Review Article

IT Medical Team
https://www.itmedicalteam.pl/

Journal of Biomedical Sciences
2254-609X

2022
Vol. 11 No. 6: 64

Recent Progress on Hepatitis C Vaccine Development: A Systematic Review

Princess Halm, Sumana Kondle*, Derek Sun

Department of Radiology and Biomedical Imaging, University of California San Francisco, 505 Parnassus Avenue, San Francisco, CA, USA

Corresponding author:
Sumana Kondle

savannahhalm@gmail.com

Tel: 2408382635

Department of Radiology and Biomedical Imaging, University of California San Francisco, 505 Parnassus Avenue, San Francisco, CA, USA

Citation: Halm P, Kondle S, Sun D (2022) Recent Progress on Hepatitis C Vaccine Development: A Systematic Review. J Biomed Sci, Vol. 11 No. 6: 64

Abstract

Chronic hepatitis C is one of the most common causes of liver disease and cancer world-wide. 20% of cases of chronic hepatitis are at high risk to develop cirrhosis and amongst them there is a 4%-5% annual incidence rate of hepatocellular carcinoma. Around the world, HCV infection is one of the leading causes of permanent liver damage, and related deaths, especially due to end-stage liver disease and hepatocellular carcinoma. Emerging data suggest that viral cure reduces, but does not eliminate the risk for hepatocellular carcinoma (HCC) development. The question that this paper seeks to find the answer to is, are there any In vitro or in vivo trials, currently being executed to discover a hepatitis C vaccine for those at risk, or already afflicted with, hepatitis C. If so, what is the perceived plausibility that an effective one is soon in the making? To find appropriate literature to assess, 70 articles were originally solicited, leaving exactly twelve remaining for data analysis through tabular format. Of these, the most promising trial vaccine was found to be a dendritic cell vaccine currently being created and tested by the Russian Academy of Sciences. The future for hepatitis C vaccine development looks bright, but there are still many continued challenges to the development of a perfectly potent therapy.

Keywords: hepatitis C; vaccine; vaccine advancements; antigenic shift; viral markers; immune response; drug therapy

Received: 27-Dec-2021, Manuscript No. IPJBS-22-12177; **Editor assigned:** 01-Jun-2022, PreQC No. IPJBS-22-12177; **Reviewed:** 15-Jun-2022, QC No. IPJBS-22-12177 **Revised:** 20-Jun-2022, Manuscript No. IPJBS-22-12177(R); **Published:** 27-Jun-2022, DOI: 10.36648/2254-609X.11.6.64

Introduction

Hepatitis C virus (HCV) is a small enveloped virus with a positive-sense, single-stranded RNA genome that encodes a large poly protein of 3010 amino acids. It belongs to the family Flaviviridae and genus hepacivirus. HCV can cause either an acute or chronic hepatitis C disease [1]. It is a blood borne virus frequently transmitted by injecting drugs through sharing needles, the transfusion of unscreened blood and sexual practices that lead to exposure to blood. HCV can be transmitted sexually or passed from an infected mother to baby. Hepatitis C is not spread through breast milk, food, water, hugging, kissing, sharing food or drinks with an infected person [2]. In addition, it is one of the most well-known viruses causing liver cancer and cirrhosis of the liver.

The acute illness is clinically mild and is typically unrecognized, undiagnosed and is not associated with any long-term sequelae. The chronic disease though, is fatal, affects more than 170 million people according to the World Health Organization, and can cause liver cirrhosis, chronic hepatitis, and hepatocellular carcinoma-a prevalent and life-threatening disease that, in contrast to diseases like hepatitis A and B, still does not have a vaccine to prevent transmission [3].

Around the world, HCV infection is one of the leading causes of permanent liver damage, and related deaths, especially due to end-stage liver disease and hepatocellular carcinoma. Recent studies suggest that viral cure reduces, but does not eliminate [4], the risk for hepatocellular carcinoma (HCC) development. Chronic hepatitis C is one of the most common causes of liver disease and cancer world-wide. 20% of cases of chronic hepatitis are at high risk to develop cirrhosis and amongst them there is a 4%-5% annual incidence rate of hepatocellular carcinoma [5]. The effects of chronic hepatitis C impact quality of life and the causes are influenced by host, viral and environmental factors, thus making it a hard disease to treat [3]. Worst of all, the major suspected reason as to why there is no vaccine available for

prevention of HCV infection is due to a high degree of strain variation. Yet, all of the above reasons necessitate how HCV needs an effective vaccine given its severe and long lasting negative health implications worldwide.

