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Hepatitis C: Recommendations for Antiviral Therapy

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Hepatitis C virus (HCV) is one of the most common blood-borne infections and causes of chronic liver disease in the United States.[1] The majority of cases result from illicit IV drug abuse (IVDA). Unlike other viral hepatides, there is no vaccination. Chronic HCV infection evolves over several decades. Approximately 15-30% of individuals recover after initial infection, while the balance progress to chronic HCV.[2] Of those developing chronic infection, the clinical outcomes are variable. The majority (70%) of patients develop chronic hepatitis that is mild to moderate. Others progress to cirrhosis, hepatic decompensation, hepatocellular carcinoma, and liver transplantation. The mortality rate is 1-5%. Because of the long delay between infection and the appearance of liver damage, the impact of HCV is expected to grow, making early diagnosis and treatment desirable.

Recommendations for Treatment

The National Institutes of Health (NIH) *Consensus Development Conference Statement: Management of Hepatitis C 2002* discusses the optimal treatment of HCV as outlined in Table 1.[3] All HCV positive persons should be evaluated for the presence and severity of liver disease.[1] Psychosocial issues should also be addressed including alcohol and illicit drug use.[1] Those negative for hepatitis A and B should be vaccinated. Antiviral therapy is recommended for patients with detectable HCV RNA 6 months or more after infection and for patients at greatest risk for progression to cirrhosis (e.g. HCV antibody positive, persistently elevated alanine aminotransferase (ALT), liver biopsy indicating portal or bridging fibrosis or moderate degrees of inflammation and necrosis). Recommendations are less clear in patients with persistently normal ALT and less severe histologic changes or decompensated cirrhosis. In these patients, progression may not occur, is often slow, or patients may not benefit from treatment. Consultation with a specialist is prudent and antiviral therapy may be deferred with careful, clinical follow-up. Follow-up may include a liver biopsy in 5 years to assess progression of fibrosis.[1]

Table 1: NIH/CDC Treatment Recommendations[3]

Should be Considered	*Should not* be Considered	Consider w/ Caution
1a. Persistently elevated ALT levels with histologic changes or 1b. Normal ALT levels with severe (grade ≥ 2) fibrosis and 2a. Detectable HCV RNA ≥ 6 months after infection 2b. Biopsy with portal or bridging fibrosis or moderate Inflammation and necrosis and 3. Compensated liver disease (no active ascites, encephalopathy, or variceal bleeding and 4. Abstinence from alcohol or IVDA for ≥ 6months	1. Pregnant or nursing women 2. Current substance or alcohol abusers 3. Concomitant/Uncontrolled: a. Cytopenias b. Hyperthyroidism c. Renal transplantation d. Evidence of autoimmune disease, other than HIV 4. Some experts assert: Life expectancy < 10 years	1. Prior psychiatric illness 2. Decompensated cirrhosis 3. Persistent ALT elevations, with less severe histologic changes 4. Age < 18 or > 60 yrs

Antiviral Therapy

Ideally, long-term goals include prevention of overt cirrhosis, hepatocellular carcinoma, liver failure and transplantation and improved quality of life. However, because the natural history of chronic HCV infection occurs over decades, the impact of therapy on these outcomes has not been studied.[4] As such, a sustained virologic response (SVR), defined as undetectable HCV RNA 6 months following treatment initiation has become the standard for measuring therapeutic efficacy.

Antiviral therapy has rapidly evolved. Prior to the advent of pegylated interferons (PEG-IFN), treatment consisted of interferon alfa-2b monotherapy and later interferon alfa-2b plus ribavirin (RBV) which produced SVRs from 40-50%.[1, 5, 6] PEG-IFN in combination with RBV is now the standard of care due to improved response rates and dosing convenience. SVRs of PEG-IFN monotherapy range from 25-39%, suggesting it does not have a significant advantage over standard IFN + RBV therapy. However, the combination of PEG-IFN + RBV has resulted in a significant improvement in response.

