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CLINICAL COMMENTARIES

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Potential cardiovascular implications of Janus kinase inhibitors in immune mediated diseases

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Dr Nehal N. Mehta is a cardiologist who won the inaugural Lasker Clinical Research Scholar award from the National Institutes of Health (NIH). He is currently the chief of Section of inflammation and Cardiometabolic Diseases at the NIH in Bethesda, MD. Dr. Mehta's lab has elucidated the critical role of innate immunity and inflammation in the development of cardiovascular and cardiometabolic diseases. Applying a trans-disciplinary approach that involves genetic epidemiology, translational medicine, and novel cardiovascular imaging approaches, Dr. Mehta and his team study how inflammation affects insulin resistance, the development of metabolic syndrome and lipoprotein dysfunction- all of which are risk factors for atherosclerosis and lead to subsequent cardiovascular disease. Dr. Mehta utilizes the chronic inflammatory state observed in psoriasis as a human model to understand potential mechanisms linking inflammation and cardiometabolic diseases. His work has led to an improvement in cardiovascular risk stratification in patients with chronic inflammatory conditions and increased our understanding of novel detection of subclinical diseases.

Inflammation in cardiovascular disease

Inflammation and the immune system are critical to atherosclerosis.[1] An augmented understanding of cytokines involved in the regulation of both inflammation and the immune system has led to the development of therapeutic monoclonal antibodies and small molecules to inhibit these cytokines or pathways. These biologics and small molecules have demonstrated efficacy in treating numerous allergic, inflammatory, and immune mediated diseases including atherosclerosis, psoriasis, rheumatoid arthritis (RA), systemic lupus erythematosus, and inflammatory bowel disease (IBD).[2,3] Despite multiple treatment options, about 10% to ≥50%[4,5] do not respond to the biologics. Janus kinase (JAK) is a family of receptor-associated tyrosine kinases involved in discrete intracellular signalling pathways, which is used by majority of Type I and Type II cytokine receptors for functional effects. In those with defective JAK pathways, severe immunosuppression in humans was observed, and collectively, these advances led to the discovery of a new class of small molecules targeting JAKs, known as JAK inhibitors (JAKinibs).

Cardiovascular disease is the leading cause of death across the world.[6] Atherosclerosis in major vascular beds (coronary and carotid) is the most common form of cardiovascular disease. Atherosclerosis is now known to be a complex process involving interplay between lipids, and both innate and adaptive immunity with inflammation at its core pathogenesis, driving the course from initiation and development to the late plaque-rupture.[7] Many biomarkers of inflammation including multiple cytokines such as interleukin-6, interleukin-1β, tumour necrosis factor-α, interferon-γ etc. have a causal and predictive role in atherosclerosis.[1] With CANTOS successfully demonstrating reduction in risk for cardiovascular disease subsequent to targeting inflammation with monoclonal antibody against interleukin-1β,[3] and with the role of JAKs in cytokine associated pathogenesis of cardiovascular disease, targeting JAK associated pathways has been proposed as a potential therapeutic target for treatment of atherosclerosis.[5] A recent Cardiovascular Research OnLife commentary detailed the basic science implications of CANTOS and discussed the role of mitigating inflammation in cardiovascular risk reduction.[8] In continuation, herein, we briefly discuss phase 2 and phase 3 clinical trials of JAKinibs for various immune-mediated diseases and their potential implications for cardiovascular disease.

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JAK inhibitors and their cardiovascular effects

