Editorial

Hepatitis C Virus: Discovery to epitaph in a life-time

When I was a resident, training in internal medicine during the 1980s, the word 'hepatitis C' was not yet a part of our vocabulary. Yes, we did learn about 'parenterally-transmitted non-A, non-B hepatitis virus'—a putative agent responsible for a proportion of patients with hepatitis, mostly subclinical, among blood transfusion recipients. The situation was no different during most of my gastroenterology training. The first time I heard the phrase 'hepatitis C virus' (HCV) was in April 1989, when two seminal papers in *Science* reported the isolation and cloning of a nucleic acid segment, believed to represent HCV, from serum of a patient with post-transfusion hepatitis,[1] and the development of a test for detection of antibodies to this virus.[2] Admittedly, the phrase had been used in some previous reports, but was known only to those who were focused on hepatitis research.

This was followed by a flurry of papers that searched for evidence of HCV infection in people with various parenteral risk factors and diseases, as well as in healthy populations around the globe. It was soon apparent that a large proportion of patients with 'cryptogenic' chronic liver disease (including cirrhosis or liver cancer) worldwide were related to HCV infection, and that several otherwise healthy persons, many with and some without parenteral risk factors, also had this infection. Studies on the natural history that followed revealed that HCV infection, though often asymptomatic, led to slowly-progressive liver fibrosis, culminating in chronic liver disease in nearly 20% of those infected. We understood the modes of HCV transmission well, and learnt that the infection could be prevented through safe blood transfusion and injection practices. However, the treatment options were virtually non-existent.

Thus, at that time, encounters with persons recently diagnosed to have chronic HCV infection typically went somewhat like: 'Do not worry. The disease progresses slowly—over several years. We do not expect anything bad to happen in the immediate future. We will assess you every year. If and when cirrhosis develops, we should be able to manage it. And by that time, liver transplantation should be available in India.' All this was said while the physician was wringing his hands beneath the table. Yes, we did have an option. Subcutaneous injections of recombinant interferon alpha for 24 weeks had been shown to provide lasting improvement in tests of liver function in nearly one-fourth of patients.[3] We did offer this treatment to those who could afford the high cost, and some did bite the bullet. However, many of them discontinued the treatment prematurely because of adverse effects, but both the patient and the physician had the satisfaction of having tried the best available option.

Slowly, the treatment advanced. First, the addition of ribavirin to interferon was shown to improve the response rates. Then, in 2001, a randomized trial showed that a combination of pegylated interferon, in which interferon was bound to polyethylene glycol (increasing the former's half-life), and ribavirin was 'highly' efficacious, achieving cure of the infection in about 50% of those treated—once considered impossible.[4] Further and importantly, this treatment needed only one injection a week than the previous three, reducing the frequency of adverse events. This was welcome news. The combination treatment was accepted worldwide and soon became the standard of care. We, in India, were happier, since the response rates were better in persons infected with genotype 3 HCV,[5] which accounted for nearly three-fourths of our patients.[6] Nature had dealt us a better hand than to the developed world, which had mainly genotype 1 virus. High cost was still an issue but at least we had a weapon. Those who could afford this treatment took it—hoping to get rid of the virus—and many did achieve cure. For those who could not,

or failed to achieve success, we still had our soothing words! And life cruised along. Adverse effects were still a problem, and the combination did not work in those who already had advanced cirrhosis.

In the early 2010s, one learnt at conferences that researchers were using the newly gained knowledge about HCV biology to develop a new group of drugs that would act specifically against this virus—the direct-acting antiviral agents (DAAs). Two new kids appeared on the block in 2011—telaprevir and boceprevir—which inhibited the protease enzyme of genotype 1 HCV. However, these were not the magic bullets that we expected them to be. Though their addition did improve the efficacy of the established treatment regimen, it also meant several tablets daily, more adverse events and a risk of developing drug-resistant strains of the virus.[7] As these drugs did not act on 'our' genotype 3 HCV, they were not marketed in India.

However, there was more in store. The tsunami finally arrived in 2014 in the form of more powerful DAAs. These newer DAAs which interfered with other HCV proteins—known as NS5a and NS5b—proved to be game-changers. Regimens that contained a DAA compound with interferon and/or ribavirin,[8] and later combinations of DAA compounds[9] for as short as 12 weeks achieved sustained virological response—an euphemism for permanent cure of HCV infection—in more than 95% of those treated. Currently, several regimens that include either two (NS5a +NS5b inhibitors) or three (in addition, a protease inhibitor) DAAs acting on different viral proteins have been shown to have cure rates exceeding 95% in those with HCV infection without cirrhosis or with compensated cirrhosis, and somewhat lower (80%–90%) cure rates in even those with decompensated cirrhosis.[10] The excellent results observed in trials have been replicated in real-life settings. Moreover, DAA combination regimens work well also in HCV-infected groups that were traditionally considered difficult-to-treat, such as those with renal failure, HIV coinfection, or those receiving immunosuppressive drugs (e.g. recipients of solid organ transplants). Recently, even shorter treatment regimens, as short as for 8 weeks, have been tested and found to have comparable efficacy.[11] Work is on to develop even shorter (3–4 weeks) regimens.

