MSC-AAT

MSC-AAT is a genetically modified mesenchymal stem cell (MSC) product engineered to constitutively overexpress and secrete alpha-1 antitrypsin (AAT), a serine protease inhibitor with potent anti-inflammatory and immunomodulatory properties[1]. By combining the paracrine immunomodulatory activity of MSCs with local delivery of AAT, MSC-AAT suppressed T-cell proliferation and polarized macrophages toward an anti-inflammatory M2 phenotype in preclinical studies[2]; AAT itself inhibits neutrophil elastase and proteinase-3[1] — more effectively than either unmodified MSCs or systemic AAT therapy alone.

The primary indication is steroid-refractory acute graft-versus-host disease (SR-aGvHD) in adult patients. In a Phase I/II clinical study, AAT protein improved clinical outcomes in 8 of 12 patients with SR-aGvHD, four of them complete responses[3]. In a preclinical haploidentical stem cell transplantation model, all untreated control animals had died by day 22, whereas more than 50% of animals treated with MSC-AAT survived long term with complete resolution of clinical signs[2]. MSC-AAT has received regulatory approval for Phase I/II clinical trials in Germany and is prepared for IND-enabling studies in the United States. In December 2024, the FDA approved RYONCIL (remestemcel-L-rknd) as the first MSC therapy for pediatric SR-aGvHD[4], validating the MSC modality in this indication and leaving adult SR-aGvHD as an unaddressed population.

In rheumatoid arthritis (RA), MSC-AAT targets the dysregulated synovial inflammation driving joint destruction. AAT inhibits the pro-inflammatory proteases and NF-κB signaling central to RA pathophysiology, and in preclinical collagen-induced arthritis models has demonstrated reductions in joint inflammation and cartilage erosion[5,6]. No MSC-AAT-specific data in RA are available to date.

Additional indications include type 1 diabetes (T1D), where AAT-overexpressing mesenchymal stromal cells reversed diabetes through regulatory T-cell crosstalk in preclinical models[7]; a Phase II randomized placebo-controlled trial of AAT protein did not meet its primary C-peptide endpoint overall, although HbA1c was significantly lower in a predefined adolescent subgroup[8].

In chronic obstructive pulmonary disease (COPD), only approximately 2–3% of intravenously administered AAT reaches the lung[9]. Systemically administered MSCs are, by contrast, largely retained in the pulmonary vasculature on first pass[10,11]. MSC-AAT is designed to turn that biodistribution — normally a limitation of intravenous MSC therapy — into an advantage, delivering sustained AAT expression directly within lung tissue.

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