JANUS KINASE INHIBITORS AND CARDIOVASCULAR EVENTS IN RHEUMATOID ARTHRITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Introduction: Janus Kinase (JAK) inhibitors represent a relatively new class of biological drugs, approved or in development for various inflammatory diseases, including rheumatoid arthritis (RA). Although adverse events in drug development were largely expected according to the drugs' mechanism of action (e.g., infections), concern on thromboembolic events in placebo-controlled trials of baricitinib (delayed approval) and tofacitinib (ongoing study) emerged, thus supporting the need to assess the cardiovascular (CV) risk of JAK inhibitors.

Methods: We conducted a systematic review of phase III randomized controlled trials (RCTs) reporting cardiovascular events with JAK inhibitors in RA, which is part of an overall systematic review comprising all inflammatory rheumatic diseases, registered in a dedicated register (PROSPERO 2018; CRD42018114920). A comprehensive search was performed in MEDLINE, EMBASE, ISI Web of Knowledge and Cochrane Central Register of Controlled Trials, using dedicated strategy. Unpublished literature was also checked (ClinicalTrials.gov, ClinicalTrialsRegister.eu, conferences proceedings/abstracts). The search was undertaken in June 2018with pragmatic searches until December 2018. Quality of included studies was assessed through Cochrane Risk of Bias tool. The outcomes of interest were: composite cardiovascular outcome (CCO, including all CV events), major adverse cardiovascular events (MACE, i.e., myocardial infarction, stroke/cerebrovascular accident, cardiovascular death), arterial thrombotic events (ATE, including myocardial infarction, stroke and coronary heart disease) deep vein thrombosis/pulmonary embolism (DVT/PE), congestive heart failure (CHF), arrhythmias and hypertension. Odds Ratios (ORs) with 95% confidence interval were calculated (heterogeneity threshold for using fixed-effect model: Cochran Q test<0.10). Different datasets were created: (I) baricitinib/tofacitinib/upadacitinib (all doses) vs control, (II) baricitinib/tofacitinib/upadacitinib (dosage comparison), (III) JAK inhibitors (week 12or 24) vs control.

Results: Out of 5211articles, 13RCTs met our inclusion criteria (seven for tofacitinib, 5and 10 mg; four for baricitinib, 2and 4mg; two for upadacitinib, 15and 30 mg), comparing JAK inhibitors to placebo, methotrexate or adalimumab. Among 6606patients with RA exposed to JAK inhibitors, 230 CV events were recorded (3.5% compared to 1.9% of patients receiving placebo/comparator). No major biases were identified (except for one study with potential detection bias). Statistical significance emerged for CCO in tofacitinib dataset (I) [OR=1.68, 95%CI=1.04-2.73], and JAK inhibitors (week 24) dataset (III) [1.62; 1.14-2.30]. Hypertension was the most frequently-reported CV event, with increased OR in tofacitinib dataset (I) [1.89; 1.13-3.17], JAK inhibitors (week 12) dataset (III) [1.98; 1.02-3.84] and JAK inhibitors (week 24) dataset (III) [1.56; 1.03-2.38]. Non-significant increased OR was found for JAK inhibitors (week 24) in dataset (III) with regard to MACE [1.60; 0.51-5.04] and ATE [1.90; 0.38-9.41], without increased risk of DVT/PE [0.76; 0.22-2.65]. No significant dose-dependent effect emerged from dataset (II). Results were consistent using Relative Risks.

Discussion and conclusion: This is the first systematic review on CV safety of JAK inhibitors in RA. Contrary to expectations, no increased risk of DVT/PE emerged, but a significant increased risk of CCO in different datasets, likely driven by the imbalance of hypertension events. Limitations of study design (only 2RCTs with 52-week follow up, and the escape design, i.e., switching from placebo to experimental drug at week 12for ethical issues) do not allow to rule out with certainty an increased risk of MACE and ATE. Long-term RCTs tailored on serious CV outcomes or MACE, and post-marketing observational studies in unselected population are warranted to further assess this risk.