] Combination therapy (PR) results in a higher rate of SVR than monotherapy with peginterferon.[1-2,9-13]

Extended therapy (not maintenance)

Extending therapy with PR to 72 weeks in patients with genotype 1 (and in one study in genotype 4 patients) who are late virologic responders (≥ 2 $\log_{10}$ decrease in HCV RNA after 12 weeks but still positive, "partial EVR") has been postulated to increase SVR. Results from published studies are

conflicting, partly because of differences in study design, population, and suboptimal doses of ribavirin.[28,74-78]

In a prospective, single-center trial, 101 treatment-naïve patients with genotype 1 infection were randomly assigned to 1.5 µg/kg/week of PegIntron and 800 to 1,400 mg/day of ribavirin for 48 weeks (Group A, n = 49) or for 72 weeks (Group B, n = 52).[77] All of the patients were slow responders, defined as attaining ≥ 2 $\log_{10}$ decrease in HCV RNA from baseline but having detectable HCV RNA at 12 weeks and undetectable HCV RNA at 24 weeks using the same assay; PCR assay with detection limit 10 IU/mL. Both groups had similar discontinuations due to dose reductions, adverse events (AEs), or laboratory abnormalities. ***Results.*** Overall, the rate of SVR (primary endpoint) was greater in patients treated for 72 weeks vs. 48 weeks (38% vs. 18%, respectively; P = 0.026). Based on subgroup analysis, African American slow responders (n = 48) had significant improvement in SVR when treatment was extended to 72 weeks (12% vs. 21%, P = 0.02 for Groups A and B, respectively). Prospective, randomized, multicenter controlled trials in a large number of patients are needed.[78]

The Study to assess Treatment with PegIntron and Rebetol in Naïve Patients with Genotype 1 Chronic Hepatitis C and Slow Virological Response (SUCCESS) was a prospective, randomized, open-label, multicenter, international study conducted in monoinfected adults (age 18 to 70 years) with compensated CHC which examined extending treatment with PegIntron and weight-based ribavirin to 72 week vs. 48 weeks.[79] Enrolled patients (n = 1,427) received PegIntron and weight-based ribavirin (800 to 1,400 mg/day) and were treated for an initial 12-week period. Further treatment duration was set in accordance with Week 12 HCV RNA levels. Slow virologic responders were classified as those with a detectable HCV RNA level and ≥ 2 $\log_{10}$ reduction in HCV RNA at Week 12, and undetectable HCV RNA at Week 24. Slow responders (n = 159 [11.1%]) were randomized to treatment for a total of 48 weeks (Group A [n = 86]) or 72 weeks (Group B [n = 73]). Eight patients in Group A and 17 patients in Group B failed to complete the study. ***Results.*** In the intent-to-treat (ITT) analysis, SVR rates (primary efficacy endpoint) were similar (non-significant difference) in Groups A and B (43% vs. 48%). ETR was 83% and 70% for the 48 and 72 week treatment-groups, respectively, in slow responders. Relapse rates were not significantly different for Group A and B (47% and 33%, respectively). SVR rates between Groups A and B did not reach statistical significance in the per-protocol analysis or in the group of patients adherent to therapy (defined as at least 80% of the planned dose for at least 80% of the assigned duration).

A prospective, partially randomized study evaluated extended duration treatment with Pegasys in treatment-naïve, monoinfected adults with genotype 1 or 4 CHC.[28] The duration of treatment was determined on the basis of the virologic response to treatment at Week 4 (based on *qualitative* HCV RNA) and Week 12 (based on *quantitative* HCV RNA). Patients with RVR (HCV RNA < 50 IU/mL at TW 4) were treated for 24 weeks (reported separately). Patients without RVR continued therapy and were assessed at TW 12. Patients with EVR (≥ 2 $\log_{10}$ HCV RNA reduction from baseline at TW 12 [or virus undetectable defined as HCV RNA < 600 IU/mL]) were randomized to complete 48 weeks (Group A) or 72 weeks (Group B) of therapy. Patients without EVR were treated until TW 24; if HCV RNA became undetectable at Week 24, treatment was continued for a total of 72 weeks (Group C). Patients with detectable HCV RNA at TW 24 (defined as ≥ 50 IU/mL) were required to discontinue treatment. All patients assigned to Group B and Group C were treated with a lower dose of Pegasys (135 µg/wk) after Week 48. ***Results.*** The rate of virologic relapse between the end of treatment and end of follow-up evaluation (primary endpoint) was significantly lower in patients treated for 72 weeks (18.5% [n = 20/108]; 95% confidence interval [CI]: 11.9, 27.6) compared with 48 weeks (33.6% [n = 36/107]; 95% CI: 24.8%, 43.4%; P = 0.0115 for the difference between Group A and B). The overall rate of SVR was 51.1% (95% CI: 42.5, 59.6) for Group A and 58.6% (95% CI: 50.3, 66.6) for Group B (P > 0.1). There was a higher overall drop-out rate in Group B (32% [n = 48/150]) as compared with Group A (18.7% [n = 26/139]). In patients without an EVR assigned to 72 weeks of treatment (Group C), 11.5% of patients (n = 9/78) continued therapy (HCV RNA undetectable at TW 24); six patients completed therapy and four achieved SVR (5.1%; 95% CI: 1.5%, 12.6%).

