Journal of Scientific Research & Reports
3(13): 1780-1792, 2014; Article no. JSRR.2014.13.006

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Intrapulmonary Administration of Autologous Bone Marrow Derived Mononuclear Cells in Congenital Heart Disease Complicated by Pulmonary Arterial Hypertension: A Case Report

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Authors' contributions

This work was carried out in collaboration between all authors. Author AL designed the study, performed the cell transplantation and evaluated the obtained results. Author IL performed clinical examination of the patient, managed a conservative therapy and performed the echocardiography examination. Author AL managed the literature searches and performed an analysis of the study. Author MR performed lung scan and interpreted the results. Author AE organized the project, implanted the cells and evaluated the clinical results. Author EJ managed thepreparation of the bone marrow derived mononuclear cells. All authors read and approved the final manuscript.

Case Study

Received 13th March 2014
Accepted 15th May 2014
Published 27th May 2014

ABSTRACT

Pulmonary arterial hypertension (PAH) is a devastating, progressive disease with increasingly debilitating symptoms that leads to right heart failure and ultimately death if untreated.

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We suggest that intrapulmonary delivery of autologous bone marrow derived mononuclear cells (BMMC-s) could be beneficial for patients with severe PAH.
We report on a patient with congenital heart disease (CHD) complicated with severe PAH, who received intrapulmonary autologous BMMC transplantation. For the examination of the results we used scintigraphy during the periods of 6, 14 and 27 months after cell transplantation and documented clinical and radiographical alleviation of PAH sypmtoms.
The obtained results suggest that intrapulmonary BMMC transplantation could serve as a new therapeutic option or supplemental therapy for deteriorating PAH, particularly in cases, when conventional therapeutic strategies have failed to provide the control of the disease.

Keywords: Pulmonary arterial hypertension; stem cells; intrapulmonary administration; children.

1. INTRODUCTION

PAH is characterized by increased pulmonary vascular resistance resulting in extensive structural heart changes, limiting exercising capacity of patients and, eventually, leading to right heart failure and death [1-2].

Currently, in accordance with the Pulmonary Hypertension clinical classification system (Dana Point 2008) by the World Health Organisation, pulmonary hypertension (PH) is divided into five groups based on aetiology, where PAH represents Group 1. Within the PAH group, there are five subgroups, based on aetiology: Idiopatic PAH (IPAH), heritable PAH (HPAH), drug and toxin induced PAH, persistent pulmonary hypertension of the newborn (PPHN) and, finally, PAH associated with different conditions and diseases like connective tissue diseases, portal hypertension, HIV, chronic haemolytic anaemia, etc. Group 2 includes PH due to left heart diseases; Group 3 includes PH due to lung diseases and/or hypoxemia; Group 4 includes chronic thromboembolic pulmonary hypertension (CTEPH); Group 5 includes PH with unclear multifactorial mechanisms.

A significant proportion of patients with congenital heart disease (CHD), in particular those with systemic-to-pulmonary shunts, would usually develop the most advanced form of PAH if left untreated. In these cases, PAH is characterized by obstruction of small pulmonary arteries that leads to progressive increase in vascular resistance. As a result, right ventricular afterload increases,that results in right ventricular failure. It is suggested by some authors that proliferation in the intima and media of arteries is the key element in developing of PAH. Such factors as vascular remodeling, vasoconstriction and thrombosis are supposed to increase pulmonary vascular resistance in PAH [3].

Based on the data obtained from experimental and clinical studies, we hypothesize, that intrapulmonary implantation of BMMC-s increase the vascular bed in the pulmonary circulation leading to alleviation of PAH. Locally implanted mononuclear cells may trigger the neovascularization process in the lung, potentially leading to a decrease of the mean pulmonary artery pressure.

This article highlights a clinical case of PAH in a patient with CHD. The case represents deteriorating PAH, despite the use of available conventional treatment strategies. Justification for the use of intrapulmonary BMMC implantation was systematically discussed

and planned by a team of cardiac surgeons and cardiologists. The Ethics Commission had granted permission to perform the procedures described in this article. A written informed consent from patient's legitimate representatives was obtained.

2. CASE PRESENTATION

A boy was admitted to the Riga Children University Hospital (Latvia) for examination and treatment at the age of 9.

