CLINICAL EFFECTS OF AUTOLOGOUS BONE MARROW DERIVED STEM CELL THERAPY FOR PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AT BACH MAI HOSPITAL

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To evaluate the clinical effects of autologous bone marrow derived stem cell therapy for patients with COPD at Bach Mai hospital. Subjectives and methods: A clinical trial follow-up with 25 patients with COPD at the Respiratory center, Bach Mai hospital from August 2018 to August 2020. Patients were treated with autologous bone marrow derived stem cell intravenously followed by checking up once a month in 12 months.Results: Average distance patient walked with the 6 minute walk test (6MWT) increased from 389.0 ± 122.2m before therapy to 427.8 ± 71.1m at the point of 6 months after the first infusion (p > 0.05) and to 435.7m at 6 months after the second infusion (p < 0.05). Average FEV1 increased from 34.8 ± 11.6% before therapy to 37 ± 11.3% at the point of 3 months after the 1st stem cells infusion and 37.2 ± 13.8% at 6 months after the 2nd infusion (p < 0.05). The BODE index decreased from 4.8 ± 2.0 before infusion to 4.1 ± 1.9 at 3 months and 4.1 ± 1.6 at 6 months after 2nd TBG infusion (p < 0.05). CAT, mMRC, SGRQ, arterial blood gas did not change significantly before and after stem cell infusion. Conclusions: autologous bone marrow derived stem cell therapy for patients with COPD after 12 months improved exertion, respiratory function, BODE index.

Keywords: stem cell, bone marrow derived stem cell, COPD

I. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a common disease representing the 4th leading cause of death in the world.[1] The burden of COPD in Asia remains a huge problem, especially when there is high prevalence of tobacco smoking.[2] Mortality related to COPD varied from 4% in New Zealand to 40% in Sri Lanka and Thailand.[2] According to the WHO estimation, prevalence of COPD in Asia was 3 times higher than in Western countries.[3] The prevalence of COPD in Hong Kong was 6.8%.[4] In 12 nations and territories in the Asia – Pacific region, the rate of moderate to severe cases of COPD accounted for 6.3% of the population over 30 year-old, with the lowest rate of 3.5% in Hong Kong and Singapore and the highest rate of 6.7% in Vietnam.[5]

The pathophysiology of COPD is complicated, in which the role of systemic inflammation has been emphasized in multiple researches, with the reaction of inflammatory cells and inflammatory mediators, ultimately leading to damaged lung parenchyma and increased mucus secretion results in narrowing, fibrosis of airways, destroying lung parenchyma and changes in the pulmonary capillary bed. These anatomical changes lead to reduced air flow and other pathological features of COPD.[6]

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Recently, according to GOLD recommendations (Global Initiative for Chronic Obstructing Lung Disease), the management of COPD includes: avoiding exposure to risk factors, pharmacological therapies (bronchodilators, corticosteroid, Phosphodiesterase 4 antagonists,etc.), pulmonary rehabilitations, oxygen therapy, mechanical ventilation with the goal of reducing symptoms and risk of exacerbations.[1] However, these treatments do not prevent systemic inflammation and disease progression, which can progress to advanced stages and lead to disabilities or death. As a result, scientists have been trying to develop new treatments to prevent and even to reverse disease progression, one of which is stem cell therapy.

Bone marrow is a good source of stem cells with the different capabilities of regeneration and differentiation, including haemopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), Endothelial Stem/progenitor cells (EPCs). MSCs are stromal cells, with the ability to regenerate and differentiate into a number of cell types. In addition, MSCs were considered to have anti-inflammatory and immune modulating capablitity.[7-9] Application of stem cells that have the potential of differentiation, immune modulation, tissue regeneration, etc. in the treatment of chronic lung diseases such as pulmonary fibrosis, COPD may be helpful to the patients by improving their quality of life.[10]

Furthermore, results from pilot studies showed promising results for safety of stem cell therapy in chronic lung diseases.[10] In Vietnam as well as all over the world, such researches are few and for a short period of time. Therefore, we decided to conduct this research with the aim of "Evaluating the clinical effects of autologous bone marrow derived stem cell therapy for patients with COPD at Bach Mai hospital".

II. SUBJECTS AND METHODS

1. Study subjects

25 COPD patients with moderate to severe stage, 40 - 80 years old at the Respiratory Centre, Bach Mai hospital, with a Forced Expiratory Volume in 1 second (FEV1) ≤ 60%, with at least 2 exacerbations or 1 hospitalised exacerbation in the previous year, and volunteered to participate in the study.