With Incivek or Victrelis

The efficacy and safety of Incivek and Victrelis in treatment-naïve adults with genotype 1 CHC were established in two randomized, international, pivotal studies: A New Direction in HCV Care: A Study of Treatment-Naïve Hepatitis C Patients with Telaprevir (ADVANCE)[49] and Serine Protease Inhibitor Therapy-2 (SPRINT-2).[37,47] In both studies, rates of SVR were improved in treatment naïve-adults with genotype 1 CHC treated with a protease inhibitor in addition to PR (triple-drug therapy). Additionally, in SPRINT-2 a cohort of Black patients and non-Black patients were assessed separately.

Response guided therapy (RGT) has been studied with both protease inhibitors and some patients are eligible for a shorter duration of therapy based on on-treatment viral response as well as the presence or absence of fibrosis at baseline. With Victrelis, all therapy is preceded by 4 weeks PR ("lead-in") followed by 24 to 44 additional weeks of PR therapy. With Incivek, all three drugs (Incivek/PR) are administered for 12 weeks followed by subsequent weeks of PR ranging from 12 weeks to 36 weeks. Not all patients are recommended for RGT including those with baseline cirrhosis/fibrosis. In SPRINT-2, treatment for 48 weeks (4 week lead-in and 44 weeks of Victrelis/PR) [fixed duration therapy (FDT)] resulted in a numerically greater response rate (SVR) in Black patients compared with RGT; this is in contrast to non-Black patients where SVR rates in patients treated with RGT were similar to FDT. Below is a summary of the data from clinical trials with the protease inhibitors in treatment-naïve adults with genotype 1 CHC.

ADVANCE randomized adults with genotype 1 CHC to one of three treatment arms: Incivek/PR for 8 weeks followed by additional weeks of PR (Incivek8) for a total duration of 24 or 48 weeks based on eRVR; Incivek/PR for 12 weeks, followed by additional weeks of PR (Incivek12) for a total duration of 24 or 48 weeks based on eRVR; or placebo/PR (control) for 48 weeks.[49] Stopping rules were implemented to prevent continuation of treatment in patients who did not have an adequate response. Patients receiving Incivek with HCV RNA > 1,000 IU/mL at TW 4 discontinued Incivek but continued PR. All patients with < 2 $\log_{10}$ reduction from baseline in HCV RNA at TW 12 discontinued treatment. If HCV RNA was confirmed to be detectable at any time between TW 24 and TW 40, treatment was discontinued. ***Results.*** The rates of SVR were 69% (difference from control 25%; 95% CI: 18, 32) and 75% (difference from control 31%; 95% CI: 24, 38) for Incivek8 and Incivek12, respectively, compared with control (44%; $P < 0.0001$ for the differences between either of the Incivek-containing regimens and control). The proportions of patients with HCV RNA undetectable at TW 4 (RVR) were 68%, 66%, and 9% for Incivek12, Incivek8, and control respectively; the proportions of patients with eRVR were 58%, 57%, and 8%, respectively (the proportions eligible for a shorter duration of therapy with subsequent PR). Among patients with eRVR assigned to receive a total of 24 weeks of therapy, 89% and 83% of patients in the Incivek12 and Incivek8 groups, respectively, met criteria for SVR. In patients with bridging fibrosis or cirrhosis, the rate of SVR was 62% for Incivek12, and 53% for Incivek8 vs. 33% for control. Although the rates of virologic failure were similar between the two Incivek groups during the first 12 weeks of the study, rates were higher after TW 12 in the Incivek 8-week treatment arm compared with the 12-week arm (10% vs. 5%, respectively).

In SPRINT-2, patients were randomized to one of three treatment groups (all therapy was preceeded by a 4-week PR lead-in): control (PR for 44 weeks), RGT consisting of treatment with Victrelis/PR for 24 weeks followed by subsequent weeks PR determined by on-treatment viral response (in patients with undetectable HCV RNA from TW 8 through TW 24, treatment commenced after 24 weeks of Victrelis/PR [TW 28]; if HCV RNA levels were detectable at any visit from TW 8 up to [but not including TW 24], PR was continued for an additional 20 weeks with placebo [TW 28 though TW 48 {total treatment duration 48 weeks}]), or FDT consisting of Victrelis/PR for 44 weeks (total treatment duration 48 weeks).[47] In all three groups, study treatment was discontinued for patients with detectable HCV RNA level at TW 24 (futility stopping rule). ***Results.*** Victrelis-containing regimens (FDT and RGT) were superior to control (PR) for the proportion of patients achieving SVR. In the overall population, SVR was achieved in 66%, 63%, and 38% of patients in the Victrelis FDT, RGT, and control groups, respectively ($P < 0.001$ for FDT vs. control and for RGT vs. control). The odds ratio (OR) for achieving SVR with Victrelis FDT vs. control was 3.5 (95% CI: 2.6, 4.9; $P < 0.001$); for Victrelis RGT vs. control

the OR was 3.1 (95% CI: 2.3, 4.3; P < 0.001). When Black and non-Black cohorts were analyzed, the pattern of SVR favoring Victrelis was significant, although overall rates of SVR were lower (53%, 42%, and 23% for FDT, RGT, and control, respectively). In the overall population, relapse was reported more frequently with PR than for either triple-drug therapy group (FDT or RGT) 22% vs. 9% (P < 0.001). The proportions of patients discontinued from therapy at TW 24 due to detectable HCV RNA were 27%, 8%, and 9% of non-Black patients and 46%, 17%, and 15% of Black patients in the control, Victrelis RGT, and Victrelis FDT groups, respectively

Retreatment (Non-responders or Relapsers to Prior Therapy for CHC)
It is estimated that 20% to 50% of patients treated with a PR will not achieve SVR.[5] There are few treatment options for patients who do not attain SVR with peginterferon (or interferon) and ribavirin. Failure to achieve SVR can be a consequence of non-response (null response or partial response), viral breakthrough, or relapse (Table 4). In addition, poor adherence and inappropriate dose reductions can contribute to poor response rates.

