

Management and treatment of hepatitis C: A review

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INTRODUCTION

Hepatitis C virus (HCV) can cause both acute and chronic hepatitis. It is a major public health problem in most countries with a considerable prevalence. In recent years the annual incidence of acute HCV infection has decreased, but chronic HCV infection is the leading cause of liver transplantations (1,2). The prevalence of HCVAb is about 0.1% in Iranian population (3) which increases up to 20% in transfusion-dependent major thalasemic patients (4). The most common subtype of HCV in Iran is 1a with the prevalence of 47% (5). Most of patients with acute HCV infection are asymptomatic or have mild course, jaundice is present in fewer than 25 percent (6). In patients with acute symptoms, it lasts for 2 to 12 weeks. Fulminant hepatic failure following acute HCV infection is very rare, but is more common in patients with underlying chronic hepatitis B virus infection (7,8). Patients with chronic infection are mostly asymptomatic or with nonspecific symptoms. It often has a progressive course and may result in cirrhosis or hepatocellular carcinoma (9).

It has been shown that 55% to 85% of patients who develop acute hepatitis C will remain HCV-

infected. 5 to 20 percent of these patients will develop cirrhosis over 20 to 25 years (10,11). Persons with HCV-related cirrhosis are at risk for developing end-stage liver disease (30% over 10 years) and hepatocellular carcinoma (1-2% per year) (12). However, acute hepatitis C is uncommonly recognized; the majority of patients already have chronic hepatitis C. In persons with persistent infection, after 20 years or more, development of cirrhosis is the main concern. Cirrhosis occurs more often in males, older ages, obese persons, HIV coinfection, those with hepatic steatosis, and those who drink more than 50 grams of alcohol each day (13-15).

Considerations before treatment

Patients should have histologic and virologic evidence of chronic infection (ie, HCV-RNA detectable in serum). Other types of liver disease should also be investigated, and other medical conditions should be evaluated. The threshold for treatment may be increased in the elderly and in patients with only mild hepatitis on biopsy who have unfavorable treatment characteristics (such as genotype 1 and a high viral load). The threshold may be decreased in patients with genotype 2 or 3 and a low viral load. (16,17)

Liver Biopsy: In whom HCV treatment is being considered, a liver biopsy has several advantages.

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Performing routine liver biopsy prior to treatment of chronic HCV has been debated, but most patients undergo liver biopsy. In 2002, NIH stated that a liver biopsy may not be necessary in all patients prior to treatment. For example, a biopsy may not be required prior to treatment of patients with genotype 2 or 3 if other etiologies of liver disease have been ruled out. Liver histology can predict the stage (table 1) and prognosis of the disease. In patients who experience adverse effects, it can assist in decisions on medication adjustment. It can show other concomitant liver diseases including hemochromatosis, alcoholic hepatitis, and hepatic sarcoidosis. Liver biopsy can also be helpful in patients who have had a sustained virologic response to treatment. In cases who do not respond, a repeat liver biopsy is reasonable two years later (16-19).

Table 1. Histological scoring systems: Ishak and Metavir system (P-P=portal-portal, P-C=portal-central)

System	Stage	Definition
Ishak	0	No fibrosis
	1	Fibrous expansion of some portal areas, with or without short fibrous septa
	2	Fibrous expansion of most portal areas, with or without short fibrous septa
	3	Fibrous expansion of most portal areas, with occasional P-P bridging
	4	Fibrous expansion of portal areas, with marked bridging (P-P or P-C)
	5	Marked bridging (P-P or P-C) with occasional nodules (incomplete cirrhosis)
	6	Cirrhosis
Metavir	0	No fibrosis
	1	Periportal fibrosis expansion
	2	P-P septa (>1 septum)
	3	P-C septa
	4	Cirrhosis

Guidelines (Selection of patients for treatment)

The guidelines were revised in 2002 to include a broader range of potentially eligible patients (11). Guidelines issued by the American Association for the Study of Liver Diseases (AASLD) are consistent with the NIH guidelines but provide additional details.

1- National Institutes of Health (NIH)

It recommends that all patients with chronic hepatitis C are candidates for antiviral therapy. Treatment should be recommended for patients characterized by the presence of measurable HCV, a liver biopsy showing portal or bridging fibrosis, and at least moderate inflammation and necrosis (11).

