Review

Rheumatoid arthritis and thrombosis

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Received on November 18, 2008; accepted in revised form on January 29, 2009.

Clin Exp Rheumatol 2009; 27: 846-855.

Key words: Rheumatoid arthritis, thrombosis, risk factors.

Competing interests: none declared.

ABSTRACT

Objective. *To review prevalence, risk factors and mechanisms of thrombosis in rheumatoid arthritis (RA).*

Methods. *Available medical literature on PubMed was reviewed and relevant information summarized.*

Results. *Patients affected by RA present an increased risk of thromboembolism, an important cause of morbidity and mortality. Research is focused on the role of disease-associated risk factors and predisposing conditions such as endothelial dysfunction, hypercoagulability, pro-thrombotic conditions, inflammatory markers, immobility and complications following major knee or hip replacement.*

Conclusions. *Thrombosis is a possible manifestation in RA patients. A number of factors are suspected to play a role in the increased thromboembolic risk. The mechanisms responsible for thrombosis in these patients remain unclear, however, the identification of the thrombophilic risk factors is clinically useful to determine in which patients occurrence is more likely.*

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology, characterized by persistent inflammation of multiple synovial joints, which results in the progressive destruction of bone and cartilage tissue and associated disability (1). Prevalence is approximately 1% of the population worldwide (2, 3).

Substantial data are available demonstrating increased cardiovascular events in RA (4). Increased risk of cardiovascular disease has been reported in RA patients compared to the general population and patients with a disease duration exceeding 10 years present a relative risk (RR) of 3.1 (CI: 1.64-5.87) (5). Moreover, an observational cohort study obtained from a large database on 2.37 million general medicine patients confirmed that RA patients present an increased risk of thromboembolic events (30%-50%) compared to the general population and to patients affected by osteoarthritis (OA) (6). Although classical risk factors for arterial disease do not seem to be crucial in explaining the increased rate of cardiovascular disease in RA, these patients are more prone to sudden death, myocardial infarction (MI) and stroke compared to the general population. Other non-classical risk factors such as chronic inflammation and treatment related factors could also be involved. The prevalence of venous thromboembolism is also greater in RA patients as has been reported by several authors (7-9). This increased risk for both arterial and venous thrombosis is not fully understood. Traditional risk factors such as smoking (10), hyperlipidemia (5), elevated homocysteine (11) hypertension (12), immobility (13) and diabetes may be important in RA (14). However, evidence indicates that it may depend on disease related factors, including the presence of systemic inflammatory disease and the concomitant vascular endothelium activation from immune disregulation and inflammation, and on treatment related factors. Furthermore, growing evidence highlights a mutual network in which inflammation, coagulation and fibrinolysis play closely related roles.

The medical literature contains multiple anedoctal or/and limited cases of thromboembolic events in RA. Presently, no comprehensive review on this subject exists. The aim of this review is to summarize the data available in different specialised medical and surgical journals, and if possible offer advice concerning the management of thrombotic risk in RA patients.

A PubMed search of articles published in English between 1960-2008 using the keyword combinations: "rheumatoid arthritis" with "thrombosis" was made. The available information regarding

thrombosis in RA was summarized. Hereditary disorders and association with connective tissue disorders are not included in this review.

Epidemiology

RA patients may suffer from thromboembolic events, which represent an important cause of morbidity and mortality (15). Despite this, the relationship between thromboembolic events and RA has rarely been investigated. Watson *et al*. (6) recently examined the incidence of all-cause mortality and all vascular events in 40+ year-old RA patients registered in the UK General Practice Research Database. RA patients showed a higher age and sex-adjusted increased risk of mortality (60%) and thromboembolic events (30%–50%) during a 5-year follow up compared to non RA patients. Similarly significant elevated risks (70% for death and 30%–40% for thromboembolic events) were seen when compared to OA patients.

Arterial thrombosis in RA

Several studies have shown that RA is associated with premature and accelerated atherosclerosis (7). RA Patients are 30%-60% more likely to suffer a CV event (16) with a statistically significant difference in the prevalence of angina compared to the general population (18% *vs*. 8% p=0.03) and chest pain (30% *vs*. 15% p=0.007) (18). The prevalence of myocardial infarction in RA patients differs from country to country, ranging between 3.6%-17.7% (19), as confirmed by other studies in which the highest rates of myocardial infarction are seen in Finland, Poland and UK while the lowest rates are reported in the Mediterranean countries (20). In contrast, the incidence and prevalence of stroke have generally been shown to be similar in both RA and in the general population (4, 15). However, a higher prevalence of stroke in RA than in controls was reported in two study (16, 17): in particular Nadareishvili et al demonstrated an increase risk of ischemic stroke in RA patients (OR: 2.66 95% IC 1.24–5.70), related to severity of the disease and comorbidity.

