Back from the Future: Treating Hepatitis C Virus with Conventional Interferon

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The last couple of decades have seen major developments that have revolutionized the therapy of chronic hepatitis C (CH-C). Conventional interferon- α (IFN- α) monotherapy with 3 million units (MU) 3 times weekly for 24 weeks and 48 weeks, the first step in the evolution of therapy of CH-C, had dismal results with sustained virological response (SVR) rates of 6% and 13–19%, respectively. Response rates improved as therapy evolved with addition of ribavirin and IFN- α /ribavirin combination therapy (IR) had SVR rates of 33% and 41% with 24 weeks and 48 weeks therapy, respectively.^{1,2} However, it was with the advent of the pegylated-interferon- α (PEG-IFN- α) and ribavirin combination, which has become the standard of care (SOC) today, that response rates improved dramatically with SVR rates of around 50% for genotype 1 and 80% for genotype 2/3 infections. For genotype 2/3, SVR rates of as much as 84–95% have been reported from some Southeast Asian countries.³ With exciting developments such as the availability of IL28B genotype testing-guided therapy, directly acting antiviral (DAA) agents and an all-oral drug combination for hepatitis C virus (HCV) therapy on the horizon, evolution to the next level for SOC treatment of chronic HCV infection is now round the corner.^{4–6}

However, excitement is dampened and the sheen of these prospects is dulled in resource-poor countries like India, where the vast majority of patients are not covered by insurance and this expensive therapy is not funded by the state. Many patients with CH-C are unable to even afford evaluation let alone therapy with PEG-IFN- α . With an estimated HCV prevalence of 1–1.9%⁷ and an estimated 12–24 million infected individuals in a population of >1.2 billion, the burden of CH-C in India is colossal. In fact, recent industry estimates suggest that <0.05–0.1% of HCV-infected individuals are being treated with <10,000

individuals currently receiving therapy for HCV in India. This gross under-treatment is primarily due to the inability of vast swathes of the Indian population to afford the prohibitive cost of proper investigation, therapy, and monitoring for CH-C. Newer advances in therapy like IL28B genotype testing and addition of DAA agents to the treatment regimen are only likely to impose an additional burden of cost. As a result, it may be a long, long time before these expensive advances in the field have any significant impact on the large HCV burden in a developing country like India.

It is with this backdrop that a paper in this issue of *JCEH* exploring alternate cheaper treatment options for Indian patients with CH-C must be viewed. Acharya et al⁸ have published, a multi-centric, prospective, randomized controlled trial comparing IFN- α -2b 3 MU/day and ribavirin 1000 mg/day (IR) with IFN- α -2b 3 MU/day and glycyrrhizin 250 mg/day (IG) in CH-C. The first Indian multicenter study of antiviral therapy in CH-C, it is a major study on genotype 3 HCV infection and one of the better designed studies to come from India in this area, in which pre-treatment and post-treatment liver biopsies have been done in almost all patients.

Essentially, this is a study involving a rigorously selected cohort of 131 patients (7.7% of 1700 patients screened) from different parts of India. They were young (mean age, 41; 44% <40 years), non-obese (mean body mass index [BMI], 24.2) men (75%) with moderate necro-inflammation (histological activity index [HAI], 5), early fibrosis (FS 2), no significant comorbidities, a favorable genotype (genotype 3, 71%), and low viral load (93% had load <2 million copies/mL). The SVR with IG combination therapy was inferior to IR (46.9% vs 65.7%, $P=0.03$). This disappointing result with glycyrrhizin for CH-C is similar to results in previously published studies.^{9,10} However, while IG was inferior to IR, results with IG were better than historical results of IFN- α monotherapy and histologic improvement, albeit rather modest, was documented in both the IG and IR arms of the study; these may suggest an antiviral effect against HCV for glycyrrhizin that was weaker than that of ribavirin. Despite the inferior results of IG compared with IR, these observations have emboldened the authors to speculate on a possible role for glycyrrhizin in the treatment of patients with CH-C who do not tolerate ribavirin.

Unfortunately, this study has not done much to clarify the place of glycyrrhizin in the therapy of genotype 3 HCV infection. From the design of the present study, it is difficult to gauge whether the increment in SVR rates seen over historical SVR rates using thrice weekly monotherapy

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Abbreviations: DAA: directly acting antiviral; IFN: interferon; PEG-IFN- α : pegylated-interferon- α ; SOC: standard of care; SVR: sustained virological response

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with IFN- α -2b 3 MU/day is attributable to glycyrrhizin or is due to the daily rather than thrice weekly administration of IFN and a meaningful antiviral role for glycyrrhizin remains a moot point in this study. Lack of side effects is a virtue only when efficacy is comparable; lack of side effects coupled with lack of efficacy smacks of the GIGO effect. The occurrence of anemia in 40% of patients in the IR arm should be construed positively, as an indicator that they had received adequate doses of ribavirin predicting good response to therapy, rather than be interpreted negatively as side effects that need to be reduced by switching to alternative combinations. Finally, though the cost benefits of replacing PEG-IFN- α with standard IFN- α are discussed, and it is mentioned that glycyrrhizin is about a third of the cost of ribavirin, the cost differential between IR and IG regimes and the quantum of savings with IG are not discussed. They are unlikely to be substantial, given that in both regimes the major cost would be of the IFN used.

