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Recent approaches in clinical trials of hepatitis C virus vaccine, challenges and future directions

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Abstract

Globally HCV infects more than 170 million individuals and is a major risk of hepatocellular carcinoma, liver cirrhosis and transplantation. Recent antiviral therapy has significant side effects and is much expensive. During the early infection with HCV, the asymptomatic characteristics have a remarkable impact which results in unknowingly spreading HCV. Recently there is no effective vaccine available. Data indicate that a considerable proportion of individuals naturally manages HCV infection through immune feedback mechanisms, suggesting that developing an effective vaccine against HCV presents a reasonable challenge. Therefore, to control this deadly virus a prophylactic vaccine is compulsory. Different types of methods are adapted to design an effective HCV vaccine which are under different human clinical trials. The current review discusses the goals of the HCV vaccine, traditional vaccine methods, vaccine approaches and challenges in the development of vaccine design.

Key words animal models, HCV, prophylactic vaccine, immune responses

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Introduction

Globally more than 71 million individuals affected with HCV are mostly treated with direct-acting antivirals (DAAs) [1] and they can attain treatment of >95% of cases [2, 3]. It was observed that there is no need for an HCV vaccine if the treatment outcomes effectual [4]. However, this justification may be widely optimistic. Early HCV infections remain mostly asymptomatic which is a possible reason for undiagnosed later cause's serious health issues. Globally it was observed that only 5% of HCV-positive individuals are screened [5, 6]. In the underprivileged countries many current and new HCV cases occur among marginalized populations like homosexuality, people who inject drugs, contaminated blood transfusion, skin piercing and incarcerated individuals [7]. Such individuals are mostly disconnecting from medical facilities with the insubstantial approach to HCV diagnosis. Meanwhile, they infect other individuals and increased the epidemic prevalence. In fact, in North America, the current sedative epidemic has been linked with the increased prevalence of HCV [8]. In underprivileged countries, medical operations remain the major challenging issue of ongoing HCV infections which contributing another risk factor among the travelers and the general population to associated areas [9]. Finally, without a prophylactic vaccine, alone DAA treatment cannot save the individual against reinfection [10]. The World Health Organization (WHO) has designed a goal to reduce the burden of new HCV infection by 90% at the end of 2030 [11]. For achieving the goal of WHO and reducing the long-term HCV prevalence an effective vaccine is the only reliable method against the viral disease by providing herd immunity, mainly among the low-income countries and vulnerable populations [12, 13]. Screening and treatment are the main principles for the elimination of HCV and enhanced immunity by the method of vaccination. Since the discovery of HCV in 1989, the question about the vaccine against this deadly virus still active, but it has been a challenging venture due to several factors such as lack of small animal models, virus genetic variability, etc. Current approaches have focused on both generating broadly neutralizing antibodies (bNAbs) that can play their role in the neutralization of viral infectivity and producing potent viral-specific T-cells that can play their role in the elimination of infected hepatocytes. For many years different kinds of vaccine regimens, adjuvants and vectors have been tested [14].

The natural history of hepatitis C infection

Globally almost 1% of the population is infected with HCV which is the major health issue [15]. The most recognized risk factor for HCV transmission is the transfusion of infected blood and skin piercing, injecting drug users (IDU) and infected surgical equipment's, etc. There is another possible risk factor for HCV transmission sexually among those individuals who have sex with other men [16]. It was estimated that after acute hepatitis C infection the infected individuals remain almost 75% RNA positive [17]. Globally 71 million individuals reported chronic hepatitis C in 2015 according to WHO guidelines and each year almost 2 million new infections were reported [18]. Once the liver cirrhosis developed it may lead to the liver end-stage or hepatocellular carcinoma, which ultimately causes the necessity for liver transplantation or leads to the death of the infected individual [19].

