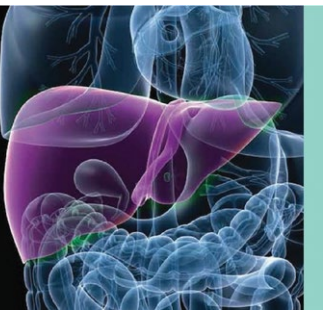

Hepatitis C Vaccine Development in the Era of Direct-Acting Antivirals

Matthew McConnell, M.D., and Joseph K. Lim, M.D.

THE NEED FOR A HEPATITIS C VACCINE

We are currently in an exciting era of hepatitis C virus (HCV) treatment in which direct-acting antiviral (DAA) therapy is associated with viral eradication rates exceeding 90%. Public health authorities, including the World Health Organization, have launched strategies for global elimination of HCV by 2030, defined by an 80% reduction in incident HCV and 65% reduction in HCV-associated mortality. As demonstrated by historical examples such as tuberculosis and syphilis, however, infectious disease eradication is not likely to be achieved by treatment alone in the absence of an effective vaccine.[1]

Persistent deficits across the HCV care cascade remain important barriers to HCV elimination in the United States and worldwide, including screening and diagnosis, linkage to care, drug access, and treatment failure. Despite support by national guidelines of the Centers for Disease Control and Prevention and US Preventive Services Task Force, birth cohort screening of individuals born from 1945 to 1965 is estimated to miss 25% of patients with chronic HCV infection.[2] Simplified regimens, improved efficacy, and decreased stigma have contributed to an increase in HCV treatment in high-risk populations, particularly people who inject drugs. However, ongoing challenges in addressing the opiate epidemic and substance abuse have been associated with rising incidence of new HCV cases, as well as a measurable rate of reinfection post-DAA therapy, ranging from 11% to 26% across several studies.[3] Furthermore, the high cost of DAA regimens has limited patient access to HCV therapy both in the United States and in multiple resource-limited regions worldwide[4] and remains a vexing barrier to global eradication. In this context, HCV vaccine development represents an important and perhaps essential tool to achieve this goal.

WHAT IS A PROTECTIVE IMMUNE RESPONSE TO HCV?

Because the complications of HCV infection arise from chronic viral persistence rather than acute infection, which is characterized by few or no symptoms, prevention of viral

Abbreviations: DAA, direct-acting antiviral; HCV, hepatitis C virus; HVR1, hypervariable region 1.

From the Section of Digestive Diseases and Yale Liver Center, Yale University School of Medicine, New Haven, CT.

Potential conflict of interest: Nothing to report.

Received July 2, 2018; accepted August 6, 2018

View this article online at wileyonlinelibrary.com

persistence represents the primary goal of vaccination.[5] The potential for achieving this goal is evident from the observation that individuals who have spontaneously cleared the virus are at a substantially reduced risk for persistent infection on reexposure.[5] Variability within the host is believed to stem from the lack of proofreading function of the NS5B RNA-dependent polymerase, which results in a high error rate per replication cycle and the development of variants known as quasispecies.[6] Other mechanisms through which HCV evades an effective host immune response include immunogenic decoy epitopes that direct the immune response away from effective targets, epitope shielding (such as by nonneutralizing antibodies), major histocompatibility complex downregulation, and direct cell-to-cell transmission.[7]

Important evidence exists for the significance of T cell–based immunity to HCV. $CD4^+$ "helper" T cells play a key role, with a broadly directed $CD4^+$ T cell response to HCV associated with spontaneous clearance of infection. Conversely, chronic infection is associated with a "defective" $CD4^+$ T cell phenotype as well as with the selection of mutants that evade the $CD8^+$ cytotoxic T cell response. Animal data provide further evidence for the importance of $CD8^+$ T cells, as chimpanzees infected with HCV after previously clearing the virus experienced prolonged viremia in the setting of $CD8^+$ T cell depletion, resolving with recovery of these cells.[8,9]

Neutralizing antibodies play a role in immunity to HCV, although the exact nature of this role is somewhat controversial. Patients with hypogammaglobulinemia are able to clear HCV infection, indicating that antibody-mediated immunity is not essential; however, antibodies are also associated with spontaneous clearance of infection in patients,[8] and passive immunization prior to HCV challenge has prevented infection in animal models.[5]