It is difficult to escape the feeling that such an immaculately planned and meticulously executed study has underachieved due to a conceptual flaw. The decision to compare IR with IG is open to criticism. Comparison of the SOC therapy in 2002, that is, IR, with SOC plus the trial drug (glycyrrhizin), that is, IR+G, would have been a superior design and would have provided valuable information, to wit, whether or not glycyrrhizin adds anything to the IR combination in treatment-naïve patients. In the present scenario, with very few new drugs emerging against genotype 3 from the overflowing pipeline of DAA agents against HCV, mainly genotypes 1 and 4, demonstration of efficacy for glycyrrhizin would have been a boon indeed. Today, it is well accepted that ribavirin is an integral part of all IFN-based antiviral combinations against HCV, playing a crucial role in ensuring high SVR rates, a fact also borne out by the results of this study, and it is difficult to justify omitting ribavirin from any IFN-based regimen against HCV. Admittedly, this is wisdom and criticism through the retrospectroscope; however, it is hard not to rue a chance that has been missed.

Nevertheless, one should not lose sight of the forest for the trees. If one stops focusing on the negative response to glycyrrhizin combination therapy, the bigger picture emerges. The real highlight of the study is the response to conventional IR therapy and the salient message that emerges is related more to the efficacy of the IR arm rather than to its comparison with the IG arm. The SVR rate of 65.7% in the IR arm (67% in genotype 3 CH-C) with standard IFN- α -2b 3 MU OD+ribavirin 1000 mg/day was nearly identical to results reported in genotype-3 patients treated with PEG-IFN (α -2a or 2b)+ribavirin for 24 weeks (SVR 67%) from a north Indian center¹¹ as well as results from a multinational genotype 3 study including Indian patients (SVR 62%).¹² Tohra et al¹¹ have reported SVR rate of 67% in 97 treatment-naïve patients with CH-C genotype 3 with PEG-IFN (α -2a or 2b)+ribavirin for 24 weeks. This

creates the impression that standard IFN- α -2b may be just as good as the PEG molecule in treatment of genotype 3 CH-C, at least in a predicted-to-do-well cohort such as the one included in this study. The relatively poor response of PEG-IFN- α +ribavirin in genotype 3 reported by Tohra et al¹¹ and the almost similar overall results reported by Acharya et al⁸ raise questions about the ideal management of genotype 3 in the Indian subcontinent as well as the role of conventional IFN- α and its dosing when cost constraints may make one alter the treatment plan.

Genotype 3 is the most prevalent genotype in India.⁷ Genotype 3 is usually considered 'easy to treat' and is lumped together with genotype 2 for therapeutic strategies by current treatment guidelines, which recommend only 24 weeks of therapy in combination with a flat lower dose of ribavirin (800 mg/day). However, genotype 3 has some distinct characteristics, which make it stand apart. Firstly, genotype 3 is associated with the occurrence of steatosis. Secondly, it is associated with a more rapid progression to fibrosis.¹³ Thirdly, a higher incidence of hepatocellular carcinoma has been reported with genotype 3.¹⁴ Fourthly, while Telaprevir monotherapy reduces levels of HCV-RNA with chronic HCV genotype 2, it has limited activity in patients with HCV genotype 3.¹⁵ Fifthly, in contrast to HCV genotype 1, where IL28B genotype has been shown to modulate early virological response to PEG-IFN- α and ribavirin therapy, the role of the IL28B genotype testing in genotype 3 remains to be defined.¹⁶ Finally, HCV genotypes 2 and 3 respond differently to anti-HCV therapy and the SVR in patients with genotype 3 are lower than those with genotype 2.^{17,18} The SVR rates with genotype 3 are 66–80% and are in between those reported with genotypes 1 and 2. The inferior response of genotype 3 may be related to steatosis and increased fibrosis. Hence, CH-C genotype 3 may not necessarily be an 'easy to treat' group,¹⁹ and larger clinical trials may further elucidate its treatment.²⁰ So keeping in mind the above poor response characteristics of genotype 3, how does one interpret these two studies from India, one with PEG-IFN- α +ribavirin¹¹ showing SVR rates in the lower reported ranges and another with conventional IFN- α +ribavirin⁸ showing almost similar SVR rates, although IR has shown lower efficacy against HCV in the past?