2- American Association for the Study of Liver Diseases (AASLD)

The AASLD recognizes three categories of patients: those in whom therapy is widely accepted, those in whom therapy should be individualized, those in whom therapy is contraindicated (20). (Table 2)

3- American Gastroenterological Association (AGA)

Persons with a reactive enzyme immunoassay for antibody to HCV, the presence of HCV RNA, and compensated liver disease are potential candidates for antiviral therapy (21,22). Currently, antiviral therapy is not recommended routinely for patients with hepatic decompensation; patients with a history of severe, uncontrolled psychiatric disorder; and/or patients with severe hematologic cytopenia. All candidates for antiviral therapy should be tested for HCV-RNA with a quantitative amplification assay and should be tested for HCV genotype. Patients in whom antiviral therapy is being considered are candidates for liver biopsy, the gold standard for determining histologic grade and stage, unless the potential for complications is unacceptably high. For patients with moderate to severe fibrosis (Ishak stage 3, METAVIR stage F2), antiviral therapy is recommended uniformly. For patients with milder histologic disease, progression may be sufficiently slow to justify monitoring without imminent therapeutic intervention in a proportion of these patients. For patients with genotypes 2 and 3, the likelihood of response is so high that the benefits of treatment may outweigh the importance of histologic considerations.

Table 2. AASLD categorization for treatment of HCV

Therapy is widely accepted	<ul style="list-style-type: none"> • At least 18 years of age • Abnormal ALT values • Liver biopsy showing chronic hepatitis with significant fibrosis (more-than-portal fibrosis: Metavir score 2; Ishak score 3) • Compensated liver disease (total serum bilirubin 1.5 g/dL; INR 1.5; albumin 3.4 g/dL; platelet count 75,000 k/mm³; and no evidence of hepatic encephalopathy or ascites) • Acceptable hematological and biochemical indices (hemoglobin 13 g/dL for men and 12 g/dL for women; neutrophil count 1.5 k/mm³; creatinine 1.5 mg/dL) • Treated previously for HCV infection • History of depression but the condition is well controlled • Willing to be treated and to conform to treatment requirements
	<ul style="list-style-type: none"> • Persistently normal ALT values • Failed prior treatment (nonresponders and relapsers) consisting of either interferon given alone or in combination with ribavirin, or consisting of peginterferon given alone • Current users of illicit drugs or alcohol but willing to participate in a substance abuse program (such as a methadone program) or alcohol support program • Liver biopsy evidence of either no or only mild fibrosis (portal fibrosis: Metavir score 2; Ishak score 3) • Acute hepatitis C • Coinfected with HIV • Under 18 years of age • Chronic renal disease (on or not on hemodialysis) • Decompensated cirrhosis • Liver transplantation recipient
Therapy should be individualized	
Therapy is contra-indicated	<ul style="list-style-type: none"> • Major, uncontrolled depressive illness • Renal, heart, or lung transplantation recipient • Autoimmune hepatitis or other condition known to be exacerbated by interferon and ribavirin • Untreated hyperthyroidism • Pregnant or unwilling/unable to comply with adequate contraception • Severe concurrent disease such as severe hypertension, heart failure, significant coronary artery disease, poorly controlled diabetes, obstructive pulmonary disease • Under 3 years of age • Known hypersensitivity to drugs used to treat HCV

Treatment of chronic HCV

Treatment objectives

It has been suggested that treatment may result in reducing progression of fibrosis and delaying evolution to cirrhosis. It has also been shown that despite an absence of virologic response to treatment, histological improvement can occur (23, 24). In treated patients who fail to clear virus, development of cirrhosis and hepatocellular carcinoma (25,26) may be decreased (table 3).