Prophylactic vaccine

Today mostly in the market the current effective vaccines are reliant on the influence of neutralizing antibodies to avoid or minimize infection [20]. Recently even for HIV-1, the human vaccine RV144 experiment was observed that the sufficient decrease of infection threat is associated with antibody feedback [21]. This strategy for the HCV vaccine generation is supported by current experiments observing that neutralizing antibodies are associated with HCV elimination [22]. In a study of a single-source HCV outbreak, Pestka et al. found that individuals who successfully cleared the HCV infection exhibited higher levels of neutralizing antibodies [23]. Antibody titer to virion proteins has also been associated with interferon therapy feedback [24]. One vaccine was planned by using recombinant glycoprotein E1/E2 with adjuvants MF59 to influence humoral feedback against HCV. This vaccine expressed efficiency in the chimpanzee model by decreasing the level of chronicity, ensuring both heterologous and homologous 1a virus tasks. In some infections, it also entirely blocks further infection against homologous tasks [25]. Essentially, if vaccination can decrease the chances of chronicity, it will be much effectual since HCV correlated disease is expressed frequently. Such recombinant glycoprotein-based vaccine safety and immunogenicity have been examined during the phase I clinical trials in humans. The outcomes of this experiment showed greater humoral and CD4l T-cell feedback and lower side effects observed among the vaccinated volunteers [14]. Generally, neutralizing antibodies were believed to be genotype-specific making it challenging to give out world protection [26]. Meanwhile, many other studies have been described in the literature which explained the broadly cross-neutralizing antibodies that inhibit infection [27]. Mostly these antibodies identify conserved regions essentially within the glycoprotein E2, while a few identifying E1 have also been reported (**Figure 1**) [28]. A few of these cross-neutralizing antibodies were proposing conformation-dependent recognition by attacking discontinuous epitopes. In chimpanzees and humans, glycoprotein-based vaccination has been observed to influence cross-genotype neutralizing activity [29]. Recently, this similar vaccine in all the major HCV genotypes has to influence broad neutralizing antibodies but with different efficiency [30]. As a result, this vaccination affects the same cross-neutralizing B-cell epitopes that have previously been reported and are currently under investigation. Moreover, it has been noted that HCV can spread from cell to cell by eluding neutralizing antibodies. Utilizing the entire infected virus to induce neutralizing antibodies is an additional alternative method for producing vaccines [31]. Several licensed vaccinations, including those for polio, Japanese encephalitis, rabies, influenza A, and hepatitis A, employ this strategy [32].

Therapeutic vaccine

Several processes are involved in the inhibition of T cells specific to HCV, which helps to restrict the spread of infection [33]. Reactivating these HCV-specific T cells could be harmful to the liver's ability to secrete cytokines that have antiviral properties as well as directly attack infected hepatocytes in the event of a therapeutic vaccine. First treating HCV infection with DAAs may theoretically increase the efficacy of these vaccinations. One therapeutic vaccination, based on recombinant HCV produced with the T-cell adjuvant IMX, was co-developed by CSL Limited and Chiron Corporation. This vaccination showed encouraging animal evidence and positive phase I experiment in healthy people volunteers [34]. The subgroup of people with chronic HCV showed a sufficient decline in viral load, according to primary outcomes as well. An enhanced vaccine has been used for transgene integration. The Ankara vector displayed the hepatitis C virus NS3, NS4a, NS5a, and NS5b genes. In a phase I clinical investigation, six out of fifteen inoculated patients reported a 0.5–1.4 log reduction in viral load after vaccination. The two patients also showed the greatest reduction in viral load and increased vaccine-specific