Inferior response to therapy for CH-C in Asians as compared with non-Asians may be because they present at an older age and have more advanced liver disease at presentation.^{21,22} The initial study of PEG-IFN- α and ribavirin in CH-C genotype 3 from India by Sood et al²³ showed an SVR of 78.9% in low-dose PEG-IFN- α and 92.6% in the standard high-dose PEG-IFN- α group. However, other workers have shown poorer response rates to therapy in the Indian population.²⁴ One of the reasons for an inferior response to PEG-IFN- α and ribavirin reported by Tohra et al¹¹ was that their population of HCV-infected genotype 3 patients included 22/97 (22.7%) cirrhotics. Patients with HCV with

advanced fibrosis and cirrhosis achieve lower SVR rates and even Sood et al²⁵ have observed a 53% SVR in cirrhotics, mostly genotype 3.

Three factors in the study by Acharya et al⁸ may contribute to the SVR rate of conventional IFN- α plus ribavirin approaching that with PEG-IFN- α and ribavirin in the study by Tohra et al.¹¹ Firstly, patients with cirrhosis were excluded from this study and the mean fibrosis score was 2.2 ± 1.52 . Secondly, 93% of the patients treated with conventional IFN- α plus ribavirin had low viral loads⁸ while almost half the patients in the study with PEG-IFN- α and ribavirin had high viral loads.¹¹ The third factor that needs to be considered is the doses of ribavirin and conventional IFN, which were used. Tohra et al¹¹ had used ribavirin at doses recommended for genotype 3 by the American Association for Study of Liver Diseases (AASLD) treatment guidelines, that is, 800 mg/day.²⁶ Acharya et al⁸ had, however, used a higher dose of ribavirin at 1000 mg/day. While current guidelines recommend low-dose ribavirin for treatment of CH-C genotype 3, there are data to suggest that higher dose of ribavirin may improve SVR in genotype 3²⁷ and with high doses of ribavirin, patients achieving rapid virological response may be treated safely with 12 weeks of therapy.²⁸

The dose of conventional IFN- α used in this study needs to be considered when analyzing the response with convention IR therapy. While some workers have shown no difference between daily and thrice weekly standard IFN- α and ribavirin,²⁹ a meta-analysis confirmed that higher doses and/or a longer duration of IFN- α monotherapy could improve the efficacy in CH-C.³⁰ Before this multicentric study was undertaken, the authors had compared thrice weekly IR with daily IR in doses of 3 MU daily in a single center study involving 65 patients. The SVR rates were 95% in daily IFN- α arm vs 64.4% in 3 times a week arm.³¹ Other workers have also shown that daily IR may be more effective than 3 times weekly I+R³² and that the results may be comparable with PEG-IFN- α + ribavirin.³³

These studies illustrate how study variables such as the presence of advanced fibrosis or cirrhosis, viral loads, dose of ribavirin, and IFN- α impact on SVR rates and may influence the outcome as much as the choice between plain and PEG-IFN- α . The suggestive equivalence of the plain and PEG molecule would have found readier acceptance had it come from a head-to-head study. While the sample-size mentioned by authors for a head-to-head study to prove this point (~700 patients in each arm) is daunting, reasons for not undertaking such a study may not be related to sample-size constraints alone, since larger studies have been done. The design of this study does not allow the speculation that plain is as good as PEG to be extended to unluckier patients who have factors such as obesity, diabetes, or advanced fibrosis, which predict a less satisfactory outcome. Short of a head-to-head study, it will be hard to dismiss the speculation that, in patients with less

favorable predictors of outcome, PEG-IFN- α may perform better.

In an era where PEG-IFN- α -ribavirin therapy, the recent SOC, has been threatened by the arrival of newer drugs and the world prepares to move on to newer, more expensive standards of care, the relevance of these observations for India, and much of the impoverished developing world that is saddled with a heavy burden of CH-C, will bear reiteration. Although, advances in treatment of CH-C have sidelined the role of conventional IR therapy, it has shown acceptable results in this study, which should make one pause and ponder before summarily dismissing it for the management of CH-C in resource-constrained settings where devising strategies for reducing cost of therapy is probably the only way to extend the benefits of therapy to the needy. The best part of this study is that it brings out the important fact that, at less than half the price of the present SOC (PEG-IFN- α + ribavirin), nearly equivalent benefit may be provided by conventional IFN- α and ribavirin to a selected subset of patients with genotype 3 infection, such as those with low viral loads and without advanced fibrosis. It highlights the fact that the IR combination remains an important and underutilized option when cost of therapy becomes a consideration. It should do much to dissuade clinicians from blind adherence to the genotype 1 SOC (PEG-IFN- α plus ribavirin) for all patients and venture to use conventional IFN- α plus ribavirin more liberally in appropriately selected patients with genotype 3 infection.

CONFLICTS OF INTEREST

All authors have none to declare.

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