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Hepatitis C Class Review

Month/Year of Review: January 2012
PDL Class: Hepatitis C Agents
Suggested Revision: Expand current Hepatitis C PDL class to include all agents for treatment of Chronic Hepatitis C (CHC) Virus

Current Status of PDL Class:
PA Criteria for Pegylated Interferon and Ribavirin (Appendix 1)
Preferred Agents: Pegasys (peginterferon alfa 2a), Pegintron (peginterferon alfa 2b)

Background:
Hepatitis C virus (HCV) infection is the leading cause of chronic liver disease and death from liver disease and leading indication for liver transplantation in the United States (U.S.). Therefore, the goal of therapy for HCV infection is to prevent complications and death.[1]

An estimated 180 million people worldwide are infected with HCV. The prevalence of HCV infection in the U.S. between 1999 and 2002 was 1.6%, or about 4.1 million people positive for hepatitis C antibody (anti-HCV).[1]

About 55% to 85% of those who develop acute hepatitis C remain infected, rather than achieve spontaneous resolution.[1] An estimated 15 to 30% of patients with CHC develop cirrhosis within 30 years. One to three percent of patients per year with HCV-related cirrhosis develop hepatocellular carcinoma.[2]

U.S. guidelines have recommended combination peginterferon alfa (P) and ribavirin (R) as the standard of care (SOC) for CHC, with the optimal duration of treatment based on viral genotype. Response to treatment (i.e., SVR) with SOC is about 50% for Caucasians and 30% for African-Americans. Guidelines for treating HCV genotype 1 (HCV-1) were updated in fall 2011, following FDA approval of the direct acting antivirals (DAA) boceprevir (BOC) and telaprevir (TVR).[1,2]

HVC is classified into at least 6 major genotypes: genotype 1 (with subtypes 1a and 1b), which is the most common in the U.S.; genotypes 2 and 3, which are the next most common; and genotypes 4, 5, and 6, which are, thus far, the least common.[1] Genotype 1 accounts for >70% of CHC in the

U.S. and Europe and has the poorest response to treatment. Genotyping HCV is useful for predicting the likelihood of response to and duration of therapy.[3]

According to AASLD guidelines, widely accepted criteria for CHC treatment include HCV RNA serum positive, significant fibrosis, compensated liver disease, acceptable blood and biochemistry indices, willingness to be adherent to therapy, and no contraindications. Criteria contraindicating therapy include uncontrolled major depression, solid organ transplant, autoimmune hepatitis or autoimmune condition exacerbated by PR, untreated thyroid disease, pregnancy, inadequate contraception, severe concurrent medical illnesses, age <2, and hypersensitivity to drug therapies. However, these are not absolute and clinical judgment should be exercised in each case.[1]

Sustained virologic response (SVR) is associated with permanent virologic cure, long-term clearance of HCV infection, as well as improved morbidity and mortality in the vast majority of patients. RVR predicts a high likelihood of achieving an SVR. Those who achieve an RVR have an SVR rate of about 90%; however, only 15% to 20% of those with HCV-1 infection achieve RVR with peginterferon alfa. Early virologic response (EVR) is the most accurate predictor of non-response, as 97 to 100% of treatment-naïve HCV-1 patients who fail to reach EVR fail to achieve SVR. While end-of-treatment response (ETR) is an inaccurate predictor of achieving SVR, ETR is necessary for SVR to occur.[1,4]

On-treatment viral kinetics is used to guide the duration of therapy.[4] Studies have previously established patients with HCV-1 should be treated for 48 weeks with PEG-2a (180 µg/week sc) plus weight-based RIB (1000 or 1200 mg per day) or PEG-2b (1.5 µg/kg sc) plus weight-based RIB (800 mg, 1000 mg, 1200 mg, or 1400 mg).[7] Treatment may be discontinued in patients who do not achieve EVR. Forty to fifty percent of patients with HCV-1 treated with PEG and the standard weight-based dose of RIB for 48 weeks achieve SVR. The two FDA-approved PEGs (Pegasys, Roche, and PegIntron, Merck) have had similar efficacy and safety profiles in head-to-head comparisons.[4]

Summary:

The standard of care for the treatment of Chronic Hepatitis C (CHC) has been pegylated interferon (alfa 2a or alfa 2b) in combination with weight-based ribavirin (PR) for either 48 weeks or 24 weeks depending on genotype[1]. The American Association for the Study of Liver Disease recently published an update on the treatment of genotype 1 chronic hepatitis c virus infection guidelines to include the new direct acting antiviral (DAA) agents of BOC and TVR.[2] These were based on a review and analysis of published literature, guideline policies, and expert opinion. There is evidence showing a significant improvement in SVR rates in patients with genotype 1 CHC but the guidelines state that the recommendations are based on new data that is still quite limited and as more studies are conducted and become available the recommendations may need to be reconsidered.[2] Both BOC and TVR have evidence showing a significant improvement in demonstrating higher rates of virologic response compared with the current standard of treatment and also both in patients who had previously failed dual therapy, but at a significantly higher cost and with safety concerns including anemia, drug interactions, skin rashes, and adverse events[5].