Table 4. Viral Response Definition.[5]

Viral Response	Definition
Breakthrough	Reappearance of HCV RNA in serum while still on therapy.
Relapse	Reappearance of HCV RNA in serum after therapy is discontinued.
Non-responder Null-responder Partial responder	Failure to clear HCV RNA from serum after 24 weeks of therapy. Failure to decrease HCV RNA by < 2 $\log_{10}$ after 24 weeks of therapy. ≥ 2 log decrease in HCV RNA but still HCV RNA positive at TW 24.

HCV – Hepatitis C virus; TW – Treatment week.

Several therapeutic options have been tried in non-responders and relapsers, with limited success. In patients with genotype 1 CHC, a protease inhibitor for HCV added to PR has improved the proportion of patients able to achieve SVR compared with retreatment with PR.[22-23] Retreatment options for non-genotype 1 patients, or for other patients not appropriate for treatment with the protease inhibitors include re-treatment with a combination of PR, longer duration of therapy, higher induction dose of peginterferon, long-term maintenance peginterferon, and daily consensus interferon regimens.[17-18] Not all of these options have demonstrated clinical benefit. In summary, depending on the type of prior non-response, SVR rates are generally lower in retreatment patients than treatment-naïve patients. Addition of a protease inhibitor to PR in retreatment patients with genotype 1 CHC has improved SVR in all retreatment populations studied. Maintenance therapy has not proven to be consistently efficacious in retreatment patients.

Details from some retreatment studies with PR as well as triple-therapy with a protease inhibitors for HCV are detailed below. Retreatment with PR in patients previously treated with interferon produces a greater rate of SVR than in patients previously treated with PR; using a different peginterferon than the patient has previously been treated with has not demonstrated greater rates of SVR and is not recommended.[5] Additional information can be found in the *Pegylated Interferon Therapy Class Summary* and the *Protease Inhibitors for Hepatitis C Therapy Class Summary*.

Without a protease inhibitor for HCV
In one study, only 18% of patients who did not respond to or had relapsed after treatment with standard interferon alfa with or without ribavirin achieved a SVR when retreated with Pegasys/ribavirin for 48 weeks.[20] Similar results were reported in another trial with PegIntron.[21]

A prospective open-label trial assessed the efficacy of PegIntron plus ribavirin in 182 adults with compensated CHC refractory to conventional interferon-based treatment regimens (nonresponders [n =

116] and relapsers [n = 66]), alone or in combination with ribavirin (minimum of 24 weeks; 84 patients had been treated for ≥ 48 weeks).[26] At baseline, 51% of previous non-responders and 52% of previous relapsers had hepatic fibrosis and 18% and 15%, respectively, had cirrhosis. The dose of PegIntron was 100 µg weekly (QW) for patients < 75 kg and 150 µg QW for patients ≥ 75 kg. The ribavirin dose was 1,000 mg/daily. Therapy lasted for 24 weeks and if serum HCV RNA was undetectable at that time, treatment was continued for an additional 24 weeks. If serum HCV RNA was detectable after the initial 24 weeks, treatment was discontinued. The primary endpoint was SVR. Most of the patients in both groups (94% of previous non-responders and 74% of previous relapsers) were genotype 1. ***Results.*** The overall SVR rate was 32% (n = 59/182); 20% for previous non-responders vs. 55% for previous relapsers (P < 0.001). SVR rates were lower for genotype 1 patients (29%, n = 45/158) compared with genotypes 2 and 3 patients (58%, n = 14/24) [P = 0.009]. In previous non-responders, SVR in patients with genotype 1 was 17% vs. 57% in genotype 2 and 3 (P = 0.03). In previous relapsers, SVR was similar in patients with genotype 1 was 53% vs. 59% with genotypes 2 and 3.

In a 48-week, open-label trial, 321 patients with CHC who were non-responders to interferon/ribavirin (n = 219) or interferon monotherapy (n = 47) or who were relapsers to combination therapy (n = 55) were randomized to PegIntron 1.5 µg/kg/week plus ribavirin 800 mg daily (Regimen A, n = 160) or PegIntron 1 µg/kg/week plus ribavirin 1,000 to 1,200 mg daily depending on body weight (Regimen B, n = 161).[27] At Week 24, 161 patients (50%) discontinued therapy due to treatment failure. ***Results.*** SVR was attained in 16% of the overall population (Regimen A, 18% vs. Regimen B, 13%; P = non-significant [NS]); in 8% of combination therapy non-responders (10% vs. 6%, respectively P = NS); in 21% of the interferon monotherapy non-responders (16% vs. 27%, respectively; P = NS), and in 42% of the combination therapy relapsers (50% vs. 32%, respective; P = NS). In non-responders to prior combination therapy, HCV RNA levels < 100,000 copies/mL at the end of the prior treatment course were associated with an increased SVR compared to levels ≥ 100,000 copies/mL (21% vs. 5%, respectively; P = 0.002). In the overall study population, patients with genotype 1 had lower SVR rates than others (14% vs. 33%, respectively; P = 0.01) and African Americans had lower SVR than Caucasians (4% vs. 18%; P = 0.01).

