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Focus on: Inflammatory State and Cardiovascular Risk Control: Towards a New Paradigm (II)

Anti-inflammatory Therapies for Cardiovascular Disease: Signaling Pathways and Mechanisms

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ABSTRACT

Cardiovascular diseases (CVD) are the clinical manifestation of atherosclerosis, a chronic inflammatory disease promoted by several risk factors such as dyslipidemia, type 2 diabetes mellitus, hypertension, and smoking. Acute CVD events are the result of an unresolved inflammatory chronic state that promotes the rupture of unstable plaque lesions. Of note, the existing intensive therapies modify risk factors but do not prevent life-threatening recurrent ischemic events in high-risk patients, who have a residual inflammatory risk displayed by increased C-reactive protein (CRP) levels. Better understanding of the role of innate and adaptive immunity in plaque development and rupture has led to intensive investigation of anti-inflammatory strategies for CVD. Some of them are being tested in specific clinical trials and use lower doses of existing medications originally developed for other inflammatory diseases such as rheumatoid arthritis and psoriasis, which have high CVD risk. Other investigations are retrospective and meta-analyses of existing clinical trials that evaluate the incidence of CVD in these inflammatory diseases. Others are based on preclinical testing such as vaccines. In this article, we summarize the main anti-inflammatory strategies and associated molecular mechanisms that are being evaluated in preclinical or clinical CVD studies.

Terapias antiinflamatorias para la enfermedad cardiovascular: vías de señalización y mecanismos

Palabras clave:
Antiinflamatorio
Terapia
Citocina

RESUMEN

Las enfermedades cardiovasculares (ECV) son una manifestación clínica de la ateroesclerosis, una enfermedad inflamatoria que se agrava en presencia de diferentes factores de riesgo como la dislipemia o la diabetes mellitus tipo 2. Los eventos cardiovasculares agudos son resultado de un proceso inflamatorio crónico no resuelto que facilita la rotura de placas inestables. Los tratamientos existentes reducen los factores de riesgo, pero no previenen los eventos isquémicos recurrentes en pacientes con riesgo residual inflamatorio caracterizado por altas concentraciones de proteína C reactiva. Una mejor comprensión del papel de la inmunidad innata y adaptativa en la ateroesclerosis ha llevado a la investigación de tratamientos antiinflamatorios para la ECV. Algunos ensayos clínicos consisten en la evaluación de dosis bajas de fármacos diseñados para otras enfermedades inflamatorias sistémicas con alto riesgo de ECV, como la artritis reumatoide y la soriasis. Otras investigaciones son estudios restrospectivos y metanálisis de la incidencia de ECV en ensayos clínicos que han evaluado diferentes fármacos en las enfermedades. Otras terapia, sin embargo, se basan en ensayos preclínicos, como las vacunas. En este manuscrito se resumen las principales estrategias antiinflamatorias y los mecanismos moleculares asociados que se están evaluando en ensayos clínicos o preclínicos.

INTRODUCTION

Cardiovascular diseases (CVD) are clinical manifestations of the atherosclerosis process, a chronic inflammatory disease that is accelerated by the presence of several cardiovascular (CV) risk factors. Currently, the participation of innate and adaptive

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Abbreviations

CVD: cardiovascular disease
LDL: low-density lipoprotein
RA: rheumatoid arthritis
VSMC: vascular smooth muscle cell

immunity is well established. The disease starts with endothelial dysfunction, which increases adhesion molecules expression and the permeability that facilitates the retention of immune cells. Monocyte-derived macrophages generate foam cells by taking up modified low-density lipoproteins (LDLs) which accumulate, forming fatty streak lesions, and perpetuate inflammation by producing cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α). In middle stages, various mediators induce a change in the phenotype of vascular smooth muscle cells (VSMCs), which become proinflammatory, migratory and proliferative and form the fibrous cap. The recruited T cells in lesions coordinate the adaptive immune response and exert diverse effects. Proatherogenic T helper-1 (Th-1) are highly proinflammatory, Th-2 are associated with secretion of anti-inflammatory cytokines. Regulatory T (Treg) cells, a minor subpopulation of $CD4^+$ T lymphocytes, have anti-inflammatory properties and suppress the activity of effector T cells. Th-17, mostly associated with chronic inflammation, has been suggested to be proatherogenic and a low Treg/Th-17 cellular ratio promotes acute coronary syndrome.[1] In later stages, proinflammatory cytokines TNF-α, interferon-γ (INF-γ), and IL-1 induce apoptosis in vascular smooth muscle cells (VSMCs) and macrophages, destabilizing plaques. These processes lead to an unresolved inflammatory chronic state generating unstable plaque lesions, which are a key feature of ischemic events. Acute-phase reactants, such as C-reactive protein (CRP), increase in patients with coronary artery disease and are known to predict adverse outcomes.[2]