Since their discovery JAKinibs have been examined in primarily immune mediated diseases with a different gamut of studies for each condition, e.g. the ORAL studies for RA, the OPAL studies for psoriatic arthritis, the OPT studies for psoriasis, and OCTAVE studies for IBD, specifically ulcerative colitis. All these studies analysed the impact of a particular JAKinib called Tofacitinib (JAK1, JAK3 selective) on disease activity. Furthermore, another set of studies in RA called RA-BEACON, RA-BUILD, RA-BEGIN, and RA-BEAM evaluated the efficacy of a different JAKinib titled Baricitinib (JAK1, JAK2 selective). Almost all of these clinical trials were randomized and placebo-controlled, while a few trials also had an additional arm with a different anti-inflammatory biological therapy such as adalimumab/etanercept (both anti-tumour necrosis factors) or methotrexate. Most of these studies demonstrated the superiority of JAKinibs over placebo using endpoints such as American College of Rheumatology guideline-based improvement in RA (ACR-50, ACR-70), and improvements in psoriasis severity and IBD activity measures. Moreover, trials that compared JAKinibs with other biological therapies demonstrated a comparable profile for Tofacitinib, whereas Baricitinib was shown to be superior to methotrexate and adalimumab with the same outcomes. Based on these studies, currently two JAKinibs have been approved by the FDA, Ruxolitinib for myelofibrosis and Tofacitinib for RA, whereas only Baricitinib is currently approved for RA by the European Union. Despite different selectivity, JAKinibs were reported to have a largely similar safety profile.[9] Almost all of them are associated with a reduction in neutrophil count and an increased risk of viral infections, specifically herpes zoster infection. Furthermore, both Tofacitinib and Baricitinib are associated with an increase in liver function tests assessed by transaminases, renal function by creatinine, and creatine phosphokinase.

Indeed, given that most of these chronic inflammatory diseases associate with an increased risk of cardiovascular disease,[10] it is imperative to separate whether any untoward effects after treatment with JAKinibs are due to the therapy and not interaction with the underlying disease. JAKinibs have been shown to increase lipid levels.[11,12] Both Tofacitinib and Baricitinib treatments led to an increase in lipids with significant dose-dependent increases in total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) cholesterol, and triglycerides.[12,13] Meta-analyses examining the extent of change in LDL in different disease states such as RA and psoriasis following treatment with JAKinibs have consistently found a mean 10–15% increase in LDL with a concurrent 5–7.5% mean elevation in apolipoprotein-B levels. Further lipoprotein subfractions analyses using nuclear magnetic resonance and advanced lipid profiling demonstrated different effects of these molecules on various particle level lipoprotein indices. Tofacitinib was associated with decreased levels of small LDL particles (*a positive impact*) at high dose and an increased HDL particle number (*a positive impact*). Baricitinib was associated with similar findings but at higher dose levels and over a longer follow-up duration of 24 weeks. While HDL associated serum amyloid A and lipoprotein (a) decreased following Baricitinib treatment (*a positive impact*), cholesterol efflux capacity did not alter with Tofacitinib therapy (a *neutral impact*).[12,13] There were no cardiometabolic untoward effects on weight or haemoglobin A1C in psoriasis patients undergoing Tofacitinib treatment. Inflammatory (high-sensitivity C-reactive protein and serum amyloid A) markers improved in psoriasis following treatment with Tofacitinib, however, these effects were found only in responders.[14] Finally, the increase in LDL was reversed with initiation of statins even when patients continued on Tofacitinib.[15]

Cardiovascular outcomes in chronic inflammatory disease patients treated with JAKinibs have been studied to understand the cardiovascular safety profile following JAKinib therapy. Tofacitinib has been used to treat RA and psoriasis patients and CV outcomes were assessed.[16,17] In RA patients, phase three studies that followed-up patients for up to 24 weeks demonstrated a *low* incidence rate for major adverse cardiovascular event (MACE) of 0.58 per 100 patient-years (23 total number of MACE). Furthermore, similar studies in RA patients but with longer term follow-up revealed a MACE incidence rate of 0.37 per 100 patient-years (32 total number of MACE), which was not higher than expected.[16] Moreover, similarly low incidence rates were found for MACE in psoriasis patients in pooled analyses, 0.32 per 100 patient-years for 10 mg twice daily dose and 0.37 per 100 patient-years for any dose.[17] However, the total number of MACE was only 19 and the median follow-up for these studies was <2 years. It is noteworthy that the mean age for patients enrolled in all the studies utilized for pooled analyses was approximately 52 years in RA patients, whereas psoriasis patients were even younger with a mean age of around 45 years.