Prevalence

Hepatitis C virus (HCV) infection is a serious global health problem that has a global prevalence of 3% and affects an estimated 170 million people. Those infected with HCV are at risk for serious liver diseases, including potentially fatal hepatic cirrhosis and hepatocellular carcinoma. Between 18-34% of infected individuals spontaneously clear HCV. At least 400,000 people die from HCV infection annually from liver failure and liver cancer caused by this disease [2].

Up to 4 million people are newly infected with HCV annually, and of those acutely infected with HCV, around 85% develop chronic infection. Approximately 70% of patients with chronic viremia develop chronic liver disease, 10-20% of which develop liver cirrhosis. One in four cases of liver cancer, results from HCV infection, making HCV one of only 7 viruses (and the only positive-strand RNA virus) known to be oncogenic in humans [6]. Outside of North America and Western Europe, many countries experience a much higher prevalence and incidence of HCV infection where implementation of a vaccine would be expected to be highly beneficial. The prevalence rate was estimated to be 5.3% in Africa (31.9 million cases), 4.6% in the Eastern Mediterranean region (21.3 million cases), 3.9% in the West Pacific region (62.2 million cases), 2.15% in Southeast Asia (32.3 million cases), 1.7% in the Americas (13.1 million cases) and 1.03% in Europe (8.9 million cases) [1].

Current treatment available

HCV infection is rarely diagnosed during the acute phase. Therefore, the treatment of acute hepatitis is very limited. However, recent studies indicate that early treatment with interferon may be beneficial. All patients with chronic HCV infection are candidates for therapy. The development of direct-acting antivirals (DAAs) has revolutionized HCV treatment by offering the prospect for the first comprehensive cure of a chronic viral infection. DAAs cure the vast majority of HCV infections after only 8 weeks of oral therapy representing an outstanding success of modern medicine [6]. In the past, the treatment of standard is interferon alone or combination of interferon with ribavirin. Interferon in combination with ribavirin results sustained viral response in 35-40% of patients. Since 2001, recombinant interferon was replaced by newly developed pegylated IFN a2a and IFN a2b. The current standard therapy for hepatitis C treatment consists of combination of several direct acting antiviral depending the viral genotypes. This combination regimen achieves HCV eradication rates of 75-90% with certain genotypes. The combination treatment can be administered to relapse cases and people who do not respond to monotherapy. However, it remains difficult to treat patients co-infected with HIV or HBV, in addition to HCV infection, in patients with solid organ transplantation, and a few other genetic conditions [1]. As of 2014, boceprevir, telaprevir, simeprevir, sofosbuvir and Harvoni are approved by the Food and Drug Administration for the treatment of HCV infections, yet these are all DAAs once again [7]. Furthermore, a large proportion of persistent HCV infections are clinically silent and will not be recognized until liver damage is advanced. Current therapeutic options for hepatitis C are limited, especially for genotype 1 [6].

Lab diagnosis

Majority of primary HCV-infected patients are asymptomatic, so using symptoms to specifically indicate HCV infection is difficult. For example, HCV viremia can still exist despite a normal serum alanine aminotransferase (ALT) level. Therefore, virological methods rather than ALT levels, or other common labs used for liver failure, are used to diagnose HCV infection [8]. The best possible indicator of effective treatment is a sustained virological response (SVR), currently defined as undetectable HCV-RNA in peripheral blood determined with the most sensitive PCR technique 24 weeks after the end of the treatment. Achievement of an SVR is associated with a reduction in portal hypertension, hepatic decompensation, hepatocellular carcinoma and liver related mortality [3]. These tests assess for hepatocellular carcinoma, liver damage, and other inflammation like cirrhosis associated with hepatitis C. However, there must be a method to assess the level of Hepatitis C outside of symptoms and labs. The World Health Organization shares another common test for diagnosing Hepatitis C. First, testing for

anti-hepatitis C virus antibodies with a serological test identify those who have the infection. If this test comes positive for presence of said antibodies, then a confirmatory test is due; 30% of people who are infected will may be randomly clear the infection without treatment, however though they show no illness they will have positive antibodies still. In this confirmatory test, Hepatitis C Virus RNA will be checked.

