Effect of Statin therapy on Erythropoietin Response in Prevelant Haemodialysis Patients

Thesis

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Submitted for Partial Fulfillment of
Master Degree ***in Internal Medicine***

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2012


بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ
أَنتَ الْعَلِيمُ الْحَكِيمُ
صدق الله العظيم
سورة البقرة آية (٣٢)

First and foremost, thanks to ***Allah*** *for giving me the will and the patience to finish this work.*
First and foremost, I'd like to thank Allah, the most kind and the most merciful.

I would like to express my sincere gratitude to ***Prof. Dr. Khaled Hussien Abo Seif*** *Professor of Internal Medicine and nephrology Faculty of Medicine, Ain Shams University ,for his kind supervision and guidance. It's great honor to work under his supervision.*

My heartiest thanks to ***Dr. Aber Halimbaki*** *Lecturer of Internal Medicine and nephrology, Faculty of Medicine, Ain Shams University, whose encouragement, expert guidance and support from the initial to the final level of this work.*

My deepest gratitude and my sincere thanks to ***Dr. Ahmed Shaaban Serag El Deen*** *Lecturer of Internal Medicine and nephrology Faculty of Medicine, Ain Shams University, for his kind supervision and support to end this work.*

I would like to thank all the Staff Members of internal medicine and nephrology department inmaadimilitirian hospital, and all those who helped me and facilitated the whole procedures to accomplish this work.

Finally, an honorable mention goes to ***my family*** *for their support to complete this project.*

Samer Magdy Hassan Aly

Contents

List of Abbreviations

ACAT	:	Acyl-CoA cholesterol acyltransferase
ACE-I	:	Angiotensin converting enzyme inhibitors
AIDS	:	Acquired Immunodeficiency Syndrome
AIHA	:	Autoimmune hemolytic anemi Apolipoprotein
APOA	:	A Apolipoprotein A
APOB	:	A Apolipoprotein B
ARBs	:	Angiotensin receptor blockers
BFU-E	:	burst forming units erythroid
CHr	:	Content of Hb in reticulocytes
CFU-E	:	Colony-forming units-erythroid
CKD	:	Chronic kidney disease
CRF	:	Chronic renal failure
CRP	:	C-reactive protein
CVD	:	Cardiovascular disease
CYP3A4	:	Cytochrome P450 3A4
DPO	:	Darbepoetinalfa
eNOS	:	Endothelial nitric oxide synthase
EPO	:	Erythropoietin
ESAs	:	erythropoiesis stimulating rate
ESR	:	Erythrocyte sedimentation rate
ESRD	:	End stage tenal disease
FPP	:	Farnesyl pyrophosphate
GFR	:	Glomerular filtration rate
GATA2	:	GATA binding protein 2
GGPP	:	Geranylgeranyl pyrophosphate
GTPases	:	Guanosinetriphosphatases
Hb	:	Hemoglobin
Hct	:	Hematocrite
HD	:	Hemodialysis
HDL	:	High-density lipoprotein

HF	:	Heart failure
HMG-CoA	:	3-Hydroxyl-3-methylglutaryl coenzyme A
ICAM-1	:	Intercellular Adhesion Molecule 1
IL	:	Iinterleukins
LCAT	:	Lecithin-cholesterol acyltransferase
LDL	:	Low-density lipoprotein
LMW	:	Low molecular weight
LVH	:	left ventricular hypertrophy
MCP-1	:	Monocyte chemotactic protein-1
NKF	:	National kidney foundation
NFκB	:	Nuclear factor kappa B
PTH	:	Parathyroid hormone
QOL	:	Quality of life
RAS	:	Renin angiotensin system
RHUPO	:	Recombinant human erythropoietin
TIBC	:	Total iron binding capacity
TGS	:	Ttriglyserides
TSAT	:	Transferrin saturation
TGFβ	:	Transforming growth factor β
TNFβ	:	Tumor necrosis factor β
SLE	:	Systemic lupus erythromatosis
VCAM-1	:	vascular cell adhesion molecule 1
VLDL	:	Very Low-density lipoprotein

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Introduction

Anaemia of end-stage renal disease patients has been effectively treated with erythropoietin (EPO). EPO therapy reduced the need for blood transfusions and improved the quality of life in maintenance haemodialysis (HD) patients**.** ***(NFK 2001),*** EPO responsiveness in patients with chronic renal failure depends on the dose, the route and the frequency of administration ***(Eschbachjw 2002)***.