CURRENT PROGRESS IN VACCINE DEVELOPMENT

HCV vaccine development is uniquely challenging due to the high level of diversity present both in the population, with seven different genotypes identified, and in individuals, in whom numerous quasispecies of the virus exist due to the high error rate in viral replication and high replication rate of the virus. This high viral diversity implies that classic antibody-mediated sterilizing immunity may not be feasible for HCV, although it remains under investigation in vaccine development.[10] The two major pathways through which candidate vaccines mediate immunity, neutralizing antibodies and T cell–mediated immunity, are listed in Table 1. An ideal HCV vaccine would prevent viral persistence, confer protection across genotypes, and generate an immune response resistant to viral evasion on an individual level.

Common targets of neutralizing antibodies in HCV infection include the envelope glycoproteins E1 and E2 or the E1E2 heterodimer.[7] E2 plays a role in virus entry, interacting with scavenger receptor class B type I and tetraspanin (CD81), and therefore most neutralizing antibodies are directed against this protein. Of interest is the hypervariable region 1 (HVR1) of E2 because antibodies to this region can mediate viral neutralization but are not broadly beneficial due to being isolate specific and exert selection pressure, resulting in the emergence of quasispecies that have evaded their neutralizing ability. Antibody binding to HVR1 of E2 may also limit the binding of other broadly neutralizing antibodies because of steric hindrance.[11] A Chiron Corporation Genotype 1a E1/E2 vaccine designed to elicit neutralizing antibodies has been tested in chimpanzees, resulting in sterilizing immunity in some animals but breakthrough infections in others; however, compared with controls, these breakthrough infections were often attenuated and more likely to resolve.[5] Current data suggest that antigenic E2 epitopes are mobile, prompting interest in the development of a novel vaccine strategy targeted at stabilization of these epitopes.[12]

Inducing T cell–mediated immunity is another important approach to HCV vaccination. $CD8^+$ T cells specific to HCV can clear the virus through the cytolytic mechanism (causing apoptosis of infected hepatocytes) or the noncytolytic mechanism (suppressing HCV replication through secreted cytokines). However, $CD8^+$ T cell exhaustion occurs in HCV infection because of upregulation of T cell–inhibitory receptors.[13] The majority of currently registered clinical trials

TABLE 1. TARGETS FOR HCV VACCINE DEVELOPMENT

Approach	Example Targets	Rationale	Challenges
Neutralizing antibodies	E1 and E2 envelope glycoproteins and their heterodimer E1E2	Known conserved epitopes bound by well-characterized neutralizing antibodies	Hypervariable regions on these proteins serve as "decoys"[12] and result in epitope shielding[7]
T cell–mediated immunity	Nonstructural proteins NS3 to NS5b	Defective virus-specific T cell response is associated with persistent infection[13]	Overcoming viral genetic diversity[18]

TABLE 2. SUMMARY OF HCV VACCINE TRIALS

Mechanism	Phase 1-4	Status	Trial(s)
Neutralizing antibodies	Phase 1	Completed	NCT00500747
T cell–mediated immunity	Phase 1	Active, not recruiting	NCT02362217
			NCT02568332
T cell–mediated immunity	Phase 1/2	Active, not recruiting or recruiting	NCT01436357
			NCT03119025
T cell–mediated immunity	Phase 1	Suspended	NCT02772003
T cell–mediated immunity	Phase 1	Completed	NCT01701336
			NCT00445419
			NCT01094873
			NCT01070407
			NCT01296451
			NCT00124215
			NCT02027116
T cell–mediated immunity	Phase 2	Completed	NCT00602784
			NCT01055821
			NCT00601770
			NCT00606086

with a known status are of vaccines using T cell–mediated immunity (Table 2) with some encouraging results from phase 2 studies.[14,15] In addition, a recent preclinical study has characterized an adenoviral vaccine using conserved, immunogenic HCV epitopes to generate HCV-specific T cell responses in mice across a range of HCV genotypes.[16] Further progress in this field is eagerly awaited.

