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REVIEW

Repurposing existing drugs for cardiovascular risk management: a focus on methotrexate

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Abstract

About 20% of patients with a history of atherosclerotic cardiovascular disease will experience further cardiovascular events despite maximal pharmacological treatment with cardioprotective drugs. This highlights the presence of residual cardiovascular risk in a significant proportion of patients and the need for novel, more effective therapies. These therapies should ideally target different pathophysiological pathways involved in the onset and the progression of atherosclerosis, particularly the inflammatory and immune pathways. Methotrexate is a first-line disease-modifying antirheumatic drug that is widely used for the management of autoimmune and chronic inflammatory disorders. There is some *in vitro* and *in vivo* evidence that methotrexate might exert a unique combination of anti-inflammatory, blood pressure lowering, and vasculoprotective effects. Pending the results of large prospective studies investigating surrogate end-points as well as morbidity and mortality, repurposing methotrexate for cardiovascular risk management might represent a cost-effective strategy with immediate public health benefits. This review discusses the current challenges in the management of cardiovascular disease; the available evidence on the effects of methotrexate on inflammation, blood pressure, and surrogate markers of arterial function; suggestions for future research directions; and practical considerations with the use of methotrexate in this context.

Keywords: arterial function, atherosclerosis, blood pressure, cardiovascular risk, inflammation, methotrexate, repurposing.

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Introduction

Atherosclerotic cardiovascular disease, particularly in the form of ischaemic heart disease and stroke, is the leading cause of morbidity and mortality worldwide. In 2013, the global risk of premature death between the ages of 30 and 70 years attributable to cardiovascular disease was 10.8% for men and 6.7% for women. The risk was highest for men in Eastern Europe and for women in Oceania and lowest for both men and women in high-income Asia-Pacific regions.[1] In 2015, ischaemic heart disease was the leading cause of health loss globally, with an estimated 7.3 million acute myocardial infarctions and 110.5 million prevalent cases of ischaemic heart disease. The prevalence of ischaemic heart disease was 290 cases per 100,000 for those 40 to 44 years of age and 11,203 cases per 100,000 for those 75 to 79 years of age. In the same year, there were an estimated 5.4 million acute first-ever ischaemic strokes. The prevalence of stroke was highest for those 74 to 79 years of age.[2]

Significant advances in the understanding of the pathophysiology of atherosclerosis have led to the concept that this disease process is characterized by a state of chronic inflammation, immune activation, and oxidative stress of the arterial wall.[3] There is also good evidence that, at some stage, virtually all cardiovascular risk factors trigger these events, favouring the onset of endothelial dysfunction and vascular damage.[4,5] For these reasons, barring the recently introduced proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors,[6] current cardiovascular drug discovery and development programmes are focused on agents that modulate the inflammatory and immune pathways, in addition

to exhibiting antiatherosclerotic and vasculoprotective effects.[7–9] However, the identification of such effects in drugs that are currently marketed would avoid the need for expensive, high-risk, and time-consuming drug development programmes, providing at the same time immediate public health benefits.[7]

This review will discuss the presence of residual cardiovascular risk as a key challenge in the contemporary management of atherosclerotic cardiovascular disease, the ongoing search for new antiatherosclerotic agents with additional anti-inflammatory effects, the emerging evidence supporting the potential repurposing of the disease-modifying antirheumatic drug (DMARD) methotrexate in this context, the opportunities for further research in this area, and the practical advantages of methotrexate treatment in the routine management of cardiovascular patients.

Residual cardiovascular risk

Despite maximal treatment with established cardioprotective drug classes, for example, statins, beta-blockers, antiplatelet agents, anticoagulants, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs), a significant number of patients with a previous atherosclerotic cardiovascular event will experience further events. Stone and colleagues prospectively studied 697 patients with acute coronary syndrome undergoing successful percutaneous coronary intervention. Upon hospital discharge, 97% were on aspirin, 97% on thienopyridines, 85% on statins or other lipid-lowering drugs, 91% on beta-blockers, and 69% on ACE inhibitors or ARBs. Barring thienopyridines, the use of cardioprotective drugs remained high, between 71 and 92%, during the follow up. However, the 3-year cumulative rate of further atherosclerotic cardiovascular events was 20%.[10] Similarly, Kaasenbrood and colleagues assessed the 10-year risk of recurrent vascular events in 6,904 patients with vascular disease. After optimal control of conventional risk factors, as per current guideline recommendations, patients with vascular disease in different arterial territories had a median estimated residual risk of 22% (interquartile range 14 to 36%).[11] Issues with poor treatment adherence in this patient group notwithstanding,[12] the available evidence suggests that approximately one in five patients with high cardiovascular risk and overt atherosclerotic cardiovascular disease will experience further cardiovascular events despite optimal pharmacological management. This observation, and the currently accepted hypothesis that atherosclerosis is an inflammatory state of the arterial wall, has led to the search for novel, more effective agents targeting atherosclerosis.

