Research Square

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Safety and preliminary efficacy of multiple intravenous infusions of human umbilical cord-derived mesenchymal stromal cells in idiopathic pulmonary fibrosis: a phase I dose-escalation trial

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Research Article

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Abstract

Background

Idiopathic pulmonary fibrosis (IPF) is a progressive disease with limited therapeutic options. Mesenchymal stromal cells (MSCs) have shown promise in preclinical models of lung fibrosis.

Methods

We conducted an open-label, multicenter, dose-escalation phase I trial (NCT06230822) to assess the safety and preliminary efficacy of intravenous human umbilical cord-derived MSCs (UC-MSCs; VUM02) in patients with IPF. Nine patients were enrolled in three dose cohorts (0.5, 1.0, and 2.0 × 10^8 cells per infusion, three infusions every 3 days) following a “3 + 3” design.

Results

No dose-limiting toxicities occurred. Seventy-four adverse events were recorded, most grade 1–2; only 13 events in four patients were considered possibly or probably related to UC-MSCs. Six serious adverse events occurred in five patients, all deemed unrelated to the investigational product. In the high-dose cohort, forced vital capacity (FVC) showed a numerical increase of 57 mL (+ 2.36%) at week 24 compared with baseline. Carbon monoxide diffusion capacity (DLCO % predicted) increased by 7.39% in the low-dose cohort at week 24. Exploratory immunological and plasma proteomic analyses suggested immunomodulatory effects and identified ribosomal protein S23 (RPS23) as a candidate biomarker that consistently decreased after treatment.

Conclusions

Multiple intravenous infusions of UC-MSCs up to 2 × 10^8 cells were well tolerated in patients with IPF. Preliminary efficacy signals, particularly the numerical FVC improvement in the high-dose group, warrant further investigation in larger controlled trials. Trial registration: ClinicalTrials.gov NCT06230822.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a disease that mainly affects elderly individuals. As a progressive chronic disease among interstitial lung diseases, its origin remains unknown to date [1, 2]. The clinical manifestations are characterized by pulmonary parenchymal fibrosis, and the pathological features include the deposition of extracellular matrix and the appearance of fibroblast foci specifically [3]. The median survival period of patients with idiopathic pulmonary fibrosis is 3 to 5 years. Of course, individual differences make the survival period of patients extremely unstable [4, 5]. As the patient mainly presented with escalating breathing difficulties and continuously declining lung function [1], the clinical course of IPF is classified into three types based on the rate of decline in forced vital capacity (FVC): i, slow deterioration (FVC decreases by less than 10% within 6 months or the disease indicators remain unchanged for a certain number of months), ii, intermittent deterioration with exacerbations, and iii, rapid deterioration (FVC decreases by more than 10% within 6 months) [6, 7]. Currently, there are two drugs, pirfenidone and nintedanib, which are designed to slow down the progression of the disease and alleviate the decline in lung function, but they cannot reverse pulmonary fibrosis [8, 9]. Although nerandomilast has been approved for sale in both China and the United States, its efficacy still requires long-term research and verification. As an illness specific to the elderly, the public health burden of idiopathic pulmonary fibrosis will become increasingly heavy with the accelerating trend of population aging in China and around the world. Therefore, the development of more effective therapeutic drugs is a major responsibility and obligation for health organizations and the pharmaceutical industry in various countries.

Studies have shown that mesenchymal stromal cells (MSCs) have great potential in anti-inflammatory, anti-fibrotic and tissue regeneration [10, 11]. Reports including animal experiments and clinical studies indicate that MSCs could migrate to the lung injury site, reduce inflammatory response, repair damage, regulate the immune environment, and facilitate the recovery of pulmonary fibrosis by being injected into the body [12–14]. Among different sources of MSCs, human umbilical cord-derived MSCs (UC-MSCs) have been widely used in regenerative medicine due to their advantages such as easy collection, high ethical acceptability, wide availability, and low immunogenicity [15]. And as an inflammatory disease, the treatment of IPF with MSCs was considered a promising treatment method [12, 16–19].

In this phase I clinical trial, we enrolled 9 patients, exploring the safety and efficacy of UC-MSCs in the treatment of IPF through intravenous infusion method. At the same time, we aim to detect the differences in protein expression of patients under UC-MSCs treatment, to identify potential biomarkers that can be used as targets through blood proteomics analysis.

Materials and methods

Study design

This study is an open-label, multicenter, multiple-dose, dose-escalation clinical trial assessing safety, tolerability and preliminary efficacy (ClinicalTrials.gov identifier: NCT06230822).

