The effect of Selenium supplementation versus N-acetylcysteine on clinical outcomes of patients with Idiopathic Pulmonary Fibrosis.

A Thesis for the Fulfillment of Master Degree in Pharmaceutical sciences

"Clinical Pharmacy"

By

Nada Hazem Abdelrehem Mohammed Farrag

BSc. in Pharmaceutical Sciences, Faculty of Pharmacy,
Misr International University

Supervised by

Dr/Ahmed Mahmoud Abdelhafeez

Assistant Professor of Chest Disease,

Faculty of Medicine, Cairo University

Dr/ Lamia Mohammed Elwakeel

Assistant Professor of Clinical Pharmacy,

Faculty of Pharmacy, Ain Shams University

Dr/ Mona Farag Schaalan

Assistant Professor of Biochemistry and Acting Head of Clinical Pharmacy and Pharmacy Practice Department

Faculty of Pharmacy, Misr International University

Faculty of Pharmacy

Ain Shams University

2015

تأثيراعطاء السيلينيوم مقارنة بالاسيتيل سيستين على المردود الاكلينيكي لمرضى التليف الرئوي مجهول السبب

رسالة

توطئة للحصول على درجة الماجيستير فى العلوم الصيدلية (الصيدلة الاكلينيكية)

مقدم من

الصيدلانية / ندى حازم عبدالرحيم محمد فراج

بكالوريوس فى العلوم الصيدلية

كلية الصيدلة – جامعة مصر الدولية

تحت إشراف

د/ أحمد محمود عبدالحفيظ

أستاذ مساعد أمراض الصدر

كلية الطب – جامعة القاهرة

د/ لمياء محمد الوكيل

أستاذ مساعد الصيدلة الأكلينيكية

كلية الصيدلة - جامعة عين شمس

د/منى فرج شعلان

أستاذ مساعد الكيمياء الحيوية والقائم باعمال رئيس قسم الصيدلة الأكلينيكية

كلية الصيدلة - جامعة مصر الدولية

كلية الصيدلة

جامعة عين شمس

2015

Acknowledgments

In the Name of Allah, the most Gracious the most Merciful

Thanks to God, all praise to Allah for the strength and his blessing in completing this thesis

Special appreciation goes to my supervisor Dr. Lamia El Wakeel, Assistant Professor of Clinical Pharmacy, Ain Shams University for her continuous support. Her constructive comments, attention to details and suggestions throughout the practical and thesis work have contributed to the success of this research.

I would like to express my deepest gratitude to Dr. Ahmed AbdelHafeez, Assistant Professor of Chest Disease, faculty of Medicine, Cairo University, for his continuous support, technical assistance in the hospital and medical knowledge regarding this topic.

I also would like to express my deepest gratitude to Dr. Mona Schalaan, Assistant professor of biochemistry and acting head of Clinical Pharmacy and Pharmacy Practice Department, MIU, for her continuous encouragement, creativity, constant support and details oriented suggestions throughout the thesis work.

I also would like to thank Dr. Samah Selim lecturer of Chest Disease, faculty of Medicine, Cairo University for her continuous help during conducting the practical part of this thesis

Sincere thanks and deepest gratitude goes to the world's best parents, brother and grandmother for their endless love, prayers, help and continuous encouragement and support.

Sincere thanks to El Kasr Ainy Chest Hospitals for allowing me to complete my practical part of the thesis within their premises

My deepest love and thanks for my family, friends and colleagues for their kindness and support the past years

List of Tables

List of Figures

List of Abbreviations

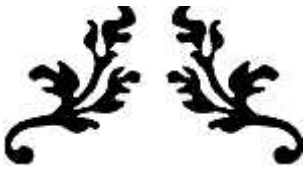
6MWT	six minute walk test
ABGs	arterial blood gases analysis
AEC	alveolar epithelial cells
ALAT	Latin- America Thoracic Society
ALT	alanine aminotransferase
AP-1	activator protein 1
ARE	antioxidant response element
ASCEND	assessment of pirfenidone to confirm efficacy and safety in idiopathic pulmonary fibrosis
AST	aspartate aminotransferase
ATS	American Thoracic Society
BAL	bronchoalveolar lavage
BUN	blood urea nitrogen
CAD	coronary artery disease
COPD	chronic obstructive pulmonary disease
Cu/zn SOD	copper/zinc superoxide dismutase
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
EC SOD	extracellular superoxide dismutase
ECM	extracellular matrix
ELF	epithelial lining fluid
ELISA	enzyme-linked immunosorbent assay
ERS	European Respiratory Society
FEF25-75%	forced mid -expiratory flow
FEV1%	forced expiratory volume in 1st second
FVC%	forced vital capacity
GER	gastroesophageal reflux
Gpx/GSH-Px	glutathione peroxidase
GR	glutathione reductase
GSH	reduced glutathione
GS-Se-Sg	selenodiglutathione
GSSG	oxidized glutathione
GS-she	glutathione selenopersilfide
H_2O_2	hydrogen peroxide
H_2Se	hydrogen selenide
HOCL	hypochlorous acid
HP	hypersensitivity pneumonitis
HRCT	high resolution computed tomography
IFIGENIA	idiopathic pulmonary fibrosis international group exploring N-acetylcysteine I annual
IGFBP-3	insulin growth factor binding protein-3
IIP	idiopathic interstitial pneumonias
IL	interleukin