Targeting inflammation and immunity in atherosclerosis

Under physiological conditions, the endothelium, through the synthesis of the key messenger nitric oxide (NO) by endothelial NO synthase (eNOS), regulates several physiological processes such as vascular tone, arterial stiffness, blood pressure, peripheral vascular resistance, and platelet activity, and it also exerts important antiatherosclerotic effects, including the inhibition of leukocyte adhesion to the arterial wall and the prevention of vascular smooth muscle cell proliferation.[13,14] According to the 'inflammatory theory' of atherosclerosis, the excessive production of pro-atherogenic cytokines, particularly tumour necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), alters the structural and functional integrity of the endothelium, favouring the formation and progression of the atherosclerotic plaque.[4,8] This has significant biological, as well as clinical, implications as both the presence and the severity of endothelial dysfunction, either singly or in combination with other markers of arterial dysfunction, independently predict adverse cardiovascular outcomes.[15] By contrast, there is good evidence that other cytokines, particularly transforming growth factor-β (TGF-β), interleukin-10 (IL-10), and interleukin-35 (IL-35), exert protective effects against atherogenesis, including the down-regulation of TNF-α and intercellular adhesion molecule-1 (ICAM-1) in endothelial cells.[16,17]

Current research focuses on the effects of targeted cytokine therapies, that is, anti-IL-1 agents, on surrogate markers of atherosclerosis as well as cardiovascular morbidity and mortality end-points in clinical trials.[7–9,18] The introduction of such therapies would represent a significant milestone in the management of cardiovascular risk. However, the agents currently under investigation, albeit marketed for other indications (e.g. the biologic agents adalimumab, etanercept, canakinumab, anakinra, and tocilizumab), are characterized by relatively high costs and potentially serious toxicity.[18–22] These issues might limit their routine use in a significant number of cardiovascular patients. Studies are also investigating the effects of currently marketed anti-inflammatory drugs, with a wider spectrum of effects on inflammatory and immune pathways, on atherosclerosis and cardiovascular risk.[7–9] The following sections will discuss the available evidence regarding the effects of the DMARD methotrexate on cardiovascular outcomes and surrogate markers of atherosclerosis and cardiovascular risk.

Methotrexate and cardiovascular risk: epidemiological evidence

Methotrexate, an analogue of the B-vitamin folic acid, is a first-line synthetic DMARD that is routinely used, at doses between 7.5 and 25 mg weekly, in the management of rheumatoid arthritis and other autoimmune, chronic inflammatory conditions.[23,24] Epidemiological studies have shown that, when compared to other synthetic DMARDs, methotrexate significantly reduces all-cause mortality in patients with rheumatoid arthritis.[25,26] Although the mechanisms responsible for this protective effect are unknown, a study has also reported a significant reduction in cardiovascular mortality (hazard ratio [HR] 0.3, 95% confidence interval [CI]: 0.2–0.7), but

not non-cardiovascular mortality (HR 0.6, 95% CI: 0.2–1.2), with methotrexate use.[25]

Rheumatoid arthritis can be regarded as a human model of chronic systemic inflammation, accelerated atherosclerosis, and vascular damage.[27] Increased concentrations of pro-atherogenic cytokines TNF-α, IL-1, and IL-6 have been well documented in patients with rheumatoid arthritis.[28] The cardiovascular risk in rheumatoid arthritis is about two-fold that of the general population and is comparable to the risk in diabetes.[29] However, in addition to inflammation, traditional risk factors are also involved in the pathophysiology of atherosclerotic cardiovascular disease in rheumatoid arthritis.[30] There is good evidence that a significant proportion of patients with rheumatoid arthritis, even those without prior evidence of cardiovascular disease, have endothelial dysfunction, altered vascular reactivity, increased platelet activation, dyslipidaemia, and insulin resistance.[31–35] Furthermore, increased arterial wave reflection and arterial stiffness, and a relatively high prevalence of hypertension, hypercholesterolaemia, obesity, cigarette smoking, type 2 diabetes, and metabolic syndrome, have been reported in this group.[35–41] From a pathophysiological point of view, a sustained increase in arterial wave reflection, arterial stiffness, and systolic blood pressure causes a significant increase in cardiac afterload. This, in turn, favours the development of left ventricular hypertrophy and dysfunction and independently predicts cardiovascular morbidity and mortality.[42–44]

