

Current Standards in the Pharmacotherapy of Chronic Hepatitis C and Local Practices

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Abstract

In the recent past, many landmark studies have come up that have substantially increased our knowledge and understanding on multiple issues related to hepatitis C pharmacotherapy. In this article, current evidence and state-of-the-art standards of chronic hepatitis C management are given followed by few suggestions for local practice. For this article, a search was made on the PubMed and Pakistan Medinet on 15/April/2008 using the keywords of 'Hepatitis C', 'Antiviral Therapy', 'Consensus Statement', and 'Guidelines'. American¹¹, Canadian¹ and Pakistani guidelines for the diagnosis and management of chronic hepatitis C were consulted.

Key Words

Chronic Hepatitis C. Antiviral Therapy. Treatment. Consensus Statement. Guidelines.

Introduction

Hepatitis C virus (HCV) HCV infection is the commonest blood-borne infection. According to World Health Organization (WHO) estimates approximately 170 million people are infected with HCV the world over¹. Although, there are no large-scale representative studies to know the true prevalence of hepatitis C in our country, based on an average seroprevalence of 6%, it is estimated that about 10 million subjects are infected with HCV in Pakistan². Some smaller studies have, however, reported a population prevalence of 16% from Lahore and 23.8% from Gujranwala³. HCV infection has already become the commonest cause of chronic liver disease and hepatocellular carcinoma, and the single most common reason for liver transplantation the world over⁴.

Objectives and Outcomes of Hepatitis C Pharmacotherapy

Eradication of HCV RNA, histologic improvement and thus prevention of complications of HCV are the main aims of antiviral treatment.

Definition of Treatment Responses:

Refer to table 1⁵.

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Table 1: Definitions of Treatment Responses:

Rapid virologic response (RVR)	Qualitative HCV RNA assay done at week 4 comes out to be negative (<50IU/mL)
Early virologic response (EVR)	Negative quantitative HCV RNA assay at 12 weeks: § Early virologic clearance (EVC) or aviremic response § Decline in HCV RNA titre (compared with pre-treatment assay) of > 2 log – called partial virologic response (PVR) or viremic response
Nonresponders	No decline in HCV RNA titre (compared with the pre-treatment assay) or a decline of < 2 log in quantitative HCV RNA assay at 12 weeks
End of treatment response (ETR)	Negative qualitative HCV RNA assay done on completion of the recommended duration of the course
Sustained virologic response (SVR)*	Negative qualitative HCV RNA assay done 24 weeks after completion of the recommended duration of the course
Relapsers	Negative qualitative HCV RNA assay done on completion of the recommended duration of the course, but turns positive 24 weeks after end-of-treatment assay.

**Achievement of SVR is generally considered as the marker of eradication. Almost all such patients show EVC or RVR on 12 weeks assay.*

The Current Standards in HCV Therapy

In all first world consensus statements / guidelines, peginterferon-ribavirin combination therapy (table 2^{5,6}) is now considered the standard drug regimen in all cases of HCV infection unless some special considerations like associated kidney disease etc warrants instituting some different regimen^{5,7,8}. In peginterferon, an inert polyethylene glycol moiety is inserted into the interferon molecule. This causes a decrease in renal clearance and thus an increase in the plasma half life (80 hrs) of the peginterferon molecule⁹. Because of the prolonged half life pegylated interferons are administered once weekly whereas the non-pegylated interferons need to be administered thrice weekly.

In multiple large, randomized, controlled trials, peginterferon-ribavirin combination therapy has proved therapeutically superior

(higher sustained virologic response rates achieved) compared to non-pegylated interferon-ribavirin combination therapy, and peginterferon monotherapy^{10,11}. The two formulations of peginterferon currently available are peginterferon alpha-2a and 2b. They differ in the size and configuration of the polyethylene glycol moiety attached to the interferon molecule. Although the two peginterferon formulations have not yet been compared head-to-head in the published controlled trails, they are generally believed to be equivalent therapies and thus can be used interchangeably.

Current standards in the management of genotypes 2, 3 and 1 are summarized in table 2^{5,6}. With the standard treatment, sustained virologic response (SVR) rates of 42-46% for genotype 1 and 72-80% for genotypes 2 and 3 have been reported¹²⁻¹⁴.