Three to six patients were enrolled in each dose group, that is, following the "3 + 3" dose escalation principle, the dosages were increased from the low-dose group to the high-dose group in sequence. The sample size can be adjusted according to the actual situation of the trial. Each subject only receives one

corresponding dose. For the first subject, the sentinel method was adopted for enrollment. That is, the first subject would complete the observation period of the dose-limiting toxicity (DLT) evaluation (from the start of the first administration to 28 days after the last administration, the definition of DLT can be found in the Supplementary Materials). If no DLT occurred, the second subject could be enrolled and administered the drug. If three subjects did not experience DLT during the DLT evaluation period in a certain dose group, and the Safety Monitoring Committee (SMC) makes a decision to increase the dose based on the reviewed data, then the next dose group trial can be initiated. The treatment was administered once every three days for a total of three times. The specific doses and groups were shown in Fig. 1. The inclusion and exclusion criteria are listed in the Supplementary Materials.

Isolation, culture and preparation of UC-MSCs

UC-MSCs (VUM02 injection) were provided by Vcanbio Cell & Gene Engineering Ltd.(http://www.vcanbio.com/business-xbzl), Tianjin, China. It has a GMP facility that had been approved by the authorities. The UC-MSCs used in this trial came from umbilical cords of full-term delivery volunteers, who understood and signed the informed consent for scientific research. The umbilical cords were cut into 1–2 cm pieces and further shredded into tissue blocks of 1–2 mm^3. These tissue blocks were then cultured in Dulbecco's Modified Eagle Medium/F12 containing 10% fetal bovine serum (ART No. 04-001-1ACS, purchased from Biological Industries, CT, United States). The resulting tissue blocks were stored at 37°C in a 5% CO_2 humidified incubator. Once the cells began to migrate, the medium was renewed every 2 days to ensure continuous cell growth. When the cultures reached 80%-90% confluence, a passage culture was performed using 0.25% trypsin-ethylenediamine tetraacetic acid solution. Subsequently, stem cell characterization and functional analyses were performed to assess the phenotype and multidifferentiation potential of MSCs. The MSCs with good growth conditions were saved for later use. Generally, the 4th or 5th generation cells are used for the production of clinical cell products.

UC-MSCs used in this trial were a frozen preparation of 10ml per bag containing 5×10^7 cells, stored in liquid nitrogen. It was a colorless suspension after re-melting.

Clinical outcome

In this trial, the safety checks conducted on the patients included vital signs, physical examination, blood routine, urine routine, four items of blood transfusion, blood biochemistry, coagulation function, blood pregnancy, 12-lead electrocardiogram, myocardial enzyme spectrum, blood gas analysis, auto-immune disease antibodies, and lung tumor markers from the screening period to the follow-up period (24 weeks after the last medication). The efficacy indicators include pulmonary function (ventilation + diffusion), 6-minute walk test (6MWT), St. George's Respiratory Questionnaire (SGRQ), and chest HRCT score, etc., in 24 weeks, as well as lymphocyte subsets. The safety assessment includes the incidence and severity of adverse events (AEs) related to the cell therapy, as well as the maximum tolerated dose (MTD) for multiple administrations. Detailed examination of the index information and visit points can be found in the Supplementary Materials.

Plasma cytokine and proteomics analysis

Blood samples were collected at baseline and at weeks 1, 4 and 12 after UC-MSCs treatment. Plasma cytokine includes TNF-α、IFN-γ、TGF-β、IL-1、IL-2、IL-4、IL-5、IL-6 and CCL2 were detected by Luminex with Luminex 200. The blood samples required for proteomics analysis had an additional 24-week sampling point compared to cytokine analysis. The mass spectrometry analysis was performed using the UltiMate 3000 RSLCnano nanoliter liquid chromatography system (Thermo) in conjunction with the timsTOF Pro mass spectrometer (Bruker).

Statistical analysis

This study was a phase I dose exploration trial, following a "3 + 3" dose escalation principle. The main objective is to determine the MTD, and to observe the safety and initial effectiveness of the cell therapy. The descriptive data include efficacy indicators and immune indices were presented as mean ± SD. Statistical analyses were performed using SAS software, version 9.4 (Cary, NC, USA). The raw data of proteomics were analyzed using the library-free mode of the DIA-NN (DIA-NN 1.9.2) software. The figures were generated by GraphPad Prism 8 software (GraphPad Inc., La Jolla, CA, USA).

