Official title: A Tolerance Clinical Study on Aerosol Inhalation of Mesenchymal Stem Cells Exosomes in Healthy Volunteers

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Study Protocol

A Tolerance Clinical Study On Aerosol Inhalation of Mesenchymal Stem Cells Exosomes In Healthy Volunteers (MEXVT)

Background

Exosomes are naturally occurring nanosized vesicles and comprised of natural lipid bilayers with an abundance of adhesive proteins that readily interact with cellular membranes. These vesicles contain cytokines growth factors, signaling lipids, mRNAs, and regulatory miRNAs. Exosomes are involved in cell-to-cell communication, cell signaling, and altering cell or tissue metabolism at short or long distances in the body, and influencing tissue responses to injury, infection, and disease.

Experimental studies have demonstrated that mesenchymal stem cells (MSCs) or their exosomes (MSCs-Exo) significantly reduced lung inflammation and pathological impairment resulting from different types of lung injury. Besides, macrophage phagocytosis, bacterial clearance, and prognosis were improved. MSCs-Exo likely has a similar therapeutic effect on inoculation pneumonia as MSCs themselves.

Previous studies have found that MSCs-Exo has no irritation to blood vessels, muscles, and no hemolysis and skin allergy were caused by MSCs-Exo. After intranasal administration of MSCs-Exo, no abnormality was found in the heart, liver, spleen, lung, and kidney of mice. These results indicated that MSCs-Exo has great safety.

At present, safety data of this product in clinical use have not been obtained. The clinical safety of MSCs has been supported by a large number of research data. Fever is the most common adverse reaction after MSCs treatment, with the highest incidence of 39% reportedly. Other symptoms such as fatigue could occur as well, which generally could remit spontaneously without treatment. No other adverse reactions related to mesenchymal stem cell therapy were reported.

MSCs-Exo has no immunogenicity due to the absence of MHC-I or MHC-II molecules on its surface. The volume of MSCs-Exo is much smaller than that of MSCs, which can avoid the obstruction and damage of capillaries. Therefore, it can be inferred that the symptoms like fever induced by MSCs-Exo will be significantly less than those of MSCs.

We designed this study to further evaluate the safety of MSCs-Exo in healthy volunteers. Cellular Biomedicine Group Ltd (Shanghai) provides the production and quality control of the research products. MSCs-Exo is secreted by mesenchymal stem cells. The MSCs used for the preparation of this product comes from the "healthy adult

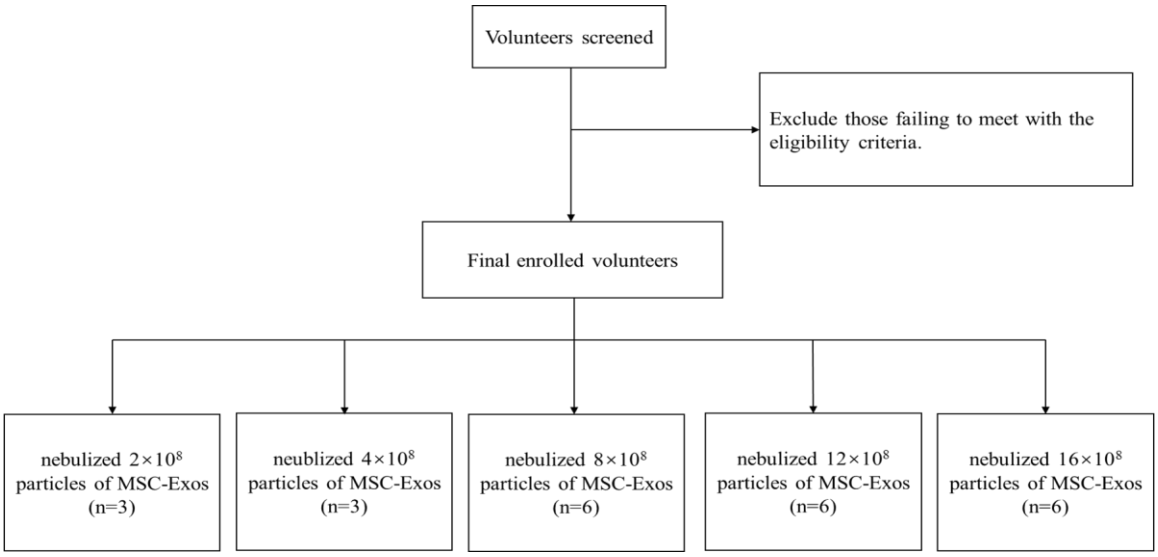
adipose stem cell bank" which meets the ethical requirements. According to the production standard of clinical research preparation, the exosomes secreted by stem cells were obtained by ultrahigh-speed centrifugation and filled aseptically. The stem cell bank has been certified by National Institutes for Food and Drug Control (NIFDC), and the "allogenic adipose mesenchymal stem cell injection" from the bank has been approved by the Center for Drug Evaluation (CDE) (No. CXSL1800109 and CXSL900075). During the whole clinical study process, we will strictly obey the relevant national regulations and ethical requirements.

