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HCV Vaccine: How Far are We?

Abstract

Worldwide, hepatitis C (HCV) is considered as an important public health problem as it is associated with severe complications and high morbidity and mortality. Majority of infections are usually asymptomatic during initial phases, however majority of the infected individuals develop symptomatic disease during the latter phase of illness. Hepatitis C virus has seven genotypes and 67 subtypes and also different quasispecies are known to circulate in one particular individual. The diagnosis is usually established by serology/ molecular tests. HCV is a RNA virus, which is associated with high mutations rate. At present newer antivirals are available that are associated with good sustained virologic response, but these are very costly and are beyond the reach of common man in developing countries. Thus, vaccine candidates are required for preventing the infection. Though, different vaccine candidates are present, but all are in clinical trials and at present no commercially available vaccine is available. In the present mini-review, recent vaccine candidates have been discussed along with a summary of challenges being faced in the development of an ideal HCV vaccine.

Keywords: HCV; Vaccine; Immune response; Animal models; Hepatitis C virus; VIPs

Mini Review

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Abbreviations: HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; HCC: Hepatocellular Carcinoma; DAA: Directly Acting Antivirals; SVR: Sustained Virologic Response; NS5: Non-Structural Protein 5; ABIR: Antibody-Mediated Immune Response; CMIR: Cell-Mediated Immune Response; HIV: Human Immunodeficiency Virus; VLPs: Virus Like Particles; Th: T Helper Cells; HADV6: Human Adeno Virus Rare Serotype 6; Chad3: Chimpanzee Ad 3; CMV: Cytomegalovirus

Commentary

Worldwide, hepatitis C (HCV) is an important public health problem. Earlier, it was mainly associated with transfusion of HCV infected blood in the developing countries. However, due to intravenous drug abuse, now it is well recognized in developed countries also. As per World Health Organization (WHO) data, approximately 170-185 million people are globally suffering from chronic HCV infection [1,2]. More than 3,50,000 individuals are expected to die every year from hepatitis C related liver diseases [3]. HCV causes more severe clinical complications as compared to other viral causes of hepatitis. Hepatitis B virus (HBV) and Hepatitis C virus shares similarity in that both are transmitted parenterally. However, the two viruses are totally dissimilar in their genetic properties, course of infection, treatment options and availability of effective vaccine. Among majority of the patients, HCV during the initial period illness is usually asymptomatic and it is only during the later course of infection that patient develops clinical manifestations.

About 15-45% of acute cases spontaneously clear the virus and around 55-85% in later period of their lives progress to chronic HCV infection, which further leads to liver fibrosis, cirrhosis and eventually hepatocellular carcinoma (HCC) in 15-30% of those having chronic hepatitis C [4]. In suspected patients diagnosis is confirmed by serology and/or molecular methods. However, majority of the patients are not diagnosed during acute phase that contributed to a pool of patients who transmit the infection *via* high-risk behavior, intravenous drug abuse, blood transfusion and organ donations. The most common indication of liver transplantation is the decompensating chronic HCV infection that alone accounts for 40-50% of liver transplants [5].

There are seven different genotypes (1-7) of HCV and 67 subtypes exist in nature [6]. The genotyping is important for deciding the treatment regimen as response to treatment and duration of treatment depends upon the specific genotype. Super infection with more than one genotype can also occur especially among high-risk groups, like injection drug users. However, genotyping methods are not widely available in developing countries and are also not affordable by all in developing countries due to limitation of resources [7,8]. Thus, research is required in the field of developing newer diagnostic tests for detecting different genotypes and nanotechnology and micro fluidics can be used to develop a point-of-care test [9,10].

Recent advances have been made in the treatment options due to the availability of new direct acting antiviral (DAA) drugs, which help in achieving sustained virologic response (SVR - a marker for cure) among 80-90% of patients after 12-24 weeks of therapy [11].

The newly approved two new DAA drugs are Sofosbuvir and Simeprevir [11]. Former drug acts by inhibiting HCV NS5B polymerase enzyme and latter one is a protease inhibitor that blocks specific protein needed by the hepatitis C virus to replicate. Moreover, efficacy of Simeprevir is markedly reduced in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism. Thus, prior to initiation of therapy, screening for this mutation

is essential. However, the current treatment is very costly and is beyond the reach of common people in developing countries. Additionally these DAAs do not cure virus induced end stage liver infections. Currently, Sofosbuvir, Ledipasvir, Velpatasvir and Daclatasvir, the non-structural protein -5 (NS5) inhibitors are regarded as the most promising drugs for HCV treatment [11-15]. However, several patients have severe irreversible liver damage or possibly liver cancer, which are not cured by available antivirals.

