A Review of Hepatitis C Virus (HCV) and the Current Management of Genotype 1 Chronic HCV Infection

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ABSTRACT

Background: Chronic Hepatitis C virus (HCV) is the primary cause of cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease. The addition of protease inhibitor with peginterferon alfa and ribavirin (triple therapy) for genotype 1 infected patients, are the current standard of care.

Method: Data was sourced from available journals and internet based search using pubmed, medline and google search.

Results: successful Treatment of Genotype 1 HCV infected patients with protease inhibitor based triple therapy has improved sustained virologic response (SVR) rates and treatment induced clearance of HCV infection.

Conclusion: significant progress in the management of chronic hepatitis C genotype 1 with the introduction of protease inhibitor (PI) in 2011 with peginterferon and ribavirin has optimized sustained virologic response (SVR).

Keywords: Hepatitis C genotype 1; Pegylated Interferon (Peg IFN); Protease inhibitors (PI), Telaprevir (TVR), Boceprevir (BOC), Ribavirin (RBV).

INTRODUCTION

Chronic Hepatitis C virus (HCV) is the primary cause of cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease. Management of chronic HCV infection is aimed at halting disease progression, preventing cirrhosis decompensation, reducing the risk of hepatocellular carcinoma (HCC).

The hepatitis C virus (HCV) is a single – stranded RNA virus of 9.5kb that belong to the flavivirus family. Six genotype of HCV have been described. Genotype 1 is the most common in North America as well as the most difficult strain to cure. In North America, genotype 1 accounts for more than 60% of infections followed by genotype 2 and 3. Genotype 4 is most prevalent in Egypt; Genotype 5 in South Africa; and genotype 6 in Southeast Asia. Genotype is associated with responsiveness to treatment. Genotype 1 is less responsive to treatment than genotype 2 and 3.

In Nigeria there is currently no data on the prevalent genotype. The standard of therapy for patients with chronic hepatitis C (HCV) infection has been the use of both peginterferon (Peg IFN) and ribavirin (RBV) which has been associated with a reduced incidence of hepatic decompensation and Hepatocellular carcinoma in addition to prolong survival. Sustained virologic response (SVR), defined as undetectable levels of HCV RNA at least 24 weeks after completion of therapy, is the primary endpoint of successful therapy, and is associated with durable clearance of virus in more than 98% of cases. In 2011, the standard of care for many patients with HCV genotype 1 infection became a combination of an oral protease inhibitor (PI), boceprevir (BOC) or telaprevir (TVR), along with pegylated IFN (PegIFN) and ribavirin (RBV). BOC and TVR represent a new era of therapy, as they are the first commercially available hepatitis C direct-acting antiviral (DAA) agents, which directly inhibit viral replication. In clinical trials of HCV genotype 1-infected patients receiving PegIFN and RBV, combined with BOC or TVR, SVR was achieved in 63-75% of treatment-naive patients, in 69-
88% of PegIFN and RBV relapsers, and in up to 33% of PegIFN and RBV nonresponders\(^3\). The key to improving outcome in management of genotype 1 chronic hepatitis C is by identifying the ideal candidate with detectable virus (HCV RNA), hepatic inflammation (elevated liver enzymes or inflammation on biopsy) with no contraindication to therapy. The treatment of genotype 1 HCV infection has become more rewarding for patients. However, triple therapy associated with more side effects requires closer patient follow-up than treatment with PegIFN and RBV alone. Stringent dosing, awareness of drug-drug interactions and management of toxicities improves treatment adherence and overall success of therapy.

**Epidemiology:**
According to World Health Organization (WHO) estimates, 3% of the world’s population or approximately 170 million people are infected with hepatitis C virus (HCV).\(^4\) The centre for the disease control and prevention (CDC) estimates that approximately 15,000 acute cases of hepatitis C occurred annually during the past decade in the USA. In the United States of America, 1.8% of the population are hepatitis C virus anti-body (anti-HCV) positive, while 2.7 million people are infected with the virus.\(^5\) In the United States, 40% of chronic liver disease is related to hepatitis C virus.\(^6\) Hepatitis C is more prevalent in blacks than in other racial groups in the USA. Persons of Hispanic ethnicity have higher rates. Hepatitis C virus is much more common in Southern Europe and Japan than in the United Kingdom.