Moreover, CVD were more prevalent in men than in women (19) and the relative risk in RA patients is highest in young patients and in those without previous CV events (21); Fifty per cent of deaths in RA are due to cardiovascular disease (22). Additionally, studies which have evaluated the severity of cardiovascular events in RA patients have shown that the severity of CV events, together with an elevated risk of atheroma, may contribute to the higher mortality rate seen in RA patients. In fact, in case control studies of patients with myocardial infarction, 40% of those with RA died, compared to 15% of patients without RA (23). Other risk factors implicated in CV disease manifestations in RA patients include the long term use of corticosteroids, age at RA diagnosis, disease duration, extra-articular manifestations and persistent disease activity (24, 25, 26). Moreover, evidence from both laboratory and epidemiologic research suggests that systemic inflammation plays a critical role (27) in the development of CVD in RA patients and may act independently of traditional risk factors to increase the risk through biologic mechanisms (28). Several studies have demonstrated that various RA disease activity and severity markers are associated with all the causes of mortality from CV events. These markers include joint swelling (22), rheumatoid factor (11), bone erosion (4), C reactive protein (CRP) (29) and high erythrosedimentation rate (ESR) levels (30). Carotid artery ultrasound and coronary angiography have shown that atheromatosis is more frequent in RA than in controls (31).

Venous thromboembolism in RA

Incidence of Venous thrombosis, comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is approximately 1/1000 annually in adult populations (32). There are only sparse data that evaluate the incidence of DVT in RA patients. In one study, the cumulative incidence of venous thromboembolic events (DVT and PE) found in a cohort study of 609 RA patients was 7.2% after adjustament for age, sex, BMI, smoking and rheumatoid factor status (7). Another study demonstrated the higher incidence of VTE and PE in hospitalized RA patients who did not have joint surgery (1.64% and 0.85% respectively), compared with patients without RA or joint operation (0.86 and 0.38% respectively) (33). Thrombosis in RA patients occurs more frequently in the deep veins of the legs and pulmonary circulation, although single cases have been described in other sites, intracardiac (34), retinal (35) and renal veins (36) but these were probably therapy related.

Another important aspect is that RA patients frequently require major orthopaedic surgery which increase the thrombotic risk. However, studies on the incidence of DVT in these patients are limited. Abernethy *et al*. (37) reports a DVT incidence of >70% and an overall Pulmonary Embolism (PE) incidence of approximately 2% in RA patients who have undergone knee replacement but who did not receive thromboprophylaxis. These figures are similar to those observed in the general population without prohylaxis (38). The risk of developing DVT appears similar for RA patients undergoing total hip or knee replacement (39). However, previous studies suggest that the incidence of VTE is 3-10 times lower in RA patients undergoing hip or knee surgery using non steroidal anti-inflammatory drugs (NSAIDs) than in OA patients (40). This protective role of NSAIDs has been confirmed in another study in which the authors present retrospective data of 103 RA patients undergoing major orthopaedic surgery procedures and found that these patients have a lower post discharge VTE risk compared to patients without RA (41).

Thrombotic tendency in RA

The etiology of thrombotic tendency in RA is still unclear due to the range of mechanisms and causal factors involved. Research is focused on the role of disease-associated risk factors and predisposing conditions such as endothelial dysfunction, hypercoagulability, pro-thrombotic conditions, inflammatory markers, immobility and complications following major knee or hip replacement. In addition, endothelial cells may be injured by high levels of plasma homocysteine. An association between hyperhomocysteinemia

and occlusive vascular disease has also been demonstrated in several studies (Table I).

Table I. Prothrombotic factors identified in RA patients.