Although more data and experience are needed to establish definite protocols regarding genotypes 4, 5 and 6, current evidence is to treat them as genotype 1 cases⁵. The SVR rates achieved in these cases fall in between those of genotypes 1, 2 and 3 i.e. 40-79%¹⁵⁻¹⁷. In patients with good prognostic signs i.e. hepatic fibrosis of 2 Metavir score and a pretreatment viral load of <800,000 IU/mL, treatment duration can be shortened to 36 weeks with results comparable to the standard 48 weeks therapy¹⁸.

Table 2: Peginterferon-Ribavirin Combination Regimen: The current standard^{5,6}:

Drug:	
Peginterferon alfa-2a (40 kd)ⁱⁱⁱ (Inj Pegasys 180 µg)	180 µg SQ once weekly regardless of the weight
Peginterferon alfa-2b (12 kd)^{iv} (Inj Peg-Intron 50/80/100/120/180 µg)	1.5 µg/kg SQ once weekly
Ribavirin^v	<i>Genotype 1:</i> Higher weight-adjusted dosage has shown better response rates (1000mg if < 75kg ^{vi} orally in two divided doses; 1200mg if >75kg) ^{vii} . <i>Genotype 2 and 3:</i> Higher dosage has not been shown in published studies to be consistently associated with better response rates. Therefore, 800mg/day orally in two divided doses is the current choice dosage regardless of the weight ^{viii} .

Abbreviations:

kd, kilodaltons;
µg, micrograms;
SQ, subcutaneously;
kg, kilograms;
mg, milligrams.

Summary of Current Standards in the Management of Genotypes 2 and 3

HCV RNA Assay:

Week 4 qualitative HCV RNA assay^{ix}

Negative assay (<50IU/mL)
i.e. a case of RVR

Positive assay

Week 24 qualitative HCV RNA assay:

Negative assay i.e. a case of ETR

Positive assay

Week 48 qualitative HCV RNA assay:

Negative assay i.e. a case of SVR

Positive assay i.e. a case of relapse

Recommendations as per the PCR results:

Shorten the standard treatment course of 24 weeks to 12-16 weeks.
Ribavirin is given at higher weight -adjusted dosage in the short courses (1000mg if ≤75 kg orally in two divided doses; 1200mg if >75 kg)^{x,x1}

Give treatment for the standard duration of 24 weeks^{xii} (may be 36-48 weeks)

Successful therapy. Needs a repeat qualitative HCV RNA assay at week 48 (24 weeks after ETR) to establish SVR.

Treatment failed

HCV infection is eradicated

Previously treated with non-pegylated interferon:
Treat with peginterferon and ribavirin.
If EVR is not achieved at week 12, stop treatment.

Previously treated with pegylated interferon:
Retreatment is not indicated even if a different type of peginterferon is administered. Consensus interferon has shown to improve responses in such cases, but it is too premature to recommend it.

Summary of Current Standards in the Management of Genotypes 1 Cases:

HCV RNA Assay:

Week 4 qualitative HCV RNA assay:

Negative assay (<50IU/mL) i.e. a case of RVR

Positive assay

Week 12 qualitative HCV RNA assay:

Negative assay i.e. a case of EVC

Recommendations as per the PCR results:

Predictors of poor response^{xiii} absent:
Shorten the treatment duration to a total of 24 weeks^{xiv,xv}

Predictors of poor response present:
Give treatment for the standard duration of 48 weeks
Continue treatment and repeat HCV RNA at 12 weeks

Continue treatment for a total of 48 weeks

HCV RNA fall by > 2 logs i.e. a case of PVR	Repeat qualitative HCV RNA at 24 weeks.
HCV RNA fall by < 2 logs i.e. a case of non-responder	Stop treatment
Week 24 qualitative HCV RNA assay (only done in cases which show PVR at week 12 assay): Negative assay (this subgroup is called 'slow responders')	Continue treatment for a total of 48-72 weeks. 72 weeks therapy has generally shown superior results as compared to 48 weeks therapy in slow responders 19-21.
Positive assay	Stop treatment as probability of attaining SVR is negligible
Week 48 qualitative HCV RNA assay: Negative assay i.e. a case of ETR	Successful therapy. Needs a repeat qualitative HCV RNA assay at week 72 (24 weeks after ETR) to establish SVR
Positive assay	Treatment failed
Week 72 qualitative HCV RNA assay: Negative assay i.e. a case of SVR Positive assay i.e. a case of relapse	HCV infection got eradicated <i>Previously treated with non-pegylated interferon:</i> Treat with peginterferon and ribavirin. If EVR is not achieved at week 12, stop the treatment <i>Previously treated with pegylated interferon:</i> Retreatment is not indicated even if a different type of peginterferon is administered. Consensus interferon has shown to improve responses in such cases, but it is too premature to recommend it.