Patients with any of the following conditions will be excluded from the study:

- Suffering from pulmonary diseases other than COPD, deficiency of a1 – antitrypsin enzyme.

- Weight < 40kg.

- Currently having viral or bacterial infection, having hospitalized exacerbations in the last 4 weeks.

- Currently smoking or recently quit smoking in the last 6 months.

- Breastfeeding, pregnant or intending to be pregnant.

- Unstable chronic conditions: Cardiovascular disease, liver disease, kidney disease, diabetes.

- Any other diseases, at the discretion of the researcher, that might put the patients at risk during the research, or can affect the efficiency analysis and safety if the disease progresses during the study.

- Has a history or is being diagnosed with cancer, hyperplasia disorders such as ovarian cysts, gastric mucosal hyperplasis, etc.

- Using TNF – inhibitors in the last 3 months, using immunosuppressants in the last 8 weeks

- Allergies to aenesthetic agents which can not be tolerated during stimulation tests.

2. Methods

- Study design: Clinical trial, follow-up.

- Sample size: 25 patients with convenient sampling.

- Study duration: from Aug, 2018 to Aug, 2020

- Study locations: Respiratory Center, Gene and Stem Cell Unit of Nuclear Medicine and Oncology Center, Hematology and Blood Transfusion Center of Bach Mai Hospital.

- Collaboration units: Institute of Scientific and Medical Research 108, National Insitute of Hematology and Blood Transfusion.

- Study protocol: COPD patients took screening tests according a unified protocol, then be consulted by the Medical council to enroll in the study of BM-derived stem cells therapy. After approval from the Medical council, 250ml – 300ml of bone marrow fluid was aspirated from the patients from bilateral posterior iliac crests, in the operating room. The bone marrow fluid was then processed by the Sepax 2 system automatically to produced 100ml of fluid containing stem cells at the Cellular laboratory of the Hematology and Blood Transfusion Center, Bach Mai Hospital.

The quality of stem cells was assessed by complete cells count test, trypan blue test to find viable rate, flow cytometry to assess the surface marker expression of CD34, MSC panel. The qualified stem cell was approved with the number of nuclear cells not smaller than 3×10^8 and viable rate not smaller than 75%.

The stem cells was then divided in half, 50 ml was infused to the patients intravenously after extraction, the other 50 ml was frozen and preserved in liquid Nitrogen at -196 degree Celsius. After the stem cells infusion, the patients were monitored in the hospital for 7 days, followed by a discharge, and a monthly check-up. At the 6 months time point post the first stem cells infusion, patients went through a second screening. If there were no abnormality and the patients satisfied the research criteria, the remaining stem cells would be taken out of the liquid nitrogen, defrosted and given immediately intravenously. All the procedures were performed under steriled conditions. After the 2nd infusion, patients are followed up monthly for the next 6 months with clinical and paraclinical data. Until August 2020, 25 patients have been followed up at least to the 6th month after the first stem cells infusion, of which 19 patients have completed 6 months following the second stem cells infusion.

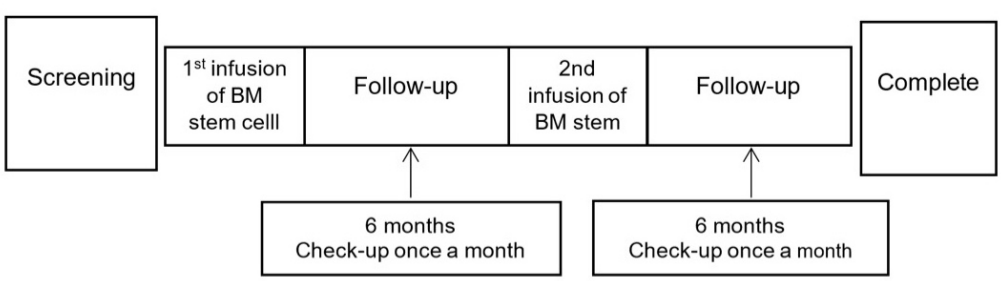

Figure 1. Study protocol

- Research variables: Evaluate clinical efficiency after stem cells infusion based on changes to CAT, mMRC, SGRQ, BODE, 6 minutes walk test, pulmonary function test (PFT), CRP, arterial blood gas. Patients filled up the questionnaire including CAT, mMRC, SGRQ every month, took PFT, CRP test and ABG test every 3 months.

