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Atherosclerosis in Systemic Lupus Erythematosus

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Abstract

Accelerated atherosclerosis and its long-term sequelae are a major cause of late mortality among patients with systemic lupus erythematosus (SLE). Traditional Framingham risk factors such as hypertension, hypercholesterolemia, diabetes, and smoking do not account in entirety for this risk. SLE specific factors like disease activity and duration, use of corticosteroids, presence of antiphospholipid antibodies, and others are important risk factors. SLE is considered a coronary heart disease; equivalent and aggressive management of all traditional risk factors is recommended. Despite their role in primary and secondary prevention in the general population, statins seem to have no effect on cardiovascular outcomes in adult or pediatric SLE populations. The use of hydroxychloroquine has a cardioprotective effect, and mycophenolate mofetil may reduce cardiovascular events based on basic science data and data from the transplant population. The role of vitamin D supplementation and treatment of hyperhomocysteinemia remain controversial, but due to the safety of therapy and the potential benefit, they remain as optional therapies.

Keywords

atherosclerosis; cardiovascular disease; autoimmunity; systemic lupus erythematosus; SLE

Atherosclerosis is a specific form of arteriosclerosis characterized by the deposition of fibrofatty lesions in the intimal lining of the large-sized and medium-sized arteries. It is the most frequent cause of death in the western world. The higher risk of cardiovascular disease (CVD) in systemic lupus erythematosus (SLE) was first recognized in 1976 by Urowitz and Gladman, who described a bimodal pattern of mortality in a Toronto SLE cohort.[1] Of 11 deaths in the cohort, 6 occurred in the first year after diagnosis, whereas 5 deaths occurred after an average of 8.6 years. The first peak in mortality was due to active lupus, and these patients had a remarkably increased incidence of infection. Mortality in the second group was associated with inactive lupus, long duration of steroid therapy, and a high incidence of myocardial infarction (MI). The first peak in mortality has decreased over the past 50 years due to advances in treatment of active lupus and its complications, especially lupus nephritis, renal failure, and infections, but cardiovascular mortality has increased slightly

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since the 1970s.[2] The latest data from the Hopkins cohort estimate the risk of cardiovascular events among patients with lupus to be 2.66 times higher compared with the general population.[3] Not only is the risk of cardiovascular events increased but the outcomes of patients with SLE who suffer an event are worse, with increased in-hospital mortality and prolonged length of hospitalization when compared with patients with diabetes and without SLE.[4] Traditional Framingham cardiovascular risk factors do not account for the entire risk in patients with SLE, with a shockingly higher risk among patients with SLE after adjusting for the following traditional risk factors: relative risk is 10.1 for nonfatal MI, 17.0 for death due to coronary heart disease (CHD), 7.5 for overall CHD, and 7.9 for stroke.[5] Besides the traditional risk factors, SLE specific risk factors have been identified, among which current disease activity, current dose of corticosteroid, renal activity, lupus anticoagulant, and anti–double-stranded DNA.[3]

PATHOPHYSIOLOGY

Although human studies have proven useful in identifying predictors of cardiovascular risk, the pathophysiologic mechanisms that underlie this risk remain elusive. The current knowledge is derived mainly from mouse models. Several single-gene knockout mouse models, like the *gld*.apoE−/− and the apoE−/− Fas−/−, were found to be more susceptible to atherosclerosis,[6] presumably due to impaired macrophage function and inadequate clearance of apoptotic bodies. Over the years, more complex models were created to address the polygenic nature of both SLE and atherosclerosis, for example, the NZM2410-derived congenic B6.*Sle* mouse strains which made it possible to examine lupus and atherosclerosis together.[7]

Role of Cytokines

Type I interferons (IFNs) interfere with vascular repair in SLE by promoting an antiangiogenic signature in SLE characterized by transcriptional repression of interleukin (IL) 1α and β, IL-1R1, and vascular endothelial growth factor A and upregulation of IL-1R antagonist and the decoy receptor IL-1R2.[8] IFN-γ, known to be a proinflammatory cytokine, influences many features of atherosclerosis, such as foam cell formation, the adaptive Th1-specific immune response, and plaque development,[9] but it may also have anti-inflammatory properties.[10] Circulating levels of tumor necrosis factor α are elevated in patients with SLE and have been associated with the severity of coronary calcium scores,[11] high triglycerides, and low high-density lipoprotein levels.[12] IL-6 is involved in the recruitment of inflammatory cells and lipid homeostasis and is associated with increased cardiovascular mortality in the general population.[13] Elevated IL-6 levels have also been associated with the atherosclerotic burden in SLE.[14] High levels of IL-17 have been reported in human SLE sera.[15] IL-17 is produced concomitantly with IFN-γ by coronary artery infiltrating T cells and they act synergistically to induce proinflammatory responses in vascular smooth muscle cells.[16] Despite the initial data that IL-17 was a proinflammatory cytokine, induction of IL-17 production in a mouse model reduced vascular T-cell infiltration and atherosclerosis development, thus indicating an atheroprotective role for IL-17.[17] The controversial role of IL-17 in atherosclerosis is a matter of intense debate, and future studies are needed to better determine the molecular mechanisms involved in the modulatory role it exerts on

