

Review

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HCV-discovery to elimination, “myth or reality”

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Abstract

Hepatitis C virus (HCV) was discovered in 1989, before that it was commonly known as transfusion associated non A non B hepatitis. It rapidly assumed the role of leading cause of cirrhosis and liver cancer and a leading indication for liver transplant globally. For over two decades the treatment was suboptimal with the use of pegylated interferon and ribavirin combination across all genotypes. The vaccine development also failed for over two decades. However a major breakthrough happened in December 2013 when the Food and Drug Administration (FDA) approved the first pan genotypic oral directly acting drug Sofosbuvir. Since then many new directly acting drugs have been approved through fast track by the FDA. Today we have directly acting antiviral agents for all HCV patients providing cure rates of over 90%. Looking into this success the World Health Organization has set targets for 2030 for HCV elimination. There are several countries which have formed strategies to achieve this goal and others are still thinking to develop their own strategies. The availability of generics have reduced the prices substantially, however the problem is so gigantic that unless proper operational strategies for elimination are developed by the developing world especially by China and Pakistan, the two counties having the largest existing pool of HCV patients, the goals of elimination may not come true.

Keywords: Hepatitis C virus, elimination, directly acting antiviral agents, Pakistan

INTRODUCTION

Year 2015 has seen the major developments on the fronts of global reawakening for curtailing down the huge burden of viral hepatitis by the World Health Organization (WHO) adopting the 2030 Agenda for Sustainable Development goals, which called on the global integrated efforts to combat viral hepatitis. It was not long when the burden of health care related to the human immunodeficiency virus (HIV) was



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enormous, but sustainable achievement of goals and target oriented approach has given this viral pandemic a breakpoint and we are seeing a decline in the global prevalence of HIV. WHO on similar grounds and experiences has acquired a target oriented approach on the issue of ever increasing burden of viral hepatitis. At the beginning it seems like a myth, but it can be made a reality with advent of new frontiers in the management of chronic viral hepatitis.

History

Viral hepatitis is one of the biggest health problems and discovery of causative viruses is one of the most significant breakthrough scientific achievements in this era. Previously identified as “Australian antigen” and later on described, as hepatitis B virus surface antigen (HBsAg), is often regarded as the initial discoveries in the history of viral hepatitis^[1]. A literature search of military records of first and second world wars revealed that “campaign jaundice” caused significant health related problem of the troops and caused a significant impact on war strategies^[2].

Discovery of non A non B hepatitis (NANBH) as hepatitis C virus (HCV) in 1988 was a milestone, a collaborative work of Centre for Disease Control (CDC) and California biotechnology company^[3]. Although the actual virus was identified later, this effort brought a novel molecular method for viral genome identification. Houghton and colleagues, the pioneers of this method, identified the unique cDNA using sera of chimpanzees and humans with NANBH that crossed with a single stranded RNA which was only extracted from NANBH patient^[4]. From the next year antibodies to HCV were measured, which laid down the foundation of blood screening for HCV in 1990^[5,6]. Major hurdle after identification of these viruses was to bring about the therapeutic measures into existence, to control their spread and eliminate them. Further developments in the form of therapeutic hepatitis vaccines and oral agents became one of the major advancements on the frontiers of treatment.

HCV characteristics

HCV has viral and genetic characteristics in common with the Flaviviridae family^[5]. The HCV surrounds its RNA with a protective coat known as the capsid, which is built from proteins. This enveloped, spherical virus of approximately 50 nm in diameter^[5], has an estimated half-life of 2.7 h^[6]. Daily, 10 trillion (i.e., 10¹²) virions are produced and cleared in an untreated individual with HCV infection^[6]. Structurally, the HCV genome is an unsegmented, linear single strand of RNA of positive sense^[5]. The genome is approximately 9.6 kilobase (kb) in length, comprising a polyprotein of about 3000 amino acid residues^[7].

HCV is a considerably heterogeneous family of viruses, with at least 6 known genotypes (genotypes 1 to 6) and numerous (> 80) subtypes^[8]. Additionally, in an individual, HCV can form heterogeneous populations of viral genomes that are closely related but different viruses^[8]. The quasispecies nature of HCV and the envelope structure of the virus may be promoting factors in its rapid mutation by allowing it to escape immune surveillance of the host^[9].

