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Original Research Paper

General Medicine

ROLE OF ANTI-COAGULANTS IN THROMBOSIS ASSOCIATED WITH SLE

Dr. Akanksha Panchal	3rd year Resident Doctor.
Dr. Hiren Makwana	Assistant Professor.
Dr. Pankaj Patil	Assistant Professor.
Dr. Ashmita Mandal	Second year resident.

ABSTRACT Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by antibodies to nuclear and cytoplasmic antigens, multi-system inflammation, protean clinical manifestations and a relapsing and remitting course. Leading cause of death associated with SLE is due to thrombosis and anticoagulants can be proven major life saving drug but till now etiopathogenesis of SLE is not completely understood so as the treatment. Therefore, in the present review, we will highlight the characteristics and mechanisms of thrombosis and focus on the anticoagulant drugs commonly used in clinical practice, thus, providing a theoretical basis for scientific and reasonable anticoagulant therapy in clinical practice.

KEYWORDS :

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with vasculopathy, as demonstrated by varying clinical presentations ranging from mild mucocutaneous disorders to multi organ involvement in patients. Women of childbearing age are usually vulnerable to this disease. Genetic factors, including polygenic and monogenic factors and genetic interactions with environmental factors, particularly UV light exposure, the Epstein–Barr virus (EBV) infection, hormonal factors, smoking or medications (such as procainamide, hydralazine, quinidine, isoniazid, TNF-α inhibitors and anticonvulsants) are associated with the pathogenesis of SLE. Thromboembolic diseases were responsible for one of every four deaths worldwide in 2010 and are the leading cause of death in patients with SLE. SLE patients have 25-to 50-fold higher incidence of thrombosis than the general population with an incidence of venous or arterial thrombosis exceeding 10%; the incidence rate exceeds 50% in high-risk patients. Men are more likely to experience thrombotic events than women and previous studies have shown that the risk of myocardial infarction is 3-fold higher in men than in women. Thrombosis is one of the most common causes of death in patients with SLE [15]. However, most studies have focused on patients with anti phospholipid syndrome (APS) or high-risk factors, ignoring that SLE itself is an independent risk factor for thrombotic events; moreover, anticoagulation therapy has also been mostly aimed at patients with APS and pregnant patients, and the need for preventive anti- coagulation therapy for patients with SLE has been rarely studied. Therefore, in the present review, we will focus on the causes of thrombosis in SLE and the commonly used anticoagulant drugs in clinical practice.

Thrombosis in SLE

Risk Factors of Thrombosis in SLE

Among varies factors that increase the thrombosis risk in SLE patients, few most important risk factors are mentioned below.

(1) Antiphospholipid Antibodies (APLAs):

Antiphospholipid antibodies (APLAs) bind to plasma proteins with an affinity for phospholipids' surfaces. Most important identified antigens are ß2-glycoprotein and prothrombin which are involved in blood coagulation. Anticardiolipin antibodies (ACA),lupus anticoagulant (LAC) are included in classification criteria, as well as anti-ß2-glycoprotein I (anti-ß2-GPI) which is known to increase thrombosis risk. It appears that about one-third of all patients with LACs have had at least one thrombotic event. Among SLE patient ACA and LAC positivity is associated with thromboembolic event in half of the patients and it's noteworthy that ACA and LAC negative status does not completely rule out risk of thrombosis. For considering patient as APLA positive one must demonstrate two episodes of positivity 12 weeks apart to rule out transient positivity. APLAs are done in SLE as they are criteria for ACR classification as well as associated with risk factor for thrombosis. Not all patients with APLA positive status develops thrombosis which makes use of anticoagulants tricky as prophylaxis therapy.

Several hypotheses have been proposed to explain the pathogenic effects of these autoantibodies and their role in the development of thrombosis. They attach to the negatively charged phospholipid surface that may induce platelet activation, interfere with coagulation inhibitors such as protein-c, inhibit antithrombin and fibrinolysis, and then initiate the formation of a thrombus. It is well established that APLAs are associated with both arterial and venous thrombosis. On one hand APLAs are associated with increased risk for myocardial infarction and stroke while on other hand approximately 40% of patients with thrombosis where tested negative for APLAs which demands to look for other involved pathophysiology of thrombosis in SLE.

