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Controlled Human Infection Model — Fast Track to HCV Vaccine?

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The discovery of hepatitis C virus (HCV) by Houghton and colleagues in 1989 capped a long journey in search of the elusive non-A, non-B hepatitis viral agent. In the ensuing 20 years, we witnessed an unparalleled transformation of the therapeutic arena that capitalized on this break-through, leveraged modern science, and led to treatment regimens that could cure more than 95% of patients infected with HCV. This tour de force represents nothing short of the best of medical science, culminating in the award of the 2020 Nobel Prize in Medicine or Physiology to Michael Houghton, Harvey J. Alter, and Charles M. Rice. While we bask in the glory of this triumph, we need to be reminded that the fight against this virus is far from over: Hundreds of thousands of people die from this disease worldwide each year, and new infections continue to ravage many parts of the world, including North America, owing to the opioid epidemic.[1] If history provides any lesson, the elimination of an infectious disease requires both an effective vaccine and a successful global vaccination strategy. For HCV, the need for a vaccine is no exception.

The road to an HCV vaccine has been fraught with difficulties, as highlighted in previous publications.[2,3] The moratorium on experimentation with chimpanzees that went into effect more than 10 years ago effectively put a stop to the use of the only viable animal model for HCV vaccine development, even though it did not explicitly forbid the use of chimpanzees for such a purpose. As a consequence of the lack of alternative animal models for preclinical testing[4] and of the perception that highly effective treatments would be sufficient for global control of the virus, new vaccine development efforts ground to a halt. The recent disappointing results of an adenovirus vector-based HCV vaccine tested in a large trial in humans[5] illustrate the challenges of developing and testing an effective vaccine

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with current approaches. Only one other vaccine candidate (based on recombinant HCV envelope proteins), which was tested in chimpanzees before the moratorium on chimpanzee experimentation began, is currently in clinical development.[3] Short of the reinstitution of the use of chimpanzees, researchers who have been involved in efforts to develop an HCV vaccine are left with few options. Although a large, controlled efficacy trial conducted in humans remains necessary, here we raise the possibility of an intermediate step — a study based on a controlled human infection model (CHIM) — for the purpose of reenergizing HCV vaccine development.

CHIMs, which involve deliberate infection of humans with infectious agents in a controlled setting for the purpose of advancing medical knowledge, especially for the purposes of vaccine development, have been in use for hundreds of years. Starting with physician Edward Jenner's testing of the smallpox vaccine in 1796, this model has been applied to more than 25 infectious diseases, including yellow fever, cholera, malaria, dengue, and, most recently, coronavirus disease 2019 (Covid-19).[6] CHIMs provide a critically important intermediate stage in vaccine development, serving primarily to reduce risk and cost and to allow the selection of more promising candidates for further testing in larger phase 2 and 3 trials.

ETHICAL CONSIDERATIONS

Although CHIMs are not fundamentally different from other clinical trials, they raise distinct challenges that depend to a considerable degree on the state of knowledge regarding the infection under consideration. Although there are no clear yardsticks, ethical considerations, such as sufficient social value, a reasonable risk–benefit profile, fair participant selection, suitable site selection, stakeholder engagement, rigorous informed consent, and appropriate compensation, need to be explored to their fullest for any proposed CHIM.[6] Without chimpanzees, CHIMs may be the only path forward to conduct rapid testing of HCV vaccine candidates and are thus justified given their high societal value.[7] However, given that CHIMs offer little benefit to participants, all risks must be mitigated to an acceptable level. Currently, the state of HCV science has advanced to the point at which an acceptable risk–benefit profile may be achieved in a CHIM involving patients with HCV. The most relevant advance is the development of highly effective, direct-acting antiviral (DAA) agents that can cure almost all those infected. However, risks to study participants and third parties still exist and should be minimized without compromising clinical evidence. A sound informed consent process is essential to dispelling mistrust and enhancing our understanding of CHIMs that involve patients with HCV.