The available evidence supporting the hypothesis that methotrexate exerts protective effects against atherosclerotic cardiovascular disease in humans, when compared to other DMARDs, comes from two systematic reviews and meta-analyses. The first, in 66,334 patients with rheumatoid arthritis, psoriasis, or polyarthritis from ten cohort studies, showed that the use of methotrexate was associated with a significantly lower risk of total cardiovascular events (risk ratio [RR] 0.79, 95% CI: 0.73–0.87, $p<0.001$) and myocardial infarction (RR 0.82, 95% CI: 0.71–0.96, $p=0.01$). Stronger inverse associations between methotrexate and cardiovascular risk were observed in studies (n=6) that adjusted for underlying disease severity (RR 0.64, 95% CI: 0.43–0.95) and those (n=4) that adjusted for treatment with other DMARDs (RR 0.73, 95% CI: 0.63–0.84).[45] The second systematic review and meta-analysis reported a significant reduction in total cardiovascular events with methotrexate treatment, when compared to other DMARDs, in eight studies of 65,736 patients with rheumatoid arthritis (RR 0.72, 95% CI: 0.57–0.91, $p=0.007$). A significant reduction in the risk of myocardial infarction was also observed in a subset of studies (n=3, RR 0.81, 95% CI: 0.68–0.96).[46] It is important to emphasize that the magnitude of cardiovascular risk reduction observed with methotrexate treatment is similar to that reported in landmark trials of cardioprotective drugs in high-risk patients. For example, in the Heart Outcomes Prevention Evaluation study, the relative risk of total cardiovascular events with the ACE inhibitor ramipril versus placebo was 0.78 (95% CI: 0.70–0.86).[47] In the West of Scotland Coronary Prevention Study, the relative risk of coronary events (non-fatal myocardial infarction or death from coronary heart disease) with pravastatin treatment versus placebo was 0.69 (95% CI: 0.57–0.83).[48]

Methotrexate and cardiovascular risk factors

Several *in vitro* and *in vivo* studies have investigated the effects of methotrexate on traditional (e.g. dyslipidaemia, diabetes, hypertension) and emerging (e.g. endothelial dysfunction and arterial stiffness) cardiovascular risk factors.

Contrasting results have been reported on the capacity of methotrexate to influence the activity of the cholesterol efflux protein and the concentrations of total cholesterol and different lipoproteins.[49–60] More recently, a study in cholesterol-fed rabbits receiving combined treatment with lipid core nanoparticles containing paclitaxel and methotrexate showed a significant regression of aortic plaque and intima areas. This was associated with a reduction of macrophage presence in aortic lesions, matrix metalloproteinase 9, and TNF-α gene expression when compared to control animals.[61]

In *in vitro* studies, treatment with methotrexate increased the expression of the glucose transporter type 4 (GLUT4) in a mouse model of diabetes. This was associated with a significant reduction in serum glucose and insulin concentrations.[62] Human studies have shown significant reductions in insulin concentrations,[63] but not glucose concentrations,[51,60,64–67] during methotrexate treatment. Contrasting results have been reported on the effects of methotrexate on glycated haemoglobin concentrations.[66–68]

Cross-sectional human studies have shown trends towards lower systolic and diastolic blood pressure values in patients with rheumatoid arthritis treated with methotrexate when compared to other DMARDs or no treatment.[51,69] Similar trends have been reported in prospective studies, albeit no placebo group was included.[70–72] Trends towards a lower prevalence of hypertension in patients with rheumatoid arthritis treated with methotrexate, when compared to other DMARDs or no treatment, have also been reported, though no formal statistical analysis was presented.[73] In a recent repeated cross-sectional study, patients with rheumatoid arthritis treated with methotrexate, with or without other DMARDs, had significantly lower clinic and 24-ambulatory systolic and diastolic blood pressure and pulse-wave velocity, a marker of arterial stiffness, when compared to patients treated with other DMARDs, but not methotrexate (n=30).[74] The association between methotrexate use and blood pressure was mediated, in univariate but not in multivariate analysis, by a single-nucleotide polymorphism (SNP) of the adenosine triphosphate (ATP)-binding cassette efflux transporter gene *ABCG2* (rs2231142).[75] In further analyses, methotrexate treatment prevented the temporal increase in blood pressure mediated by arterial stiffness.[76]

