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Cardiovascular risk in patients with rheumatoid arthritis receiving targeted synthetic and biological disease-modifying antirheumatic drugs: a multi-centre retrospective cohort study

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Background

Biological and targeted synthetic DMARDs (b/tsDMARDs) unfolds the new chapter of RA management and being moving towards to be the standard treatment[1] for patients who have inadequate responses to conventional synthetic DMARDs[2]. The mortality of ***RA patients*** is 1.2 to 3.0 folds greater compared with the general population, which ***half of the excess mortality are attributed to cardiovascular (CV) diseases***[3,4]. It is commonly recognized that ***chronic inflammation*** alters body composition, insulin sensitivity and lipid profile, of which *mediates premature atherosclerosis*[3,5-7]. Abundance literature have suggested the **beneficial CV effect** of bDMARDs, especially the tumor necrosis factor inhibitor (***TNFi***), through the *reduction of systemic inflammation*[8-12]. However, the effects of other bDMARDs such as *IL-6 inhibitor*, still *paradoxical*[13]. Studies found IL-6 inhibitors increased circulating low-density lipoproteins (LDL) levels[14] but not the risk of major cardiovascular events[11,15,16].

Janus Kinase inhibitors [JAKi, tofacitinib (in 2012), baricitinib (in 2018) and upadacitinib (in 2019)] are typical and the *only category of tsDMARDs* approved for the management of RA[17,18]. **JAKi** are ***small molecules*** targeting the *intracellular transduction pathways*, the Janus kinases/signal transducers, and activators of transcription (***JAK/STAT***), which are essential signals in down streaming inflammatory molecules with ***wide spectrum of cytokines***[19,20]. Comparing to bDMARDs, tsDMARDs are with *lower rates of immunogenicity* and can be administrated orally [21], which is a more *convenient dispense route* that potentially increase patients compliance. Despite its safety and convenience of administration, **tsDMARDs neither not be free of side effects risk. *JAK/STAT pathway is deeply involved*** in several largely unknown regulatory networks influencing hundreds of cytokines, as a result, *inhibiting this pathway* may in addition ***dysregulating inner organs***, such as cardiovascular system[13]. What's more, considering of JAKi is a small compound that leads to blocking the physiological response of hundreds of genes[13], the effects of tsDMARDs on cardiovascular system are still not conclusive[22,23]. Limited evidence suggested that JAKi-based therapy positively modifies the risk of cardiovascular disease[24,25], while **a growing body** of literature indicated that JAKi **adversely affect** several cardiovascular risk factors (such as serum lipid profile and platelet count) and potentially increase thrombotic risk [26-29].

To our knowledge, current evidences on cardiovascular events and tsDMARDs are from RCT studies or non-comparative observational studies without conclusive outcomes and there are limited studies[11,30] comparing the risk of cardiovascular events with tsDMARDs to other bDMARDs through real-world data. Whether JAKi would cause increased risk of cardiovascular events and whether doctors should evaluate the risk of cardiovascular events before they prescribe this class of drug to RA patients need further investigation in real-world practice.

Hypothesis to be tested

There is *scattered evidence from current literature* comparing the cardiovascular events (CVE) among b/tsDMARDs. We propose to evaluate and compare *the risk of CVE* among patients with RA firstly treated by b/tsDMARDs in real-world clinical settings. We hypotheses that tsDMARDs and IL-6 inhibitors have higher risk of CVE compared to TNFi bDMARDs, especially in patients with exist cardiovascular risk factors (old age, hypertension, obesity, diabetes etc.).

Study objectives

1. To describe the overall incidence rate of CVE among patients with RA using multiple databases in Asia Pacific Areas
2. To compare the risk of CVE among patients with RA receiving JAK inhibitors, IL-6 inhibitors and TNF inhibitors, with TNF inhibitors as reference group, using cohort study design and international electronic medical records databases

Methods

Data source from Asia-Pacific areas

Hong Kong Clinical Data Analysis and Reporting System (CDARS) is the territory-wide EHR database developed and managed by the HA of Hong Kong. HA[31] is a unique statutory body that manages all public hospitals and their ambulatory clinics serving a population of 7.4 million through 43 hospitals and institutions, 49 specialist outpatient clinics, and 73 general outpatient clinics in HK. EHRs including demographics, date of registered death and cause, date of hospital admission and discharge, prescriptions, diagnoses, immunization history etc. are all centralized in CDARS routinely for research and audit purposes. Coding accuracy and records quality of CDARS has been demonstrated through many high-quality epidemiology and health service studies published using this database [32,33]. Patient records are anonymised to protect patient confidentiality and identity.

