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Regenerative Therapy for Chronic Obstructive Pulmonary Disease, a Retrospective Study of Benefits and Safety

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ABSTRACT

This is a retrospective case series of 568 patients suffering from Chronic Obstructive Pulmonary Disease (COPD) treated with autologous cells and platelet rich plasma (PRP) during 2015. Our objectives were to determine any benefits of treatment as well as any risks to the patient. Quality of Life (QoL) was measured using the Clinical COPD Questionnaire (CCQ). There was a statistically significant improvement in the average self-reported improvement greater than 0.4, in all of our protocols. The proportion of patients experiencing significant improvement in QoL at the 6-month follow-up ranges from 68.2 to 80.0%, depending on the treatment protocol. This study shows that autologous cell therapy with PRP positively affected the QoL of 73% of patients treated using our protocols. Pulmonary function was also measured but no significant changes were observed in the Forced Expiratory Volume at 1 second (FEV1) or the FEV1 to Forced Vital Capacity (FVC) ratio: (FEV1/FVC) values from baseline. Neither age nor gender correlated with the QoL response. There were no complications related to the therapy noted in any patient. We postulate that the natural history of the disease in responding patients was positively changed during the duration of therapy and with little, if any, risk to the patient.

Keywords

Autologous cells, Chronic obstructive pulmonary disease, Platelet rich plasma.

Introduction

COPD is a general term for a complex group of diseases such as chronic bronchitis and emphysema characterized by airflow obstruction, destruction of alveoli and progressive deterioration of lung function over time resulting in impaired gas exchange, hypoxemia and respiratory failure as a result of chronic inflammation of the tissue [1]. Left untreated it will result in the patient's death.

It is a global public health problem with 210 million people diagnosed world-wide and the World Health Organization (WHO) estimates that by 2020 COPD will be the third leading cause of death on the planet. In the United States an estimated 25 million people are diagnosed with COPD with many millions not yet diagnosed. It is estimated that by the year 2030, COPD will be the fourth leading cause of death in the United States, and the financial burden to both patients and the health care system is growing [2]. In 2010 700,000 hospitalizations and 1.5 million emergency room visits were attributed to COPD with direct treatment costs of $32 billion and indirect costs such as missed work and disability of $4 billion [3].

New approaches to the management of COPD are needed urgently. The field of regenerative medicine for lung diseases, including investigative therapies, has emerged in recent years as an alternative to conventional treatment which typically involves various oral and inhaled medications, including steroids, lung reduction surgery and lung transplants. With the exception of lung transplants all of these modalities help with symptoms but do not alter the course of the disease. Lung transplant is considered curative but rejection reactions and the medications used to control them can have a significant negative impact on quality of life.

Autologous cell therapy is a nontraditional alternative to medical care for COPD, and the lungs are a ripe organ for cell applications [4-7].

Recent advances in the field of regenerative medicine in lung disease have demonstrated that cell therapy may reduce inflammation and aid in the maintenance and/or repair of damaged lung tissue [7,8]. As a result, many patients have elected to undergo autologous therapy utilizing their body's own cells and other healing factors in an effort to control their chronic lung disease.

This study retrospectively examines the self-reported outcomes of patients who have undergone elective cell therapy and their pre- and post-treatment quality of life scores. The aim is thereby to inform the community of clinicians about the potential mechanisms, outcomes and safety of this emerging therapy.

Methods

Cell therapy is done using a patient's own adult stem cells, other reparative cells as will be described and PRP, known for its ability to aid in healing tissues [9]. In the case of this study, cells were harvested from the patient by either the bone marrow or peripheral blood, isolated and concentrated using centrifugation, and then returned to the patient the same-day via the venous side of the peripheral circulation. As circulation occurs, the cells enter the right heart and are then disseminated into the lungs, becoming trapped in the lung's microcirculation. Here, the cells begin to produce bioactive factors such as cytokines and anti-inflammatory mediators. Several growth factors are released by activated platelets becoming homing signals to attract cells for healing within the tissue. The exact long-term mechanism of action of stem cells and PRP in the lungs remains under investigation but a discussion of potential functions of these cells in the lungs will be discussed later.

