New Era in Hepatitis C Therapy

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Because of its propensity to become chronic in 80-85% of cases, high incidence of long term chronic sequelae including cirrhosis and hepatocellular carcinoma (HCC), substantial cost of the current antiviral therapy coupled with serious side effects and an uncertain outcome in a significant number of treated cases, Hepatitis C poses a great therapeutic challenge to the medical profession and a tremendous economic burden to the community. Discovered in 19891, Hepatitis C Virus (HCV) - an enveloped, positive sense, single stranded RNA virus - exhibits significant sequence heterogeneity in its 9.6 kb-long genome, leading to the recognition of six distinct genotypes, 1 – 6, with numerous subtypes2. Over the years HCV genotypes have come to be recognized as having important implications in terms of treatment outcomes and relative risk of developing cirrhosis and HCC. It is now well established that genotype influences response to the standard combination therapy of Pegylated Interferon (PEG-IFN) plus Ribavirin (RBV), with the potential for shorter durations (6 months) and higher SVR (Sustained Virologic Response) rates for genotypes 2 and 3 as compared to genotype-1 which requires one year of treatment3. (SVR defined as: a negative HCV RNA test three or six months after the end of treatment). Furthermore, chronic infection with certain HCV genotypes, notably type-3, may be the strongest predictor of development of cirrhosis and HCC4.. Along with viral load, HCV genotype determination has therefore assumed a crucial role in predicting not only the prognosis but also the probable outcome of therapeutic intervention in individual patients.

HCV affects more than 185 million individuals worldwide, of whom about 350,000 die every year5. Based on the current estimates of 4 – 5 % HCV prevalence in Pakistan, we may have a disease burden of more than 8 million HCV infected individuals in our population6. Studies on genotype determination in our country have been few and far between. The available information however indicates genotype 3 to be the most prevalent (80-90%) followed by genotype 1 and 4 (7% and 5% respectively)7. Experience at Islamabad Diagnostic Centre indicates a similar pattern, with 78% genotype 3 followed by type 1 (8%) and type 4 (3%) (Unpublished data).

As mentioned above, because of a less than optimal response to PEG-INF/RBV combined therapy and a high incidence of miserable side effects, huge research efforts had long been underway to find an alternative to interferon. Recent breakthrough in the discovery of Direct Acting Antivirals (DAA) has ushered in a new era of interferon-free Hepatitis C treatment.

HCV genome encodes a single polyprotein cleaved into three structural envelope glycoproteins (C, E1, and E2) and seven nonstructural proteins (NS1, NS2, NS3, NS4A, NS4B, NS5A, NS5B)2. The non-structural (NS) proteins include proteases (necessary for viral proteins synthesis) and RNA polymerase (crucial for viral replication). The DAAs, all orally administered, have been developed specifically to target these enzymes effectively blocking the viral replication8.

Four DAAs have so far been licensed for HCV therapy: three protease inhibitors (PI), Telaprevir, Boceprevir and Simeprevir – and one NS5B inhibitor Sofosbuvir9. The PIs boceprevir and telaprevir, used in combination with PEG-IFN and RBV, have substantially increased SVR rates in persons with genotype 1 HCV infection. Bristol-Myers-Squibb have recently completed phase III trials of their NS5A inhibitors – Daclatasvir and Asunapavir – with SVR rates of above 90% against HCV genotype 1b after 24 weeks of therapy. In a recently reported phase III trial, combination of Sofosbuvir plus Ladipasvir used as a single pill has shown a cure rate of 95% after an 8 weeks course in chronic Hepatitis C without cirrhosis10.

Sofosbuvir (trade name Sovaldi) , developed and marketed by Gilead Science Inc, has shown the greatest promise. It inhibits the viral RNA-dependent nucleotide polymerase, NS5B, which is the most...
important non-structural viral protein, having the key function of replicating HCV genome by using the positive RNA strand as its template. Presently the only all-oral regimen approved by FDA, sofosbuvir given per oral once daily, alone or in combination with ribavirin for 12 weeks achieves SVR in a high percentage of genotype 2 and 3 infections. The drug, in combination with PEG-INF and ribavirin, has also been approved for genotypes 1 and 4. In this rapidly evolving scenario Hepatitis C is now virtually a curable disease. With more than 40 new DAAs in the development pipeline, it is fondly anticipated that “interferon-free, all-oral treatment regimens of shorter duration and broadest spectrum of activity (pangenotypic), with fewer side effects” will become available in the near future. However, the greatest impediment appears to be the exorbitant cost ($84000 for a 12 weeks course of sofosbuvir in the US). It is understandable that the companies need to recover the R & D expenses and make some profit too. But there has to be some way of passing the immense benefit of these drugs to patients in low and middle income countries. It has been suggested that one way of doing this would be for the patent owners to license the medicine to generic producing companies. As an example, price of drugs for HIV/AIDS came down almost 100-fold through the introduction of generics. While there seems to be some progress toward this end, lot more concerted efforts are needed on the part of the national and international agencies, civil society organizations and pharmaceutical companies to work together toward achieving this humanitarian goal.

References

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