2) Effect of inflammation and activity of disease on thrombosis

All three stages of inflammation are affected by inflammation which are initiation, propagation and regulation. inflammation induces the expression of tissue factors which is important step of the initiation of coagulation. The presence of inflammation reduces the fibrinolytic activity through up regulation of the production of plasminogen activator inhibitor (PAI). Further, the anticoagulant effect of the protein C pathway is impaired due to down-regulation of thrombomodulin and a decrease of protein S. Inflammatory cytokines promote endothelial damage, plaque formation and vascular smooth muscle hypertrophy [62].

Pro-inflammatory cytokines which activate endothelial and vascular smooth muscle cells include interleukin 1 (IL-1), interleukin 6 (IL-6), tumor necrosis factor (TNF) and vascular endothelial growth factor (VEGF), all of which are increased in active lupus, particularly lupus nephritis.Inflammation induces thrombosis via endothelial cell dysfunction, tissue factor mediated activation of coagulation, platelet activation, impaired function of anticoagulants and suppressed fibrinolytic activity [55]. These effects all play a role in venous thrombosis in lupus.

(3) Thrombophilic risk factors:
Multiple mechanisms contribute to hyper-coagulability in SLE and thrombosis is due to multiple hits to the clotting system (the multiple-hit theory). elevations of procoagulant factors in combination have an additive effect on thrombosis. In lupus, this includes lupus-specific and non- specific thrombogenic factors. Lupus nonspecific factors contributing to hyper-coagulability in SLE includes hyperhomocysteinemia, and elevated plasminogen activator inhibitor-1 (PAI-1) which decreases fibrinolytic activity, as well as deficiencies of anticoagulant factors such as protein C, protein S and tissue plasminogen activator (tPA)which activates the fibrinolytic system. The plasma homocysteine level is an independent risk factor for atherosclerosis, arterial thrombosis, and possibly, venous thrombosis. Elevated plasma homocysteine levels are attributed to deficiencies of vitamins B12 or B6 or folic acid, chronic renal failure, hypothyroidism, certain malignancies, drugs, and inherited enzyme abnormalities. Hyperhomocysteinemia is detected in around 15% of lupus patients. The prevalence of hyperhomocysteinemia is significantly higher in SLE patients with thrombosis. Raised levels of homocysteine are demonstrated in 27.3% of SLE patients with thrombosis compared to 16.9% in those without thrombosis .Lupus-specific procoagulant factors include antiphospholipid antibodies, antibodies to factor XII , prothrombin and annexin V.

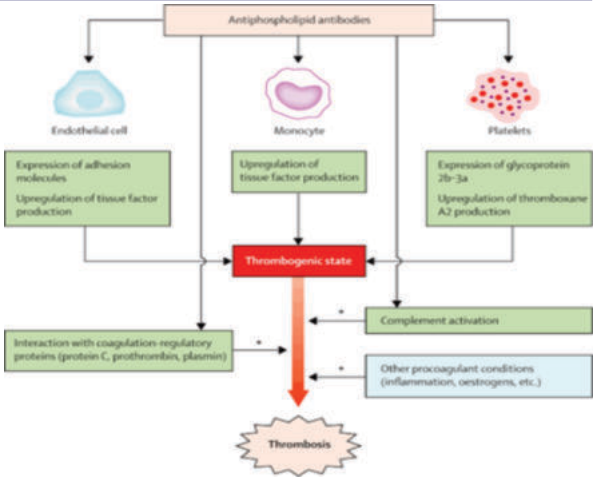
(4) Traditional risk factors:
Smoking is consistently associated with increased risk of developing thrombotic events particularly venous in nature. Smoking is known for inducing endothelial damage, which results in the activation of the endothelium and the initiation of a cascade of events leading to thrombosis. Others are Hypertension, Diabetes mellitus, and dyslipidemia which have been demonstrated to be associated with thrombosis in SLE. Increasing age is also associated with more vascular morbidity and occurrence of thrombotic events.

