SUSTAINED EXPRESSION WITH PARTIAL CORRECTION OF NEUTROPHIL DEFECTS 5 YEARS AFTER INTRAMUSCULAR rAAV1 GENE THERAPY FOR ALPHA-1 ANTITRYPSIN DEFICIENCY.

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Alpha-1 antitrypsin (AAT) deficiency is a common monogenic disorder resulting in emphysema, which is currently treated with weekly infusions of protein replacement. We previously reported achieving plasma wild-type (M) AAT concentrations at 2.5-3.8% of the therapeutic level at 1 year after intramuscular (IM) administration of 6×10^{12}vg/kg of a recombinant adeno-associated virus serotype 1 (rAAV1)-AAT vector in AAT-deficient patients, with an associated regulatory T cell (Treg) response to AAV1 capsid epitopes in the absence of any exogenous immune suppression. Here, we report sustained expression at greater than 2% of the therapeutic level for 5 years after one-time treatment with rAAV1-AAT in an AAT-deficient patient from that study, with partial correction of neutrophil defects previously reported in AAT-deficient patients. There was also evidence of an active Treg response (FoxP3+, Helios+) and an exhausted cytotoxic T cell response (PD-1+, LAG-3+) to AAV1 capsid. These findings suggest that muscle-based AAT gene replacement is toleragenic and that very stable levels of M AAT may exert beneficial effects at lower concentrations than previously anticipated.

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