CLINICAL CONSIDERATIONS

The prospect of using CHIMs is possible only because of the remarkable advances in HCV therapy gleaned through the development of highly effective, safe, pan-genotypic DAA regimens. With both sofosbuvir–velpatasvir and glecaprevir–pibrentasvir, administered for 8 to 12 weeks, the incidence of virologic cure is consistently above 98% in clinical trials and real-world cohorts in patients with chronic HCV infection who do not have cirrhosis.[8,9] For the few persons who have relapse after a complete course of therapy, retreatment with

sofosbuvir–velpatasvir–voxilaprevir is almost universally successful.[10] In the registration trials, there were no virologic failures in patients without cirrhosis, the group most likely to be enrolled in a CHIM.

Small studies have confirmed that these same pan-genotypic regimens are equally effective when used to treat patients with acute HCV infection.[11] In the largest known trial of acute infection, patients were randomly assigned to receive sofosbuvir–velpatasvir for 6 or 12 weeks.[12] The trial was stopped prematurely because of a higher incidence of relapse in the 6-week group, but, more important, there were no virologic failures in the 60 patients who received treatment for 12 weeks. Organ transplantation from HCV-positive donors to uninfected recipients has also shown that immediate treatment of HCV infection, even in the context of immunosuppression, is highly efficacious; although long-term follow-up data are lacking, no adverse effects of short-term HCV infection have been reported.[13,14] Collectively, these data strongly suggest that treatment of a recently infected participant in the context of a CHIM, who according to enrollment criteria does not have preexisting liver disease, will almost certainly be successful, with the promise of retreatment in the extremely unlikely case of relapse. To add further confidence, one could restrict the challenge inoculum to a patient who has already been successfully cured with a DAA regimen.

Even if the cure of infection in the context of CHIM is almost a certainty, other important clinical considerations remain. Although acute HCV infection is typically associated with a mild or even subclinical course, fulminant HCV infection has been reported. The true incidence of fulminant, acute HCV infection is unknown, but it is probably rare.[15] Early reports suggested that it occurred more frequently in Asia, where it has been most commonly reported in patients with genotype 2 infection. Increased risk of HCV infection has also been reported in patients with preexisting infection with hepatitis B virus.[16] Other host and viral factors have not been identified, making the occurrence of fulminant HCV infection hard to predict.[17] Reassuringly, the treatment of fulminant HCV infection is likely to be effective. Fibrosing cholestatic hepatitis, a very severe form of acute HCV infection that is seen in patients with immunosuppression — and that was almost universally fatal before the advent of DAA agents — can now be treated effectively.[18] Cases of severe, acute HCV infection successfully treated with DAA agents have also been reported.[19] Thus, although unlikely to occur, a severe course of acute infection would still very likely be curable and without long-term complications.

Beyond the immediate clinical effects, the potential consequences of acute infection followed by cure need to be considered. There have been reports of rare instances of the detection of HCV RNA in serum with the use of a highly sensitive polymerase-chain-reaction assay long after curative therapy. HCV RNA has also been detected in mononuclear cells in peripheral blood and liver specimens obtained years after patients have had successful treatment. In some instances, the HCV RNA could be transmitted to chimpanzees by means of inoculation with a large volume of serum, raising the possibility that a persistent reservoir of virus remains.[20,21] However, there was no evidence of residual liver disease in these patients, which indicates that the minuscule amount of virus or viral RNA detected is probably of little clinical consequence. Also reassuring are

clinical data showing that late relapse after sustained virologic response, even with potent immunosuppression, is extremely rare (occurring in <1% of patients). As compared with hepatitis B virus, there have been no known reports of reactivation of HCV infection in patients with immunosuppression once a sustained virologic response with a DAA agent has been achieved.[22]