Challenges in vaccine development

HCV is highly heterogeneous because the genome of HCV is highly mutable, its RNA-dependent RNA polymerase lacks proofreading ability. Mutations give rise to HCV antigenic variation, which may allow the virus to escape immune response and cause chronic or persistent infection in infected persons. Various viruses can be differentiated by RNA sequence analysis into at least 6 major genotypes (clades) and more than 100 subtypes. In sum, the genetic variability can be attributed to the high mutation rate in the envelope gene [9]. A key challenge for vaccine development and for understanding the pathogenesis of HCV-caused liver disease is the lack of appropriate animal models because predictive in vivo models of vaccine efficacy are crucial to prioritize vaccine candidates before initiation of costly clinical development [10]. The current lack of detailed knowledge concerning the correlates of immune protection is another major roadblock for devising vaccination strategies that overcome viral escape mechanisms [6]. In susceptible groups where HCV is prevalent, such as within the injection drug users community, prophylactic DAA treatment might in principle be considered, similar to a strategy pursued for HIV infection control. However, such a strategy will most likely increase the risk for the selection of DAA-resistant HCV variants and will be considered unaffordable. Second, DAAs are expensive, especially for most high-prevalence countries, which

are often resource limited. Thus it will likely remain out of the reach of a majority of infected persons worldwide for many years. Although costs have been lowered due to competition in the HCV drug market or facilitated access to generic drugs in some high-prevalence countries, a global eradication will not be possible unless these drugs become widely available with no strings attached. Third clinically relevant antiviral resistance now relatively uncommon will likely increase with broader use of DAAs. Fourth, protective immunity after viral clearance is most often insufficient and reinfection with HCV, in the absence of a vaccine, is all too easy following curative DAA therapy [6]. Fifth, the therapy is expensive and often associated with side effects, like leucopenia, thrombocytopenia, neutropenia, depression, fatigue, and "flu-like" symptoms, that may lead to discontinuation of therapy in 20% of patients. Finally, eliminating HCV infection with DAAs does not eliminate the risk of developing liver cancer. The most challenging treatment approach is resembled by previously difficult to cure patients [1].

Objectives

The purpose of this literature review is to review recent studies performed to manufacture a vaccine, focusing primarily on the challenges of developing a hepatitis C vaccine, the current reasons for the difficulty in producing a vaccine, and suggesting areas that should be of major focus in overcoming the difficulties of creating an effective hepatitis C vaccine. In addition, we will also be systematically reviewing the hepatitis C vaccines currently in trial, or within the last decade. Specifically, we have an interest in assessing the effectiveness of the vaccine to mount protective antibodies in the participants. The question that this paper seeks to find the answer to is, "Are there any in vitro or in vivo trials currently being executed to discover a hepatitis C vaccine for those at risk, or already afflicted with hepatitis C. If so, what is the one with the most perceived plausibility for maximum efficacy?"

Methods

To elicit methodology the group roughly followed the suggestions provided in the PRISMA diagram. To begin with we will discuss eligibility criteria used in our study. To determine eligibility, the abstract of the studies were measured up to our specific PICO type question, where we separately compared the study's patient/problem, intervention specified, and outcome to that of our study's own objectives. In terms of patient/problem we are focusing on those at risk for hepatitis C transmission and need prophylaxis or, people who are already afflicted with hepatitis C and need a complete cure. In regard to intervention of choice, we are specifically seeking for hepatitis C vaccination development. Finally, we wanted some alignment with outcome as previously mentioned above checking for effectiveness of vaccine to mount protective antibodies to the study participants. Because this is a study focused on the development of a therapy and/or prevention for the incurring of hepatitis C, the PICO method was used as a guiding light to define our search. As a result we initially began our search for Randomized Controlled Trials and some journal articles for background and supplemental material, through Pubmed and Google Scholar, EBM Reviews, Medline, Elsevier, National Institute of Health (NIH) website, World Health organization (WHO) website, ScienceDirect, Mendeley, and most of all clinical trials.gov, with the above mentioned key words, and in various combinations.

The inclusion criteria used was as follows: only randomized controlled type studies for vaccine identification. The type of studies that are included for review only include free or otherwise accessible, English-written peer reviewed journal articles within the last 10 years. The exclusion criteria included secondary research publications, predatory publications, studies that do not explicitly focus on the development of a hepatitis C vaccine, were published more than ten years ago, that do not mention the factors that give hepatitis C immunity or protection from immune system responses, non-clinical research trials. Some irrelevant terms that we intentionally excluded in our search included hep b/a; non vaccine intervention, and "cohort" or "Case control" type studies. After that, we continued on to use the highly acclaimed PRISMA method to provide guidelines for official methodology of literature review. The type of study emphasized in our finalized list of articles to review were intended to be randomized controlled trials and other literature reviews on the subject were also reviewed for guidance in writing this paper as well as offering further support to claims made in the background and discussion. The only factor separating this paper from the heaps of systematic reviews available [11], is the timing, and therefore compilation and newness of articles synthesized for this paper in comparison to the relative antiquity of others'.

