www.medscape.com

Cancer Drug Neratinib Halts Beta-Cell Death in Diabetic Mice

Marlene Busko

December 11, 2019

Neratinib, a small molecule approved by the US Food and Drug Administration (FDA) to treat breast cancer, inhibited a critical regulator of pancreatic beta-cell death in preclinical proof-of-concept experiments.

If the researchers can produce a more selective and better-tolerated molecule, then ultimately this could be trialed as the first in a new class of drugs to treat, or reverse, type 1 diabetes or treat later-stage type 2 diabetes.

Specifically, this early study, published in *Nature Communications,* found that neratinib inhibited mammalian sterile 20-like kinase 1 (MST1) in mouse models of type 1 and type 2 diabetes, and it also prevented apoptosis of insulin-producing beta cells in human pancreatic islets grown in diabetes-like conditions in the lab.

"Neratinib is a previously unrecognized inhibitor of MST1 and represents a potential beta-cell-protective drug with proof-of-concept in vitro in human islets and in vivo in rodent models of both type 1 and type 2 diabetes," Amin Ardestani, PhD, University of Bremen, Germany, and colleagues summarize in their article.

However, this particular agent has side effects that would not be considered acceptable in a chronic condition such as diabetes, for example severe diarrhea, so the team is now working to design a molecule that is more specific that they hope to trial in humans in the next couple of years.

A Fundamentally Different Approach to Preserve and Regenerate Beta Cells

Fellow supervising authors Kathrin Maedler, PhD, from Bremen University, along with Matthew Tremblay, PhD, and Weijun Shen, PhD, from Calibr, the drug development arm of Scripps Research, in La Jolla, California, and other scientists collaborated on the research that was funded by JDRF, a nonprofit organization dedicated to finding a cure for type 1 diabetes.

"Targeting beta cells with a small molecule provides a fundamentally different approach to preserve and regenerate endogenous beta cells," Shen told *Medscape Medical News,* adding that if this approach were to be successfully developed, this could ultimately "have a profound effect" on diabetes treatment, especially for type 1 diabetes.

Typically, when a person is diagnosed with type 1 diabetes, 10% to 20% of their pancreatic beta cells are still producing insulin, and the scientists hope that this research could help preserve this capacity.

"We are funded by JDRF and our primary goal is type 1 diabetes," Shen said, "because beta cell loss is early in the course of type 1 diabetes."

The same event occurs much later in type 2 diabetes (insulin resistance and then beta-cell loss), Shen said.

Accelerated Research Path, More Preclinical Work Needed

However, these are early days, Shen emphasized.

Although this research saved time by investigating a known molecule that was tolerated in phase 2 and 3 studies for cancer in humans, neratinib has side effects that would likely not be acceptable for a chronic condition like diabetes.

And it does not only inhibit MST1.

As the researchers observe, "the identification of neratinib as an MST1 inhibitor" which was not known before, "amounts to an accelerated path to a preclinical proof of concept," and what is needed next is a continued research program "aimed at retaining the drug-like properties of neratinib but improving upon its selectivity and safety."

The current article is based on work completed 3 years ago.

In the interim, the group has continued to try to design a better molecule and they plan to publish these new results soon.

If everything works out, they expect to test a better MST inhibitor in humans in about 2 years.

"Repurposing" Drugs: Why the Molecule Needs to Be Tweaked

The researchers had previously identified that MST1 is a critical regulator of beta-cell apoptosis. In the current study, after high-throughput screening of 641 drug-like kinase inhibitors, they identified that neratinib is a potent MST1 inhibitor.

"Repurposing of FDA-approved drugs has been a topic of great interest amidst the escalating costs of new drug development, particularly in the case of diseases with high unmet medical need," such as type 1 diabetes, the authors write in their article.

Neratinib was already known to inhibit epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2).

Based on those effects, as previously reported, neratinib (*Nerlynx*, Puma Technology) was approved by the FDA in July 2017 to treat breast cancer in women with HER2+ breast cancer who had already been treated with trastuzumab (*Herceptin*, Roche/Genentech).

But in February 2018, the European Medicines Agency rejected neratinib for this same use, citing its unfavorable risk/benefit profile; 40% of the patients had grade 3 diarrhea, according to data presented in 2015.

In the ongoing work to investigate neratinib as a potential treatment for diabetes, "we needed to make an MST1-selective compound," Shen noted. "The first thing we needed to do is to get rid of EGFR activity, which is causing the grade 3 diarrhea side effect."

The next move is to make the molecule more selective for MST2.

For a chronic life-long condition such as diabetes, patients will need a drug with a much more "pristine" tolerability and safety profile, Shen concluded.

Nat Commun. Published online November 1, 2019. Full text

For more diabetes and endocrinology news, follow us on Twitter and Facebook.

Send comments and news tips to news@medscape.net.

Cite this: Cancer Drug Neratinib Halts Beta-Cell Death in Diabetic Mice - *Medscape* - Dec 11, 2019.