Indian National Association for Study of the Liver (INASL) Guidance for Antiviral Therapy Against HCV Infection: Update 2016

Pankaj Puri [*], Vivek A. Saraswat [†], Radha K. Dhiman [‡], Anil C. Anand [§], Subrat K. Acharya [¶], Shivaram P. Singh [**], Yogesh K. Chawla [‡], Deepak N. Amarapurkar [‡‡], Ajay Kumar [§§], Anil Arora [¶¶], Vinod K. Dixit [***], Abraham Koshy [†††], Ajit Sood [‡‡‡], Ajay Duseja [‡], Dharmesh Kapoor [§§§], Kaushal Madan [¶¶¶], Anshu Srivastava [****], Ashish Kumar [¶¶], Manav Wadhawan [§§], Amit Goel [†], Abhai Verma [†], Shalimar [¶], Gaurav Pandey [†], Rohan Malik [††††], Swastik Agrawal [‡‡‡‡]

[*]*Department of Internal Medicine, Armed Forces Medical College, Pune 411040, India,* [†]*Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow 226014, India,* [‡]*Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India,* [§]*Department of Gastroenterology and Hepatology, Indraprastha Apollo Hospital, New Delhi 110076, India,* [¶]*Department of Gastroenterology, All India Institute of Medical Sciences, New Delhi 110029, India,* [**]*Department of Gastroenterology, SCB Medical College, Cuttack 753007, India,* [‡‡]*Department of Gastroenterology, Bombay Hospital, Mumbai 400020, India,* [§§]*Department of Gastroenterology and Hepatology, Fortis Escorts Liver and Digestive Diseases Institute, New Delhi 110076, India,* [¶¶]*Department of Gastroenterology and Hepatology, Sir Ganga Ram Hospital, New Delhi 110060, India,* [***]*Department of Gastroenterology, Banaras Hindu University, Varanasi 221005, India,* [†††]*Department of Hepatology, Lakeshore Hospital, Cochin 682304, India,* [‡‡‡]*Department of Gastroenterology, Dayanand Medical College, Ludhiana 141001, India,* [§§§]*Department of Gastroenterology, Global Hospital, Hyderabad 500004, India,* [¶¶¶]*Department of Gastroenterology, Artemis Hospital, Gurgaon 122001, India,* [****]*Department of Pediatric Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow 226014, India,* [††††]*Department of Pediatrics, All India Institute of Medical Sciences, New Delhi 110029, India and* [‡‡‡‡]*Department of Gastroenterology, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala, India*

India contributes significantly to the global burden of HCV. While the nucleoside NS5B inhibitor sofosbuvir became available in the Indian market in March 2015, the other directly acting agents (DAAs), Ledipasvir and Daclatasvir, have only recently become available in the India. The introduction of these DAA in India at a relatively affordable price has led to great optimism about prospects of cure for these patients as not only will they provide higher efficacy, but combination DAAs as all-oral regimen will result in lower side effects than were seen with pegylated interferon alfa and ribavirin therapy. Availability of these newer DAAs has necessitated revision of INASL guidelines for the treatment of HCV published in 2015. Current considerations for the treatment of HCV in India include the poorer response of genotype 3, nonavailability of many of the DAAs recommended by other guidelines and the cost of therapy. The availability of combination DAA therapy has simplified therapy of HCV with decreased reliance of evaluation for monitoring viral kinetics or drug related side effects. (J Clin Exp Hepatol 2016;6:119–145)

There have been revolutionary changes in the management of chronic hepatitis C (CH-C) over the last few years. Pegylated interferon alfa (Peg-IFNα) plus ribavirin (RBV) therapy, which till the recent past was the standard of care, has been eclipsed by the arrival of newer directly acting antiviral agents (DAAs). Not only do the DAAs have better efficacy, they are also associated with lower side effects, have better tolerability, a shorter duration of therapy, and have simpler administration.

In the recent guidelines issued by the American Association for the study of Liver Diseases (AASLD), in collaboration with the Infectious Diseases Society of America[1] and the European Association for Study of the Liver z (EASL),[2] the role of Peg-IFNα/RBV therapy in the management of HCV has been relegated to second-line, backup status. These newer guidelines, however, cannot be implemented in India as many of the recommended drugs are yet to be marketed in India. Other considerations for the treatment of HCV in India are a predominance of

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Address for correspondence: Vivek A. Saraswat, Professor and Head, Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareli road, Lucknow 226014, India.
E-mail: profviveksaraswat@gmail.com

Abbreviations: ALT: alanine aminotransferase; ANC: absolute neutrophil count; anti-HCV: antibody to HCV; AST: aspartate aminotransferase; CH-C: chronic hepatitis C; CTP: Child-Turcotte-Pugh; DAA: directly acting antiviral agents; DCV: daclatasvir; EIA: enzyme immunoassay; ESRD: end-stage renal disease; EVR: early virological response; FCH: fibrosing cholestatic hepatitis; GT: genotype; HCV: hepatitis C virus; HCWs: healthcare workers; HIV: human immunodeficiency virus; INASL: Indian National Association for Study of the Liver; IU: international units; LDV: ledipasvir; LT: liver transplantation; NSI: needlestick injury; NS: nonstructural protein; PCR: polymerase chain reaction; Peg-IFNα: pegylated interferon alfa; RBV: ribavirin; RVR: rapid virological response; SOF: sofosbuvir; SVR: sustained virological response; ULN: upper limit of normal

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genotype (GT)-3 and the considerations of the cost of management of HCV.