After searching we found 70 relevant articles from all the databases. In the second phase we screened through abstracts and excluded 30 based on lack of direct relevance or mention of current antibody or antiviral therapies, rather than holistic approaches. Of the 40 remaining we discarded 10 because they were either not directly related to our PICO or not free for full article access, leaving 30. Remaining of the 30, 13 of them were directly relevant clinical trials. The other 17 were utilized for overall exposure, background knowledge, and literary fodder for the background and discussion portions of this paper. No specific mathematical summary measures will be used in this study. Instead, a compilation of qualitative data through discussion will be the only means of data collection and analysis offered in this simple literature type review/compilation. Of course it is evident as usual that there must be certain levels of inherent bias that must be done, but for the most part we targeted studies that had an even distribution of race, gender, and age throughout the study population. There was a limitation of publication bias inherent to our accumulation of studies. This is because many of the populations affected with Hepatitis C are Asian and Southeast Asian populations; however, many of the journals stemming from these regions are notorious for poor publishing standards; as a result these such publishers did not make the final cut for data to be analyzed. Instead, a majority of the trials assessed came from clinicaltrials.gov, and additional supporting information found from Elsevier, Clinical Direct, and the National Institute of Health (NIH).

Results

Referring to (**Table 1**) respectively, the first clinical trial was a

Table 1. Clinical trials.

References	Year	Country	Type of antigen used	Developer	Phase of trial	Limitations
12,13	2012-2018	USA	Recombinant vaccine vectors, AdCh3NSmut1/MV A-NSmut	National institute of allergy and infectious diseases	Both Phase I and Phase II	Lost of follow up and may have serious adverse effects from treatment
14	2016-2020	USA	DNA Plasmid Encoding Interleukin-12 INO-9012	National Cancer Institute, Inovio Pharmaceutica ls	Phase I	Not enough participants
15	2017-2022	UK	Adenovirus (ChAd) vectored chimpanzee vaccine against HCV	Centre Fo Universiy of Oxford	Phase I	Not enough participants
16	2014-2017	UK	Chimpanzee Adenovirus and modified vaccinia virus Ankara (MVA)	University of Oxford	Phase I	Nonrando mized, not enough participants
17	2014-2017	South Korea	VGX-6150 Plasmid	GeneOne Life Science, Inc., Inovio Pharmaceutica ls	Phase I	Nonrando mized, may have severe adverse effects of antigen
18	2018	Russia	Dendritic cell vaccine that has a core of HCV with NS3 proteins and made in the presence of IFN alpha/GMSF.	Russian Academy of Medical Sciences	Both Phase I and Phase II	Lost of follow up, may have severe adverse effects, not enough participants
19	2016-2020	USA	DNA plasmid encoding interleukin-12, HCV DNA Vaccine INO-8000,Electroporation- Mediated Plasmid DNA Vaccine Therapy	National cancer institute	Phase I	Not enough participants
20	2015-2018	USA	Recombivax This is made from the HbsAg produced in a yeast cell	Charles Rice, Rockefeller University	Phase IV	Nonrando mized, extremely low number of participants
21	2006-2009	Vietnam	Conventional therapy with PEIT, TOCE, PEIT + TOCE, TOCE + RFA for hepatocellular carcinoma or Entecavir for hepatitis B virus.MGN-3/Biobran treated with an extract taken from Shiitake mushrooms	The 108 Military Central Hospital	N/A	Study did not accept healthy volunteers
22	2017	USA	HCV-virus like particles, plasmid DNA and viral vectors encoding HCV-virus like particles	University of Melbourne, Parkville, VIC, Australia.	Preclinical	Genetic variability of HCV
23	2010-2016	U.K	human (Ad6) and simian (AdCh3) adenoviral vectors MVA encodes for malaria antigen ME-TRAP	ReiThera Srl	Phase I	Nonrando mized
24	2002-2004	Austria	immunization with HCV antigen peptide vaccine with polyarginine and IC41	Valneva Austria GmbH	Phase II	Lost of follow up

phase 1- phase 2 clinical randomized trial. The experiment was double blind. There were 548 participants in the study design. The interventional treatment used was AdCh3NSmut1, MVA-NSmut, along with a placebo. The study used IV drug abusers and injected the interventional treatment intramuscularly. After 6 months researchers checked the subjects viremia. After each vaccination when 1 month passed, researchers collected blood for assessment of alanine transferase (ALT) (SGPT), hemoglobin, creatinine, white blood cells (WBC), and platelets. According to clinical.gov"A laboratory AE was defined for ALT as greater than 1.25 times the upper limit of normal" [12]. At the very end of the experiment interferon gamma was measured; if the patient had a positive response to the pool of antigenic peptides used this was a positive response and treatment worked. This vaccine was not developed [13]. The vaccine was not developed.