Results

Safety evaluation

Nine patients were enrolled in the study, the basic characteristics were shown in **Table 1**. No DLT occurred in any of the three dose groups during the trial period as determined by SMC. Therefore, a total of 9 patients were enrolled in this study, with 3 patients in each group. 74 AEs occurrences were recorded during the trial. They mainly included hypoproteinemia, infectious pneumonia, fever, diarrhea, oral mucositis, etc. Among them, 66.2% improved or were cured in a short period of time **(Table 2)**. AEs related to UC-MSCs were 4 cases with 13 occurrences, with an incidence rate of 44.44%. As a whole, 5 patients experienced serious AEs (SAEs) 6 times, and they all were determined to be unrelated to UC-MSCs **(Table 2)**. Overall, the safety of UC-MSCs infusion in each dose group was good.

Preliminary effectiveness analysis

We found that the FVC of patients decreased by only 7 ml (0.29%) compared to the baseline at week 12, while it increased by 57 ml (2.36%) at week 24 **(Fig.2A, Table S1)** in the high-dose groupthrough the analysis of clinical indicators, forced expiratory volume in 1 second (FEV_1) increased by 80 ml (3.94%)

at week 12 and by 53 ml (2.61%) at week 24 **(Fig.2B, Table S2)**compared to the baseline in the high-dose group at the same time. Of course, FEV_1/FVC (%) was higher at week 12 and week 24 **(Fig.2C, Table S3)**. Additionally, we found that 6MWDT and SGRQ score show a stable improvement trend in the high-dose group **(Fig.2D and E, Table S4 and S5)**. The lung function of patients in the low-dose group showed certain improvement based on the results of carbon monoxide diffusion capacity (DLCO) and alveolar ventilation (VA) **(Fig.S1A-C, Table S6 and S7)**. While the chest HRCT scores indicated that patients in the medium-dose group benefited more **(Fig.S1D, Table S8)**.

The result of lymphocyte subsets showed that the number of $CD3^+$ and $CD4^+$ cells decreased, while $CD8^+$ cells increased. Correspondingly, the ratio of $CD4^+$ to $CD8^+$ also decreased, especially in the high-dose group **(Fig.3A-D)**. IFN-γ was increased, and IL-4, TGF-β (TGF-β1 and TGF-β2) were decreased in the low-dose and high-dose groups according to the plasma cytokine detection **(Fig.3E and F)**. The results of other lymphocyte subsets and cytokines did not show a favorable improvement trend **(Fig.S2)**.

We conducted proteomic analysis on blood samples from 9 patients to screen for differential proteins. Results showed that RPS23 decreased at week 1, 4, 12 and 24 compared to W0 (baseline) **(Fig.4)**.

Discussion

This phase I trial is, to our knowledge, one of the first completed studies evaluating repeated intravenous administration of allogeneic UC-MSCs in patients with IPF. The primary objective was met: no dose-limiting toxicities were observed across the tested dose range up to 2×10^8 cells per infusion, and all SAEs were judged unrelated to the investigational product by the SMC. One additional subject died of pneumonia at month 12 after end of treatment, which assessed as unrelated to UC-MSCs by SMC. These findings align with the favorable safety profile reported for MSC therapy in other lung diseases and reinforce the low immunogenicity of UC-MSCs.

Although this study was not powered for efficacy, several observations merit discussion. In the high-dose cohort, mean FVC increased by 57 mL (+ 2.36%) at week 24 relative to baseline, contrasting with the expected annual decline of approximately 150–200 mL in untreated or antifibrotic-treated IPF patients [20, 21]. Similarly, DLCO % predicted in the low-dose group rose by a mean of 7.39% at week 24. It was significantly better than the existing drugs nintedanib and pirfenidone [22–24]. At the same time, the stable improvement trend of FEV_1, FEV_1/FVC, 6MWDT and SGRQ score in high-dose group and the HRCT score in low-dose group also verified the therapeutic effect of UC-MSCs. While these changes must be interpreted cautiously given the small sample size and open-label design, they represent encouraging signals that warrant confirmation in placebo-controlled studies.

According to previous studies, reducing the accumulation of $CD3^+$ T-cells was beneficial for alleviating pulmonary fibrosis [25]. Meanwhile, the ratio of $CD4^+/CD8^+$ in the bronchoalveolar lavage fluid of elderly patients was significantly increased compared with young normal volunteers [26]. Interestingly, exploratory immunological assessments revealed a decrease in $CD3^+$ and $CD4^+$ T-cell proportions and an increase in $CD8^+$ cells, particularly in the high-dose group, accompanied by a reduced $CD4^+/CD8^+$ ratio after UC-MSCs injection. These shifts were associated with increased plasma IFN-γand reduced IL-4, TGF-β1/TGF-β2 levels, consistent with a shift away from a profibrotic immune environment. For the relevant studies [27] indicated that the increase in the proportion of $CD8^+$ cells promotes the expression of IFN-γand inhibits IL-4, which could reduce the degree of pulmonary fibrosis, and the decrease of TGF-β was also [28–30]. Therefore, we believe that UC-MSCs could improve the immune environment by regulating the proportions of immune cells and immune factors, thereby alleviating pulmonary fibrosis and enhancing lung function. Compared with the clear trends of IFN-γ and TGF-β, the changing trends of other cytokines such as TNF-α and IL-1 did not clearly reflect the role of UC-MSCs in improving immune function, which may be related to the time limit of UC-MSCs acting on the lung organ. Animal experiments have shown that after intravenous infusion of MSCs, cell activity decreased from 27.0-33.5% immediately after the image to 2.0-5.4% on the 10th day [31]. This may be the main reason why the expression levels of some inflammatory factors returned to near baseline values at week 4 and week 12.