Diagnosis: Ventricular septal defect (VSD). Cardiopulmonary insufficiency (NYHA IV). Pulmonary hypertension. Chromosome 21 trisomy. Chronic uncompensated hypoxemia.

The medical history revealed repeated episodes of dizziness, even at minimal exercise, fatigue, malaise, severe dyspnea. Acrocyanosis, watch-glass nails. During the last year, voice hoarseness had appeared,suggesting compression of the left laryngeal nerve by the dilated pumonary artery.

It was also known that the diagnosis of VSD complicated by PAH was established in the patient at the age of 4. From that time, the patient received symptomatic treatment with sildenafil, accupro, aspirin, propanolol. No surgical procedures were performed as the patient's parents refused. During the following 5 years, the patient's relatives never approached a doctor for help and had previously refused hospitalization. During the last two years, the care was provided by an orphanage, as the child's parents had been deprived of the rights of the child.

Clinical examination: Auscultation of the heart revealed rhythmic heart sounds and systolic murmurs, characteristic for the shunt due to the VSD, complicated by tricuspid insufficiency. Despite the expressed dyspnea, auscultation of the lungs revealed normal sounds, though slightly diminshed. The liver was palpable 3 cm below the costal margin in the midclavicular line, increased tendereness.

Laboratory examination (complete blood count): Leucocytes 3,3 th/cmm, Erythrocytes 5,34 mln/cmm, Hemoglobin 141 – 15,7 g/dL; Hematocrit 42 – 49%; Platelets 268 th/cmm. Oxygen saturation 88%.

Electrocardiography: Strongly expressed dextrogram (+180º), right ventricular hypertrophy and right axis deviation by 85%. PR 0,14 sec.; QRS 0,11 sec.; QT 0,36 sec.

Chest radiography revealed symetric aeration, enhanced pulmonary structures paracardially with poor presentation in the peripheral parts of the lungs and increased right side of the heart with accentuated conus pulmonalis. Cardiothoracic index 0,6 (See Fig. 1).

Transthoracic doppler echocardiography revealed ventriculoarterial concordance, normal drainage of the pulmonary veins. A diameter of the ventricular septal defect was 22 mm, featuring a shunt during systole from the left side to the right of the heart, followed by opposite direction of the blood flow during diastole. Measurements revealed hypertrophy of the right ventricle, moderate pulmonary valve regurgitation and severe tricuspid valve regurgitation with calculated pressure in the right ventricle 90 mmHg. Left ventricle dimension in diastole was 37 mm, FS 44%, EF 77% . Intact aortic and mitral valves. Normal left sided aortic arch. No ductus arterious patency.

During cardiac catheterisation, blood oxygen saturations were taken from the SVC and IVC through to pulmonary artery. Step-ups in oxygen saturations of more than 10 % from one chamber/vessel to the next were registred and itindicated to the presence and position of an intracardiac shunt.

Right ventricle 87/21 mm/Hg (with the mean of 46 mm/Hg), oxygenation 68%; pulmonary artery 89/42 mm/Hg, (mean 62), oxygenation 68%; right atrium 16/12 mm/Hg (mean 14), oxygenation 40%; left ventricle 82/13 mm/Hg, oxygenation 90%.

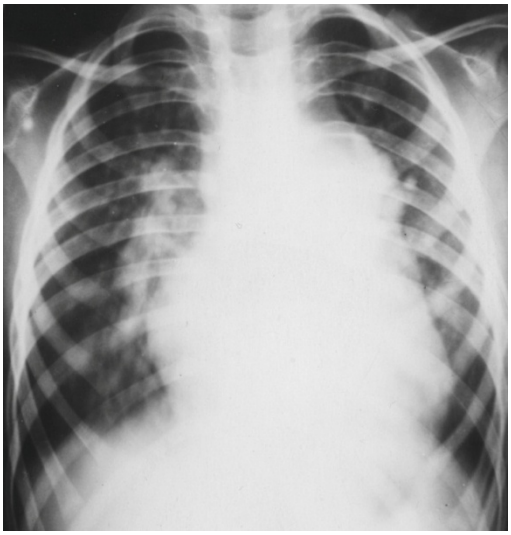

Fig. 1. Plain chest radiography (AP projection) upon admission to the hospital

Pulmonary angiography revealed distinct features of pulmonary hypertension, decreased vascularization in the peripheral parts of the lungs in particular (See Fig. 2).

