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The JAK–STAT pathway: an emerging target for cardiovascular disease in rheumatoid arthritis and myeloproliferative neoplasms

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Inflammation contributes centrally to cardiovascular diseases, and anti-inflammatory treatments can reduce cardiovascular events. The JAK–STAT pathway is an emerging target in inflammation, mainly in rheumatoid arthritis (RA) and chronic myeloproliferative neoplasms (MPNs), disorders that heighten cardiovascular risk. The aim of this study was to review the international literature on the relationship between dysregulation of the JAK–STAT pathway in RA/MPNs and cardiovascular risk and on the potential cardiovascular effects of JAK–STAT inhibitors. The JAK–STAT pathway sustains inflammatory and thrombotic events in autoimmune disorders such as RA and MPNs. Here, an imbalance exists between pro- and anti-inflammatory cytokines [increased levels of interleukin (IL)-6, IL-1-β, tumour necrosis factor-α, decreased levels of IL-10] and the over-expression of some prothrombotic proteins, such as protein kinase Cε, on the surface of activated platelets. This pathway also operates in atherosclerotic cardiovascular disease. JAK–STAT inhibitors may reduce cardiovascular events and related deaths in such conditions, but the potential of these agents requires more studies, especially with regard to cardiovascular safety, and particularly for potential prothrombotic effects. JAK–STAT inhibitors merit consideration to curb heightened cardiovascular risk in patients with RA and MPNs, with rigorous assessment of the potential benefits and risks.

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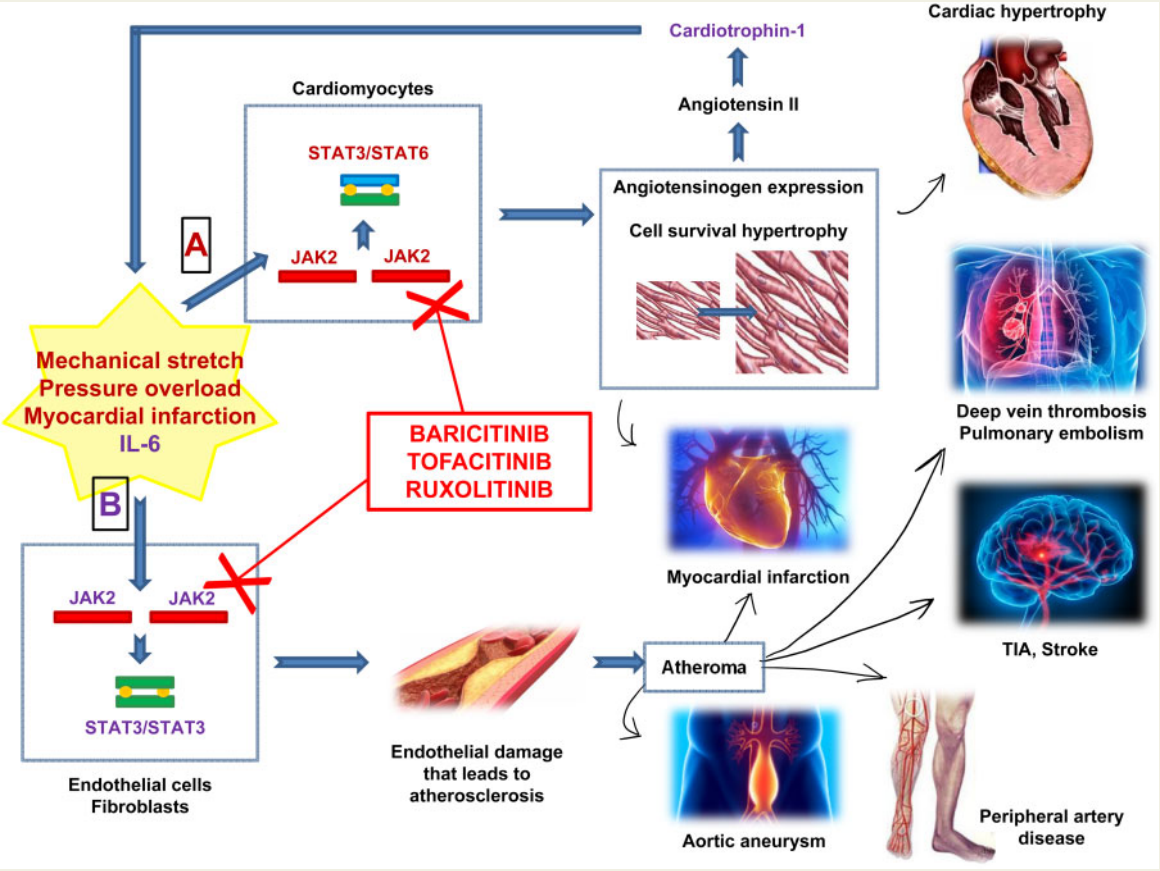
Graphical Abstract



Clinical effects of JAK–STAT pathway activations and JAK–STAT inhibitors. (*A*) Stimuli, such as mechanical stretch, pressure overload and myocardial infarction, activate the JAK2/JAK2-STAT3/STAT6 pathway. This way allows the expression of the angiotensinogen gene promoter in cardiac myocytes. Angiotensinogen eventually leads to the production of angiotensin II that in turn induces the production of cardiothropin-1, a member of the IL-6 family, ultimately producing cardiac hypertrophy. The clinical effects of this pathway are cardiac hypertrophy or myocardial infarction (both could result in heart failure). Cardiotrophin-1 in turn allows the activation of the B-pathway. (*B*) Cytokines, such as IL-6, could activate the JAK2/JAK2-STAT3/STAT3 pathway in fibroblasts and endothelial cells. They are responsible for the endothelial damage that leads to atherosclerosis, with the formation of atheroma. There are several events linked to atherosclerotic cardiovascular disease, such as myocardial infarction, deep vein thrombosis and pulmonary embolism, cerebrovascular events (transient ischaemic attack, stroke), peripheral artery disease, and the formation of aortic aneurysms. JAK–STAT inhibitors, through the inhibition of the JAK–STAT pathway, may represent a way to prevent these adverse cardiovascular events. Baricitinib (JAK1/JAK2 inhibitor), tofacitinib (JAK1/JAK2/JAK3 inhibitor) and ruxolitinib (JAK1/JAK2 inhibitor) are treatment approved in RA and in MPNs that are hypothesized to have potential cardiovascular benefit.