Factors that contribute to EPO hyporesponsiveness include iron deficiency, infections, inadequate dialysis, chronic blood loss, hyperparathyroidism, aluminum toxicity, malnutrition, vitamin deficiency, malignancy and others ***(Drueke T 2002).***

Drugs (including angiotensin converting enzyme inhibitors or angiotensin II receptor blockers)have been identified as contributory factors to EPO resistance**(raoDS,et al 2003)**. Inflammation has also been reported as a factor contributing to EPO hyporesponsiveness ***(Gunell G, et al. 1999).***

C-reactive protein (CRP), an acute phase protein, is the most well-investigated representative marker of inflammation in the general population and in chronic kidney disease (CKD) patients ***(Yeun JY, et al. 2000)*** CRP predicts the risk of cardiovascular evevts and may play arole in the atherosclerotic process in general population ***(Koenig W Loelh, Baumert 2004).*** CRP also predict mortality in HD patients, and high

levels of CRP have been associated with resistance to EPO therapy in HD patients, possibly by indicating the presence of some micro inflammation ***(Locatelli F, et al. 2006).***

The prevalence of dyslipidemia in end-stage renal disease is greater than that in the general population ***(Kasiske BL, et al. 2002).*** Lipid abnormalities may result in atherosclerotic vascular disease and statin therapy could lower the risk of cardiovascular events by reducing plasma cholesterol and triglycerides both in general population and HD patients ***(Seliger SL, et al 2002).*** Moreover, statins seem to exert other pleiotropic effects on inflammation, the immune system and thrombosis ***(DavignonJ, et al. 2004).***

Statins may reduce CRP levels in the general population patients.***(Vernaglione Let al.2004)***. It has also been suggested that statins by reducing CRP levels have a positive impact on EPO responsiveness ***(Dornbrook-Lavender KA, et al 2005)***.

Aim of the Study

Evaluate the effect of statin therapy on Erythropoietin responsiveness in prevalent Haemodialysis patients.

Chapter I

Anemia in CKD and Role of Erythropoietin

Anemia of CKD is one of the first signs of kidney dysfunction, yet it often goes undetected because of its insidious onset. Anemia develops gradually as kidney function declines and the GFR drops to 70 ml/min in male patients and 50 ml/min in females. Epidemiologic data indicate that two-thirds of patients in the early stages of kidney failure are also anemic, with a hemoglobin level of less than 11 g/dl, yet only one-third of these patients have ever received erythropoietin stimulating agents (ESAs) to treat their anemia ***(Taliercio, 2010)***.

Definition of Anemia:-

Anemia is defined as a decrease in the number of circulating red blood cells (RBCs), a reduction in the amount of Hb in the RBCs, or a combination of both. Although there are natural variations in laboratory values, and Hb varies by age and gender, the average normal ranges of Hb in adult men and women are as follows: 14 to 18 g/dl in males, and 12 to 16 g/dl in females ***(Basile, 2007)***.

Anemia in CKD, as defined by The National Kidney Foundation (NKF), is hemoglobin (Hb) concentration < 12 g/dl for women and < 13.5 g/dl for men. Conversely, the European Best Practices Guidelines for the Management of

Anemia in Patients with Chronic Renal Failure defines anemia according to age and sex. Anemia is defined as an Hb concentration of < 11.5 g/dl in women, < 13.5 g/dl in men ≤ 70 years of age, and < 12 g/dl in men > 70 years of age ***(O'Mara, 2008)***.

Prevalence of Anemia:-

Anemia is very common in patients with chronic kidney disease and probably causes many of its symptoms. Physicians should start thinking about anemia when their patient's glomerular filtration rate (GFR) declines to 60 mL/minute/1.73 m^2 or less. In the third National Health and Nutrition Examination Survey, the prevalence of anemia in stage 3 chronic kidney disease (ie, a GFR of 30 to 59 ml/ minute/1.73 m^2) was 5.2%, rising to 44.1% in stage 4, and becoming almost universal in stage 5. African Americans and patients with diabetes have even higher rates of anemia at each stage of kidney disease ***(Nurko, 2006)***.

How kidney failure leads to anemia?

Insufficient erythropoietin production is the primary cause of anemia in patients with CKD. Various secondary causes can contribute to anemia, including a deficiency of iron, folate, or vitamin B12, gastrointestinal bleeding, severe hyperparathyroidism, inflammatory conditions and shortened red blood cell survival due to uremia. Deficiencies of folate and vitamin B12 cause macrocytic anemia. Elevated parathyroid hormone concentrations and acute and chronic