Last September, scientists, doctors, advocates and people with hemophilia gathered in Washington, DC, for the National Hemophilia Foundation’s (NHF) 15th Workshop on Novel Technologies and Gene Transfer for Hemophilia.

The amazing number of studies presented demonstrated the start of the payoff from more than two decades of hard lessons learned. “We saw the first clinical studies of gene therapy in hemophilia start in the late 1990s, shortly after we started these workshops in 1996,” said Glenn Pierce, MD, PhD, co-chair of the workshop.

Looking back over the workshops, “the speed of development, of advancement, is astonishing,” said David Lillicrap, MD, from Queen’s University in Ontario, Canada, and the workshop’s other co-chair. “For those of us who’ve been part of this meeting for a long time, it’s really incredible where this field has gone in a short period of time.”

“The recent progress has left a number of clinical trial participants independent of the need for factor replacement, but more work remains before these technologies will be widely available.”
LASTING EFFECTS OF GENE THERAPY

Lessons learned from early studies have led to a proliferation of successful clinical trials, some of which shared long-term results at this year’s workshop.

Both hemophilia A and B are caused by defects in a single gene. If a working copy of that gene could be delivered to liver cells—the gene for factor VIII (for hemophilia A) or factor IX (for hemophilia B)—gene therapy could theoretically provide a lifelong novel treatment.

Participants in previous workshops shared strategies for improving gene therapies, including raising the amount of clotting factor produced by the replacement genes.

The big boost for gene therapy for hemophilia B came with the discovery of a naturally occurring variation in the gene that produces factor IX (FIX). This gene variation increases FIX activity by seven times compared with the normal FIX gene. Several pharmaceutical companies swapped this hyperactive gene in for regular FIX. This led to factor levels after gene therapy jumping from about 5% to approximately 30% or more on average.

For hemophilia A, researchers had long been thwarted by the physical size of the gene that produces factor VIII (FVIII). Its large size made it difficult to pack into the viruses used to deliver the gene to liver cells.

Over the last decade, researchers discovered they could cut out a portion of the gene and still have it produce useful FVIII. This, plus other improvements, allowed the first successful delivery of gene therapy for hemophilia A.

At the workshop, investigators presented results from four clinical trials of gene therapy for hemophilia B and three trials for hemophilia A. Some trials have been completed and are following participants for safety and long-term effectiveness, and some are still enrolling volunteers. But all show promising results.

Ongoing trials of both FIX and FVIII gene therapy have achieved levels of factor expression high enough to allow some participants to discontinue prophylactic factor replacement therapy. For example, in an ongoing trial of FVIII gene therapy from St. Jude Children’s Research Hospital and University College London (UCL), participants who received the highest treatment dose gained factor expression levels between 46% and 74% of normal. Participants with hemophilia A in the BioMarin trial have also achieved independence from clotting factor therapy, lasting for at least three years to date.

Several of the therapies presented are in phase 3 clinical trials, which is the last step before applying for Food and Drug Administration approval. One is preparing to submit results to regulatory agencies by the end of the year.

Promisingly, gene therapy appears to be durable, meaning that factor levels have stayed steady over time. Some of the
trials presented have followed their participants for one to three years, and some for even longer. Participants in the first FIX gene therapy trial, run by St. Jude and UCL, have now been tracked for five to almost nine years. Their modified liver cells continue to produce FIX.

Adrian Rothenfluh, PhD, who was born with severe hemophilia B, was one of those participants. “I had a lot of bleeds in my lifetime; probably over 1,000, I’d guess,” he told conference attendees. “Seven years ago, I enrolled at the trial, (and) since becoming a genetically modified organism, I’ve had one bleed a year. So it has made a tremendous difference,” he said.

Conference attendees also shared information about long-term follow-up from dogs and nonhuman primates with hemophilia who had received gene therapy in the lead-up to human studies. All dogs studied continued to express clotting factor for their entire lives. When they died of natural causes, the researchers found no gene therapy-related damage to their livers—only changes normally seen with old age.