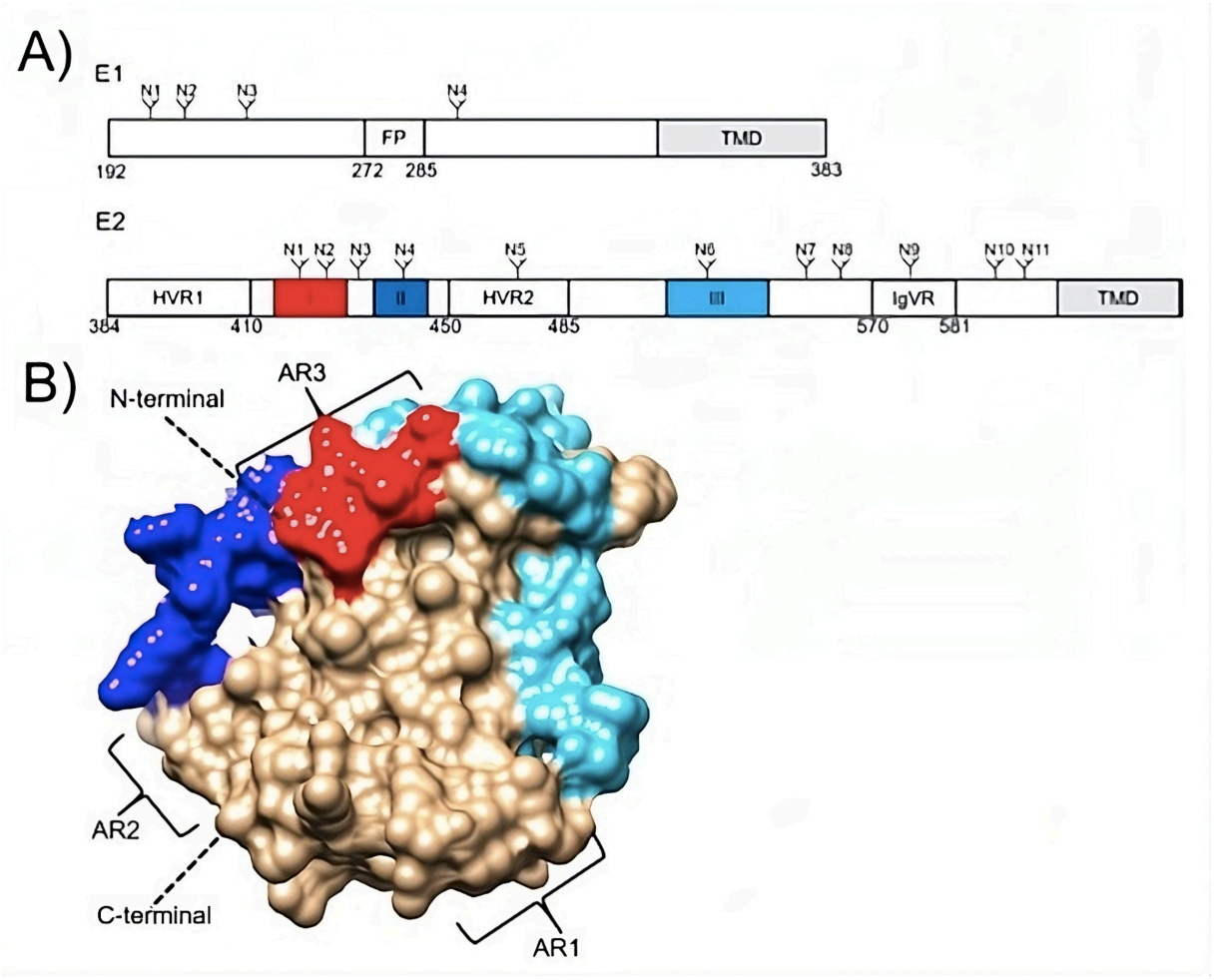

Figure 1. (A) Schematic representations of the N-linked glycosylation sites (N), transmembrane domains (TMDs), and the E1 fusion peptide (FP) of the hepatitis C virus envelope glycoproteins E1 and E2. The intergenotypic variable region (IgVR) and the E2 hypervariable regions (HVRs) 1 and 2 are also shown. The colors red, dark blue, and light blue, respectively, are used to emphasize linear epitopes I, II, and III. (B) E2 configuration (PDB: 6MEH). The associated schematic shows the highlighted linear epitopes I, II, and III. Moreover, antigenic regions (ARs) are displayed [73].

T-cell feedback [35]. Transgenes recently reported from a phase II clinical trial that HCV-positive patients who had ribavirin and INF-a treatment first shown a higher virological response (64% vs to 30% in the control group) after receiving the vaccine [36]. But this mutual treatment was shown to have serious negative effects, making this process problematic [37]. The Swedish business ChronTech used a different technique called electroporation encrypting the HCV proteins 3/4a. This vaccination strategy is currently in phase II clinical investigation [38]. The effectiveness of interferon-free DAA treatment in conjunction with therapeutic vaccinations will be interesting to watch.

