The Uphill Climb Toward a Hepatitis C Vaccine

Will we ever have a vaccination for the virus?

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Behind the excitement surrounding the new, highly effective treatments for hepatitis C virus (HCV) lies a separate, arguably more important struggle to combat the global epidemic: the quest for a vaccine, which isn't anywhere near achieving such success.

The first and only study to test a hep C vaccine among at-risk humans began in March 2012. Results are expected after its scheduled wrap-up in January 2016. With sites at Johns Hopkins University in Baltimore, the University of California, San Francisco, and the University of New Mexico, this National Institutes of Health (NIH)–sponsored Phase I/II study includes 450 injection drug users (IDUs), who all receive counseling and referral to drug treatment programs.

The vaccine under investigation includes one injection that primes the immune system by delivering key genetic information to cells and a second shot as a booster. The goal is to prompt both a CD4 and CD8 immune cell reaction to the virus. In an earlier trial among what are known as "healthy" volunteers, the vaccine showed promise in eliciting a robust immune response.

All other hep C vaccine research is in earlier stages. Much of the scientific effort is in basic search-and-discovery work: trying to better map and understand the structure of the virus, and to identify weaknesses a vaccine might exploit.

A recent study, also out of Johns Hopkins, tested 18 antibodies against 19 strains that make up about 94 percent of the genetic variability of genotype 1. (There are six main genetic variants, or genotypes, of hep C in the world.) They found that the strains had differences in key proteins on their surfaces. These differences made it so that each virus was vulnerable to a certain numbers of antibodies, but remained resistant to others. In sum, this meant that there was no one antibody that could knock out every strain.

According to the study's lead investigator, Justin Bailey, MD, PhD, an assistant professor of medicine at Johns Hopkins, he and his colleagues' findings were "bad news for vaccine development." Their research illuminated the vast challenge of prompting antibodies to fight the virus. (Such a tactic is a main alternative means of developing a vaccine from the immune-priming

response approach pursued in the current Phase I/II clinical trial.) Any discouragement notwithstanding, Bailey does believe that a vaccine that elicits multiple antibodies could ultimately prove successful.

Numerous factors have held research back and littered obstacles across the road to even a partially successful vaccine. For starters, there is the matter of time: Hepatitis C was only identified and named 1989 (before then it was known, rather obliquely, as “non-A, non-B hepatitis”). Then there’s the matter of will: Unlike HIV, which has had a vociferous activist community fighting for scientific progress for over three decades, HCV lacks such fierce political advocacy to fight for funding. Only an estimated one in six of the 3 million to 4 million Americans living with the virus is aware of the fact, and those who are haven’t been as likely to publicize it. For the most part, people with hep C are baby boomers, who likely aren’t keen to be identified as having a stigmatizing disease they likely contracted from a youthful dalliance with injection drugs. Otherwise, most people with hep C are active IDUs, or are either in prison or have a history of incarceration—two marginalized and perhaps less vocal demographics.

Today, the success of treatments like Gilead Sciences’ Harvoni (ledipasvir/sofosbuvir) have led some to suggest that a vaccine is no longer necessary. But Rajen Koshy, PhD, program officer for viral hepatitis at the National Institute for Allergies and Infectious Diseases, part of the NIH, believes such a mindset is based on flawed reasoning.

“There is no instance that I can think of where the availability of a drug that cures a disease eradicates that disease,” Koshy says. “We have 150 million to 180 million people in the world who are infected chronically with this virus and who have all got to be treated before you can eradicate the virus. And with treatment running upward of $100,000 per course, we’re not going to see big numbers of people being treated anytime soon in this country. You don’t even think about that happening in countries where the greatest burden exists. So to eradicate the virus you need a vaccine that prevents infection.”

Preventing infection is highly difficult given the crafty, evasive nature of the virus itself. Like HIV, hep C is quick to mutate, owing to its rapid, sloppy self-copying. The mistakes the virus makes in its replication process lead to mutations that ultimately help the overall viral population evade immune attacks.

Also, the fact that there are multiple genotypes of the virus makes developing a vaccine that works on a global scale far more difficult. Every genotype attacks the liver and leads to similar outcomes, but each one is distinct enough that a vaccine for one wouldn’t necessarily work to prevent another. Most current research focuses only on genotype 1, which is the most common in the United States. (The same has held true for the development of hep C medications; only now are pharmaceutical companies paying close attention to the other genotypes.)

“When you say, ‘I want to design a vaccine to protect against hepatitis C,’ the question is: Which hepatitis C?” says Andrea Cox, MD, PhD, an associate professor of medicine at Johns Hopkins who is one of the two lead investigators of the Phase I/II vaccine trial.

“There’s also a lot of variation [of the virus] within an infected individual,” Bailey points out. “It’s hard to induce an antibody with a vaccine that would neutralize all those potential variants.”

Another problem facing vaccine scientists is that until recently they lacked the technology to grow enough of the mass quantities of virus needed for their research. Furthermore, researchers lack of a proper animal in which to study a vaccine’s effects. Influenza vaccines, for example, are grown in embryonated chicken eggs. This is feasible because both chickens and humans can be infected by the flu virus. But the only animal that can be infected with hep C is the chimpanzee. And as a result of a successful animal rights campaign, in 2011 the NIH placed a moratorium on the new use of chimps for research in the United States.

Cox is keeping her ambitions modest for her vaccine research.

“What one can hope is that, if we don’t hit the ball out of the park the first time,” she says, “we learn how to play the game a little bit better so that we could, if necessary, design a better vaccine.”

If the current phase of the vaccine trial is a success, the chances of its moving into the kind of large-scale, multi-year trial necessary to prove the its efficacy to the U.S. Food and Drug Administration (FDA) are challenged by financial as well as practical concerns. GSK (GlaxoSmithKline), which owns the rights to the vaccine, may decide that such a sizable investment is unlikely to lead to a significant monetary payout and shelve the vaccine. Then there’s the matter of finding a population to participate in the trial, one whose members would need to be at high risk of contracting hep C. In the United States, this primarily means IDUs, who can be a challenging group to work with and perhaps less likely to remain in a long-term study. While there is also the possibility of testing a vaccine among prisoners, this group tends to move in and out of incarceration and be difficult to monitor; also, their hep C infection rate may not be high enough.

Should a vaccine receive FDA approval—a feat Cox for one believes will happen within a decade, but the timing of which Bailey stresses is very difficult to predict—it is less likely that it would achieve what is known as sterilizing immunity: the ability to totally prevent the virus. Bailey believes that the best hope may be “partially protective” vaccine that would reduce, but not totally eliminate, the risk of infection. Considering that about 20 percent of people who are infected with hep C clear the virus on their own in a few months, he hopes that an eventual vaccine would help expand that effect to a higher proportion of the population.

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