Table 3. Definition of treatment responses

Response	Time assess	to Definition	Implication
RVR	4 wk	HCV RNA undetectable by PCR or TMA	Higher chance of SVR; may respond or as well with only 24 wk of treatment
EVR	12 wk	HCV RNA decreased by \geq two logs from baseline	Failure to achieve SVR and treatment or HCV RNA can usually be undetectable stopped
ETR	End of treatment	HCV RNA undetectable by PCR or TMA	On treatment response; observe
SVR	24 wk after treatment	HCV RNA undetectable by PCR or TMA	Eradication of virus

RVR: Rapid viral response; PCR: Polymerase chain reaction; TMA: Transcription-mediated amplification; SVR: Sustained virologic response; EVR: Early virologic response; ETR: End-of-treatment response

Initial treatment

Standard interferon

Alpha interferons have been extensively prescribed in treatment of chronic B, C, and D. IFN is directly antiviral to all of these viruses, but the exact mechanism of action of IFN in these infections is unknown. In HBV treatment, it appears to stimulate a cellular immune response. Interferons may have effects on the cytokine cascade, and so may have antiinflammatory

properties (27). In patients with chronic HCV, it improves liver tests, reduces the level of HCV-RNA, and decrease hepatic inflammation on liver biopsy (28). Alpha subtypes include (treatment outcomes seem to be similar with the different types):

Interferon alfa-2b: For HCV treatment, it has been approved at a dose of 3 MU (million units) subcutaneously three times weekly for 24 months and 12 months in the United States and the European Union, respectively (29). Compared to control groups, Interferon alfa-2b has resulted in greater biochemical ETR (47% versus 4%), virologic ETR (29% versus 5%), and histologic response (73% versus 38%) (30).

Interferon alfa-2a: It differs from interferon alfa-2b by a single amino acid. For HCV treatment, it has been approved at a dose of 3 MU subcutaneously three times weekly for 12 months in the United States. While, the dose approved by the European Union is 3-6 MU subcutaneously or intramuscularly three times weekly for six months, followed by 3 MU three times weekly for six months (29). It has similar effects as interferon alfa-2b in the treatment of chronic HCV infection (31).

Interferon alfacon-1 or consensus interferon: It is a non-natural recombinant interferon. It is approved in the United States at a dose of 9 µg subcutaneously three times per week for 6 months. The dose for non-responders or relapsers is 15 µg three times per week for 6 months (29).

Interferon alfa-n1: It is a combination of nine interferon subtypes. It has been approved by the European Union at a dose of 5 MU subcutaneously or intramuscularly three times weekly for 48 weeks (but not in the United States) (32).

Pegylated interferon

Peginterferons are produced by binding of the polyethylene glycol moiety to interferon molecules. The attachment of polyethylene glycol to a protein (pegylation) results in reduced absorption following subcutaneous injection, reduced renal

and cellular clearance, and decreased immunogenicity of the protein. All of these effects tend to enhance the half-life of the pegylated versus the native protein. On the other hand, pegylation may also interfere with the ability of a protein to bind to its receptor thereby decreasing its biologic effect. Thus, the true biologic effect of the pegylated protein is determined by the balance of these competing properties (33-37). Due to its prolonged half life, it can be administered once weekly by subcutaneous injection. There are two peginterferon formulations, the alfa-2b (12-kd) and the alfa-2a (40-kd) (38). Pegylated interferon has largely replaced standard interferon in the treatment of chronic hepatitis C.

Pegylated interferon monotherapy has a role in patients who cannot tolerate ribavirin (such as patients with renal failure, hemoglobinopathies, or those who develop severe anemia while on therapy).

Side effects

Side effects are neutropenia, thrombocytopenia, depression, hypothyroidism and hyperthyroidism, irritability, concentration and memory disturbances, visual disturbances, fatigue, muscle aches, headaches, nausea and vomiting, skin irritation, low-grade fever, weight loss, insomnia, hearing loss, tinnitus, and interstitial fibrosis and hair thinning. Flu-like symptoms and depression appeared to occur more frequently with peginterferon alfa-2a (39). These side effects, which found in approximately 75% of patients, are more severe in the first weeks of treatment. They can be managed with analgesics (acetaminophen or nonsteroidal anti-inflammatory drugs), antidepressants (serotonin uptake inhibitors) or growth factors. Currently, routine administration of growth factors in order to prevent side effects of interferon alfa and ribavirin is not recommended (20,39).

Ribavirin

Ribavirin is a nucleoside analog which has antiviral activity. It inhibits the replication of RNA

viruses in cell culture. In a dose-dependent manner, it appears to decrease hepatitis C virus infectivity (40). Ribavirin has been used in treating RNA virus infections. However, it is ineffective in eliminating HCV RNA, although it may reduce HCV RNA levels in some patients (41). In combination with standard or pegylated interferon alfa, it improves the rate of SVR (42-44).