The Indian National Association for Study of the Liver (INASL) had previously reviewed the epidemiology of HCV in India[3] and formulated the guidelines for HCV in India relevant to the available therapy in India. The initial guidelines were based on Peg-IFNα/RBV therapy.[4] Following the availability of the nucleoside NS5B inhibitor sofosbuvir (SOF) in India with effect from March 2015, INASL had revised the guidance for antiviral therapy against HCV.[5] However, while SOF was the sole DAA in the Indian market, efficacy of the all-oral regimen (SOF/RBV) was limited. Now with the arrival of two new DAAs [NS5A replication complex inhibitors, ledipasvir (LDV) and daclatasvir (DCV)] in the Indian market in December 2015, the recommendations for management of CH-C must accordingly change.

The availability of these newer DAAs is an exciting development in the management of HCV in India. Not only will they provide higher efficacy, but combination DAAs as all-oral regimen will also obviate the reliance on Peg-IFNα/RBV therapy, which had significant side effects.

EVALUATION OF HCV IN THE ERA OF DAA

With Peg-IFNα/RBV therapy, there is a high reliance on laboratory monitoring not only for monitoring the side effects of therapy but also for efficacy and decision for duration of therapy. Repeated testing of HCV RNA for viral kinetics was done to look for rapid virologic response (RVR, undetectable HCV RNA after 4 weeks of treatment) and early virologic response (negative HCV RNA at 12 weeks), which are predictors of sustained virologic response (SVR). However, unlike Peg-IFNα-based therapy, with DAA, there is limited role for repeated HCV RNA testing for RVR or EVR for residual viremia and response-guided therapy. The need for repeated viral load testing for response-guided therapy is obviated, as is the frequent blood sampling for monitoring adverse effects. This simplification of antiviral therapy for HCV and lower laboratory requirements are an advantage in resource-constrained settings.[6]

Diagnosis of HCV Infection

Antibodies to hepatitis C (anti-HCV antibodies) are the screening test for HCV infection. However, these antibodies may be negative early in acute HCV infection, in immunosuppressed individuals, or years after resolution of HCV infection.[7,8] Hence, in patients with suspected acute hepatitis C, HIV infection, organ transplant recipients, and in patients on immunosuppressive drugs, HCV RNA may be required for the diagnosis of HCV infection if anti-HCV is negative.

Anti-HCV antibodies only indicate prior exposure to HCV infection and detection of active viral replication by either HCV core-antigen (HCV core-Ag) or HCV RNA testing is needed to differentiate between active and resolved HCV infection. Traditionally, HCV RNA testing has been used for this purpose and for following the response to antiviral therapy. A simpler alternative to HCV RNA testing is the estimation of HCV core-Ag, a protein with highly conserved sequence, by enzyme immunoassays.[9] Newer, more sensitive assays of HCV core-Ag have now become available. Automated platforms, such as Abbott Architect®, are able to rapidly perform anti-HCV and HCV core-Ag together in a short period of time. The major advantages of HCV core-Ag testing are that it is simple to perform, does not require highly skilled manpower, is cheaper, and can be performed at the same time as the anti-HCV test. HCV core-Ag testing has been shown to be valuable in detection of active HCV infection, HCV infection in seronegative hemodialysis patients, early treatment monitoring, and as a cost-effective alternative to nucleic acid technology for the identification of blood donors in the preseroconversion window.[10–14]

The arrival of DAAs has reduced the need for pretreatment viral load measurement. Detection of HCV replication prior to therapy and its absence 12 weeks after end-of-therapy may be sufficient for diagnosis and monitoring of the treatment. HCV core-Ag may be useful in resource-limited settings and provides smaller laboratories with the capacity to detect active HCV infection where HCV RNA testing may not be feasible.[15] Algorithms incorporating HCV core-Ag testing have been proposed for the evaluation and management of patients with chronic hepatitis C (CH-C).[16,17] However, further evaluation of HCV core-Ag testing is required to guide its use in the management of CH-C in the absence of HCV RNA testing.

Assessment Prior to Treatment

Prior to starting treatment, the following evaluation should be done:

- A detailed history and physical examination is essential, including history of alcohol consumption and drug abuse. Cardiac, pulmonary, and psychiatric evaluations should be done, if indicated.
- Baseline tests include complete hemogram and liver biochemistry [alanine aminotransferase (ALT), aspartate aminotransferase (AST) alkaline phosphatase, bilirubin, gamma-glutamyl transpeptidase (GGT), prothrombin time or INR, albumin], renal function tests, and thyroid function tests.
- Investigations for viral coinfections: Hepatitis B surface antigen, anti-HIV.
- Evaluation for other causes: The causal relationship between HCV infection and liver disease should be established and tests for additional etiologic factors may be done as indicated, e.g., antimitochondrial antibodies, antinuclear antibodies, anti-smooth muscle antibodies, serum ceruloplasmin, serum ferritin, etc.
- Serum HCV RNA (quantitative) and HCV genotyping.
- Cardiac, pulmonary, and psychiatric evaluations, if indicated.
- In women of childbearing age, urine pregnancy test should be done.