Over the past few years, some research has focused on identifying and applying biomarkers to accurately diagnose, predict prognosis, and treat IPF. Biomarkers offer the potential to improve diagnostic accuracy and identify IPF at an early stage [32]. Longitudinal plasma proteomics identified a sustained reduction in ribosomal protein S23 (RPS23) expression after UC-MSC administration (PXD072340) in this trial,. Recent preclinical evidence suggests that reduced RPS23 hydroxylation is linked to MSCs senescence [33]; the observed decrease may reflect enhanced endogenous MSC function or direct regulation by infused cells, though mechanistic studies are needed.

Compared with prior MSCs trials in IPF (predominantly bone marrow or placental sources, single infusion), our repeated-dosing regimen and use of UC-MSCs achieved comparable safety while showing numerical lung function stabilization or improvement not consistently reported elsewhere. These differences may relate to cell source, dosing schedule, infusion frequency, or patient baseline characteristics. We believe that the frequency of infusion was also quite important except the source of cells. Relevant research reports [34–36] showed that MSCs could stably exert their functions and achieve better therapeutic effects only when they were infused three or more times.

Limitations include the small sample size, absence of a placebo arm, and relatively short follow-up for a chronic progressive disease. Nevertheless, the safety profile and preliminary efficacy signals justify progression to a randomized phase II trial, which is currently in preparation.

Conclusion

Multiple intravenous infusions of allogeneic human UC-MSCs (up to 2×10^8 cells/dose × 3) were safe and well tolerated in patients with idiopathic pulmonary fibrosis. Exploratory analyses revealed encouraging numerical improvements in FVC and DLCO, together with immunomodulatory effects and a sustained decrease in plasma RPS23. These findings support further evaluation of UC-MSCs in larger, placebo-controlled studies to confirm safety and efficacy in IPF.

Abbreviations

IPF
Idiopathic pulmonary fibrosis
MSCs
Mesenchymal stromal cells
UC-MSCs
Umbilical cord-derived mesenchymal stromal cells
FVC
Forced vital capacity
DLCO
Carbon monoxide diffusion capacity
RPS23
Ribosomal protein S23
SMC
Safety Monitoring Committee
DLT
Dose-limiting toxicity
6MWT
6-minute walk test
SGRQ
St. George's Respiratory Questionnaire
AEs
Adverse events
SAEs
Serious adverse events
MTD
Maximum tolerated dose
FEV_1
forced expiratory volume in 1 second
VA
Alveolar ventilation

Declarations

Competing of interest

All authors declare that they have no known competing interests or personal relationships that could have appeared to influence the work reported in this paper. The authors declare that they have not use AI-generated work in this manuscript.

Ethics approval and consent to participate

The trial received ethical committee approval from institutions including a main center (the First Affiliated Hospital of Guangzhou Medical University) and three sub-centers (Peking University Third Hospital, West China Hospital of Sichuan University, and the First People's Hospital of Kashgar Prefecture). Among, the trial was approved by the Medical Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University on October 10, 2023. The approval number is EC-2023-073(YW)-03 and the trial name is “An open-label clinical study to explore the safety, tolerability and preliminary efficacy of VUM02 injection in the treatment of idiopathic pulmonary fibrosis (IPF)”. All the participates signed the informed consent form and then received the treatment.

Supplementary data

The relevant definitions, admission and exclusion criteria, as well as supplementary charts in the main text can be found in the Supplementary Materials.

Author Contribution

Jianyu Li drafted the initial version of the experimental scheme. Jianxing He, Qian Han, Yu Zhang and Shunjun Jiang were responsible for the review and revision of the experimental scheme, coordinate and manage the progress of the experiment and review of the overall quality of the manuscript. Qun Luo, Fengming Luo, Li Li, and Yongchang Sun peformed most of the experiments, collected relevant data, and revised the manuscript . Jiaxing Huang, Shu Xia,

and Bingpeng Guo participated in the implementation of the experiment and collected some of the data. Guangjie Luo created charts and wrote the initial manuscript. Li Wan and Tengyun Dong coordinated the communication and liaison among all relevant personnel.