Three pivotal clinical trials of 3,935 treatment-naïve patients with compensated chronic HCV are described in Table 2. Important results were that several factors predictive of achieving SVR were identified (Table 3). Also evident was that weight-based RBV dosing and 48 weeks of treatment is preferable in patients with genotype 1, whereas RBV 800mg qd and 24 weeks of treatment is sufficient in patients with genotypes 2 and 3.[7] Study differences such as patient demographics, severity or stage of disease, protocols for dose reduction and discontinuation, HCV RNA assays, and RBV dosing prevent definitive comparisons among PEG-IFN brands and ribavirin brands.[8] Head-to-head clinical trials have not been conducted. Comparative costs are shown in Table 4.

Table 3: Factors Predictive of a Sustained Virologic Response

- ♣ Non-Genotype-1 infection
- ♣ Low HCV RNA titers
- ♣ Undetectable or 2-log decrease in HCV RNA at week 12
- ♣ Low hepatic iron stores
- ♣ Absence of cirrhosis or minimal hepatic fibrosis
- ♣ Short duration of disease post-infection
- ♣ Younger age

Safety

Interferon-RBV therapy is not benign. Influenza-like symptoms, nausea, anorexia, depression, anemia and neutropenia are common adverse effects (AE) and may result in the use of complementary alternative medical treatment or antiviral nonadherence. In clinical trials, withdrawals due to AEs (most often depression) ranged from 14-32%. RBV-induced anemia is also problematic. In one trial, the mean decrease in Hgb was 2.5g/L and resulted in 9-13% of withdrawals.[10] The product labeling recommends dose-reduction in the presence of anemia. This reduction has *not* been shown to significantly reduce SVR upon completion of a full treatment course. Interest in the use of hematopoietic growth stimulators (epoetin alfa and filgrastim) is emerging in subpopulations such as in those with cirrhosis and HIV/HCV co-infection. Although published clinical trials currently do not support this practice and it cannot be recommended. Proper identification of good candidates, education and support, and close follow-up is critical.

Conclusion

The current standard of care, PEG-IFN + RBV produces SVRs of 50-80%. It is associated with significant adverse effects and is costly. Treatment may not be appropriate or safe in many individuals. Patient selection should be highly individualized based on the severity of disease, likelihood of response, potential for serious adverse effects, and patient motivation. Education, continued support and close follow-up are critical. Baseline genotyping is used to predict a patient's response to therapy and to determine the duration of therapy. Liver biopsy is used to guide treatment in patients with genotype 1 who are negative for HBV and HIV co-infection or who do not have a history of alcohol abuse. Genotype 1 requires 48 weeks of treatment and RBV doses of 1000-1200mg qd to achieve SVR. Genotypes 2 & 3 are inherently more likely to respond and 24 weeks of interferon-therapy with RBV dose of 800mg qd is sufficient.[13, 14, 15] Evaluation of viral response via quantitative PCR HCV RNA is recommended at 12 weeks as a means of reducing antiviral treatment morbidity and costs.

Because of the complexity of antiviral therapy, patients should be managed under the care of clinicians well-educated and experienced in interferon-based therapy. In remote areas of Oregon, access to trained providers may be problematic. However, through the efforts of the Hepatology section at OHSU, providers in select remote areas have been formally trained in interferon-based therapy to address this need. In January 2004, the Statewide Viral Hepatitis Planning Group (SVHPG) was formed to address HB 2451 which mandates the Department of Human Services to design a plan for statewide education, prevention, and management of Hepatitis C by January 2005. For more information, visit http://www.dhs.state.or.us/publichealth/acd/svhpg/index.cfm .

