European Respiratory Society
Annual Congress 2013

Abstract Number: 815

Publication Number: 226

Abstract Group: 3.2. Airway Cell Biology and Immunopathology

Keyword 1: Experimental approaches **Keyword 2:** Interstitial lung disease **Keyword 3:** Morphology

Title: Comparative effects of inhaled and intravenous mesenchymal stem cells in bleomycin-induced pulmonary fibrosis in rabbits

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Body: Purpose: To determine the survival rate of inhaled MSCs via different types of nebulizers, and their effect on bleomycin-induced pulmonary fibrosis Methods: We evaluated the survival rate of MSCs nebulized ex vivo via 3 types of nebulizers – ultrasound, jet and mesh nebulizers. Subsequently we used a nebulizer which showed the best result in cells viability. At the next stage 15 rabbits received instillation of bleomycin solution 2,5 mg/kg in the posterior lobe of the right lung through the ultrathin bronchoscope. The next day 5 rabbits were intravenously introduced 2 x10^6 MSCs, other 5 animals inhaled an equivalent respirable dose of MSCs, the rest ones were used as control. At 28 days we assessed the morphological changes and cytokine levels in bronchoalveolar lavage fluid (BALF). Results: The highest survival rate of MSCs was detected after using jet nebulizer (72%). Morphologic and ELISA data are presented in the table and figure.

Morphologic fibrosis score and BALF cytokines in study groups

	Healthy control	Bleomycin control	Bleo+MSCs iv	Bleo+ MSCs inh
Ashcroft fibrosis score (point)	0.24±0.11	4.15±1.8	2.34±1.6	2.11±1.3
TNF-α (pg/ml)	Not detected	122±65	95±77	101±36
TGF-β1 (pg/ml)	26±11	56±32	44±24	51±18

Conclusion: Inhalation of MSCs via jet nebulizer provides a significant antifibrotic effect in a bleomycin induced lung fibrosis similar with benefits of intravenous MSCs transplantation.