Taiwan National Health Insurance Research Database (NHIRD) exemplifies a population-level data source for generating real-world evidence to support clinical decisions and health care policy-making. By the end of year 2014, NHIRD covered 99.9% of the Taiwanese population. Up to year 2018, over 2,700 peer-reviewed studies have been published using NHIRD data[34].

Korea Health Insurance and Review Assessment (HIRA), also called National Health Insurance (NHI) data covered all citizens in South Korea. HIRA contains comprehensive and rich information pertaining to healthcare services such as treatments, pharmaceuticals, procedures, and diagnoses. HIRA provides a high value in answering a wide spectrum of research questions in health research encompassing outcomes, public health, epidemiology, biostatistics, health informatics and health economics[35].

We will use distributed network approach to analyse the data from different sites and pool the result using meta-analysis. Data source and estimated number of patients are detailed in

Table 1 Data source and estimated number of patients

Data source	Country/ regions	Patient recruitment period	Follow-up end date	Number of patients with RA	Estimated number of patients using TNFi[a]	Estimated number of patients using ILi[a]	Estimated number of patients using JAKi[a]
CDARS	Hong Kong	2010-2020	12-31-2020	17,628	598	162	294
NHIRD	Taiwan	2010-2018	12-31-2018	396,485	2775	508	545
HIRA	South Korea	2010-2020	12-31-2020	2,196,992	2476	599	732

Note: [a] Excluded patients with systemic lupus erythematosus, psoriasis, spondylarthritis, multiple sclerosis, and inflammatory bowel disease

Study design

This will be a retrospective cohort study based on multiple population-based electronic medical records databases. Study population will be patients with a recorded diagnosis of RA [identified with ICD-9-CM codes (714.0); ICD-10 M05 and M06] between 2010 and 2020 (or feasible timespan) for each database. We will further identify patients who have not responded to the first-line treatment (csDMARDs) and then first treated with b/tsDMARDs (biologics naïve patients) as the target population of the cohort analysis. Patients with other autoimmune diseases (systemic lupus erythematosus, psoriasis, spondylarthritis, and inflammatory bowel disease) will be excluded to avoid data contamination. Based on modes of action, biological and targeted synthetic DMARDs assessed in this study includes **TNF inhibitors** (TNFi)(etanercept, infliximab, adalimumab, certolizumab pegol and golimumab), **interleukin-6 inhibitors** (IL-6i) (tocilizumab, sarilumab), and **JAK inhibitors** (JAKi) (tofacitinib, baricitinib and upadacitinib), whichever available in each data base.

Targeted patients will be followed-up from the index date (prescription start date of the first b/tsDMARDs treatment) until censoring - occurrence of outcome, treatment discontinuation (treatment gap more than 6 months), death, treatment switch to another b/tsDMARDs with different modes of actions, or study end date (December 31, 2020), whichever comes first.

Outcome

The primary outcome of interest is the composite of first hospitalized CVE, after b/tsDMARDs treatment. CVEs considered in this study include coronary heart diseases, stroke (ischemic or hemorrhagic), heart failure (HF), VTE, systemic embolism (SE) (ICD-9-CM and ICD-10-CM codes are listed in appendix table)[11,36].

Statistical analysis

Crude incidence rates of CVE with 95% confidential interval will be estimated for each group (TNFi, ILi and JAKi) using Poisson distribution. Using ***TNFi as reference group***, we will use Cox proportional-hazards models or generalised linear regression model (Poisson distribution) to adjust confounding factors (including age, sex, disease duration and Charlson Comorbidity Index) and estimate the Hazards Ratios (HRs)/Incidence Rate Ratios (IRRs) of cardiovascular events for ILi and JAKi, respectively. Subjects' age, sex, disease duration (defined as years since RA diagnosis to the first treatment of b/tsDMARDs); stage of RA [early RA (disease duration less than or equal to 2 years) and established RA (disease duration longer than 2 years)], medical histories, Charlson Comorbidity Index (CCI), and recent one-year medication usage [csDMARDs, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroid, and cardiovascular drugs] before index date are covariates to be reported as baseline characteristics.