- i Peginterferons are therapeutically superior to non-pegylated interferons.
- ii Because of the lack of randomized control trials, currently there is no data available to assess the relative efficacies of the two interferons. Thus both are recommended interchangeably.
- iii Peginterferon-ribavirin combination therapy is therapeutically superior to peginterferon monotherapy as well as non-pegylated interferon-ribavirin combination therapy.
- iv More studies are needed to ascertain that whether or not the treatment outcomes with 1000mg and 800mg ribavirin in patient's 75kg weight are comparable.
- v It is not yet clear whether or not patients heavier than 88 kg will have better outcomes on 1400mg of ribavirin than on 1200mg.

Table 3: Monitoring of Anti-viral Therapy 5;6:

<i>Fortnightly:</i>	CBC at weeks 1, 2, 4, 6, 8 and then monthly
<i>Week 4:</i>	Qualitative HCV RNA assay at week 4 in both genotype 1 and 2&3 cases to assess for RVR
<i>Every month:</i>	Pregnancy assay in a sexually-active female of child bearing age
<i>Week 12:</i>	Quantitative HCV RNA assay at week 12 in genotype 1 cases only to assess for EVR
<i>Every 3 months:</i>	LFTs, INR, albumin, creatinine, urinalysis, glucose and TSH
<i>Week 24:</i>	§ Qualitative HCV RNA assay at week 24 in only those genotype 1 cases who attained EVR at week 12 § Qualitative HCV RNA assay at week 24 in genotype 2&3 cases to determine ETR
<i>Week 48</i>	§ Qualitative HCV RNA assay at week 48 in genotype 2 and 3 cases to determine SVR § Qualitative HCV RNA assay at week 48 in genotype 1 cases to determine ETR
<i>Week 72</i>	§ Qualitative HCV RNA assay at week 72 in genotype 1 cases to determine SVR

Predictors of good response with treatment:

- § Strongest predictor = HCV genotype (genotypes 2 and 3 respond better than genotype 1).
- § Lower the pre-treatment HCV RNA titer (< 800,000 IU/mL), better the response.
- § Lesser the fibrosis on liver biopsy, better the response. Absence of bridging fibrosis and cirrhosis are encouraging histological signs.
- § Younger (<40yrs) the age and lesser the body weight (<75kg), better the response.

Predictor of good response during the course of the treatment:

- § Achievement of rapid virologic response (RVR)/early virologic response (EVR)
- § means high probability of achieving sustained virologic response (SVR), and vice versa.

- vi More studies are needed to ascertain whether or not the heavier patients yield better results with >800mg of ribavirin dose in genotypes 2 & 3 cases.
- vii The newly recommended week 4 qualitative HCV RNA assay helps modify the duration of the therapy based on viral kinetics. On one hand, this approach helps maximize SVR rates and on the other hand, limits the toxicities and cost associated with extended treatment courses. Achievement of RVR means that we can consider shortening the treatment course.
- viii With the shortened treatment courses in subjects who show

- RVR, SVR rates of 80-100% have been reported in genotype 2 cases and 77-85% in genotype 3 cases.
- ix In case of relapse, retreatment with the standard 24 weeks course is recommended.
 - x SVR rates achieved in this subgroup are poor, particularly in genotype 3 cases – 41-58%. In genotype 2 cases, the results are relatively better - 50-89%. Because of the poor SVR rates, prolonged therapy (>24 weeks) may be considered in this subgroup, although more evidence is needed at this time for a definite recommendation.
 - xi Old age (>50yrs); male gender; African American race; obesity; alcoholism; HIV confection or immunosuppression; more-than-portal fibrosis on liver biopsy (Metavir =2 or Ishak = 3); a pretreatment viral load of >800,000IU/mL.
 - xii SVR rates of 80-89% can be achieved in this subgroup.
 - xiii In case of relapse, retreatment with the standard 48 weeks course is recommended.

Suggestions for Local Practice

Diagnostic workup:

1. The newly introduced week 4 qualitative HCV RNA assay helps modify the duration of the therapy based on viral kinetics. On the one hand, this approach helps maximize the SVR rates and on the other hand, limits the toxicities and cost associated with the extended treatment courses. It is recommended that week 4 qualitative HCV RNA assay will help us identify patients who have achieved RVR at this stage warranting shortening of the treatment course to 12-16 weeks (instead of the standard 24 weeks) in genotypes 2&3 cases.
2. Qualitative HCV RNA assays at the completion of treatment course and 24 weeks thereafter to determine ETR and SVR respectively should be done as otherwise.

