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Treatment of Chronic Hepatitis C Virus Infection Using Pan-Genotypic Combinations of Direct Acting Antiviral Agents: A Laudable Paradigm Shift.

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Abstract: *Hepatitis C virus (HCV) infection is a preventable cause of death that affects people all over the world. World Health Organization (WHO) estimated that in the year 2015 alone, 71 million persons in various nations of the world had chronic hepatitis C Virus infection. In the same year, cirrhosis of the liver and hepatocellular carcinoma caused by HCV infection was responsible for the death of 399,000 people around the world. Although HCV, a positive stranded RNA virus of the genus Hepacivirus, was discovered about 3 decades ago, there is no vaccine yet for prevention of the disease that it causes.*

Treatment of chronic hepatitis arising from HCV infection had been with pegylated interferon alfa and ribavirin until drug trials established the superior efficacy and tolerability of appropriate combinations of Direct Acting Antiviral agents (DAAs). A few months ago WHO published laudable new guidelines for the treatment of chronic hepatitis C infection using combinations of DAAs.

In this paper we highlight the public health significance of HCV infection and the recently recommended curative regimens using pan-genotypic combinations of DAAs.

Key words: *Hepatitis C virus, chronic hepatitis, treatment, direct-acting antiviral agents.*

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I. Introduction

HCV a major cause of chronic hepatitis and morbidity globally

Hepatitis C virus (HCV) infection is a major global public health problem. It affects people of both genders and of all age groups in both developed and developing countries all over the world. There has been challenging epidemics in various parts of the world including the Sub-Saharan African, Eastern Mediterranean and the European regions [1, 2, 3, 4]. It was after HCV was discovered in 1989 that it was realized that what had been known as post-transfusion viral non-A non-B hepatitis was caused by HCV [2].

WHO estimated that in the year 2015 alone, 71 million persons in various nations of the world had chronic hepatitis C Virus infection. In the same year, cirrhosis of the liver and hepatocellular carcinoma caused by HCV infection was responsible for the death of 399,000 people around the world. As much as 3% of the world's human population have been infected HCV though the majority of the new infections are occurring in poor developing nations [5, 6, 7]. HCV infection is the most common indication for liver transplantation in technologically advanced countries [8]. It has been reported that of all persons that get infected with HCV, 15% self-resolve while 85% go on to develop chronic liver disease with viraemia, and subsequently fibrosis, cirrhosis and, in about 30% of patients, hepatocellular carcinoma [9, 10].

About 325 million people globally are living with chronic hepatitis due to both hepatitis C virus and Hepatitis B virus infections. Out of the five well known forms of viral hepatitis, HCV and HBV account for 96% of the overall deaths due to viral hepatitis globally [5]. Whereas deaths from tuberculosis are declining worldwide, new infections are being recorded for HCV and increasing deaths are arising from viral hepatitis worldwide [5]. These statistics call for more concerted action to control and eventually eradicate viral hepatitis globally.

Hepatitis C virus: a pathogen that produces a subtle but potentially devastating illness.

Hepatitis C virus is a positive stranded RNA virus of the genus Hepacivirus and of the Flaviviridae family. This family of viruses includes the yellow fever virus and the dengue virus [11, 12]. It is an icosahedral enveloped virus. HCV replication is very dynamic with viral half-life of 2-3 hours [13]. Its primary host the non-human primate chimpanzee.[2, 11] As chimpanzees are the only animal models for HCV research [2, 11], the development of genetically modified HCV-permissive mice became necessary for widespread use in HCV research [15, 16].

HCV has wide genetic heterogeneity [17, 18, 18]. It has at least 7 genotypes and several subtypes. There are variations in geographical spread of the various genotypes of the virus. The responses of various genotypes to some antiviral agents also vary. Interestingly too, the propensity for HCV infection to progress to chronic liver disease and other complications has also been variable, depending on the genotype of the infecting Hepatitis C virus [3, 20, 21, 22]. Hence, HCV genotype testing was routinely required to guide the choice of medicines for all patients.

