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Review Article

Treatment of chronic hepatitis C: What is new?

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ABSTRACT

Hepatitis C Virus infection is a global problem that leads to development of chronic hepatitis, cirrhosis and hepatocellular carcinoma. So far this infection was being treated with interferon and ribavirin combination which has a large number of adverse effects. Last few years have seen availability of a large number of new molecules that are revolutionising the treatment of hepatitis C. Some of these newer drugs like sofosbuvir have been called game changer because they have changed the way we think of HCV treatment. The cost and availability of these newer drugs in India remains a problem so far. Efforts are on to bring these drugs within the reach of people at an affordable cost, but it is not clear as to how much time it will take. Till then, in our setting, we may continue to recommend the treatment that was standard of care for whole world before these game changers came in. In fact we also explore cheaper options, which are equally effective to make treatment within reach of poorer patients. It may be prudent to withhold treatment for patients with low levels of fibrosis (F1 or F2, with genotype 1 or 4 infection), and for patients who are non-responders to initial therapy, Interferon intolerant, those with decompensated liver disease, and patients in special populations such as stable patients after liver and kidney transplantation, HIV co-infected patients and those with cirrhosis of liver.

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1. Introduction

The management of chronic hepatitis C (CH–C) is rapidly evolving and recent introduction of Sofosbuvir in the armamentarium has brightened the prospects for patients' suffering from HCV infection. So far, the standard of care for most genotypes of HCV infection was treatment with a combination of pegylated interferon alpha (Peg-IFNα2) and ribavirin with or without addition of first generation protease inhibitors. This later therapy led to response rates around 50–80% in various genotypes. The therapy though successful to some extend was associated with several undesirable adverse effects making the regimen uncomfortable and even dangerous in some situations. Newer 'directly acting antiviral' (DAA) drugs are safer and highly effective in achieving cure but have brought in different kind of controversies.

There are currently multiple guidelines on the management of CH–C, which have been issued by leading authorities.[1–4] In Indian setting, one needs to consider type of genotype, the stage of disease and cost/affordability of treatment before implementation of any such guideline for the management of CH–C. The most prevalent genotype of HCV in India is genotype 3 unlike in western countries where

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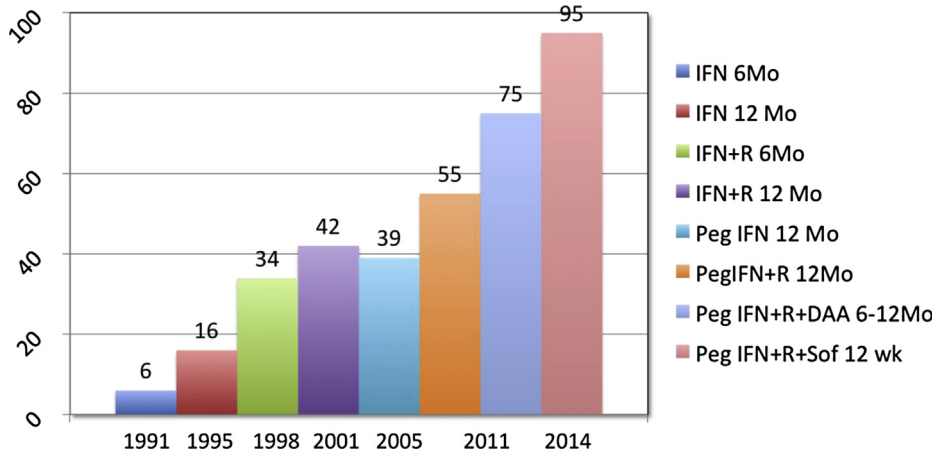

Fig. 1 – Sustained viral response rates for hepatitis C treatment over years, as the treatment has evolved. Figure shows mainly the results related to genotype 1, which is more commonly seen in Western countries. Numbers near the top of bars indicate response rates in percentage, while numbers along the horizontal axis above indicate year of introduction of regimen. Note: IFN = Interferon, PegIFN = Pegylated interferon, Sof = sofosbuvir, Mo = months and wk = weeks.

genotype 1 is more common. Most guidelines have clubbed genotype 2 and 3 together and labeled them easy to treat often for shorter duration and with lower and flat dose of ribavirin (800 mg/day). Our experience shows that genotype 3 is associated with higher steatosis, has a more rapid progression to fibrosis,[5] and has higher incidence of hepatocellular carcinoma.[6] Its treatment responses are poorer as compared to genotype 2 and therefore it needs to be considered separately.

1.1. *Evolution of HCV treatment so far*

The treatment of hepatitis C virus (HCV) infection was started even before the virus was discovered when it was called a parentrally transmitted non-A, non-B virus.[7] Initial results of treatment were measured as a durable normalization of transaminases and were seen in about 10% of patients without a relapse. In 1991 ribavirin was discovered and was shown to have antiviral effect against Flaviviruses.[8] Around this time, we also learned that virus has six genotypes, which behave in different manner and have different patterns of response to treatment.[4] A combination of ribavirin with interferon alpha increased therapeutic responses to around 40%.[9] Some time later, pegylated forms of interferon were developed and it boosted the sustained virological response (SVR, as the response is now measured after discovery of HCV RNA) to around 55%.[10] Soon thereafter in-vitro models of HCV replication were developed and the full cycle of HCV replication and its enzymes was understood which made it possible to design newer drugs to interfere with RNA replication.[11] In the year 2011, first generation of antiproteases, Boceprevir and Telaprevir were added to Pegylated interferons + ribavirin (PR) regimen and it increased the SVR by additional 25–30%. Latest introduction of Sofosbuvir has taken the response rates to 90% and above.[12] (Fig. 1) The results with newer drugs are so good that it may be worthwhile waiting for them to become available in many situations, rather than starting treatment with available drugs.[13]

The reason for suggesting this strategy is abundance of adverse reactions with existing regimens. Pegylated Interferon and ribavirin (PR) combination therapy for CH–C produces a number of troublesome side effects, which include fatigue, influenza-like symptoms, hematologic abnormalities, and neuropsychiatric symptoms such as depression. Combination therapy with pegylated interferons (peg-interferon alpha-2a and alpha-2b) yields an adverse event profile similar to standard interferon. Some 10–14% patients may discontinue therapy on account of such side effects.[14] Most adverse events however can be safely and effectively managed by dose reduction using predetermined criteria. The most common reason for dose reduction is hematologic abnormalities, such as anemia, thrombocytopenia and neutropenia, with the latter two more frequent with peg-IFNα2 treatment. If one adheres to a prescribed treatment regimen, better antiviral responses are achieved. Strategies to maximize adherence have been developed with selective use of hematopoietic growth factors to ameliorate hematologic abnormalities.[15] First generation protease inhibitors Telaprevir and Boceprevir have added their own side effects to above list. They can enhance fatigue, anemia nausea and add diarrhea, anal itching, change in sense of taste and distressing skin rashes.[16]

However, so far, treatment has been recommended with above drugs despite adverse effects because of benefits it can give to patients. Questions have been raised about usefulness of above regimes. There were two main reasons why usefulness of this therapy was doubted. Firstly, Cochrane database systematic review had shown that SVR as a virological biomarker is universally used to evaluate treatment efficacy in both clinical practice as well as in drug development. Conclusive evidence for the clinical benefit of antiviral therapy or validity of SVR as surrogate marker, as derived from trials randomizing patients to a treatment or control arm, is lacking.[17] Secondly, 'hepatitis C antiviral long-term treatment against cirrhosis' (HALT-C) trial recently showed an increased mortality rate among interferon treated patients compared to untreated controls. Therefore, the recommendation to treat

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