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Table 2: Pegylated Interferon/Ribavirin Pivotal Trials

Study /Design	Subjects	Duration	Drug Regimens	1˚ Endpoint	% SVR
Manns et al.[14] R, DB, AC	1530 Mean Age: 43y %Male: 65.5 Mean HCVRNA: $2.7x10^6$ Median ALT: $2.3x10^{-6}$ G 1 (68%); G 2,3 (20%); G 4,5,6 (2.9%) Knodell score: 7.9 Bridging fibrosis/cirrhosis: 29%	48 wk	1. PI 1.5 mcg/kg/wk + RBV 800 mg qd (n=511) 2. PI 1.5 mcg/kg/wk x 4 wk, then 0.5mcg/kg/wk x 44wk + RBV 1000-1200mg qd (n=514) 3. IA 3mu tiw + RBV 1000-1200mg qd (n=505)	SVR 24-wk post treatment	Regimen 1 2 3 G 1 42* 34 33 G 2,3 82 80 79 G 4,5,6 50 59 53 Overall: 54* 47 47 * p < .05 for comparison to standard IFN
Fried et al. [9] R, DB, AC	1121 Mean age: 42.5y %Male:70.6 Mean HCVRNA:$6.0 x10^6$ Median ALT:$6.0x10^{-6}$ G 1 (64.9%); G 2,3 (31.6%) G 4,5,6 (3.5%) Bridging fibrosis/cirrhosis: 12.8%	48 wk	1. PS 180mcg/wk + RBV 1000-1200 mg qd (n=453) 2. IA 3mu tiw + RBV 1000-1200mg qd (n=444) 3. PS 180mcg/wk + Placebo qd (n=224) (≤ 75kg: RBV 1000mg, > 75kg: RBV 1200mg)	SVR 24-wk post treatment	Regimen 1 2 3 G 1 46* 36 21 G 2,3 76* 61 45 G 4 77* 36 44 Overall: 56* 44 29 *p< 0.05 for comparison to standard IFN
Hadziyannis, et al.[15] R, DB, AC	1284 Mean age: 42.2y %Male:65 Mean HCVRNA: $5.9x10^6$ Mean ALT:86.5 u/l (divided by upper limit of normal for local laboratory) G 1 (57.6%) G 2,3 (38.3%) Bridging fibrosis/cirrhosis: 25%	24-48 wk	1. PS 180mcg/wk + RBV 800mg qd x 24 wk n=207) 2. PS 180mcg/wk + RBV 1000-1200mg qd x 24wk (n=280) 3. PS 180mcg/wk + RBV 800mg qd x 48 wk (n=361) 4. PS 180mcg/wk + RBV 1000-1200mg qd x 48wk (n=436) (≤ 75kg: RBV 1000mg, > 75kg: RBV 1200mg)	SVR 24-wk post treatment	48 vs. 24 wks of treatment Odds Ratio p G 1 2.19 (1.52-3.16) <0.0001 G 2,3 0.89 (0.56-1.42) >0.2 RBV 1000-1200mg vs. RBV 800mg Odds Ratio p G 1 1.55 (1.14-2.10) 0.005 G 2,3 1.00 (0.63-1.61) >.02

AC=active controlled, DB=double-blind, G=genotype, IA=Intron-A, PI=Peg-Intron, PS=Pegasys, R=Randomized, RBV=ribarivin, tiw=three times/week

Table 4: Cost of Therapy

Generic	Brand	Cost/unit	Dose	Cost/24 wks	Cost/48 wks
Interferon alfa-2b	Intron-A	$43/dose	3 MIU SQ tiw	$3070	$6139
Peginterferon alfa-2b	Peg-Intron	$369/dose $388/dose $407/dose $428/dose	50 mcg SQ qwk 80 mcg SQ qwk 120 mcg SQ qwk 150 mcg SQ qwk	$8859 $9301 $9767 $10,271	$17,717 $18,602 $19,533 $20,541
Peginterferon alfa-2a	Pegasys	$1528/month	180 mcg SQ qwk	$9167	$18,333
Ribavirin	Rebetol	$11/capsule	800-1200 mg qd	$7419 - 11,128	$14,838 - 22,257
Ribavirin	Copegus	$7/capsule	800-1200 mg qd	$4462 - 6693	$8924 - 13,386
Ribavirin	Ribasphere	$19/capsule	800-1200 mg qd	$6673 - 10,009	$13,346 - 20,019
Interferon alfa-2b + Rebetol	Rebetron	$804/ 2 week box	Intron-A 3 MIU SQ tiw + Rebetol 1000mg qd	$9652	$19,304

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