atherosclerosis.[18] IL-12 and IL-18 are proatherogenic cytokines associated with the helper T cell (T_H1) response,[19] but their role in SLE models has not been studied.

B Cells

Recent data suggest that the effects of B cells on atherosclerosis may depend on their subtype and the antibody subclass they produce. B-1 cells produce immunoglobulin (Ig) M antibodies, whereas conventional B-2 cells are the main source of IgG antibodies.[19] Natural IgM autoantibodies seem to be atheroprotective,[20] whereas IgG autoantibodies exhibit proatherogenic properties through the formation of oxLDL-containing immune complexes and the subsequent activation of macrophages and resident cells via specific Fc receptors.[21]

T Cells

The role of T_H17 cells has been studied in the context of their signature cytokine IL-17 that was described above. The only T-cell subset that was clearly identified as atheroprotective are the T regulatory (Treg) cells.[22] Evidence from studies using transgenic atherosclerosis-prone mice suggests that regulatory T cells tune down experimental atherosclerosis: Treg deficiency in LDLr−/− mice leads to enhanced atherogenesis and transfer of Tregs into Treg-poor apoE−/− mice attenuated atherosclerosis and reduced T-cell accumulation within the lesions of the mice.[23]

Dendritic Cells

CCL17 is a dendritic cell (DC)–derived chemokine and CCL17+ DCs have been shown to accumulate in atherosclerotic lesions.[24] CCL17 deficiency led to a Treg-dependent reduction of atherosclerosis, expression of CCL17 by DCs limited the expansion of Tregs and precipitated atherosclerosis, whereas a CCL17-blocking antibody expanded Tregs and reduced progression of atherosclerosis in a mouse model.[25]

TRADITIONAL CARDIOVASCULAR RISK FACTORS IN SYSTEMIC LUPUS ERYTHEMATOSUS

Smoking

Smoking is directly related to increased rates of the following: MI, sudden death, aortic aneurysm formation, peripheral vascular disease, and stroke in the general population.[26] Smoking among patients with SLE increases the risk of having a cardiovascular event 3-fold compared with nonsmokers with SLE.[27,28] Smokers had significantly higher disease activity compared with ex-smokers and never smokers in a multivariate analysis.[29] Smoking also interferes with the efficacy of antimalarial therapies[30–32] although the exact mechanism is unknown. Interestingly, nicotine has been shown to strongly inhibit the uptake of chloroquine in cultured cells, but whether this effect occurs in vivo is unknown.[33]

Hypertension

Hypertension is a risk factor for coronary artery disease (CAD), heart failure, chronic kidney disease, stroke, intracerebral hemorrhage, transient ischemic attack, and peripheral arterial disease. Blood pressure is strongly and directly related to vascular (and overall) mortality in

the general population, without any evidence of a threshold down to at least 115/75 mm Hg.[34] Hypertension is a major problem in patients with SLE. Seventy-five percent of patients in the Hopkins Lupus cohort are hypertensive. The presence of hypertension in SLE increases the risk of cardiovascular events 2.66-fold[3]; increases the progression of carotid plaque[35]; and increases the risk of CAD,[3] stroke,[36] and poor renal outcomes.[37] Only 9% of hypertensive patients with lupus reach a goal blood pressure of less than 120 mm Hg with antihypertensive therapy.[38]

Hyperlipidemia

Studies have shown hypercholesterolemia to be a significant risk factor for CVD in patients with SLE.[39–42] On an average, total cholesterol increases the risk of CVD 1-fold to 2-fold. Within 3 years of diagnosis, 40.3% of patients in the Toronto cohort developed sustained elevated total cholesterol, which was a good predictor of future cardiovascular events.[43] Patients who developed hypercholesterolemia tend to have a higher cumulative dose of steroids, were not on antimalarial therapy, and had an age of onset of SLE >35 years. Triglyceride (nonfasting and fasting) levels are also predictive of CAD in patients with lupus.[39]

