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Perspective

Focusing on the Negative Response to Glycyrrhizin Combination Therapy

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PERSPECTIVE

Major advancements in the treatment of chronic hepatitis C have occurred over the previous two decades (CH-C). The first step in the evolution of CH-C therapy, conventional interferon-Alfa (IFN-) immunotherapy with 3 million units (MU) 3 times weekly for 24 weeks and 48 weeks, had poor outcomes, with sustained biological response (SVR) rates of 6% and 13–19%, respectively. With the addition of ribavirin, response rates improved, and IFN-/ribavirin combination therapy (IR) had SVR rates of 33% and 41% with 24 weeks and 48 weeks of therapy, respectively Response rates improved considerably with the introduction of the paginated interferon alfa (PEG-IFN-) and ribavirin combination, which is now the standard of care (SOC) for genotype 1 and genotype 2/3 infections, with SVR rates of roughly 50% for genotype 1 and 80% for genotype 2/3 infections. SVR rates of 84–95% have been recorded for genotype 2/3 in various Southeast Asian countries. 3 With promising advancements such as IL28B genotype testing-guided therapy, directly acting antiviral (DAA) drugs, and an all-oral medication combination for hepatitis C virus (HCV) therapy on the horizon, SOC treatment of chronic HCV infection is about to evolve to the next level.

However, in resource-poor nations like India, where the great majority of patients are not covered by insurance and this expensive therapy is not financed by the government, excitement is tempered and the lustre of these prospects is tarnished. Many patients with CH-C cannot afford even an examination, let alone PEG-IFN-therapy. The burden of HCV in India is massive, with an estimated HCV prevalence of 1–1.9% 7 and 12–24 million infected individuals in a population of >1.2 billion.

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The SVR with IG combo therapy was lower than that with IR (46.9% *vs.* 65.7%, P= 0.03). This poor result with glycyrrhizin for CH-C is consistent with earlier research findings. 9,10 While IG was inferior to IR, the results were better than previous IFN- immunotherapy outcomes, and histologic improvement was recorded in both the IG and IR arms of the research, albeit modestly; this could indicate that glycyrrhizin has a lower antiviral effect against HCV than ribavirin. Despite the fact that IG had poorer results than IR, the authors were encouraged to speculate on a prospective function for glycyrrhizin in the treatment of CH-C patients who could not tolerate ribavirin. Unfortunately, this study did not contribute much to the understanding of glycyrrhizin's role in the treatment of genotype 3 HCV infection. Because of the study's design, it's impossible to say whether the increase in SVR rates reported with thrice weekly immunotherapy is comparable to previous SVR rates. With IFN—2b, 3 MU/day is due to glycyrrhizin or the daily rather than thrice weekly dose of IFN, and a major antiviral role for glycyrrhizin is a moot point in this investigation. Only when efficacy is equivalent is lack of side effects a virtue; lack of side effects combined with lack of efficacy reeks of the GIGO effect. Rather than being interpreted negatively as side effects that need to be reduced by switching to alternative combinations, the occurrence of anaemia in 40% of patients in the IR arm should be interpreted positively as an indicator that they had received adequate doses of ribavirin, predicting good response to therapy.

Finally, while the financial benefits of replacing PEG-IFN with conventional IFN are acknowledged, and it is indicated that glycyrrhizin is about a third of the cost of ribavirin, the cost difference between the IR and IG regimes, as well as the amount of money saved with IG, are not discussed. They are unlikely to be significant, considering that the principal cost in both regimes would be the IFN utilised. It's impossible not to get the idea that

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such a precisely planned and conducted study fell short owing to a conceptual problem. The decision to compare IR with IG has been questioned. A comparison of SOC therapy in 2002, IR, with SOC plus the trial drug (glycyrrhizin), IR + G, would have been a better design and would have produced significant information, such as whether glycyrrhizin contributes anything to the IR combination in treatment-naive patients. Demonstration of efficacy for glycyrrhizin would have been a blessing in the current context, with relatively few new medications arriving against genotype 3 from the overflowing pipeline of DAA agents against HCV, particularly genotypes 1 and 4.