Transmission of HCV to man is mainly by parenteral routes including blood transfusion, reuse of injection needles, organ transplantation, tattoos, hospital procedures, as well as through sexual contact [23, 24, 25, 26].

The entry of HCV into liver cells is known to be mediated by viral glycoproteins E1 and E2. The binding of viral glycoprotein E2 to receptor CD81 of host cell is vital to the entry of HCV into host cell and for the establishment of infection in man[27, 28, 29, 30].

Hepatitis C Virus in itself is not directly cytopathic in the liver. Injury to liver cells results from host immune responses to the invading pathogen and the attendant local inflammatory processes leading to fibrogenesis, fibrosis, and liver cirrhosis [31].

Most cases of HCV infection (50-90%) are asymptomatic. However with chronic hepatitis, liver cirrhosis or liver cancer, symptoms do arise. The difficulty in diagnosing HCV at its early phase is a major constraint to curbing the prevalence of liver cirrhosis and cancer arising from HCV infection [8, 31].

There is spontaneous clearance of HCV infection in 15% of infected people owing to the combined innate and adaptive immune responses of the body. This occurs in human hosts who are able to mount ample and broad cytotoxic T-lymphocyte response [2, 10.]

Treatment of HCV infection

With the advent of direct acting antivirals (DAAs) which are better tolerated by patients and which have been shown to produce high cure rates when used in combination for HCV infection [26], the World Health Organization (WHO) recently simplified guidelines for the treatment of HCV infection which had hitherto involved pegylated interferon alfa and ribavirin in the main [2, 33, 34].

Directacting antiviral agents for the treatment of hepatitits C virus infection:

The development of DAAs was made possible by in-depth knowledge of the biology of hepatitis C virus and its life cycle [35]. DAAs target specific vital steps within the life cycle of the virus. Multiple DAAs target specific nonstructural proteins of HCV leading to failure of viral replication. In appropriate combinations DAAs achieve not only high cure rates but also reduced treatment duration. Their improved efficacy and tolerability compared to older therapies for HCV infection have been established by clinical trials [36, 37, 38]. Several other research reports point to DAAs being effective therapeutic agents for treatment of HCV infection [39, 40].

The four classes of DAAs

There are four classes of DAAs based on their mechanism of action and therapeutic target:

Nucleoside and nucleotide NS5B polymerase inhibitors: The Nucleoside and nucleotide NS5B polymerase inhibitors directly target HCV to stop it from replicating in the liver. They attach to viral RNA to block viral multiplication. An example is Sofosbuvir.

NS5A inhibitors: These agents block NS5A, a viral protein that HCV requires in order to reproduce and to establish itself within the human cells. Examples are: Ombitasvir, Velpatasvir, Pibrentasvir and Daclatasvir.

Non-nucleoside NS5B polymerase inhibitors: A Non-nucleoside NS5B polymerase inhibitor inhibits HCV reproduction by inserting itself into the virus thereby stopping other pieces of from attaching to it. An example is Dasabuvir.

NS3/4A protease inhibitors: The mechanism of action of NS3/4A protease Inhibitors is that they inhibit a viral enzyme (protease), that HCV requires in order to survive and replicate within human cells. An example is Glecaprevir.

WHO's new guidelines for the treatment of HCV infection.

The World health Organization this year released new guidelines for the treatment of Hepatitis C virus infection [4, 41.]

The hallmark of the new guidelines from WHO is that all persons who are 18 years or older who are infected with HCV should be offered a pan-genomic combination of DAA. The DAAs in the right combinations are efficacious, produce less adverse effects, and achieve viral clearance within a period of 12 weeks.

For such persons aged 18 years and above who do not have liver cirrhosis, WHO recommends any of the following pangenotypic combination of DAAs: 12 weeks treatment with Sofosbuvir/velpatasvir or Sofosbuvir/daclatasvir; or 8 weeks treatment with Glecaprevir/pibrentasvir[41] . Slightly modified regimens have been recommended for adults with chronic HCV infection and compensated cirrhosis of the liver. For children less than 12 years who have HCV infection, the recommendation is for their treatment to be deferred until they are up to 12 years.