Diabetes Mellitus

Presence of diabetes confers an equivalent risk to aging, 15 years, an impact higher than that of smoking.[44] The rates of future cardiovascular events compared with individuals without diabetes are 2-fold to 8-fold higher. Eighty percent of all deaths in patients with diabetes result from CVD.[45] Surprisingly, there is a paucity of data in regard to the association of diabetes with SLE. Cortes et al[46] found a prevalence of only 1.9% of an overlap SLE/diabetes mellitus (DM) in their cohort. In the Hopkins Lupus Cohort, presence of diabetes doubled the risk of cardiovascular events compared with the baseline SLE risk.[3]

Obesity

Obesity may soon overtake cigarette abuse as the leading cause of preventable death in the United States.[47] It increases the risk of developing type 2 DM, hypertension, dyslipidemia, heart failure, CHD, atrial fibrillation, obstructive sleep apnea/sleep-disordered breathing, proteinuria, and osteoarthritis.[48] Obesity has not been frequently examined in relation to CVD risk in populations with SLE. In a pediatric population with SLE, increased body mass index was associated with increased carotid intima-media thickness (IMT).[49]

Homocysteine

Homocysteine is an amino acid derived from the demethylation of dietary methionine. Elevated homocysteine may result either due to dietary or genetic factors. Homocysteine is an independent risk factor for progression of atherosclerosis,[50] stroke, and thrombotic events in patients with SLE.[51]

SLE-SPECIFIC RISK FACTORS

Disease Activity and Duration

The incidence of cardiovascular events was significantly higher in patients with high SLE disease activity in the Hopkins cohort.[3] Increasing duration of SLE was also associated with increased risk of all types of vascular events in the LUMINA cohort study,[27] but in the Hopkins cohort, there was no association of either disease duration or age at diagnosis with the rate of cardiovascular events.[3] Disease duration is significantly associated with coronary calcium scores,[52] whereas longer disease duration and higher Systemic Lupus International Collaborating Clinics (SLICC) damage index have been shown to be independent predictors of carotid plaque.[53]

Renal Disease

In the general population, the role of kidney disease as a risk factor for atherosclerosis is well defined. Worsening renal function as expressed by a decrease in estimated glomerular filtration rate (eGFR) is associated with increasing rates of death, cardiovascular events, and hospitalizations.[54] Proteinuria is also an independent risk factor for cardiovascular mortality.[55] As expected, multiple studies have shown that an increasing level of serum creatinine and the presence of proteinuria are strongly associated with cardiovascular events in SLE.[56–58]

Glucocorticoid Therapy

Glucocorticoid use has been associated with atherosclerosis in SLE,[3] at least partly through a dramatic increase in the risk of multiple traditional cardiovascular risk factors. In a meta-analysis of 93 studies, DM and hypertension occurred 4 times more commonly in patients treated with steroids compared with controls.[59] In an observational population-based study that included patients with inflammatory arthritis, inflammatory bowel disease, and chronic obstructive pulmonary disease, the rate of cardiovascular events was 17 per 1000 person-years among 82,202 nonusers of glucocorticoids and 23.9 per 1000 person-years among 68,781 glucocorticoid users. A dose of prednisone of 7.5 mg or more was associated with a 2.56-fold increased risk of cardiovascular events.[60] In patients with SLE, a change in prednisone dose of 10 mg was associated with a change in cholesterol of 7.5 ± 1.46 (SE) mg %, a change in mean arterial blood pressure of 1.1 mm Hg, and a mean weight change of 5.50 ± 1.23 (SE) lb.[61] In the Hopkins Lupus Cohort, the effect of corticosteroids is independent of disease activity and traditional cardiovascular risk factors.[3]

Antiphospholipid Antibodies

A high anticardiolipin antibody level is an independent risk factor for MI and cardiac death.[62] The presence of anti-phospholipid antibodies was associated with a greater than 4-fold increased risk of MI, stroke, or peripheral vascular disease in a study of 182 patients with SLE who were followed for a mean of 8.3 years.[63,64]