Long-term follow-up of patients who are positive for HCV antibodies but negative for HCV RNA and have cleared the virus spontaneously has shown that after controlling for risk factors and coexisting conditions associated with HCV infection, such as drug use, those with spontaneously resolved infection have a probability of survival that is similar to that of the general population when matched for age and sex.[23] The authors of one recent study reported persistent epigenetic changes in the liver after successful HCV treatment, a profile that was also found, and with greater frequency, among patients in whom hepatocellular carcinoma developed after treatment.[24] These findings arouse concern that persistent viral-induced changes may be prooncogenic. However, in this study, among persons with HCV that was treated successfully with a DAA agent, hepatocellular carcinoma occurred only in those who had cirrhosis before they had a sustained virologic response, a finding consistent with extensive data showing that the risk of hepatocellular carcinoma is not increased among persons with spontaneous HCV clearance or among those with chronic infection and minimal or no liver fibrosis. Collectively, these data suggest that although there may be some alterations in the liver of a patient with chronic infection that persists after HCV clearance, these alterations are unlikely to be an issue after a short duration of acute infection, as would be the case for participants in a CHIM.

REGULATORY CONSIDERATIONS

Any infectious agent that is used in a CHIM is considered to be both a biologic product and a drug and thus requires an investigational new drug application under the Food and Drug Administration. All of the following are part of the regulatory process: preclinical toxicology studies; proof-of-concept studies assessing efficacy and risks to participants; chemistry, manufacturing, and controls; environmental concerns (e.g., transmission); and approval by an institutional review board. Typically, regulatory authorities will not make a judgment regarding the social value of a proposed CHIM. For an HCV CHIM, a challenge inoculum is particularly complex in the context of regulatory standards and would need to be thoroughly tested and characterized. Features such as genetic composition, the production process, clinical information, antiviral susceptibility, and the purity, potency, and stability of the product must meet certain standards before human testing. All regulatory authorities require a fully vetted clinical protocol by an institutional review board that incorporates many of the above-described ethical and clinical issues.

CHALLENGE INOCULUM

Robust HCV cell culture and animal models have been established to generate and propagate recombinant HCV, and thus they provide potential sources of viruses suitable for the CHIM. A human hepatoma cell line (Huh7) has been adapted to propagate and produce high-titer

HCV. Cell-culture–generated HCV can also be genetically manipulated to obtain certain advantageous features for CHIMs, such as increased susceptibility to antiviral agents.

Molecular clones of HCV genomes have been generated and propagated in cell culture as infectious virus,[25] but virtually all of them require adaptive mutations in order to replicate efficiently in cell cultures that can lead to attenuation in vivo. JFH1 and its chimeric derivatives remain the only strains that can replicate to sufficiently high levels to be potentially useful as a CHIM challenge inoculum.[26] JFH1-derived viruses can infect chimpanzees and have low pathogenicity,[27,28] and thus they may not be representative of circulating HCV in the human population. Similarly, cell-culture–adapted viruses of other genotypes appear to infect and replicate poorly or not at all in chimpanzees or humanized mouse models.[29] Thus, virus propagated in vitro may be attenuated for in vivo infection and may not be suitable for a challenge inoculum. However, easy genetic manipulation of cell-culture–generated viruses does offer a potential advantage.

Neither the Huh7 cell line nor its highly permissive sublines have been approved for the generation of biologic products for human use, and thus they would need to be extensively characterized before regulatory approval. Finally, HCV exists in nature as a quasi-species, and the use of molecularly cloned virus does not fully represent the physiologically relevant diversity of a natural infection, which may be critical for the assessment of vaccine candidates.

HCV can also be propagated in primary human hepatocytes and human stem cell–differentiated hepatocyte-like cells,[30] but replication tends to be low and transient. Like cell lines, these primary cells would also need to pass a high regulatory bar for human use.

Humanized chimeric immunodeficient mouse models engrafted with human hepatocytes can support HCV infection to a level similar to that in humans[4] and thus could be potentially used to propagate viral inocula. Stored serum from chimpanzees infected with HCV may also be a source, but viruses obtained from animals pose a potential exposure to unknown contaminating pathogens and animal proteins that may be viewed as an unacceptable risk by regulatory authorities. It is conceivable that HCV could be purified from these sources; however, isolation with adequate purity that does not affect infectivity may not eliminate the concern regarding contamination by pathogens or proteins.