Global burden

Viral hepatitis is a global health burden and a leading cause of death worldwide, according to WHO 1.34 million death was estimated to occur in 2015 as a result of HCV infection. These numbers are comparable to or exceed the number of deaths caused by tuberculosis and HIV. Mortality due to viral hepatitis has seen new peaks in the recent years and most deaths in the context of viral hepatitis in 2015 were due to chronic liver disease (720,000 deaths due sequelae of decompensated cirrhosis) and primary liver cancer (470,000 deaths due to hepatoma). During the same year, approximately 257 million people were chronically infected with hepatitis B virus, and chronic hepatitis C (CHC) infection was responsible for 71 million infections^[10]. The ongoing HCV epidemic is affecting all regions with major differences between and within countries. The WHO 2015 report has described Eastern Mediterranean Region and the European Region as showing the

rising reported prevalence of HCV. After the population shifts and migrant crisis due to current geopolitical scenario in the northern African countries and Arab world, reported prevalence in the bordering areas is again increasing^[10]. On the other hand China and Pakistan are placed in the 2017 WHO report as the areas of world with highest prevalence of CHC, which claims 350,000 lives every year in the world. The global burden of chronic hepatitis B is around 350 millions, killing around 600,000 people yearly^[11].

With the advent of highly successful therapy (> 90% success rates) for CHC as directly acting antiviral agents (DAAs), the treatment duration has shrunk to 8-12 weeks for most of the time, despite this major advancement, as of 2015 out of 71 million people infected with CHC, only 7% had access to this therapy^[12].

For United States of America, CDC described that 3 to 4 million people are infected currently with HCV. While in Egypt, the situation was very grave till early 2015 when Egypt was ranked as the country with highest prevalence, with a prevalence rate well above 10%. The prevalence of infection is greater than 10% in certain parts of Asia with high rates found in certain geographic regions of Taiwan, Japan and Italy. However, there are a number of countries/regions where data are not available^[13,14].

Hepatitis C epidemic in Pakistan

Situation in Pakistan is grave, as it's been placed among highly prevalent countries. Recently Pakistani researchers have increased their focus on studying endemic patterns of HCV infection and genotype distribution leading to publication of eighty six relevant studies^[15]. This data on increasing prevalence have been comprehensively reviewed previously^[15-17]. Pakistan has the second largest burden of hepatitis C^[11], prevalence data published locally in last seven years has shown alarming figures with an almost 40% increase in HCV antibody detection rates in general population as per the recent review published in 2016 by Umer *et al.*^[15]. This all translated into high nosocomial transmission rates, highest burden in economically disadvantaged areas and in marginalized communities. A shift in relative distribution of genotypes in Sindh and Khyber Pakhtunkhwa provinces is seen, which the predominant areas are dealing with migrant crises and internally displaced peoples (IDPs). A nationwide survey on prevalence of hepatitis B and C was done in 2007-2008 which estimated that approximately 8 million people are exposed to HCV^[18], and 2010 saw a landmark step as the establishment of hepatitis sentinel sites nationally and surveillance system located in provincial and federal capitals^[19]. Despite these landmark developments, still they are far behind than what was expected from these centres in terms of their clear task of bringing about an integrated service model for identifying what is beneath the tip of the iceberg of HCV epidemic in Pakistan, as more recent estimates suggests that Pakistan is home to one-tenth of the global HCV burden^[20].

Between 2016 and 2030, it is estimated that Pakistani population will be around 250 million, and prevalence of HCV will rise from 3.9% to 5.1%, with a disturbing figure of 1.4 million deaths among those over 20 years of age. Burden of this endemic infection will continue to rise with 12.6 million prevalence of CHC and a projected 1.1 million new infections with each passing year^[21].

HCV-elimination strategies

Global hepatitis strategy by WHO defined a goal to eliminate viral hepatitis by 2030 has been adopted, which can be achieved by reducing incidence by 90% and mortality by 65%, calling for integrated and collaborative work and dedication by the policy makers and health care providers.

The World Health Assembly endorsed a Global Health Sector Strategy (GHSS) on viral hepatitis 2016-2021, in May of 2016. This will translate into the elimination of viral hepatitis by 2030.