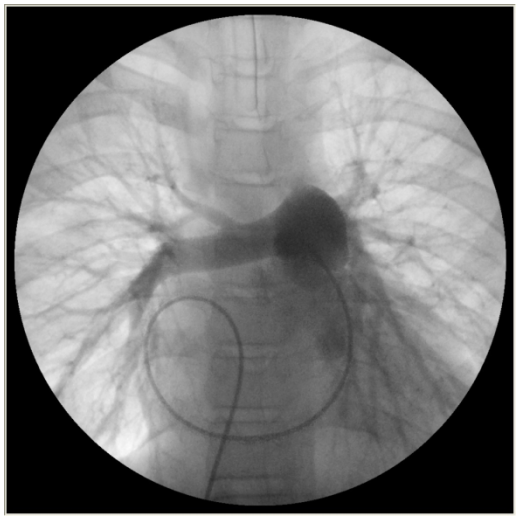

Fig. 2. Pulmonary angiography image obtained after intravenous administration of contrast material

Based on the data obtained from cardiac catheterization, ratio between pulmonary vascular resistance (PVR, a measure of the pulmonary blood vessel resistance to blood flow) and systemic vascular resistance (SVR, a measure of peripheral blood vessel resistance to blood flow and the arterioles) was 2:1. A normal PVR is approximately one sixth of the normal SVR.

Lung perfusion scintigraphy (LPS) helped to evaluate the distribution of pulmonary arterial blood flow. For the LPS we used IV injection of radiopharmaceutical Tc-99m-MAA (macro-aggregated albumin) in a dose of 55MBq with Siemens - ECAM SPECT camera. We used a SPECT protocol to obtain a 3-dimensional evaluation of the perfusion.

2.1 Lung Scans Using a SPECT Technique

The examination results revealed perfusion defects in the upper dorsal and lateral segments of the right lung. Slightly lower perfusion was detected also in the upper segments of the left lung (See Fig. 3). The second study performed 6 months after the mononuclear cell implantation procedure (See Fig. 4) demonstrated remarkable improvement of perfusion in the upper segments of the right lung, as well as a small positive dynamics in the lateral segments of the right lung. Further investigations carried out 14 and 27 months after the mononuclear cell transplantation (See Figs. 5 and 6), demonstrated the trend of improving perfusion of the right lung in particular. None of the performed consecutive studies revealed considerable changes in perfusion of the left lung after the BMMC implantation.

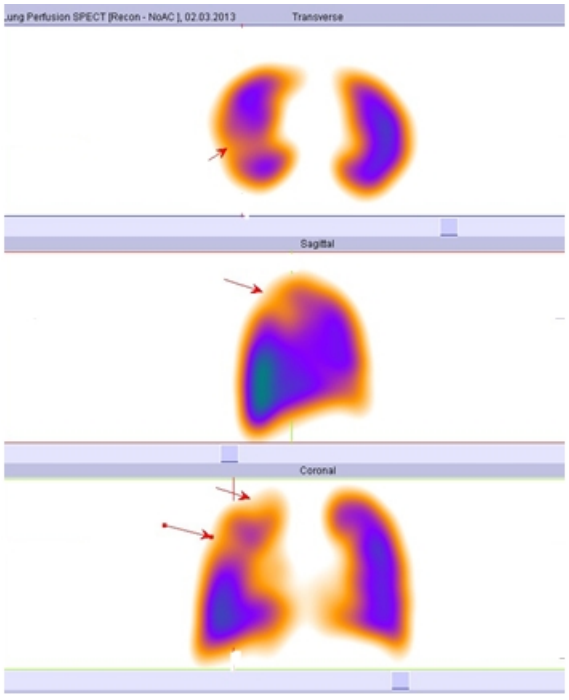

Fig. 3. Lung perfusion before the BMMC transplantation. Arrows (in red) indicate the areas with decreased lung perfusion