Nonsteroidal Anti-Inflammatory Medications

Nonsteroidal anti-inflammatory drug (NSAID) treatment predisposes to nonfatal and fatal cardiovascular events.[65] Rofecoxib is associated with the highest risk of MI; ibuprofen with the highest risk of stroke; and diclofenac with the highest risk of cardiovascular death. Naproxen seems least harmful.[66] The association of NSAIDs with cardiovascular events in patients with SLE was studied by Hill et al[67] and was found to increase cardiovascular events. Besides the cardiovascular risk, NSAID use in patients with SLE increases the risk of worsening glomerular filtration and we advise avoiding the use of any NSAIDs in patients with compromised renal function.[68]

Vitamin D Deficiency

Low serum levels of 25-hydroxyvitamin D have been associated with stroke,[69] MI,[70] hypertension,[71] DM,[72] hyper-triglyceridemia,[71] obesity,[72] and the metabolic syndrome.[73] In SLE, low vitamin D levels are associated with increased atherosclerotic burden,[74] high disease activity and dyslipidemia,[75] higher body mass index, and insulin resistance.[76]

C-reactive Protein

Several studies in the general population have shown that using high sensitivity C-reactive protein (hsCRP) in addition to established risk factors (age, gender, blood pressure, cholesterol, smoking, and diabetes) does not improve the estimation of risk of CVD to a clinically important degree.[77] The addition of 10 different biomarkers including hsCRP to the standard CVD predictive models that included age, sex, and traditional risk factors did not improve their predictive power.[78] In patients with SLE, hsCRP had no association with cardiovascular damage in the Hopkins Lupus cohort,[79] but it was associated with damage to various organs, particularly those of the pulmonary and musculoskeletal systems.

PREVENTION AND TREATMENT

Recommendations for therapy are based on prevention guidelines for the general population, because no formal guidelines exist for the prevention or treatment of CVD in the context of SLE. SLE should be considered a CHD equivalent[80] and aggressive screening and management of traditional CVD risk factors should be pursued. Whether this approach reduces the CVD risk in patients with SLE to the same degree as in the general population is not known. The currently available data, especially in relation to statins, have been discouraging, as described below.

Smoking Cessation

This is the single most important intervention in preventive cardiology. It reduces cardiovascular mortality by 36% as compared with mortality in subjects who continue smoking. Low-yield cigarettes do not seem to reduce the risks of MI and their use should be discouraged. A combination of counseling and pharmacotherapy is more effective than either one and both should be offered. As part of counseling, we prefer to underline the importance of social support and especially encourage smoking cessation by the patient's spouse, which decreases a person's chance of smoking by 67%.[81] The first-line evidence-based pharmacological options include: bupropion, nicotine replacement therapy (gum,

inhaler, lozenge, nasal spray, or patch), and varenicline. There is no concern with the use of any of these pharmacotherapies in patients with SLE.

Hypertension

Treatment of hypertension in SLE is based on the Seventh Report of the Joint National Committee.[82] Because SLE is a CAD equivalent, the JNC7 recommendations are to maintain a BP less than 130/80 mm Hg. However, in the Hopkins Lupus Cohort, the risk of cardiovascular events increased with any elevation above 120 mm Hg[3] so a more aggressive approach may be warranted. The first-line antihypertensives according to JNC7 guidelines are thiazide diuretics, which are a safe option in patients with SLE. Physicians need to be aware of their potential metabolic side effects including hypercholesterolemia, hypertriglyceridemia, and hyperglycemia.[83] Thus in patients with SLE, angiotensin converting enzyme (ACE) inhibitors are our preferred first-line agents. ACE inhibitors have a long track record of safety and efficacy and have been studied in patients with lupus nephritis and severe hypertension, where they were shown to improve renal function in 64% of the patients although also improving BP control.[84] The β-blockers may precipitate or worsen Raynaud's phenomenon[85] and can rarely cause drug-induced lupus[86,87] so they are used as second-line agents.

As primary prevention of CVD in patients with hypertension, aspirin reduced MI, increased the risk of bleeding, and did not reduce strokes or total cardiovascular events,[88] but was associated with a 4.1% absolute reduction in vascular events compared to placebo when used in secondary prevention. There are no randomized, controlled trials of aspirin use as primary or secondary prevention of CVD in patients with SLE. In a study that examined mortality reduction in SLE, aspirin was associated with a 70% reduction of all-cause mortality, and antiphospholipid antibodies were not associated with increased mortality.[89] In the absence of contraindications, we recommend the use of aspirin in any patient with SLE who has a history of CVD, positive antiphospholipid antibodies, or lupus anticoagulant; history of hypertension, DM, hypercholesterolemia; and a history of smoking.[90]

Hydroxychloroquine

Antimalarial medications are a mainstay of treatment in SLE and they have multiple benefits directly or indirectly pertaining to CVD and cardiovascular events in SLE. Hydroxychloroquine has been shown to be cardioprotective.[91] Positive metabolic effects include lowering total cholesterol in patients receiving steroids[92] and lowering fasting blood glucose concentration.[93] Antimalarials have also been shown to reduce the incidence of thrombotic events[94] and to improve overall survival in patients with SLE.[95] Thus we recommend hydroxychloroquine for every patient with SLE in the absence of contraindications.