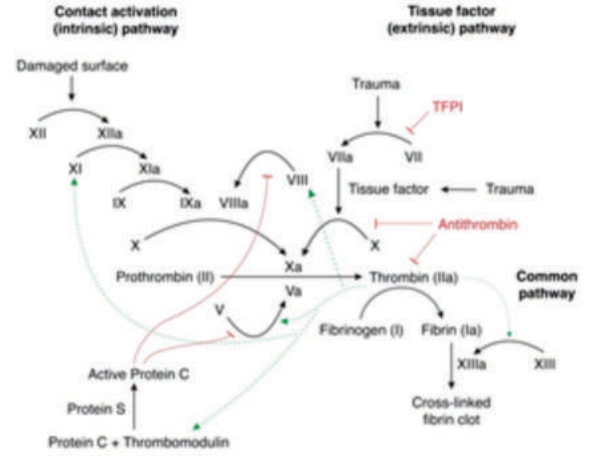
(5) Thrombosis and drugs in SLE
glucocorticoids are commonly used as the first line treatment of lupus because of their strong anti-inflammatory effects and immunosuppressive properties. Glucocorticoid aggravate coagulation abnormalities by releasing coagulation factors, increasing endothelial injury and inhibiting fibrinolysis by increasing levels of clot factor VII, VIII, XI, and PAI-1. They can also aggravate the hyperlipidemia and further contribute to hyper-coagulable state. Therefore it's recommended that during maintenance phase of treatment dose of glucocorticoid should be limited to less than 7.5 mg/day and tapered as early as possible or use of glucocorticoid should be eliminated by using immunomodulatory agents.

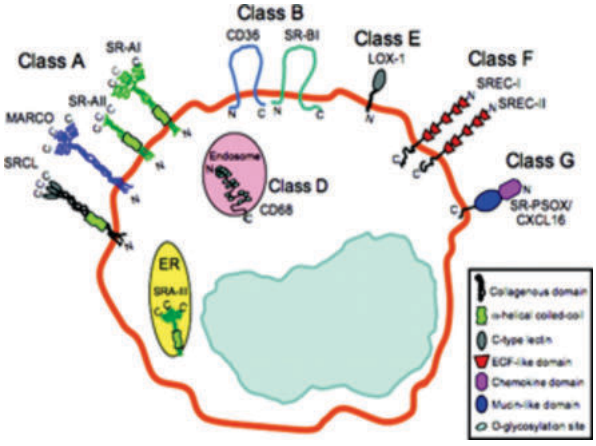
PATHOGENESIS OF THROMBOSIS ASSOCIATED WITH SLE

(1) Anti-Endothelial Cell Antibody(AECA)-Mediated Vascular Endothelial Injury: being a heterogeneous group of antibody AECA acts by binding to antigens through Fab2 region of endothelial cell associated antigenic structures such as heparin like compounds,DNA and DNA-histone complexes, fibronectin, ribosomal proteins, which in turn promotes tissue factor(TF) production leading to vascular damage. ANCA positivity has shown to be strongly associated with renal involvement, pulmonary hypertension, vascular lesions and thrombosis in SLE.

(2) Anti phospholipid Antibody(APLA) Mediated Endothelial Injury:
APLAs can induce the expression and procoagulant activity of TF in monocytes and endothelial cells. Higher level of expression of TF increases the production of activated coagulation factors VII, X, and thrombin which contribute to the development of a hypercoagulable state and an increased risk of thrombosis.