We will aggregate HR/IRR estimates results from each data resources with meta-analytic estimates using a random-effects meta-analysis [37,38]. Pooled analyses and visualisation of crude and adjusted IRRs will be conducted through Review Manager (RevMan) (Computer programme, Version 5.4. The Cochrane Collaboration, 2020). We are going to conduct data analysis via R (version 4.1.4, R Foundation for Statistical Computing, Vienna, Austria) and SAS (version 9.4, SAS Institute, Cary, NC, USA).

Sample size estimation

Sample size of the proposed study is calculated with the software authorized by Open Source Epidemiologic Statistics for Public Health[39]. We assume the percent of CVE in TNFi treatment group is around 7% [8,11,40]. To detect a relative risk of 1.2 [30,41] in the CVE outcome with 80% power, we estimated the total subjects should be around 16,836 with equal sample size (n=5612) in each treatment group.

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Supplementary Table 1. Classification of Diseases, Ninth & Tenth Revision, Clinical Modification (ICD-9-CM & ICD-10-CM) codes of included diseases

	ICD-9-CM	ICD-10-CM
Autoimmune disease		
Rheumatoid arthritis	714.0	M05, M06
Systemic lupus erythematosus	710.0	M32
Inflammatory Bowel Disease	555, 556	K50, K51
Multiple sclerosis	340	G35
Psoriasis	696	L40
Spondylarthritis	720.0	M45
Cardiovascular events		
Venous thromboembolic	453.0, 453.1, 453.2, 453.3, 453.4, 453.8, 453.9, 415.1, 451.1, 451.2, 451.9, 451.81, 453.5	I80, I81, I82, I26
Systemic embolism	444	I74
Congestive heart failure	428, 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93	I099, I110, I130, I132, I255, I420, I425-429, I43, I50, P290
Acute coronary heart disease	410, 411, 413	I20-I24
Stroke	430, 431, 433.x1, 434.x1, and 436	I60, I61, I630-I635, I64, I678
Baseline comorbidities		
Atrial fibrillation/flutter	427.3	I48
Chronic ischaemic heart disease	412, 414	I25
Cerebrovascular disease	430-438	I60-I69, G45-46, H340
Chronic obstructive pulmonary disease	490-496, 500-505, 506.4	J40-47, , J60-67, J684, J701, J703
Chronic renal failure	582, 585, 586, 588, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7	N032-037, N052-057, N18-19, N250, Z490-492, Z940, Z992
Dementia	290	F00-03, F051, G30, G311
Diabetes	250	E10-14
Hypertension	401- 405, 437.2	I10 - I16
Hyper lipoid	272.0-272.4	E780 - E785
Liver disease	571.2, 571.4, 571.5, 571.6, 456.0, 456.1, 456.2, 572.2, 572.3, 572.4, 572.8	K70, K713-715, K717, K72-74, K76
Malignancy	140-149, 150-159, 160-165, 170-172, 174-176, 179-189, 190-195, 200-208	C00–C26, C30–C34, C37–C41, C43, C45–C58, C60–C76, C81–C85, C88, C90–C97
Peripheral vascular disease	441, 443.9, 785.4	I70, I71, I731, I738, I739, I771, I790, I792, K551, K558, K559, Z958, Z959
Comorbidities for Charlson Comorbidity Index		
Acquired Immune Deficiency Syndrome (AIDS)	042	B20-24
Cerebrovascular disease	430-438	I60-I69, G45-46, H340
Chronic obstructive pulmonary disease	490-496, 500-505, 506.4	J40-47, , J60-67, J684, J701, J703
Chronic renal failure	582, 585, 586, 588, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7	N032-037, N052-057, N18-19, N250, Z490-492, Z940, Z992
Dementia	290	F00-03, F051, G30, G311
Diabetes without chronic complication	250.0, 250.1, 250.2, 250.3, 250.7	E100, E101, E106, E108-111, E116, E118-E121, E126, E128-131, E136, E138-141, E146, E148, E149
Diabetes with chronic complication	250.4, 250.5, 250.6	E102-105, E107, E112-115, E117, E122-125, E127, E132-135, E137, E142-145, E147
Myocardial infarction	410	I21, I22, I252