3. Data analysis

Data was entered and analyzed by the SPSS software. Results were displayed in percentage ± standard deviation. Evaluate the changes after intervention by paired-sample T-test. When comparing, difference is considered statisticially significance with $p < 0.05$.

4. Research ethnics

All patients participating in the research were given appropriate information about te purpose, methods, benefits and risks of the research, signed the Consent forms to voluntary participate in the study and have the right to withdraw at any time.

The research has been approved by Bach Mai Hospital Ethnics Committees with the certificate 86/HDDD signed 12/10/2016 and Ethnics Commission of Biomedical Research of the Ministry of Health with the certificate 61/CN-HDDD signed 27/7/2018.

III. RESULTS

1. General characteristics of studied patients

Table 1. General characteristics of studied patients

Index	Results (n = 25)
Age, year (min, max)	64.2 ± 7.9 (50, 79)
Male, n (%)	25 (100%)
History of smoking, pack-year (min, max)	23.7 ± 11.0 (5, 50)
Staging of GOLD D, n (%)	25 (100%)
BMI, kg/m2 (min, max)	21.0 ± 2.1 (17.3, 26.6)
Hypertension, n (%)	5 (20%)
Diabetes, n (%)	2 (8%)
Dyslipidemia, n (%)	22 (88%)
History of other diseasesa, n (%)	7 (28%)

[a] Appendectomy, resection of 2/3 stomach due to gastric ulcer, inguinal hernia operation, stomachace, knee osteoarthritis

Out of 25 patients in the research group, 100% were male, the average age was of the sixth decade of life, highest being 79 years old. Average pack-year of tobacco smoking was quite high, with the highest being 50 pack-year, however according to the criteria, no patient smoke over the previous 6 months. 100% of patients were categorized at GOLD D class according to GOLD 2016. There were several patients having hypertension, diabetes but blood pressure and blood glucose level were under control, 22 patients (88%) with dyslipidemia, as well as a few patients with other conditions but no serious risks to the general health at the time of research.

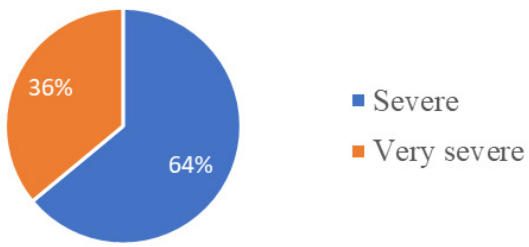

Figure 2. Obstructive level of COPD patients

All patients had airway obstruction classified of severe and very severe level, of which nearly 2 third of patients had severe obstruction (FEV1 < 50%) and the rest had very severe obstruction (FEV1 < 30%).

Table 2. Paraclinical features of COPD patients (n = 25)

Index	Mean	Min	Max
SpO2 (%)	95.5 ± 1.6	92	99
ESR 1st hour (mm)	10.0 ± 8.8	2	41
ESR 2nd hour (mm)	21.2 ± 15.2	6	73
Erythrocyte (T/L)	5.09 ± 0.52	4.34	6.56
Neutrophil (G/L)	7.43 ± 1.45	4.69	10.66
Hemoglobin (g/l)	148.3 ± 9.9	130	165
Hematocrit	0.45 ± 0.03	0.40	0.50
Platelets (G/L)	261.2 ± 72. 6	98	396
D-dimer (mg/l)	0.653 ± 1.158	0.106	5.70
HbA1c (%)	5.8 ± 0.4	4.9	6.5
Acid uric (µmol/l)	396.6 ± 87.8	260	565
Creatinin (µmol/l)	79.1 ± 11.4	65	100
AST (U/L)	23.1 ± 5.5	13	38
ALT (U/L)	21.8 ± 9.9	9	43
Bilirubin total (µmol/l)	10.4 ± 3.3	3.8	18.9
Cholesterol TP (mmol/l)	5.40 ± 1.10	3.02	7.49
LDL-C (mmol/l)	3.19 ± 0.94	1.55	4.95
HDL-C (mmol/l)	1.46 ± 0.44	0.52	2.32
Triglycerid (mmol/l)	1.71 ± 1.36	0.59	7.03
Natri (mmol/l)	140.4 ± 3.5	132	146

Kali (mmol/l)	3.8 ± 0.3	3.1	4.3
Clo (mmol/l)	101.1 ± 4.1	91	110
Troponin T (ng/l)	4.66 ± 3.12	1.074	9.510
Pro-BNP (pmol/l)	3.65 ± 2.26	0.59	9.12
EF (%)	68.8 ± 6.9	57	81
Pulmonary arterial pressure (mmHg)	32.6 ± 6.8	20	47

100% of patients were screen – tested according to a unified protocol, with table 2 displaying the average, highest and lowest figure of a number of important tests. We can see that 100% of patients did not have hypoxemia, no liver failure, kidney failure or heart failure before the stem cells infusion.