Current CVD treatments modulate traditional risk factors and consist of hypolipemiants, hypoglycemics, antiplatelet strategies and anticoagulants, which prevent and delay plaque formation. Of note, these treatments, which include statins and antidiabetic drugs, metformin and incretin-based therapies, also exert anti-inflammatory effects. However, these intensive therapies do not prevent life-threatening recurrent ischemic events in patients at highest risk, who display a residual inflammatory risk with enhanced CRP levels.[3] Anti-inflammatory interventions might represent potential novel CV treatments with additional beneficial effects in patients at highest risk. The following sections provide a summary of the main therapeutic strategies.

CLASSIC ANTI-INFLAMMATORY DRUGS WITH POTENTIAL USE FOR CVD TREATMENT

Colchicine

Colchicine is an anti-inflammatory drug designed to treat gout and chronic familial Mediterranean fever but studies have shown that can be used to treat atherosclerosis.

Colchicine blocks microtubule polymerization by binding to free tubulin dimers affecting cellular migration, trafficking of vesicles and cytokine release.[4] Colchicine also diminishes E- and L-selectin expression in endothelial cells and chemotaxis in neutrophils.[4,5] A reduced secretion of IL-1β and IL-18 cytokine by inhibiting the activation of the (NOD)-like receptor protein 3 (NLRP3) by gout crystals has been also proposed.[6] At high doses, it can induce depolymerization of microtubule, affecting all processes with need of cytoskeleton intervention, such as cell division or deformation of neutrophil for its activity.[7] Colchicine treatment associates with TNFα-receptor downregulation in macrophages and endothelial cells.[8] NLRP3 is activated by cholesterol crystals in atherogenesis, and colchicine prevents this process.[9] It also impairs granulocyte, platelet-monocyte and platelet-neutrophil aggregations during acute events and promotes anti-inflammatory macrophages.

Colchicine has been used to treat pericarditis and a potential protection of the drug has been observed in cardiac survival and remodeling after myocardial infarction (MI).[4] Retrospective and follow-up studies in gout patients have shown a reduced incidence of MI stroke and transient ischemic attack compared with those taking other medications.[4] Several other studies in nongout diseased patients have shown that a low-dose colchicine reduced lesion volume. In postacute coronary syndrome patients with intensive lipid-lowering therapy, colchicine provoked a change in plaque morphology through a marked decrease in high-sensitivity CRP.[10]

Low-dose colchicine is undergoing detailed evaluation for safety and efficacy in large randomized controlled trials. The LoDoCo2 (Low Dose Colchicine2) clinical trial showed that colchicine decreases recurrent acute coronary syndrome events in patients with coronary artery disease.[11] The ongoing COLCOT (Colchicine Cardiovascular Outcomes Trial) clinical trial also evaluates the effects of long-term treatment with colchicine on CV events in MI patients. The use of colchicine is being tested in 2 randomized clinical trials in acute and recurrent pericarditis,[8] the Colchicine for Acute Pericarditis (COPE) trial and Colchicine for Recurrent Pericarditis (CORE). In both trials, colchicine significantly reduced the risk for recurrence and enhanced symptom-free interval compared with aspirin or prednisone.[12,13]