Side effects

It is generally well tolerated. Side effects are hemolytic anemia, fatigue, depression, itching, insomnia, vertigo, anorexia, nausea, rash, sinusitis, birth defects, or gout. Using contraception methods is mandatory during treatment and for a period of 6 months after treatment. Anemia (hemoglobin <10g/dL) requiring dose reduction occurs in 10 to 15 percent of patients. The hemolysis is reversible

after discontinuing the drug (45-47).

Other medical therapies

Combination therapy for 12 weeks with telaprevir, peginterferon alfa-2a and ribavirin produced better virologic response at weeks 4 and 12 compared with standard peginterferon alfa-2a/ribavirin combination therapy in treatment-naïve patients with chronic HCV genotype 1 infection (Telaprevir an investigational oral inhibitor of HCV NS3/4 A protease.) Based on previous trials, phlebotomy (48,49), Amantadine (50-54), or interleukin-10 (55) has shown to be of no benefit.

Alternative therapy

Alternative and complementary medicine (such as natural and herbal preparations) have no role in the treatment of chronic hepatitis C (21,22).

Table 4. Drugs used in the treatment of chronic hepatitis C

	Generic (Trade Name)	Recommended Dose
Combination peginterferon regimens with ribavirin	<i>Peginterferon</i> Peginterferon alfa-2a (40 kd) (Pegasys, Hoffmann-La Roche, Nutley, NJ)	180 µg SQ once weekly regardless of weight
	Peginterferon alfa-2b (12 kd) (Peg-Intron, Schering-Plough Corporation, Kenilworth, NJ)	1.5 µg/kg SQ once weekly
	<i>Ribavirin</i> (Rebetol, Schering-Plough Corporation, Kenilworth, NJ; Copegus, Hoffmann-La Roche)	800–1200 mg PO daily (in 2 divided doses), dose depending on infection, genotype, and patient weight
Regimens used in certain clinical circumstances	<i>Peginterferon alfa-2a</i> (40 kd) (Pegasys) as monotherapy	180 µg SQ once weekly regardless of weight
	<i>Peginterferon alfa-2b</i> (12 kd) (Peg-Intron) as monotherapy	1.0 µg/kg SQ once weekly
	<i>Interferon alfa-2b + ribavirin</i> (Rebetron, Schering-Plough Corporation)	Interferon alfa-2b SQ 3 mU t.i.w. Ribavirin 1,000 mg PO daily ≤75 kg or 1,200 mg daily if >75 kg (in 2 divided doses)
	<i>Interferon alfa-2a</i> (Roferon-A, Hoffmann-La Roche)	3 mU SQ t.i.w.
	<i>Interferon alfa-2b</i> (Intron-A, Schering-Plough Corporation)	3 mU SQ t.i.w.
	<i>Interferon consensus</i> (Infergen, InterMun, Brisbane, CA)	9 µg SQ t.i.w.; 15 µg t.i.w. in nonresponders

Abbreviations: kd, kilodaltons; µg, micrograms; SQ, subcutaneously; kg, kilograms; mU, million units; t.i.w., three times per week; PO, per mouth; mg, milligrams.

Table 5. Recommended thresholds for drug dose reductions in patients treated with PEG-IFN and ribavirin for chronic hepatitis C

Hematologic threshold	Dose reduction ^a
Absolute neutrophil count (/mm ³)	
500-750	Reduce PEG-IFN dose ^b
<500	Withhold PEG-IFN
Platelet count (/mm ³) ^c	
25,000-50,000	Reduce PEG-IFN dose ^c
<25,000	Withhold PEG-IFN
Hemoglobin (g/100 mL)	
≤10	Reduce ribavirin dose ^d
≤8.5	Discontinue ribavirin ^d

► These recommendations may be useful in monitoring therapy but do not represent absolute guidelines; those who treat patients with chronic hepatitis C rely on discretion and close monitoring of their patients. Attempts can be made to reinstitute therapy or to resume full/higher-dose therapy after cytopenias improve or resolve.

► *a* The magnitude of dose reductions differs between the 2 PEG-IFN preparations, as noted in the following footnotes.