In animal studies, treatment with methotrexate caused a significant impairment of endothelium-dependent (acetylcholine-mediated), but not endothelium-independent

(nitroprusside-mediated), vasodilatation.[77] By contrast, no significant changes in endothelial function were observed in patients with rheumatoid arthritis or psoriasis treated with methotrexate.[70,78] Other studies reported a significant improvement in endothelial function with methotrexate in patients with rheumatoid arthritis and other types of inflammatory arthritis.[79,80]

A significant reduction in measures of arterial stiffness was observed in patients with rheumatoid arthritis treated with methotrexate and infliximab, but not with methotrexate alone.[71] By contrast, another study reported no significant changes in arterial stiffness with methotrexate.[81]

Despite the conflicting results reported in several studies, the available evidence suggests that methotrexate might exert beneficial effects on some measures of cardiovascular risk, particularly insulin resistance, blood pressure, and, possibly, arterial stiffness.

Putative mechanisms mediating the effects of methotrexate against atherosclerosis

A number of mechanisms might account for the potential antiatherosclerotic, blood pressure lowering, and vasculoprotective effects of methotrexate, particularly cytokine modulation, adenosine accumulation, and activation of 5′ adenosine monophosphate-activated protein kinase.

Cytokine modulation

Methotrexate has been shown *in vitro* to increase the release of soluble TNF receptor p75 from the cell surface, with potential inhibition of the pro-inflammatory effects of TNF-α.[82,83] In other studies, methotrexate treatment prevented the TNF-α-induced expression of ICAM-1 and vascular cell adhesion molecule 1, both involved in favouring the adhesion of leukocytes to the endothelium in the early stages of atherosclerosis.[84] In animal studies, methotrexate significantly reduced the circulating concentrations of IL-6 and TNF-α. This was paralleled by a significant increase in endothelium-dependent vasodilatation and a reduction in vascular cell adhesion molecule 1.[85] In another study, the expression of IL-6 and TNF-α was also significantly reduced by methotrexate treatment. These effects were associated with an improvement in endothelium-dependent vasodilation in rat aorta.[86] The inhibitory effects of methotrexate on TNF-α, IL-1, and IL-6 have also been recently reported in human macrophages.[87] Notably, there is also preliminary evidence that the effects of methotrexate on pro-inflammatory cytokines are associated with a reduction in plaque burden. Four-week intravenous administration of methotrexate-loaded spherical polymeric nanoconstructs significantly reduced the production of IL-6 and TNF-α in apolipoprotein E–deficient ($ApoE^{-/-}$) mice receiving high-fat diet. These effects were associated with a 50% reduction in plaque burden.[88]

Other studies have reported beneficial effects of methotrexate treatment on antiatherogenic cytokines. In 24 patients with plaque psoriasis, 12-week treatment with subcutaneous methotrexate caused a trend towards an increase in IL-10, but not TGF-β, concentrations.[60] In patients with chronic heart failure, 12-week treatment with methotrexate significantly increased the plasma concentrations of IL-10.[89] A significant increase in IL-10 concentrations after 4- or 12-week methotrexate treatment was reported in rabbit models of in-stent neo-atherosclerosis and cardiac allograft vasculopathy, and in post-myocarditis rats.[90–92] Methotrexate treatment has also been shown to increase the local adipose tissue concentrations of IL-10 in obese mice fed with high-fat diet.[93]

Adenosine accumulation and activation of 5′ adenosine monophosphate-activated protein kinase

The intracellular polyglutamate forms of methotrexate inhibit the activity of the enzyme aminoimidazole carboxamide ribonucleotide (AICAR) transformylase (ATIC).[94] The consequent accumulation of the substrate AICAR, in turn, inhibits the enzymes adenosine deaminase and adenosine monophosphate deaminase, involved in the catabolism of adenosine.[94] Adenosine exerts blood pressure lowering effects through increased eNOS, direct vasodilation, and central nervous system pathways.[95–97] Furthermore, in human studies, the pharmacological inhibition of adenosine receptors, particularly A_1 and A_{2A},[98] has been shown to increase blood pressure and arterial stiffness.[99] There is also evidence that adenosine A_{2B} receptor activation prevents the formation of atherosclerotic lesions and reduces the plasma concentrations of cholesterol and triglycerides, possibly through the reduced activation of the transcription factor sterol regulatory element-binding protein 1 in the liver.[100,101]