The next clinical trial used plasmids from bacteria and then with reverse transcriptase or using a cDNA library and then PCR they could multiply selective DNA out of the RNA. The study does not specify how they were able to make the interventional treatments which were: DNA Plasmid Encoding Interleukin-12 INO-9012,electroporation-mediated plasmid DNA Vaccine Therapy, HCV DNA vaccine INO-8000.This study only had 32 participants. Also,the trial never left the phase 1 stage. The study sought to measure the interferon gamma levels when finished with the clinical trial at 26 weeks [14]. Another measurement this study planned to use the hepatitis C ribonucleic protein to observe if the levels went down. The hepatitis C vaccination was not developed.

In relation to the chart in the third clinical trial the interventional treatment was ChAd3-hliNSmut, MVA-hliNSmut, and was administered intramuscularly [15]. There was 25 participants;this was a phase 1 clinical trial. This was a nonrandomized clinical trial. There were three experimental groups and each group was subjected to different conditions. Group 1 received a low dose

of chimpanzee adenovirus vector vaccine and modified vaccinia ankara (MVA) vectored vaccine against HCV, group 2 was given a higher dose, group 3 were individuals who previously had HCV and were cured with DAA. This experiment used dosages of the two vectored vaccines to see if in higher amounts of vectored vaccine, if the immune response against the HCV vaccine will be increased. The results for this experiment was not noted. Moreover, the vaccination was not developed. The fourth clinical trial's objective was to determine if the HCV potential vaccine ('NSmut') and the HIV potential vaccine ('HIV.consv') if it was inserted into ChAd(chimpanzee adenovirus) and MVA (modified vaccinia virus ankara) would create an efficacious vaccine against the HCV vaccination. There were 33 subjects in this experiment. The groups were divided into 3 and then in a period of 2 months the individuals were given 2-4 intramuscular injections. This experiment was nonrandomized. The study was not complete, the results were not listed and the vaccination was not developed.

The next trial had only 18 participants, it was nonrandomized. VGX6150 plasmid was the interventional treatment. This was a phase 1 experiment. Three different groups had increasing doses of the DNA plasmid VGX6150 intramuscularly. The first group had 1mg, the second group had 3 mg, and the last group had 6 mg. This could have been a second line therapy to treat hepatitis C, according to this study that is why the study was done. Again this study failed to report the results of the experiment. Furthermore the vaccine was not developed.

The sixth trial had 10 participants the interventional treatment was a dendritic cell vaccine that had a core of HCV with NS3 proteins, and made in the presence of IFN alpha/GMSF.CBC count was monitored after each vaccination at month 2,7, and 13 months after the 1st vaccination 18.Also after the 2,7,10 months the HCV RNA viral node was measured. The participants in this experiment were all caucasions. Patients were getting injections under the skin along with hiL 218.This vaccine was not developed.

The following trial used HCV antigen DNA.The HCV antigen DNA used INO-800 and INO-9012; this consists of a DNA plasmid that encodes interleukins. This experiment treated some individuals with one DNA plasmid with interleukins or a mix to see if it would be efficacious in killing the HCV virus. This clinical trial had 32 subjects. There was no results posted and the vaccine was not developed.

The next clinical trial only had 6 participants. The interventional treatment was Recombivax which is a drug 20.This clinical trial got to phase 4. Recombivax was given to healthy people and individuals that had HCV. At 0, 1, and 6 months recombivax was injected. This clinical trial used an HBV vaccine to see if HCV would be able to be extinguished. At 8 months the HbsAg antibody titers were measured, using RNA sequence with an interferon stimulated gene list and a cytokine panel. CD4 T cells were also measured. No results were posted for this experiment. Moreover there was no limitations listed; a vaccine for hepatitis C was not developed.