The ideal vaccine requirements

Various methods, as outlined in **Table 1**, have been applied to overcome the numerous challenges in developing HCV vaccines. There are three basic properties for the successful and therapeutic preventive vaccine strategies established such as:

- These vaccines have the potential to deal with the viral genetic diversity and normally they required conserved viral regions as a target.
- The 'magnitude' of viral control correlated with antiviral immunity is not exactly explained. However, humoral, broad, functional T cell immune feedback will be essential.
- To be harmless, an effective vaccine will be required to eliminate HCV from the liver without influencing liver immunopathology. Human experiments up till now described that this is a faithful idea.

Vaccine approaches

Recombinant protein vaccines

Recombinant protein use as a potential vaccination approach may consider that enhancing the immune response to fewer viral epitopes is an appropriate way to develop defensive immunity. Finding the gene encoding the necessary protein and cloning it into yeast, bacteria, or mammalian cells is the major objective of this approach. It is possible to create recombinant proteins using culture material or transfected cells. However, certain recombinant proteins are readily available alone, whilst others need adjuvant therapy to possibly elicit an immune response. Protein-based strategies generally elicit CD4+ T-cell and antibody responses.

Core proteins

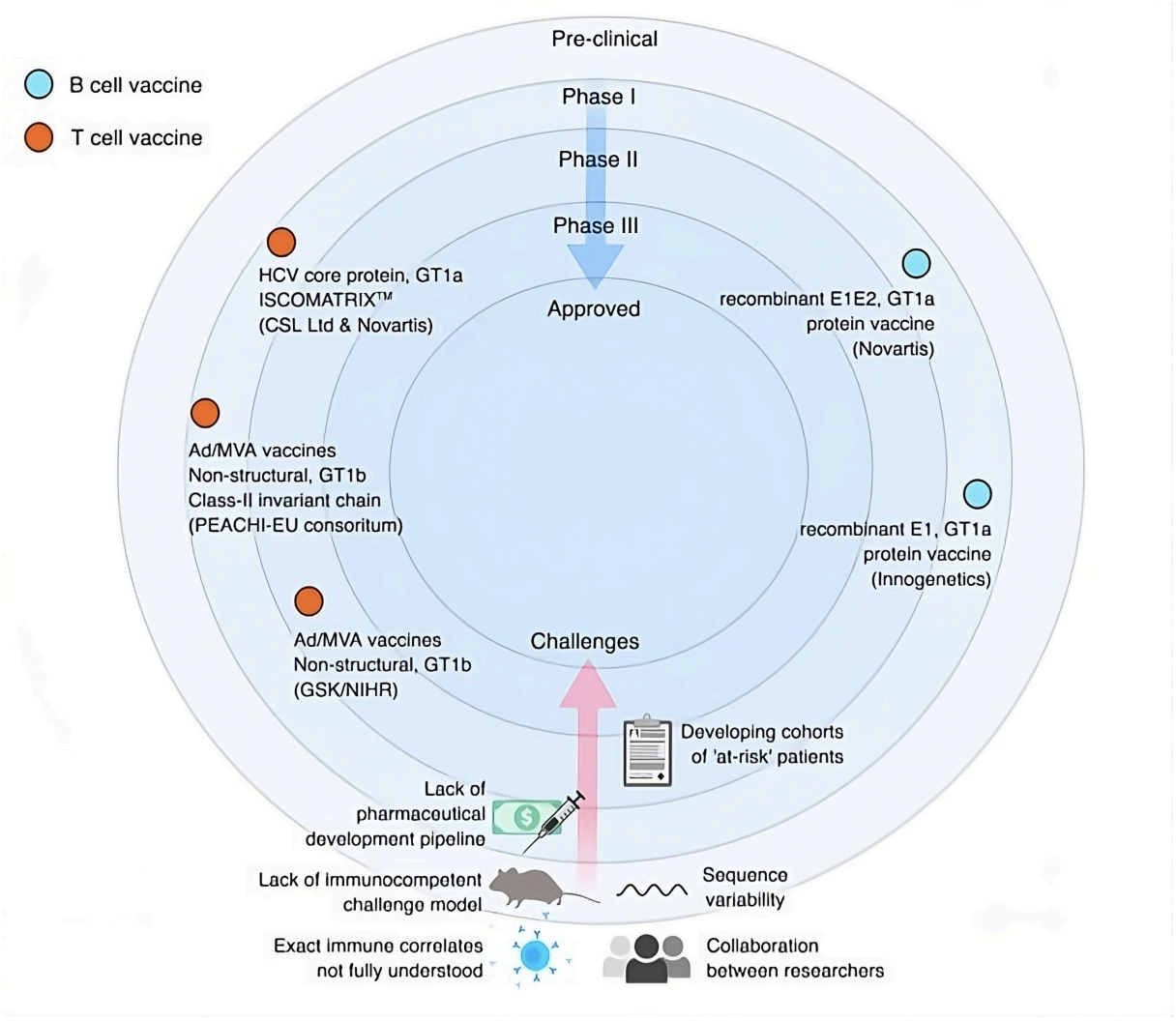

Figure 2. Clinical route and obstacles for the HCV vaccine development [74].

As a therapeutic vaccine approach (GI5005) heat-killed yeast cells (Saccharomyces cervisiae) have experimented which showed core-NS3 fusion protein [39]. During Phase II placebo-controlled experiment in 66 chronic HCV-1 patients, GI5005 was integrated with excellent therapy (PEG-IFN/ ribavirin). The procedure consisted of 12-week excellent therapy administered subcutaneously with average weekly doses for 5 weeks then used for 2 months for one dose monthly of GI5005 vaccine. Previously non-responder acquired 72 weeks of excellent treatment but treatment-experienced patients acquired 48 weeks. For immunological feedback, no statistics have been issued. However, in those homozygous for the IFN-l3 risk alleles, the researcher saw a rise in persistent virological response rates [40]. In a Phase I investigation, healthy volunteers received a vaccination containing the conserved HCV core protein