		References
Endotelial disfunction	Inflammation	42
	HLA DR1 and inusual genotype	43, 44
	Increased expression of adhesion molecules (VCAM-1, ICAM1)	80
	Increased level of IL1, TNF-α	46
	Increased von Willebrand factor level	47
Hypercoagulability	Excessive deposition of fibrine in synovial membrane	50, 51
	Anticardiolipin antibodies	53, 54, 55
	Dyslipidemia	60
	Higher levels of Lp(a)	61, 62
Prothrombotic conditions	Decreased in ATIII, protein C, protein S	70
	Increased fibrinogen levels	42
	Hyperhomocysteinemia	48, 77, 78
	Higher level of microparticles	73, 83, 84
Inflammatory markers	Increased levels of PCR, D-dimer, acute phase reactant	18, 28, 88

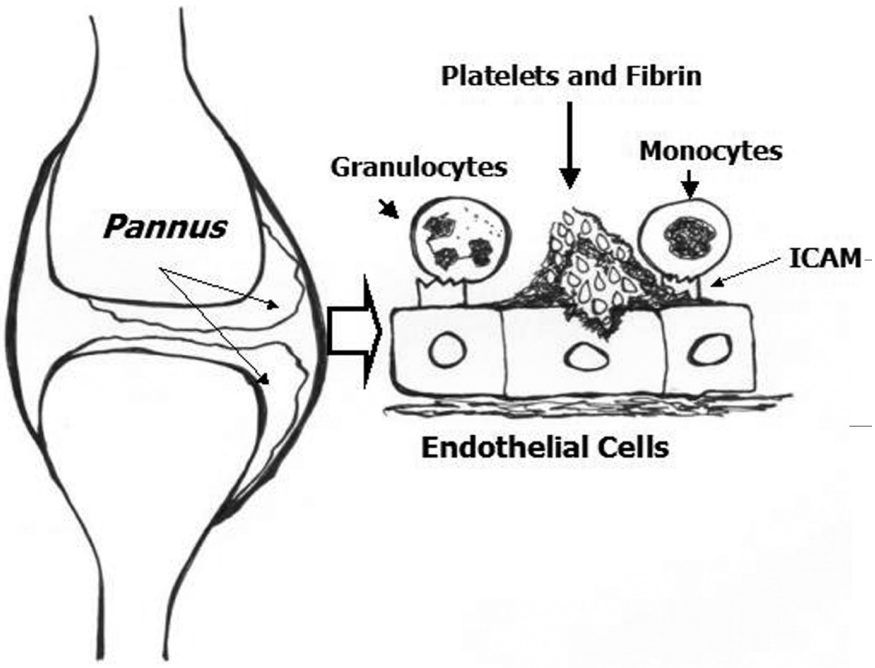

Fig. 1. Articular inflammation (pannus) can induce expression of adhesion molecules (ICAM) on the surface of the endothelial cells. Granulocytes and monocytes are involved in this phenomenon. These cells can both activate blood coagulation and damage the endothelium with secondary platelet adhesion and aggregation.

Endothelial dysfunction

Recent studies have demonstrated impaired endothelial function in RA patients, even in early stages of the disease. The injury and activation of endothelium leads to altered endothelial permeability and to increased leukocyte and platelet adhesion. Endothelial dysfunction is related to inflammation (42) and HLA-DR1 (43), unusual genotype (44) and improves with infliximab therapy (45, 46). Whereas the healthy endothelium prevents mononuclear cell adhesion, monocyte-adhesion is promoted by the expression of the adhesion molecule (VCAM-1), the intercellular adhesion molecule (ICAM-1) during inflammation. This expression is induced by pro-inflammatory cytokines such as interleukin (IL)1 beta and tumor necrosis factor (TNF)-α and C-reactive protein (CRP). As all of these factors are present at increased levels in the systemic circulation in RA, it appears possible that they might be associated with cardiovascular risk factor and vascular events. In addition, coagulation factors such as increased von Willebrand Factor levels (vWF) and plasminogen activator inhibitor-(PA-)1 (47), are important and may play a significant role in both RA and thrombosis (48) (Fig. 1) .

Hypercoagulability

Hypercoagulability identifies an imbalance in the coagulation cascade toward pro-coagulant forces as a result of an excessive activation of coagulation enzymes without clinical signs of thrombosis. There is ample evidence that coagulation processes are active in RA both at extra and intravascular sites (49). Tissue Factor (TF) expression in arthritic synovial tissue favours extravascular coagulation and may play a role in inflammation. These pathways has been investigated by various authors. Functional TF activity was significantly increased in synovial membranes from RA patients and is linked to fibrin deposition; evidence demonstrates that TF, a transmembrane glycoprotein, binds the zymogen, factor VII (FVII), and activated FVII (FVIIa). Different studies have shown that on FVIIa binding, TF acts as a neoangiogenesis regulator. Angiogenesis has been shown to take place in the growing arthritic synovial tissue and it has recently been shown that intrarticular injection of recombinant human TF into mice induces synovial inflammation (50). TF is constitutively expressed on fibroblast and epithelial cells and its expression on endothelial cells and monocytes is induced by inflammatory stimuli such as lypopolisaccharide and TNF-α. In the context of arthritis, the persistence of fibrin iduced by deposition has been shown to potentiate synovial inflammation (51), but also to pro-