Human serum–derived virus would approximate natural infection closely and thus is the most viable challenge inoculum. Human blood products have been used routinely in clinical practice, and there are well-established procedures in place to ensure safety. High-titer HCV human plasma could be obtained from HCV-infected volunteers in a relatively large quantity (several hundred milliliters per volunteer) through simple procedures such as blood donation. Genotype 1 would be the preferred initial viral genotype because it is common globally and persons with this genotype have the highest response rate to current DAA regimens. Other genotype inocula may eventually be needed to test the breadth of protection of candidate vaccines. Potential inocula should be screened by means of deep sequencing to eliminate those harboring drug-resistant strains or other pathogens. Transmission studies can then be performed in humanized chimeric mouse models to assess infectious titer. Ideally,

patients from whom plasma is obtained should then be treated with a highly effective pan-genotypic DAA regimen to document the effectiveness of therapy against this strain. Plasma can then be tested in healthy volunteers to determine the transmissibility and infectivity of the inoculum. Once infected, these participants would be treated with the same DAA regimen to ensure a high response rate.

CLINICAL TRIAL DESIGN

The crucial issues in the design of a clinical trial based on CHIM for HCV vaccine development are the test population, the dose of the inoculum, post-challenge monitoring, the timing of treatment, and the definition of efficacy. For ethical reasons, it may be appropriate to recruit persons who inject drugs, since this population is at high risk for infection and may benefit from vaccine testing. Conversely, this population may be difficult to follow and may include some persons who have had previous or recurrent HCV infection, who may be more likely to transmit infection to others, or who may have other medical conditions. However, these concerns are not insurmountable in a clinical trial. Selection of young and healthy participants who do not have coexisting conditions would ensure the highest likelihood of treatment response. Both men and women should be recruited, since it would be important to discern any differences in vaccine response that are related to sex. Potential harm to others, such as sexual spread by all participants and vertical transmission in women of childbearing age, should be thoroughly explained and carefully monitored in all participants, although the risk of transmission by either route is low.

The inoculum dose should be carefully selected, initially based on the in vivo infectious dose in animal models, and then later validated in the CHIM. It is also important to consider the amount of virus that is typically transmitted from person to person, such as the residual amount of contaminating blood that is transmitted in a shared syringe.[31]

Clearly defined end points are critical in trial design. An effective HCV vaccine candidate can either induce sterilizing immunity (no infection) or prevent chronic infection. On the basis of existing evidence, the former goal may be difficult to achieve and the latter more realistic.[2,3,5] It is conceivable that sterilizing immunity could be obtained by targeting the requisite immune responses with highly potent immunogens. Questions remain regarding what constitutes protective immunity; extensive evidence points to the importance of the induction of strong, multispecific, cell-mediated immunity and high-titer, broadly neutralizing antibodies.[3]

If prevention of chronic infection is the goal, the design would be more complicated and would have to account for chronicity, which is typically defined as persistent viremia 6 months after infection.[5] This definition would require waiting as long as 6 months before initiating treatment, which may be difficult to justify ethically. However, with treatment administered during the acute phase of HCV infection, possibly up to 12 months after infection, it is still possible to reliably achieve a response rate of 100%.

Development of an effective HCV vaccine that can be readily mobilized for use in both high- and low-income countries is one of the last goalposts in the journey toward control

of this global health threat. Considering the enormous resources and time required to test an HCV vaccine candidate, as illustrated by the only preventive HCV clinical trial known to have been completed to date,[5] it behooves the scientific community to ponder and pursue alternative paths. The chimpanzee model should be reconsidered for this purpose, but in its absence, the CHIM is perhaps the most viable alternative road to achieving the goal of an HCV vaccine. Although daunting challenges and controversies remain, it is time to begin a dialogue regarding this model as an intermediate step between the present and a future in which there will be an HCV vaccine. We urge interested parties to engage in a concerted effort — through public–private partnership and investment — to spur the preclinical development of HCV vaccine candidates, perhaps by leveraging the highly successful platforms of the recently developed Covid-19 vaccines, and to explore the development of an HCV CHIM before engaging in large-scale testing in humans.

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