Additionally the development of resistance in HCV in response to the currently used treatment modalities also of a major concern. Hence, the development of a prophylactic vaccine against HCV is the need of the hour.

The hope to develop HCV vaccine comes from the fact that spontaneous resolution occurs in 15% of the patients infected with HCV [16]. It occurs due to the strong innate immune response along with adaptive immune response mounted against HCV in the form of antibody-mediated immune response (ABIR) and the cell-mediated immune response (CMIR) [17-19]. Developing a pan-genotypic vaccine against HCV is a major challenge due to the high genetic divergence of the virus, which has seven distinct genotypes and at least 30% genetic sequence variability. However, development of a vaccine against a single predominant genotype will also be a breakthrough. HCV has evolved number of strategies to evade the antibody mediated neutralization such as E2 region of the envelope protein has two hypervariable regions, which are the major targets of neutralizing antibodies.

Therefore, research is required to find out the immunogenic conserved epitopes which is a challenging task. The same strategy has been applied in designing a vaccine against human immunodeficiency virus (HIV) [20]. Currently, many researchers are targeting the E2 region of HCV for designing monoclonal antibodies, with a hope of developing neutralizing antibodies against it [21-23]. The mechanisms of blocking the HCV entry into the hepatocytes by specific antibodies may provide a way for developing such vaccine candidates as many such receptors are known now [24]. Recently a genetically humanized mouse was developed, which facilitated the measurement of vaccine-induced humoral responses [25]. The key antibody epitopes of the E2 ectodomain of HCV along with their molecular structure has also been resolved [26]. Recently, Jong et al. [27] demonstrated that established HCV infection in human liver chimeric mice could be cured by neutralizing antibodies that have been expressed in recombinant adeno-associated virus.

It is a well-known fact that for effective vaccine development against HCV, generation of HCV specific T cell response is a major challenge. The protective role of $CD8^+$ and $CD4^+$ T cells in controlling HCV infection was supported by the studies of T cell depletion experiments in chimpanzee model, where a lack of either of these cells during exposure and early infection was associated with persistent viraemia [28]. The lack of proliferation of HCV-specific $CD4^+$ T cells that proliferate after antigenic stimulation *in-vitro* is the hallmark of persistent HCV infection. Several researchers reported that the frequency of proliferation of HCV-specific $CD8^+$ T cells are much higher compared to $CD4^+$ T cell responses.

There are different methodologies by which vaccine can be developed. These vary from conventional approaches to the use of reverse vaccinology. However, conventional approaches have failed in developing successful candidates and only tested with varying results among animal models. The different approaches used for development of HCV vaccine include the use of recombinant E1 and E2 proteins, synthetic peptide, virus like particles (VLPs), recombinant non-pathogenic live vectors, DNA vaccines, dendritic cell-based vaccination and prime-boost strategies [16]. However, till date no effective vaccines have been discovered against HCV that is commercially available. There are two different concepts behind HCV vaccine development, first is the development of a prophylactic vaccine, which can be administered prophylactically to prevent the acquisition of HCV infection [29]. Another type of HCV vaccine is the therapeutic vaccine, which can be administered to decrease the severity of illness in an already infected person. Therapeutic vaccines can also be used along with anti-viral treatment regimens so as to increase the chances of achieving the SVR [30].

Modern technologies involving the concept of reverse vaccinology may provide success in short span of time as by using bioinformatics tools, large number of HCV peptides can be searched which appear to be present at surface of HCV and are found to be immunogenic by B cell and T cell epitope prediction [31-33]. Later on these can be tested *in vivo* for their immunogenicity and efficacy. Other technologies may involve use of nanotechnology to increase the immunogenic potential of the vaccine candidates as compared to conventionally used adjuvants [34,35].