List of Abbreviations

ILD	interstitial lung disease
INPULSIS-1	safety and efficacy of BIBF 1120 at high dose in idiopathic pulmonary fibrosis patients
INPULSIS-2	safety and efficacy of BIBF 1120 at high dose in idiopathic pulmonary fibrosis patients II
INR	international normalization ratio
IPF	idiopathic pulmonary fibrosis
IPFnet	Idiopathic Pulmonary Fibrosis Clinical Research Network
JRS	Japanese Respiratory Society
K	potassium
kPa	kilopascal
LAP	latency association protein
MDD	multidisciplinary discussion
Mm Hg	millimeter mercury
MMP 1	matrix metalloproteinase 1
MMP 7	matrix metalloproteinase 7
MMPs	matrix metalloproteinases
Mn SOD	manganese superoxide dismutase
MPO	myeloperoxidase
MT-MMPs	membrane type matrix metaloprotienase
MUC5AC	mucin gene 5AC
Na	sodium
NAC	N-acetylcysteine
NADPH oxidase	nicotinamide adenine dinucleotide phosphate-oxidase
Nalp3	nacht domain-, leucine-rich repeat-, and PYD-containing protein 3
NFκB	nuclear factor- kappa B
NO	nitric oxide
NOS	nitrogen oxide synthase
NOXs	mono nitrogen oxides
Nrf2	nuclear factor-erythroid 2-related factor 2
OH	hydroxyl radical
OTC	over the counter
$PaCO_2$	partial pressure of arterial carbon dioxide
PANTHER-IPF	prednisone, azathioprine, and *N*-acetylcysteine: a study that evaluates response in idiopathic pulmonary fibrosis
PaO_2	partial pressure of arterial oxygen
PH	acidity
PUFA	polyunsaturated fatty acids
RAs	retinoic acids
RNS	reactive nitrogen species
ROO	peroxy
ROS	reactive oxygen species
SaO_2	arterial blood oxygen saturation
SCr	serum creatinine
Se	selenium

List of Abbreviations

Sec	selenocysteine
SHH	sonic hedgehog
SLB	surgical lung biopsy
SMA	smooth muscle actin
SOD	superoxide dismutase
Sp-1	specify protein 1
SPSS	statistical package for social sciences
SST	serum separation tube
TBB	transbronchial lung biopsy
TGFβ	transforming growth factor β
TIMPS	tissue inhibitor of metalloprotienases
TNF a	tumor necrosis factor a
UIP	usual interstitial pneumonia
WHO	World Health Organization



ABSTRACT

Abstract:

Objectives: To evaluate the impact of selenium supplementation on oxidative stress and clinical outcome of IPF patients and to assess selenium efficacy, safety and tolerability in addition to conventional therapy in IPF patients.

Patients and methods: A prospective, randomized, controlled study conducted at the Chest Department Kasr El-Ainy, Cairo, Egypt. The study included forty clinically and radiologically diagnosed cases of IPF and twenty healthy controls. Eligible IPF patients were randomized to either, Group 1 (Control); 20 IPF patients received N-acetyl cysteine 600 mg/3 times + Prednisone 0.5 mg/Kg/day, or Group 2 (Test); 20 IPF patients received Selenium 200 mcg/day + Prednisone 0.5 mg/Kg/day, both for 6 months. Assessment of MMP, GPx, 6-minute walk test, and spirometry was performed for both groups at baseline, 3 and 6 months.

Results: The 2 groups were comparable at baseline with significantly lower GPx levels and higher MMP7 levels versus healthy. After 6 months of selenium supplementation, the test group showed a significant increase in GPx, PO_2 and SaO_2 levels versus control. MMP7 levels significantly decreased in test versus control at 3 and 6 months intervals ($p=0.004$, $p<0.001$, respectively). Spirometric parameters (FEV1, FVC, and FEF 25-75%), 6MWT and Borg scale significantly increased in test group versus control. No remarkable side effects or drug interactions were observed in both groups.

Conclusion

The administration of 200µg selenium to IPF patients for six months was accompanied by an improvement in lung functions, pulmonary oxygenation, exercise tolerance and oxidative stress and a decrease in MMP7 levels versus control. Selenium was tolerable with no significant side effects or drug interaction occurrence during the 6-month treatment regimen.

Key Words: Idiopathic Pulmonary fibrosis; Selenium; Spirometry, oxidative stress, MMP7.

INTRODUCTION

Idiopathic pulmonary fibrosis is a rare disease and recent epidemiologic studies suggest an increasing incidence. The mean survival rate is 3-5 years and it's worse than many types of cancer ***(Flynn & Kass, 2015)***. IPF presents with a chronic and progressive scarring of the lung parenchyma characterized histologically by the usual interstitial pneumonia (UIP) pattern. It is a disease that is limited to the lungs and lacks a well-defined etiology ***(Flynn & Kass, 2015)***. IPF has a poor prognosis, occurring primarily in older male adults. The clinical course of individual patients varies from slow to rapid progression. Unpredicted acute exacerbation that develops in some patients is often fatal ***(Matsuzawa et al., 2015).*** Typical clinical presentation of IPF is, unexplained exertional dyspnea, cough, bibasilar respiratory crackles and finger clubbing ***(Raghu et al., 2011).***

It has been long believed that pulmonary fibrosis begins with alveolar inflammation and that chronic inflammation modulates fibrogensis ***(Matsuzawa et al., 2015)***. But, therapeutic studies that target inflammation failed to show clinical benefit and other association between inflammatory cells and disease progression ***(Kliment & Oury, 2010).*** It has been found that oxidative stress is increased in IPF and is involved in its pathogenesis. It was found that cells in the bronchoalveolar lavage fluid (BALF) produced oxidants and myeloperoxidase at higher concentration in IPF patients than in control patients. In addition to increased peroxidase activity that was involved in the epithelial injury in IPF. Moreover, an increased free radicals activity that lead to