amphotericin lozenges for 6 weeks. Cotrimoxazole was given for 6 months and acyclovir if there was a cytomegalovirus recipient-donor mismatch. HLA mismatches varied from 1 to 11. Cytotoxicity tests between donor serum and recipient cells were negative in all cases. HLA mismatches varied from 1 to 11. Cytotoxicity tests between donor serum and recipient cells were negative in all cases.

In case 2, the biopsy was not typical of rejection. Two patients had episodes of impaired renal function. In case 2, the biopsy was not typical of rejection. Two patients had episodes of impaired renal function.

All 13 patients have sustained function in their allografts between 6 and 11 months after surgery, and 12 are receiving low-dose cyclosporin. One patient, case 8 (table), is taking a dose aimed to produce maintenance through concentrations 75–125 μg/mL. 500 mg methylprednisolone was given intravenously 30 min before the first dose of campath 1H to minimise reactions to cytokine release. Lymphocyte cytotoxicity tests between donor serum and recipient cells were negative in all cases. HLA mismatches varied from 1 to 5.

Strategies to establish tolerance will probably require the initial use of immunosuppressive agents, an induction treatment to prepare the immune system for active graft acceptance by almost, or the Latin equivalent prope, tolerance, and then very low-dose maintenance immunosuppression to guard against rejection.

How many lymphocyte depletion have helped engraftment in our patients? We speculate that the reduced number of cell numbers inhibited the opportunity for T cell to T cell interactions that are required for rejection. In the absence of initial aggression and inflammation, the healed graft may lose its capacity to immunise and may instead behave as a tolerogen.

We are currently studying the in-vitro reactivity of the repopulated lymphocytes in the renal recipients in an attempt to determine how tolerant these graft recipients have become after having received campath 1H. A randomised trial is planned to compare the protocol described in this report with conventional treatment.

Efficient and persistent gene transfer of AAV-CFTR in maxillary sinus

John A Wagner, Thomas Reynolds, Mary Lynn Moran, Richard B Moss, Jeffrey J Wine, Terence R Flotte, Phyllis Gardner

Cystic fibrosis is a common, lethal, genetic disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), and it is an attractive target for gene therapy. Adeno-associated virus (AAV) is a naturally replication-deficient single-stranded DNA parovirus. Preclinical studies showed that CFTR transcripts and protein can be detected up to 6 months after transduction with an AAV-CFTR vector, suggesting that AAV performs well as a gene transfer vehicle for CFTR. The maxillary sinuses are attractive for evaluating new treatments of cystic fibrosis because they have ion-transport systems and microbiology similar to those of the lower respiratory tract. Recurrence of maxillary sinusitis may prove to be a surrogate for infectious exacerbations characteristic of cystic fibrosis lung disease.

Ten patients who had undergone bilateral endoscopic antrostomies were treated with AAV-CFTR in a phase I, randomised, non-blinded, dose escalation protocol. Five patients received one dose of vector and five were treated with an initial low dose followed by a second, higher dose in the contralateral maxillary sinus. The figure reveals semiquantitative PCR of sinus biopsies from patients treated with 100 000 replication units of AAV-CFTR. At this dose, DNA transfer was observed at 0·1–1 vector copy per cell in biopsies done 14 days after treatment. Persistent DNA transfer was noted in patients 8 and 9, both of whom...
No evidence of vector transcripts was obtained by reverse transcriptase PCR after AAV-CFTR treatments, but a major difficulty with PCR in this setting is discrimination between vector DNA and vector RNA; no sequence present in the vector mRNA is not also present in vector DNA. An alternative measure of expression, transenepithelial potential differences, may be useful. The baseline potential difference is −45 (SD 15) mV, which depolarises upon addition of amiloride (by 57.5 [26.5] % in 72 previously untreated sinuses). There is no response to isoproterenol in previously untreated sinuses, as expected in cystic fibrosis. All six sinuses treated with 50 000 and 100 000 units of AAV-CFTR exhibited by day 14 hyperpolarisations in response to superfusion with isoproterenol, amiloride, and low-chloride-containing solutions, as would be expected if functional CFTR is being expressed. Similar results were observed at day 7 but isoproterenol-induced hyperpolarisations were absent by day 28.

Vector administration did not change the endoscopic appearance of the maxillary sinuses or the acute inflammation present in maxillary sinus biopsies at day 14. All patients had detectable levels of antibodies to AAV capsid, but no consistent change in antibodies was seen after treatment with AAV-CFTR. Eight serious adverse events were observed in four patients; there were six subacute pulmonary deteriorations requiring hospital admission and intravenous antibiotics (typical for cystic fibrosis patients), one patient required revision sinus surgery, and one had a recurrent episode of cholelithiasis requiring medical treatment. Adverse events did not seem to be related to AAV-CFTR.

This phase I study suggests that AAV-CFTR administration to the maxillary sinuses results in safe, successful, dose-dependent gene transfer to the maxillary sinus and alterations in sinus potential suggestive of a functional effect, with little or no host immune response. AAV vectors may prove useful for CFTR gene transfer and other in-vivo gene-transfer therapies.

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Department of Molecular Pharmacology, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94305-5332, USA; J A Wagner & Targeted Genetics Corp, Seattle, WA; Division of Clinical Pharmacology, Department of Medicine, Division of Otologyngology, Department of Surgery, and Division of Allergy-Pulumonary, Department of Pediatrics, Stanford University School of Medicine; Cystic Fibrosis Research Lab, Department of Psychology, Stanford University; and Departments of Pediatrics, Molecular Genetics, Microbiology, and the Gene Therapy Center, University of Florida, Gainesville