mote activation of the coagulation cascade which is therefore closely associated with synovial inflammation. There is also evidence that the blockade of the coagulation pathway at multiple levels can reduce the inflammation process in chronic diseases (52) and may be beneficial in arthritis. Hypercoagulability may commonly be secondary to the presence of anticardiolipin antibodies (aCL) and abnormal lipid profile. In 2006 Olech and Merrill (53) reviewed published data to evaluate the occurrence of anti phospholipid antibodies in RA and calculated both median and mean prevalence. Estimates were 22% and 28% respectively. Positivity of aCL in patients affected by autoimmune disorders correlates strongly with the risk of the concomitant appearance of arterial and venous thromboembolic complications (54, 55). Seriolo *et al*. (1999) (56) reported increased concentrations of aCL and decreased levels of protein S, a natural anticoagulant which belongs to the protein C system (57), with an increased rate of different vascular complications, including arterial or venous thrombosis, in RA patients (58).

However, the mechanism by which aCL increase and their relationship to thrombotic events have not been clearly established (58). APL antibodies may induce a pro-inflammatory, pro-adhesive and pro-coagulant status in endothelial cells, platelets and monocytes. Abnormal platelet aggregation, decreased endothelial cell prostacyclin production, inhibition of protein C, possibly by eliminating the enhancing effect of phospholipids on thrombomodulin, decreased fibrinolysis by unopposed tissue plasminogen activator-inhibitor or prekallicrein inhibition and complement activation, have all been proposed as a possible cause of the pathogenic role of antiphospholipid antibodies (59).

A large number of patients are affected by RA associated to dyslipidemia and the presence of aCL and an altered lipid profile may be important risk factors for thrombotic events in these patients. Lipoprotein profiles that predispose RA patients to the development of cardiovascular disease include high levels of total cholesterol (TC) or low density lipoprotein cholesterol (LDL-C), low levels of high density lipoprotein cholesterol (HDL-C) and higher levels of lipoprotein(a) [Lp(a)] (60). Studies have shown that plasma levels of Lp (a) in RA are influenced by several acquired factors, including administration of certain drugs (61) and inflammation status (62). It is thought that the correlation observed in aCL positive RA patients between high levels of Lp(a) and the incidence of thrombotic events, may well be due to the presence of aCL as a consistent risk factor and the thrombosis promoting effect exerted by Lp(a) (63). These findings may be of interest since Lp(a) has been shown to be a risk factor for peripheral vascular disease, independently of other risk factors, including LDL and HDL cholesterol with implications in thrombogenic processes (64, 65). The protein of human Lp(a) is composed of Apolipoprotein B_{100} and the unique, highly glycated glycoprotein, apolipoprotein (a). It has been suggested, because of the striking similarity between apoliporotein (a) and plasminogen, that Lp(a) may interfere with the conversion of plasminogen to plasmin and inhibiting plasminogen activation in a dose dependent manner (66), thereby inhibiting fibrin clot lysis. Elevated plasma Lp(a) has also been found to be a risk factor for venous thromboembolism in adults (67) and children (68). Indeed, the detection of Lp (a) in RA patients with an absence of the traditional and thrombophilic risk factors (69) is considered a contributing factor to the development of venous thromboembolism.

Pro-thrombotic conditions

Pro-thrombotic condition is defined as an increase in the risk factors for thrombosis and/or a decrease in anticoagulant factors (70). Homocysteine (Hcy) is a non essential amino acid produced during normal metabolism and has also been implicated in the pro-thrombotic tendency observed in RA. Hyperomocysteinemia is a pathological condition characterized by an increase in plasma concentration of total Hcy (71).