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Vcanbio Cell & Gene Engineering Co. Ltd. was responsible for all the expenses as the sponsor of this clinical phase I trial.

Data Availability

The mass spectrometry proteomics data have been deposited to the ProteomeXchange Consortium via the iProX partner repository with the dataset identifier PXD072340

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Tables

Table 1 Characteristics of the Patients

Group	Subject number	sex	Age (years)	Height (cm)	Weight (kg)	Smoking history	Supplemental-oxygen therapy
Low-dose	1	male	69	160.0	63.6	Former smoker	Yes
	2	male	77	166.0	65.5	Former smoker	Yes
	3	male	69	168.9	81.2	Former smoker	Yes
Medium-dose	4	male	66	159.7	57.7	Former smoker	Yes
	5	male	66	154.7	52.5	Former smoker	Yes
	6	male	56	171.0	73.0	Former smoker	Yes
High-dose	7	male	58	172.2	75.2	Former smoker	Yes
	8	male	64	157.0	66.7	Former smoker	Yes
	9	male	55	170.0	64.0	Former smoker	Yes

Table 2 Statistical analysis of adverse events

	Low-dose (N=3)			Medium-dose (N=3)			High-dose (N=3)			Summation (N=9)		
Events	**frequency**	**case**	**occurrence rate (%)**	**frequency**	**case**	**occurrence rate (%)**	**frequency**	**case**	**occurrence rate (%)**	**frequency**	**case**	**occu rate (**
AEs	22	3	100.00	28	3	100.00	24	3	100.00	74	9	100.(
AEs related to MSC	0	0	0.00	4	2	66.67	9	2	66.67	13	4	44.4
SAEs	4	3	100.00	2	2	66.67	0	0	0.00	6	5	55.5
SAEs related to MSC	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
SAEs that led to or prolonged hospitalization	0	0	0.00	0	0	0.00	0	0	0.00	0	0	0.00
SAEs resulting in death	1	1	33.33	0	0	0.00	0	0	0.00	1	1	11.1