2. Clinical features after stem cell transfusions

Table 3. CAT, mMRC, BODE, SGRQ and 6MWT before and after stem cell therapy

Index	Before infusion (n = 25)	3 months after 1st infusion (n = 23)	P	6 months after 1st infusion (n = 25)	P	3 months after 2nd infusion (n = 19)	P	6 months after 2nd infusion (n = 19)	P
CAT, mean (SD)	22.1 (6.2)	22.0 (6.8)	0.867	22.2 (4.6)	0.932	21.9 (5.1)	0.871	21.0 (4.8)	0.480
mMRC ≥ 2 n (%)	17 (68%)	18 (78.3%)	0.599	18 (72%)	0.468	14 (73.7%)	0.764	16 (84.2%)	0.364
6MWT, mean (SD) (m)	389.0 (122.2)	400.0 (98.8)	0.649	427.8 (71.1)	0.092	402.1 (107.3)	0.025	436.7 (108.0)	0.002
BODE mean (SD)	4.8 (2.0)	4.5 (1.9)	0.192	4.1 (1.9)	0.101	4.1 (1.2)	0.027	4.1 (1.6)	0.007
SGRQ mean (SD)	53.9 (14.7)	56.1 (14.3)	0.173	54.3 (14.7)	0.878	57.4 (15.9)	0.995	51.0 (13.5)	0.122

p: calculated based on paired-sample T-test, comparing the changes between before infusion and those at each follow-up of CAT, 6MWT, BODE, SGRQ.

p: calculated based on Chi-square test, comparing the changes of percentage of patients having mMRC ≥ 2 between before infusion and those at each follow-up.

Table 3 shows changes in symptoms-related data, dyspnea level, exertion capacity, quality of life score before stem cells infusion and 3 months, 6 months after the first infusion and 3 months, 6 months after the 2nd infusions. Average CAT score at all times were high (> 10), proportion of patients with mMRC > 2 at all times were also high accounting for 65% and there was no significant change before and after stem cell infusion. Likewise, the SGRQ score at all times was still high, a small decrease in the last time (51.0) compared to before infusion (53.9) with no statistical significance.

Interestingly, the average 6MWT increased from 389 m from before the infusion to 402.1 m at the 3-month mark after the 2nd infusion and up to 435.7m at the 6-month mark after the 2nd infusion with $p < 0.05$. the BODE index also improved with a drop from 2.8 before infusion to 4.1 at the 3 month and 6-month mark after the 2nd stem cell infusion with $p < 0.05$.

Table 4. Laboratory features before and after stem cell therapy

Index	Before infusion (n = 25)	3 months after 1st infusion (n = 23)	P	6 months after 1st infusion (n = 25)	P	3 months after 2nd infusion (n = 19)	P	6 months after 2nd infusion (n = 19)	P
FEV1 %, mean (SD)	34.8 (11.6)	37.0 (11.3)	0.024	38.3 (12.7)	0.052	35.4 (10.8)	0.09	37.2 (13.8)	0.045
Gaensler, mean (SD)	0.43 (0.08)	0.44 (0.08)	0.128	0.44 (0.09)	0.632	0.44 (0.09)	0.128	0.44 (0.09)	0.168
CRP, mean (SD) (mg/dl)	0.28 (0.31)	0.25 (0.25)	0.854	0.23 (0.22)	0.466	0.38 (0.76)	0.445	0.52 (0.97)	0.244
pH, mean (SD)	7.42 (0.03)	7.43 (0.02)	0.377	7.42 (0.02)	0.534	7.42 (0.02)	0.436	7.41 (0.03)	0.060
pCO2, mean (SD)	43.9 (5.9)	42.7 (5.6)	0.035	44.4 (4.9)	0.608	44.3 (5.3)	0.246	45.5 (4.5)	0.656
pO2, mean (SD)	72.90 (8.0)	72.3 (8.0)	0.144	74.1 (10.7)	0.587	68.1 (8.8)	0.058	73.0 (12.4)	0.953

p: calculated based on paired-sample T-test, comparing the changes between before infusion and those at each follow-up of indexes.