Five key pillars of global health sector strategy include strategic information, interventions equity, financing and innovation. These key elements are devised for facilitation of progress monitoring globally, regionally

and nationally. This will enhance the methodological calculation of impact of different interventions and tools used to reduce rates of new infections and saving precious human life between 2016 and 2030. These strategic parameters are aligned with plans and strategies of other relevant programs including those for sexually transmitted infections, HIV, blood safety, safe injections, vaccines, tuberculosis and non-communicable diseases. This integrated model will give an end to viral hepatitis and net result on elimination of the disease.

Hepatitis C treatment

Risk of disease progression in patients living with CHC can be prevented by effective screening and diagnostic modalities and by proper implementation of care linkage, and provision of highly effective anti viral therapy. HCV patients with risk behaviors should be targeted and effectively engaged in the linkage to care and should be offered sound counseling, this will help reduce further spread of infection. This is the key element that has been stressed by different hepatology society guidelines. Engaging communities in screening activities and linking counseling with care and treatment strategies are needed for combating HCV epidemic. Treatment affordability as a major barrier for successful strategy is another concern apart from other barriers.

With the advent of DAAs, cure rates exceeding 90% even with newer 8 weeks pangenotypic regimens have been reported in large trials. Despite this astonishing success in the therapeutic armamentarium of CHC the low and middle income countries are not able to handle the problem with success as the national strategic plan for the elimination of Hepatitis C by 2030 for most of the countries is not developed.

Economics

A few impressive calculations determined that treating patients annually with a number exceeding 328,000 persons by 2018 could reduce the prevalence of HCV by 94% and liver-related mortality by 75% by 2030. Calculations regarding disability-adjusted life year (DALY) with or without cirrhosis also given this therapy high cost effectiveness, while taking into consideration the indirect costs, this intervention is again cost saving^[22]. Requirements for meeting the WHO targets include removal of restrictions for treatment by treating all the patients, providing access to everyone and screening at mass levels, so that 80% of infected persons will be diagnosed by 2030 and 260,000 patients would continue to be treated per year. This methodological approach will curtail down infections by 90% and prevent nearly a quarter million mortality in next 13 years. While challenges have been encountered persistently in the developing world due to poor and reliable data management mechanisms and quality of hepatitis services provided and a limited timely intervening capacity. Apart from these, safe and necessary injection practices and disposal of waste in effective manner are also among the major barriers.

Strong government commitment to new treatments is necessary to ensure universal coverage. According to the European Liver Patients Association (2017), national plans must be developed and include forecasting and budgeting to expedite unrestricted access to treatment, in order to succeed in eliminating HCV.

Global strive towards elimination of HCV

After WHO's 2030 elimination goal was laid down in 2015, till now only 9 countries are on the track of achieving this goal. While 22 countries are working towards the direction of achieving on-track policies, the rest of the world is still far behind the laid down parameters^[11].

A glimpse of global policy making; European and Australia: Universal access to DAAs

Only a few of the countries reviewed, have granted universal coverage for DAAs. Australia, Portugal, Germany, and since 2017, France and Italy, offer access to DAAs for all patients, regardless of their level of fibrosis. Scotland and England do not have fibrosis requirements, but have limits on numbers of patients

who can be treated each year, so usually only patients with higher fibrosis levels receive treatment. Other countries such as Spain, Belgium, and Switzerland only provide treatment for patients with a certain fibrosis level by prioritizing severe cases. Some of these countries are already considering broadening access to additional fibrosis levels. For instance, in Spain access has been broadened to all fibrosis levels in some regions and commitment to broaden it at national level has been recently announced; and in Belgium access was extended to second stage fibrosis (F2) patients in January 2017, and full access is expected by 2019.

Patients who inject drugs, a European and Australian approach

The European Monitoring Center For Drugs and Drug Addiction (EMCDDA) has been working since the era of HIV. It has published different policies on its website and those were heavily cited and were taken into consideration by major health providers. It has recently been presenting its data describing insights for policy making to halt the HCV prevalence in the EU and Turkey but also the strategies for meeting the 2030 elimination goal.

According to EMCDDA report 2017^[23], 14 EU countries plus Norway have HCV policies in place, which are very effective. Thirteen of them were adopted recently between 2013 and 2017. Nine EU countries have clinical guidelines limiting treatment access to people who use drugs.

After effectively bringing down the prevalence in general population of EU countries, and providing treatment to all patients who are chronically infected with the exception of a few EU countries. Now the focus is on patients who inject drugs (PWIDs), which includes lifting the ban from those who are actively injecting and treating this population apart from providing them more syringes to break the transmission chain^[24].