Figures

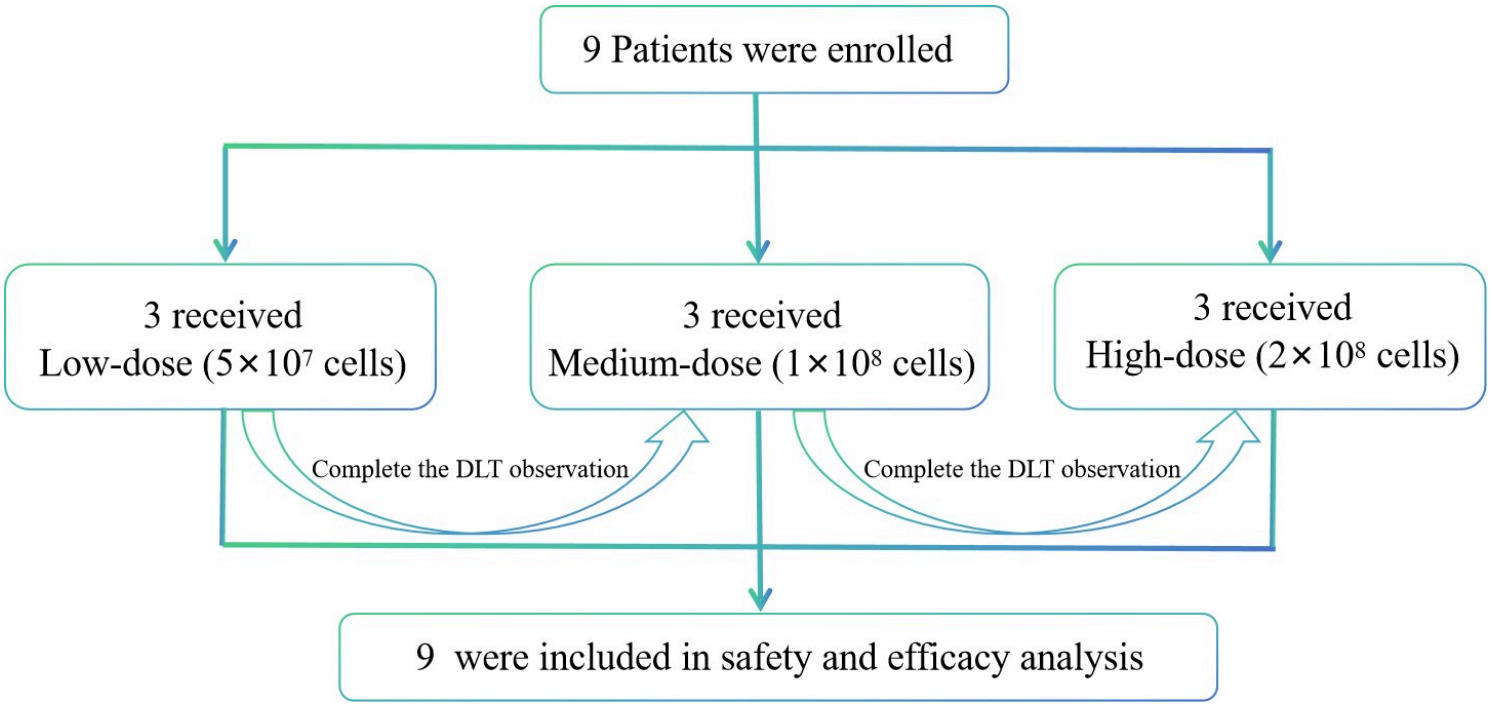

Figure 1

Flowchart of the study

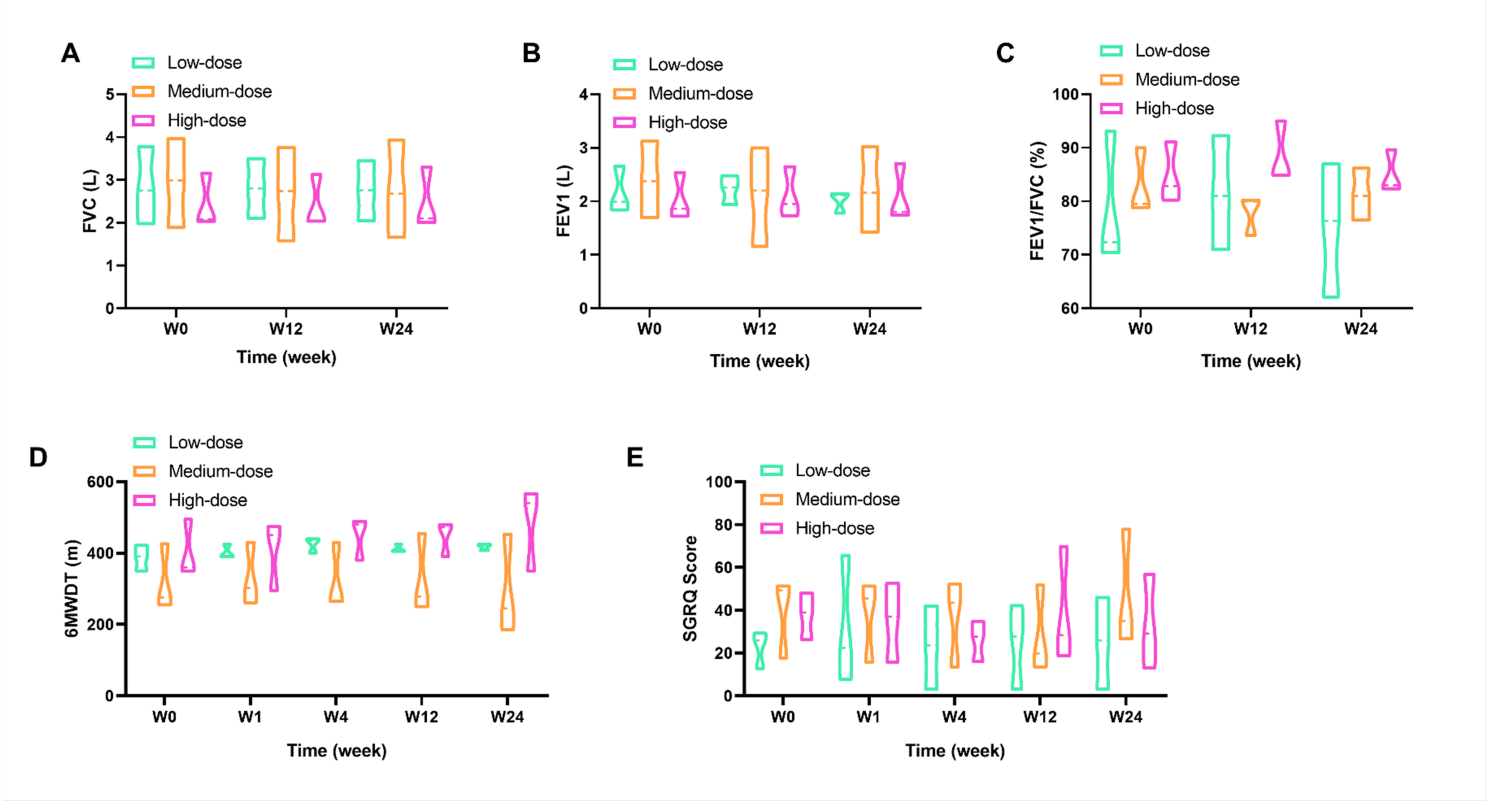

Figure 2

The value of several clinical outcome at different times with three dose groups

A-E, The value of FVC, FEV_1, FEV_1/FVC, 6MWDT and SGRQ score at W0, W12 and W24 with Low-dose, Medium-dose and High-dose groups. FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; 6MWDT: St. George's Respiratory Questionnaire. W0, W12 and W24 represent week 0 (baseline), week 12 and week 24 respectively.