Keywords Cardiovascular disease • Rheumatoid arthritis • Inflammation • Atherosclerosis • Myeloproliferative neoplasm • JAK–STAT pathway • Tofacitinib • Baricitinib • Ruxolitinib

Introduction

Cardiovascular diseases cause nearly one-third of deaths worldwide.[1] Atherosclerosis is the most important substrate for cardiovascular diseases, with acute myocardial infarction (MI), stroke, and ischaemic cardiomyopathy being major causes of death and disability.[2] The participation of inflammation in cardiovascular diseases has come into focus as clinical trials have validated a large body of biomarkers and experimental work. Immune-inflammatory cells foster the initiation and subsequent development of atherosclerosis. Individuals at risk of developing cardiovascular diseases have increased levels of inflammatory cytokines or biomarkers of their activation, such as C-reactive protein (CRP).[3,4] These findings have encouraged clinical research in targeting inflammatory molecules, with the aim of reducing cardiovascular risk.[5–10]

From this perspective, the JAK–STAT inflammatory pathway has recently attracted interest. The JAK–STAT pathway participates in the pathogenesis of several autoimmune diseases including

rheumatoid arthritis (RA)[11–13] and myeloproliferative neoplasms (MPNs),[14] but it also operates in cardiovascular diseases.[15] Recently, several JAK–STAT inhibitors have become available for the treatment of RA[16] and MPNs[17] and are under evaluation for other rheumatological disorders including systemic lupus erythematosus,[18,19] autoinflammatory diseases and giant cell arteritis.[12] Considering that both rheumatological and haematological disorders are themselves characterized by increased cardiovascular risk[11–15,20,21] the use of JAK inhibitors in these conditions affords a unique opportunity to understand their therapeutic role in atherosclerosis.

We here therefore review the evidence for the hypothesis that these inhibitors benefit cardiovascular diseases in the two specific conditions, RA and MPNs, where they have been most studied.

The JAK–STAT pathway in physiology and disease

Janus kinases (JAKs) comprise a family of intracellular non-receptor tyrosine kinases. Originally named 'just another kinase', these enzymes were subsequently renamed 'Janus kinases' from the name of Janus, the two-faced Roman god of beginnings, endings and duality. This is because JAKs possess two nearly identical phosphate-transferring domains: one exhibiting kinase activity and the other one inhibiting the kinase activity of the former. There are four currently listed JAK proteins—JAK1, JAK2, JAK3, and TYK2—involved in signalling activated by various members of cytokine receptor families.[22]

Members of the *signal transducer and activator of transcription* (STAT) protein family are intracellular transcription factors that mediate many aspects of cellular immunity, proliferation, apoptosis, and differentiation. There are seven STAT proteins—STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6—activated by different combinations of cytokines or growth factors in addition to the JAK proteins.[22] STATs require activation by the recruitment of a receptor complex, consisting of two JAK combinations and several cytokines, growth hormones, or growth factors.

Signalling through the JAK–STAT pathway (*Figure 1*) begins when a cytokine binds to its corresponding receptor. This ligation leads to conformational changes in the cytoplasmic moiety of the receptor, activating receptor-associated members of the JAK family. These JAK proteins, in turn, mediate the phosphorylation at specific tyrosine residues of the receptor's cytoplasmic domains, which then serve as docking sites for STATs and other signalling molecules. Once recruited to the receptor, STATs also become phosphorylated by JAKs on a single tyrosine residue. Activated STATs then dissociate from the receptor, dimerize, translocate to the nucleus, and bind to members of the gamma-activated site family of enhancers. This event allows the transcription of different portions of DNA-targeted genes that encode molecules involved in processes of proliferation, differentiation, and apoptosis.[23] Modulators of the signal transduction to the nucleus include inhibitory molecules, such as *suppressors of cytokine signalling* (SOCSs) and *protein tyrosine phosphatases* (PTPs). SOCSs act by negative feedback, binding to JAK proteins or to the cytokine receptors, and limiting STAT phosphorylation. PTPs remove phosphate groups from phosphorylated tyrosine residues on JAKs and STATs.[24]

In several pathological states, the JAK–STAT pathway does not operate in a physiological manner. This is because of mutations—sporadic or inherited—of the signalling elements involved directly in the pathway or in regulatory molecules. Different clinical manifestations may then occur, depending on which combination of ligands, JAK and STAT proteins, DNA sequences, or regulatory proteins are defective compared with the physiological situation. Consequently, derangements of the pathway may contribute to rheumatological diseases or to MPNs.[25]

Several aspects of the JAK–STAT pathway still require full elucidation. These include cell-intrinsic and -extrinsic factors that govern its activity, molecular, and genomic mechanisms with epigenetic and transcriptional effects, causes that induce and maintain JAK mutations, and the correlation between biology and clinical manifestations of dysregulated JAK–STAT signalling. Nevertheless, the rapidly accumulating knowledge on these aspects should lead to development of novel possible pathway-targeting drugs and their practical implementation in disease states.[23]

Atherosclerosis, inflammation, and the JAK–STAT pathway

The relationship between cardiovascular diseases, atherosclerosis, and inflammation has gained wide recognition over the past 20 years[26] and provides a background for the role of the JAK–STAT pathway in modulating cardiovascular risk. Inflammatory activation of the arterial endothelium occurs early in the development of atherosclerosis. Inflammatory cytokines, such as *interleukin* (IL)-1, IL-6, and *tumour necrosis factor* (TNF)-α, which orchestrate the clinical course of RA and other inflammatory diseases, play a pivotal role in endothelial activation and dysfunction, inhibiting the production of nitric oxide and cyclooxygenase-1.[27] Endothelial activation in turn increases vascular permeability, leucocyte adhesion, and propensity to thrombosis. After monocyte adhesion to the activated, 'inflamed' endothelium, these cells migrate into the intima, mature into macrophages, and accumulate lipids, forming foam cells.[28] Smooth muscle cells can undergo metaplasia to acquire characteristics of foam cells as well.[29] Platelets can also adhere to the endothelium, leading to the release of several mediators. These stimuli, in concert with molecules derived from macrophages and activated T lymphocytes, induce smooth muscle cell migration, proliferation, and increased production of extracellular matrix.[30] These processes result in the formation of atheromata, dynamic lesions consisting of dysfunctional endothelial cells, modulated smooth muscle cells, and admixed T lymphocytes and macrophages of various subtypes.[31] These various leukocytes can each release mediators that promote further changes in the vessel wall. As lesions progress, cell death releases lipids and necrotic debris.[26] The net result of macrophage and T-cell activation is the local production of cytokines and chemokines that further activate inflammatory cells, such as polymorphonuclear neutrophils. In advanced or disrupted human atheromata, neutrophils may contribute to lesion inflammation through release of numerous mediators such as myeloperoxidase, calgranulins, and formation of neutrophil extracellular traps (NETs).[32–37] Activated macrophages actively produce reactive oxygen species that enhance low-density lipoprotein (LDL) oxidation and elaborate growth factors driving smooth muscle