Allopurinol

Allopurinol is a gout prescription to reduce uric acid synthesis that acts as an inhibitor of xantine oxidoreductase (XOR), a rate-limiting enzyme in uric acid synthesis during purine metabolism.[14] XOR can also catalyze xenobiotics acting as a detoxifier in the liver and can oxidize endogenous metabolites, thus generating oxygen radical species (ROS). XOR has been shown to exert proinflammatory and prothrombotic activities of vascular endothelial cells through enhanced ROS and uric acid production.[14] In fact, serum levels of uric acid are an independent risk factor for CVD including hypertension, heart failure, and ischemic heart disease.[15] Because of these findings and retrospective studies, allopurinol was proposed as an anti-inflammatory therapy for CVD.[16] In a meta-analysis in CVD and gout patients, allopurinol treatment was associated with improved endothelial function and was even more effective in patients with normal uric serum levels,[17] which is consistent with a decrease in vascular oxidative stress independently of uric acid levels.[18] Allopurinol has also been shown to improve energy metabolism in heart failure by increasing the concentrations of myocardial high-energy phosphates and adenosine triphosphate flux.[19] In experimental animals, the drug decreases atherosclerosis development in apoE-/- mice by impairing macrophage foam cell formation[20]

and attenuates atrial structural and electrical remodeling by diminishing ROS in a rabbit model with diabetes and heart dysfunction.[21] An ongoing clinical trial in the UK (ISRCTN32017426) is currently evaluating the impact of allopurinol on CV outcomes in patients with ischemic heart disease.

Methotrexate

Methotrexate is a chemical analog of folic acid and interferes with purine and pyrimidine synthesis by inhibiting folate-dependent enzymes, such as dihydrofolate reductase through which the growth of several cell types decreases. The drug was initially developed to treat some types of cancer and is currently used for the treatment of psoriasis and rheumatoid arthritis (RA). The anti-inflammatory effects of methotrexate are attributed to the increased extracellular concentrations of adenosine and subsequent immunosuppression through binding to the A_2 adenosine receptor.[22] By adenosine binding to the A_2a receptor, the drug diminishes lymphocyte proliferation and the production of inflammatory cytokines, such as TNF-α, IL-6, IL-8, IL-10 and IL-12, being one of the most important anti-inflammatory mechanisms.[22]

In humans, a systematic review and meta-analysis showed an association between methotrexate use and a lower risk of CVD in patients with chronic inflammation.[23] Likewise, in another study in RA patients, methotrexate use was associated with decreased CVD outcomes.[24] This led to the design of the Cardiovascular Inflammation Reduction Trial (CIRT)[25] to evaluate the potential anti-inflammatory effect of low-dose of methotrexate on CV events in stable atherosclerotic patients at highest risk and with aggressive lipid-lowering therapies. However, the recently published data from this clinical trial failed to show a reduction in IL6, IL1β or CRP or in the incidence of CV episodes in methotrexate-treated patients compared with those in placebo-treated participants.[26] Of note, the authors suggested that, given the lack of effect on CRP, methotrexate could only be effective in CVD events through CRP-dependent reductions. In fact, there are associations between methotrexate and a low incidence of vascular events in patients with highly inflammatory diseases like psoriasis and RA with high CRP levels.[23,24]

Salsalate

Salsalate is a nonacetylated salicylate used in the treatment RA and osteoarthritis conditions. Salsalate compared with salycilates such as the aspirin weakly inhibits cyclooxygenase but strongly inhibits nuclear factor-κB (NFκB) activity by binding to IκB (IκK) kinase which, in normal conditions, frees the inhibitor IκK from NFκB.[27] Its potent anti-inflammatory actions are due to the decreased NFκB-mediate gene expression of proinflammatory cytokines IL-6, TNF-α and CRP.[28]

In mouse models deficient in AMPKβ1, salsalate reduced nonalcoholic fatty liver disease by an AMPK-indepent mechanism via mitochondrial uncoupling.[29] Similarly, in atherosclerotic APOE*3Leiden cholesteryl ester transfer protein (CETP) transgenic mice, salsalate improved dyslipidemia, insulin resistance and nonalcoholic steatohepatitis by downregulation of inflammatory NFκB pathways and TGF-β signaling.[30]

Studies in humans reported that salsalate reduces HbA1c levels and glycemic control in type 2 diabetes mellitus patients; however, increased urine concentration was observed.[31] In another study, salsalate therapy was associated with a reduction in early glycated end products but paradoxically with increased pentosidine levels indicative of augmented oxidative stress.[32]