In endemic areas such as Egypt, more than 10% of the population is infected. In Nigeria most studies on hepatitis C are not community based with majority of reported studies among blood donors, patients with chronic liver disease, sickle cell disease and hepatocellular carcinoma.\(^7\) The incidence of acute HCV infection has decreased by more than 80% since the early 90s, with the screening of blood donors likely contributing to the greatest proportion of this decrease.\(^8\) However, even in resource-rich regions of the world, HCV transmission continues to occur by injection drug use.\(^9\) The most common mode of HCV transmission is the percutaneous route through intravenous drug use and previously from blood transfusion. Nosocomial transmission and needle stick exposures have been shown to result in viral transmission. Hemodialysis has been associated with high rates of infection while sexual transmissions have been found to occur though not a common mode of spread of HCV infection. Mother to infant or vertical transmission is known to occur; in an average of 5% - 6% of deliveries from HCV infected women\(^\text{10}\). The incidence is higher (14%-17%) in patients co-infected with HIV. The risk for vertical transmission is higher if the mother is co-infected with the HIV or if the mother has a high titre of HCV RNA in late pregnancy.

**Pathogenesis:** The replication of HCV occurs via an RNA-dependent RNA polymerase, which is error-prone resulting in the formation of quasispecies within a patient. The formation of quasispecies and the high rate of replication complicate treatment of the hepatitis C. The pathogenesis of chronic hepatitis C is unclear. Liver damage in chronic HCV infection stems from a cellular immune response, because HCV itself is not cytopathic, rather HCV-specific helper and cytotoxic T cells recognize HCV proteins leading to the production of inflammatory cytokines.

**Natural History**
The average incubation period of HCV infection is 6-7 weeks, with a range of 2-26 weeks.\(^\text{11}\) Acute infection is asymptomatic in 60% to 70% of patients, although 20% to 30% will develop jaundice. Chronic HCV infection develops in 50% to 85% of patients and the course of chronic HCV infection is prolonged and usually insidious with few symptoms or signs if any for the first 20 years.\(^\text{12}\) Cirrhosis develops in 15% to 20% of patients with chronic HCV infection.\(^\text{13}\) Hepatocellular carcinoma occurs in 1% to 4% of patients per year during the first five years after cirrhosis has been established.\(^\text{14}\) Alcohol use, male sex, age over 40 years at time of infection, steatosis, elevated serum alanine transaminase, and greater hepatic inflammation promote
progression of chronic hepatitis C. Co-infection with HIV and/or HBV is associated with earlier and more severe liver disease. Patients who develop cirrhosis may continue in a compensated state or decompensate overtime with ascites, jaundice, hepatic encephalopathy, variceal bleeding or hepatocellular carcinoma.

**Pretreatment Assessment in patients with Chronic HCV Infection**

The medical history is an important part of pretreatment assessment. The history is useful in evaluating for complications of liver disease and the presence of significant extra hepatic disease e.g. Nephrotic syndrome, Glomerulonephritis, thrombocytopenia, Diabetes mellitus, thyroid disease, etc. A history of past or ongoing psychiatric disease and substance abuse disorders is important in evaluating the ability of compliance with treatment, the route of transmission, the patients risk for disease transmission and the screening of contacts if necessary. Uncontrolled depression or active suicidal ideation is an absolute contraindication to IFN-based therapies. Patients with stable psychiatric disorders should be evaluated by a mental health professional before therapy with anti-viral treatment. Screening for depression and alcohol use is also an important component of the clinical evaluation. Severe psychiatric adverse reaction may manifest in patients receiving interferon. Depression and suicidal ideation may occur in patients with or without previous psychiatric illness.

The testing for biochemical makers of liver injury such as the liver enzymes and serum proteins gives an indication of the presence of ongoing hepatic inflammation and disease chronicity. A complete blood count which evaluates for anemia and a low platelet count which is associated with an increased risk of bleeding. Patients with HCV infection could have thrombocytopenia. The evaluation of thyroid stimulating hormone, renal function test and blood glucose level are also important in excluding extra hepatic manifestation.

Exacerbation of autoimmune diseases have been reported in patients receiving interferon therapy hence the need to test anti-thyroid antibody. Diabetes mellitus has been observed in patients treated with alfa interferon.