There were many experimental interventions for "Randomized Clinical Study of Arabinoxylan Rice Bran (MGN-3/Biobran) for the Treatment of Hepatocellular Carcinoma and Hepatitis B and C Infection". The experimental interventions were: PEIT, TOCE, TOCE plus PEIT, TOCE plus RFA, MGN-3 which is a dietary supplement from shiitake mushrooms which has shown anticancer activity in mice, and Entecavir an antiviral drug. PEIT is an ethanol injection 21. TOCE is transarterial oily chemoembolization, RFE is radiofrequency ablation. This randomized trial had 130 participants. This randomized clinical trial compared conventional therapy to experimental therapy. The conventional therapy was all the other combinations excluding MGN-3, and the experimental therapy included MGN-3 with: PEIT and TOCE. This study also compares HBV and HCV. There was no results posted, and also the vaccine was not developed.

Next is a preclinical study that talks mostly about viral like particles. NCBI states, "The HCV core, E1 and E2 proteins can self-assemble into immunogenic VLPs". To create a VLP one would need to clone the gene of interest first. Also this preclinical study portrays that each system would show the limitations and strength of the VLP. For example if one used a bacterial system it is way cheaper but there may be many genes of interest that are recombinant. Nevertheless this preclinical study never made it to a phase 1 clinical trial and no vaccine was developed. This preclinical study does state though that HBV's VLP could have epitopes that could lead to a HCV vaccination and could induce a strong T cell response.

Latterly, there were 55 participants for this clinical study. There was no randomization and the intervention treatment was MVA-NSmut, AdCh3NSmut, AdCh3NSmut. This was a stage 1 clinical trial. Human and simian adenoviral vectors were used for this clinical trial. There are nonstructural HCV proteins in both the human and simian adenoviral vectors. NSmut is an inactivated genetic polymerase gene which supports the adenoviral vectors. These were used to see if these factors could induce a spontaneous resolution of HCV. Modified Vaccinia Ankara encodes for the malaria antigen. This would increase the T cell response as this is supposed to protect one from malaria.In this clinical trial. The outcome being tested for is T cell response for each treatment. The effect of these agents on HCV were not noted. Also there was no vaccine developed. Finally, in the last clinical trial was a phase 2 clinical trial. This was a randomized clinical trial with 66 participants. The intervention treatment was IC41 and polyarginine. IC41 is a new vaccine that decreases viral load in hepatitis C. There were 66 participants in this study. This experiment was double blind and immunological assays were used. Injections of mixtures of polyarginine and IC41 or one or the other in different doses, were given in the arm every 4 weeks subcutaneously. RNA and HCV were also supposed to be measured. However the results were never recorded and the vaccinations for hepatitis C was not developed.

Discussion

This literature review demonstrated that the most conventional methods of developing a hepatitis C vaccine that were relying on engineering a vaccine that induces antibody formation upon exposure to hepatitis C antigens, using reverse transcriptase to engineer a DNA vaccine that will induce lower levels of hepatitis C virus RNA and antigens, and using vectors and

recombinant proteins to give patients immunity or the ability to mount an immune response against already existing hepatitis C infection. The results of analysis of the studies included in this review indicate that there are a number of promising avenues that researchers can pursue in order to develop a functioning hepatitis C vaccine. Recent progress that involves using dendritic cells as antigen presenting cells to elicit immune responses in patients with hepatitis C especially show progress in improving symptoms of hepatitis C, as do experimental vaccines that use hepatitis C DNA to act against the hepatitis C virus in order to generate an immune response to combat hepatitis C virus. Currently, however, a vaccine for hepatitis C that can be regularly used and that can prevent hepatitis C does not exist, and more research is required to develop such a vaccine. The ability of hepatitis C to shift and modify its antigens to avoid recognition by any experimental vaccine is the major factor that explains why developing a hepatitis C vaccine is so far still not possible. None of the current treatments studied in the review showed sufficient improvement in symptoms of hepatitis C or offered enough prophylaxis to prevent healthy patients from contracting hepatitis C.

Engineering antibodies to counter the effects of hepatitis C antigens remains a popular method of obtaining a vaccine against hepatitis C. In one research project[12] conducted by the National Institute of Allergy and Infectious Diseases, a two stage, phase I/II, double-blinded, randomized, placebo-controlled study [13] of 548 hepatitis C virus uninfected male and female injection drug users aged 18 to 45 was launched to test the efficacy of two experimental hepatitis C vaccines dCh3NSmut1 and MVA-NSmut, compared to placebo when administered to HCV-uninfected injection drug users and to determine if AdCh3NSmut1 and MVA-NSmut HCV vaccines will reduce incidence of chronic HCV infection compared to placebo among HCV-uninfected. This study revealed that while some immunogenicity against hepatitis C virus was provided by the two experimental vaccines, complete prophylaxis against hepatitis C was not achieved.