along with an adjuvant made of phospholipid, cholesterol, and saponin (named ISCOMATRIX®). The vaccination proved to be innocuous and among the volunteers who received the highest dose (50 μg), there was a specific humoral response to the core protein. Consequently, HCV-specific CD8+ T cells have been seen in the two patients. To analyze this strategy as a therapeutic vaccine further trial are intended by the same researcher among the HCV-infected patients. One is the feasible method to observe the genomic proteins functions of HCV for the appropriate vaccine to target this virus, the distinct properties of these proteins are shown in the **Table 2**.

Vector vaccines

The intriguing possibility of spreading HCV RNA via viral vectors is present. In the chimpanzee model, adenoviral vectors have been demonstrated to potently generate HCV-specific T-cell feedback and to lower the peak HCV load during the initial infection [41]. The vaccine's immunogens are not HLA constrained; hence this strategy might affect viral epitopes more than the peptide-based strategy. Modified vaccinia Ankara (MVA), a highly attenuated strain of the poxvirus, has been safely used in a number of vaccine approaches, including those for melanoma, HIV, TB, and colorectal cancer. The primary conclusions from the 2009 European Association of Liver Disease meeting [42]. Nine of the fifteen chronically infected HCV patients had a fourth treatment six months after the first three weekly injections. The HCV viral load decreased in six out of the fifteen patients (0.5–1.4 log10), and there was also a notable CD8+ T-cell feedback. Constructed a phase II trial that contrasts the immunization with conventional therapy [43]. In the Phase I vaccination study, NS HCV proteins (NS3–5B) are also being transferred to 36 healthy volunteers using adenovirus vectors. In order to further improve vaccination safety, the polymerase activity of the NS proteins is deactivated

and genetically engineered vaccine vectors are used, rendering them incapable of replicating [44]. Ad6 and the simian vector AdCh3, which are used to manage the challenges of pre-existing anti-adenoviral antibodies that may limit vector efficiency, are uncommonly seen in humans. The American Association of Liver Disease published main results from this investigation in 2009, explaining that the particular priming injection that this technique ensures is highly immunogenic in healthy volunteers (Ad6) [45]. Advanced studies are planned with HCV-positive subjects.