Pre-treatment quality of life scores were recorded on each participant using the Clinical COPD Questionnaire (CCQ), a ten-item self-report Likert scale measuring three domains: symptoms, functional state and mental state that has been validated in the literature as an effective measure for perceived illness perception in chronic lung disease and endorsed as a valid measure by the Global initiative for chronic Obstructive Lung Disease (GOLD) committee [10-12]. All scores range from 0 to 6, with 6 being the most impairment. The total score is averaged resulting in a final score of 0 to 6. Domain scores determined the Quality of Life (QoL) score.

Patients in the study were treated on an outpatient basis with one of four self-selected protocols. Patients underwent either single venous harvest with venous reinfusion, double venous harvest with venous reinfusion or bone marrow harvest with venous reinfusion. For those patients whose disease began to progress again a "booster" treatment was offered which consisted of repeating the single venous treatment. Patients who elected the venous harvest protocol were treated with this protocol each day on three consecutive outpatient days. Patients who elected the double venous treatment were treated on three consecutive days then returned after three months for an additional three days. Patients who elected the bone marrow harvest protocol received one day of venous harvest with venous reinfusion followed by one day of bone marrow harvest followed by venous reinfusion and on the third day the wound was checked prior to discharge from the clinic.

Patients who were on prescribed blood-thinners, those with osteoporosis or other contraindications did not qualify for the bone marrow option. Most of the patients elected the venous option. There were no placebos given. Patients were also given a nebulizer of the mucolytic glutathione during each of the three treatment days. This was not administered to patients with a history of asthma due to the potential for bronchospasm. Glutathione was discussed and recommended, but not required, for use after discharge for each patient.

Three and six months after treatment, each patient was called on the phone and the CCQ was re-administered and scored. The pre- and post- CCQ scores were entered into a computerized database for later extraction. Demographic data, smoking history, oxygen use, GOLD COPD scale and baseline FEV1 data were also collected pre-treatment on each patient. Data was stored in and collected from an encrypted and password-protected internal database and de-identified prior to analysis.

Informed consent was obtained from each patient prior to starting treatment. The consent indicated that a response to treatment is not guaranteed. The facility works closely with an independent Institutional Review Board. The IRB ensures that the treatment facility follows the accepted ethical, scientific, and medical standards under the World Medical Association Declaration of Helsinki, which protects the rights of patients undergoing investigative therapy. These standards include policies on privacy and confidentiality, informed consent, post-care follow-up, and the audit of established quality controls.

Of the 1,210 cases reviewed, only 568 patients with COPD GOLD stages 1-4 and, meeting the criteria of FEV1/FVC<0.7 to confirm a diagnosis of COPD, were able to be included in the analysis. Basis of exclusion included: radiographic findings of diffuse lung disease suggesting a process other than COPD and/or an obstructive lung disease having a ratio of FEV1/FVC>0.7. Pulmonary function tests were measured pre-treatment and were recommended to be done at 6 months post-treatment although the rate of return for post- treatment PFTs was poor.

All analysis was conducted utilizing Statistical Package for the Social Science 21.0 (SPSS). Overall summary statistics were calculated in terms of means and standard deviations. The effective level of significance was 0.05 for all reported P values. Differences in mean PRP group scores at discrete follow-up time points compared with those at baseline were determined significant according to the 0.4 cut-off suggested by Alma et al. Analysis of covariance (ANCOVA) was conducted to assess the significance

of treatment protocol and baseline CCQ score in explaining the variance of follow-up measurements.

Results

Baseline demographics of the study sample are included in Table 1. This information is further broken down in tables 2, 3 and 4 for greater clarity. None of the baseline characteristics were significantly associated with the self-selected treatment protocols indicating this population was relatively homogenous. On average, the patients included in the sample were 70 years old, had a FEV1% predicted value of 31 signifying a GOLD stage of 3, and a Quality of Life (QoL) score of 3.6.

		Venous (N=495)	Bone Marrow (N=36)	Double Venous (N=17)	Booster (N=30)	P-Value
Age, y		70.4 (7.6)	69.3 (7.6)	70.1 (9.8)	71.2 (7.0)	0.76
Gender, Nu (%)	Male	294 (59.4)	18 (50.0)	11 (64.7)	18 (60.0)	0.69
	Female	201 (40.6)	18 (50.0)	6 (35.3)	12 (40.0)	-
CXR/ CT Results, Nu (%)	COPD	402 (82.0)	33 (91.7)	15 (88.2)	23 (92.0)	0.26
	No COPD changes	88 (18.0)	3 (8.3)	2 (11.8)	2 (8.0)	-
	FEV1/ FVC	0.43 (0.11)	0.40 (0.09)	0.43 (0.12)	0.44 (0.12)	0.62
	FEV1%	30.8 (13.9)	28.6 (12.4)	31.3 (15.8)	29.8 (11.9)	0.82
GOLD Stage, Nu (%)	1	-	-	-	-	0.96
	2	55 (11.5)	2 (5.9)	2 (13.3)	3 (10.7)	-
	3	155 (32.5)	12 (35.3)	4 (26.7)	8 (28.6)	-
	4	267 (56.0)	20 (58.8)	9 (60.0)	17 (60.7)	-

Table 1: Demographics.