► *b* For PEG-IFN alfa-2b, reduce dose by 50%; for PEG-IFN alfa-2a, reduce dose to 135 µg.

► *c* The platelet thresholds cited appear in the product insert for PEG-IFN alfa-2a (dose reduction to 90 µg); in the product insert for PEG-IFN alfa-2b, the platelet threshold for dose reduction is 80,000/mm³ (dose reduction 50%) and for drug discontinuation is 50,000/mm³.

► *d* For PEG-IFN alfa-2b, a dose reduction of 200 mg is recommended; for PEG-IFN alfa-2a, reducing the dose to 600 mg/day is recommended.

Alternatively, erythropoietin can be administered.

Treatment duration

The decision about discontinuation of therapy is based on the toleration of therapy, the severity of the underlying liver disease, and degree of biochemical or virologic response. Quantitative HCV RNA should be determined before the initiation of therapy and at week 12. In patients with genotype 1 who do not achieve an early virologic response (at least a 2-log decline from baseline of the HCV RNA level) at week 12, treatment can be discontinued (20).

According to a previous study (patients in the 4 groups received either 24 or 48 weeks of ribavirin at doses of either 800 mg or the higher, weight-based dose of 1,000 or 1,200 mg daily plus peginterferon alfa-2a at a dose of 180 µg), in patients with genotype 1 with low-level viremia (≤2x10⁶ copies/mL), the SVR was highest in

those who had received the higher ribavirin dose (1,000 or 1,200 mg daily) and who were treated for 48 weeks (61 percent). This regimen was also optimal for patients with genotype 1 and a high viral load: 46 percent achieved an SVR. In contrast, in patients with genotype 2 or 3, regardless of the pretreatment viral load, no differences were detected between groups, suggesting that peginterferon alfa-2a plus ribavirin at a dose of 800mg given for 24 weeks is adequate (56,57).

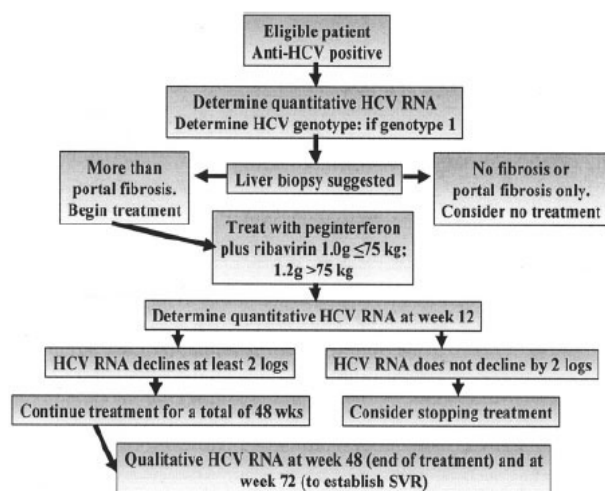
Response to treatment

In addition to compliance, several patient and viral characteristics have been associated with the likelihood of response. Genotype of HCV is the strongest predictor of response (higher response in genotypes 2 and 3 compared with 1). In one hand, based on studies of peginterferon alfa-2b and ribavirin, SVR were higher in patients who had genotype-2 or genotype-3, lower pretreatment HCV RNA levels (a baseline viral load ≤2 X 10⁶ copies/mL [approximately 800,000 IU/mL]), younger ages, lower body weights, and absence of bridging fibrosis, cirrhosis or significant (>33%) steatosis (23,39,56). On the other hand, in patients who were treated with peginterferon alfa-2a together with ribavirin, the independent variables associated with an SVR included genotype non-1, age less than 40 years, and body weight less than 75 kg (39). SVR rate in genotype-1 infections were 42-46%, while in genotype 2 or 3 were 76-82% (23,39). Several studies have demonstrated that the likelihood of achieving a SVR can be predicted based upon the change in viral load during the course of treatment (23,39,58-61). For example, it has also been shown that a high viral load (>2x10⁶ copies/mL, equivalent to ≈800,000 IU/mL) will influence the SVR as well. In the study of peginterferon alfa-2a with ribavirin, 65% of patients with an EVR subsequently achieved an SVR (39). In another study that used peginterferon alfa-2b together with ribavirin, 72 percent ultimately achieved an SVR (59).