Ribavirin (RBV) is potentially teratogenic therefore a pregnancy test should be obtained from women of childbearing age before initiation of HCV treatment. Women who are pregnant or attempting to conceive should not be treated. Pregnancy also must be avoided in the partner of an HCV infected male patient receiving treatment. IFN is contra-indicated in pregnancy. Other key investigations are HIV serology, serum HBsAg, anti HBC, anti HBS, anti HAV (total), Quantitative HCVRNA and the HCV genotype. A liver biopsy will only be necessary if the result will influence the management, while IL28B genotyping is a robust pretreatment predictor of SVR to peginterferon alfa and ribavirin as well as to protease inhibitor based triple therapy in patients with genotype 1 chronic hepatitis C virus infections.

In patients with pre existing cardiac disease an electrocardiogram (ECG) should be performed, because cardiac disease may be worsened by ribavirin induced anemia. Alcohol and illicit drug use may affect HCV treatment adherence and response to therapy however; patients who have recently become abstinent can be treated successfully. Patients with past or recent substance abuse disorders often require close monitoring.

Following the pretreatment evaluation, it should be noted that HCV antiviral therapy should be used only in patients with preserved liver function serum bilirubin < 1.5mg/dl; international normalized ratio < 1.5; Albumin > 3.0g/dl and no evidence of hepatic encephalopathy or ascites along with adequate

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Adapted from Ghany MG et al Hepatology 2009; 49:1335-1374
The screening of patients for chronic HCV infection is an important strategy in the early detection of HCV infection. People for whom HCV screening is recommended include persons who have injected illicit drugs in the recent or remote past; prior recipients of transfusions or organ transplants prior to July 1992; persons with conditions associated with a high prevalence of HCV including persons with human immunodeficiency virus (HIV) infection; persons with hemophilia who received clotting factor concentrate prior to 1987, persons who have ever been on hemodialysis; persons with unexplained abnormal aminotranferase levels; children born to HCV-infected mothers and health care, emergency medical and public safety workers after a needle stick injury or mucosal exposure to HCV-positive blood.

**Treatment of HCV.**

The treatment of HCV is classified into two groups. Treatment naïve and treatment experienced patients.

**Treatment-naïve patients:** Patients with cirrhosis treated with either boceprevir or telaprevir in combination with peg IFN and RBV, should receive therapy or a duration of 48 weeks. The recommended dose of boceprevir is 800mg with food three times daily together with PIFN alfa and weight-based RBV for 24-44 weeks preceded by 4 weeks of lead-in treatment with peg IFN alfa and RBV alone.

Patients without cirrhosis treated with Boceprevir, PegIFN and RBV this should be preceded by 4 weeks of lead-in with PegIFN and RBV, whose HCVRNA levels at week 8 and 24 is undetectable; consider a shortened duration of 28 weeks in total (4 weeks lead-in with peg IFN and RBV followed by 24 weeks of triple therapy.

Stop treatment with all three drugs (Boceprevir, Peg IFN alfa and RBV) if the HCVRNA level is > 1000 iu/ml at treatment week 4 or 12 and/or detectable at treatment week 24.

**Telaprevir:** The recommended dose of telaprevir is 750 mg with food three times daily. Together with peg IFN alfa and weight-based RBV for 12 weeks followed by an additional 12-36 weeks of peg IFN alfa and RBV.

For patients without cirrhosis treated with telaprevir, PegIFN and RBV whose HCV RNA level at weeks 4 through 12 is undetectable; consider a shortened duration of 24 weeks.

Stop treatment with all three drugs (telaprevir, Peg IFN alfa and RBV) if the HCVRNA level is > 1000 iu/ml at treatment week 4 or 12 and/or detectable at treatment week 24.

**Treatment – Experienced Patients:**

Re-treatment with boceprevir or telaprevir, together with PegIFN alfa and weight-based RBV, can be recommended for patients who had virological relapse or were partial responders after a prior course of treatment with standard interferon alfa or PegIFN alfa and/or RBV.

Re-treatment with telaprevir, together with pegIFN alfa and weight-based RBV, may be considered for prior null responders to a course of standard interferon alfa or pegIFN alfa and/or weight-based RBV.

Consider response-guided therapy of treatment-experienced patients using either a boceprevir or telaprevir-based regimen for relapsers for boceprevir, for telaprevir for partial responders but not for null responders. This regimen should not be used for null responders.

