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Alpha-1 antitrypsin treatment of new-onset type 1 diabetes: An open-label, phase I clinical trial (RETAIN) to assess safety and pharmacokinetics.

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Abstract

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.

KEYWORDS: C-peptide; autoimmune diseases; **diabetes** mellitus; **pharmacokinetics**; serine proteinase inhibitors; **type 1 diabetes**

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