Pegylated Interferon Criteria for Use

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The following recommendations are dynamic and will be revised, as new clinical data become available. These criteria are not intended to interfere with clinical judgment. Rather, they are intended to assist practitioners in providing cost effective, consistent, high quality care.

The use of interferon therapy for chronic hepatitis C may decrease viral load, which could decrease the risk of complications (e.g., cirrhosis, liver failure, liver cancer). Recent guidance from the National Institutes of Health can assist in determination of which patients to treat with interferon therapy. (Internet link http://www.consensus.nih.gov/cons/116/116cdc_intro.htm) Interferons have been proven to provide a sustained virologic response (SVR), as defined by the absence of detectable HCV RNA in the serum as shown by an HCV RNA assay with a lower limit of detection of 50 IU/ml or less at 24 weeks after the end of treatment. Trials comparing interferon alfa and pegylated interferon documented a larger percentage of patients with SVR in the pegylated interferon treatment group. This may be the result of pegylation increasing molecule size, which slows the absorption, prolongs the half-life, and decreases the rate of interferon clearance. Thus, the duration of biological activity is increased with pegylated interferon over nonpegylated interferon. Tolerability of the pegylated interferons is comparable to the nonpegylated formulations. Combination therapy with ribavirin appears more effective than monotherapy. Studies comparing peginterferon alfa-2b and peginterferon alfa-2a in the treatment of chronic Hepatitis C have not been performed. Treatment decisions should be based on patient specifics and tolerability of interferon-based preparations in combination with ribavirin.

I. Combination therapy with pegylated interferon and ribavirin

a) In treatment naïve patients, the following regimens are recommended:

Genotype 1 and 4: Peginterferon alfa-2a 180 ug/week or peginterferon alfa-2b 1.5 ug/kg/week plus ribavirin 1,000 to 1,200 mg/day based on body weight (1,000 mg for ≤75 kg, 1,200 mg for >75 kg in two divided doses daily)

Genotype 2 or 3: Interferon alpha 3 million units three times weekly plus ribavirin 1,000 to 1,200 mg/day based on body weight (1,000 mg for ≤75 kg, 1,200 mg for > 75 kg in two divided doses daily). For selected patients peginterferon alfa-2a 180 ug/week or peginterferon alfa-2b 1.5 ug/kg/week plus ribavirin 800 mg/day may be considered, keeping in mind the risks, benefits and costs of the therapy. Limited data suggest the pegylated regimen may have minimally better response rates.

b) Patients who are classified as a relapser (elevation of serum alanine aminotransferase concentration within one year of the end of interferon therapy and detectable HCV RNA) or nonresponder (defined by the presence of detectable HCV RNA in the serum as shown by a qualitative HCV RNA assay with a lower limit of detection of 50 IU/ml at 24-48 weeks of therapy) may be considered for retreatment. Given that only 15-20% of nonresponders to standard interferon plus ribavirin will achieve a SVR with pegylated interferon/ribavirin, clinicians should consider the risks, benefits and costs associated with re-exposing a non-responder to this therapy.

Recommendation	Source	QE	Overall quality	R
Combination therapy	Manns 2001 Zeuzem, 2000 Fried, 2002 Ferenci, 2001	I	Good	A
Nonresponder	Davis, 1998 Keeffe, 1997	I	Good	A
Genotype 1	Trepo, 2000 Manns 2001 Fried, 2002	I	Fair Good Good	B A A
	NIH Consensus, 2002	III	Good	B

II. Monotherapy with pegylated interferon

In patients who have a contraindication or are intolerant to ribavirin, peginterferon alfa-2a 180 ug/week or peginterferon alfa-2b 1.0μg/kg/week can be given for 48 weeks. In patients with end-stage renal disease requiring hemodialysis, dose reduction of peginterferon alfa-2a to 135 ug/week is recommended. A decision to continue or withdraw therapy after 24 weeks is based on the virological response, regardless of the infecting genotype.

Contraindications to ribavirin therapy:

a) Decreased baseline hemoglobin (< 13 gm/dL for men, <12 gm/dL for women)
b) History of thalassemia or other hemoglobinopathies
c) Evidence of significant cardiac disease such as ischemia on stress testing or ECG, significant arrhythmias, cardiac failure, angina, recent coronary surgery or myocardial infarction within the past 12 months.
d) Men whose female partners are or are at high risk of becoming pregnant or females of child-bearing age not using appropriate contraception. Neither, interferon or ribavirin should be used in women who are pregnant or at risk of becoming pregnant due to the abortifacient (interferon) and teratogenic (ribavirin) properties of these compounds.

Recommendation	Source	QE	Overall quality	R
Monotherapy	Lindsay, 2001 Poynard, 1995	I	Fair	B
Monotherapy	NIH Consensus, 2002	III	Fair	B

III. Treatment Duration

Patient response while receiving interferon-based preparations plus ribavirin should be assessed at 12 weeks. In those who are HCV RNA negative and/or who have achieved a 2 $\log_{10}$ or greater drop in HCV RNA levels at 12 weeks, treatment should be continued for a total of 24 weeks for genotype 2 or 3 infection and 48 weeks for genotype 1 and 4 infection. In patients who have less than a 2 $\log_{10}$ decrease in HCV RNA levels at 12 weeks, consider discontinuing treatment because SVR with continued treatment is rare.