Withdraw from all therapy patients re-treated with boceprevir plus PegIFN alfa RBV who continues to have detectable HCV RNA >100 IU/ml at week 12 because of the high likelihood of developing antiviral resistance. Withdraw from all therapy patients re-treated with telaprevir plus PegIFN alfa RBV who continues to have detectable HCV RNA >1000 IU/ml at weeks 4 or 12 because of the high likelihood of developing antiviral resistance.

Side effects of HVC therapy: The incidence and severity of side effects including rash, anemia, anorectal problems and dysgeusia have increased due to the introduction of protease...
inhibitors and the potential for drug-to-drug interactions.

Skin rash occurs in approximately 24 – 28% of patient being treated with PIFN/RBV, with the exception of injection site reaction; these rashes are primarily due to RVB. The rash is not a significant problem for patient taking BOC triple therapy, however rash has been reported in 56% of patients taking TVR triple therapy and may occur with or without pruritus.

Stephen Johnson syndrome and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome has also been reported in patients on triple therapy. 6% of patients require discontinuation of TVR due to rash. 1% of patients require termination of triple therapy due to rash while rash resolution may take weeks. Serious rash occur infrequently, TVR must never be dose-reduced and once TVR has been discontinued it must never be restarted.

Anemia is a common side effect of HCV therapy. The anemia associated with PIFN is due to bone marrow suppression whereas the anemia associated with RBV is due to dose-dependent red cell hemolysis in addition to down regulation of erythropoietin receptors. Anaemia associated with RBV typically occurs during the first 4 weeks of therapy with hemoglobin reduction ranging between 2-3gm/dl. RBV associated hemolysis is usually the primary reason for dose reduction and treatment termination due to anemia in patients taking PIFN/RBV. The addition of BOC or TVR to PIFN/RBV increases the incidence of anemia which is due to PI induced bone marrow suppression.

Sulkowski et al found that patients who developed anemia while on PIFN/RBV were more likely to achieve SVR compared to patients without anaemia during combination therapy, a trend that was similarly found in BOC triple therapy but not in TVR triple therapy. The anaemia associated with HCV therapy can be managed using erythropoietin (EPO). This has been shown to improve the quality of life in anemic patients during therapy.

Anorectal Disorders: Anorectal events including hemorrhoids pruritus, pain, burning diarrhea occur more commonly in TVR-based regimens compared to PIFN/RBV alone and has not been a significant problem with BOC-based regimes. The exert mechanism of anorectal events are unknown. Dysgeusia: Dysgeusia, an altered taste sensation has been shown to occur in approximately 40% of patient taking BOC triple therapy and in 10% of those patients taking TVR triple therapy. Oral zinc supplementation has been a treatment option for dysgeusia.

Future therapies involving second generation HCV PI's are on clinical trials with the hope of broader genotype coverage, with fewer side effects and shorter duration of action.

CONCLUSION
The Successful treatment of HCV genotype 1 chronic hepatitis with protease inhibitor based triple therapy has lead to a substantial improvement in sustained virologic response (SVR) rates and treatment induced clearance of HCV infection. Hepatitis C virus (HCV) infections are thus the only known example of a chronic viral infection that can be completely cleared from an infected individual by treatment. The standard of therapy for patients with chronic hepatitis C (HCV) infection has been the use of both peginterferon (Peg IFN) and ribavirin (RBV). These drugs are administered for either 48 weeks for HCV genotypes 1,4,5 and 6 or for 24 weeks for HCV genotype 2 and 3; indicating sustained virologic response (SVR) rates of 40% - 50% in those with genotype I and 80% or more in those with genotype 2 and 3 infections. The current addition of protease inhibitor (PI) in 2011 to pegylated interferon plus ribavirin, has enhanced genotype 1 HCV patients capable of achieving a sustained virologic response (SVR), defined as HCV RNA undetectable 24 weeks after treatment termination, however patients management has been complex with increasing side effects and severity.

From the foregoing it is obvious that significant progress has been made in the management of viral hepatitis. The management of chronic hepatitis C genotype 1 has improved with the
introduction of newer agents (Protease inhibitor). The optimal response to therapy is the sustained virologic response which implies becoming seronegative for HCVRNA while on therapy and remaining negative for at least six months after stopping treatment. Sustained virologic response (SVR) is associated with cure of chronic HCV, and results in improved liver outcomes and prolonged survival.

It is hoped that in the near future PI's will be the mainstay of treatment of hepatitis C viral infection.

REFERENCES

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