The Evaluation of PegIntron in Control of Hepatitis C Cirrhosis (EPIC 3) trial[21] was a prospective, open-label study, in 2,333 patients with CHC and significant fibrosis/cirrhosis who had previously failed treatment for CHC (relapsers or non-responders) with nonpegylated or pegylated interferon with ribavirin. Patients received treatment with PegIntron (1.5 µg/kg/week) plus weight based ribavirin for up to 48 weeks. Patients with HIV co-infection, hepatitis B or decompensated liver disease were excluded. The majority of patients were previously treated with nonpegylated interferon alfa with ribavirin (62%), and 61% were non-responders to their previous treatment; most patients were White (84%); 80% had genotype 1 CHC. ***Results.*** Overall, 22% of patients attained SVR after retreatment with PegIntron and ribavirin. Among both non-responders and relapsers, patients previously treated with interferon alfa and ribavirin responded better to retreatment than those previously treated with a PR. Additionally, patients who had prior treatment with PegIntron or Pegasys had similar response rates (17% and 18%, respectively). Concordant with other studies, relapsers responded better to retreatment than non-responders.

<u>With Incivek or Victrelis</u>

The efficacy and safety of Incivek and Victrelis in retreatment patients with genotype 1 CHC have been established in two, randomized, double-blinded, placebo-controlled, multinational studies: Retreatment of Patients with Telaprevir-based Regimen to Optimize Outcomes (REALIZE) and Retreatment with HCV Serine Protease Inhibitor Boceprevir and PegIntron/Rebetol-2 (RESPOND-2), respectively.[22-23] The pivotal retreatment study with Incivek (REALIZE) enrolled partial non-responders, relapsers and also enrolled prior null-responders (patients with < 2 $\log_{10}$ reduction in HCV RNA after 12 weeks of therapy).[22] RESPOND-2 enrolled patients who had a previous non-response (partial response only) or had relapsed after treatment with peginterferon.[23]

REALIZE randomized patients (n = 662) to one of the following treatment regimens: Incivek/PR for 12 weeks followed by PR for 36 weeks ("simultaneous start"); PR for 4 weeks followed by Incivek/PR for 12 weeks, then PR for 32 weeks ("lead-in"); or placebo/PR for 48 weeks (control).[22] At baseline, 53% of patients had a previous relapse, 19% had a partial response, and 28% had a null-response to prior therapy. ***Results.*** The proportion of patients with SVR was significantly higher in the two Incivek treatment groups compared with PR for patients who had a prior relapse (83% [simultaneous-start] and 88% [lead-in] vs. 24%) and for prior non-responders (41% [for both simultaneous-start and lead-in] vs. 9%), including those who had a partial response (59% [simultaneous-start] and 54% [lead-in] vs. 15%) and those who had a null-response (29% [simultaneous-start], and 33% [lead-in] vs. 5%) [P < 0.001 for Incivek comparisons vs. peginterferon/ribavirin].

RESPOND-2 randomized patients (n = 403) to one of three treatment groups (all treatment was preceded by a 4-week PR lead-in). Group 1 ([control]; n = 80) received placebo/PR for 44 weeks (total treatment duration, 48 weeks). In Group 2 ([Victrelis RGT]; n = 162) patients received Victrelis/PR for a total of 32 weeks.[23] In the Victrelis RGT arm, if HCV RNA level was undetectable at TW 8 *and* TW 12 treatment commenced following completion of the 32-week Victrelis/PR treatment (total treatment duration 36 weeks); patients with a detectable HCV RNA level at TW 8 (but an undetectable level at TW 12) received an additional 12 weeks of PR plus placebo following the 32 week Victrelis/PR treatment period (total treatment duration 48 weeks). Group 3 ([Victrelis FDT]; n = 161) received Victrelis/PR for 44 weeks (total treatment duration 48 weeks). In all three groups, failure to achieve an undetectable level HCV RNA at TW 12 was considered treatment failure and resulted in discontinuation of all treatment and advancement to follow-up (stopping rule for futility). ***Results.*** The overall rates of SVR (full analysis set) were significantly greater with Victrelis FDT (66%) and RGT (59%) compared with control (21%; P < 0.001 for either Victrelis group vs. PR). Relapse was reported in 12%, 15%, and 32% of patients in the Victrelis FDT, RGT, and control groups, respectively (no statistical analysis provided). Patients with prior relapse to therapy had higher rates of SVR with Victrelis than those with prior non-response, as would be expected. Table 5 provides additional study details.

Table 5. RESPOND-2: Patients with SVR According to Treatment Group Analysis.[23]

Patient Population	SVR % (n/n)		
	Control	Victrelis RGT	Victrelis FDT
Primary analysis population[a]	21% (17/80)	59% (95/162)[†]	66% (107/161)[‡]
Secondary analysis population[b]	22% (17/78)	61% (95/156)[α]	67% (107/160)[γ]
Prior relapse [β]	29% (15/51)	69% (72/105)	75% (77/103)
Prior non-response [β]	7% (2/29)	40% (23/57)	52% (30/58)
Poor response to interferon[c]	0 %(0/12)	33% (15/46)	34% (15/44)
Good response to interferon[d]	25% (17/67)	73% (80/110)	79% (90/114)

SVR – Sustained virologic response; RGT – Response guided therapy; FDT – Fixed duration therapy; [a]Primary analysis population – patients who received at least one dose of any study medication; [b]Secondary analysis population – patients who completed the lead-in phase and received at least one dose of boceprevir or placebo; [†]Absolute difference RGT vs. peginterferon and ribavirin (PR): 37.4%, 95% confidence interval (CI): 25.7, 49.1, P < 0.001; [‡]Absolute difference FDT vs. PR: 45.2%, 95% CI: 33.7, 56.8, P < 0.001; [α]Absolute difference Victrelis RGT vs. Control: 39.1%, 95% CI: 27.2, 51.0, P < 0.001; [γ]Absolute difference FDT vs. PR: 45.1%, 95% CI: 33.4, 56.8, P < 0.001; [c]Poor response to interferon defined as < 1 $\log_{10}$ IU/mL decrease in HCV RNA after the 4-week lead-in; [d]Good response to interferon defined as ≥ 1 $\log_{10}$ IU/mL decrease in HCV RNA after the 4-week lead-in; [β]No statistical analysis provided (forest plot graphic shows odds ratio > 1 and 95% CI does not contain 1 for FDT vs. PR and RGT vs. PR, respectively).