However, it is recommended that adolescents aged 12-17 years with chronic HCV infection should have HCV genotyping in order to identify the appropriate combination of DAAs to use. In this subpopulation of HCV infected patients, WHO recommends a combination of Sofosbuvir with any of the following: Ledipasvir for 12 weeks (for HCV genotypes 1, 4, 5, or 6); or with ribavirin for 12 weeks (for genotypes 2) or with ribavirin for 24 weeks (for genotype 3) [41].

For some other patient sub-populations with special characteristics such as people with HCV/HIV co-infection, people already having liver cirrhosis, or HCV/HBV co-infection WHO recommends that they receive a personalized prescription to take into consideration the possibility of drug-drug interaction and other factors [41].

This new guideline has made genotype testing unnecessary for persons aged 18 years and above. The new recommendation has also made the use of Pegylated interferon alfa for the treatment of HCV infection obsolete. Ribavirin may be used only for adolescents from 12-17 years old diagnosed with HCV genotypes 3 or 4 in combination with the DAA Sofosbuvir.

Access to Direct-Acting Antiviral Agents

Access to Direct-Acting Antiviral Agents (DAAs) is another key challenge to potential users especially those living in resource-poor countries. The drugs are expensive and not within the reach of the poor.[30] There is an urgent need for more effort to be made to make these medicines available subsidized prices or free of charge to persons diagnosed with HCV infection in resource constrained nations [6, 42].

Relevant laboratory tests available but exorbitant.

The laboratory investigations for HCV infection include serological assays for detection of serological evidence of past or present infection for the initial diagnosis. Where serological test is positive, qualitative or quantitative Nucleic Acid Testing (NAT) would be required to establish whether the patient has a current or viraemic HCV infection or not. These tests are at present too expensive for patients who are poor or who lack health insurance coverage for such laboratory tests. In the past some patients' treatment could not be commenced owing to inability to carry out the required tests [42]. Nonetheless, there is also an urgent need for arrangements to be put in place to make these relevant tests accessible to patients living in low income countries of the world.

Global need for Anti-HCV vaccine.

The effectiveness of vaccines in combating infectious diseases has been well established. Several promising vaccine candidates are in the pipeline for HCV infection but none has yet been licensed for clinical use. The constraints to vaccine development include the complex biology and life cycle of HCV as well as the difficulty in obtaining an efficient in-vitro model or culture system in which HCV replication could easily occur and in which ample production of a vaccine that contains the requisite HCV antigenic epitopes could occur.

An effective anti-Hepatitis C Virus vaccine is bound to significantly decrease the incidence and prevalence of HCV all over the world along with its deleterious hepatic complications. Such a vaccine, ideally, should be affordable and capable of effectively stimulating strong cellular immune response and eliciting strong neutralizing antibodies to protect the recipients in various regions of the world from various HCV genotypes [30, 43, 44, 45].

Considering that millions of HCV infected patients lack access to prompt and affordable requisite diagnostic and therapeutic services, HCV vaccine is a dire need.

II. Conclusion

We applaud the new treatment guidelines recommended by the WHO this year for the treatment of Hepatitis C Virus infection. It is a major positive development. It also paves the way for several patients to be treated without any compulsion to wait for HCV genotyping services which had been inaccessible to many. The new treatment regimen also eliminates the need for procurement and use of either pegylated interferon alfa or ribavirin for the majority of adult patients who have no complications.

However, there is no gainsaying it that there is still a great need to have an affordable and effective anti-HCV vaccine to further contribute towards the elimination of HCV infection globally because a significant proportion of HCV infected people are unaware of their HCV status, and a significant proportion of those who know their status in developing countries lack the capacity to procure the recommended combination of curative antiviral medicines.

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