OBJECTIVE: To determine the safety and pharmacokinetics of alpha-1 antitrypsin (AAT) in adults and children.

RESEARCH DESIGN AND METHODS: Short-term AAT treatment restores euglycemia in the non-obese mouse model of type 1 diabetes. A phase I multicenter study in 16 subjects with new-onset type 1 diabetes studied the safety and pharmacokinetics of Aralast NP (AAT). This open-label, dose-escalation study enrolled 8 adults aged 16 to 35 years and 8 children aged 8 to 15 years within 100 days of diagnosis, to receive 12 infusions of AAT: a low dose of 45 mg/kg weekly for 6 weeks, followed by a higher dose of 90 mg/kg for 6 weeks.

RESULTS: C-peptide secretion during a mixed meal, hemoglobin A1c (HbA1c), and insulin usage remained relatively stable during the treatment period. At 72 hours after infusion of 90 mg/kg, mean levels of AAT fell below 2.0 g/L for 7 of 15 subjects. To identify a plasma level of AAT likely to be therapeutic, pharmacodynamic ex vivo assays were performed on fresh whole blood from adult subjects. Polymerase chain reaction (PCR) analyses were performed on inhibitor of IKBKE, NOD1, TLR1, and TRAD gene expression, which are important for activation of nuclear factor-κB (NF-κB) and apoptosis pathways. AAT suppressed expression dose-dependently; 50% inhibition was achieved in the 2.5 to 5.0 mg/mL range.

CONCLUSIONS: AAT was well tolerated and safe in subjects with new-onset type 1 diabetes. Weekly doses of AAT greater than 90 mg/kg may be necessary for an optimal therapeutic effect.

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