“Combining Traditional Medicine, Regenerative Treatment and Current Technology to Optimize Care of Patients with Chronic Obstructive Pulmonary Disease (COPD)”

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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 worldwide and the World Health Organization (WHO) estimates that by 2020 COPD will be the third leading cause of death worldwide. In the United States an estimated 16 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].

Conventional treatment for COPD typically involves various oral and inhaled medications, including steroids, oxygen therapy and lung reduction surgery. Current management of COPD may alleviate symptoms but no conventional pharmacologic treatment can modify the progressive course of the disease except lung transplant which, although considered curative, has significant quality of life issues and mortality related to rejection reactions and the medications used to control them.

Besides medical and surgical approaches to COPD management other behavioral interventions are also useful. Smoking cessation is the most common and important behavioral change that COPD sufferers are encouraged to make by their primary care physicians and is an effective means of reducing the rate of disease progression including rate of decline of lung function.[4] Immunizations, awareness, evaluation and treatment of other co-morbidities such as anxiety, depression, sleep disorders and pulmonary hypertension are well managed in the community. Pulmonary Rehabilitation has been known for some time to be beneficial but not everyone has taken advantage of these programs for reasons to be discussed.

Despite all of these interventions COPD continues to be a progressive disease which is frustrating to patients, families and those caring for these patients. Many COPD patients are marginalized once conventional treatment has failed. New approaches to the management of COPD are needed urgently. The aim is thereby to inform the community of clinicians about the potential mechanisms, outcomes and safety of this emerging therapy utilizing combined protocols to optimize outcomes.

Method 1 – Regenerative Treatment

The field of regenerative medicine for lung diseases, including investigative therapies, has emerged in recent years as an alternative or adjunct to conventional treatment for COPD. Autologous cell therapy along with activated platelets may safely affect chronic airflow obstruction by reducing inflammation and aid in promoting maintenance and/or repair of damaged lung tissue.[5-8] The long-term mechanism of action is not yet completely known and remains under investigation.

400 patients underwent cellular therapy with their own cells and platelet rich plasma (PRP-PC) harvested from peripheral blood. Patients underwent pre-treatment spirometry for baseline which included Forced Expiratory Volume in 1 second (FEV1) %. FEV1 is a direct reflection of the severity of obstruction and is the standard for determining a patient’s COPD GOLD (**Gl**obal Initiative for Chronic **O**bstructive **L**ung **D**isease) Stage (stages I-IV with I being mild and IV being very severe obstruction). As COPD worsens, FEV1 decreases. After 3 months, patients underwent post-treatment spirometry to detect any change after treatment.

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 illness perception in chronic lung disease and endorsed as a valid measure by the GOLD committee. [9,10,11] All scores range from 0 to 6, with 6 being the most impairment. So the lower the score the better the patient is doing. The total score is averaged resulting in a final score of 0 to 6. Domain scores determined the Quality of Life (QoL) score.

Informed consent was obtained from all patients prior to collecting any data. All participants signed informed consent which indicated that response to treatment is not guaranteed. Due to additional regulations required in the state of Texas, our Dallas clinic and protocols are reviewed and accredited by a third-party, independent Institutional Review Board, Advarra IRB, that is accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). Our procedures and protocols are consistent across all clinics.

Patients in the study were treated on an outpatient basis with what we call a “double venous” protocol. Patients underwent venous harvest with venous reinfusion of the product the same day. The second day they did the same thing. The patients returned to the clinic three months later and repeated the same process.

There were no placebos given. Patients were also given a nebulizer of the mucolytic glutathione during each of the treatments.[12] 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.

Results 1 – Regenerative Therapy

400 patients underwent autologous cellular therapy with their own cell and PRP-PC harvested from their peripheral blood. The mean sample age was 71 years. 239 subjects were male and 169 were female. 87% were former smokers and none of the subjects were smoking at the time of the treatment.

All analysis was conducted utilizing Statistical Package for the Social Science (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.

224 (56%) of subjects had an improvement in their FEV1 with the mean improvement being 6.2%. 140 (35%) of subjects had a decline in their FEV1 with a mean of 3%. 36 (9%) of subjects had no change in their FEV1. Because the ultimate goal of this treatment is to stop the disease progression and/or improve lung function one could argue that the 36 patient with no change in FEV1 should be included with the 224 subjects with improvement however, because of the short time frame of three months it was felt that these two groups should remain separate.

The CCQ results showed 308 (77%) had improved quality of life at 3 months, 36 (13%) had a decline in their quality of life and 40 (10%) had no change in their quality of life. The meaningful difference cut off was at < or > 0.4.

In addition to these treatments patients were instructed to follow up with their primary care physicians regarding being evaluated for pulmonary hypertension and participate in a Pulmonary Rehabilitation program. Despite this documentation shows that 19 patients out of 400 started a program with 7 completing it. Of those that did complete the program 86% (6/7) had a positive change in their FEV1. 57% (4/7) had a change of +4% or greater and the average change for the group was +5%. So even though the numbers are small they do show the benefit of the program.

None of the patients treated in this series had any complication or morbidity directly related to the treatment.

Method 2 – Pulmonary Rehabilitation

Pulmonary Rehabilitation (PH) programs have been available to patients for many years but in the last few years more stress has been placed on their value to COPD patients. They have a positive impact on endurance, shortness of breath and quality of life for these people.[13] It has also been shown to significantly stop the decline of FEV1 over time.[14] Studies have also shown physical activity through metabolic, mechanical and hormonal stimuli can increase activation, mobilization and differentiation of stem cells.[15] These programs are typically offered by and carried out in medical centers or other outpatient rehabilitation centers. While the majority of COPD patients could benefit from these programs, access and compliance is limited due to several factors. Many patients with moderate to severe COPD suffer from significant deconditioning, making it difficult to get to facility-based programs. Additionally, traditional pulmonary rehabilitation programs are typically located in larger medical centers and hospitals, which may be located hours away from some patients making consistent engagement nearly impossible. On top of transportation issues, insurance may cover a set number of visits, but many times the out-of-pocket co-pays or costs after the covered visits have been utilized are too high for patients to continue participating. The result is that only an estimated 2-3% of COPD patients have access to the facility-based programs available today.

