Practice Guidelines

PSG Consensus Statement on management of Hepatitis C Virus Infection - 2003

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Introduction

The hepatitis C virus (HCV) was identified in 1989 and subsequently tests were developed for diagnosis.[1] Since then, HCV has been recognized as a major public health problem all over the world, including Pakistan. Approximately 160 million people are estimated to be infected with HCV by the World Health Organization, the large majority of whom reside in the developing countries of the world.[2] Even in developed countries, the burden of HCV related liver disease is increasing so that HCV has become the single most important reason for liver transplantation.[3]

Over the last decade, important and extensive information has accumulated regarding the epidmiology, natural history, diagnosis and treatment of chronic HCV infection. Even so, a number of areas remain controversial in the management of chronic HCV infection. Accordingly, many professional societies and health agencies have attempted to develop a consensus to address the important issues in this area. The most widely followed amongst these include the ones from the National Institutes of Health USA[4], the European Association for Study of the Liver and the British Society of Gastroentorology.[5] These documents provide excellent reviews of the epidemiology and management of HCV infection. However all these statements are based generally on information obtained from the developed regions of the world and do not take into account the peculiar differences that may exist in the developing countries, particularly in relation to epidemiology of disease and local economic and cultural conditions. Even the Asia-Pacific consensus, developed by the Asian Pacific Association for study of Liver in 2000[6], deals with a large region which has great ethnic, cultural and economic diversity. A need was therefore felt to develop a consensus statement for the management of chronic HCV infection by the Pakistan Society of Gastroenterology, which would be particularly relevant to the management of HCV infection in Pakistan. The over riding concern in the development of these guidelines has been to recommend the most cost effective and yet efficacious care for our HCV infected patients.

Methodology

A total of 30 of the most prominent gastroenterologists from all over the country were invited to attend a two-day conference. On the first day, the invited speakers were asked to present a comprehensive review of the available national data pertaining to HCV infection. Topics included prevalence, mode of transmission, natural history, diagnosis, treatment and prevention of hepatitis C. On day two, the data presented was critically analyzed by the panel of experts and a consensus was derived for the management of chronic HCV infection in Pakistan. Particular attention was paid to the economic and cultural difficulties faced in the management of such patients. Where good local data was not available, recommendations from the international guidelines were adopted. Accordingly, this document concerns itself more with issues that are peculiar to the management of HCV patients in Pakistan rather than provide a comprehensive overview of the subject.

Epidemiology of HCV in Pakistan

Accurate epidemiological information for chronic HCV infection is still scanty from Pakistan. However, based on the data presented, the following observations can be made.

Community Prevalence

Few population based studies are available, the most comprehensive being that of Luby et al[7], which tested a representative sample from a population of 150,000 in Hafizabad and found an overall seroprevalence of 6%. This increased to 30% with increasing age. The same group also found a 16% sero-prevalence rate in household members of HCV infected cases.[7] Other smaller studies have reported a population prevalence of 16% from Lahore and 23.8% from Gujranwala.[8] Based on an average prevalence rate of 6%, it could be estimated that approximately 10 million people are infected with HCV in Pakistan.[9]

The sero-prevalence of HCV in children appears to be low in Pakistan, with 0.2% and 0.4% children infected under the age of 12 and between 12-19 years respectively.

Ethnic differences in the sero-prevalence of HCV in the country are suggested in some studies, but more data is needed to confirm this observation.

Volunteer Blood Donors

There is more extensive data on HCV sero-prevalence in volunteer blood donors from across the country, even though figures may vary from 0.13% to

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5%.[10-12] A meta analysis of the available data suggests that HCV sero-prevalence among volunteer blood donors in the country is between 3-4%.[9] However up to 20% of paid blood donors are anti HCV positive.[13]

Burden of HCV related chronic liver disease

The burden of HCV related chronic liver disease (CLD) clearly seems to be increasing with time. Whereas earlier studies showed that of all patients presenting with CLD 16.6% were anti-HCV positive[14], more recent data shows nearly 60-70% patients with CLD to be positive for anti-HCV.[15,16] The number of admissions to hospital related to chronic HCV infection also show a nearly linear increase over time.[17]

HCV and Hepatocellular Carcinoma

Although data is limited, more recent studies show that nearly 50% patients with HCC in Pakistan are anti-HCV positive.[18] More data is urgently required in this area.

Modes of transmission of HCV in Pakistan.

