

Patients suffering from emphysema associated with alpha-1 antitrypsin (AAT) deficiency can benefit from augmentation therapy. AAT is administered to the patient once a week via intravenous infusion by a healthcare professional. However, only 2 % of the AAT dose reaches the lungs following intravenous infusion. Inhalation of AAT might be a convenient and effective alternative to intravenous infusion. Yet, it has shown limited therapeutic efficacy in a recent clinical trial. Here, we assessed the impact of these routes of AAT administration on AAT pharmacokinetics, lung distribution and therapeutic efficacy in mice. PEGylation of the serpin was employed to improve its therapeutic value. Intravenous injection of AAT or its local administration to the lungs resulted in a similar exposure of AAT in the lung parenchyma with however an AAT dose delivered to the lungs 45 times lower than the injected dose. Conjugation of AAT to a 2-armed 40 kDa polyethylene glycol (PEG) chain prolonged its half-life in plasma and lungs by 1.6-times, decreased its penetration in the lung tissue by both routes of administration but did not markedly affect the lung exposure to AAT. The PEG moiety in PEG-AAT was cleared more slowly than the protein moiety and high PEG quantities remained in the lung tissue and alveolar macrophages several days after intratracheal instillation. Pulmonary administration and PEGylation both improved AAT efficacy to prevent lung injury and inflammation in a murine model of chronic obstructive pulmonary disease where lung inflammation was induced by delivering porcine pancreatic elastase and lipopolysaccharide locally to the airways. Anti-AAT and anti-PEG antibodies were generated by AAT and PEG-AAT administration, as expected for a foreign protein. However, anti-PEG antibodies did not significantly contribute to the overall anti-drug antibody titers against the conjugate. AAT and PEG-AAT showed good stability to jet nebulization. This study provides new insights into the impact of administration route and PEGylation on lung exposure, clearance, therapeutic efficacy, and safety of AAT. It highlights that inhalation of AAT might effectively replace its intravenous infusion in augmentation therapy.