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TRIAL WATCH

Pioneering RNAi therapy shows antitumour activity in humans

Alnylam Pharmaceuticals and collaborators have published encouraging Phase I results of their novel first-in-class lipid nanoparticle (LNP)-formulated RNA interference (RNAi) therapeutic — ALN-VSP — in the treatment of advanced solid tumours with liver involvement (*Cancer Discov.* 28 Jan 2013; doi:10.1158/2159-8290.CD-12-0429). ALN-VSP was demonstrated to be safe and well tolerated, displaying antitumour activity, including complete regression of liver metastases in a patient with endometrial cancer.

Gene silencing by RNAi forms the basis for a potential new class of anticancer therapeutics that may offer several advantages over existing therapies. Anil Sood, University of Texas MD Anderson Cancer Center, explains: "There are many novel targets that are simply not druggable by existing approaches. In addition, specificity of RNAi would be greater than many current approaches and there is tremendous variability in current drugs with regard to bioavailability, and so on; with RNAi, that kind of variability could be reduced substantially."

However, several issues have hindered the clinical translation of this approach. "Arguably, the biggest challenge has been safe and effective delivery. Many of the delivery systems used have either been toxic or not particularly effective," says Sood. "Historically, there was a disconnect between what the materials scientists were doing and what the translation/clinical needs were, and some of the platforms were so complex that one could never make a practical drug with them. However, there are now several biocompatible platforms under investigation," he adds.

A promising approach involves packaging small interfering RNAs (siRNAs) into nanoparticle-based delivery systems, such as liposomes, dendrimers and polymeric nanoparticles. "One potential advantage, particularly relevant for the use of RNAi-based therapeutics for cancer, is that several siRNAs can be combined into a nanoparticle to simultaneously attack multiple targets without additive toxicities," says Mark Davis, California Institute of Technology. Alnylam's ALN-VSP is an example: it uses LNP technology comprising two siRNAs targeting two genes that are critical for the growth and development of cancer cells — vascular endothelial growth factor and kinesin spindle protein.

"The current trial is the first to show that two siRNAs can be safely delivered to cancer patients," notes Davis.

The ALN-VSP Phase I trial was a dose-escalation study involving 41 patients with advanced solid tumours and liver involvement who had failed to respond to or progress after standard treatment. The primary objective was to evaluate the safety, tolerability and pharmacokinetics of intravenously administered ALN-VSP given every 2 weeks. RNAi was demonstrated in liver biopsy samples taken from patients. The study showed that ALN-VSP was generally safe and well tolerated up to a dose of 1.0 mg per kg, with the most common adverse events being low-grade fatigue, nausea and fever.

A total of seven patients in whom disease had not progressed by CT scan after four cycles of therapy continued treatment on an extension study, in which they received bi-weekly treatments of ALN-VSP at the same dose level that they had been safely treated with in the initial study. Striking results were achieved in four patients; one patient with endometrial cancer achieved a complete response after 20 months of treatment at 0.7 mg per kg and remained in remission upon completion of 26 months of therapy; two patients with renal cell carcinoma treated at a dose of 1.0 mg per kg had stable disease at all sites for ~8–12 months; and one patient with a pancreatic neuroendocrine tumour treated at a dose of 1.0 mg per kg continued on the extension study for 18 months with stable disease.

These results demonstrate the therapeutic potential of systemically delivered siRNAs in human cancer, adding to the Phase I success previously reported with CALAA-01 (Calando Pharmaceuticals), a targeted cyclodextrin-based nanoparticle containing an siRNA that targets ribonucleoside-diphosphate reductase subunit M2, which was shown to localize to melanoma metastases following intravenous administration and specifically inhibit target expression by RNAi.

"These results are a very important step forward in realizing the true potential of RNAi therapy in the clinic. More such studies are needed and are underway," concludes Sood.

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