Hcy is independently associated with the development of peripheral vascular disease and DVT in the general population. Pro-thrombotic activities may be attributed to either a direct or indirect toxic effect on the endothelium: one possible mechanism is a relative lack of endothelium-derived NO, which could lead to enhanced platelet hyperactivation (72, 73). Another possible pro-thrombotic mechanism may be related to a decreased expression of the anticoagulant protein, thrombomodulin, which is expressed on the luminal surface of endothelium and is essential for anticoagulant protein C activation (74). In addition, it is also possible that hyperhomocysteinemia may predispose patients to thrombosis via up-regulation of tissue factor on endothelium or monocytes (75). Hyperomocisteinemia may mediate endothelial dysfunction, LDL-C oxidation, cause vascular smooth muscle proliferation, and affect hemostasis (76). Several studies have demonstrated that in RA patients the degree of inflammation is correlated to plasma concentration of Hcy (77, 78, 48). A positive relationship was found between the Hcy concentration and some bio-humoral parameters of inflammation, such as the circulating levels of soluble receptors for different cytochines (IL-2sRα, sTNF-R75) (79), adhesion molecules (sICAM-1) (80), and CPR (81).

In addition, there is another mechanism which could be implicated in determining a prothrombotic condition in RA: the role of the cell component called "microparticles"(MP). MP are small (o,1-1μm) membrane-bound vesicles that circulate in the blood and mediate inflammation and thrombosis (73). The most abundant MP in the blood come from platelets, although MP in the periphery can also arise from lymphocytes, monocytes and endothelial cells among other sub-cellular structures such as apoptotic bodies and exosomes (82). In a study of RA patients (83), platelet MP levels in the blood were elevated and correlated to disease activity measured using the Disease Activity Score (DAS)-28. MP derived from granulocytes and monocytes have been found in the synovial fluid of RA patients (84). Synovial MP from RA patients stimulate tissue factor/factor VII-dependent thrombin generation. This local hypercoagulability could play a role in intra-articular inflammation and

the formation of fibrin clots, known as "rice bodies" (85). MP have different properties that could promote the pathogenesis of thrombotic disorders. Phosphatidylserine and tissue factor are both exposed on MP outer membrane and are central players in the coagulation cascade. In addition MP interact with factors Va, VIII and IXa, facilitating assembly of prothrombinase complex (86, 87).

Inflammatory markers

In RA, inflammatory status increases thrombotic risk in several ways: by increasing platelet count and activity, activating the coagulation cascade, impairing anticoagulant and fibrinolytic activities, and leading to hyperhomocisteinemia. It is not clear whether the relationship between elevated inflammation markers and athero-thrombosis is one of cause or effect. Plasma levels of several inflammation markers have been found to be associated to prothrombotic risk. These markers include fibrinogen, D-dimer (18), cytokine and C-reactive protein (CRP). CRP, an acute-phase reactant has been identified as a new independent risk factor for atherothrombotic disease (88). CRP may be elevated resulting from the acute phase response to vascular injury. There is some evidence that elevated CRP may mediate cardiac damage by complement activation, and inflammation may have some procoagulant effect (89). There is also evidence of an inverse relationship between CPR levels and HDL-C values, which has been demonstrated in untreated RA patients (62). Additionally, TNF-α plays a crucial role in determining the inflammatory status in RA patients (90). In particular, TNF-α can cause both endothelium damage (91) and promote blood coagulation *via* monocyte activation by exposing the TF on the cellular membrane and promotes the subsequent blood coagulation *in vivo* (92). This cycle may well be involved in the pathogenesis of vascular complications (93) thus increasing in cardiovascular risk in RA patients. Ferraccioli and Gremese (90) stated that TNF-α blockers should decrease cardiovascular risk; if that is so, this would further enhance the crucial role of inflammation in determining cardiovascular complications.

Complications after major orthopaedic surgery

Venous thromboembolism is a common complication following major hip or knee replacement. The peak of DVT incidence is observed around the fifth postoperative day (39). After the first postoperative week a second coagulation process occurs, as demonstrated by an increase of thrombin-antithrombin III complexes and D-dimer, markers of coagulation activation, which may persist for up to six weeks or longer (94). Data on the risk of RA patients undergoing major orthopaedic surgery developing VTE are conflicting and there is no consensus about whether, nor for how long thromboprophylaxis should be given to these patients following hospital discharge (95). Data suggests that the risk of RA patients developing VTE might be lower than in OA patients (40). This is likely to depend on many factors: RA patients tend to be younger, have lower body weight and lower haemoglobin levels. Another explanation might be the frequent use of non-steroidal anti-inflammatory drugs (NSAIDs), with their antiplatelet activity. Only one study on the incidence of post-discharge VTE in RA patients has been published (41). The authors present retrospective data on 103 RA patients who underwent major orthopaedic surgery and found symptomatic VTE only on the 17th postoperative day. The authors suggest that post discharge thromboprophylaxis might not be necessary in RA patients undergoing major orthopaedic surgery, because these patients have a lower post-discharge VTE risk owing to the use of NSAIDs. In addition the COX-2 inhibitors might replace conventional NSAIDs because they have a more favourable benefit/risk profile. However, these compounds seem to have a much lower antithrombotic efficacy, which might lead to a higher postoperative VTE risk than with conventional NSAIDs (96). A proposed mechanism to explain this observation is that non selective NSAIDs have a cardioprotective effect, due to tromboxane A2 inhibition, but cycloxygenase 2 inhibitors (COX-2) have no inhibitory effect on tromboxane and lower the beneficial vascular effect of prostacyclin. This imbalance of tromboxane and prostacyclin potentially interferes with homeostatic functions and may accelerate the risk of spontaneous thrombotic events in predisposed patients (97)