Mild liver disease	571.2, 571.4, 571.5, 571.6	B18, K700-703, K713-715, K717, K73, K74, K760, K762-764, K768, K769, Z944
Moderate-severe liver disease	456.0, 456.1, 456.2, 572.2, 572.3, 572.4, 572.8	K704, K72, K761-768, I85
Metastatic solid tumour	196-199	C77-80
Malignancy	140-149, 150-159, 160-165, 170-172, 174-176, 179-189, 190-195, 200-208	C00–C26, C30–C34, C37–C41, C43, C45–C58, C60–C76, C81–C85, C88, C90–C97
Paralysis	342, 344.1	G041, G114, G801, G802, G81, G82, G830-834, G839
Peripheral vascular disease	441, 443.9, 785.4	I70, I71, I731, I738, I739, I771, I790, I792, K551, K558, K559, Z958, Z959
Rheumatoid arthritis and other inflammatory polyarthropathies	710.0, 710.1, 710.4, 714.0, 714.1, 714.2, 714.81, 725	M05, M06, M315, M32-34, M351, M353, M360
Ulcers	531-534	K25-28

Supplementary Table 2. Drug identification

	Hong Kong, drug molecular
RA related drugs	
TNFi	etanercept infliximab adalimumab certolizumab pegol golimumab
IL-6i	tocilizumab sarilumab
JAKi	tofacitinib baricitinib upadacitinib
csDMARDs	methotrexate Hydroxychloroquine leflunomide sulphasalazine
corticosteroid	triamcinolone, betamethasone dexamethasone, fludrocortisone hydrocortisone, methylprednisolone prednisolone
NSAIDs	celecoxib, diclofenac, etoricoxib febuxostat, piroxicam, ibuprofen indomethacin, sulindac, mefenamic acid naproxen, penicillamine
Diuretics	amiloride, bumetanide, dyazide eplerenone, frusemide, hydrochlorothiazide, indapamide mannitol, metolazone, moduretic spironolactone
Anti-arrhythmic	amiodarone, atropine, disopyramide dronedarone, flecainide, mexiletine procainamide, propafenone, quinidine
Beta-adrenoceptor blocking drugs	atenolol, bisoprolol, carvedilol esmolol, labetalol, metoprolol nadolol, propranolol, sotalol
Hypertension and heart failure	captopril, ambrisentan, clonidine amlodipine, enalapril, bosentan enalaprilat, candesartan, hydralazine doxazosin, lisinopril, iloprost losartan, methyldopa, irbesartan minoxidil, nitroprusside dihydrate sodium macitentan, perindopril, sacubitril phenoxybenzamine, selexipag phentolamine, sildenafil, prazosin telmisartan, predonium, telmisartan ramipril, valsartan, terazosin
Antianginal drugs	amlodipine, cilostazol, diltiazem ginkgo biloba extract, felodipine er ivabradine, glyceryl trinitrate

	lercanidipine, naftidrofuryl oxalate isosorbide dinitrate, nifedipine isosorbide mononitrate, oxpentifylline nicardipine, nicergoline, nifedipine nimodipine, verapamil
Sympathomimetics	adrenaline, dobutamine, dopamine ephedrine, isoprenaline, metaraminol midodrine, noradrenaline, norepinephrine phenylephrine
Anti-thrombotic therapy	argatroban, apixaban, dabigatran edoxaban, enoxaparin, epoprostenol heparin, nadroparin, protamine sulphate rivaroxaban, sodium citrate, tinzaparin warfarin, aspirin, clopidogrel dipyridamole, eptifibatide, prasugrel ticagrelor
Antifibrinolytic and Haemostatic drugs	tranexamic acid, emicizumab factor ix/viia/viii/viii inhibitor bypassing fraction prothrombin complex concentrate ethanolamine oleate sodium tetradecyl sulphate
Lipid-regulating drugs	alirocumab, atorvastatin, cholestyramine evolocumab, ezetimibe, fenofibrate gemfibrozil, rosuvastatin, simvastatin