The European Liver Patients' Association (ELPA) is also providing a platform for policy making as is reflected by the Hep-Core 2017^[25] study, which is acting as a benchmark for monitoring changes in European policy landscape.

As per the current policies, EU and Australia will achieve the WHO target much earlier than 2030.

Egyptian model, an eye opener for the middle to low income countries

In the middle and low income countries the Egyptian model is the best strategy for combating HCV. Egypt was regarded as one of the countries with the highest prevalence till 2015 according to WHO report^[11]. This was the outcome of mass treatment with unsterilized syringes for schistosomiasis during 1960s to 1980s, which has represented the largest ever iatrogenic spread of blood borne infection in the history^[26]. After this mammoth burden with an estimated 10% seroprevalence^[27], the agreement of Gilead Sciences, than Bristol-Meyers-Squibb and Ministry of Health, brings down cost of Sofosbuvir and Daclatasvir and making local brands in much cheaper cost. Then with continuous efforts of opening up of health care provision, treatment centres and web based appointment system, Egypt is regarded as being on the right path as per latest estimates from local and international audits^[28]. Egyptian model is not only cost efficient but also easily acquirable. Egypt is the only low- and middle-income country, among nine of countries which are on the track of WHO 2030 elimination program.

Situation in Pakistan

According to latest estimates^[11] Pakistan has the second largest viremic pool of HCV patients after China, with ever increasing morbidity and mortality due to this highly prevalent infection in the country. With the advent of DAAs, like the Egyptian strategy of getting Sofosbuvir in low cost, Gilead Sciences gave the similar licensure to Ministry of Health, Pakistan, by this effort and now with the availability of the generic

Sofosbuvir and Daclatasvir, generic brand is available here in Pakistan in < than \$50/month of therapy, while generic Sofosbuvir with ribavirin is reaching below \$20/28 day therapy^[24]. Due to lack of continuous health surveys in a country of 220 million population, the estimates available only show the tip of the iceberg^[28]. Health care system is still in the phase of continuous evolution and ongoing acquisition of web based system, striving to achieve smooth data collection and management which is the key element in assessing the population at risk and marginalized communities. As per Polaris observatory^[11] Pakistan is among those countries which are not on the track yet.

The training in emerging advances in the management of CHC infection for healthcare professionals in Pakistan (Teach-Pak) project

The Teach-Pak has started a large scale physician training module system for management of liver disease. Every year two to three batches of physicians based all over Pakistan are been trained via this program and this has started showing its impact. These trained physicians then educate the physician community in their respective area of practice^[29].

The concept of micro-elimination of HCV, a Pakistani perspective

There are multiple welfare and philanthropic organizations, which are working extensively on the marginalized communities, i.e., prisoners, trans genders, PWIDs, for promoting health care seeking behavior, awareness of health risk practices and exposures and treating them free of cost with latest available options in the developing world for both hepatitis B and C.

Similarly Pakistan has seen the major disruption of its health care system after the historical migration of Afghans during the era of 1980s, and again during 2000s and till now IDPs, that is the main driving force of disruption of health care provision and substantial additional burden on economics of already resource-poor setup. This community is a challenge; it is extremely difficult to engage them in the health care assessment due to persistently changing dynamics, lack of education and religious and cultural taboos.

Despite all the hurdles, Pakistan has developed strategic HCV elimination program as per WHO guidelines in October 2017, but the country is striving to come up with a proper implementation of healthcare policies providing free of cost DAAs in government hospitals. It will be evident from the upcoming national survey that how far the goal of WHO elimination program is from current strategies observed in Pakistan.

CONCLUSION

With the discovery HCV in 1989 and development of all oral hepatitis C therapy 2014, the world is looking at the rise and fall of a virus, which became a global epidemic. It played a major havoc globally especially in the low and middle income countries. With appropriate provision of health care delivery, early detection, universal treatment of all chronically infected, close follow up and special attention towards marginalized communities, the WHO 2030 elimination goal will not be regarded as a myth but a reality.

DECLARATIONS

Authors' contributions

Concept and design, critical revision and finalizing of the manuscript: Jafri W

Data acquisition: Siddiqui B

Data analysis: Awan S

Manuscript preparation: Awan S, Siddiqui B

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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