The Miami Herald

HEALTH & FITNESS

NOVEMBER 17, 2015

5 ways to tackle Type I diabetes — mixed into a potent drug cocktail

UM team working on a proposed drug therapy study
The drugs have been used in other diabetes studies
Goal is for patients to control blood sugar with less intrusive insulin regimen

Rick Dronsky, of Cooper City, discusses a clinical trial with Dr. Jay Skyler of the Diabetes Research Institute. **DANIEL BOCK** FOR THE MIAMI HERALD

BY CAMMY CLARK

Special to the Miami Herald

A 12-person team at the University of Miami Health System has developed a cocktail of five potent drugs that it thinks could stabilize and possibly reverse the progression of Type I diabetes in newly diagnosed patients.

The team believes that combining the different therapies is necessary to combat the complex disease that usually strikes during childhood and has been frustrating doctors and researchers from around the world for decades.

If the cocktail works the way the team at the Diabetes Research Institute at UM optimistically thinks it should, patients who take it over the course of one year may be able to control their blood sugar with a less intrusive insulin regimen and possibly with no insulin at all.

To put the cocktail to the test, the UM team has been working on a proposed study it calls DIPIT: Diabetes Islet Preservation Immune Treatment. It requires the participation of 42 people ages 18 to 35 who have been diagnosed within four months of new onset Type 1 diabetes.

One big hurdle already has been cleared: Food and Drug Administration approval.

“Everybody said the problem with combination therapies is that the FDA would never let you do that. These are relatively healthy people with new onset diabetes and you are going to give them five potent drugs. You have got to be crazy. The FDA will say: ‘No way, Jose,’ ” said Dr. Jay Skyler, associate director at the Diabetes Research Institute and spokesman for the study.

But in September, the FDA surprised many in the field and sent the Diabetes Research Institute a letter with only three minor revisions to its protocol and a reminder to adhere to all reporting regulations. It is the FDA’s version of consent to conduct the study.

The UM team now is working to get drug manufacturers Genzyme, Amgen, Prometheus and AstraZeneca to supply the cocktail’s five drugs and the placebos. The drugs — Thymoglobulin, Neulasta, Embrel, Proleukin and Bydureon – all are FDA-approved for other medical uses.

The UM team also is working to get the $7 million to $8 million study undertaken by the federally funded TrialNet, an international network of diabetes researchers. Skyler helped lead the network and was its first chairman, serving in that role for 22 years before stepping down in June.

TrialNet has a central pharmacy and the infrastructure to enroll the participants, administer the drugs, monitor the participants and gather the data for analysis, Skyler said.

Last month, he presented TrialNet with the multitherapy concept proposal.

“It takes months and months to vet,” said Julie Ford, clinical research administrator at TrialNet, “but Dr. Skyler has been our leader for many, many years. We have a tremendous amount of respect for him. He has taken us to where we are today.”

Type 1 diabetes is a chronic disease in which there is a high level of sugar (glucose) in the blood. This is caused because the immune system attacks the pancreas' beta cells, which produce insulin. Why the immune system attacks is still unknown.

Insulin is a hormone that moves blood sugar into cells, where it is stored and later used for energy. With the beta cells unable to produce enough or any insulin, glucose builds up in the bloodstream, creating a condition called hyperglycemia. A person with the disease must inject insulin several times daily or continuously use an insulin pump to live.

The five drugs chosen for the cocktail all have been used in other Type 1 diabetes studies, and usually with new onset patients, Skyler said.

"In the past, these drugs have shown at least transient benefit, but the problem is we haven't had the home run yet," he said.

From past failures, Skyler said it has been learned that the evolution of Type 1 diabetes involves several immune pathways.

"Really, it is the whole immunological army that is attacking the beta cell," Skyler said. "If we stop the artillery, then the cavalry steps in. If we stop the cavalry, the artillery attacks."

This complicates the design of an ideal therapeutic strategy to both control the immune system and prevent the loss of beta cell function and beta cell mass.

"So we have one drug to stop the cavalry; one drug to stop the artillery; two drugs that help bring in supports systems that favor the immune response; and one drug that helps beta cell health so they can resist the attack better," Skyler said.

In addition to the five drugs showing some promise in previous Type 1 diabetes studies, four of the five were used together with favorable results in a recent clinical study in which islet cells (which include the insulin-producing beta cells) were transplanted in the pancreas, Skyler said.

"The immune system has proven to be a formidable opponent," said Dr. Robin Nemery, pediatric endocrinologist at Joe DiMaggio Children's Hospital in Hollywood. "We think we get somewhere and then some unseen factors trump our efforts and we have to go back to the drawing board. Unfortunately, so far the immune system seems to be smarter than us."

She said she agrees that because of the immune system's complexity, "you have to attack it on many levels in order to hope to see any results."

At the time most people develop the disease, they have lost about 70 to 80 percent of their insulin-producing beta cells.

“What we want to do is preserve that 70 to 80 percent that is left and ideally allow some of the pancreas to recover by reducing the attack on it,” Skyler said. “Maybe if we can recover another 20 to 30 percent of the beta cells, a person can get by with little to no insulin therapy.”

If that occurs, the risk of long-term complications from the disease is also reduced.

The peak of developing Type 1 diabetes is between ages 10 and 14, but due to the novelty and potency of the five-drug cocktail the participants must be at least 18 years old. “So they can think about it and give consent,” Skyler said.

The study will begin with only six participants, of which some will get the drugs and some will get the placebos. After 90 days, an independent data safety committee will make sure no unusual side effects occurred before deciding whether to give the rest of the study the green light.

The drugs are not given all at once, but in precise sequences at particular times during one year.

The first drug in the protocol is given for two days. During this time, participants are kept in the hospital due to known possible side effects from other studies. These include fever, sweating and low blood pressure. They also will receive Benadryl and Tylenol, which can reduce those symptoms.

Other drugs can cause nausea. One drug can cause the spleen to rupture. Flu shots and other immunizations should be taken before the drug regime begins.

“And there always is a risk of serious infection whenever you are dealing with the immune system,” Skyler said, “but we are going to be watching these people very closely and really spending a lot of time to do everything necessary to protect the patient.”

The study is randomized. About 28 of the 42 participants will get the drugs, with the others receiving the placebos.

Skyler is hopeful the study can begin enrolling participants in the next three months. The patients receive the drugs or placebos for the first year, seeing the researchers about every two weeks. During the next year, they receive no drugs but are monitored for the long-term affects of the cocktail therapy.

Skyler said he knows it’s a big commitment for patients, whom he calls “research partners.” “But hey, they can say I’m not only doing it for myself — if it works I will benefit — but I am also doing it for the community at large to really see if this kind of strategy actually works the way the crazy guys at UM think it potentially will do.”