These new developments have energized hepatologists as well as public health communities worldwide. They now believe that, given the high rate of permanent cure with current highly-efficacious and safe treatment regimens, it should be possible to eliminate hepatitis C as a public health problem. Thus, in May 2016, the World Health Assembly endorsed WHO's Global Health Sector Strategy for Viral Hepatitis which envisages elimination of hepatitis C,[12] which is defined as: (i) 90% reduction in new cases of HCV; (ii) detection of HCV infection in 90% of those infected; and (iii) treatment and cure of HCV infection in 80% of persons eligible for current treatments. Successful achievement of these targets would reduce the mortality due to hepatitis C worldwide by 65% by the year 2030. This would have been unimaginable even 5 years ago.

So, what would it take for this rosy picture to become a reality? First, easy and wide availability of the DAAs all over the world, and at reasonable prices. These drugs entered the market at a high cost—an astounding US$ 84 000 for a 12-week regimen. In developed countries, though the prices have come down somewhat, these drugs continue to remain beyond the reach of many patients. Fortunately, these drugs are available in India through licensing agreements between the original manufacturers and several Indian generic drug manufacturers at about ₹30 000 for a complete 12-week regimen. The licensing agreements permit the marketing of these 'generic' drugs in several low- and low-middle-income countries, but this can happen only after these drugs have been approved by the national drug regulatory authorities in these countries.

The prices of these drugs in India are a huge bargain. Using a mathematical modelling technique, we have shown that HCV treatment at this cost is not only cost-effective, but actually cost-saving.[13] This implies that the cost of treatment will be more than offset by savings in future healthcare costs, thus leading to an overall monetary saving while improving survival; a win-win situation.

Second, even these 'cheap' drugs are beyond the reach of many in India and other developing countries, and hence novel solutions are needed to improve access. Since the treatment with generic DAAs is cost-saving, governments in countries with such low drug prices should ideally use public money to pay for this treatment. It is noteworthy that governments of some Indian states have already started such initiatives. For instance, the Punjab government is currently providing free HCV treatment to all eligible persons,[14] and has been able to buy the drugs at prices much below the market prices indicated above. Even when this is not possible because of budgetary limitations, governments can help by

(i) providing a partial subsidy on drug cost; or (ii) by purchasing the drugs in bulk (which would allow for better discounts to be negotiated with pharmaceutical companies) and then making these available to patients at prices lower than that in the market.

Third, we need to find HCV-infected persons who would benefit from treatment. HCV infection is largely asymptomatic, and hence most of those infected with the virus are unaware of their status. Thus, we will need to first find those infected using large-scale HCV screening programmes, initially among those with identifiable risk factors for HCV infection, and later in the general population. For us, in India, blood transfusion prior to 2000, when HCV screening of donated blood became mandatory, is possibly the best such identifier.

And finally, the large number of HCV-infected persons (about 7 million in India) cannot be treated by hepatologists and gastroenterologists alone. To make a major impact, it is imperative that the medical profession undertakes a major task-shift, whereby the diagnosis and treatment of HCV infection moves into the hands initially of internists and later non-specialist doctors. This poses a major challenge. One can foresee resistance from the specialists—because task-shift means income-shift; also, willingness of the other groups to take on this responsibility remains unclear. Hopefully, the medical community would realize that such opportunities do not present often in the field of medicine, and all would rise to the occasion.

What about an HCV vaccine? We know that vaccines have led to marked reductions in morbidity and mortality caused by several infectious agents. For instance, the vaccines against hepatitis A virus and hepatitis B virus have led to major reductions in the disease burdens caused by these pathogens. However, development of a HCV vaccine has faced major technical challenges. Fortunately, the routes of transmission of HCV are easily amenable to simple interventions. And now we have an additional tool available for this purpose—'treatment as prevention'. It is believed that increasing use of DAA-based treatment and successful cure of infection would lead to reduced opportunities for the transmission of HCV not only in high-risk groups (e.g. injecting drug-users) but also in the general population, thereby reducing the number of new cases. In fact, we may soon face a situation where, if a vaccine is developed against HCV, we may not have much use for it.

In the end, let me fast forward to 2030, when I will be ready for retirement from active professional work. Hopefully, by then, hepatitis C would be a much smaller public health problem. If WHO's vision succeeds, we would have cut the annual mortality due to HCV infection by two-thirds. So, within my professional life span, I would have seen it all—from 'the beginning' to at least the 'beginning of the end', if not 'the end'. What a satisfying journey it would have been!

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