A survey of blood banks in the large urban centers of the country, shows that only about 25% of them tested blood and blood product donations for HCV infection[19], the main reason for not testing being the higher cost of a blood donation. It can be safely assumed that testing for HCV in the rural areas of the country is even less frequent, making blood transfusions still the major cause of HCV transmission in the country.

A number of studies also show the relationship between therapeutic injections using non-sterile needles and transmission of HCV.[20] There is enormous dependence on parentral therapy for treatment, both in the form of injections and infusion of drips, driven by cultural beliefs in the power of parenteral therapy.

Additional risk factors that are peculiar to a developing country and may be important modes of transmission are excessive use of barbers for shaving[21], ear piercing and non-sterile surgical and dental practices of unqualified health care workers (quacks). However studies are needed in these areas to confirm this fact.

Screening strategies for HCV.

Based on the prevalence of infection and risk factors, universal screening of all adults in Pakistan for HCV infection may be the best strategy. However this cannot be recommended because of cost constraints. We therefore recommend that, in addition to the already well-defined high risk groups, all individuals who have ever received a blood transfusion or multiple therapeutic injections should be screened for HCV infection.

HCV Genotype distribution in Pakistan

Multiple studies confirm that type 3 is the predominant HCV genotype in Pakistan, with a prevalence of between 75-90%.[22,23] The rest are mostly type 1 and occasionally type 2, with no evidence for other genotypes. Amongst the type 3 infections, subtype 3a is the commonest followed by 3b.

Natural History of HCV

Local natural history data is lacking, so no definitive statements could be made in this regard. The natural history of chronic HCV infection is presumed not to be any different to that described in other populations, so that the classic view of disease progression holds true for our population as well. The only difference in natural history may come from the observation that few patients have a concomitant history of alcohol intake, due to religious and cultural beliefs.

Diagnosis of HCV Infection

The following tests are recommended for the diagnosis of HCV infection.

HCV antibody test

The 3rd generation ELISA tests are easy to use and extremely accurate for the diagnosis of HCV infection.[24] These are recommended as the only standard serological test to be used to make a diagnosis of chronic HCV infection.

Qualitative HCV RNA

A qualitative PCR for serum HCV RNA should be used to confirm the diagnosis of HCV infection, particularly prior to starting interferon therapy. Confirmation by a qualitative PCR may not be necessary in a patient who has clinical evidence of chronic liver disease and obvious risk factors for HCV infection, particularly if treatment is not being considered.

It is recommended that for routine patient care, all laboratories should use only one of the commercially available assays and that use of in-house assays should only be limited for research purposes. This is important because many laboratories across the country use non- standardized assays and this complicates patient care due to non-reproducible results.

Quantitative HCV RNA

Quantitation of HCV RNA in serum by PCR is particularly helpful for management of patients infected with HCV genotype 1, as the total duration of treatment may vary with the quantity of virus present. However for HCV type 3 infection, the recommended length of treatment remains six months irrespective of the level of viremia. As

the large majority of our HCV patients are genotype 3, the use of Quantitative HCV RNA is not recommended in the routine treatment of our patients. Moreover standardization of Quantative HCV RNA is even more problematic in our country.

HCV Genotyping

The treatment schedule of chronic HCV infection with interferon varies with the genotype being treated. Accordingly determination of HCV Genotype is considered important before initiation of therapy. However, as the large majority of our patients are infected with HCV genotype 3, testing for HCV genotypes may not be necessary as a routine prior to initiation of therapy in our patients.

Liver Biopsy

Liver biopsy provides a unique source of information on fibrosis and also the possible role of iron, steatosis and alcohol on the progression of chronic HCV infection. The degree of fibrosis observed on a liver biopsy is an important parameter to determine the need for anti viral therapy. The use of clinical parameters to predict cirrhosis is inaccurate, with a correct histological diagnosis in less than one third of cases.[25] However, since a favorable response to treatment is expected in up to 80% of patients with genotype 3 infection, it may not be always necessary to perform liver biopsies in these patients to make a decision to treat. Liver biopsy is therefore recommended, but not considered mandatory, prior to treatment in our chronic HCV patients.

Treatment of Naïve Patients with Chronic HCV Infection

Criteria for Anti-Viral Therapy

The following criteria are recommended for treatment of chronic HCV infection:

a) Raised ALT for 6 months or more. (1.5 - 2 times ULN)

b) Positive HCV antibody by 3rd generation ELISA.

c) Positive HCV RNA in serum by a standardized qualitative PCR.

d) Liver biopsy (if available) showing active disease with early fibrosis.