Based on these actions, salsalate has been tested as an anti-inflammatory CVD treatment. In the TINSAL-CVD clinical trial, salsalate added to statin treatment did not affect coronary plaque in patients with coronary heart disease,[33] although a limitation of that study was the absence of plaque progression in the placebo group. On the other hand, results obtained from clinical trials suggest that salsalate therapy might prevent type 2 diabetes mellitus in obese participants by improving glycemic control.[34] Similarly, in other clinical trials, 1-month salsalate-treatment improved glucose and lipid homeostasis, which are risk factors for atherosclerosis,[35] and, in participants with carbohydrate metabolism derangement, salsalate-treatment reduced inflammatory and glycemic markers.[36] By contrast, salsalate therapy increased CVD risk by diminishing endothelium-dependent vasodilation.[37] Therefore, although inhibition of NFκB might reduce the inflammatory components of metabolic diseases, its effect on CVD and acute-associated events is less clear.

PHARMACOLOGIC TREATMENTS TARGETED TO SPECIFIC INFLAMMATORY MEDIATORS

TNF-α inhibitors

TNF-α antagonists were developed for the treatment of RA and there are 5 biological drugs that target TNF: infliximab, etanercept, adalimumab, certolizumab, and golimumab. Retrospective studies in RA patients under TNF-α blocking therapies have provided support for considering these drugs as anti-inflammatory agents for CVD.[38]

Serious adverse effects have been shown for TNF-α inhibitors, such as increases in total, LDL and high-density lipoprotein (HDL) cholesterol and triglycerides.[39] While long-term infliximab therapy might be proatherogenic, etanercept and adalimumab can exert beneficial effects on lipid levels.[40] TNF-α is a potent proinflammatory and proatherogenic cytokine, which, by binding to its receptor, activates NFκB and p38 mitogen-activated protein kinases, inducing the transcription of proinflammatory genes in atheroma plaque cells, lymphocytes, macrophage, endothelial cells, and VSMCs.[41] TNF-α can influence plaque vulnerability by promoting apoptosis of endothelial cells and proliferation of VSMCs.[42] In mouse models, treatment of apoE -/- mice with TNF-α-binding protein reduced plaque development[43] and double deficiency in TNF-α and apoE diminished atherosclerotic plaque formation.[44] Consistently, mice deficient in TNF receptors showed reduced vascular recruitment of immune cells and decreased atherosclerosis in LDL receptor-deficient mice.[45]

RA patients are at increased risk of the development of atherosclerosis and have a 2-fold risk of MI.[46] Observational cohort studies with patients showed that the incidence of CVD is lower in patients receiving anti–TNF-α therapy than in those receiving alternative treatments.[47,48] In psoriasis patients, treatment with anti–TNF-α inhibitors was associated with decreased intima-media thickness (IMT).[49] In RA patients, use of etanercept or adalimumab diminished aortic inflammation and inversely correlated with aortic stiffness.[50] Long-term TNF-α blockade decreased pulse wave velocity and carotid IMT in participants with inflammatory arthropathies[51] and acute CV events in participants with RA.[52] A systematic review in participants with RA and psoriatic arthritis treated with TNF-α antagonists showed decreased subclinical atherosclerosis and

arterial stiffness.[53] In in vitro studies, human serum from adalimumab-treated RA participants improved cholesterol transport in THP1 macrophages, increased serum HDL levels and increased scavenger receptor class B type I-mediated cholesterol efflux, thereby showing anti-atherosclerotic activity by preventing foam cell formation.[54]

All these findings together suggest that TNF blockade could be useful for CV prevention, although it should be reserved for high-risk individuals because of its potential adverse effects. It is necessary to promote additional studies to investigate whether agents targeting TNF-α signaling might prevent CVD.

Anti–IL-6 inhibitors

IL-6 is a key mediator of inflammation involved in many processes, including atherosclerosis and rheumatic diseases and is a unique pleiotropic cytokine, exhibiting both pro- and anti-inflammatory properties depending on the target cell type. Prospective studies have shown a detrimental effect of IL-6 receptor (IL-6R)-dependent signaling on CVD. Thus, loss-of-function of IL-6R polymorphisms results in reduced CV events.[55,56] IL-6 blockade therapies, tocilizumab and sarilumab, tested in the MONARCH and MOBILITY RA clinical trials, reported efficacy as RA therapy[57] in patients at high risk of CVD.