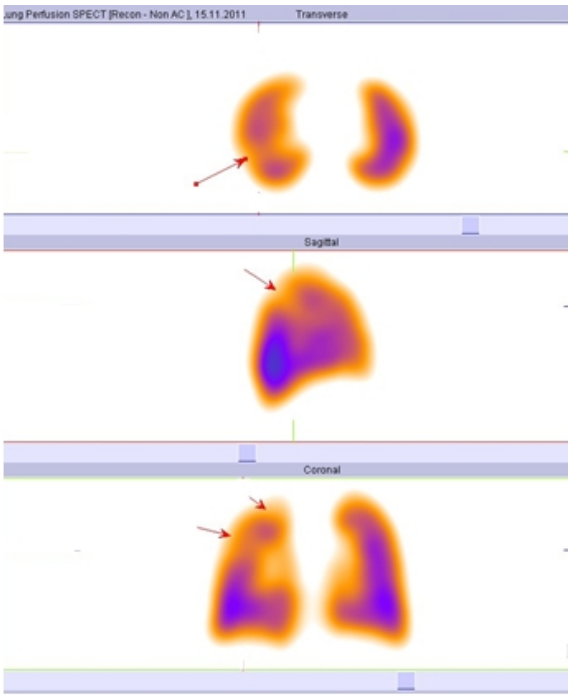

Fig. 4. Lung perfusion 6 months after the BMMC transplantation. Arrows (in red) indicate the areas with decreased lung perfusion

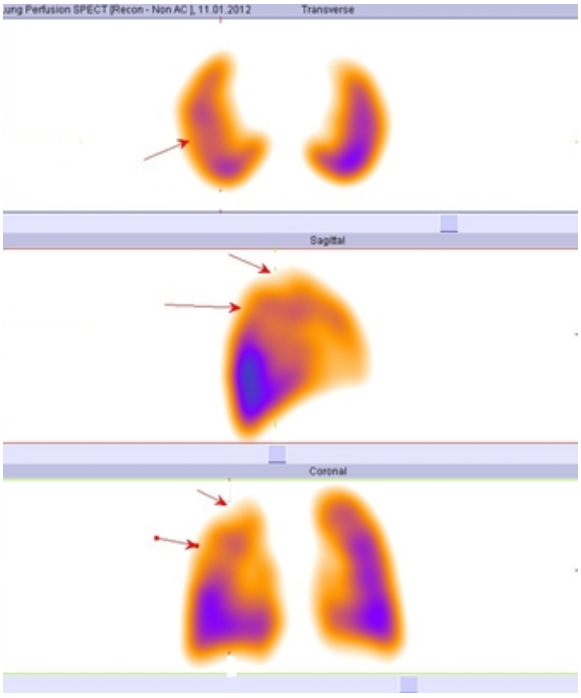

Fig. 5. Lung perfusion 14 months after the BMMC transplantation. Arrows (in red) indicate the areas with decreased lung perfusion

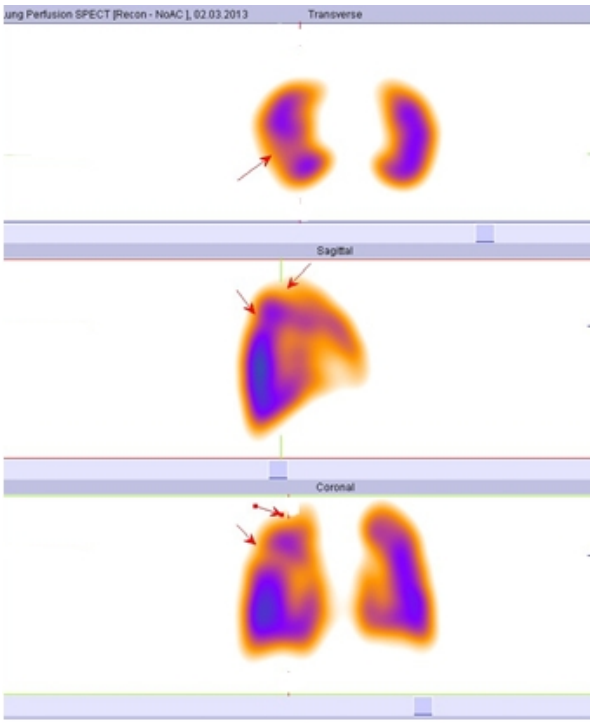

Fig. 6. Lung perfusion 27 months after the BMMC transplantation. Arrows (in red) indicate the areas with decreased lung perfusion

2.2 Preparation of BMMC-s for Transplantation

We aspirated 30 milliliters of bone marrow from the iliac crest to isolate around 100 million bone marrow cells. We took samples for flow cytometry from 15 ml of mononuclear cell fraction and prepared for transplantation. Then we carried out preparation of the isolated cells by using Stem-kitTM reagents (Cat. Nr. IM3630; Beckman Coulter) that contained CD34-PE, CD45-FITCm isotype control, 7AAD (viability dye) and Stem-Count Fluorospheres, followed by FACS analysis on FC-500 (Beckman Coulter), using CXP analysis software. Each measurement contained at least 50 000 events. Maximum number of events was 100 000. The obtained numbers of cells/μL were calculated for the total number of all mononuclear cells within the transplantation material.