Special Populations with CHC

Compensated Cirrhosis

Limited information is available on the efficacy of PR in patients with cirrhosis. Some clinical trials have included small numbers of patients with cirrhosis or bridging fibrosis.[12-14,26]

In a prospective study, 271 previously untreated patients with CHC and compensated cirrhosis or bridging fibrosis were randomized to 48 weeks of therapy with interferon alfa-2a (Roferon-A [no longer manufactured]) 3 million IU three times weekly [TIW] (n = 88), Pegasys 90 µg QW (n = 96), or Pegasys 180 µg QW (n = 87).[9] There was a 24-week follow-up period. Treatment was completed by 64, 78, and 67 patients, respectively. ***Results.*** Using ITT analysis, SVR was attained in 8%, 15%, and 30% of patients treated with interferon alfa-2a and with 90 µg and 180 µg of Pegasys, respectively (P = 0.001 for comparison between 180 µg of Pegasys and interferon alfa-2a). A response to therapy at Week 12 predicted a sustained response; at Week 12, all of the 26 patients who had a SVR with 180 µg of Pegasys had a decrease in viral load by a factor of ≥ 100 compared with baseline, and 23 of these patients had undetectable HCV RNA. The rates of biochemical response at Week 72 were 15%, 20%, and 34% in patients on interferon alfa-2a and with 90 µg and 180 µg of Pegasys, respectively (P = 0.004 for 180 µg of Pegasys vs. interferon alfa-2a). In a subgroup of 184 patients with paired liver biopsy specimens, the rates of histologic response at Week 72 were 31%, 44%, and 54%, respectively (P = 0.02 for comparison of 180 µg of Pegasys and interferon alfa-2a). A histologic response was correlated with a SVR: among the patients with a virologic response at Week 72, 80% of those on interferon alfa-2a also had a histologic response as did 100% on 90 µg Pegasys and 88% of those on 180 µg of Pegasys. The virologic response was similar in patients with bridging fibrosis and cirrhosis. A histologic response occurred in 26%, 33%, and 35%, respectively of patients who did not have a SVR.

In a prospective open-label trial, 126 treatment-naïve patients with HCV-related advanced fibrosis/cirrhosis (Ishak score F4-F6, Child-Pugh score ≤ 7) were randomized to 48 weeks of 180 µg of Pegasys QW and either ribavirin 1,000 or 1,200 mg or 600 or 800 mg daily.[29] ***Results.*** SVR rates were 52% and 38%, respectively, but were not statistically significantly different (P = 0.153). The probability of SVR was ≤ 7% if viremia had not decreased by ≥ 2 $\log_{10}$ or to undetectable levels after 12 weeks. Dose reductions were required for intolerance in 78% and 57% of patients, respectively and therapy was stopped early in 23% and 27% of patients.

Liver Transplantation

Pre-transplantation. There are almost no data from randomized trials on antiviral therapy in patients with decompensated cirrhosis where treatment is not recommended outside of a clinical trial and liver transplantation is the treatment of choice.[31]

Post-transplantation. A prospective, multicenter, open-label randomized study (PHOENIX) compared the efficacy, safety and tolerability of an escalating-dose regimen of Pegasys with ribavirin for 48 weeks in two situations: prophylactic initiation (before significant histological recurrence) within 26 weeks after liver transplantation and initiation upon HCV recurrence in adult patients who had undergone liver transplant due to HCV infection. Prophylaxis patients were treated for 48 weeks with Pegasys (135 µg/week for 4 weeks followed by 180 µg/week for 44 weeks) and ribavirin (dose escalated from 400 mg/day increased by 200 mg every 4 weeks to 1,200 mg/day for patients ≥ 75 kg). Observation patients were observed without treatment for up to 48 weeks; however, patients meeting the predefined endpoint of significant HCV recurrence were treated with the same antiviral regimen as was used for prophylaxis patients. This study was designed to enroll 300 patients; however slow enrollment lead to only 115 patients being randomized to either observation or prophylaxis (ITT population). ***Results.*** The primary endpoint, significant histological HCV recurrence (defined as histological activity index [HAI] inflammation grade ≥ 3 and/or a fibrosis stage score ≥ two 120 weeks after randomization) was reported in a similar proportion of prophylaxis and observation patients (61.8% and 65%, respectively). The majority of patients in both groups (n = 25/34 patients and n = 32/39 patients in the prophylaxis and observation groups, respectively) had missing biopsy results at Week 120, and therefore were classified as having recurrence due to missing data, not based on proven recurrence. In the per-protocol (PP) population, an analysis of treatment completers showed that fewer prophylaxis patients experienced HCV recurrence than observation patients (16% vs. 40.5%, respectively; 95% CI for the difference -24.5: -45.9, -3.2; P = 0.041) when any available post-baseline biopsy data were used rather than only data falling within the Week 120 window. Other secondary endpoints such as patients and

graft survival rates and the rates of biopsy-proven acute cellular rejection were similar in the two study arms. A low proportion of patients overall in both arms achieved SVR (22.2% and 21.4% for prophylaxis and observation, respectively).