Study purpose

Recruit healthy adults as participants. Every subject inhale different doses of the exosomes derived from allogenic adipose mesenchymal stem cells (MSCs-Exo), starting from the initial small dose. This clinical study will be performed to evaluate the safety and tolerance of aerosol inhalation of MSCs-Exo in healthy volunteers, and to provide the reference basis for formulating the clinical treatment dose range for the follow-up clinical research on the treatment of severe pulmonary diseases.

Study design

Study Type: Interventional
Primary Purpose:Treatment
Study Phase:Phase 1
Interventional Study Model: Parallel Assignment
Number of Arms: 5
Masking: None (Open Label)
Allocation: Non-Randomized
Enrollment: 24



Study Process

	Follow-up visit			
	V1	**V2**	**V3**	**V4**
	-7D-D0	**Day 1**	**Day 2**	**Day 7**
		Nebulation		**±1d**
Sign informed consent	X			
Basic information	X			
Medical history collection	X			
Physical examination	X			
Infectious disease detection	X			
Coagulation	X			
Blood pregnancy test	X			
eligibility criteria	X			
enrollment	X			
Skin-test of MSCs-Exo		X		
nebuliztion		X		
Vital signs	X	X	X	X
Blood routine	X			X
Urine routine	X			X
Blood biochemistry	X			X
Immunology	X			X
Electrocardiogram	X			X
AE/SAE		X	X	X
Summary				

Eligibility Criteria

Inclusion Criteria:

1) Healthy volunteers.
2) Age: 19-45, males and females.
3) The weight is within ± 10% of the standard weight [standard weight (kg) = 0.7 × (height cm-80)].
4) Examination indices of heart, liver, kidney and blood are all within the normal range.
5) According to Good Clinical Practice (GCP), volunteers who understand and voluntarily sign the consent form before this study.

Exclusion Criteria:

1) Women in pregnancy or lactation.
2) Primary diseases of important organs.

3) Mentally or physically disabled patients.
4) Suspected or definite history of alcohol and drug abuse.
5) According to the investigator's judgment, there is a low possibility of enrollment (such as frailty, etc.).
6) Volunteers who are allergic to the components of this medicine, or have a history of allergies to two or more drugs or food.
7) Volunteers who have diseases (such as insomnia) and are using other preventive and therapeutic drugs before this study.

Statistical Analysis

The statistical analysis will be completed by statisticians and the content includes:

1) Unless otherwise specified, all statistical tests are two-sided tests, and statistical significance is judged with the first type error of 0.05 (α value).

2) Describe quantitative data with number of cases, median, mean, standard deviation and range description.

3) Describe qualitative data with frequency, composition ratio or percentage.

4) Statistical description: including laboratory tests and etiological parameters.

5) Statistical test: firstly, parametric statistical method is considered. If the data distribution is different from the requirements of hypothesis test, nonparametric statistical method is used.