Virus-like particles

Virus-like particles (VLPs) have been extensively researched as a potential HCV vaccine and are an attractive avenue for vaccine development [46]. As of right present, the VLP approach is being used commercially for both the HPV and the hepatitis B virus (HBV) vaccines. Virus-like particles (VLPs) are produced in a genome-independent manner when the structural proteins of a virus assemble to create a particle that mimics the virus but cannot replicate. Due to their intricate structure and ability to drain into lymph nodes, VLPs exhibit greater immunogenicity compared to soluble proteins [47]. Baumert et al. were the first to describe HCV-LPs, noting their appearance in the insect cell line Sf9 following transduction with a recombinant baculovirus containing HCV core, E1, and E2 structural proteins [48]. These HCV-LPs were found to induce the production of HCV-specific IgG, IFN-γ-secreting CD4+ T cells, and CD8+ T cell responses in both mice and baboons [49]. In a study, all four chimpanzees that received four doses of HCV-LPs exhibited CD4+ and CD8+ T cell responses. When later challenged with homologous HCV, vaccinated animals demonstrated lower viral loads compared to controls, two of which tested negative for HCV for up to two years post-challenge [50]. However, in three of these animals, humoral feedback in chimpanzees was not observed and seems to have been missing during the decrease of viremia. Since this initial trial in chimpanzees, further research on this approach has not been developed. Therefore, it is an ideal approach for upcoming HCV vaccine research, as is expressed using an experimental VLP vaccine approach the viral clearance can be accomplished. Despite work on this approach stopping, HCV-LPs persistently are to be examined. Recently, an HCV-LP method has been recognized through the recombinant adenovirus encrypting the structural genes of HCV with transduction of the human hepatoma cell line Huh 7 [51]. Primarily intended using the H77 isolate, advance progress has extended by producing HCV-LPs using the important sequences of dissimilar isolates demonstrating Gt1b, 2a and 3a subtypes to generate HCV-LPs with a configuration close to that the wild type virus [52]. Experiments of this approach in mice indicated the stimulation of nAbs and triggering of both CD4+ and CD8+ T cell feedback and recently this trial was also observed in vaccinated Landrace pigs [53]. As yet, humoral feedback analysis has illustrated that this vaccine provokes nAbs with undertaking towards homologous strains. For this approach, heterologous neutralisation data have not been described. Immunized animals with this quadrivalent vaccine against the different genetic variants of HCV after sera analysis from animals would be of special interest not only for this approach but to update upcoming vaccine programs.

DNA vaccine

A very new vaccination technology is the DNA-based immunization strategy. Compared to other common vaccinations like live attenuated viruses and recombinant protein vaccines, DNA vaccines have a far higher efficacy [54]. Numerous advantages of DNA-based vaccination include the ability to produce the vaccine, the ease with which DNA may be modified, and the immunological response that comes primarily from several sources, such as helper T cells, CTLs, and antibody feedback. Additionally, DNA vaccines are suitable for progressive immunization since early-existing antibody titers to the vector do not control their function [55]. The genetically varied HCV virus poses a significant challenge to the creation of an HCV vaccination [56]. Since many researchers have concentrated on the specific CTL feedback initiated by C and NS3 region proteins and defensive antibodies triggered by HCV E proteins, the NS3 gene is moderately conserved and plays a significant role in HCV elimination by influencing specific T cell feedback. This makes it an appropriate approach for T cell-based vaccines [57]. The HCV core should be harmed by the application of a particular vaccination under the influence of immunological response. It is a strong immunogen with anti-core immune feedback at the early stages of infection [58]. Since the HCV core protein is the most highly conserved region of the translated HCV genome throughout the many HCV genotypes, it may be the observable route for a therapeutic T-cell-based vaccination. However, different studies expressed that adaptive and innate immune responses can interfere with the core protein [59]. DNA-based vaccines substandard as compared to the conventional vaccines like subunit vaccine since the DNA vaccines concentration to regulate the immune feedback has been comparatively weak, thus efforts are focused towards the generation of novel technologies such as co-delivery of unique cytokine IL-18, IL-15, IL-12, IL-7 and IL-2 adjuvants for evading this limitation [60]. Among the current development in viral infections, HCV identification is the most significant. Researchers into the generation of new therapeutic approaches are emphasized on the study of molecular effects of the virus due to the clinical consequence of the disease. An effectual HCV vaccine should regulate the different features of the immune system such as CTL, humoral and T helper feedback. Due to the greater HCV genetic diversity and mutagenicity, developing a therapeutic or prophylactic vaccine for HCV is still a major issue. Earlier studies explained that the cellular immune responses might be crucial for an effective vaccine. Human phase I/II clinical trials are under underway for a number of HCV vaccine approaches, including vector-based, DNA, recombinant protein, and peptide vaccines, all of which have been demonstrated to give a number of benefits. It can be challenging to assess these techniques' efficacy in diseased or at-risk populations, despite the fact that many of them offer both healthy and infected volunteers' substantial immunity.