Definition of abbreviation: Y=years, Nu=Number, CXR=Chest X-Ray, CT=Computed Tomography, QoL=Quality of Life, Tx=Treatment, Avg.=Average, SD= Standard Deviation, CCQ=Clinical COPD Questionnaire, N=Sample Size.

		Venous (N=495)	Bone Marrow (N=36)	Double Venous (N=17)	Booster (N=30)	P-Value
Age, y		70.4 (7.6)	69.3 (7.6)	70.1 (9.8)	71.2 (7.0)	0.76
Gender, Nu (%)	Male	294 (59.4)	18 (50.0)	11 (64.7)	18 (60.0)	0.69
	Female	201 (40.6)	18 (50.0)	6 (35.3)	12 (40.0)	-

Table 2: Age and gender vs. protocol.

		Venous (N=495)	Bone Marrow (N=36)	Double Venous (N=17)	Booster (N=30)
GOLD Stage, Nu (%)	1	-	-	-	-
	2	55 (11.5)	2 (5.9)	2 (13.3)	3 (10.7)
	3	155 (32.5)	12 (35.3)	4 (26.7)	8 (28.6)
	4	267 (56.0)	20 (58.8)	9 (60.0)	17 (60.7)

Table 3: GOLD Stage vs. Protocol.

Baseline QoL scores were found to be significantly correlated with other COPD assessment tools, such as predicted FEV1% and GOLD Stage, however no other baseline predictors were analyzed in the current study. The change in QoL from baseline to the 6-month follow-up was not associated with any variables besides the CCQ results. The ANCOVA test could not determine that the varying treatment protocols significantly explained the variance in the change in QoL from baseline to 6-month follow-up.

		Symptoms Domain		Functional State Domain		Mental State Domain	
		Avg. (SD)	% Improved	Avg. (SD)	% Improved	Avg. (SD)	% Improved
Venous, N=265	CCQ Pre-Tx	3.5 (1.1)	-	3.7 (1.3)	-	3.8 (1.6)	-
	CCQ 3-Month	2.2 (1.3)*	78.9	2.7 (1.5)*	70.2	2.1 (1.6)*	76.6
	CCQ 6-Month	2.2 (1.4)*	75.8	2.8 (1.5)*	66.8	2.3 (1.8)*	70.6
Bone Marrow, N=22	CCQ Pre-Tx	3.0 (1.0)	-	3.7 (1.3)	-	3.6 (1.8)	-
	CCQ 3-Month	1.9 (1.2)*	72.7	2.5 (1.4)*	59.1	2.4 (1.9)*	68.2
	CCQ 6-Month	1.9 (1.2)*	77.3	2.7 (1.6)*	63.6	2.0 (2.0)*	68.2
Double Venous, N=5	CCQ Pre-Tx	2.9 (0.8)	-	2.7 (1.6)	-	4.2 (1.6)	-
	CCQ 3-Month	2.1 (0.9)*	80.0	2.9 (1.0)	40.0	1.9 (1.7)*	100.0
	CCQ 6-Month	1.4 (1.2)*	100.0	1.9 (1.2)*	60.0	1.9 (1.6)*	100.0
Booster, N=16	CCQ Pre-Tx	2.9 (0.9)	-	3.2 (1.3)	-	3.3 (1.6)	-
	CCQ 3-Month	2.2 (1.7)*	62.5	2.4 (1.3)*	75.0	1.8 (1.9)*	81.3
	CCQ 6-Month	2.4 (1.3)*	62.5	2.5 (1.1)*	50.0	1.8 (1.7)*	68.8

Table 4: QoL Change by CCQ Domains.