AASLD recommended treatment

Genotype-1: Peginterferon plus ribavirin (1,000 mg for those ≤ 75 kg in weight and 1,200 mg for those more than 75 kg) for 48 weeks. Quantitative serum HCV RNA should be performed at the initiation of treatment and at week 12. Treatment may be discontinued in patients who do not achieve an EVR at 12 weeks. Persons whose treatment continues through 48 weeks, and whose qualitative measurement of HCV RNA at that time is negative, should be retested for HCV RNA 24 weeks later to document an SVR (figure 1).

Figure 1. Management and treatment of HCV genotype-1

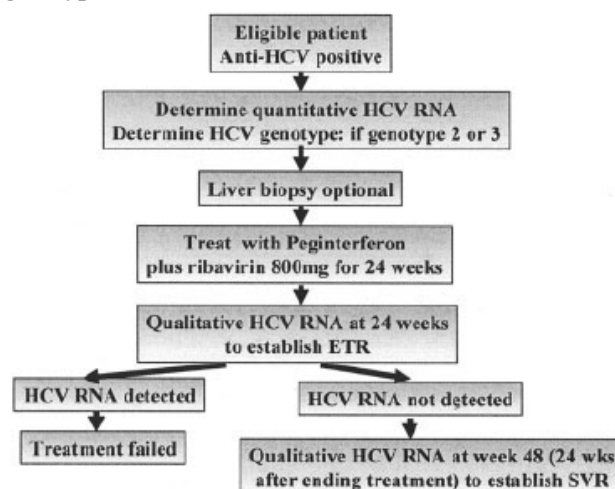


Genotype-2 or 3: Peginterferon plus ribavirin (800 mg) for 24 weeks. Persons whose treatment continues for the full 24 weeks, and whose qualitative measurement of HCV RNA at that time is negative, should be retested for HCV RNA 24 weeks later to document an SVR (figure 2).

Retreatment

Partial responders: In these patients factors associated with a higher likelihood of response to retreatment included genotype non-1, lower baseline HCV RNA levels, lesser degrees of fibrosis, and Caucasian race (62).

Figure 2. Management and treatment of HCV genotype-2 or 3



Nonresponders: In 25-40% of patients who did not to respond to monotherapy with interferon alfa and in 10% who failed to respond to interferon alfa and ribavirin, will respond to retreatment with peginterferon alfa and ribavirin (62).

Relapsers: These patients generally respond to retreatment. Genotypes 2 and 3 and a low HCV RNA load are favorable predicting factors. About 50% of relapsers following a regimen of interferon without ribavirin, almost will respond to retreatment with interferon alfa and ribavirin for 24 weeks (63).

Recurrence after transplantation: Recurrence correlates with HCV RNA levels at the time of transplantation, the age of the organ donor, and the degree of immunosuppression in the post-transplant period. The risk of progression and complications is higher in post-transplant HCV patients with cirrhosis compared to immunocompetent patients with cirrhosis (64).

AASLD recommends that retreatment with peginterferon plus ribavirin should be considered for nonresponders or relapsers who have significant fibrosis or cirrhosis and who have undergone previous regimens of treatment using nonpegylated interferon (20).

NIH states that 15-20% of nonresponders treated with interferon-ribavirin combinations achieved an SVR on retreatment using pegylated interferon with ribavirin. NIH recommends that decisions regarding retreatment should be based on: previous type of response, the previous therapy and the difference in potency of the new therapy, the severity of the underlying liver disease, viral genotype and other predictive factors for response, and tolerance of previous therapy and adherence. For the retreatment of patients with intermediate degrees of fibrosis (bridging fibrosis or cirrhosis with minimal disease activity), clinicians should consider the factors enumerated above in determining whether or not to retreat. Patients with advanced fibrosis or cirrhosis have an increased risk of hepatic decompensation and should be considered for retreatment, especially if they were originally treated with interferon monotherapy (64).