Both AICAR and adenosine monophosphate deaminase activate the 5′ adenosine monophosphate-activated protein kinase (AMPK).[102] AMPK protects endothelial cells against oxidative stress and apoptosis and inhibits vascular smooth muscle cell proliferation.[103–105] There is increasing evidence that AICAR and/or AMPK activation stimulates NO synthesis in the endothelium, enhances endothelium-dependent and endothelium-independent vasodilation, reduces blood pressure, prevents vessel restenosis, and increases cholesterol efflux capacity.[106–111] Furthermore, AMPK stimulates cellular glucose uptake, through GLUT-1 and GLUT-4 transporters, and glycolysis, providing beneficial effects on glucose homeostasis.[112]

Current and future research directions

Further experimental and clinical studies are required to support the repurposing of methotrexate for the management of patients with atherosclerotic cardiovascular disease.

In particular, studies should investigate the effects of methotrexate on different cardiovascular end-points and also determine the role of pro- and antiatherogenic cytokines, adenosine, AMPK activation, methotrexate polyglutamate concentrations (a robust marker of methotrexate intracellular exposure), and genetic polymorphisms of methotrexate transporters and target enzymes,[75,113] in mediating these effects. While appropriately powered trials, using either placebo or other DMARDs as comparator, should ultimately test the hypothesis that methotrexate reduces cardiovascular morbidity and mortality both in patients with and without autoimmune disorders, a number of trials addressing this issue are already in progress or have recently been completed. The results of a relatively small (n=84) study have been disappointing. The Effects of Methotrexate Therapy on ST Segment Elevation Myocardial Infarctions trial (TETHYS, clinicaltrials.gov identifier NCT01741558), investigated the role of methotrexate in reducing infarct size when administered within the first 6 hours of admission for ST-elevation myocardial infarction. Methotrexate was given as intravenous bolus, 0.05 mg/kg, immediately before percutaneous coronary intervention, followed by 0.05 mg/kg/hr for 6 hours. The infarct size in patients treated with methotrexate was not significantly different from that of patients receiving placebo. Furthermore, in univariate analysis, the left ventricular ejection at 3 months was lower in the methotrexate group when compared to the placebo group.[114] Another study is currently investigating the effects of methotrexate carried by a lipid nanoemulsion, 40 mg/m^2 single dose intravenously, on left ventricular remodelling in 50 patients with anterior wall ST-elevation myocardial infarction (clinicaltrials.gov identifier NCT03516903). The recruitment for the Cardiovascular Inflammation Reduction Trial (CIRT, clinicaltrials.gov identifier NCT01594333), a large randomized placebo-controlled trial investigating whether methotrexate, 15–20 mg weekly as single oral dose, reduces a composite primary end-point of myocardial infarction, stroke, and cardiovascular death in 7,000 patients with type 2 diabetes or metabolic syndrome and stable coronary artery disease, has been prematurely stopped in April 2018. The trial has accrued enough data to answer the main question of the study and it is anticipated that the results will be presented by the end of 2018.[115] The Inflammation and Coronary Endothelial Function in Patients with Coronary Artery Disease Trial (clinicaltrials.gov identifier NCT02366091) is investigating the effect of 15 mg oral methotrexate weekly, colchicine, and their combination on coronary endothelial function in 120 patients with established ischaemic heart disease. Furthermore, the Methotrexate, Blood Pressure and Arterial Function Study (clinicaltrials.gov identifier NCT03254589) is investigating the effects of methotrexate treatment, 7.5–25 mg weekly, on clinical and 24-hour peripheral and central blood pressure in 124 patients with rheumatoid arthritis. The results of these studies will provide important additional information to support, or refute, the possible role of methotrexate in the management of patients with atherosclerotic cardiovascular disease.