Challenges to hepatitis C virus vaccine design

The primary obstacle to the effective development of a vaccine against the hepatitis C virus is its genetic diversity (**Figure 2**). HCV has more subtypes than HIV-1 and has seven identified genotypes, making it more heterogeneous than HIV. About 30% of the amino acids in distinct HCV genotype strains vary, but only about 15% of the amino acids in different subtypes vary. In addition, the virus speaks in quasispecies. Improved results may result from vaccination strategies that target conserved epitopes, T cell feedback, and cross-reactive antibodies. According to available data, two HCV vaccines that are currently in development can cause these kinds of reactions; nevertheless, in order to improve vaccination attention, more methods to boost the vaccines' immunogenicity and expand the response are needed. Finding excess antigen design techniques that employ mosaic, ancestral, and consensus sequences to potentially regulate HCV heterogeneity is also important. **Table 3** lists a few of the main issues along with suitable remedies.

Immunogens designed rationally to induce cross-reactive

neutralizing antibodies

For the production of an effective HCV vaccine, the literate rational design of immunogens will be important. As development in the exploration of antibody repertoires is allowing substantial notion into the types of nAbs which can be related to SVC, there's the opportunity to use these records to generate immunogens that propose the improvement of those kinds of antibodies. E2 epitope I region is an example of such a process. They adopt three individual conformations when in association with nAbs and this linear epitope is organizationally flexible. Primarily epitope I make a prolonged configuration in association with the rat nAb 3/11, β-hairpin configuration is detected when to human nAb HCV-1 or AP33 and a transitional configuration happens when in association with the human nAb HC33.1 [61]. As discussed before by the action of glycan shift HCV may discharge epitope I concentrated on nAbs. However, this method does not revoke and an alternative to boost the influence of HC33.1 [62]. Due to this attention, the rational plan of an immunogen might attempt to extant the epitope I vicinity in an intermediate configuration to influence the humoral feedback to provoke HC33.1-like nAbs. As but this has now no longer been explored, however, struggles have been assumed to extant epitope I in β-hairpin configuration using cyclic peptides depends on θ-defensin which approves a related configuration. Such methods influence nAb feedback when confirmed in mice, but these have been inferior paralleled to mice immunized with E2 [63]. In this way, the rational strategy of HCV epitopes is precisely interesting and is inadequate for directing linear epitopes. Furthermore, the provision of cyclic peptides will require additional expansion which will increase the immunogenicity and initiate better titers of nAbs.

Table 2. Hepatitis C virus genomic proteins functions.

Protein	Functions
E1 and E2	Design envelope glycoprotein
P7	Polyprotein maturation, viral association
NS3	Helicase action
NS2/NS3	Protease action
NS4B	Replication complex
NS3/NS4A	Serine protease action
NS5B	Development of replication complex

Absence of a pipeline for pharmaceutical development

Different industries share in DAAs with massive financial profits have unfocussed consideration from HCV vaccine development

Table 1. Recent approaches for the development of hcv vaccine.

