Indian National Association for Study of the Liver (INASL) Guidance for Antiviral Therapy Against HCV Infection in 2015

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Overall prevalence of HCV infection in India has been estimated to be approximately 1.3% in the general population. Recent introduction of sofosbuvir in India at a relatively affordable price has led to great optimism about prospects of cure for these patients. This drug is likely to form the backbone of current and future treatment regimes for HCV infection, displacing pegylated interferon. Availability of directly acting antiviral drugs (DAAs) has necessitated revision of INASL guidelines for the treatment of HCV published in 2014, as has happened across the world. 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. Since only one DAA, sofosbuvir, is available in India, only two sofosbuvir-based regimes are possible: either dual drug therapy in combination with ribavirin alone for 6 months or triple drug therapy in combination with ribavirin and pegylated interferon for 3 months. The utility of these regimes in various situations has been discussed. Availability of a few other newer DAAs, expected in 2016, is expected to lead to more widespread use of these agents. Current guidance will be updated once newer DAAs, newer evidence with DAAs and 'real-life experience' with use of DAAs accumulate in India. (J Clin Exp Hepatol 2015;5:221–238)

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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; EIA: enzyme immunoassay; ESRD: end stage renal disease; EVR: early virological response; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IFN-α: interferon alfa; INASL: Indian National Association for Study of the Liver; PCR: polymerase chain reaction; Peg-IFNα: pegylated interferon alfa; RBV: ribavirin; RVR: rapid virological response; SOC: standard of care; Sof: sofosbuvir; SVR: sustained virological response; ULN: upper limit of normal

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The management of chronic hepatitis C (CH-C) evolved gradually in the 1990s; it had been almost static from 2001 to 2011, when pegylated interferon alfa (Peg-IFNα) with ribavirin (RBV) became the global standard of care for CH-C, but evolution has become a revolution in the last five years. Introduction of triple therapy in 2011, with the addition of protease inhibitors boceprevir or telaprevir to Peg-IFNα/RBV, increased sustained virological response (SVR) rates in genotype 1 infection. However, these advances were eclipsed in 2013 by the arrival of another new directly acting antiviral agent (DAA), sofosbuvir (Sof), the first-in-class pangenotypic NS5B nucleotide polymerase inhibitor.

In consonance with the rapidly accumulating new evidence in the management of CH-C, there have been a spate of new guidelines and guidance in this area. The American

Association for the Study of Liver Diseases (AASLD), in collaboration with the Infectious Diseases Society of America (IDSA), revised their guidelines for testing and treating hepatitis C in December 2014, less than a year after the original guidelines were released, and these were further updated online in June 2015.[1,] In March 2014, the World Health Organization (WHO) released its first ever set of global guidelines for hepatitis C virus (HCV) treatment were updated at the APASL meeting in Istanbul in March 2015.[2,] The European Association for Study of Liver Diseases (EASL) has updated its HCV management guidelines issued in August 2014 at its annual meeting in Vienna in April 2015.[3,] Similarly Canadian (January-February 2015),[4,] Dutch (October 2014),[5,] and NICE (February 2015)[6] guidelines have all been published recently.

However, uncritical implementation of these guidelines in India may neither be appropriate nor possible. Considerations in India include the prevalent genotype and its response to therapy, availability of drugs, and cost of therapy. Many of the DAAs recommended for management of CH-C are either not approved for use in India or not likely to be available in India in the near future or can be imported only at a prohibitive cost.

The Indian National Association for Study of the Liver (INASL) has recently reviewed the epidemiology of HCV infection in India[7,] and has formulated guidelines for treating HCV infection with Peg-IFNα/RBV, the standard-of-care (SOC) till 2014.[8] Anticipating the imminent arrival of DAAs in India, these guidelines had recommended that it would be prudent to consider deferring treatment in patients with no or minimal fibrosis or with poor likelihood of response to Peg-IFNα/RBV therapy.

The arrival of oral DAAs has been eagerly awaited in India. Not only is the efficacy of Sof-based therapy expected to be higher than of Peg-IFNα/RBV therapy, but fewer side effects, better tolerability, shorter duration of therapy, simpler administration, easier monitoring and, importantly, reduction in the cost of therapy anticipated with the newer DAAs, are also advantages likely to significantly increase access to antiviral therapy among Indian patients.[9] It is expected that effective drugs will obviate need for response-guided therapy and will reduce need for repeated blood tests to monitor viral load and adverse effects. However, a word of caution is important. A combination of DAAs has been recommended in most situations and therapy with a single DAA-with-RBV combination may not be successful in all patient groups, especially in difficult-to-treat situations. Full benefits of oral, interferon-free antiviral therapy against hepatitis C are likely to be reaped only after a second potent DAA becomes available in India.

The arrival of Sof in the Indian market in March 2015 has mandated a revision of the INASL 2014 recommendations for the management of CH-C in India, recognizing that further changes are likely in these recommendations, as the fast-paced scenario of changing HCV therapy unfolds in India.

CURRENT CLINICAL PRACTICE IN INDIA

It has been estimated that India has a burden of 8.7 million patients with HCV viremia who are candidates for therapy. About 20% have advanced stages of disease with F3-F4 fibrosis, compensated cirrhosis, decompensation or HCC. Fewer than 5% have ever been diagnosed and less than 0.2% have ever received treatment.[10,11] In 2014, it was estimated that approximately 17,000 received treatment with Peg-IFN/RBV, which was the SOC then, and about 65% of them achieved SVR. With the availability of Sof in India at an affordable price, a dramatic increase in the number of patients being prescribed therapy was anticipated, as several barriers to interferon-based therapy were likely to be breached and a large number of 'warehoused' interferon ineligible patients and relapsers were likely to be offered treatment. That this is indeed happening, and at a pace anticipated by few, is suggested by data from pharmaceutical industry sources for the first three months after Sof became available, ending June 30th, 2015, according to which more than 19,000 patients have been prescribed Sof-based treatment, including ~6600 prescribed triple therapy (personal communication). Results of therapy are likely to be available soon.

LABORATORY TESTING OF HCV IN THE ERA OF DAA

Investigations for patients with HCV include serological assays for antibodies to hepatitis C (anti-HCV) and assays to check for viral nucleic acid and viral genotype besides investigations for status of the infected liver, including evaluation of the stage of hepatic fibrosis.

Viral Kinetics in the Era of DAA

Studying HCV kinetics during treatment with Peg-IFNα/RBV has allowed clinicians to develop response-guided therapy paradigms. A rapid viral decline early during therapy with undetectable HCVRNA by highly sensitive assays after 4 weeks of treatment (rapid virologic response, RVR) and negative HCVRNA at 12 weeks (early virologic response, EVR) are important predictors of sustained virologic response (SVR), that is, cure of HCV infection. These terms should be restricted to responses on therapy with Peg-IFNα/RBV. Traditionally, with Peg-IFNα-based therapy, SVR referred to the absence of detectable virus 24 weeks after the completion of therapy (SVR24). However recent data suggest that absence of detectable virus at 12 weeks after completion of therapy (SVR12) is concordant with SVR24.[12,] Concordance of SVR4 and SVR8 with SVR24 and SVR12 has also been assessed for Sof therapy, however, they have not been found to be adequate.[13]