In another approach to inducing protective immunity, research continues into the role that HCV-like particles may be able to play in vaccination. Virus-like particles, collections of viral structural proteins that form structures mimicking viruses but without the necessary components for infection, are attractive in HCV vaccination because of their improved safety profile over killed or live-attenuated viruses. A number of preclinical studies have produced HCV-specific neutralizing antibody and T cell responses using these particles, and there is hope that continuing research will yield promising results with vaccines amenable to human trials.[3,17]

CONCLUSION

Despite transformative advances in the efficacy of DAA regimens, global HCV eradication remains a vexing challenge because of ongoing deficits across the care cascade, as well as new concerns for rising incident infection and reinfection in high-risk populations, including people who inject drugs. HCV vaccine development remains a vitally important component of HCV elimination strategy and will require ongoing investment in basic and translational research. Significant advances in our understanding of HCV immunology provide optimism that effective vaccines may be developed, and several are currently under investigation in clinical trials.

CORRESPONDENCE

Joseph K. Lim, M.D., Professor of Medicine, Director, Yale Viral Hepatitis Program, Section of Digestive Diseases and Yale Liver Center, Yale University School of Medicine, 333 Cedar Street, LMP 1080, New Haven, CT 06520-8019. E-mail: joseph.lim@yale.edu

REFERENCES

1) Strom BL, Buckley GJ, eds. A National Strategy for the Elimination of Hepatitis B and C: Phase Two Report. Washington, DC: National Academies Press; 2017.

2) Shiffman ML. Universal screening for chronic hepatitis C virus. Liver Int 2016;36(Suppl. 1):62-66.

3) Torresi J. The rationale for a preventative HCV virus-like particle (VLP) vaccine. Front Microbiol 2017;8:2163.

4) Edlin BR. Access to treatment for hepatitis C virus infection: Time to put patients first. Lancet Infect Dis 2016;16:e196-e201.

5) Walker CM. Designing an HCV vaccine: A unique convergence of prevention and therapy? Curr Opin Virol 2017;23:113-119.

6) Trucchi C, Orsi A, Alicino C, et al. State of the art, unresolved issues, and future research directions in the fight against hepatitis C virus: perspectives for screening, diagnostics of resistances, and immunization. J Immunol Res 2016;2016:1412840.

7) Pierce BG, Keck ZY, Foung SK. Viral evasion and challenges of hepatitis C virus vaccine development. Curr Opin Virol 2016;20:55-63.

8) Freeman ZT, Cox AL. Lessons from nature: understanding immunity to HCV to guide vaccine design. PLoS Pathog 2016;12:e1005632.

9) Shoukry NH, Grakoui A, Houghton M, et al. Memory $CD8^+$ T cells are required for protection from persistent hepatitis C virus infection. J Exp Med 2003;197:1645-1655.

10) Torres-Cornejo A, Lauer GM. Hurdles to the development of effective HBV immunotherapies and HCV vaccines. Pathog Immun 2017;2:102-125.

11) Fauvelle C, Colpitts CC, Keck ZY, et al. Hepatitis C virus vaccine candidates inducing protective neutralizing antibodies. Expert Rev Vaccines 2016;15:1535-1544.

12) Fuerst TR, Pierce BG, Keck ZY, Foung SKH. Designing a B cell-based vaccine against a highly variable hepatitis C virus. Front Microbiol 2017;8:2692.

13) Shi J, Li Y, Chang W, Zhang X, Wang FS. Current progress in host innate and adaptive immunity against hepatitis C virus infection. Hepatol Int 2017;11:374-383.

14) Klade CS, Wedemeyer H, Berg T, et al. Therapeutic vaccination of chronic hepatitis C nonresponder patients with the peptide vaccine IC41. Gastroenterology 2008;134:1385-1395.

15) Di Bisceglie AM, Janczweska-Kazek E, Habersetzer F, et al. Efficacy of immunotherapy with TG4040, peg-interferon, and ribavirin in a phase 2 study of patients with chronic HCV infection. Gastroenterology 2014;147:119-131.e3.

16) von Delft A, Donnison TA, Lourenço J, et al. The generation of a simian adenoviral vectored HCV vaccine encoding genetically conserved gene segments to target multiple HCV genotypes. Vaccine 2018;36:313-321.

17) Masavuli MG, Wijesundara DK, Torresi J, Gowans EJ, Grubor-Bauk B. Preclinical development and production of virus-like particles as vaccine candidates for hepatitis C. Front Microbiol 2017;8:2413.

18) Swadling L, Capone S, Antrobus RD. et al. A human vaccine strategy based on chimpanzee adenoviral and MVA vectors that primes, boosts, and sustains functional HCV-specific T cell memory. Sci Transl Med 2014;6:261ra153.