Benefits of treatment beyond one year in preventing long-term complications of liver disease are under investigation. Long-term suppressive therapy cannot be recommended until such data are available.

IV. Ribavirin Dose

Based on preliminary data combination therapy with pegylated interferon and ribavirin, the optimal ribavirin dose appears to be 1,000 to 1,200 mg/day in patients with genotype 1 infection and 800 mg/day in genotype 2 or 3 infection. The use of "weight-based" doses of ribavirin at 10.6 mg/kg or higher in combination with peginterferon alfa-2b is under evaluation prospectively.

Ribavirin is not effective as a single agent.

Recommendation	Source	QE	Overall quality	R
Dose	Manns, 2001 Hadziyannis, 2002 Fried, 2002 McHutchinson, 1998	I	Good	A
	NIH Consensus, 2002	III	Good	B

V. Comparative Costs

	Cost per week	Cost for 48 wks	Cost of ribavirin Component/week
Monotherapy			
Peginterferon alfa 2b 1.0ug/kg/week (Peg-Intron®)	$152.59	$7324.32	
Peginterferon alfa 2a 180ug/week (Pegasys®)	$166.70	$8001.60	
Combination Therapy			
Peginterferon alfa 2b 1.5 ug/kg/week (Peg-Intron®) Ribavirin 800 mg QD	$326.80	$15,686.40	$170.52
Peginterferon alfa 2a 180ug/week (Pegasys®) Ribavirin 800 mg QD	$337.22	$16,186.56	$170.52
Peginterferon alfa 2b 1.5 ug/kg/week (Peg-Intron®) Ribavirin 1000 mg QD	$368.52	$17,688.96	$213.15
Peginterferon alfa 2a 180ug/week (Pegasys®) Ribavirin 1000 mg QD	$379.85	$18,232.80	$213.15
Interferon alfa 2a 3 mU TIW (using multi dose pen injector) Ribavirin 1000 mg QD	$194.14	$9318.72	
Interferon alfa 2a 3 mU TIW (using multi dose pen injector) Ribavirin 1200 mg QD	$215.90	$10,363.20	

Doses based on 70 kg patient, there is currently no FSS price available for Co-Pegasys®
Cost of ribavirin 1200mg/day for 1 week is $255.78

References

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National Hepatitis C Program http://www.va.gov/hepatitisc/index.htm June 25, 2002

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RATING THE EVIDENCE

TABLE 1: Quality of Evidence [QE]

I	At least one properly done RCT
II-1	Well designed controlled trial without randomization
II-2	Well designed cohort or case-control analytic study
II-3	Multiple time series, dramatic results of uncontrolled experiment
III	Opinion of respected authorities, case reports, expert committees.

TABLE 2: Overall Quality

Good	High grade evidence (I or II-1) **directly linked** to health outcome
Fair	High grade evidence (I or II-1) **linked to intermediate** outcome or Moderate grade evidence (II-2 or II-3) directly linked to health outcome
Poor	Level III evidence or no linkage of evidence to health outcome

TABLE 3: Net Effect of the Intervention

Substantial	More than a small relative impact on a frequent condition with a substantial burden of suffering – or - A large impact on an infrequent condition with a significant impact on the individual patient level.
Moderate	A small relative impact on a frequent condition with a substantial burden of suffering - or - A moderate impact on an infrequent condition with a significant impact on the individual patient level.
Small	A negligible relative impact on a frequent condition with a substantial burden of suffering - or - A small impact on an infrequent condition with a significant impact on the individual patient level.
Zero or Negative	Negative impact on patients - or - No relative impact on either a frequent condition with a substantial burden of suffering - or - An infrequent condition with a significant impact on the individual patient level.

TABLE 4: Grade the Recommendation

A	A strong recommendation that the intervention is always indicated and acceptable
B	A recommendation that the intervention may be useful/effective
C	A recommendation that the intervention may be considered
D	A Recommend that a procedure may be considered not useful / effective, or may be harmful.
I	Insufficient evidence to recommend for or against – the clinician will use their clinical judgment

Abstract of the USPSTF:

- Once assembled, admissible evidence is reviewed at three strata: (1) the individual study, (2) the body of evidence concerning a single linkage in the analytic framework, and (3) the body of evidence concerning the entire preventive service. For each stratum, the Task Force uses explicit criteria as general guidelines to assign one of three grades of evidence: good, fair, or poor.
- Good or fair quality evidence for the entire preventive service must include studies of sufficient design and quality to provide an unbroken chain of evidence-supported linkages, generalizable to the general primary care population, that connect the preventive service with health outcomes. Poor evidence contains a formidable break in the evidence chain such that the connection between the preventive service and health outcomes is uncertain.
- For services supported by overall good or fair evidence, the Task Force uses outcomes tables to help categorize the magnitude of benefits, harms, and net benefit from implementation of the preventive service into one of four categories: substantial, moderate, small, or zero/negative.
- The Task Force uses its assessment of the evidence and magnitude of net benefit to make a recommendation, coded as a letter: from A (strongly recommended) to D (recommend against). It gives an "I" recommendation in situations in which the evidence is insufficient to determine net benefit

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