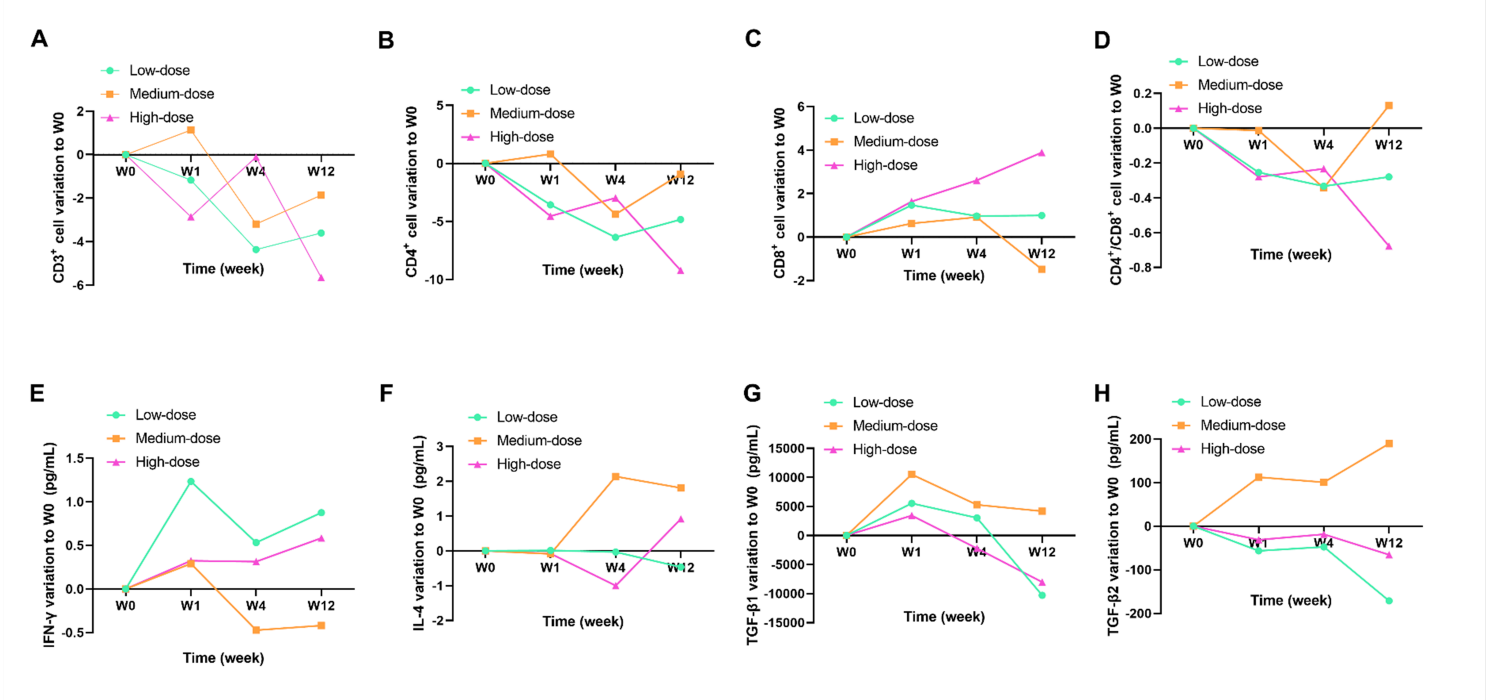

Figure 3

The expression of immune cell subpopulation and plasma cytokines at other times compared to W0

A-C, The percentage of $CD3^+$, $CD4^+$ and $CD8^+$ cell at week 1 , week 4 and week 12 compared to W0; D, The ratio of $CD4^+/CD8^+$ cell at week 1, week 4 and week 12 compared to W0; E-H, The expression of IFN-γ, IL-4, TGF-β1 and TGF-β2 at week 1 , week 4 and week 12 compared to W0. W0, W1, W4 and W12 represent week 0 (baseline), week 1, week 4 and week 12 respectively.