Vaccine	HCV strain	HCV target	Tested species	CD8 T cell response	CD4 T cell response	Antibody response	Ref.
pVax-N3-NS5b	Gt1b, Gt3a	NS3, NS4, NS5b	mice	N.D	yes	homologous, heterogeneous towards Gt1a, 1b, 2a, 2b, 3a, 4a, 5, 6	[64]
DREP- HCV/MVA-HCV	Gt1aH77	core, E1, p7, NS2, NS3	mice	yes	yes	non-neutralising IgG	[65]
pVax-sE1E2-IMX313P	Gt1b	E1, E2	mice	yes	yes	N/A	[66]
HCVp6-MAP	Gt4a ED43	E1, E2, NS4b, NS5a, NS5b	mice	yes	yes	homologous, heterologous towards JFH1	[67]
P7	Gt1b J4	P7	mice	yes	yes	N/A	[68]
ChAd3/MVA-Nsmut	Gt1a BK	NS3, NS4a, NS4b, NS5a, NS5b	humans	yes	yes	N/A	[69]
HBV/HCV-LPs	Not stated	linear E1 and E2 epitopes	mice	N.D	N.D	heterologous towards Gt1a, 1b and 2a	[70]
HBV/HCV-LPs	Gt1a H77	E1, E2	rabbit	N.D	N.D	homologous, heterologous towards Gt1a and 1b	[71]
Core, E1, E2 from Gt1a, 1b, 2a and 3a	Gt1a H77, Gt1b BK, Gt2a JFH1, Gt3a	core, E1, E2	mice, pigs	yes	yes	homologous neutralising antibodies	[53]
H77 $sE2_{\Delta 123}$	Gt1a H77	E2 core	pigs	N.D	N.D	homologous and heterologous	[72]
HCV-1 rE1E2	Gt1a HCV-1	E1, E2	humans	yes	yes	homologous and heterologous	[72]

N.D (not determined) and N/A (not applicable).

Table 3. Challenges and solutions in HCV vaccine development.

Challenges in HCV vaccine development	Clarification
Viral genetic variability	I. Develop mixed or multiple genotype vaccine II. Genotype specific vaccine targeting to that region where genotype dominates III. For multiple genotype design vaccine with novel immunogens
Lack of animal models	I. Development in the novel small animal models II. Speculation in phase- I/ II human research
Lack of human challenge models	Could be considered now
For phase-II/III studies well characterized cohorts	Financial assistance for cohort studies
Lack of pharmaceutical investment	To ensure funding by government and non-government organizations

(Gilead Sciences assessed financial profit in 2015 was around £15 billion). For the HCV vaccine development, there is limited privately funding despite the crucial demand for an approved vaccine being promoted by the research society. For publically sponsored healthcare organizations, an accessible vaccine delivers an inexpensive alternative to excessively costly DAAs which may attract sponsorship from governments and donations. In the absence of a prophylactic vaccine, not any pathogen has been eliminated and considering the main barriers facing recent HCV administration, there is a dire need to develop a prophylactic vaccine. It can be possible to promise the land but only with large-scale funding in the vaccine pipeline. According to all the barriers and obstacles in the current HCV treatment and to get effective outcome there is a dire need to develop a prophylactic vaccine.

Conclusion

Since the discovery of HCV in 1989, the question about the vaccine against this deadly virus still active, but it has been a challenging venture due to several factors such as lack of small animal models, virus genetic variability, etc. Despite the significant efficiency of DAA therapy against HCV, it is impossible that the virus will be eliminated without a prophylactic vaccine. Promisingly, struggles by using new technologies continue for effective vaccine and exploration into a range of methods have produced remarkable outcomes. The major improvements in the small animal models especially in vitro models revealed out some aspects about nAbs functionality, apprising rational vaccine design. The current review also explained about patient-derived E1E2 sequences for vaccine approach to influence nAbs which have the potential to target circulating HCV variants. Assessing the current method will provide the more laborious tool for understanding the nAbs feedback which will be an important characteristic for an effective HCV vaccine. However, the recent advancement about HCV E1E2 glycoprotein part and the human antibodies produced by HCV infection will permit the rational antigen-based design to provoke bnAbs.

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Ethics approval

No applicable.

Data availability

The data will be available upon request.

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Authors' contribution

Muhammad Shoaib Akhtar contributed to draft and critical revision of the article and approved the final version to be submited.

Competing interests

None.

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