Tocilizumab is a monoclonal antibody of IL6R approved for use in combination with other antirheumatic drugs or as monotherapy in patients with RA and other related diseases.[58] Tocilizumab blocks the binding of IL-6 to the IL-6R, preventing inflammatory manifestations of elevated IL-6[59] and decreasing disease severity.[60] Although tocilizumab causes significant perturbations in lipid and cholesterol homeostasis, such as increases in LDL and total cholesterol,[61] it also displays beneficial effects on surrogate markers of vascular risk.[62] A recent multicenter population-based cohort study showed no evidence of increased CV risk among RA patients treated with tocilizumab.[63] Other clinical trials with a large cohort of RA patients receiving tocilizumab in a postmarketing setting have shown low rates of major adverse CV events.[64,65]

Anti-IL-17 inhibitors

IL-17 cytokine plays a key role regulating the innate and adaptive immune system in chronic inflammation, host defense, and autoimmune diseases. Therapeutic strategies to block the IL-17-signaling-pathway[66] to treat psoriasis, psoriatic arthritis and other autoimmune diseases characterized by a dramatic production of cytokines have been developed. IL-17A, the leading IL-17 cytokine, induces and synergizes other cytokines playing a central role in inflammation.[67] However, potential negative consequences of targeting IL-17 have been also described.

The drugs developed to block IL-17 are secukinumab, which is a fully human anti–IL-17A monoclonal antibody, ixekizumab and the fully human anti–IL-17 receptor A monoclonal antibody, brodalumab. Results from clinical trials have shown that these strategies are highly effective in treating psoriasis,[67] RA, psoriatic arthritis, and ankylosing spondylitis.[66,68] A more recent drug, bimekizumab, producing dual neutralization of IL-17A and IL-17F in the BE ABLE1 trial, showed substantial clinical improvements in patients with psoriasis.[69]

Although studies in atherosclerosis led to conflicting results about the role of IL-17 in plaque lesion development,[70,71] many studies have demonstrated an increased risk of CVD in psoriasis and psoriatic arthritis patients, characterized by augmented IL-17.[72] In addition, atherosclerosis subrogate markers such as carotid IMT and arterial stiffness were independently associated with psoriasis. On the grounds that both CVD and psoriasis share mechanisms involving the IL-17 cytokine, the impact of anti–IL-17 therapies in CVD in psoriatic patients is being currently evaluated.[72] In 1 study, secukinumab is being investigated in an ongoing prospective clinical trial in psoriatic patients that evaluates vascular inflammation (Vascular Inflammation in Psoriasis-Secukinumab). In addition, the clinical Trials UNCOVER-1, UNCOVER-2, and UNCOVER-3, analyzed the impact of ixekizumab treatment for 60 weeks in CVD in psoriatic patients, showing a neutral impact on CV-related parameters.[73] However, a major limitation of this latter study was the lack of data from echocardiograms. All together, these findings suggest that anti–IL-17 strategies might be a potential therapy for CVD but further progression and analysis of these and other clinical trials are needed to evaluate the their potential beneficial effects.

IFN-γ inhibitors

IFN-γ is a proinflammatory cytokine produced mainly by macrophages and T cells that coordinates innate and adaptive immunity. It is highly abundant in atheroma lesions and is associated with plaque progression. In macrophages, it induces the release of TNF-α, IL-6 and MCP1 cytokines, induces oxidative stress damage, and promotes lipid uptake and foam cell formation. In endothelial cells, it enhances the expression of adhesion molecules favoring the adhesion, retention and migration of immune cells. In VSMCs, it induces an inflammatory, migratory and proliferative phenotype.[74] It also promotes macrophage apoptosis in advanced lesions leading to plaque rupture.