Pegasys monotherapy (n = 26) for 48 weeks was compared to no therapy (n = 28) in one multicenter, prospective trial for prophylaxis (i.e., within 3 weeks of transplantation to prevent recurrence).[19] Patients on Pegasys had significantly lower HCV RNA levels and more favorable changes in liver histology compared to untreated patients, but only two treated patients (8%) attained an SVR

In a small study (n = 24), PegIntron plus ribavirin was started in the acute phase of HCV genotype 1 reinfection.[80] SVR was attained in 34.7% of treated patients (8 of 23 patients reaching Week 24 after completing treatment) vs. no patients (0%) in the control group (this was not a randomized trial).

Studies have shown that PR treatment results in an SVR rate of 18% to 45%. Small non-comparative, open-label studies with great variability in patient selection, endpoints, doses, and immunosuppressive regimens indicate therapy with peginterferon plus ribavirin may be beneficial in some patients.[20,51,53-54, 58,81-84] Many patients are unable to complete therapy for reasons unrelated to antiviral therapy.

CHC/HIV co-infection

In the US up to 8% of individuals with CHC may be co-infected with HIV.[5] The course of liver disease in this patient population is more rapid and there is an approximately 2-fold increased risk of cirrhosis. Treatment of CHC may improve the tolerability of highly active antiretroviral therapy (HAART) because CHC infection increases the hepatotoxicity risk from HAART. Achievement of SVR is generally lower in patients co-infected with HIV and CHC.[1,32-33,35-36,38-39] It is uncertain if the reasons for the lower response rates are due to the patient population having more factors associated with a poor response (e.g., high viral load, Black race) or if the HIV infection itself diminishes the SVR rate. Pegasys is indicated for use in patients co-infected with chronic CHC and HIV; PegIntron has also been studied in co-infected patients. Some of the studies in co-infected patients are summarized below. There are no fully published studies with the protease inhibitors for HCV in HIV co-infected patients. Limited information is available on retreatment with peginterferon/ribavirin in patients co-infected with HIV and CHC.[42-44] In small observational studies, these patients have been treated with Pegasys or PegIntron/ribavirin.[40-41] About 20% of patients with genotype 1 co-infected patients achieved SVR.

Children

Pegasys (alone or in combination with ribavirin) and PegIntron (in combination with ribavirin) are indicated for the treatment of CHC in patients ≥ 5 years and ≥ 3 years of age, respectively with compensated liver disease previously untreated with interferon alfa.[1-2, 46, 50,] Limited data are available for retreatment in children.[48]

Guidelines

The AASLD has two set of guidelines for the management of patients with hepatitis C that are endorsed by the Infectious Diseases Society of America (IDSA) and the American College of Gastroenterology (ACG). For patients with non-genotype 1 CHC and for patients with genotype 1 CHC for whom a protease inhibitor for HCV is not appropriate, the 2009 guidelines for the diagnosis, management, and treatment of hepatitis C remain current.[5] An updated guideline (2011) from the AASLD for the treatment of genotype 1 chronic HCV infection was published following the approval of the NS3/4A protease inhibitors for HCV (Victrelis and Incivek) and is the current guideline for patients with genotype 1 CHC.[18] Treatment recommendations are summarized below:

Genotype 1 CHC with Protease Inhibitor

In general, for genotype 1 CHC, optimal treatment consists of three drugs: Victrelis or Incivek and PR.[18] Victrelis and Incivek should not be used without PR.

Treatment-naïve

In *treatment-naïve patients* treated with Victrelis, following a 4-week lead-in with PR, Victrelis is administered in combination with PR for 24 to 44 weeks. In *treatment-naïve* patients *without cirrhosis*, who have undetectable HCV RNA at TW 8 and 24, a shortened course of therapy (28 weeks in total) is recommended (4 weeks of PR lead-in followed by 24 weeks of triple-drug therapy). In *treatment-naïve* patients *with cirrhosis*, the duration of PR therapy is 48 weeks. Treatment with all three drugs (peginterferon alfa, ribavirin, and Victrelis) should be stopped if HCV RNA is > 100 IU/mL at TW 12 or detectable at TW 24.

Treatment-naïve patients with genotype 1 CHC *without cirrhosis* treated with Incivek are eligible for a shortened duration of therapy (24 weeks) if HCV RNA level at TW 4 and 12 is undetectable (eRVR).[18] In *treatment-naïve* patients *with cirrhosis*, the duration of PR is 48 weeks. Treatment with all three drugs (peginterferon alfa, ribavirin, and Incivek) should be stopped if HCV RNA is > 1,000 IU/mL at TW 4 or 12 and/or detectable at TW 24.

Retreatment

Retreatment with Victrelis or Incivek together with peginterferon alfa and weight-based ribavirin, is recommended for patients who had virologic relapse or were partial responders after a prior course of treatment with standard interferon alfa or peginterferon alfa with or without ribavirin.[18] Retreatment with Incivek (as triple-drug therapy) may be considered for prior null-responders to a course of standard interferon alfa or peginterferon alfa with or without weight-based ribavirin. In treatment-experienced patients using either Victrelis or Incivek-based regimens, RGT can be considered for relapsers and may be considered for partial responders, but cannot be recommended for null-responders (applies to Incivek). Patients retreated with Victrelis/PR who continue to have detectable HCV RNA > 100 IU at TW 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance. Patients retreated with Incivek/PR who continue to have detectable HCV RNA > 1,000 IU at TW 4 or 12 should be withdrawn from all therapy because of the high-likelihood of developing antiviral resistance.