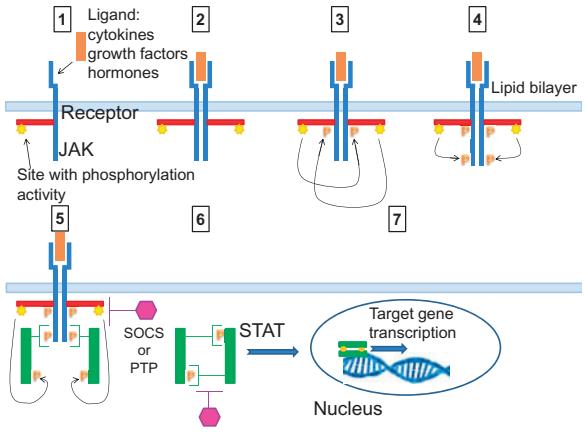


Figure 1 Signalling through the JAK–STAT pathway. (1) The signal through the JAK–STAT pathway is initiated when a ligand (e.g. cytokines, growth factors, hormones) binds to its corresponding transmembrane receptor. (2) Ligand binding causes receptor dimerization. (3) This leads to the activation of the receptor-associated members of JAKs through proximity-mediated trans-phosphorylation. (4) JAKs are endowed with a phosphorylation site. This mediates the phosphorylation of a specific tyrosine residue of the receptor, which then becomes a docking site for latent cytoplasmic STAT proteins. (5) Inactive STAT proteins associate with the phosphorylated receptor, allowing the JAK protein to phosphorylate its C-terminus on a single tyrosine residue. (6) Activated STATs then dissociate from the receptor, dimerize, and translocate to the nucleus. (7) Here, they bind to nuclear DNA. This allows the transcription of specific DNA-targeted genes that encode for molecules involved in processes of proliferation, differentiation, and apoptosis. (8) The signal transduction to the nucleus is turned-off by inhibiting molecules, such as suppressors of cytokine signalling and protein tyrosine phosphatases.

cell proliferation and extracellular matrix production.[38] This connective tissue typically forms a fibrous cap beneath the luminal surface that overlies a central core of lipid-laden cells and fatty debris that may then accumulate calcium mineral. The accumulation of cholesterol crystals and free fatty acids in macrophages and other cells also leads to activation of pattern recognition receptors and cytosolic innate immune receptors. The latter include components of inflammasomes, multiprotein oligomers of the innate immune system that mediate inflammatory responses.[39,40] Inflammasome activation leads to the maturation of IL-1β and IL-18, pro-inflammatory mediators that promote further leucocyte recruitment, including monocytes, and activated T lymphocytes.

The intimal plaque grows initially abluminally, preserving the lumen calibre, but may progressively encroach on the arterial lumen often accompanied by a thinning of the underlying tunica media. Rupture of the fibrous cap that separates the necrotic core from the flowing blood or superficial erosion may eventually cause an acute thrombotic event[41–43] due to the sudden exposure of the highly thrombogenic material in the plaque to the blood, with the release of subendothelial von Willebrand factor, collagen, tissue factor (TF), as well as an array of mediators including platelet-derived thromboxane A_2.[44] Locally produced and circulating plasminogen activator inhibitor-1 can limit endogenous thrombolysis, favouring thrombus accumulation.

Inflammatory biomarkers to assess cardiovascular risk

Elevated plasma concentrations of pro-inflammatory mediators, such as cytokines and chemokines, adhesion molecules (*intercellular adhesion molecule-1, vascular cell adhesion molecule-1*), and acute-phase reactants (CRP, fibrinogen), have undergone extensive study, delineating them as markers of different phases of atherosclerosis and overt cardiovascular diseases. Many cell types can produce cytokines that mediate and regulate immune and inflammatory reactions, not only leukocytes but also endothelial, epithelial, and mesenchymal cells. These molecules circulate in the bloodstream and can affect distant tissues.[45] Their plasma concentrations can serve, therefore, to predict their peripheral action and the severity of ensuing tissue injury. For example, CRP is a biomarker that—alone or in combination with clinical and other serum markers—can predict the occurrence of a first acute MI and ischaemic stroke in healthy humans.[46,47] CRP derives largely from the liver in response to IL-6. This cytokine contributes causally to atherosclerotic events, while CRP is a downstream readout of IL-1β/IL-6 production and of the activation of other inflammatory pathways and most likely does not contribute directly to atherosclerotic disease.[48,49] CRP detected by a high-sensitivity assay (high-sensitivity CRP) has emerged as the benchmark biomarker for inflammatory risk in atherosclerotic disease.[50,51]

Interleukin-6 and the JAK–STAT pathway: a two-faced Janus cornerstone in atherosclerosis and cardiovascular diseases

Among the atherosclerosis-related stimuli of JAK–STAT signalling, interferons and cytokines figure prominently. Interferon gamma (IFN-γ) augments atherosclerosis and signals through JAK1 and JAK2.[52–54] IL-6 participates in many biological processes, including the activation of B cells, haematopoiesis and oncogenesis, as well as in the regulation of cell growth, gene activation, proliferation, survival,

and differentiation.[55] IL-6 may have direct pro- and anti-atherogenic effects and contributes causally to human atherosclerotic events.[56] IL-6 signalling is complex:[57–59] *classical signalling* involves engagement of the canonical IL-6 surface receptor (CD126) found primarily on hepatocytes and leukocytes by the soluble ligand IL-6. After binding IL-6, CD126 associates with gp130 that signals to JAK–STAT components downstream. Cleavage of CD126 by proteinases of the ADAM (short for *a disintegrin and metalloproteinase*) family generates a circulating soluble form of CD126 that can bind IL-6 and partner promiscuously with gp130, expressed by many cells, a pathway designated *trans signalling*. The roles of *trans*- and *classical* IL-6 signalling in atherosclerosis have engendered controversy.[59,60] Recent human data, however, support a net pro-inflammatory effect of IL-6 signalling in humans.[61]

Binding of IL-6 to its receptor initiates several cellular events, including the activation of JAK- and Ras-mediated signalling. Activated JAKs phosphorylate and activate STAT transcription factors, particularly STAT3 and Src homology-2 domain-containing tyrosine phosphatase (SHP2).[62] Phosphorylated STAT3 then forms a dimer and translocates to the nucleus to induce the transcription of genes containing STAT3-responding elements, dealing with cell survival and cell-cycle transitions.[63] In addition to eliciting acute phase protein production in hepatocytes, IL-6 induces lipolysis and fat oxidation[57,63] (*Figure 1*).