An ideal HCV vaccine should be able to induce strong cellular immune response, including both $CD4^+$ and $CD8^+$ T cells and a strong cross-neutralizing antibody response against HCV envelope proteins. Thus, for developing effective prophylactic vaccine, structural proteins such as core, E1 and E2 should be selected in such a way that they must induce high titers of neutralizing antibodies, which help in blocking the viral access to the target cells. The non-structural proteins such as NS3, NS4 and NS5 must also be selected so as to mount a strong T-cell response targeting infected cells [30,36,37].

Though, efforts are being made to develop a successful HCV vaccine but only few HCV vaccine candidates have reached clinical phase trials. The synthetic peptide vaccine IC41 (proposed by Intercell AG; Vienna, Austria) containing 7 relevant HCV T-cell epitopes and the helper cell (Th)1/Tc1 adjuvant poly-L-arginine can induce HCV-specific IFNγ secreting $CD4^+$ and $CD8^+$ T cells in healthy volunteers and among patients who are difficult to treat [38,39]. This vaccine has successfully completed phase II trial. Another peptide vaccine consisting of HCV core region (C35-44) along with ISA51, an emulsified incomplete Freud adjuvant has completed phase I trial [40].

The recombinant E1E2 vaccine derived from HCV1a was also approved for phase I clinical trial in humans [41]. Another HCV vaccine tested in Phase I human clinical trials is based on the use of human adeno virus rare serotype 6 (HADV6) and chimpanzee Ad 3 (ChAd3) expressing the HCV non-structural proteins [42]. T cell responses targeted multiple proteins and were able to recognize heterologous strains. Booster dose with heterologous

adenoviral vector mounted a sustained immune response even after one year.

Therapeutic vaccines like viral-vector-based vaccine are similar to DNA vaccines which encodes target protein or peptide but are reported to be more immunogenic than DNA-based vaccines [16,42]. TG4040 (by transgene) proved to induce HCV-specific cellular immune response and reduced viral load in chronic HCV infected patient in phase I clinical trial [43]. Ad6Nsmut (by Okairos) containing NS3-5B proteins expressed in adenovirus vector has cleared Phase I trial but their results are not published yet [44].

The major hurdle in the development of HCV vaccine is the presence of high rate of mutations due to the absence of proof reading capability of the NS5B viral polymerase, which is required for HCV replication [45]. HCV has a short half life of 2-3 hours and generates an estimated 10^{-5}-10^{-4} errors/nucleotide/ replication cycle [46,47]. It results in the development of the quasispecies, which evades the immune system of the host. The highest level of genetic heterogenicity within E2 is present at hypervariable region-HVR1 [48]. Though, HVR is highly immunogenic but it is not essential for viral entry. Another important hurdle is limited availability of animal model that can be used for vaccine challenge studies.

The best animal model available is the chimpanzee but due to various bioethical restrictions, these are difficult to procure to carry out research [49]. There is also difficulty faced in enrolling the people at risk of getting HCV such as intravenous drug abusers in vaccine trials. Moreover, there is a lack of correlation of protection in terms of immune response. Thus, efforts are required to develop a universal vaccine, which can provide lifelong immunity against different genotypes/ serotypes at an affordable price without any side effects.

Recently several researches are also focusing on synthesizing dendritic cell based vaccines against HCV. Here dendritic cells are modified *ex vivo* to express foreign proteins and these have are been regarded as safe and promising tools for the development of more effective therapeutic vaccines. However, in phase 1 trials, hese vaccines failed to influence the viral load and the level of HCV specific cytokines. Therefore, much needs to be accomplished to achieve therapeutic efficacy of these vaccines [50,51].

Another very promising field for vaccine development is DNA based vaccines containing naked plasmid DNA molecules that express HCV proteins capable to induce a viral-specific immune response. CIGB-230 DNA vaccine containing core/E1/E2 is one of the DNA vaccines that reached the clinical evaluation [52,53]. Though, many vaccine candidates are available but still the modifications are required so as to develop an ideal vaccine which can provide lifelong immunity with no side effects against multiple genotypes. Another vaccine candidate ChronVac-C [plasmid DNA encoding NS3/NS4A under the control of cytomegalovirus (CMV) immediate-early promotor] was found to be safe and significantly improved IFNγ producing responses to HCV NS3 [54].

Conclusion

To date, a few vaccine candidates have been progressed to phase I/II trials, but published data on both the efficacy and safety of these vaccines is limited, and none of them has yet reached a phase III clinical trial. Thus, we still are far away from an ideal HCV vaccine candidate.

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