IFN-γ is increased in animal models and in humans with MI. Interestingly, its levels decrease in participants with acute MI undergoing percutaneous coronary intervention.[75] By contrast, IFN-γ has been shown to attenuate cardiac hypertrophy in vivo and in cultured cardiomyocytes[76] and exerts a protective role in cardiac hypertrophy induced by pressure overload through STAT5-dependent signaling.[77]

The involvement of IFN-γ in inflammatory bowel disease, ulcerative colitis and Crohn's disease led to the development of therapies aiming to block IFN-γ. However, these have been limited by adverse effects such as an increased risk of infection. A systematic review and a meta-analysis indicated that anti–IFN-γ strategies are safe and effective in Crohn's disease.[78] Fontolizumab, a humanized anti–IFN-γ antibody was proven to be safe and well tolerated and increased disease remission in Crohn's disease.[79] In another phase 2 clinical trial, several doses of fontulizumab decreased CRP levels, suggesting a biological effect with potential for disease remission.[80]

Whether anti–IFN-γ strategies might add benefits to CVD has not been properly explored. Nevertheless, the increasing prevalence of inflammatory bowel disease in several countries has been shown to be a risk factor for CVD.[81] The reason could be that systemic inflammation leads to oxidative stress and cytokine release and that the compromised intestinal mucosa facilitates the translocation of bacteria/endotoxins, which, by exacerbating the inflammatory response will enhance arterial stiffening, atherosclerosis, ischemic heart disease, and MI. The impact of these mechanisms is just beginning to be elucidated. Studies and prospective analyses of inflammatory bowel disease participants

receiving anti–IFN-γ therapies will elucidate whether these anti-inflammatory therapies might be of use for CVD treatment.

VACCINES AS A THERAPEUTIC TOOL FOR THE TREATMENT OF CVD

The immune reaction of atherosclerosis consists of enhanced $CD4^+$T cell and antibody production and therefore immunization has been a logical therapeutic strategy to pursue. In fact, studies in humans with MI have described an inverse correlation between circulating immunoglobulin G antibody levels against apoB and the severity of coronary atherosclerosis.[82]

Given that the strongest immune reaction is against the proatherogenic LDL lipoprotein particles, potential atheroprotective-specific antigens within LDL and apoB100 have been used to boost the immune reaction. Thus, experimental settings using vaccines with whole LDL, oxidized LDL or apoB have consistently shown atheroprotection in preclinical studies. However, due to the complexity of whole particles, smaller peptides within the particle have been more closely investigated.[83] Among the LDL peptides with antigenicity, p210 decreased up to 70% of atherosclerosis burden and plaque inflammation in hypercholesterolemic mice. p210 was also shown to elicit $CD4^+$T cell response, reduce activated $CD4^+$T cells and enhance the levels of $CD4^+CD25^+Foxp3^+$ Treg cells in lymph nodes.[84] Other apoB-derived peptides are $ApoB_{3501-3516}$ and $ApoB_{978-993}$, which reduced atherosclerosis in apoE-/- mice by increasing IL10.[85] Immunizing apoE-/- mice with a vaccine with a TRBV31-derived peptide, which was a receptor from hybridoma $CD4^+$T cells responding to apoB immunization, decreased atherosclerosis by blocking recognition of apoB by T cells.[86]

Other strategies include vaccination with IgM antibody recognizing the epitopes in oxidized LDL and phosphorylcholine in apoptotic cells, heat sock proteins (HSP65)-based vaccines, and immunization against CETP, which all decreased atherosclerosis in animal models by decreasing immune responses, increasing IL-10, or augmenting $CD4^+Foxp3$ T cells.[84]

In humans, the clinical study GLACIER (Goal of Oxidised LDL and Activated Macrophage Inhibition by Exposure to a Recombinant Antibody) tested MLDL1278A (BI-204), an antibody against oxidized LDL. The clinical trial, however, which was a multicenter study to evaluate the effect of the drug in patients with standard care for atherosclerosis and with plaque inflammation, was halted in 2016 as it did not meet the primary endpoint.[87]

CONCLUSIONS

Recurrent CVD and ischemic events in patients at high risk are related to the high residual inflammatory risk. Current therapies are based on the modification of classic risk factors, such as dyslipidemia, hypertension and diabetes, but the incidence of CVD events remains unacceptably high. Therefore, specific anti-inflammatory drugs are needed to decrease this residual risk. The analysis of recurrent CVD events in patients with systemic inflammatory diseases such as RA and psoriasis treated with various anti-inflammatory drugs has provided relevant information about potential anti-inflammatory treatments for CVD. However, additional studies in inflammatory disease patients under certain treatments as well as specific clinical trials testing new drugs and new preclinical studies targeting the immune system are needed to provide effective new anti-inflammatory therapies.

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CONFLICTS OF INTEREST

None declared.

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