Definition of abbreviation: QoL=Quality of Life, Avg.=Average, SD= Standard Deviation, CCQ=Clinical COPD Questionnaire, Tx=Treatment, N=Sample Size.Note. Utilized the 0.4 cut-off point suggested by Alma et al. to determine the frequency of significant improvement in QOL from Pre-treatment CCQ.

QoL measure at baseline, 3 months and 6 months was measured for each of the four protocols and presented in figure 1.

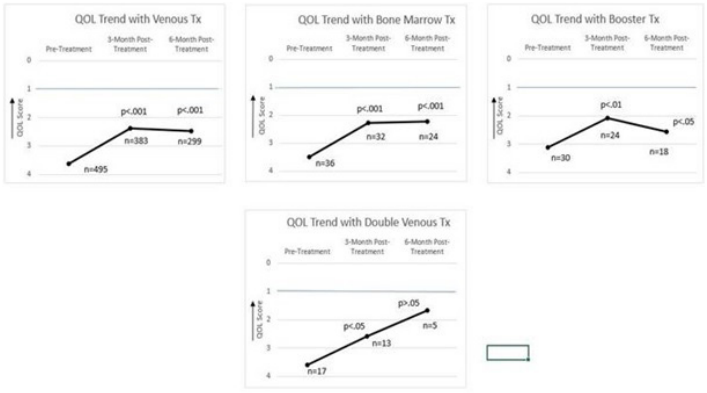

Figure 1: QoL trends by treatment protocol.

When broken down by CCQ domains the domain scores tended to parallel the QoL trends. The single venous and bone marrow

protocols had very similar results at 6 months. The booster result at 6 months was the worst of the four. The need for a booster may reflect a more aggressive disease state and/or COPD morbidity combined with age related decline in pulmonary function. The double venous protocol had the best result at 6 months.

None of the patients treated in this series had any complication or morbidity directly related to the treatment. Those that did not respond had no decrease in their lung function or QoL as a result of treatment.

Discussion

The effect of the treatment is based on the interactions of cellular and non-cellular materials to repair damaged tissue or cells and calm inflammation. The exact molecular pathways that regulate these repair responses have not been defined [13] nor has the ability to administer induced pulmonary stem cells to damaged lungs. Although there is a variety of cells harvested, especially from the bone marrow, it is generally felt that hematopoietic stem cells (HSCs) or hematopoietic progenitor cells (HPCs), mesenchymal cells (MSCs), endothelial progenitor cells (EPCs) and platelets play a major part in the cellular activity of repair. The primary non-cellular component is PRP with its many circulating factors.

These cells when removed from their usual environment, such as their niche for stem cells or the perivascular location in the case of MSCs, can become very responsive to their new environment and can help stimulate the quiescent endogenous progenitor cell population in the lung and induce proliferation as well as differentiation in response to tissue injury [14]. These cells can also respond to damage and work via paracrine, immunomodulatory, anti-inflammatory and/or stimulate other reparative cells in the lung. Stem cells appear to work via these effects rather than engraftment and differentiation [15-19].

When a vessel is damaged, MSCs come off and dock at the site of injury. Platelet-derived growth factor (PDGF) attaches MSCs to the vessel wall. PRP is rich in enzymes that break down PDGF which contracts the MSC and causes it to come off the vessel wall. MSCs have yet to be defined interactions between epithelial cells and MSCs in the reparative niche as cross talk between these cell types is known to be essential to proper development of the lung [13]. MSCs are enormously sensory and sensitive to their environment and have a milieu specific response. Because of their ability to respond differently in different environments some of their functions may seem contradictory. They release cytokines for repair. It has been shown that MSCs are able to home in on damaged areas of the lung and may differentiate into various cell types including epithelial, endothelial fibroblasts and myofibroblast cells [20]. Ex Vivo expansion of the cells can result in decreased differentiation potential and protective effects [21]. MSCs from aged [22] or diseased subjects are profoundly impaired [23]. One would like to be able to standardize MSCs to disease, site, genotype specific but we cannot do that now.

PRP contains high concentrations of platelet derived growth factors (PDGF) AA, AB, and BB, Vascular endothelial growth factor (VEGF), transforming growth factor (TGF) β1, and β-2, as well as pro-inflammatory cytokines such as interleukin (IL)-4, IL-8, IL-13, IL-17, tumor necrosis factor (TNF)-α (which promotes EC homing and angiogenesis) [24], and interferon (IFN)-α. The VEGF signal pathway is involved in the anti-apoptotic effects of EPCs as well as in proliferating effects. There is a direct relationship between the VEGF and circulating EPC levels and endothelial cells [25].