Acute calf tenderness diagnosis in RA patients

RA patients with acute calf pain and swelling pose a common diagnostic problem. In fact, acute calf tenderness with or without swelling may be caused by various conditions such as a ruptured popliteal Baker's cyst or venous thrombosis. The similarity between the symptoms of a ruptured popliteal cyst and thrombophlebitis are such that the former is defined as "the pseudo thrombophlebitis syndrome"(98). Baker's cyst is a formation frequently secondary to RA, resulting from an excessive collection of synovial fluid within the gastrocnemius-semimembranosus bursa, which communicates with the knee joint (99). The majority of the cysts remain asymptomatic, some are presented as a localized mass behind the knee. Occasionally they can compress the popliteal vein or rupture spontaneously and mimic DVT. Pseudothrombophlebitis is described as a clinical picture eliciting an inflammatory response secondary to herniation or extravasation of popliteal cyst contents into the soft tissue. The clinical manifestations reveal subcutaneous edema, cutaneous erythema, swelling and tenderness of the calf. Baker's cyst rupture is clinically important because of the difficulty in discriminating the clinical picture from DVT. Treatment for these two clinical conditions is completely different. The administration of anticoagulants in pseudothrombophlebitis causes bleeding into the soft tissues, which provokes contracture and fibrosis of the calf muscle (100). Nevertheless, Baker's cyst and DVT can co-exist are referred to as "pseudopseudothrombophlebitis" (101).

Therapy and thromboembolic risk in RA

RA patients are frequently treated with a variety of medications, includ-

ing NSAIDs, corticosteroids, and disease modifying antirheumatic drugs (DMARDs), to provide symptomatic relief and to slow disease progression. Collectively, the drugs used to treat RA have a number of effects on vascular function, coagulation and cellular repair.

Pain management in RA increases cardiovascular risk. Relative data are not yet available and the potential atherothrombotic risk of any NSAID or selective COX-2 inhibitor must be taken into account when selecting therapy. In fact, a previous study has shown an increased myocardial infarction risk in patients using NSAID and COX-2 inhibitors, especially with rofecoxib (102).

Controversy surrounds the effect of glucocorticoids on the cardiovascular system. Their effect on blood pressure, insulin resistance, lipid profile, body weight and coagulation proteins might significantly increase the risk of CVD in RA patients (103). Although studies have shown that larger cumulative doses of glucocorticoids are associated with increased carotid plaque and poor indices of arterial compressibility in patients with RA (104), it is accepted that there in no evidence linking low dose therapy and CVD in RA patients (105).

Methotrexate (MTX) has been most commonly used in conventional therapy for the treatment of RA over the past 20 years. It inhibits the homocysteine-methionine pathway and its use can be associated with hyperomocysteinemia, a known risk for CVD. Folic acid, which reduces homocysteine plasmatic levels, is taken by many patients treated with MTX. In one study, the use of MTX was associated with increased mortality for CVD compared with other DMARDs (106). However, in several studies the use of MTX is associated with a significantly lower risk for CVD in RA patients compared to patients who had never used DMARDs (107, 108). Long term follow-up of RA patients has shown that the use of MTX is related to reduced CV mortality (109), probably related to a reduction of disease activity.

Among other classical disease modifying antirheumatic drugs, antimalarials appear to have a beneficial effect in patients with systemic lupus erythematosus as they decrease the serum cholesterol and low density proteins and also reduce interleukin-6 levels (110). Hypertension is a widely recognized side effect in both cyclosporine and leflunomide. The increase in risk that we observed may be due to drug-induced hypertension, but it might also be a reflection of the suboptimal control of inflammation by these agents (21).