Many cell types involved in atherogenesis or myocardial diseases express STAT family members including cardiac myocytes, fibroblasts, and endothelial cells. Various stimuli that activate hypertrophic growth of cardiac myocytes or provide cardioprotection, as well as those occurring after mechanical stretch, pressure overload or MI, can activate the JAK–STAT signalling.[64] Profound alterations in the JAK–STAT signalling pathways can occur in patients with end-stage dilated cardiomyopathy, where tyrosine phosphorylation of JAK2 is diminished, while increased gp130 phosphorylation occurs, indicating impaired downstream activation of this critical pathway.[65] Activation of JAK leads to phosphorylation and activation of STAT substrates. JAK2 phosphorylates STAT3 or STAT6, which then activate the angiotensinogen gene promoter in cardiac myocytes. Angiotensinogen eventually leads to the production of angiotensin II that in turn induces the production of cardiotrophin-1, a member of the IL-6 family, ultimately producing cardiac hypertrophy.

On the other hand, several studies have demonstrated that STAT3 also mediates cardioprotective signalling when the pathway is activated by the anti-inflammatory cytokine IL-10.[66,67] This activation may exert protective effects in the heart, such as compensatory hypertrophy or a reduction in apoptosis.[15] Thus, the JAK–STAT pathway, in keeping with the reminiscence of Janus, can either promote or protect diseases of the myocardium and the coronary arteries.

Anti-inflammatory therapies and cardiovascular diseases

Several recent studies have highlighted the central role of inflammation in provoking cardiovascular events by targeting inflammatory pathways. Although statins exert anti-inflammatory activity independent of LDL lowering, analyses cannot rigorously deconvolute the relative contribution of these two actions. Trials of agents that act primarily as anti-inflammatory agents in cardiovascular disease have studied the anti-IL-1β monoclonal antibody canakinumab, as well as methotrexate and colchicine and the anti-IL-6 receptor monoclonal antibody tocilizumab (*Table 1*).

Particularly, it is still debated whether tocilizumab, an IL-6 receptor inhibitor used in active RA, exerts any influence on cardiovascular risk. Current literature has not yet proven a clinically relevant cardioprotective effect for tocilizumab in RA. However, tocilizumab appears to reduce ApoLp(a) within LDL particles despite increasing their serum levels and increases protective HDL.[74] Tocilizumab also decreases leptin levels in RA patients, another potentially beneficial cardiovascular effect in such patients.[75]

Rheumatoid arthritis: a main emerging arena for JAK–STAT inhibitors

RA exemplifies a disease in which inflammation, and in particular the JAK–STAT pathway, plays a central role, and for which agents, such as JAK–STAT inhibitors, may play a role in curbing the associated cardiovascular risk. RA is a chronic inflammatory autoimmune disorder characterized by a chronic synovitis of the joints, but also fostering significant cardiovascular morbidity and mortality.[21,76–78] The threads that link joint damage and increased cardiovascular risk in RA include the participation of multiple cytokines (i.e. IL-6, IL-1, TNF), the downstream signalling of which crucially involves JAK–STAT.[79] In RA, the JAK–STAT pathway appears to be constitutively activated, thus leading to the progression of joint damage through a higher expression of matrix metalloproteinase genes, chondrocyte apoptosis, and apoptosis resistance in the synovial tissue.[80] In particular, among inhibitors of the JAK–STAT pathway, SOCS proteins appear deficient in RA,[81,82] promoting the pathway constitutive activation. The same inflammatory cascade that affects the joints can mediate RA-associated endothelial inflammation, contributing to the development of cardiovascular complications.[83,84]

Blockade of JAK–STAT signalling can improve the clinical manifestations and progression of RA.[85] Accordingly, the US Food and Drug Administration (FDA) already in 2014 approved the first JAK1/3-selective small molecule inhibitor (SMI) tofacitinib for the treatment of RA.[86] Currently, three oral JAK inhibitors (tofacitinib, baricitinib, and upadacitinib) have received FDA approval for the treatment of RA. Baricitinib is a selective oral JAK1/2 inhibitor with moderate activity against TYK2 and significantly less inhibition of JAK3,[87] whereas upadacitinib is an oral JAK1-selective inhibitor.[88,89] In Japan, peficitinib, another pan-JAK inhibitor, has received approval,[90] and the pipeline now lists several other molecules, such as filgotinib and decernotib.[91] Overall, phase II and III randomized controlled trials (RCTs) have demonstrated the efficacy of JAK inhibitors in both RA patients with inadequate response to conventional synthetic drugs or disease-modifying antirheumatic drugs (DMARDs) and in patients with inadequate response or intolerance to TNF inhibitors.[85] According to the European League Against Rheumatism (EULAR) recommendations, JAK inhibitors, either combined with a

Table 1 Main trials of anti-inflammatory strategies to avert cardiovascular events

First author and reference	Study name	Year of start and follow-up duration	Study population	Intervention	End points	Results
Ridker *et al.*,[68] USA	JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosurvastatin)	2003, median follow-up of 1.9 years (maximum, 5.0)	Healthy people with high levels of hsCRP (≥2 mg/L), but LDL-C 130 mg/dL (3.4 mmol/L)	Rosuvastatin 20 mg daily	MI, stroke, arterial revascularization, hospitalization for unstable angina, or death from CV causes	Rosuvastatin reduced LDL-C levels, hsCRP levels, and the main CV outcome
Ridker *et al.*,[69] USA	CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study)	2011, median follow-up of 3.7 years	Patients with previous MI and hsCRP ≥2 mg/L	Canakinumab 50 or 150 or 300 mg every 3 months	Nonfatal MI, nonfatal stroke, or CV death	The 150 mg dose of canakinumab every 3 months led to a rate of recurrent CV events significantly lower than placebo
Kleveland *et al.*,[70] Norway	Effect of a single dose of the IL-6 receptor antagonist tocilizumab on inflammation and troponin T release in patients with NSTEMI	2011, follow-up of 6 months	Patients with NSTEMI	Single dose of 280 mg of tocilizumab	hsCRP and hsTnT	Tocilizumab attenuated the inflammatory response and TnT release
Ridker *et al.*,[71] USA	CIRT (CV Inflammation Reduction Trial)	2013, median follow-up of 2.3 years	Patients with previous MI or multivessel coronary disease who additionally had either type 2 diabetes or the metabolic syndrome	Methotrexate 15–20 mg weekly	Composite of MI, stroke, CV death or hospitalization for unstable angina that led to urgent revascularization	Methotrexate did not reduce levels of IL-1β, IL-6, or hsCRP and did not result in fewer CV events than placebo
Nidorf *et al.*,[6] USA	LoDoCo (Low-Dose Colchicine)	2013, median follow-up of 3 years	Patients with stable coronary disease receiving aspirin and/or clopidogrel and statins	Colchicine 0.5 mg daily	A composite of acute coronary syndrome, cardiac arrest or ischaemic stroke	Colchicine 0.5 mg daily was safe and effective in reducing the risk of CV events
Nidorf *et al.*,[9] USA	LoDoCo2	2014, 30-Day run-in phase	Patients with stable coronary disease receiving aspirin and/or clopidogrel and statins	Colchicine 0.5 mg daily	Reduce the incidence of composite acute coronary syndrome, cardiac arrest or ischaemic stroke	Confirmation of the safety and benefit of colchicine 0.5 mg daily for secondary prevention of CV events
Hennessy *et al.*,[72] Australia	LoDoCo-MI (Low-Dose Colchicine after Myocardial Infarction)	2015, follow-up of 30 days	Patients with acute MI	Colchicine 0.5 mg daily	Proportion of patients with residual hsCRP level ≥2 mg/L after 30 days of treatment	The treatment was safe and well tolerated, but it was not associated with a