Medication

1. Many recent landmark studies have consistently shown that pegylated interferon therapy is therapeutically superior to nonpegylated therapy in terms of RVR, ETR and SVR rates achieved in all genotype cases. Pegylated interferons, however, are considerably more expensive than the nonpegylated interferons routinely used in Pakistani patients. It is the need of the hour to conduct a multicenter, population-based, statistically representative study in our population to know whether or not the results of nonpegylated interferons are comparable to those of pegylated interferons and whether RVR, ETR and SVR rates are achieved or not.
2. Relapse has been shown to occur in almost 40% of the pegylated interferon-ribavirin combination therapy treated HCV cases shortly after cessation of antiviral therapy despite an earlier normalization of aminotransferase levels, disappearance of HCV RNA from the circulation and histologic improvement²²⁻²⁵. Disease relapse has occurred

even after protracted pegylated interferon-ribavirin courses of 12-24 months^{26;27}. Considering such a high relapse / reinfection rate following pegylated interferon therapy in multiple international studies, one could assume that nonpegylated interferon therapy would yield SVR rates of >50% in Pakistani population. This needs scientific verification and validation by representative local studies.

3. Ribavirin dose of 10.6 mg/kg is most probably an under-dosage. All recent major, randomized, control trails have shown that the optimal dose of ribavirin in genotypes 2 and 3 is 800mg/day given in two divided doses regardless of body weight. Studies have shown that genotypes 2 and 3 cases who achieve RVR at week 4 and are thus selected for shorter treatment courses of 12-16 weeks (instead of the standard 24 weeks), show better results if higher weight-adjusted ribavirin dose is given i.e. 1000mg for 75kg and 1200mg for >75 kg. Also some studies have shown that heavier (>75 kg) patients yield better results with >800mg of ribavirin dose in genotypes 2 and 3 cases, although this observation needs to be validated by further studies. Likewise, it is shown in few studies that genotype 1 patients who are heavier than 88 kg yield better results if 1400 mg ribavirin is given instead of the currently recommended 1200mg in all >75 kg cases. Based on these trials, both current American and Canadian guidelines recommend a ribavirin dosage of 800mg/day in all genotypes 2 and 3 cases regardless of the body weight. With 10.6mg/kg dose regimen, only those Pakistani patients having a body weight of =75 kg get the benefit of 800mg/day ribavirin.

Non-responders / relapsers

1. Patients who are non-responders to an initial course of interferon and ribavirin therapy need further work up for HCV genotype, quantitative HCV RNA and liver biopsy. Notably, not all treatment failure cases are non-responders or relapsers. In fact many secular factors like administering low-potency nonpegylated interferon, interferon monotherapy, suboptimal ribavirin dosing and early withdrawal are significant contributors to treatment failure, and not necessarily indicate non-response or relapse. Other contributory factors may include nonadherence, development of side effects, lack of patient education, physician inexperience and the presence of bad prognostic signs - genotype 1; more-than-portal fibrosis on liver biopsy; high pretreatment viral load of >800,000 IU/mL; thrombocytopenia; coinfection with HIV; continued alcohol use; and comorbidities like depression, hyperthyroidism, renal insufficiency, autoimmune disease, hemochromatosis, uncontrolled diabetes mellitus/hypertension and associated/superadded hepatitis B infection. In nonresponders and relapse cases, the investigative workup and therapeutics should cater for all these secular contributory factors. These must be kept in mind in order to avoid treatment failure.

2. For cases previously treated with non-pegylated interferon, the treatment of choice should be peginterferon-ribavirin combination therapy. For those previously treated with pegylated interferon-ribavirin combination therapy, retreatment is not indicated even if a different type of peginterferon is administered. In a recent study, consensus interferon (CIFN) has been shown to improve responses in such cases but it is premature to definitely recommend its use.
3. In all cases that have non-responded/relapsed after nonpegylated-ribavirin combination therapy, it is recommended to go for a quantitative HCV RNA assay before the start of the treatment and 12 weeks into therapy regardless of the genotype. If week 12 quantitative HCV RNA assay fails to show achievement of EVR, there is 100% reported probability that SVR will not be achieved in such cases. Therapy may therefore be terminated in these patients at week 12.

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