Other Recommendations

Other recommendations concerning treatment with the protease inhibitors as triple-therapy (with PR) in patients with genotype 1 CHC include close monitoring of the HCV RNA level and discontinuation of therapy if virological breakthrough (> 1 log increased in serum HCV RNA above nadir) is observed.[18] In addition, patients who fail to have a virological response, patients who experience virological breakthrough, or *patients who relapse on one protease inhibitor should not be retreated with the other protease inhibitor*.

CHC Without a Protease Inhibitor

General recommendations for treatment in patients with viral genotypes other than genotype 1 (and in genotype 1 when a protease inhibitor is not appropriate) the treatment of choice is PR.[5] PR is also recommended for patients with bridging fibrosis or compensated cirrhosis, providing no contraindications are present. AASLD recommends that HCV RNA should be tested by a highly sensitive quantitative assay at the initiation of or shortly before treatment and at Week 12 of therapy.

In *treatment-naïve* patients with *genotype 1 CHC infection (without a protease inhibitor for HCV) and genotype 4 CHC infection* treatment with PR should be planned for 48 weeks. Treatment *may* be discontinued in patients who do not achieve an EVR at 12 weeks; for patients who have *delayed virus clearance*, (HCV test becomes negative between Weeks 12 and 24), consideration should be given to extending therapy to 72 weeks. In patients continuing treatment through 48 to 72 weeks and whose measurement of HCV RNA is negative at the end of treatment, HCV RNA should be tested 24 weeks later to evaluate SVR. *Treatment-naïve* patients with *genotype 2 or genotype 3 CHC infection* are recommended to receive treatment with PR for 24 weeks. Patients whose treatment continues for the full 24 weeks, and whose qualitative measurement of HCV RNA at that time is negative, should be retested for HCV RNA 24 weeks later to document SVR.

Retreatment with PR in persons who did not achieve SVR after a prior full course of PR is not recommended even if a different type of peginterferon is administered.[5] Retreatment with PR can be considered for nonresponders or relapsers who have previously been treated with non-pegylated interferon with or without ribavirin or with peginterferon monotherapy, particularly if there is significant fibrosis or cirrhosis.

Special patient groups that are recommended for therapy with PR include children, patients with HIV co-infection, patients with compensated or decompensated cirrhosis/solid organ transplantation and acute HCV infection. In *children* aged 2 to 17 years who are infected with CHC and are considered appropriate candidates for treatment the recommended duration of treatment with PR is 48 weeks. AASLD guidelines, recommend treatment with PegIntron in children ages 2 to 17 years with CHC infection (Pegasys was not indicated in children when the recommendation was made). Additionally, 48 weeks of treatment is recommended in children regardless of genotype; the committee felt the evidence was insufficient (in 2009) to recommend a shorter duration of therapy. PegIntron was approved in children at the time the guidelines were published; however, the AASLD notes using either product in children with genotype 1 is substantiated.[5] In patients with *HIV/CHC co-infection* treatment is recommended in for patients in whom the likelihood of serious liver disease and a treatment response are judged to outweigh the risk of morbidity from the AEs of therapy. Initial treatment of hepatitis C in most HIV-infected persons is PR for 48 weeks. AASLD also recommends, when possible, patients with HIV co-infection receiving zidovudine and especially didanosine be switched to an equivalent antiretroviral before beginning therapy with ribavirin. Patients with HCV-related *compensated cirrhosis* (Child-Pugh class A) can be treated with the standard regimen of PR but require close monitoring for AEs. Patients with clinically *decompensated cirrhosis* should be referred for consideration of liver transplantation. Interferon-based therapy may be initiated at a lower dose in patients with decompensated cirrhosis (Child-Pugh class B or C) as long as treatment is administered by experienced clinicians with vigilant monitoring for AEs (preferably in patients who have already been accepted as candidates for liver transplantation). Treatment of HCV-related disease following *liver transplantation* should be initiated in appropriate candidates after demonstration of recurrent histologic disease but should be undertaken with caution because of the increased risk of AEs and should be performed under the supervision of a physician experienced in transplantation. Peginterferon alfa with or without ribavirin should be the preferred regimen when treating patients with hepatitis C after liver transplantation. Interferon based therapy should not be used in recipients of *heart, lung, and kidney* grafts, except for patients who develop fibrosing cholestatic hepatitis.

Patients with *acute HCV* should be considered for interferon-based antiviral therapy.[5] Although excellent results were achieved in reported uncontrolled studies using standard interferon monotherapy, it is appropriate to consider the use of peginterferon because of its improved ease of administration. For acute HCV, no recommendation can be made about the addition of ribavirin, and the decision will therefore need to be considered on a case-by-case basis. In the absence of controlled study data, no definitive recommendations can be made about the timing of treatment initiation (for acute HCV); however, it seems reasonable to delay treatment for 2 to 4 months after acute onset to allow for spontaneous resolution. No definitive recommendation can be made about the duration of treatment needed to treat acute HCV; however, it seems reasonable to continue treatment for at least 12 weeks, and 24 weeks may be considered.