Continued

Table I *Continued*

First author and reference	Study name	Year of start and follow-up duration	Study population	Intervention	End points	Results
						significant reduction of hsCRP level
Tardif *et al.*,[8] Canada	COLCOT (Colchicine CV Outcomes Trial)	2015, median follow-up of 22.6 months	Patients within 30 days after an MI	Colchicine 0.5 mg daily	A composite of death from CV causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization	Colchicine produced a 23% lower composite efficacy endpoint but did not lower hsCRP level compared to placebo
Giles *et al.*,[73] USA	ENTRACTE (A Clinical Outcomes Study to Evaluate the Effects of IL-6 Receptor Blockade With Tocilizumab in Comparison With Etanercept on the Rate of CV Events in Patients With Moderate to Severe Rheumatoid Arthritis)	2016, follow-up of 4.9 years	Patients with active RA who had inadequate response to conventional synthetic disease-modifying antirheumatic drugs and who had at least 1 CV risk factor	Tocilizumab 8 mg/kg/month or Etanercept 50 mg/week	Comparison of time to first occurrence of a major adverse CV event	Tocilizumab was associated with a relative risk of 1.43 for the occurrence of major CV events compared to etanercept

CV, cardiovascular; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NSTEMI, non-ST elevation MI; RA, rheumatoid arthritis.

conventional synthetic DMARD or in monotherapy, are now indicated as second-line treatment for moderate-to-severe active RA in patients with an inadequate response or intolerance to methotrexate.[92]

Cardiovascular risk in patients with rheumatoid arthritis

Patients with RA have an incidence of cardiovascular events threefold higher than the general population.[93] RA patients suffer about the double of cardiovascular disease-associated deaths compared with control subjects.[83,94] Traditional cardiovascular disease risk factors, including smoking, hypertension, insulin resistance, obesity and physical inactivity, play an important role in explaining the higher cardiovascular disease risk in RA.[95] The lipid profile in RA patients is characterized by the so called 'lipid paradox': indeed, RA patients with active disease feature lower levels of total cholesterol (TC), LDL-cholesterol, and HDL-cholesterol (HDL-C) than treated patients with normal acute-phase reactants.[96] The reduction in HDL-C levels occurring in RA patients leads to a high atherogenic index of TC/HDL-C ratio, that in turn may contribute to cardiovascular risk.[97] However, conventional cardiovascular risk factors do not completely explain cardiovascular morbidity in this disease.[98] The increased cardiovascular risk extends beyond patients with established RA, as rheumatoid factor-positive patients with early inflammatory arthritis also have increased cardiovascular mortality.[99] Elevated concentrations of cytokines, such as TNF-α, IL-6, and IL-1β, can mediate activation of both synovial and vascular cells and contribute to both pannus formation in the joints and associated higher carotid artery intima-media thickness or increased prevalence of carotid plaques in comparison with controls.[100] Pro-inflammatory IL-6 and TNF-α are significantly involved in the 'lipid paradox' up-regulating LDL receptors on hepatocytes, thus decreasing circulating LDL. Interestingly, recent studies have shown a decrease in LDL catabolic clearance in patients treated with tofacitinib or anti-IL-6 inhibitor.[101–103]

Myeloproliferative neoplasms as disorders of JAK/STAT pathway dysfunction

Activation of the JAK–STAT pathway also plays a pivotal pathogenetic in chronic Philadelphia-chromosome-negative MPNs, through the presence of mutated, constitutively activated tyrosine kinases, such as JAK2, the thrombopoietin receptor (*monophosphoryl lipid A*) and calreticulin.[104–109] Under physiological conditions, haematopoietic growth factors act on progenitor cells by binding their surface receptors and activating tyrosine kinases in a controlled manner. In contrast, in MPNs the mutated tyrosine kinases circumvent the physiological control of haematopoiesis, thus leading to continued proliferation and survival of progenitors.[110] This phenomenon gives rise to polycythemia vera (PV), characterized by excess production of erythrocytes; essential thrombocythemia (ET), where platelet number exceeds 400 × 109/L; or myelofibrosis (MF), where collagen overproduction in the bone marrow associates with cytopenia in various lineages and progressive splenomegaly.[111,112] Gain-of-function mutations in the JAK2 kinase-like domain are frequent in MPNs, the most common being the V617F mutation—a valine-to-phenylalanine substitution at residue 617 of the *JAK2* gene[113]—that characterizes more than 95% of cases of PV,[114] and about 50% of cases of ET and MF.[110] When mutated, JAK2 binds to homodimeric cytokine receptors,[115] unrestricted signalling occurs via the STAT 3/5, the phosphatidylinositol-3-kinase/AKT, and the RAS/mitogen-activated protein kinases pathways, with consequent uncontrolled expansion of myeloid lineages. STAT proteins are differentially activated in MPNs: increased STAT5 and STAT3 phosphorylation occurs in PV, increased STAT3—but reduced STAT5—phosphorylation are reported in ET, and reduced phosphorylation of both STAT5 and STAT3 characterizes MF.[116] JAK V617F can also trigger the *absent in melanoma 2* (Aim2) inflammasome and generate mature IL-1β.[117]

