Hepatitis C (HCV) is prevalent in Pakistan with an estimated number of about 8 - 10 million patients. The virus affects liver and causes hepatitis which can progress to cirrhosis and ultimately hepatocellular carcinoma. Treatment with interferon and antiviral agents has been shown to reduce its progress to cirrhosis and hepatocellular carcinoma.

From early 90s, the treatment has been standard interferon and ribavirin. After the introduction of Pegylated Interferon (PEG-IFN), various formulation of PEG along with ribavirin had become the standard of care and had given reasonable response. However, the treatment is accompanied with significant side effects including hematological and neuropsychiatric symptoms.

The life cycle of hepatitis C virus had prompted the scientists to work on the various stages of replication of virus. By now, several Direct Acting Antivirals (DAA) like Protease inhibitors and Polymerase inhibitors have been introduced for combination therapy of HCV infection. The first generation Protease inhibitors included telaprevir and boceprevir which have been particularly useful treatment of genotype-I infection. However, they have low genetic barrier to resistance, have cumbersome side effects and multiple daily dosing schedule. More recently, second generation Protease inhibitor simeprevir was introduced and its combination with PEG and ribavirin had given satisfactory result, especially in genotype-1 patients. This has fewer side effects, convenient dosing schedule helping in patient compliance and has pan genotypic activity.

The introduction of DAA nucleotide polymerase inhibitor HCV NS5B, sofosbuvir has been a breakthrough in the management of HCV. This combined with PEG and ribavirin has given more than 90% response in genotype-1 patients. However, its combination with ledipasvir, an NS5A Proteinase inhibitor, in a fixed-dose single tablet combination of 400 mg of sofosbuvir and 90 mg of ledipasvir given once daily for 12 weeks resulted in 99% Sustained Virological Response (SVR) in HCV genotype-1 patients. It has also been possible in difficult-to-treat patients who have advanced liver disease and who have previously failed on the treatment resulting in 94% SVR. Addition of ribavirin did not give additional response. Although sofosbuvir alone is not effective, a combination of sofosbuvir with ribavirin has been used for genotype-3 patients resulting in 85% response.

With second generation protease inhibitors and polymerase inhibitors, there have been large number of drugs that have been already available for use in the clinical practice and some of the newer ones have already been approved for use in Japan. Many pharmaceutical companies are in a race to develop effective combinations of protease inhibitors and polymerase inhibitors and many are in the final stages of development.

These DAA currently fall into four categories: (1) NS3/4A protease inhibitors: faldaprevir, asunaprevir, vedroprevir, danoprevir, vaniprevir, sovaprevir, narlaprevir, simeprevir, telaprevir, boceprevir, (2) NS5A protease inhibitors: daclatasvir, ledipasvir, (3) NS5B nucleoside type polymerase inhibitors: sofosbuvir, mericitabin and (4) NS5B non-nucleoside type polymerase inhibitors: deleobuvir, tegobuvir, strobuvir.

There is going to be increasing popularity of these drugs because they are likely to obviate the need of interferon and side effects are minimal, very acceptable and the response rates are near 90 to 100% in certain cases. Their side effects have generally been mild and acceptable like headache, fatigue, nausea and pruritis, rarely necessitating need for their discontinuation.

Combination of two or more of DAAs may be helpful with the aim to achieve pan genotypic HCV activity and little or no risk of resistance, shorter duration may be around 12 weeks and a better SVR. Newer trials are aiming for an interferon free regimen of just 4 weeks. The use of these drugs may not completely eliminate the need of interferon which may still be indicated in certain specific reasons where the combination of these agents with interferon may be helpful.

Interferon was once considered backbone of therapy of HCV and remained for nearly 20 years and with various combinations resulted in fairly satisfactory response. Pegylated interferon will now have a smaller role. It may be helpful as a part of quad therapy where two DAAs and ribavirin may be used for non-responders or for patients who fail DAA regimens with multi-drug resistance to HCV. In resource limited region like Pakistan, where the DAAs may be unaffordable, PEG...
still may have a role and it may also be ultimate salvage therapy when there is no response to DAAs.

Current recommendations for HCV therapy for genotype-3 in rapidly evolving DAA era is use of sofosfovir with ribavirin for 24 weeks in naïve patients and PEG with sofosfovir and ribavirin for 12 weeks in patients who did not respond to PEG and ribavirin. Patients with cirrhosis who cannot tolerate PEG should be treated for 24 weeks (Table 1).

While the use of these drugs will become more popular, we must consider various factors that should be kept in mind. First of all, the experience has been short and the reported side effects have been minimal; one will have to keep in mind for any unexpected side effects that may arise with more extensive clinical use. Secondly, the trials in genotype-3, which is encountered in our country, are sparse and its efficacy as reported may not be quite applicable in our case. Thirdly, the treatment regimen recommended for genotype-3 may not prove as thought. Therefore, we may need to generate local data for these drugs. Fourthly, as many of these regimens are going to be interferon free regimens, there is a possibility of unscrupulous use of these agents. This may result in the development of resistance of the virus. Moreover, we need to develop certain protocols for the use of these agents and they should not be freely available to be advised by untrained professionals.

Finally, the most important problem with these new drugs is the cost factor and this has become a major issue in US and European countries, not to talk of less developed countries like Pakistan. However, there are programs in which the drugs may be made available in the less developed countries in a much lower cost, as compared to the cost in the US. Several strategies for access to DAAs in low income countries have been suggested. These have included creating novel international funding streams (e.g., the Global Fund to Fight AIDS, Tuberculosis, and Malaria and the US President’s Emergency Plan for AIDS Relief) on the line of antiretroviral drugs for AIDS.

It has been estimated that with the use of these agents HCV may be eliminated by 2040 in US and Europe. With all oral regimens for HCV management are making their entry into clinical practice, situation in Pakistan, public awareness and the cost factor will still have to be worked out. And when will we be able to eliminate HCV from Pakistan is a major question.

REFERENCES