TNF-α has an important role in the initiation and progression of inflammation as well as in the mechanism implicated in accelerated atherosclerosis in RA (111). A recent study suggested that the risk of developing any CV event in RA is lower in patients who receive TNF-α blockers (112). Chimeric monoclonal anti-TNF-α antibody infliximab alone or in combination with low doses of MTX is an effective therapy in severe RA (113). One study reported that TNF-α blockade using infliximab improves endothelial function after 12 weeks of therapy. This improvement depends on the clinical improvement of the joint manifestations and on a decrease in the C reactive protein and erythrocyte sedimentation levels (114). Other studies have shown the potential effect of short-term adalimumab therapy on endothelial function in RA patients with long-standing disease refractory to infliximab (115).

Prophylaxis of thromboembolic events in RA patients: which and when?

Prophylaxis for arterial thrombosis

Various factors appear to play a relevant role in determining an increased risk of thrombosis in RA patients and many appear related to disease activity. Indeed, as already demonstrated, inflammation and higher ESR values may increase the thrombotic risk.

RA vasculitis and the presence of lung disease disease are specific predictors of cardiovascular mortality (116). As a consequence, major efforts to prevent thrombotic complications and reduce cardiovascular events in RA patients should focus on correcting inflammatory status with early intervention and control of disease activity (117).

Prophylactic antithrombotic treatment should be started in all clinical conditions that are associated with a greater risk for thrombosis, such as active diseases. Daily aspirin (ASA) doses of 75-325 mg are regarded as suitable for inhibiting platelet aggregation as a means of cardioprophylaxis in patients at risk for acute MI, angina, stroke, peripheral vascular disease. Although primary prophylaxis *per se* in RA is not recommended, ASA appears to be important in the prevention of CV events in RA patients with increased CV risk (118). When ASA is used it should be recognized that it is very difficult to propose contemporary administration of NSAIDs since the latter limit the cardioprotective effects of ASA; in fact, studies show that the concomitant use of ibuprofene in patients with increased CV risk may limit the cardioprotective effect of ASA (119), whereas other NSAIDs such as diclofenac or drugs with a lower COX-1 inibitory effect, such as meloxicam, do not interfere with ASA (120). However, ASA is associated with increased risk of gastrointestinal bleeding and death from gastrointestinal events is higher in RA than in the general population, perhaps due to use of NSAIDs or corticosteroids (121).

However, if the general and related disease risk factors are present, chronic aspirin administration could be suggested, provided that rheumatologists use NSAIDs, which do not interfere with ASA, and the use of proton-pump inhibitor should also be considered (Fig. 2).

Prophylaxis for venous thrombosis

The use of routine thromboprophylaxis in RA patients is not generally indicated. However, it can be useful in patients with previous VTE affected by acute arthritis of the legs or other acute disabling medical illnesses (122, 123). Since RA is a medical condition with increased risk of venous thrombotic events, the use of prophylaxis with heparin to prevent venous thrombosis should be limited to periods of immobilization; not only for immobilization *per se,* but because immobilization is related to disease activity and inflammation. This point is crucial as inflammation can be considered a thrombophilic condition. For example, a 65-year-old

patient with poliarticular RA, with important disabilities, and increased ESR and RCP levels, may be given (LMWH) heparin as primary prophylaxis for the limited period of disease flare up. As for RA patients undergoing knee or hip replacement, studies have shown that short term subcutaneous LMWH is an adequate, simple and safe method to prevent thrombosis in these patients (41); there is also evidence suggesting that the use of spinal rather than general anaesthesia, graded compression stockings and early immobilization reduces the incidence of VTE (12). Although ASA is not indicate in profylaxis of VTE, some authors also consider ASA to be useful to prevent VTE (124, 125), reporting a significant risk reduction of 39% in high-risk medical patients or in patients undergoing orthopaedic surgery (125). This is probably related to the anti-inflammatory properties of ASA and to its capability to modulate the coagulation process by reducing thrombin formation in clotting blood (126, 127) (Fig. 3).

