Thrombin Activatable Fibrinolysis Inhibitor in Thrombotic Complications of Systemic Lupus Erythematosus

Thesis

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SUMMARY AND CONCLUSION

Systemic lupus erythematosus is a chronic multisystem autoimmune disease with a broad range of clinical manifestations. The prevalence of vascular events in SLE patients ranges between 10% and 30%, for symptomatic coronary artery disease 6–20%, stroke 2–15%, and subclinical coronary artery disease 30–40%.

Thrombin activatable fibrinolysis inhibitor (TAFI) has an antifibrinolytic action by removal of the C-terminal lysine residues of fibrin,which acts as template onto which both tPA and plasminogen bind thereby enhancing the catalytic efficiency of plasmin formation. , further enhances plasmin formation and is a better substrate for tPA. Elevated TAFI levels in plasma are correlated with an elevated risk for venous thrombosis.

Also it has anti-inflammatory action through removal of C-terminal arginines so it inactivates several inflammatory mediators, including bradykinin, the anaphylotoxins C3a and C5a, and osteopontin . The inhibition of plasmin generation is also part of the anti-inflammatory activity of TAFI.

The present study aimed to assess plasma concentrations of TAFI and its association to different

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Jackline Samir Kamal Fahim

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List of Abbreviations

Abbrev.	Full term
ACA	Anticardiolipin antibody.
ACR	American College of Rheumatology.
ADP	Adinosine diphosphate.
Ag	Antigen.
AI	Autoimmune .
ANA	Antinuclear antibody.
Anti- SSA	Anti Sjogren syndrome antibody.
Anti-sm	Anti smooth musle.
Anti-TPO	Anti thrombopoietin.
AP	Antiplasmin.
APC	Activated Protein C.
APC	Antigen presenting cell.
APL	Acute promyelocytic leukemia
aPL	Antiphospholipid antibody.
APLS	Antiphopholipid antibody syndrome.
APS	Antiphospholipid sundrome.
AT	Antithrombin.
CABG	Coronary Artery Bypass Grafting.
CAD	Coronary artery disease.
CD	Cluster of differentiation.
C-lys	C- terminal lysine.
CPN	Carboxypeptidase N.
CR	Complement receptor.
DM	Diabetes mellitus.
DNA	Deoxyribo nucleic acid.
ds-DNA	Double strand- Deoxyribo nucleic acid.
DVT	Deep Venous Thrombosis.
ECG	Electrocardiograph.

List of Abbreviations (Cont'd)

Abbrev.	Full term
ECs	Endothelial cells.
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme linked immunosorband assay
EPCR	Endothelial Protein C Receptor.
F	Factor
Fc	Fragment crystallizable.
GEMSA	Guanidino ethylmercaptosuccinic acid.
GPI	Glycoprotein I.
HLA	Human leucocytic antigen.
IBD	Infilammatory bowel disease.
IS	Ischaemic stroke
KD	Kilodalton.
LAC	Lupus anticoagulant.
MAU	Microalbuminuria.
MERGEPTA	2-Mercaptomethyl-3-guanidinoethyl-thiopropanoic acid
MI	Myocardial infarction.
MMP	Matrix metallopeptidase
MPD	Myeloproliferative disorders.
MRI	Magnetic resonanace imaging.
NAU	Normal albuminuria.
OPN	Osteopontin.
P CPB	Pancreatic carboxypeptidase B.
PAI	Plasminogen Activator Inhibitor.
PAR	Protease Activated Receptor.
PC	Protein C
PCR	Polymerase chain reaction.
PL	Phospholipid
PNH	Paroxysmal nocturnal heamoglobinuria.

List of Abbreviations (Cont'd)

Abbrev.	Full term
PS	Protein S.
QOL	Quality of life
RBC	Red blood cell.
RNA	Ribonucleic acid.
RNP	Ribonucleoprotein.
ROC	Receiver-operating characteristic
RT	Reverse transcriptase
SLP	Systemic Lupus Erythematosus.
TAFI	Thrombin Activatable Fibrinolysis Inhibitor.
TF	Tissue Factor.
TFPI	Tissue Factor Pathway Inhibitor.
TH	T helper
TM	Thrombomodulin.
T-PA	Tissue Plasminogen Activator.
TRAP	Thrombin receptor activating peptide.
TTM	Thrombin thrombomodulin complex.
U-PA	Urokinase.
VTED	Venous thromboembolic disease.
vWF	von Willebrand Factor.
ZPI	Protein Z dependent protease inhibitor.