Treatment of other patient populations (special groups)

Acute hepatitis C: Acute HCV infection is usually asymptomatic and clinically inapparent (65-67), and patients who do have symptoms are more likely to resolve spontaneously (65,68). The diagnosis of acute hepatitis C in patients with new-onset, unexplained liver disease should be confirmed by measuring HCV RNA in serum (20). It has been recommended that for those with symptomatic acute hepatitis, treatment should be delayed for the first 12 weeks to permit spontaneous resolution and avoid unnecessary treatment, but for those with asymptomatic hepatitis, treatment should begin as early as possible (69). Moreover, many authorities would initiate treatment within no later than 2-3 months after the onset of acute hepatitis and would extend combination therapy for at least 24 weeks (70). Although interferon monotherapy has been associated with satisfactory outcomes in previous

studies, it is appropriate to consider the use of peginterferon because of its improved ease of administration (20).

Children: Children are less likely to progress to end-stage liver disease, less likely to have symptoms, more likely to have spontaneous viral clearance, and more likely to have normal or near-normal aminotransferase values (71-75). Characteristic histological findings are the same as in adults (76-78). Periportal fibrosis occurs in around 70% of children (76,78). Based on previous studies, the FDA has approved the use of interferon alfa-2b 3MU/m² plus ribavirin (Rebetron) 15mg/kg for the children (79-82). Children tolerate interferon well without overt serious adverse effects (83,84). New HCV infections in children are primarily the result of vertical (perinatal) transmission and the risk of HCV transmission at the time of delivery is 1-5% (85). AASLD recommends that treatment of children under the age of 3 years is contraindicated (20).

Normal serum aminotransferase: These patients generally have less severe liver disease (86,87). Biopsies have revealed bridging fibrosis or cirrhosis in 1-10% of cases, and at-least-portal fibrosis in a greater proportion (88-90). The response rate to interferon alfa and ribavirin appears to be similar to patients with abnormal values (91). The decision to initiate therapy with interferon and ribavirin should be individualized based on the severity of liver disease by liver biopsy, the potential of serious side effects, the likelihood of response, and the presence of comorbid conditions (20).

Renal disease: In one hand, patients with renal disease are at increased risk of acquiring HCV; and hepatitis C is also the most common liver disease in renal dialysis patients. On the other hand, HCV has been associated with cryoglobulinemia that may lead to membranoproliferative glomerulonephritis (92). HCV has also an adverse effect on survival after renal transplantation (93-96). Although there is a theoretical increased risk

of bleeding following liver biopsy in patients on hemodialysis, but side effects have rarely been reported (97, 98).

In patients with HCV-induced glomerulonephritis not on dialysis, HCV-infected patients on hemodialysis, patients with mild renal disease and superimposed HCV infection, or peri- or post-renal transplantation infected patients, treatment of HCV should be considered (20). Ribavirin is not recommended in persons with creatinine clearances of less than 50 mL/min. Moreover, it is contraindicated in this group because the drug is not removed during conventional dialysis and leads to hemolytic anemia (that correlates with baseline creatinine clearance) (99-101). For patients on hemodialysis, treatment with peginterferon alfa-2a monotherapy at a dose of 135 µg SQ/wk may be considered, with close monitoring for interferon toxicity (20,102-108).

Cirrhosis: In patients with compensated HCV-related cirrhosis with preserved hepatic synthetic function and sufficient platelet and white blood cell counts, hepatitis C antiviral therapy is clearly indicated. In contrast, in patients with decompensated cirrhosis who have clinical complications of liver chronic disease (such as ascites, encephalopathy, bleeding from varices secondary to portal hypertension, or impaired hepatic synthetic function), thrombocytopenia or leukopenia, therapy is dangerous because of the increased likelihood of life-threatening infection. Moreover, treatment might accelerate hepatic decompensation. Liver transplantation is the treatment of choice for these patients (109-111). Therefore, antiviral therapy may be initiated at a low dose in patients with only mild degrees of hepatic compromise. In cases of anemia or leucopenia following treatment, growth factors such as epoetin or G-CSF/GM-CSF can be used to limit the need for antiviral dose in these patients (20).

HIV coinfection: Before HCV treatment of HIV/HCV-coinfected patients, HAART is usually

initiated to stabilize CD4⁺ count. However, patients with advanced liver disease or intact immune system (ie. high CD4⁺ counts and no history of opportunistic infection) might require HCV treatment first to prevent hepatotoxicity from HIV treatment (112).