Table 4 shows important paraclinical tests of COPD patients. Pulmonary function tests of the patients group showed significant FEV1 increase from 34.8% before infusion to 37% 3 months after the first stem cell infusion and up to 37.2% at the 6-month mark after the 2nd stem cell infusion ($p < 0.05$). Other tests such as CRP, pH, pCO2, pO2 did not show any significant changes before and after the therapy. Average CRP was 0.28, 0.25, 0.23, 0.38 and 0.52 at the time before, 3 months and 6 months after 1st infusion, 3 months and 6 months after 2nd infusion respectively.

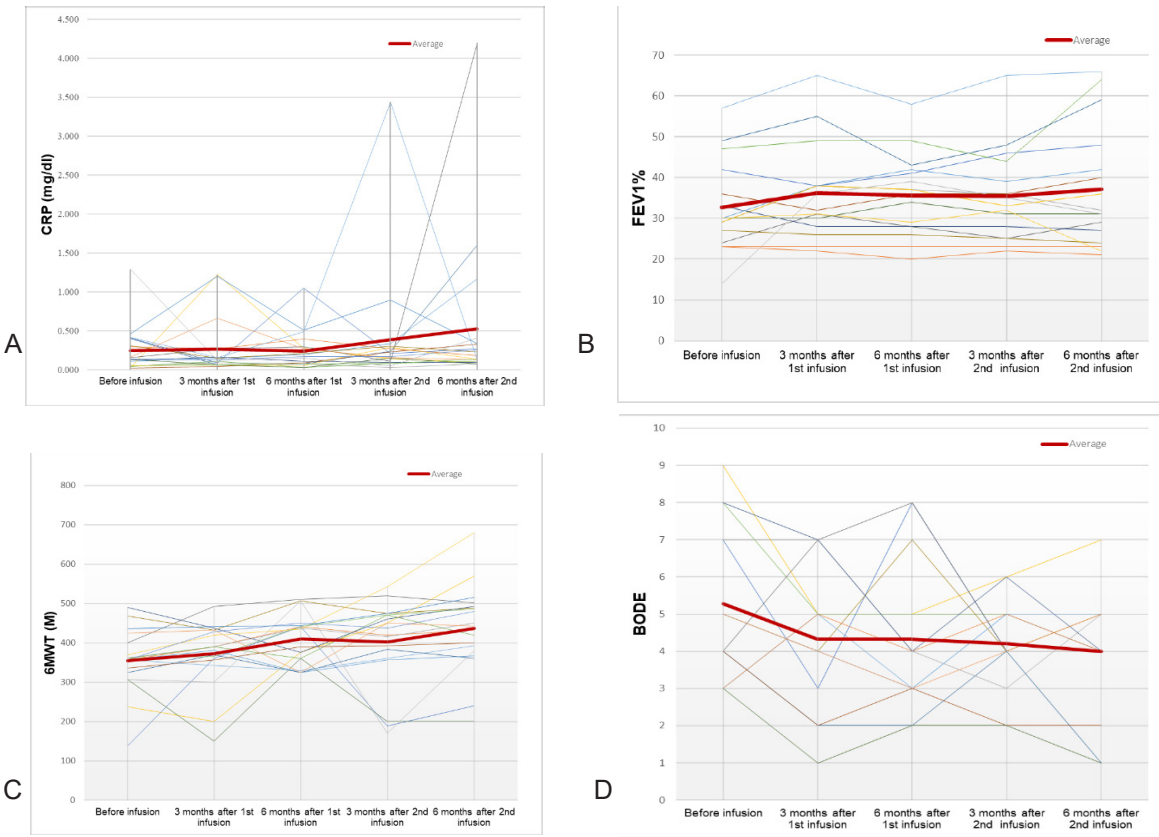

Figure 3. Changing trend in clinical and paraclinical data before and after stem cell infusion, measured every 3 months.

A: CRP (n = 19), B: FEV1% (n = 16), C: 6MWT (n = 19), D: BODE index (n = 15)

Figure 3 expresses changes in clinical and paraclinical indexes of COPD patients after 2 stem cells infusion. FEV1, 6MWT and BODE showed significant improvements after 12 months of follow-up ($p < 0.05$). There was no significant change in CRP.