The updated guidelines state:

1. The optimal therapy for genotype 1, chronic HCV infection is the use of boceprevir or telaprevir in combination with peginterferon alfa and ribavirin. (Class 1, Level A)
2. Boceprevir and telaprevir should not be used without peginterferon alfa and weight-based ribavirin. (Class 1, Level A).

The combination of pegylated interferon and ribavirin remains the standard of care for all other genotypes.[1] Oregon reviewed the interferons for CHC previously and developed PA criteria for treatment with peginterferon and ribavirin shown in Appendix 1. Both Peg-Intron and Pegasys are listed as preferred agents. There is comparative effectiveness evidence demonstrating that there are no significant differences in efficacy or safety between the two agents.[4] The introduction of these long-acting peginterferons has become the standard of care and have replaced the older non-pegylated infererons[1].

In 2010, the FDA approved an expanded indication for interferon alfacon-1 (Infergen) for retreatment of CHC in combination with ribavirin after failure to previous treatment with a pegylated interferon and ribavirin[6]. This approval was based on a single study (DIRECT trial) which was a randomized, open-label, study comparing the safety and efficacy of two doses of interferon alfacon-1 plus ribavirin in previous nonresponders[4]. The AASLD guidelines do not demonstrate any role of interferon alfacon-1 in the treatment of CHC and there is limited data to support its use.

There is currently no comparative evidence evaluating if there is a difference in either efficacy or safety between BOC and TVR. There were also differences in how the drug studies were conducted as well as major differences in side effect profiles, making a direct comparison difficult. Only telaprevir was studied in prior null responders to PR therapy, BOC was studied in combination with peginterferon alfa-2b while TVR was given with peginterferon alfa-2a, and although there is a high incidence of anemia associated with both drugs it was managed differently in clinical trials. Use of erythropoietin stimulating agents (ESAs) was excluded from TVR studies while ESAs were allowed for the management of anemia at the discretion of the clinician in the BOC studies.[2,3] Ongoing studies are further evaluating how the management of anemia including ESA use or R dose reduction affects outcomes with BOC treatment.

Recommendations:

- Expand current Hepatitis C antiviral PDL class to include all agents for treatment of Chronic Hepatitis C Virus
- Recommend to maintain either one or both of peginterferon alfa-2a (Pegasys) and peginterferon alfa-2b (PegIntron) as preferred pegylated interferon products depending on price. These two agents are recommended in the current guidelines and have shown to be similar in terms of safety and efficacy.
- Designate interferon alfacon-1 (Infergen) as a non-preferred agent due to the lack of recommendations for use in current treatment guidelines.
- Develop PA criteria to support the judicious use of the oral protease inhibitors in patients with genotype 1 CHC in combination with pegylated interferon and ribavirin.

APPENDIX 1: Prior authorization criteria for pegylated interferon and ribavirin

Pegylated Interferon and Ribavirin

Goal(s):

Cover drugs only for those clients where there is medical evidence of effectiveness and safety

Length of Authorization: 16 weeks plus 12-36 additional weeks or 12 months

Requires pa: All drugs in HIC3 = W5G

Approval Criteria		
1. Is peginterferon requested preferred?	**Yes:** Go to #3.	**No:** Go to #2.
2. Will the prescriber consider a change to a preferred product? Message: - Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Health Resources Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml	**Yes:** Inform provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml.	**No:** Go to #3.
3. Is the request for treatment of Chronic Hepatitis C? Document appropriate ICD9 code: (571.40; 571.41; 571.49)	**Yes:** Go to #4.	**No:** Go to #10
4. Is the request for continuation of therapy? (Patient has been on HCV treatment in the preceding 12 weeks according to the Rx profile)	**Yes:** Go to "Continuation of Therapy"	. **No:** Go to #5
5. Does the patient have a history of treatment with previous pegylated interferon-ribavirin combination treatment? Verify by reviewing member's Rx profile for PEG-Intron or Pegasys, PLUS ribavirin history. Does not include prior treatment with interferon monotherapy or non-pegylated interferon.	**Yes:** Forward to DMAP Medical Director	**No:** Go to #6
6. Does the patient have any of the following contraindications to the use of interferon-ribavirin therapy? • severe or uncontrolled psychiatric disorder • decompensated cirrhosis or hepatic encephalopathy • hemoglobinopathy~~cytopenias~~ • untreated hyperthyroidism • severe renal impairment or transplant	**Yes:** Deny; Pass to RPH (Medical Appropriateness)	**No:** Go to #7