Activation of the JAK–STAT pathway also increases the formation of NETs, which can aggravate thrombosis. Indeed, mice with the *JAK2* V617F mutation overexpress PAD4, a protein that contributes to NET formation. Administration of the JAK1/2 inhibitor ruxolitinib limits NET formation and reduces venous thrombus formation, as seen in mice.[118] NETs link thrombosis[119] to inflammation[120] observed in MPNs. Indeed, high levels of pro-inflammatory cytokines (IL-6, IL-8, TNF-α, IFN-α, transforming growth factor-β) might contribute to the endothelial–mesenchymal transition,[121] thus favouring the evolution of ET/PV into secondary MF.[122] Indeed, high levels of IL-6 correlate with a higher incidence of cardiovascular events also in other chronic myeloid neoplasms.[123] Especially in MF, 'inflammatory' symptoms are very relevant, with significant impairment of patients' quality of life: in a survey involving 904 patients, half of responders reported a decline in the ability to work caused either by symptoms, such as itching, or the occurrence of thrombotic events.[124] *JAK2* mutations can also increase circulating levels of the coagulation initiator TF, promoting a prothrombotic milieu,[125] and augment venous thrombosis through the increased adhesion of granulocytes to endothelium via β_1 and β_2 integrins.[126] Such findings help explain the well-known high risk of thrombosis and thrombosis recurrence that characterizes MPNs.[20] In a series of 494 patients affected by PV or ET, thrombosis recurred in about one-third, especially involving the central nervous system and the heart. Leukocytosis and age (>60 years) predict thrombosis recurrence, the incidence of which decreases after starting cytoreductive therapy.[127] Moreover, in about 15% of cases, portal or mesenteric vein thrombosis precedes the diagnosis of MPN.[128]

Many studies have now investigated the relationship between *JAK2* mutations and the occurrence of thrombotic events in MPNs, offering some interesting pathogenetic hypotheses.[129–131] For example, the protein kinase Cε, which is also over-expressed in platelets from patients with acute MI and cardiac hypertrophy, appears to be abundant on platelets from patients affected by MF, with significant correlation with a history of cardiovascular events and disease aggressiveness.[132] It has been clearly demonstrated that hyperactivation of the JAK–STAT pathway induces significant biological changes in megakaryocytes and platelets that could contribute to the increased thrombotic risk observed in MPNs.[133] In particular, two different transgenic murine models were used to demonstrate that megakaryocytes from *JAK2* mutated animals show increased ploidy and mobility, that JAK–STAT activation leads to increased formation

of more active pro-platelets, and that platelets from *JAK2* mutated mice show increased aggregation, spreading, and propensity to thrombus formation. For a better understanding of the cause for these observations, the authors performed gene expression profiling experiments, confirming that in *JAK2* mutated mice several pathways known to be important in thrombosis are upregulated.[134,135] Translated in the human context, it has been reported that platelets from subjects affected by *JAK2*-mutated ET or with a previous history of thrombosis show higher P-selectin expression[136] and higher levels of TF-positive platelets.[137]

All these data clearly suggest that JAK–STAT pathway hyperactivity might significantly affect different cellular pathways potentially involved in the activation of the hemostatic system, which might contribute to explain the increased risk and cardiovascular events observed in patients with MPNs.

Cardiovascular risk in patients with myeloproliferative neoplasms

Many studies available from the literature clearly show that MPNs are significantly associated with a heightened cardiovascular risk and with a higher incidence of cardiovascular thrombotic events.[138] The incidence of cardiovascular events in MPN patients is about 10 times higher than in the general population, as reported by the Swedish group that matched 9429 MPN patients with 35 820 controls. Here, in the MPN cohort, arterial thrombotic events were thrice higher than in the control population, while the ratio of occurrence of venous thrombosis was even 9.7, and across all age groups.[139] Moreover, the hearts of MPNs patients harbouring JAK2 mutations accumulate collagen fibres, and cardiac myocytes become hypertrophic.[140]

In PV, the European Collaboration on Low-dose Aspirin in Polycytemia Vera (ECLAP) study reported that cardiovascular mortality accounted for 41% of all deaths, mainly due to coronary heart disease (15%), congestive heart failure (8%), non-hemorrhagic stroke (8%), and pulmonary embolism (PE) (8%).[141] The maintenance of a haematocrit level <45% significantly reduced the occurrence of cardiovascular events.[142] PV is the MPN subtype more frequently associated with arterial and venous thrombosis,[143] abnormal coronary flow, and myocardial ischaemia.[144,145]

In ET, the rate of thrombotic events ranges from 2% to 4% patient/year, with arterial events being 2–3 times higher than venous ones.[146] In a series of 891 patients with a median follow-up of 6 years, 12% experienced arterial or venous thrombosis. At multivariable analysis, arterial thrombosis was predicted by age >60 years, history of previous thrombosis, 'conventional' cardiovascular risk factors (tobacco use, hypertension, diabetes mellitus), leukocytes $>11 \times 10^9$/L, platelet count $>1000 \times 10^9$/L and presence of the *JAK2*V617F mutation.[146] Patients with ET also experience a higher rate of ischaemic strokes, attributed to increased platelet activation, coagulation changes, endothelial and leucocyte activation.[147,148]

In MF, the overall cumulative rate of cardiovascular death and non-fatal thrombotic complications was 2.2%/year. Here age >60 years, hyperleukocytosis and the presence of *JAK2* mutations were significantly associated with thrombosis occurrence. When *JAK2* mutation was present along with leukocytosis, the rate of thrombosis increased up to 3.9% person/years.[20] Serum uric acid levels have also been reported to be associated with shorter times to thrombotic events, independent of the Dynamic International Prognostic Staging System score or age.[149]

Finally, in about 15% of cases the diagnosis of MPN is made following that of a thrombotic event, especially when occurring at an 'atypical' site: for example in a study involving 1062 patients with the Budd–Chiari syndrome and 855 patients with portal vein thrombosis, the prevalence of MPNs resulted to be 40.9% and 31.5%, respectively.[128]

Available data on the cardiovascular safety of JAK–STAT inhibitors

Pathophysiological considerations illustrated above suggest viability for the hypothesis of favourable effects of JAK–STAT inhibitors on cardiovascular disease affecting RA and MPNs. Safety concerns with the use of any new class of drugs, however, require careful consideration. This is even more so because, despite a rather solid rationale—and perhaps paradoxically—some observations have raised concern on possible prothrombotic effects of JAK inhibitors. We therefore searched and analysed PubMed-indexed studies, the EULAR documents reporting on treatments with JAK–STAT inhibitory drugs and adverse reactions connected with their use, as well as post-marketing safety documents specifically focusing on three currently used such agents—tofacitinib, baricitinib, and ruxolitinib—to identify cardiovascular events connected with their extended use in patients with RA or MPNs.