Hypercholesterolemia

In the general population, the approach to treatment of hypercholesterolemia is outlined by the NCEP ATP III guidelines.[96] SLE is considered a CAD equivalent with a goal low-density lipoprotein (LDL) of less than 100 mg/dL. The first-line medications in the treatment of hypercholesterolemia are statins. They have a role in both primary and

secondary prevention of CVD in the general population. They reduce CVD events and stroke and may reduce all-cause mortality in patients without CVD.[97] Statins also reduce mortality and MI in patients with established CAD.[98] It is thus understandable that there was much anticipation in regard to the effects this class of medications would have in SLE, but the Lupus Atherosclerosis Prevention Study (LAPS) trial showed no benefit in the primary (coronary artery calcium) or secondary (carotid IMT, carotid plaque) atherosclerosis outcomes of patients with SLE.[99] A similar trial in a pediatric SLE population also did not show any effect of atorvastatin on the progression of carotid IMT.[49] Despite the negative results of the LAPS trial, statin treatment to goal LDL levels is recommended.

Omega-3 fatty acids have no conclusive evidence of benefit in primary or secondary prevention of coronary vascular events.[100] Furthermore, they have been shown to increase LDL levels up to 45%,[101,102] so we recommend against their use in patients with SLE. The AIM-HIGH trial[103] showed no clinical benefit from the addition of niacin to statin therapy during the 36-month follow-up period despite significant improvements in HDL cholesterol and triglyceride levels. There was also an unexpected rate of ischemic stroke among patients in the niacin group. Until larger trials evaluate this risk, we tend to avoid niacin use in our patients.

Hyperhomocysteinemia

Lowering homocysteine levels with folic acid, vitamin B6, and B12 in patients at risk for CVD does not reduce the risk for MI, stroke, or overall mortality.[104] Despite the lack of evidence in the general population, we do recommend treating hyperhomocysteinemia in patients with SLE due to the simple, effective, and safe therapy until data from larger trials in this specific population will be available.

Diabetes Mellitus

Diabetes is a CAD equivalent, so its presence in patient with SLE mandates an aggressive therapeutic approach. One of the most important causes of diabetes in SLE is the use of prednisone. Corticosteroid use increases the risk of developing diabetes 4-fold,[59] thus minimizing corticosteroid use is imperative. Intensive glycemic control defined as an HgbA1c less than 7% may reduce the risk for amputation, nephropathy, and retinopathy but does not seem to reduce mortality, MI, or end-stage renal disease in the general population.[105] From a treatment standpoint, there are no contraindications to the use of any antidiabetic medications in SLE. According to the American Diabetes Association guidelines,[106] the first-line glucose-lowering therapy for type 2 diabetes is metformin, unless the patient is significantly symptomatic or the HgbA1c and blood glucose are markedly elevated. The most important contraindication for the use of metformin is renal insufficiency, namely a serum creatinine ≥1.4 mg/dL for women and ≥1.5 mg/dL for men.[107] If metformin alone does not adequately control the hyperglycemia, a second oral agent may be added or the patient may be started on a glucagon-like peptide 1 receptor agonist or insulin.[106]

Vitamin D Deficiency

Whether vitamin D supplementation modifies the risks linked to its deficiency is currently not known. Until further data are available, we recommend treatment of vitamin D deficiency with a goal 25-hydroxyvitamin D level of 40 ng/mL or more.[108]

C-reactive Protein

In the JUPITER trial, rosuvastatin was shown to reduce the chance of developing clinically important cardiovascular event in patients with elevated C-reactive protein, but normal cholesterol levels,[109] and it was proposed that the effect was secondary to the reduction of hsCRP. Unfortunately, an entire range of drugs that have been shown to clinically reduce hsCRP levels, including fibrates, ezetimibe, glitazones, and niacin had a highly inconsistent impact on cardiovascular events in the general population,[77,110–114] thus casting doubt on the clinical importance of reducing hsCRP levels.[77] In the LAPS trial, atorvastatin not only failed to reduce measures of atherosclerosis more than 2 years in patients with SLE but also did not reduce the levels of hsCRP.[99]