IV. DISCUSSION

COPD has been a huge burden for the patients, their families and society. Despite the continuous researches of new medicine to treat COPD, the effects are still limited. The results from our research showed that bone marrow derived stem cell therapy can help increase lung function, exertion, prognosis of COPD patients. In recent years, several researches on stem cell therapy for chronic lung diseases have been conducted on animal models and human, using stem cells from bone marrow and adipose tissue.[10] But until now, 3 clinical trials of COPD patients had been completed and published.[11-13] Among those, 1 trial used allogeneic BM-MSCs, the other two used autologous BM-derived stem cells. In Vietnam, 1 latest research has just been published, using umbilical cord MSCs.[14]

In our study, all 25 patients were male, average age of 64.9, with severe and very severe airway obstruction. Similar to researches from Weiss et al (2013),[11] Stolk et al (2016),

[12] Ribeiro-Paes et al (2011) [13] or Le Thi Bich Phuong et al (2020),[14] the majority of COPD patients were old, with moderate to very severe COPD. Stem cells therapy is a new treatment with many potential risks,[10] therefore COPD patients with fewer symptoms do not want to take this treatment out of fear for risks that might occur while undergoing stem cell therapy.

To evaluate clinical efficiency, symptoms such as cough, breathlessness, chest tightness, sputum, etc. were quantified by CAT and mMRC score, with exertion measured by 6MWT. We observed that at the 6-month mark after the first stem cell infusion, both CAT, mMRC and 6MWT had no significant improvements. But at the 6-month mark after the 2nd infusion, 6MWT achieved a significant change. CAT and mMRC had no statistically significant improvement. Similarly, BODE index that indicated the prognosis of COPD patients did not have significant improvement 6 months after the first infusion, but 6 months after the second infusion it was reduced significantly. This could be said to be a positive sign indicating the potential of bone marrow derived stem cell therapy to treat COPD. In addition, while stem cells were administrated intravenously, they could affect other organs in the body, leading to overall efficiency. This could guide future researches. When comparing to 3 other bone marrow derived stem cell therapy for COPD patients, the authors did not conclude anything about the changes in clinical symptoms, and the limitations of those were small sample size (4, 7, 32 patients perspectively).[11-13] However, in a recent research of Le Thi Bich Phuong et al with 20 COPD patients treated with umbilical cord stem cells, the symptoms improved significantly after 6 months with mMRC from 1 to 0, CAT from 10.5 to 2.0 ($p < 0.05$). However, the baseline symptoms in our research were much more severe with percentage of patients having mMRC > 2 taking up 68% and the average CAT of 22.1. Also, the different sources of stem cells could relate to their different characteristics.[15]

To evaluate the difference of lung function before and after stem cell therapy, the pulmonary function test of patients showed positive signs as FEV1 increased from 34.8% before infusion to 37% 3 months after the 1st infusion and to 37.2% 6 months after the 2nd infusion ($p < 0.05$). This result was similar to Ribeiro-Paes's research on 4 patients, which showed increase in FEV1 at the 1-month and 3-month mark after treatment.[13] On the contrary, researches from Weiss and Le Thi Bich Phuong showed no improvement of FEV1 compared to before the stem cells infusion.[11,14]

In our research, CRP before and after stem cells infusion had no statistically significant change ($p < 0.05$). Meanwhile Weiss et al reported improvements to CRP 1 month after stem cells infusion, while at other follow-up there were no clear conclusions. Also, the 2 other researches using BM stem cells did not conclude about changing in inflammatory markers.[11-13] Le Thi Bich Phuong reported no significant changes to CRP 6 months after stem cells infusion from umbilical cord blood in COPD patients both at GOLD C and GOLD D.[14]

Health related quality of life of patients was judged by the SGRQ scale, higher score indicated a poorer quality of life. There was no significant improvement in SGRQ. Research from Ribeiro-Paes in 2011 on 4 patients reported improved quality of life among patients.[13] However, the number of patients were too small to represent for one therapy.

Until now, our research was just a very first step of researching about stem cell therapy, with limited sample and follow-up time, it showed

improvement in the clinical aspect of COPD outcome, but we continue our researching to prove if the effect of this therapy can last for a long time. It would take a longer follow-up to conclude about the effects and the adverse effects of this therapy, to be sure if it can be applied in clinical practice widely.

V. CONCLUSION

Bone-marrow derived stem cell therapy as a treatment of COPD initially showed an increase in patients' exertion, lung function and BODE index. Even though the sample size was limited, the results of this research are the first step for continous research, open up new directions to find and optimize new treatment options for patients with COPD.

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