In primates, an initial decline in factor expression was seen over a year or two, but then it stabilized over time. Like in dogs, there was no liver damage from gene therapy seen in samples taken after death.

“The million-dollar question is: Will expression be lifelong in patients after gene therapy?” asked Thierry VandenDriessche, PhD, from the Free University of Brussels in Belgium and a member of the workshop organizing committee. While this question remains open in people, “it’s very nice to see this long-term data... (with) sustained effects for more than 10 years (in dogs) and more than six years in primates,” he said.

Workshop attendees discussed the need for liver biopsies from people who have undergone gene therapy, to get physical proof of what happens in their livers over time. Clinical trials of gene therapy have not routinely required biopsies, because of concerns that people would be hesitant to participate if asked to undergo this invasive procedure.

NHF’s Medical and Scientific Advisory Council (MASAC) has put out a call asking companies to include voluntary biopsies as part of future trials, said MASAC Chair Steven Pipe, MD, a workshop organizing committee member.

“We can’t wait 10, 20 years (to understand) long-term effects in humans,” Pipe said. “If there are things we can be looking for in liver specimens that would give us an early signal of a potential adverse risk that might develop later, we can then act on those and make changes to the strategies that we bring to clinical trials.”
As gene therapy gets closer to the clinic, discussion at the workshop also focused on making sure that people’s expectations are aligned with the likely results from these first-generation treatments. Several attendees stressed that not all people who undergo first-generation gene therapy will achieve freedom from factor replacement, and all will probably need support in extreme cases, such as surgery.

“There is enormous benefit to achieving something higher than what we’re getting now. The first gene therapies that come to market are going to be ‘Gene Therapy 101,’ and there will be other advances,” said Mark Skinner, a MASAC member who has severe hemophilia A. “But this shouldn’t hold people back from trying the first treatments that come to market if they have what they need to make an informed decision,” he added.

WORKING TO BUILD ALTERNATIVE DELIVERY METHODS

In addition to improving the genes used for gene therapies, researchers have been working on new ways to get these genes into cells. All the ongoing trials use modified versions of a virus called adeno-associated virus (AAV). Its safety and ability to get genes into cells is long established. But it has limitations.

A substantial number of people are naturally exposed to forms of the virus early in life. This exposure results in lifelong antibodies to AAV, which could destroy a gene therapy using the virus before it enters the liver.

AAV is also thought likely to be suboptimal for gene therapy in children. AAV does not insert the gene it carries directly into a cell’s genetic code. Therefore, as cells divide, the gene could be left behind and expression of clotting factor could be lost. Children’s liver cells divide rapidly as they develop. To date, no gene therapy trials have enrolled children.

Researchers have been working to develop another type of virus called a lentivirus for gene therapy. Since it is based on HIV, almost no one is exposed early in life. It’s also a bigger virus, meaning that larger genes can be packed inside after most of the viral genes are removed. Lentiviruses insert the genes they carry directly into a cell’s genetic code.

Promising results from animal studies of lentiviral vectors were presented at the workshop, including one in nonhuman primates. So far, though, lentiviruses have proved difficult to manufacture.

Several novel approaches to modify cells in the lab to express clotting factor and then put them back into the body after modification were also presented.

Researchers also discussed methods to deliver genes to cells without using viruses at all. Gene editing—repairing a broken gene within liver cells instead of replacing it—is
also being studied for the treatment of hemophilia. These techniques are still experimental.

MORE THAN JUST GENE THERAPY

Gene therapy isn’t the only way that scientists are trying to eliminate the need for lifelong clotting factor replacement.

New therapies hold particular promise for patients with inhibitors to factor replacement products. Inhibitors are antibodies produced by the immune system that destroy factor as soon as it’s infused and are a dreaded complication of current factor-based treatments.

One such drug whose development had been tracked through previous conferences is now approved for clinical use. Emicizumab is approved for the treatment of people with hemophilia A, both with and without inhibitors. It works by replacing the function of FVIII in the clotting cascade but doesn’t structurally resemble the factor. Therefore, it’s not recognized by inhibitors.