2.3 BMMC Transplantation

We used two approaches for delivery of BMMC-s into the lungs (See Fig. 7).

Intravasal injection of the BMMC-swas performed by catheterization of both pulmonary arteries via superior vena cava (dots 1 and 4, Fig. 7). For delivery of the cells right into the tissues of the upper and lower lobe (dots 2 and 3, Fig. 7) of the right lung, we used a standard transcutaneous, transthoracal injection technique, followed by punction (0.95 mm × 220 mm OptiMed CHIBA needle) of the lung parenchyma and injection of 1 ml of the mononuclear cell suspension, performed under chest radiological control. A minsicule (1 cm thick) pneumothorax resolved within 24 hours after the procedure.

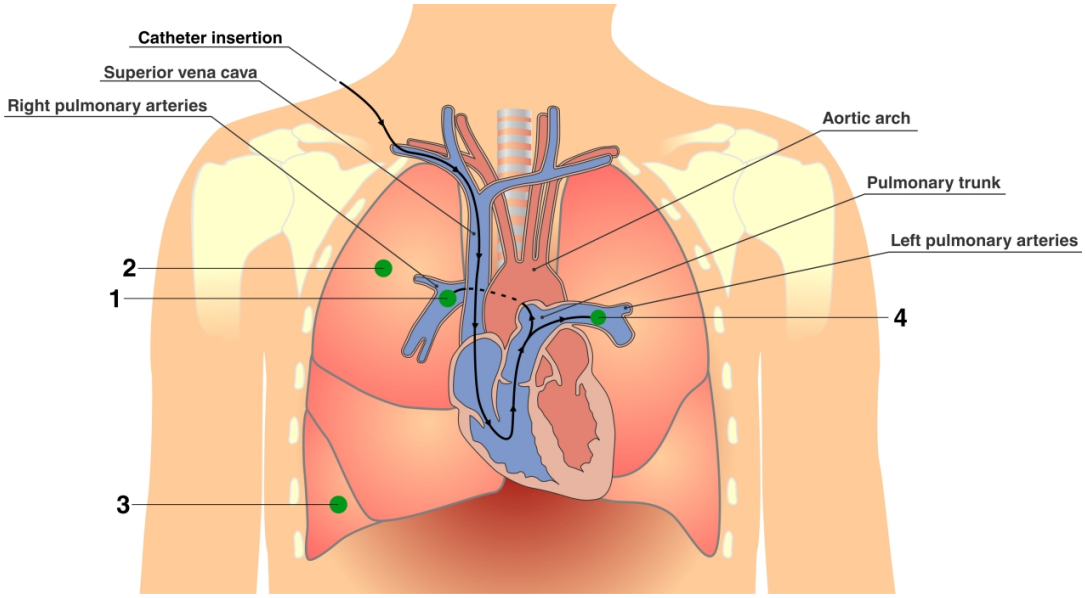

Fig. 7. Intrapulmonary transplantation of BMMC-s. Dots (1-4): sites for injection

Echocardiography 27 months after the BMMC transplantation revealed no relevant changes in anatomical findings as compared with the intial status. Left ventricle dimension in diastole was 40 mm, FS 33%, EF 62%. Calculated pressure in the right ventricle was 85 mmHg.

Clinical and laboratory examination 27 months after the BMMC transplantation also did not reveal crucial changes. A general condition of the patient was compensated, oxygen saturation 89%.

3. DISCUSSION

Prior to the cell transplantation,our patient received symptomatic treatment with medicines approved for the use in PAH, such as sildenafil, accupro, aspirin, propanolol. Unfortunately, the lung transplantation is not available for children in Latvia. Therefore, the BMMC transplantation was being applied as the last resort after other available treatment options had failed, serving as a bridge to the potential lung transplantation in the future.

The data obtained from the lung perfusion studies suggest that a combined intrapulmonary delivery (both directly into the lung tissues and pulmonary arteries) of BMMC-s caused detectable changes in perfusion of the (right) lung, compared with insignificant improvements of the (left) lung perfusion followed by intravasal injection of BMMC-s alone.