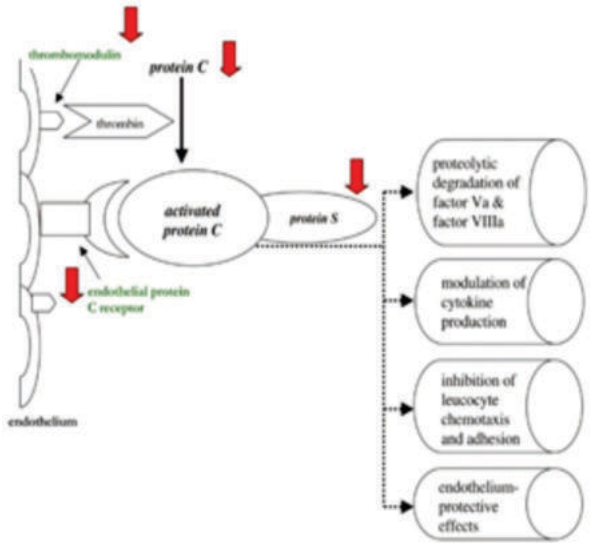




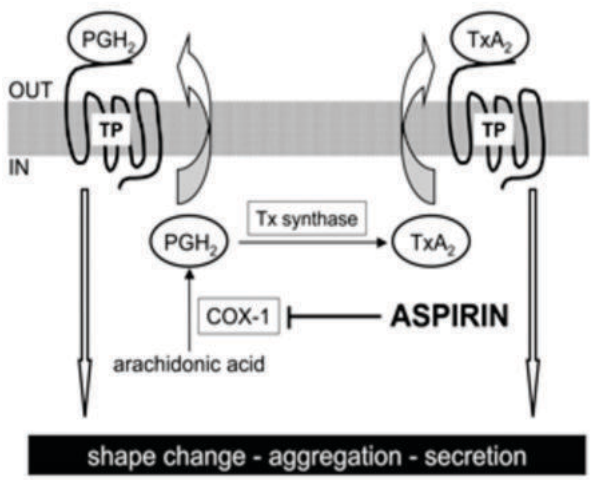
(3) Coagulation System Activation
Endothelial cells are natural barriers which provides no thrombotic environment for platelets and other blood cells to prevent coagulation cascade. The above mentioned autoantibodies damages the endothelial cells leading to activation of coagulation pathways. The initial response to vascular injury is vasoconstriction which in turn slow downs the blood flow which is the first and most important hemodynamic response for subsequent hyper-coagulation process. Furthermore the extrinsic pathway is activated by TF and the intrinsic pathway is activated by collagen underlying the endothelial cell. This collagen acts as a magnet for circulating platelets and attaches with them through GP Ia/IIa surface receptors. von Willebrand factor (vWF) further enhances this connection while activating the platelets. Activated platelets secrete ADP, serotonin, platelet activating factor (PAF), vWF, and thromboxane A2 (TXA2) into plasma which subsequently activates more platelets. Spherical shape

of circulating platelet is changed to stellate shape once activated and through GP IIb/IIIa receptors fibrinogen is cross linked with platelet and which in-turn contributes to aggregation of adjacent platelets. All this processes adds up to platelet aggregation and lead to increased risk for thrombosis.

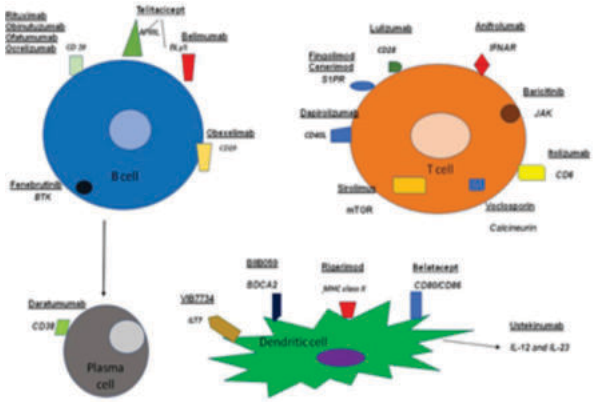
(4)NETs: Being one of the first cytokines to be recruited at the site of endothelial injury, neutrophils are known to cause immune thrombosis by releasing NETs,which are network of chromatin fiber made of histones, anti microbial peptides and oxidising enzymes such as neutrophil elastase and myeloperoxidase. It is observed that in patients with SLE, natural potential of NETs to cause endothelial damage and induction of dendritic cells for production of interferon is enhanced leading to stronger autoimmune response thereby participating in platelets adhesion and fibrin generation.



(5) Macrophage Scavenger Receptors:
Scavenge receptor are superfamily of membrane bound receptors and structurally diverse having seven classes(A-G) according to multi domain structure of individual members. Having wide rang of functions scavenge receptors are mainly involved with antigen presentation, lipid metabolism, phagocytosis and apostolic cell clearance. Current studies have shown that CD36 which is transmembrane glycoprotein of class B SR family has pro-atherogenic properties in pathogenesis of SLE. As oxLDL promotes platelet activation and creates prothrombotic state by Stimulating CD36 on surface of platelets, a novel drug blocking CD36 activity can be an upcoming target for pharmacological intervention.



(6) Protein C Pathway:
Regulation of coagulation and fibrinolysis as well as prevention of thrombosis is mainly a function of natural anticoagulant protein. The pathway includes thrombin, thrombomodulin, endothelial cell protein C receptor (EPCR), protein C, and protein S. Interference of anti phospholipid antibodies (APLAs) with protein C pathway as well as formation of anti-thrombomoduline antibodies are associated with increased risk of thrombosis. Increased protein S clearance in patients with SLE are attributed to formation of antiPS autoantibodies therefore modulation of this pathway can be proven beneficial for treatment strategies.