To address these concerns Sparo, Inc. (St. Louis, MO) has developed the Lift Pulmonary Rehab© program – an online, low cost, home-based pulmonary rehabilitation program available via smartphone, tablet or computer. The program is designed for patients with COPD and includes not only daily guided classes, but also access to a COPD support group on Facebook for its members to connect with, encourage, and support each other.

Results 2 – Lift Program

In a study of 8 patients who completed Lift’s 0-to-10 Minute 40-day buildup program, the CCQ was self-administered at the beginning of the program and after completion of the program. The exercise capacity was also measured at both time points by self-reported duration of continuous walking in minutes. The mean CCQ pre-program was 3.17 and post-program was 1.21, a significant decrease. This translated to a 37% improvement in Quality of Life as measured by CCQ domain scores. The mean walking duration pre-program was 3.88 minutes and post-program was 7.19 minutes. The mean improvement in walking duration represents a 142% improvement in exercise capacity.

In another study of the Lift program 92 COPD patients participated in the Lift maintenance program for 4 months. Pre- and post-program walking duration was measured. A 150% mean improvement in walking duration was found in this study.

Conclusions

Our retrospective study showed improvement in FEV1 and significant CCQ and QoL improvements in COPD patients who were treated with our protocol. 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.

Some perceived drawbacks of our results are 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, some would say that placebo effect cannot be definitely excluded. The counter argument is that the pre- and post-treatment CCQ difference is greater than the minimal clinically important difference (MCID) for the CCQ for COPD which has been determined to be 0.4.16 It has also been shown that “placebo effects are largely confined to patient-reported subjective outcomes and do not influence physiologic measures” such as FEV1.[17,18]

The lack of access and compliance to Pulmonary Rehabilitation for this group of patients is a significant limitation in providing optimal care that achieves the best outcomes for patients with COPD. The introduction of the Lift program provides an alternative to facility-based programs that is more accessible to the majority of COPD patients and should result in many more patients being able to participate in Pulmonary Rehabilitation. This program is being incorporated into our patient protocols with the goal of improving the results of both treatments when used together.

It is also important that conventional medical therapies not be abandoned. This disease process is multivariate in its etiology and pathophysiology so it is logical that every methodology that can be integrated to the treatment of the problem will help in achieving better control and hopefully a cure at some point. Another potential benefit of a more integrated treatment protocol is the possible economic impact of reduced medication use, oxygen use, emergency room visits, imaging studies and hospitalizations to name a few. This type of data is difficult to collect and it generally takes time to do so but the effort is being made.

The combination of conventional medical therapy with Regenerative Medicine based treatment and the application of current interactive communication technology to improve patient compliance with Pulmonary Rehabilitation will result in more effective control of COPD and improvement in patients’ quality of life.

HISTORY OF SMOKING

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid		40	10.0	10.0	10.0
	No	12	3.0	3.0	13.0
	Yes	348	87.0	87.0	100.0
	Total	400	100.0	100.0	

GENDER

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Female	161	40.3	40.3	40.3
	Male	239	59.8	59.8	100.0
	Total	400	100.0	100.0	

PRE-FEV1, 3 MONTHS POST-FEV1, CHANGE FROM BASELINE (MEAN IMPROVEMENT OF 1.95%)

	N	Range	Minimum	Maximum	Mean	Std. Deviation
FEV1_PRE	400	81	9	90	33.17	15.609
FEV1_3MO	400	81	8	89	35.12	16.613
FEV1_CHANGE	400	67	-22	45	1.95	7.389
Valid N (listwise)	400					

T-TEST OF STATISTICAL SIGNIFICANCE OF CHANGE

	N	Mean	Std. Deviation	Std. Error Mean
FEV1_CHANGE	400	1.95	7.389	369

ONE-SAMPLE TEST

	Test Value = 0					
	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
FEV1_CHANGE	5.285	399	.000*	1.953	1.23	2.68

*FEV1 change from baseline is statistically significant at the α=0.05 level

FEV1 STATUS OF IMPROVEMENT, NO CHANGE OR DECLINE

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	IMPROVED 1-5%	138	34.5	34.5	34.5
	IMPROVED 6-10%	46	11.5	11.5	46.0
	IMPROVED 11-15%	25	6.3	6.3	52.3
	IMPROVED 16-20%	8	2.0	2.0	54.3
	IMPROVED >20%	7	1.8	1.8	56.0
	NO CHANGE	36	9.0	9.0	65.0
	DECLINED 1-5%	102	25.5	25.5	90.5
	DECLINED 6-10%	30	7.5	7.5	98.0
	DECLINED 11-15%	5	1.3	1.3	99.3
	DECLINED 16-20%	1	.3	.3	99.5
	DECLINED >20%	2	.5	.5	100.0
	Total	400	100.0	100.0	

FEV1 OVERALL SAMPLE SUMMARY

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	IMPROVED AT 3 MONTHS	224	56.0	56.0	56.0
	DECLINED AT 3 MONTHS	140	35.0	35.0	91.0
	NO CHANGE AT 3 MONTHS	36	9.0	9.0	100.0
	Total	400	100.0	100.0	

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