Practical considerations with the use of methotrexate in cardiovascular risk management

Methotrexate is a relatively old drug that has been used, at high doses, for the treatment of different types of cancer and, more recently, at lower doses, for the treatment of several autoimmune disease states.[116–118] Treatment with high- and low-dose methotrexate is associated with gastroenterological, haematological, renal, neurological, pulmonary, and mucocutaneous toxicity of different severity.[119,120] However, with appropriate dosing and monitoring, the main side effects of methotrexate, particularly hepatic, gastrointestinal, and haematological toxicity, are infrequent and rarely severe. In a naturalistic study of 673 patients with inflammatory arthritis receiving methotrexate, mainly rheumatoid arthritis, 74% remained on treatment after 5 years. Methotrexate was stopped in 10.7% because of inefficacy or patient choice. Serious adverse events included liver abnormalities in 5.5% and haematological abnormalities in a further 5.5%.[121] In the CareRA study of 379 patients with rheumatoid arthritis randomized to 1-year treatment with methotrexate + other DMARDs and/or corticosteroids, 2.1% reported serious adverse events.[122] The safety profile of methotrexate in these studies compares favourably with trials of conventional cardioprotective drugs, for example, antihypertensive agents, in patient populations without autoimmune conditions. For example, in the Systolic Blood Pressure Intervention Trial in 9,069 patients with high cardiovascular risk, 9.8% (intensive treatment arm) and 7.2% (standard treatment arm) had serious adverse events.[123] In the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial in 25,620 patients with vascular disease or high-risk diabetes, serious adverse events leading to treatment discontinuation occurred in 7.2% of those randomized to ramipril, 5.1% of those randomized to telmisartan, and 12.0% of those randomized to combination treatment.[124]

A potential advantage associated with methotrexate treatment is the once-weekly administration, either orally or subcutaneously. By contrast, virtually all cardiovascular drugs currently used require daily administration. The less-intense treatment schedule with methotrexate has the potential to increase treatment adherence, which remains a significant issue in the routine management of patients at high cardiovascular risk. For example, a recent study showed that only 49% of older patients after an acute myocardial infarction (n=90,869) were adherent to three standard therapies: ACE inhibitors or ARBs, beta-blockers, and statins. Notably, the lack of adherence to these therapies was independently associated with increased mortality (HR 1.65, 95% CI: 1.54–1.76).[125] Similarly, a systematic review and meta-analysis reported that the non-adherence rate to secondary prevention treatment after a stroke is 30.9% (95% CI: 26.8–35.3).[126]

Repurposing methotrexate for cardiovascular risk management, at doses similar to those currently prescribed

in patients with autoimmune disorders, would also be highly cost effective. For example, in Australia the Prescribing Benefits Scheme cost of methotrexate 7.5–25 mg once a week is $94.8–109.68/year per individual patient. This is less than half of that of atorvastatin ($222.48–258.60/year) and perindopril ($222.60–256.68/year), the most commonly prescribed statin and ACE inhibitor in Australia, respectively. The corresponding cost figures for methotrexate, atorvastatin, and perindopril in the United Kingdom are £8.35–55.64/year, £7.95–22.42/year, and £64.60–80.18/year, respectively. Notably, the yearly costs of anakinra, a marketed IL-1 antagonist for the treatment of rheumatoid arthritis currently under investigation as antiatherosclerotic agent, are $514.91 in Australia and £9,568.21 in the United Kingdom.

Conclusions

The recognition that atherosclerosis is a chronic inflammatory disease of the arterial wall and that significant residual cardiovascular risk exists in a substantial number of patients despite maximal treatment with established drugs such as statins, beta-blockers, antiplatelets, anticoagulants, ACE inhibitors, and ARBs, justifies the need for novel, effective therapies that target multiple pathways, including inflammation. Recent studies have highlighted the beneficial effects of currently marketed anti-inflammatory drugs, such as colchicine and hydroxychloroquine, in reducing cardiovascular events in patients with stable coronary artery disease and in patients with rheumatoid arthritis.[127–130] Methotrexate has also the potential to be repurposed for the management of patients with atherosclerotic cardiovascular disease and residual cardiovascular risk treated with currently recommended cardioprotective agents, in view of a unique combination of anti-inflammatory and, possibly, blood pressure lowering and vasculoprotective effects. In this context, the identification of the patients who are most likely to benefit from methotrexate treatment might require additional stratification by measuring pro-atherogenic, and possibly antiatherogenic, cytokine concentrations. However, only after the completion of several prospective studies investigating the effects on surrogate cardiovascular end-points as well as morbidity and mortality, can the exact therapeutic role of methotrexate be established in this context.

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