TREATMENT OPTIONS FOR SLE

Over the past decades, the treatment of SLE has shifted from the use of hydroxychloroquine (HCQ), glucocorticosteroids, and conventional immunosuppressive drugs to biological agents, among which belimumab is the first and only biological agent approved for treating SLE to date and many more are under trial which are depicted in this figure . With application of newer biological agents prognosis of SLE patients has significant improved but on other hand prolongation of survival increases risk of thrombosis. Treatment strategies are focused on controlling active disease with available drugs by weighing benefits over accumulating adverse effect. However if we are considering only anticoagulant treatment strategies we have limited options. So here's some commonly used anticoagulant and their mechanism of action.

(1)Aspirin: aspirin is nonsteroidal drug with antipyretic, anti-inflammatory and analgesic properties. At low doses aspirin produces antithrombotic effect by inhibiting cyclo-oxygenase activity of prostaglandin H synthase-1 (COX-1), which inhibit TXA2 synthesis.

A long-term retrospective cohort study showed the use of low-dose aspirin as the primary pro- phylaxis for cardiovascular events in patients with SLE. Multiple meta-analyses and EULAR recommended that low- dose aspirin reduces the risk of first thrombotic events in asymptomatic aPL individuals, patients with SLE, and pregnant women with APS. Low dose of aspirin also restored the placental hCG secretion which was abolished by aPL in a model of experimental study on mice. Considering all this study it is evident that we should use low dose aspirin as prophylactic therapy unless and until there are contraindications of the same.

(2) Warfarin
By antagonising vitamin K warfarin interferes with production of factor II, VII, IX and X, as well as proteins C and S. Use of warfarin in patients with SLE is less evident but it's commonly used in patients with APS. A prospective multicenter research trial showed that warfarin (1–5 mg/day) started at the same time as a steroid therapy for at least 3 months can prevent the occurrence of osteonecrosis associated with SLE. Monitoring prothrombin time (PT) during warfarin administration is

warranted because of high risk of bleeding. As far as pregnancy and warfarin use is concerned, one should keep in mind that warfarin crosses placenta and exposure of warfarin during 6-12 week of gestation causes fatal warfarin syndrome which is dose dependent and <5 mg daily is associated with lowest risk.

(3) Heparin:
In current practice commonly used heparins are unfractionated and low-molecular weight heparin. Under normal circumstances, antithrombin III (ATIII) inactivates thrombin (factor IIa) and factor Xa. This process occurs at a slow rate. Administered heparin binds reversibly to ATIII and leads to almost instantaneous inactivation of factors IIa and Xa The heparin-ATIII complex can also inactivate factors IX, XI, XII and plasmin. The mechanism of action of heparin is ATIII-dependent. It acts mainly by accelerating the rate of the neutralization of certain activated coagulation factors by antithrombin. Heparin is not a thrombolytic or fibrinolytic. It prevents progression of existing clots by inhibiting further clotting.

Compared to lower molecular weight heparin, unfractionated heparin has a highly variable dose response relationship so we need to monitor aPTT levels frequently. Where as LMWH shows little nonspecific binding to endothelial cells and plasma proteins thereby reducing risk for thrombocytopenia, severe bleeding and osteoporosis which is seen with heparin. Therefore LMWH is known for improving outcomes in pregnant female with SLE. Based on in viva studies it is noted that pro-coagulant effect of aPL are amplified by C3 and C5 activation and heparin appears to prevent aPL-induced pregnancy loss by inhibiting C3 and C5 activation rather than its anticoagulant effect.

(5)HCQ.
Originally being an anti malarial drug HCQ is hydroxylated analog of chloroquine. It has manny proposed mechanism of action including blockage of antigen presentation, reduction in T cell activation, inhibit the production of proinflammatory cytokines and angiogenesis, multiple hematological mechanisms, including reduction in red blood cell sludging, blood viscosity, and platelet aggregation, which may explain its benefit as an antithrombotic agent. A very short outline of pathogenesis of SLE (left) and possible pathways of interference of hydroxychloroquine (right) is depicted in above flow chart. Given that HCQ has been shown to be beneficial in patients with lupus by delaying the onset of damage in general and increasing long-term survival, it is recommended for all patients with lupus but long tern use should be warned of because of serious side effect like retinopathy and which mandate regular assessment for ophthalmological complications.

CONCLUSION

In conclusion, majority of patients with SLE are likely to have thrombotic event and current management of anticoagulation relies on opinion of experts because of lack of solid evidence from trials. As long as HCQ is concerned, taking consideration of its broad spectrum beneficial effect it is recommended for all lupus patients, So as the low dose aspirin. In future more evidence based studies are needed to weigh the risk benefit and outcome considerations of overall prophylaxis strategy.

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