Previous workshops have also followed the progress of a drug called fitusiran, which increases the circulation of a protein in the clotting cascade called thrombin. Fitusiran is in phase 3 trials, and data on its safety is not yet available.

The next generation of such drugs is now in the pipeline. Examples presented at the 2019 workshop included marstacimab, concizumab and SerpinPC. All work to boost the clotting process by blocking molecules that normally inhibit clotting. Because they don’t change FVIII or FIX levels, they may be less likely to provoke the development of inhibitors compared with standard factor replacement products.

These experimental treatments are either in clinical studies in people or about to start human trials in people with and without inhibitors.

AS MANY QUESTIONS AS ANSWERS

The run of successes presented at the 2019 conference raised as many questions as answers in a discussion that closed out the second day.

No ongoing gene therapy trials have as yet enrolled children. But once they do, some doctors in the audience expressed concerns about the ethics of parents being asked to make such a decision for their children.

Two parents of children with hemophilia who participated in the discussion said it would be a difficult choice to make, especially if their child’s factor levels remained relatively steady with available treatments.

“But I think the other side of it is that the population that would stand to benefit the most from a correction would be the youngest children, before they have bleeds and before they have joint disease,” commented Guy Young, MD, a...
hematologist at Children’s Hospital Los Angeles, who spoke at the conference.

The amount of protection offered to children by newer therapies such as emicizumab will have to be part of that discussion as more is known about them, commented Nigel Key, MD, from the University of North Carolina.

The issue of how much factor production will be “enough” for a person to choose gene therapy also came up. “We’ve really gone through the glass ceiling” of expectations, Key said. “A few years ago, we were talking about ‘2%, 5%, wouldn’t that be great?’ Now we’re saying (that) 30% or 40% is not enough.”

The fact that gene therapy still produces significant variability in factor levels among people remained a sticking point for many of the workshop attendees with hemophilia. While some people could gain factor levels above 50%, others might get 5% or less.

The floor of “enough” is likely to vary between individuals. Rothenfuh only went from having 0.5% FIX to 5%. “But to me, that made a huge difference” in quality of life, he said.

The topic of quality of life after gene therapy or with novel drugs—and whether that can be measured with standard outcomes such as the number of bleeds a year—was also discussed.

Declan Noone, who has severe hemophilia B, currently experiences no bleeds with prophylactic factor replacement. If he chose to undergo gene therapy, “I’d go from zero bleeds a year to zero bleeds a year,” he said. “But quality of life could be completely different.”

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What to Ask Before Taking Part in a Clinical Trial
Clinical trials are an important step in developing new therapies for bleeding disorders. In a trial, study subjects receive a new treatment under close supervision by medical experts. As you weigh whether to participate in a trial, get answers to the following questions from the research team:

WHAT IS THE PURPOSE OF THE TRIAL?
How is the treatment being tested different from what’s available now, and how might it benefit you more than your current treatment?

WHAT ARE THE POSSIBLE RISKS?
Be sure you understand the possible short- and long-term side effects of the treatment being tested and how those side effects will be addressed during the trial.

WILL I HAVE TO STOP TAKING MY CURRENT FACTOR PRODUCT?
Some trials require participants to stop taking other medications.

WILL I HAVE TO TRAVEL FOR TREATMENT?
In some trials, treatments may be done at home or in a doctor’s office. Others require participants to travel to a specific location for treatment. If you need to go to a hemophilia treatment center (HTC), for example, ask how often—and whether transportation assistance will be provided.

WHO WILL BE IN CHARGE OF MY CARE?
Can you keep seeing your own doctor? Will researchers keep your doctor informed about your participation in the trial? Will you be informed about the trial’s progress?

ARE THERE COSTS?
Will you have to pay for any parts of the study? Who will pay if you are injured during the trial? Does insurance cover any of the costs?

CenterWatch (centerwatch.com), a clinical trials resource center, offers more questions to ask. If you are interested in taking part in a clinical trial, speak with your healthcare team at your HTC. Search for trials on ClinicalTrials.gov, a US National Library of Medicine database of publicly and privately funded clinical studies around the world.