Rheumatoid arthritis

Data regarding the cardiovascular safety of JAK inhibitors in RA remain inconclusive, as they derive primarily from short-term RCTs. Observational studies without randomized allocation of treatments and those without rigorous adjudication of cardiovascular events can prove misleading (*Table 2*). Data from six phase III studies and two open-label long-term extension (LTE) studies of tofacitinib in patients with RA and inadequate response to DMARDs show that tofacitinib treatment associates with a low incidence of cardiovascular events.[150] In a *post hoc* analysis of six phase III and two LTE studies over 7 years including 4076 patients, the same authors found that, after 24 weeks of tofacitinib treatment, increased HDL-C, but not higher LDL or total cholesterol, appeared to be associated with a lower rate of subsequent cardiovascular events.[151] Tofacitinib may also reduce carotid intima-media thickness after 54 weeks of treatment in patients with increased carotid intima-media thickness at baseline.[152] Similarly, pooling data from nine clinical trials with baricitinib, no difference in the incidence of major adverse cardiovascular events was found in patients treated with baricitinib in comparison with placebo; six events of deep vein thrombosis (DVT)/PE occurred in patients treated with 4 mg baricitinib, but no cases of DVT/PE were reported in the placebo group. During longer-term evaluation, the incidence of DVT/PE was similar between the baricitinib dose groups.[153] Finally, in a recent meta-analysis of 26 RCTs, no significant differences regarding the risk for cardiovascular events in RA patients treated with JAK inhibitors were found in general, and specifically

Table 2 Main studies on JAK-inhibitors and cardiovascular safety in patients with rheumatoid arthritis

First author and reference	Objectives	Methods	Results
Charles-Schoeman *et al.*[150]	To evaluate the incidence of CV events, including major adverse CV events (including CV death, as coronary, cerebrovascular, cardiac, and non-cardiac vascular events, and non-fatal CV events, as MI and cerebrovascular events) and CHF	Data from six phase III studies and two LTE studies of tofacitinib (administered alone or with non-biological DMARDs) in patients with RA and inadequate response to DMARDs	Lower incidence of major adverse CV events and CHF; lipid levels increased in the first 3 months and stabilized thereafter; blood pressure remained stable
Charles-Schoeman *et al.*[151]	To evaluate the incidence of major adverse CV events (including MI, stroke, CV death)	*Post hoc* analysis of six phase III and two LTE studies over 7 years, in patients with RA and inadequate response to DMARDs, after a 24-week treatment with tofacitinib	Lower incidence of major adverse CV events; HDL-scholesterol increased, but not LDL-cholesterol or total cholesterol
Kume *et al.*[152]	To analyse the effects of tofacitinib on atherosclerosis, comparing the CIMT at the baseline and 54 weeks after	Open-label prospective study in which patients with RA received tofacitinib 10 mg/day for 54 weeks	The CIMT had a signifcant decrease after the observation period
Taylor *et al.*[153]	To evaluate the incidence of major adverse CV events (including MI, stroke, and CV death) and other CV events (hospitalization for unstable angina, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, or coronary revascularizations); ATE (MI and ischaemic stroke); DVT/PE; CHF	Data from nine studies, placebo comparison up to 24 weeks included data from six studies. Randomized dose comparison between baricitinib doses of 2 and 4 mg used data from four studies and from the associated long-term extension study	No association between baricitinib and the incidence of major adverse CV events, ATE or CHF. DVT/PE occurred in patients treated with 4 mg baricitinib, but there were no cases of DVT/PE in the placebo group
Xie *et al.*[154]	To evaluate the incidence of major adverse CV events (including MI, ischaemic, and haemorrhagic strokes) or cardiovascular death, and DVT/PE	Systematic review and meta-analysis of 26 randomised controlled trials comparing tofacitinib 5 mg against 10 mg, baricitinib 2 mg against 4 mg, upadacitinib 15 mg against 30 mg	No significant differences regarding the risk for major adverse CV events were found; baricitinib at the dose of 2 mg appeared to be safer than 4 mg

ATE, arterial thrombotic events; CHF, congestive heart failure; CIMT, carotid intima-media thickness; DVT/PE, deep vein thrombosis/pulmonary embolism; DMARDs, disease-modifying antirheumatic drugs; LTE studies, open-label long-term extension studies; MI, myocardial infarction.

with tofacitinib, baricitinib, upadacitinib, peficitinib, or decernotinib. The authors did not observe any significant difference in the occurrence of major adverse cardiovascular events in patients receiving JAK inhibitors with respect to placebo.[154] This meta-analysis, which evaluated the risk of thromboembolic events comparing tofacitinib 5 mg against 10 mg or upadacitinib 15 mg against 30 mg, showed no significant overall risk of thromboembolic events. Conversely, however, baricitinib at dose of 2 mg appeared to be safer than 4 mg.[154]

There are indeed some concerns about the occurrence of thromboembolic events attributable to JAK inhibitors at higher dosage. A recent post-marketing ongoing safety trial (study A3921133) aroused concerns regarding increased risk of PE and death in RA patients older than 50 years with at least one cardiovascular risk factor when treated with high-dose tofacitinib (10 mg twice daily). Current recommendations suggest avoiding such high doses continuously in patients with augmented risk of thrombosis (older or obese subjects, patients undergoing hormone replacement therapy, patients with previous history of DVT or PE).[155] More reliable results should soon become available. Similar data have been reported for baricitinib in Europe,[156] and the US FDA did not approve the 4-mg dose once daily of baricitinib due to unclear additional benefit vs. the 2-mg dose once daily, and also due to concern of a dose-related effect on safety outcomes, particularly thromboembolism.[87]

In summary, existing data raise concern regarding the safety of high-dose JAK inhibitors with respect to thromboembolism, but further randomized and well-controlled studies are required to determine if this is a class effect and if a threshold and a dose–effect relationship exists.[157] Such studies should definitely also clarify if the anti-atherosclerotic effects hypothesized above might counterbalance such potential risks.

Myeloproliferative neoplasms

The JAK1/2 inhibitor ruxolitinib was initially approved for treating patients with MPNs of intermediate-2 or high risk, according to the International Prognostic Scoring System.[158] Since 2015, expanded indications include treatment of patients with PV resistant or intolerant to hydroxyurea. Two phase III pivotal trials (COMFORT-I[159] and COMFORT-II[160]) have compared ruxolitinib to placebo or to the