Implications for basic science

A recent study demonstrated that the late remote ischaemic pre-conditioning, a signal transducer, and activator of transcription 5 (STAT5) dependent mechanism, prevented myocardial ischaemia–reperfusion injury in mice with STAT5 knocked out. These effects were anti-apoptotic signalling dependent. Another study evaluated the effects of inhibiting JAK-STAT pathways in preventing atrial fibrosis using a canine model, which showed reduced *in vivo* left atrial fibrosis and post-myocardial infarction remodelling. *In vitro* studies demonstrated attenuated profibrotic effects of platelet derived growth factor stimulation, and authors concluded that decreased STAT3 activation may have a role in preventing the atrial fibrosis. With effects on cardiomyocytes, fibroblasts, impact during the cardiac remodelling process, and the inherent anti-inflammatory activity, JAKinibs certainly provide exciting avenues related to these findings.

The only JAKinibs tested thus far have been the non-selective agents. However, non-selective JAKinibs may prevent upstream activity of both pro- and anti-inflammatory cytokines. As such, there is still scope for research in analysing the cellular and molecular level impact of more selective JAKinibs, specifically, JAK1 inhibitors that primarily affect T-cell proliferation. These selective agents may have different effect on cardiovascular profile compared with the non-selective JAKinibs. As such, further research should focus on assessing their impact on endothelial function, their role in plaque level inflammation, and possible effects on HDL efflux. Furthermore, studying the effects of JAKinibs using integrated-omics approaches (e.g. genomic, proteomic, metabolomic, lipidomic) may provide insights into their cumulative effect on cardiovascular risk profile.

Conclusions

With the aforementioned known biological effects of JAKinibs, there are several aspects for developing our understanding of the effects of these therapies on cardiovascular research. Foremost, selective inhibition of

JAK and the differential effects should be studied *in vitro* utilizing several human cell lines. Furthermore, using emerging-omics data, studies should evaluate the downstream effects of JAKs in cardiometabolic pathways including adipose tissue and human vascular tissue. Careful *in vitro* characterization of changes in signaling following selective JAK pathway knockout in several cell types are needed to improve our understanding of biological effects of the JAKnibs. Finally, of most importance would be performing a simple trial of approved JAKinibs on cardiovascular surrogate outcomes including coronary plaque studies and cardiometabolic parameters. While LDL increase with JAKinibs may pose a concern, the reversibility with statins is promising. The increase in HDL with no change in HDL efflux suggests neutral effects, especially given the failure of pharmacological interventions raising HDL in mitigating subsequent cardiovascular risk.[18,19] In view of the promise of JAKinibs, it is timely to test these medications in enhanced cohorts with the ability to decipher all these changes in a single set of patients to confirm the observed findings. Furthermore, longer-term follow-up with use of surrogate cardiovascular outcomes such as vascular inflammation by fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) or coronary artery disease evaluation by coronary computed tomography angiography should be undertaken to provide much needed context to the changes in lipoprotein, cardiometabolic, and cytokine profiles. Only by utilization of multiple phenotypes over time will the true effect of JAKinibs on cardiovascular disease be realized. Anti-TNF therapy reduced myocardial infarction over an 8-year observational study but recently was shown not to improve subclinical vascular disease. However, cardiovascular biomarkers changed favourably.[20] This experience demonstrates that many clinical studies are needed before any adjudication of cardiovascular effects can be made with great certainty. A novel set of studies assessing the impact of various biological therapies on vascular inflammation by FDG PET/CT (the 'VIP' studies NCT01553058, NCT01866592, NCT02187172, NCT02690701) or coronary computed tomography angiography as in psoriasis patients should be considered using JAKinibs in order to assess the risk of cardiovascular disease comprehensively, while treating the underlying immune-mediated disease processes. With the recent success of the strategy of targeting inflammation to curb cardiovascular risk, JAKinibs indeed provide an exciting avenue for future research with a focus on the assessment of their efficacy as immunomodulators, while delivering critical insights into the underlying mechanisms of immune-mediated diseases.

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