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a systemic illness of autoimmune etiology characterized by either acute or chronic inflammation of multiple organs ***(Bernatsky et al., 2007).*** It has also a kind of a vasculitis associated with a thromboembolic tendency. Accelerated atherosclerosis and early coronary artery disease are important causes of death and hospitalisation in SLE patients nowadays ***(Manger et al., 2003).***

In epidemiological studies, the risk of acute myocardial infarction (AMI) was 2.67 to 10 times higher among patients with SLE than the general population. Some studies combined AMI with other vascular diseases such as stroke or peripheral arterial disease ***(Avolas et al., 2008).***

Fibrinolysis is an essential step of the haemostatic process for it leads to the removal of the haemostatic plug once the vascular lesion has been repaired. Moreover, along with the physiological inhibitors of coagulation, it contributes to maintaining vessel patency by preventing the pathological accumulation of fibrin ***(Heylen et al., 2011).***

A key event of fibrinolysis is the binding of plasminogen and its activator (t-PA) to the fibrin surface, which occurs through the recognition of C-terminal lysines on partially degraded fibrin. The colocalization of the

fibrinolytic enzymes on the fibrin surface is necessary to activate plasminogen, to protect t-PA and plasmin from their respective inhibitors, and to confine the proteolytic activity of plasmin ***(Colucci and Semeraro, 2011).***

Thrombin Activatable Fibrinolysis Inhibitor-(TAFI), also called procarboxypeptidase B or carboxypeptidase U and carboxypeptidase R, is formed in the liver as a unichain glycoprotein of molecular weight of 60000 Da and circulates in the blood in the form of zymogene (pro-TAFI) ***(Waldemar et al., 2007).***

It plays an important role in the delicate hemostasis balance between coagulation and fibrinolysis. TAFI is converted to an active carboxypeptidase (TAFIa) by thrombin, plasmin, trypsin, and more efficiently the thrombin-thrombomodulin complex. Activated TAFI inhibits fibrinolysis by removing carboxy-terminal lysine residues that appear during proteolysis of the fibrin polymers during the process of clot lysis. These residues are important for binding and activating plasminogen. Thus, TAFI leads to a potent inhibition of tissue plasminogen activator–induced fibrinolysis ***(Emile et al., 2011).***

Therefore it is clear that plasma TAFI levels are major determinants of clot lysis because of the down regulation of plasminogen activation and fibrinolysis ***(Vercauteren et al., 2010).***

AIM Of THE WORK

To study the clinical utility of thrombin activatable fibrinolysis inhibitor as an indicator of thrombotic complications in patients with Systemic Lupus Erythematosus.

OVERVIEW OF HAEMOSTASIS

Haemostasis is a physiological mechanism that controls blood fluidity and has the potential to rapidly induce haemostatic plug formation at sites of injury in order to stop or limit bleeding ***(Furie, 2009).*** The normal haemostatic response to vascular damage depends on closely linked interaction between the blood vessel wall, circulating platelets and blood coagulation factors (**Figure 1**) ***(Hoffbrand et al., 2011).***

An efficient and rapid mechanism for stopping bleeding from sites of blood vessel injury is clearly essential for survival; however such a response needs to be tightly controlled to prevent extensive clots developing and to break down such clots once damage is repaired. The haemostatic system thus represents a delicate balance between procoagulant and anticoagulant mechanisms allied to a process for fibrinolysis ***(Weisel, 2010 a*****nd** ***Hoffbrand et al., 2011).***

A. Phases of Haemostatic Process

There are three distinct phases of the haemostatic process **(primary haemostasis, coagulation and fibrinolysis)** which are closely linked to each other and are strictly regulated in order to efficiently close vessel wounds and promote vascular healing ***(Segers et al., 2007).***

1. Primary Haemostasis

Primary haemostasis is initiated by the adhesion of platelets to collagen fibers underlying the vascular endothelium, which have become exposed following vascular injury. This adhesion is mediated by a specific platelet collagen receptor (glycoprotein Ia/IIa) and von Willebrand factor (vWF), which forms links, between the platelet and collagen fibers ***(Angiolillo et al., 2010).***

As a result of the interaction with collagen, the platelets are activated and release a number of different coagulation and platelet activating factors, which in turn activate other platelets and white blood cells. The platelets adhere to each other via adhesion receptors (integrins) that bind to the same receptor on adjacent platelets via a central fibrinogen molecular bridge, which results in the formation of a haemostatic platelet plug ***(Varga-Szabo et al., 2008).***

Platelet activation further results in the activation of several phospholipid transporter proteins, which causes the transport of negatively charged phospholipids from the inner to the outer leaflet of the platelet membrane. These negatively charged phospholipids provide a catalytic surface that is crucially important for efficient propagation of the coagulation through binding of several blood coagulation factors ***(Segers et al., 2007).***