Researchers use RNAi to silence genes that cause transthyretin amyloidosis

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(Medical Xpress)—An international team of researchers has discovered a way to silence the genes that cause transthyretin amyloidosis—a fatal genetic disease. In their paper published in the *New England Journal of Medicine*, the team describes how they developed a new treatment called ALN-TTR02 to prevent the creation in the body of a type of protein that causes problems in patient's nerves and heart.

Transthyretin amyloidosis is a condition where the liver produces more of the protein transthyretin than the body can use. This results in a buildup in nerves and the heart, leading to death after a few years. Currently, the only treatment is a liver transplant. In this new effort, the researchers used a new technique to stop the liver from producing the protein.

The new treatment involves using RNA interference (RNAi) to prevent the creation of the protein responsible for the deadly condition. RNA is, of course, the means by which protein creation is regulated in the body. Thus, RNAi is a process by which the normal course of protein creation is disrupted. In this case it was done by adding small amounts of molecules to existing RNA. In this new effort, the researchers infused RNA in patients with what are known as small interfering RNAs (siRNAs) that have been developed over many years. The molecules were delivered to the liver by hiding them in lipid capsules to prevent them from being destroyed by enzymes sent by the immune system.

The researchers tested the new therapy on 32 sick patients and 17

healthy volunteers. After waiting 7 days, all of those given the therapy were tested for transthyretin levels. Those with amyloidosis saw an average decline of the protein by 38 percent, while the control group experienced a whopping 78 percent drop. The results show that the siRNAs were able to silence the production of transthyretin by the liver.

Because the trials are still so new, it's not known if the lowered levels in the body will remain that way, and thus if the new therapy will prevent amyloidosis in patients with a genetic disposition. The team intends to find out of course by monitoring protein levels in all of the volunteers over time. They expect it will take at least 15 months to reach any definite conclusions.

More information: Safety and Efficacy of RNAi Therapy for Transthyretin Amyloidosis, *N Engl J Med* 2013; 369:819-829, August 29, 2013. DOI: 10.1056/NEJMoa1208760

ABSTRACT

BACKGROUND
Transthyretin amyloidosis is caused by the deposition of hepatocyte-derived transthyretin amyloid in peripheral nerves and the heart. A therapeutic approach mediated by RNA interference (RNAi) could reduce the production of transthyretin.

METHODS
We identified a potent antitransthyretin small interfering RNA, which was encapsulated in two distinct first- and second-generation formulations of lipid nanoparticles, generating ALN-TTR01 and ALN-TTR02, respectively. Each formulation was studied in a single-dose, placebo-controlled phase 1 trial to assess safety and effect on transthyretin levels. We first evaluated ALN-TTR01 (at doses of 0.01 to 1.0 mg per kilogram of body weight) in 32 patients with transthyretin

amyloidosis and then evaluated ALN-TTR02 (at doses of 0.01 to 0.5 mg per kilogram) in 17 healthy volunteers.

RESULTS
Rapid, dose-dependent, and durable lowering of transthyretin levels was observed in the two trials. At a dose of 1.0 mg per kilogram, ALN-TTR01 suppressed transthyretin, with a mean reduction at day 7 of 38%, as compared with placebo (P=0.01); levels of mutant and nonmutant forms of transthyretin were lowered to a similar extent. For ALN-TTR02, the mean reductions in transthyretin levels at doses of 0.15 to 0.3 mg per kilogram ranged from 82.3 to 86.8%, with reductions of 56.6 to 67.1% at 28 days (P