Table 3 Studies on ruxolitinib reporting on cardiovascular risk

First author and Reference	Title	Type of study	Results
Verstovsek *et al.*[159]	Long-term treatment with ruxolitinib for patients with myelofibrosis: 5-year update from the randomized, double-blind, placebo-controlled, phase 3 COMFORT-I trial	5-year update of COMFORT I phase-III trial: ruxolitinib ($n = 155$) vs. placebo ($n = 154$)	Myocardial infarction 2.7%
Verstovsek *et al.*[161]	Long-term survival in patients treated with ruxolitinib for myelofibrosis: COMFORT-I and -II pooled analyses	Pooled analysis	The update of results at 5 years reported 0.9% of myocardial infarction at 2 years and 2.7% at 4 years. Overall, by 48 months of therapy 6.2% of patients receiving ruxolitinib presented cardiac failure
Harrison *et al.*[160]	Long-term findings from COMFORT-II, a phase 3 study of ruxolitinib vs. best available therapy for myelofibrosis	5-year update of COMFORT II phase-III trial: ruxolitinib ($n = 146$) vs best available therapy ($n = 118$).	Cardiac failure 2%
Barraco *et al.*[162]	Real-world non-interventional long-term post-authorisation safety study of ruxolitinib in myelofibrosis	Real-world experience	Occurrence of cardiac failure in only 1.6% of treated subjects
Samuelson *et al.*[165]	The impact of ruxolitinib on thrombosis in patients with polycythemia vera and myelofibrosis: a meta-analysis	Meta-analysis	Rates of thrombosis were significantly lower among patients treated with ruxolitinib (risk ratio 0.45, 95% confidence interval 0.23–0.88)
Masciulli *et al.*[166]	Ruxolitinib for the prevention of thrombosis in polycythemia vera: a systematic review and meta-analysis	Meta-analysis involving four randomized trials with 663 patients	Thrombosis risk ratio of 0.56 for ruxolitinib vs. best available therapy, corresponding to an incidence of 3.09% and 5.51% patients per year
Saliba *et al.*[167]	Association between myelofibrosis and thromboembolism: a population-based retrospective cohort study	Population-based retrospective study; 1 469 790 adults were followed from 2007 until 2016 for the occurrence of myelofibrosis	One-third of myelofibrosis patients received ruxolitinib: no significant association was found between JAK-2 inhibitor treatment and the risk of venous or arterial thromboembolism, indirectly suggesting a favourable role of this drug from the CV
Colafigli *et al.*[168]	The advantages and risks of ruxolitinib for the treatment of polycythemia vera	Expert opinion: authors searched Medline, Embase, archives from the European Hematology Association and the American Society of Hematology annual congresses from 2014 to 2020 about ruxolitinib treatment in polycythemia vera patients and safety	Thromboembolic events per 100 patient-years of 1.8 in the ruxolitinib vs. 8.2 in the best available therapy arm and 2.7 in the cross-over cohort

best available therapy, respectively. For the first time in the history of MF, a drug prolonged overall survival reducing the risk of death by 30% and proving to be quite safe also from the cardiovascular standpoint. Indeed, the 5-year update of results from these trials reported an incidence of only 0.9% of MI at 2 years, and of 2.7% at 4 years.[161] More recently, a post-marketing safety study confirmed the occurrence of heart failure in only 1.6% of treated subjects.[162] Other authors have evaluated the possible adverse effects of ruxolitinib on lipid metabolism. This inhibitor apparently increases cholesterol levels[163] and alters the lipid structure of the cell membrane, but without damaging cell membrane integrity.[164] A compilation of studies reporting on the cardiovascular safety of ruxolitinib is provided in *Table 3*.

Concerning the possible cardiovascular 'protective' effect of ruxolitinib, one meta-analysis reported the halving of arterial and venous thrombosis in MF and PV.[165] A more recent meta-analysis including more than 600 PV patients has reported an annual incidence of thrombosis of 5.5% in the control arm vs. 3% in the ruxolitinib

arm.[166] Although this difference was not statistically significant, both meta-analyses suggest that ruxolitinib protects MPN patients from cardiovascular events. Another study matched 642 MF patients with 2568 controls and followed them for 10 years for thrombotic events. As expected, the MF cohort had an increased risk of DVT and PE, especially in subjects with a history of previous venous thromboembolism and atrial fibrillation. Interestingly, atypical sites of thrombosis occurred in these patients compared with controls (26.1% vs. 4.0%). In this study one-third of patients received ruxolitinib: those receiving this JAK2 inhibitor showed no significantly higher risk of venous or arterial thromboembolism, although one has to recognize that non-randomized observational studies are subject to multiple sources of confounding.[167]

In PV as well, ruxolitinib has so far appeared safe and protective: the pivotal phase III RESPONSE trial, which included 110 patients followed for a median of 80 weeks, reported a rate of thromboembolic events of 1.8% patient-years in the ruxolitinib vs. 8.2% in the best available therapy arm and 2.7% in the crossover cohort, again suggesting that this JAK inhibitor may play a role in reducing cardiovascular and thrombotic events in MPN patients.[169] The *JAK2* V617F mutation can cause clonal haematopoiesis, associated with increased cardiovascular risk, particular in younger individuals.[170] Targeting JAK2 inhibitors to bearers of *JAK2* V617F clonal haematopoiesis thus has a strong rationale.[118]

Conclusions

Patients affected by rheumatological and haematological diseases, such as RA and MPNs, share a pro-inflammatory state and concomitantly higher cardiovascular risk and increased prevalence of cardiovascular disease-related deaths than the general population.[171,172] In these conditions, the JAK–STAT pathway contributes fundamentally, as demonstrated by the efficacy of JAK inhibitors, now extensively used in clinical practice.

Several research groups are now assessing the cardiovascular safety of JAK inhibitors. Treatment with tofacitinib seems to be associated with a lower incidence of cardiovascular events.[150] There are some concerns about the occurrence of thromboembolic events attributable to JAK inhibitors at higher dosage (study A3921133). There appears to be an increased risk of PE and death in RA patients older than 50 years with at least one cardiovascular risk factor when treated with a high dose of tofacitinib (10 mg twice daily). Current recommendations suggest avoiding such high doses in patients with high risk of thrombosis. Similar concerns have been reported for baricitinib.[153] Baricitinib at dose of 2 mg appeared to be safer than 4 mg.[154]

The use of tofacitinib and baricitinib in patients with autoimmune diseases and a high thromboembolic risk requires caution. Favourable observations in treatment of COVID-19[173,174] support the possibility of using these drugs proactively to reduce cardiovascular events in patients at high thrombotic risk by reducing the underlying chronic inflammatory state.

Treatment with ruxolitinib improved the quality of life of MPN patients, but further studies are necessary to definitively ascertain if the use of these drugs in early disease prevents the occurrence of cardiovascular events. Results from trials on this drug reported a lower incidence of MI and heart failure in treated subjects.[159,162] There are also possible adverse effects on lipid metabolism, with an increase in cholesterol levels.[163] Other studies showed a lower incidence of thrombosis in patients treated with ruxolitinib, but these data are not statistically significant.[166,167] In a study on PV, ruxolitinib appeared safe and protective with a lower incidence of thromboembolic events in patients treated with ruxolitinib vs. the best available therapy.[169]

Thus, with a word of caution, and recollecting the troublesome story of two previous drug strategies also aimed at reducing atherosclerosis—hormone replacement therapy[175] and cyclooxygenase 2 inhibitors (coxibs)[176]—and then found harmful because of the increased thrombotic risk, currently available data support the hypothesis of a net clinical cardiovascular benefit of JAK–STAT inhibitors due to anti-atherosclerotic effects (*Graphical abstract*). This possibility requires rigorous investigation in well-conducted, randomized, and adequately powered trials to balance potential benefit and harm.

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