Another study [14] conducted by the National Cancer Institute takes a different approach by pursuing a vaccine by DNA vaccine therapy against hepatitis C infection. This phase I trial studied the side effects and ideal dosage of deoxyribonucleic acid vaccine therapy in treating 32 patients with hepatitis C virus infection that persists or progresses over a long period of time. Vaccines made from DNA via using the enzyme reverse transcriptase to engineer DNA from hepatitis C viral RNA may help the body build an effective immune response to kill cancer cells that express HCV infection. The goal of the study was to determine the safety profile of the hepatitis C DNA vaccine, consisting of INO-8000 (HCV antigen DNA) alone or co-administered with INO-9012 (interleukin [IL]-12 adjuvant DNA) (DNA plasmid encoding interleukin-12 INO-9012), and researchers gave injections of the vaccine to see if the vaccine induced substantial decreases in measured levels of hepatitis C virus RNA, antibody response to hepatitis C virus antigen, and sustained viral response. These measures were analyzed to indicate if the DNA vaccine had any effect against the activity of hepatitis C virus, and early results have not shown any appreciable decrease in the variables measured, suggesting that a DNA vaccine against hepatitis C is still not feasible for preventing or treating hepatitis C.

Another research study [15] examined 25 patients who were injected with candidate vaccines against hepatitis C that had been inserted into the carrier viruses chimpanzee adenovirus and modified vaccinia virus Ankara. Participants were studied for six months to see if any T cell response to hepatitis C epitopes occurred and if any cellular immune response against hepatitis C appeared as a result of the experimental vaccines given. Final data released by the study indicated that no long lasting or statistically significant increase in cellular immune response occurred as a result of the vaccines, meaning that this approach to creating a hepatitis C vaccine has not succeeded and that further research is required for a successful vaccine to be produced.

One particularly novel approach to hepatitis C vaccine development is harnessing dendritic cells to produce antigens that will elicit a strong cellular immune response against hepatitis C through the innate and adaptive immune responses. In one study conducted by the Russian Academy of Medical Sciences, 10 patients suffering from chronic hepatitis C were given initiating and maintaining courses of autologous monocyte-derived dendritic cells, generated in the presence of IFN-α/GM-CSF and pulsed with recombinant hepatitis C Core and NS3 proteins, and were monitored for any improvement in their symptoms for thirteen months. The final results of the study showed that none of the patients suffered any adverse effects from the treatment that they received, and a majority of patients showed some improvement in their symptoms of chronic hepatitis C. However, no patients showed any complete recovery from hepatitis C, and the results of the study do not confirm that this vaccine is a definite treatment for the disease. Of all of the studies analyzed in this literature review, none of the studies delivered any vaccine that is guaranteed to provide prophylaxis or effectively treat hepatitis C. While some of the conclusions of the study demonstrate some recent progress in ameliorating the symptoms of hepatitis C, and some studies explore new pathways in treating hepatitis C and developing a vaccine, a true vaccine remains elusive, and more research needs to be conducted that builds on the progress that was made in the studies included in this review. The host T cell response is most important in determining the outcome of acute hepatitis C infection, but humoral and innate immune responses are also important. During chronic hepatitis C infection, the host hepatitis C specific T-cell response is impaired. So far, no research project or study has succeeded in producing a completely reliable vaccine against hepatitis C that is widely used in clinical settings. The key problems present in creating an effective vaccine for hepatitis C mainly include the ability of the hepatitis C virus to evade the natural host immune response through a number of mechanisms, including genetic variation. There are several promising vaccine trials currently recruiting patients that will undoubtedly further expand our understanding of the complex interplay of hepatitis C and host immunity and our ability to modulate this in favor of the host. New therapeutic hepatitis C vaccine approaches are likely to continue to be explored in combination with standard medical therapy rather than in isolation. The new directly acting viral protease inhibitors that will become available in the next few years will further influence this process. While these drugs will improve treatment outcomes

for patients with HCV genotype-1 infection, their high cost will limit availability.