These patients have high risk of cirrhosis and rapid course of liver disease (113,114). All HIV-infected persons should be tested for HCV, but around 6% of them do not show HCV antibodies. So, in HIV-positive patients with unexplained liver disease and negative HCV-antibody, HCV RNA should be tested (115,116). Making decision for treatment of HIV/HCV coinfecting person is based on the results of the liver biopsy and the stage of HIV infection. Patients with decompensated liver disease should be considered for liver transplantation (117).

Possibility of achieving an SVR is lower in HIV/HCV-coinfecting persons. Data from previous studies show that SVR rates are higher in patients receiving peginterferon alfa (alfa-2a or alfa-2b) and ribavirin than standard interferon alfa and ribavirin. Most existing studies have treated HIV-infected persons for 48 weeks (118,119). Interferon alfa therapy causes a dose-related reduction in the white blood cell count and the absolute CD4⁺ lymphocyte count, but the percentage of CD4 cells remains essentially unchanged, and its use is not associated with the development of opportunistic infections (120-123). As a result of limited myeloid reserves in HIV patients, anemia is a greater problem with ribavirin (124). Ribavirin also potentiates didanosine anti-HIV activity and increases toxicity (125,126). Fatal hyperlactatemia have been also reported (126). Although clinically important interactions have not been shown between ribavirin and zidovudine, zalcitabine, or stavudine, these patients should be carefully monitored (121,122,127). HCV infection increases the risk of hepatotoxicity from highly active antiretroviral therapy (128). There are no FDA-approved medications for the treatment of hepatitis C in HIV-infected persons.

Alcoholism: Alcoholism has been shown to be associated with progressive liver disease in patients with chronic hepatitis C (65,129-132). Excessive alcohol use reduces the likelihood of a response to therapy (133-136). Therefore, treatment is not recommended for patients who were not abstinent from alcohol for at least 1–2 years; and alcoholism has been considered as a contraindication to antiviral therapy (1). National Institutes of Health stated that 1)abstinence should be recommended before and during antiviral treatment because continued alcohol abuse affects the response to therapy adversely, 2) treatment of alcohol abuse should be linked with efforts to treat hepatitis C in alcoholic patients, 3) even moderate alcohol consumption can have a deleterious effect on the progression of liver disease in patients with chronic hepatitis C (64,134).

Injection drug users: Illicit injection drug use is the predominant mode (60%) of HCV transmission (68). Methadone use does not directly influence the management of HCV infection (137,138). Based on AASLD recommendations, treatment should not be withheld from those who currently use illicit drugs or those on a methadone maintenance program provided that they wish to be treated and are willing and able to maintain close monitoring and practice contraception. Additionally, the decision of whether to treat should be made considering the anticipated risks and benefits for the individual (20).

Thalassemia: Hepatitis C infection can intensify the progression of liver disease caused by iron overload in thalassemic patients (139). Studies show that around 12-75% of these patients are infected with HCV virus (140). In these patients, chronic anemia is a contraindication for antiviral regimens and ribavirin-induced hemolytic anemia should be considered (6,70). For thalassemic patients with substantial hemosiderosis, iron overload should be treated before antiviral therapy. Based on a study (but with small number of cases), interferon and ribavirin combination therapy has

resulted an SVR rate equal to 72% in these patients (141).

Hemophilia: Response rates to interferon monotherapy or interferon and ribavirin combination therapy has been reported to be similar to or lower than those in the nonhemophiliac population (142-150). No clinical trial has been done on the use of peginterferon and ribavirin combination therapy. The duration of therapy should be guided by genotype. Liver biopsies can be done safely by experienced teams working. Treatment should be adapted from the nonhemophiliac population (149,151).

Conclusion

Chronic hepatitis C is a potentially progressive disorder that may progress to cirrhosis and hepatocellular carcinoma. Significant morbidity and mortality from its complications have made it as a global health problem. Treatment of chronic hepatitis C has always been under debate. Based on clinical research in this area, new recommendations appear with increasing frequency. Over the past decades, antiviral therapy for this infection has progressed considerably. Described above was a review on the currently acceptable recommendations on diagnosis, selection of patients for treatment, and the recommended treatments of patients with hepatitis C infection. However, these guidelines should be updated in the future as additional information becomes available.

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