Based on the HALT-C Trial, the AASLD guidelines note that *maintenance* low dose Pegasys is not indicated in patients with hepatitis C who have bridging fibrosis or cirrhosis and who have not responded to a standard course of peginterferon and ribavirin therapy; decisions to undergo retreatment should be individualized.[5]

Other Guidelines

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) practice guidelines for the diagnosis and management of hepatitis C infection in infants, children and adolescents (2012) recommend that children with hepatitis C who demonstrate persistently elevated

serum aminotransferases or those with progressive disease (i.e., liver fibrosis) should be considered for treatment.[7] The NASPGHAN guidelines state that the recommended therapy for children ages 3 to 17 years of age is with PR. The recommended length of therapy is 48 weeks for children with genotype 1 or 4 CHC and 24 weeks for genotype 2 or 3 CHC. There are limited data for the treatment of children with HIV or hepatitis B co-infections; however, if treated, the recommended duration of therapy is 48 weeks. Close clinical monitoring is warranted.

Compensated Cirrhosis

The International Liver Transplantation Society Expert Panel proposed guidelines for the use of interferon-based therapy in patients with HCV cirrhosis who are awaiting liver transplantation are based on Child-Pugh and Model for End-Stage Liver Disease (MELD) scores.[30] According to their recommendations, therapy should be strongly considered if the Child-Pugh score is ≤ 7 or the MELD score is ≤ 18 and possibly considered in select cases with Child-Pugh score 8 to 11 or MELD score 18 to 15.

Liver Transplantation

Liver disease caused by HCV is the main indication for liver transplantation in Western countries and re-infection post-transplantation significantly impairs patient and graft survival.[34] CHC infection is estimated to develop in 75% to 90% of post-transplant patients, and ultimately progresses to cirrhosis within 5 years in 5% to 30% of post-transplant patients. Antiviral therapy can be administered before transplantation to suppress viral replication and reduce the risk of HCV early post-transplantation as well as prevent the progression of hepatitis (pre-emptive or prophylactic therapy). Both pre-transplantation and prophylactic post-transplantation antiviral treatment is limited by poor tolerance and drug side effects.

Pre-transplantation. In some patients with CHC on the waiting list for liver transplantation, a low, accelerating dose regimen (LADR) is recommended.[30,45] Using this regimen, dose adjustments are made every 2 weeks.[30] The interferon dose is increased as tolerated to achieve full dose treatment within in 2 to 4 weeks. Next the ribavirin dose is increased every 2 weeks as tolerated to achieve an estimated optimal effective dose (10.6 mg/kg/day). Frequent hematologic and biochemical assessments are required (every 2 weeks) until the dose is stabilized (monthly assessments after a stable dose is achieved). The viral titer is recommended to be monitored every 3 months. Guidelines recommend to discontinue therapy in patients who fail to respond to 12 weeks of treatment with at least a 2 $\log_{10}$ reduction in HCV RNA. After the optimal doses of interferon and ribavirin are achieved, the expected duration of initial treatment is recommended to be 6 months for genotypes 2 or 3 and 12 months for genotype 1; however, guidelines note additional data are needed to support these timelines. Similar to patients with CHC not on the waiting list for liver transplantation, the desired outcome of treatment is attainment of SVR. However, relapse rates in liver transplant candidates with advanced cirrhosis may be greater than those in non-cirrhotic patients with CHC, particularly with genotype 1, because of the inability to achieve optimal doses of both interferon and ribavirin. In patients who relapse after treatment is stopped, it may be appropriate to consider reinstitution of antiviral therapy Reinstitution of therapy should be considered in patients who relapse. An alternative approach could be continuation of antiviral therapy for patients with genotype 1 and with on-treatment viral clearance up to the time of transplantation. The European Association for the Study of the Liver (EASL) notes that approximately 75% of patients who are HCV negative at the time of transplantation remain negative post-transplantation.

The role of peginterferon (or standard interferon) with or without ribavirin in patients with decompensated CHC cirrhosis has been investigated in a small number of published studies.[34] All have been single-center, many have been uncontrolled and the endpoints assessed have varied greatly. The goal of pre-transplantation hepatitis C antiviral therapy is not to reduce viral load at transplantation, rather it is to achieve an SVR at transplantation or on-treatment negative serum HCV RNA at transplantation. The best candidates for therapy remain Child-Pugh class A. In Child-Pugh

class B patients, treatment should be discussed on a case-by-case basis according to baseline factors for potential response such as non-genotype 1, low viral load, good-response *IL28B* genotype, treatment-naïve or patients who have relapsed from previous antiviral therapy. In patients for whom there is no virologic response at TW 4 or 12, therapy can be discontinued. There is no experience on the efficacy and safety of the protease inhibitors for HCV (Victrelis and Incivek) in patients with decompensated cirrhosis, and therefore these drugs should not be used outside of carefully designed clinical trials in this population.

Post-transplantation. Pre-emptive or early post-transplant antiviral therapy should be initiated soon after liver transplantation, optimally within 1 month (when viral load is at its lowest level and fibrosis is absent).[34] However, in the early post-transplant period, antiviral therapy may be less effective because of the high level of immunosuppression and tolerance is low because of high risk of poor hematological tolerance, of rejection and sepsis. Antiviral therapy is usually given when there is histological evidence of recurrent HCV in the post-transplant setting.[34]

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Billing Coding/Physician Documentation Information

N/A Pegylated Interferons are a pharmacy benefit.

Additional Policy Key Words

5.01.540

Related Topics

N/A

Policy Implementation/Update Information

03/2013 New policy titled Pegylated Interferons
03/2014 Reviewed – no policy changes