Approaches for non genotype 1 strains also need some consideration given the major genetic divergence of the six major genotypes and their distinct immunoreactivity. Vaccines that produce substantial antiviral T-cell responses are being developed, but in the absence of a clear correlate of protection, efficacy will need to be demonstrated in clinical trials. The organization and monitoring of these is a substantial issue for the field, but moves to harmonize studies of at-risk and acutely infected cohorts might accelerate this process. Many promising vaccine approaches have reached clinical trials including peptide, protein, DNA and vector-based vaccines. A successful T-cell vaccine strategy will need to induce a broad and strong T cell response. Adenoviral vectors are highly immunogenic in healthy volunteers; it is not yet known if these vaccines can adequately recover T-cell responses in HCV-infected patients. Well-characterized cohorts of at-risk and acutely infected HCV patients are required to move Phase I vaccine studies forward into studies of efficacy.

Conclusion

Significant advances in genomics and proteomics in recent years have enabled a variety of new hepatitis C vaccine approaches to reach clinical trials. The most popular and promising methods of developing a working hepatitis C vaccine include engineering DNA from hepatitis C viral RNA via reverse transcriptase to create a working vaccine, antibody therapy to counter antigens, peptides, recombinant protein, and vector-based methods, which have all been explored with varying degrees of success. Of all the vaccine research approaches studied in this literature review, therapy relying on dendritic cells to produce antigens that result in an immune response to hepatitis C viral infection showed the largest decrease in viral levels and highest rates of improvement in health for patients with hepatitis C, suggesting that it is the most promising mode of therapy for a future vaccine. Recombinant protein vaccines that induce anti-envelope antibody responses are unlikely to provide sterilizing immunity owing to the genetic variability of the HCV envelope region, but may play a role in attenuating the course of primary infection or serve as an adjunct to a T-cell-based vaccine. Peptide and protein-based T-cell vaccines have induced weak T cell responses only. This approach is likely to progress with the development of novel adjuvants. DNA vaccines with additional techniques to enhance delivery and immunogenicity show some promise and have been shown to decrease viral load in some chronically infected patients. Adenoviral vectors appear to be highly immunogenic in healthy volunteers and Phase II studies in at-risk populations are required to assess efficacy. Because hepatitis C infection can be cleared by an appropriate immune response, vaccination remains a realistic goal. At this current point, an effective and widely used vaccine against hepatitis C remains in development and does not yet exist, so further research is necessary to reach the goal of engineering a vaccine against hepatitis C.

References

1 Ashfaq UA, Javed T, Rehman S, Nawaz Z, Riazuddin S (2011) An overview of HCV molecular biology, replication and immune responses. Virol J 8: 161.

2 World Health Organization Hepatitis C (2019).

3 Westbrook RH, Dusheiko G (2014) Natural History of Hepatitis C. J Hepatol 61: S58-S68.

4 Baumert TF, Zeuzem S (2014) Overcoming the Roadblocks in Hepatitis C Virus Infection. J Hepatol 61: S1-S2.

5 Ansaldi F, Orsi A, Sticchi L, Bruzzone B, Icardi G (2014) Hepatitis C virus in the new era: Perspectives in epidemiology, prevention, diagnostics and predictors of response to therapy. World J Gastroenterol 20: 9633-9652.

6 Bartenschlager R, Baumert TF, Bukh J, Houghton M, Lemon SM, et al. (2018) Critical challenges and emerging opportunities in hepatitis C virus research in an era of potent antiviral therapy: Considerations for scientists and funding agencies. Virus Res 248: 53-62.

7 Ogholikhan S, Schwarz KB (2016) Hepatitis Vaccines. Vaccines 4: 6.

8 Chigbu DI, Loonawat R, Sehgal M, Patel D, Jain P (2019) Hepatitis C Virus Infection: Host–Virus Interaction and Mechanisms of Viral Persistence. Cells 8: 376.

9 Lapa D, Garbuglia AR, Capobianchi MR, Porto PD (2019) Hepatitis C Virus Genetic Variability, Human Immune Response, and Genome Polymorphisms: Which Is the Interplay? Cells 8: 305.

10 Bukh J (2016) The history of hepatitis C virus (HCV): Basic research reveals unique features in phylogeny, evolution and the viral life cycle with new perspectives for epidemic control. J Hepatol 65: S2-S21.

11 Baumert TF, Schuster C, Cosset F-L, Dubuisson J, Hofmann M, et al. (2016) Addressing the next challenges: A summary of the 22nd international symposium on hepatitis C virus and related viruses. J Hepatol 64: 968-973.

12 Staged Phase I/II Hepatitis C Prophylactic Vaccine (2019).

13 Department of Health and Human Services. Experimental Hepatitis C Vaccine Trial Concludes.

14 DNA Vaccine Therapy in Treating Patients With Chronic Hepatitis C Virus Infection.

15 Class II Invariant Chain HCV Vaccine Study.