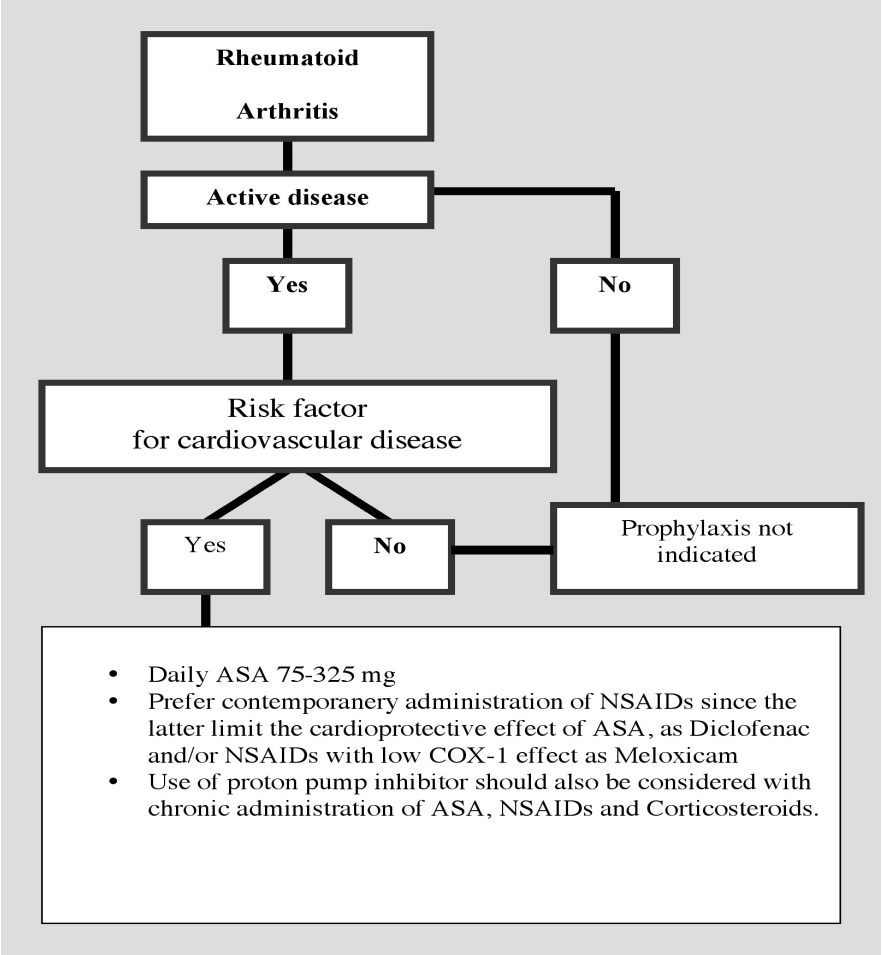

Fig. 2. Propose for prophylaxis for arterial thrombosis in rheumatoid patients.

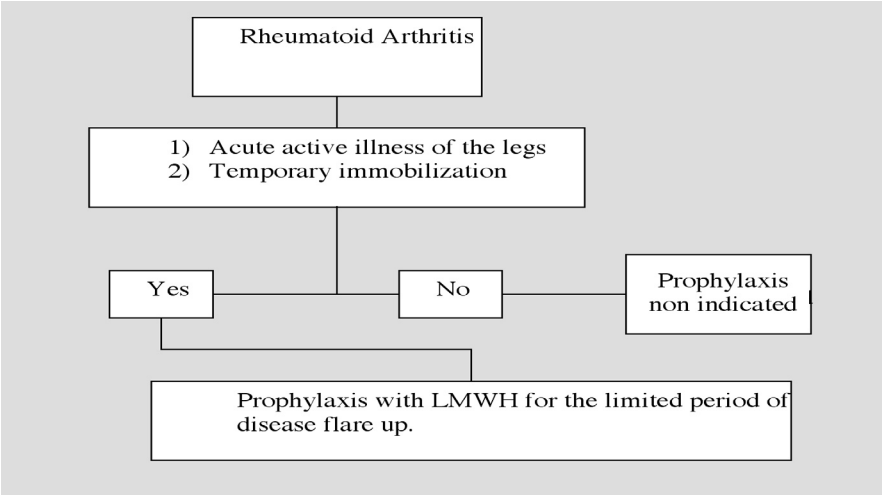

Fig. 3. Prophylaxis for venous thrombosis in rheumatoid patients.

Conclusions

Thrombosis is a possible manifestation in RA patients. A number of factors are suspected to play a role in the increased thromboembolic risk. The precise mechanism responsible for thrombosis in these patients remains unclear, however, the identification of the thrombophilic risk factors is clinically useful to determine in which of these patients its occurrence is more likely.

At present, the elimination of removable risk is recommended in RA patients.

Finally, data in literature suggests chronic administration of ASA may be useful to reduce risk and prevent arterial thrombosis in RA patients with cardiovascular risk. However, administration of heparin in prophylaxis for VTE should be limited to periods of disease flare up, prolonged patient inactivity or surgical procedures.

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