Optimal Therapy

In naive patients, the combination of interferon alpha (3 million units three times a week) and ribavirin (10.6 mg/kg body weight) is recommended for a period of six months. It is important that therapy should be initiated by a specialist physician who has a particular interest in viral hepatitis, and not by general practitioners or family physicians.

In patients who are non responders to an initial six month course of interferon and ribavirin therapy, further work up should be instituted. HCV genotype should be determined at this stage to rule out the possibility of genotype one infection, and if this is confirmed, a quantitative HCV RNA should be determined.

Monitoring response to Therapy

Response to treatment is defined as follows:

End of Treatment Response (EOT): When, at the end of the treatment period, serum ALT is normal and PCR is negative.

Sustained Response: When serum ALT remains normal and PCR negative, six months after stopping treatment.

Relapse: When PCR becomes positive again, with or without raised serum ALT.

Non-responder: When PCR remains positive, with or with out raised serum ALT, at the end of treatment.

During treatment, hemoglobin, white cell and platelet counts should be checked at least every four weeks. This is necessary to prevent and treat therapy related side effects.

Response to therapy should be determined by a monthly serum ALT level. If serum ALT levels remain normal during therapy, we do not recommend an HCV PCR. In such a case, a qualitative HCV PCR should be done only at the end of therapy to document a virologic response.

During follow up, a serum ALT level and a PCR should be repeated at 6 months after stopping treatment to determine if the patient has had a sustained response or not. It is recommended not to measure ALT and PCR before 3 months after end of treatment as this is unlikely to lead to a treatment decision.

Re-treatment of relapsers or non-responders

We recommend the use of pegylated interferons, in combination with ribavirin, for re-treatment of patients who relapse after standard treatment.[26] The dose of pegylated interferon can be either fixed (for PEGASYS, 180 micrograms once weekly) or weight based (for PEGINTRON, 1.5 micrograms per kg once weekly). When used in combination with pegylated interferons, ribavirin can be used in a standard dose of 800 mg/day. Treatment is given for six months, with the same monitoring as for standard therapy.

It is recognized that pegylated interferons are expensive and may not be afforded by many of our patients. A more cost effective alternative may be triple therapy with standard interferon, ribavirin and amantidine (100 mg twice daily) for a period of six months. Although initial data of efficacy is available[27], further studies are needed before

triple therapy can be clearly recommended.

Summary and Recommendations

1. Based on an average prevalence rate of 6%, it could be estimated that approximately 10 million people are infected with HCV in Pakistan.

2. The sero-prevalence of HCV in children appears to be low in Pakistan (0.2% - 0.4%).

3. A meta-analysis of the available data suggests that HCV sero-prevalence among volunteer blood donors in the country is between 3-4%.

4. Nearly 60-70% patients with CLD and 50% patients with HCC in Pakistan are anti-HCV positive.

5. Only about 25% of blood banks adequately test blood and blood product donations for HCV infection.

6. There is a strong relationship between therapeutic injections using non-sterile needles and transmission of HCV in the country.

7. All individuals who have ever received a blood transfusion or multiple therapeutic injections should be screened for HCV infection.

8. Type 3 is the predominant HCV genotype in Pakistan, with a prevalence of between 75-90%.

9. PCR assays for HCV RNA need to be standardized, as many laboratories across the country use non- standardized assays which complicates patient care.

10. As the large majority of our HCV patients are genotype 3, the use of Quantitative HCV RNA is not recommended in the routine treatment of our patients.

11. Testing for HCV genotypes may not be necessary as a routine prior to initiation of therapy in our patients, as the large majority is expected to be infected with genotype 3.

12. Liver biopsy is recommended, but not considered mandatory, prior to treatment in our chronic HCV patients.

13. In naive patients, the combination of interferon alpha (3 million units three times a week) and ribavirin (10.6 mg/kg body weight) is recommended for a period of six months.

14. Therapy should be initiated by a specialist physician who has a particular interest in viral hepatitis

15. A qualitative HCV PCR should be repeated only at the end of therapy, in order to document a virologic response.

16. A serum ALT level and a PCR should be repeated at 6 months after stopping treatment to determine if the patient has had a sustained response.

17. 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.

18. The use of pegylated interferons, in combination with ribavirin, is recommended for re-treatment of patients who relapse after standard treatment or do not respond.

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