The cells and PRP are infused into a peripheral vein and carried to the lungs where they trapped in what has been described as the "Pulmonary First Pass Effect" simply the "Pulmonary Trap" [26]. The same studies showed that the size of the cells (15 to 19 um for MSCs) is a factor in the trapping effect as well as adhesion abilities involving P-selectin and a counter ligand. There is also evidence, at least in their rat model, that there may be receptor mediated MSC entrapment as well to extracellular matrix components such as collagen, laminin, fibronectin and vitronectin as well as integrin expression [27]. How long this lasts for MSCs is not well defined for humans. Platelet derived microparticles transfer attachment receptors (e.g.,glycoproteins IIb/IIIa, Ib, aIIa, P-selectin, CCXR4) to the HPC cells and by doing so make the latter's attachment to endothelial cells more efficient [28]. Interaction in the form of adhesion of HPC cells to MSCs and stroma has been demonstrated [29,30].

Conclusion

Our retrospective study showed a significant QoL improvement in COPD patients who were treated with our protocols as measured using the CCQ. The findings are in agreement with the recommended goals of the GOLD Executive Summary of relieving symptoms and improving perceived exercise tolerance and health status. A QoL improvement may suggest a reduction in risk of disease progression and also prevention of exacerbations. These questions can be answered with longer term follow up. Nevertheless, significant improvement in the QoL of patients should be of utmost consideration in practitioners involved in treatment of debilitating chronic conditions.

A major drawback of our results are lack of objective evidence in the way of pulmonary function test changes. We had no problem performing testing on our patients prior to treatment. But because many of our patients come to us from several hours away we often must depend upon their physician at home to provide us with follow up testing. Unfortunately cooperation in doing that for us has been negligible. We hope to overcome that problem by implementing newer, FDA approved, cell phone based technology for follow up evaluations.

This study is also limited by the lack of a control group and is rather observational in nature, though not all important and effective medical innovation is bred from clinical trials. Although the results are promising and a significant number of patients reported a response to therapy indicating that something has occurred, the placebo effect cannot be definitely excluded. Because of the favorable outcomes in this retrospective study both in patient

response and patient safety further prospective studies, including randomized controlled trials, are under way.

The current restrictions in the United States regarding cell manipulation may also be impeding more effective treatments. Doing studies to overcome these obstacles are time consuming and expensive but, fortunately, some have the resources to press forward in these areas.

Our thinking may have to change from the concept of a single treatment to control the disease. This methodology is not a cure for these diseases but an attempt to slow or arrest the progression. It has already been demonstrated by some of our patients that this control may not be permanent, hence the need for boosters. By observation anything that can cause new inflammatory response in the lungs such as pulmonary infections or exposure to irritants such as cigarette smoke may cause a flare up of the lung disease. So rather than taking a "one and done" approach to patient care we may have to realize that many of our patients might benefit more in the long term to a periodic or maintenance therapy approach.

We also need to keep our eyes on potential future trends such as more effective delivery of drugs or cytokines utilizing "trained" MSCs or cell derived products such as microvesicles. Better targeting or delivery of cells utilizing selective vascular administration, robotic surgery technology for cell placement or scaffold placement or nanotechnology along a local or systemic pathway. Currently scaffolds are being created for such things as tracheal replacement and can be of organic or inorganic materials, 3-D printed using biocompatible or biodegradable materials. Efforts at removal of all antigenic materials from donor tissues to prevent graft versus host disease or creation of de novo scaffolds seeded with cells controlled by DNA inserted by retroviruses and "organ in a dish" created transplantable organoids are all technologies that hold promise for our patients

There remains a lot to be learned about the long-term effects of autologous adult cell therapy. The treatments presented are a beginning. They show a degree of effectiveness but reasons for non-response must be determined and addressed. The results of this study demonstrate that some patients may experience an improvement in their perceived quality of life following therapy. Cell therapy using a body's own cells was shown to be very safe and should be an elective option for those patients who wish to use their own cells and cell products for potential healing. Actual cure is some time off but the ability to control is within our grasp. Further work needs to be done to bring the most effective methodology to bear on these patients and that methodology must be effective, simple and affordable. Informing the larger medical communities about this treatment option is imperative in advancing the field.

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