Based on our findings, we believe that BMMC transplantation has helped to prevent deterioration of clinical symptoms during the last 2 years and led to a stabilisation of progressive PAH in our patient.

It is still not clear what stem cells have to do with pulmonary hypertension, but it is an area of great interest and much ongoing research. There are numerous publications showing

remarkable benefits for using various kinds of stem or progenitor cells in experimental models of PAH. However, as regards the humans, there is quite limited clinical experience with progenitor cell therapy in patients with PAH, as there have been performed very few definitive and rigorously designed trials so far. Thus, it would be fare to say that the potential benefits and risks of progenitor cell therapy for PAH are largely unknown. Therefore, this type of therapy has been widely recognized only in the context of a research study that would help to provide answers for further study. Prior to the stem cell treatment,it is necessary to assess possible advantages of available conventional treatments by evaluating expected benefits and risks, as well as possible ethical problems.

Although important advances in symptomatic treatments have occurred, many lung diseases including emphysema, pulmonary fibrosis, cystic fibrosis, and others have no cure [1].

A conventional therapy of PAH consists of non-specific drugs, including oral anticoagulation and diuretics, as well as PAH specific therapy, including prostanoids (epoprostenol, trepoprostenil, iloprost), endothelin receptor antagonists (bosentan, ambrisentan) and phosphodiesterase type 5 inhibitors (sildenafil, tadalafil) [2].

One of the most commonly used non-medical treatment strategies is atrioseptostomy that is applied to create artificial communication to decrease the right heart volume. The surgical creation of a right-left shunt decreases right auricular pressure and increases systemic blood flow, followed by reduction in right ventricular wall tension. However, atrioseptostomy has never been studied in controlled clinical trials and its role on long term survival has not been established. Based on the data published by several researchers, it can be concluded that immediate mortality is high, reaching 14% during the first week, in the case of severe desaturation and right heart failure in particular [4-6].

Lung transplantation still remains the treatment of choice for severe PAH patients, in the case when conservative treatment does not provide sufficient results [7]. Unfortunately, this type of surgery can be offered just to a small proportion of patients with PAH and its long term benefits remain unsatisfactory. It is partly due to complications by acute and chronic rejection that requires lifelong immunosuppression with approximately 50% survival at 5 years and the donor graft induced antigenicity and extremely common infections, owing to the immunological and anatomical features of the lungs [8-9]. Besides, there is a critical shortage of donor lungs. All the above mentioned arguments suggest that new approaches for lung diseases, including PAH, are highly needed.

At the same time, significant results in this area can be mentioned with regards to animals.There have been convincing results obtained from experimental studies with regeneration of damaged pulmonary vasculature with exogenously administered stem cells in dogs [9]. According to the researchers, neovascularization in the lung could increase the volume of the vascular bed in the pulmonary circulation and thus reduce the development of PH. It allows presuming that endothelial-like progenitor cells (EPCs) might be a potential cell source for neovascularization. The obtained results suggest that EPC transplantation into the lung is effective at preventing the progression of dehydromonocrotaline-induced PH in dogs, posing a new therapeutic option for PH. Similar results have been obtained from studies with rats. Using a similar model of PAH (monocrotaline-induced), authors achieved restoration of the microvasculature structures and function of the artificially damaged lungs. Authors conclude that the regeneration of lung vascular endothelium by injecting progenitor cells may represent a novel treatment paradigm for patients with PAH [10]. Similar conclusions have been made based on results obtained from many other studies [11-14].

The latest data shows that paracrine effects and secretion of growth factors are mainly responsible for stimulation of native angiogenesis, not just the EPCs as it was suggested by earlier studies. Whatever mechanism is behind these alterations, both anatomic and physiologic improvement in pulmonary hypertension has been clearly documented in animal models. It has been established that autologous implantation of bone marrow derived progenitor or stem cells leads to structural repair and regeneration of the lung.

Currently there have been performed very few studies on effects of autologous stem cell administration to PH in humans [15]. However, preliminary clinical trials using EPC-based therapies in patients with pulmonary hypertension show benefit of this approach, thus revealing EPCs as potential therapeutic targets [16-18]. There is also available information on two ongoing trials of cell therapy in PAH patients, which are being conducted in China and Canada. The results of these trials will be available in the forth-coming years.