• autoimmune disease • pregnancy • unstable CVD		
7. If applicable, has the patient been abstinent from IV drug use or alcohol abuse for ≥ 6 months?	**Yes:** Go to #8	**No:** Deny; Pass to RPH (Medical Appropriateness)
8. Does the patient have a detectable HCV RNA (viral load) > 50IU/mL? Record HCV RNA and date:	**Yes:** Go to #9	**No:** Deny; Pass to RPH (Medical Appropriateness)
9. Does the patient have a documented HCV Genotype? Record Genotype:	**Yes:** Approve for 16 weeks with the following response: Your request for has been approved for an initial 16 weeks. Subsequent approval is dependent on documentation of response via a repeat viral load demonstrating undetectable or 2-log reduction in HCV viral load. Please order a repeat viral load after 12 weeks submit lab results and relevant medical records with a new PA request for continuation therapy. Note: For ribavirin approve the generic only	**No:** Deny; Pass to RPH (Medical Appropriateness)
10. Is the request for Pegasys and the treatment of confirmed, compensated Chronic Hepatitis B?	**Yes:** Go to #11	**No:** Deny; Pass to RPH (Medical Appropriateness)
11. Is the patient currently on LAMIVUDINE (EPIVIR HBV), ADEFOVIR (HEPSERA), ENTECAVIR (BARACLUDE), TELBIVUDINE (TYZEKA) and the request is for combination Pegasys-oral agent therapy?	**Yes:** Deny; Pass to RPH (Medical Appropriateness)	**No:** Go to #12
12. Has the member received previous treatment with pegylated interferon?	**Yes:** Deny; Pass to RPH (Medical Appropriateness) Recommend: LAMIVUDINE (EPIVIR HBV) ADEFOVIR (HEPSERA)	**No:** Approve Pegasys #4 x 1ml vials or #4 x 0.5 ml syringes per month for 12 months (maximum per lifetime).

Continuation of Therapy- HCV

1. Does the client have undetectable HCV RNA or at least a 2-log reduction (+/- one standard deviation) in HCV RNA measured at 12 weeks?

Yes: Approve as follows:

Approval for beyond quantity and duration limits requires approval from the medical director.

Genotype	Approve for	Apply
1 or 4	**An additional 36 weeks** or for up to a total of 48 weeks of therapy (whichever is the lesser of the two).	Ribavirin quantity limit of 200 mg tablets QS# 180 / 25 days (for max daily dose =1200 mg).
2 or 3	**An additional 12 weeks** or for up to a total of 24 weeks of therapy (whichever is the lesser of the two).	Ribavirin quantity limit of 200 mg tab QS# 120 / 25 days (for max daily dose = 800 mg).
For all genotypes and HIV co-infection	**An additional 36 weeks** or for up to a total of 48 weeks of therapy (whichever is the lesser of the two)	Ribavirin quantity limit of 200 mg tablets QS# 180 / 25 days (for max daily dose = 1200 mg).

No: DENY
(Medical Appropriateness)

Treatment with pegylated interferon-ribarvirin does not meet medical necessity criteria because there is poor chance of achieving an SVR.

Clinical Notes:

- Serum transaminases: Up to 40 percent of clients with chronic hepatitis C have normal serum alanine aminotransferase (ALT) levels, even when tested on multiple occasions.
- RNA: Most clients with chronic hepatitis C have levels of HCV RNA (viral load) between 100,000 (10^5) and 10,000,000 (10^7) copies per ml. Expressed as IU, these averages are 50,000 to 5 million IU. Rates of response to a course of peginterferon-ribavirin are higher in clients with low levels of HCV RNA. There are several definitions of a “low level” of HCV RNA, but the usual definition is below 800,000 IU (~ 2 million copies) per ml.(5)
- Liver biopsy: Not necessary for diagnosis but helpful for grading the severity of disease and staging the degree of fibrosis and permanent architectural damage and for ruling out other causes of liver disease, such as alcoholic liver injury, nonalcoholic fatty liver disease, or iron overload.

Stage is indicative of fibrosis:			Grade is indicative of necrosis:	
Stage 0	No fibrosis			
Stage 1	Enlargement of the portal areas by fibrosis		Stage 1	None
Stage 2	Fibrosis extending out from the portal areas with rare bridges between portal areas		Stage 2	Mild

Stage 3	Fibrosis that link up portal and central areas of the liver		Stage 3	Moderate
Stage 4	Cirrhosis		Stage 4	Marked

The following are considered investigational and/or do not meet medical necessity criteria:

- ✓ Treatment of HBV or HCV in clinically decompensated cirrhosis
- ✓ Treatment of HCV or HBV in liver transplant recipients
- ✓ ~~Re-treatment of HCV or HBV previous non-responders or relapsers~~
- ✓ Treatment of HCV or HBV > 48 weeks
- ✓ Treatment of advanced renal cell carcinoma
- ✓ Treatment of thrombocytopenia
- ✓ Treatment of human papilloma virus
- ✓ Treatment of multiple myeloma

References:

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3. Food and Drug Administration Center for Drug Evaluation and Research. Application Number: 202258Orig1s000 summary review. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202258Orig1s000SumR.pdf. Accessed September 26, 2011.

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6. Infergen Package Insert. Kadmon Corporation, LLC. Available at: http://kadmon.com/files/infergen-pi.pdf.