Immunosuppressants

In a mouse model of accelerated atherosclerosis in lupus, treatment with mycophenolate mofetil (MMF) reduced the atherosclerotic burden.[115] There is evidence in the transplant population that MMF reduces coronary allograft vasculopathy[116] and decreases cardiovascular mortality by 20% in renal transplant recipients compared with azathioprine.[117] These data bring up the intriguing possibility that MMF may prove beneficial in prevention and treatment of CVD in SLE. However, a 2-year prospective study of 25 patients with SLE treated with MMF showed no evidence of a decrease in the progression of atherosclerosis as measured by carotid IMT or coronary artery calcium compared with patients with SLE who were not treated with MMF.[118]

In contrast to MMF, data from the Hopkins cohort showed that methotrexate use was highly associated with noncalcified plaque in SLE in a multivariate analysis.[119] The homocysteine levels did not differ compared with the patients who were not on methotrexate. This was a surprising finding due to the well-documented reduced risk of cardiovascular events in patients with rheumatoid arthritis who were treated with methotrexate.[120–122]

Data from several trials are awaited with great interest. The CANTOS trial is a phase 3 clinical trial evaluating the use of canakinumab, an IL-1β inhibitor, in stable post-MI patients with persistent hsCRP elevation.[123] In mouse models, the IL-1 pathway inhibition is mediated by type I IFNs and is responsible for an antiangiogenic effect in SLE mouse models,[8] thus the role of further IL-1 inhibition in preventing progression of atherosclerosis in SLE may prove limited. The cardiovascular inflammation reduction trial[124] is a phase 3 clinical trial of low-dose methotrexate (10 mg/wk) in stable patients with CAD with persistent elevations of hsCRP, but due to the association of methotrexate with noncalcified plaque in patients with SLE, this is unlikely to be a treatment option in SLE. B cell depletion strategies primarily with antibodies targeting CD20 are being investigated and their impact on B-2 and B-1 cells and on CVD needs to be determined.[19] Further strategies targeting B cells that are investigated are inactivation of B-cell–activating factor of the tumor necrosis

factor family (BAFF) and of a proliferation-inducing ligand pathways, or the use of neutralizing antibodies against the B-cell surface markers CD19 and CD22.[125] Belimumab is a humanized monoclonal antibody that inhibits the binding of BAFF and could potentially find application in the context of atherosclerosis.[126] Several experimental treatment options are emerging: maraviroc, a CCR5 antagonist approved for use in HIV, reduced the progression of atherosclerosis profile in an ApoE$^{-/-}$mouse model by interfering with inflammatory cell recruitment into plaques and by reversing the proinflammatory.[127] The specific role of CCR5 in progression of atherosclerosis in SLE has not been studied, but studies in lupus nephritis mouse models have shown that CCR5 is upregulated before inflammatory cell infiltration is observed and its generation is restricted to sites of subsequent inflammatory cell infiltration.[128] Whether a similar process occurs in atherosclerotic plaques and whether maraviroc may have a beneficial effect in SLE remains to be seen. Other experimental approaches include blocking the CD40-TRAF6 interaction, blocking the macrophage migration inhibitory factor receptor binding, inhibition of CCL5-CXCL4, and blocking CCR2,[129] but none of these approaches have been tested in lupus models.

CONCLUSIONS

Accelerated atherosclerosis and its long-term sequelae are the major cause of late mortality among patients with SLE. Treatment strategies include an aggressive approach in therapy of traditional cardiovascular risk factors with targets equivalent to the ones used for established CVD. Smoking inhibits the effect the antimalarials and should be immediately addressed. In the absence of contraindications, hydroxychloroquine should be used in every patient. Despite the negative results of the LAPS trial, statins remain the mainstay of treatment of hyperlipidemia, whereas fish oil and niacin use are discouraged. ACE inhibitors should be used as first-line agents for treatment of hypertension to a goal of less than 120 mm Hg systolic. Aspirin should be used in any patient with SLE who has a history of CVD, positive antiphospholipid antibodies or lupus anticoagulant, history of hypertension, DM, hypercholesterolemia, and a history of smoking. Despite the lack of conclusive benefit, the treatment of vitamin D deficiency and hyperhomocysteinemia is encouraged. The role of immunosuppressives, including MMF and methotrexate, in the treatment of atherosclerosis remains to be elucidated.

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