Therefore, many questions still have to be answered. For instance, the question about the best way for administration of the stem cells in patients with PH still remains controversial. It is not yet established whether these cells can engraft and acquire phenotype of structural lung cells following either systematic or intratracheal or local injection. It is also not clear, which is the best cell source (bone marrow versus peripheral blood) and the best cell type (endothelial or haematopoietic progenitor cells or mesenchymal stem cells (MSC) to be used. It is still not established whether cell therapy is effective in idiopathic PAH alone or in associated PH as well, and which is the best disease stage for cell therapy to be applied.

Data from experimental studies suggest that bone marrow cell transplantation reduces the development of PH by increasing vascular beds in pulmonary circulation [17-18]. Although, the underlying mechanism is not yet determined and several factors are expected to contribute, namely, cellular differentiation, transdifferentiation, paracrine and cell-cell effects [19]. These results led to human studies of pro-angiogenic cell transplantation that demonstrate significant clinical improvement in patients with PAH [17-18]. Cell therapies using various stem cells have been extensively evaluated. Available research data indicate to possible reparative roles of exogenously administered stem cells through paracrine and immunomodulatory effects and encourage further exploration of MSCs and EPCs in clinical studies of PH [1,20,21].

Despite sufficient evidence supporting the endobronchial [22] and intravenous [23-24], administration routes we suppose they are not optimal. As recognized by the researchers, an assumption that endobroncial infusion of stem cells may lead to morphological alterations in the vascular bed of the lung is highly speculative and needs further exploration before applying in critically ill patients, who suffer from chronic lung disorder [22]. We support an argument that an acceptable safety profile is a very important criterion when thinking about innovative treatment options. However, a safety profile should not be the main or only criterion to be considered in the case of rapidly deteriorating PH, when available conventional treatment strategies have failed.

In fact, available scientific data from both experimental and clinical studies suggest that concentration of implanted stem cells in the target tissues rapidly decreases shortly after the intravascular injection. Poor uptake of stem cells is explained by recirculation of the implanted cells by the blood flow [25-26].

Substantial experimental evidence points to the role of the circulating progenitor cells in vascular pathology, which characterizes chronic PH. However, it is widely recognized that

more study is needed to determine the types of progenitor cells involved in vascular remodeling and their specific functions, once they take up residence in the vessel wall. Much study is needed to determine the factors involved in their recruitment and retention. [27-29].

It has been reported that the hemodynamic alterations that is, normalization of pressure and blood flow preferentially directed to the transplanted lung, occuring with single-lung transplantation, may result in regression of the characteristic findings of PH in the native lung for primary PH patients [30]. We hypothesise that clinical and radiographical improvements of PAH after intrapulmonary implantation of stem cells can be reached by improvement of lung perfusion due to neovascularization of lung tissues. As demonstrated by the case report in this article, intrapulmonary injections directly into the lung parenchyma may lead to even better results, if compared with injection into the lung arteries. These results may be explained by higher concentration of the injected stem cells in the target tissues. As the mechanism of this action is still not clear, we also presume that injected cells trigger a neovascularization process in the lung that further affects much larger areas than those directly exposed to the implanted cells. The achieved results might be explained by the upregulation of hypoxia-inducible factor in vascular cells, leading to the production of bone marrow-mobilizing factors that recruit pro-angiogenic progenitor cells to the pulmonary circulation where they contribute to angiogenic remodeling of the vessel wall in PAH [31]. It still remains to be explored, if andwhy the effects of intrapulmonary injection of stem cells is not extended to the contralateral lung.

In summary, it has to be recognized that the optimal route of administration of stem cells is not known. The optimal dosage regimen, including the lower effective doses, is also unclear. The true potential for different types of stem cells remains obscure. The issues concerning the group of PH patients benefiting most from the treatment and particular point in time for the treatment to be successful remain uncertain [32-33]. No long term benefits have been established as well. The above mentioned discussion suggests that more studies are necessary for most crucial questions to be answered. Until the prognosis for PAH remains unsatisfactory, stem cell therapy poses a new promising therapeutic option that requires deeper understanding of underlying processes and long term effects caused by it.

4. CONCLUSION

Potential benefits provided by the stem cell therapy should encourage multidisciplinary teams to think beyond the conventional and develop newer innovative strategies to obtain the control of deteriorating PAH.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
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