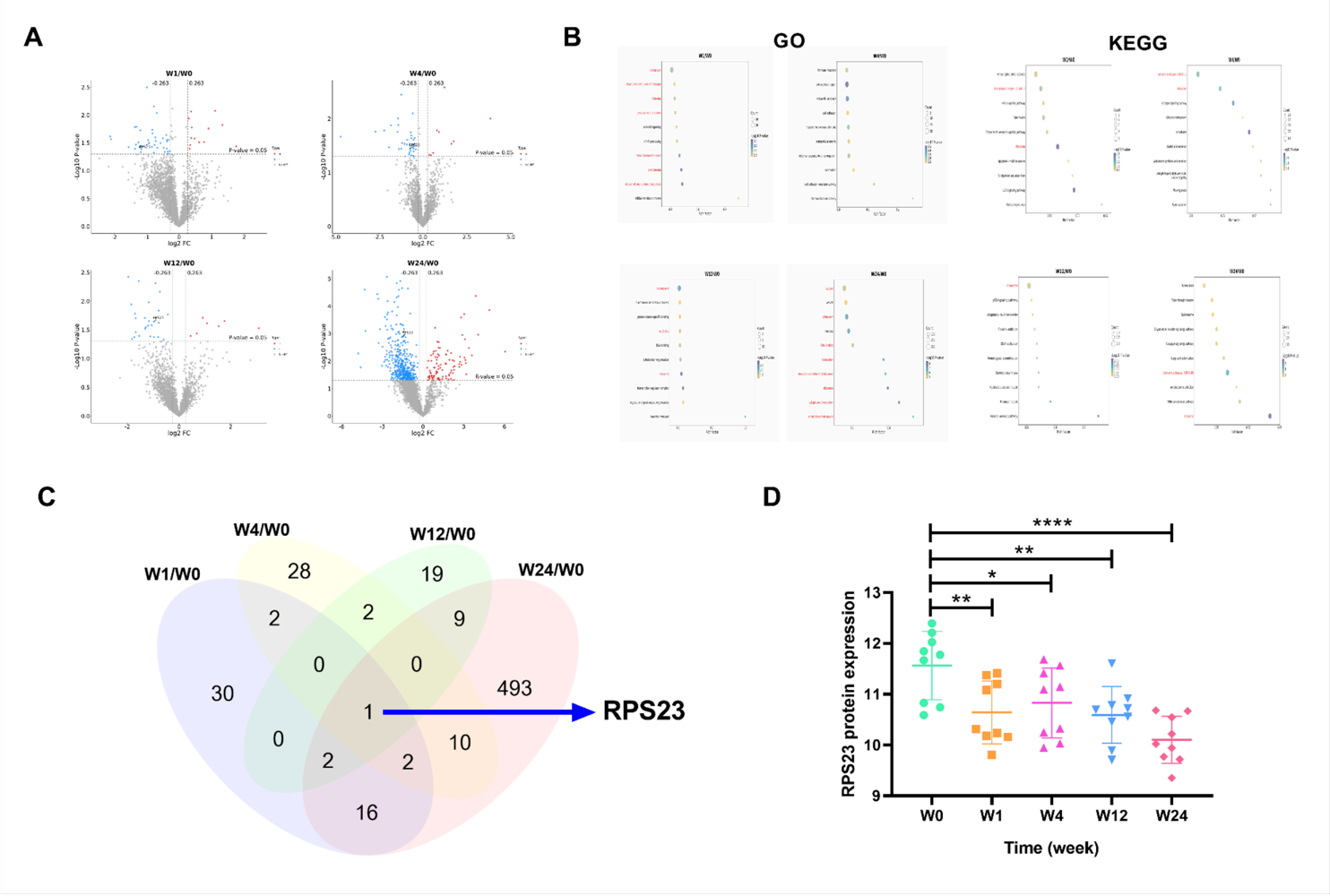

Figure 4

The result of proteomics analysis

A, The volcano plots of W1, W4, W12 and W24 compared to W0. B, The GO/KEEG enrichment analysis of W1, W4, W12 and W24 compared to W0 (the red path was where RPS23 located, PXD072340). C, The veen diagram of W1, W4, W12 and W24 compared to W0. D, The expression of RPS23 at W0, W1, W4, W12 and W24. W0, W1, W4, W12 and W24 represent week 0 (baseline), week 1, week 4, week 12 and week 24 respectively.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarytable.docx
- Supplementarymaterials.docx