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Clinical science

Effectiveness of JAK inhibitors in biologics-naïve patients with RA: a population-based study

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Abstract

Objective: We evaluated drug retention rates to compare the effectiveness of Janus kinase (JAK) inhibitors *vs* TNF inhibitor (TNFi) biologics and non-TNFi biologics in biologics-naïve RA patients, and assessed intra-class differences among JAK inhibitors.

Methods: We conducted a cohort study using Taiwan's National Health Insurance Research Database, including RA patients initiating TNFi biologics, non-TNFi biologics or JAK inhibitors. We followed patients from index date until outcome, death or end of 2-year study period. To evaluate retention rate, we used treatment change defined as discontinuation or switching of medications. We calculated hazard ratios of treatment change to compare the effectiveness of JAK inhibitors *vs* biologics, using JAK inhibitors as reference group.

Results: Of 16 212 patients, 2654 (16.37%) received JAK inhibitors, 10 080 (62.18%) received TNFi biologics, and 3478 (21.45%) received non-TNFi biologics. We found TNFi biologics were associated with a higher risk of treatment change than JAK inhibitors (hazard ratio = 1.38; 95% CI: 1.25–1.53). We found no significant difference between JAK inhibitors and non-TNFi biologics. The risk of treatment change among JAK inhibitors (tofacitinib, baricitinib) was similar.

Conclusion: Our findings reflected drug effectiveness by the duration that patients maintained the regimen, considering both therapeutic effects and adverse events. We found JAK inhibitors had better effectiveness than TNFi biologics, with no significant difference compared with non-TNFi biologics in biologics-naïve patients. Intra-class comparison of JAK inhibitors indicated similar effectiveness for both tofacitinib and baricitinib. These findings supported the use of JAK inhibitors in RA patients after failure of conventional DMARDs treatment.

Keywords: biological therapies, RA, JAK inhibitors, outcome measures, DMARDs, observational studies.

Rheumatology key messages

- Among biologic-naïve users with RA, JAK inhibitors were more effective than TNFi biologics.
- No significant difference was observed between JAK inhibitors and non-TNFi biologics among biologic-naïve users.
- Our findings supported the use of JAK inhibitors for patients after the failure of conventional DMARDs.

Introduction

Janus kinase (JAK) inhibitors represent a novel therapeutic class for patients with RA, particularly those who are intolerant to or have an inadequate response to conventional DMARDs. These small molecules are administered orally, providing a convenience advantage over injectable biologics. Unlike biologics, JAK inhibitors do not induce anti-drug antibodies (ADA), potentially reducing the risk of secondary failure. In randomized controlled trials (RCTs), the efficacy and safety of tofacitinib or baricitinib were comparable to biologics [1–3]. However, participants in RCTs do not adequately represent patients in real-world settings. Several factors not measured in RCTs may influence drug effectiveness in real-world settings, such as pain relief and administration routes. Post-hoc analyses of RCTs have reported that baricitinib can bring pain relief faster than TNF inhibitor (TNFi) biologics [4, 5]. The convenience of oral administration also offers advantages over parenteral administration and may contribute to the better

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effectiveness of JAK inhibitors over TNFi biologics in real-world settings.

Efficacy results from RCTs do not always translate into corresponding clinical outcomes [6]. The length of time patients maintain a regimen of biologics or JAK inhibitors can serve as a measure of effectiveness, as time to treatment-change is a composite measure of therapeutic outcomes, including adverse reactions and loss of efficacy. Non-compliance and psychological influences may also affect how long patients stay on the treatment. Therefore, time to treatment-change can provide a holistic view of drug effectiveness [6, 7].

Previous studies have compared the effectiveness of JAK inhibitors with biologics in clinical practice, by measuring drug-survival, or the time to treatment-change [8–12]. Most studies generally report that JAK inhibitors are more effective than TNFi biologics; however, results regarding drug survival differences between JAK inhibitors and non-TNFi biologics have been inconsistent [8, 10, 12, 13]. None of the studies discussed patients directly switching to biologics or JAK inhibitors after failure of the first-line DMARD regimen, defined as biologics-naïve patients [14, 15]. Notably, in previous studies, JAK inhibitors were likely used for those who had already received biologics, raising concerns of confounding by indication when compared with biologics. Additionally, intra-class comparison of JAK inhibitors was limited by sample sizes. Since JAK inhibitor approvals have varied across different countries, the study population of JAK inhibitor has differed by country. Our nationwide population-based study aimed to compare the effectiveness of JAK inhibitors with that of TNFi biologics or non-TNFi biologics in biologics-naïve patients with RA, and furthermore to evaluate and compare JAK inhibitors intra-class. We measured the effectiveness by the drug retention rate, which can be interpreted as a global assessment of drug therapeutic effects, adverse events and tolerability from both clinician and patient perspectives. This approach has previously been used in several pragmatic trials and observational studies [11, 13, 16]. Because in Taiwan biologics and JAK inhibitors are both considered second-line therapies for patients in whom traditional immunosuppressant therapy has failed, we specifically selected patients naïve to any biologics or JAK inhibitors, in order to address the issue of confounding by indication residual from previous studies.

Materials and methods

Data source

We used the National Health Insurance Research Database (NHIRD) for this study [17, 18]. The NHIRD is derived from National Health Insurance claims data in Taiwan and covers 99.9% of the population. The database contains patient demographic information, diagnosis claims and prescription records from inpatient, outpatient and emergency room visits. Patients using biologics and JAK inhibitors had thoroughly confirmed RA diagnoses, as use of these medications needed review and approval by a second rheumatologist. Previous studies have shown that we could capture all reimbursement records for biologics and JAK inhibitors, thereby ensuring a high level of completeness [19]. Approval from an independent institutional review board of National Cheng Kung University Hospital (A-ER-111–197) was obtained, and informed consent was waived, as the study was retrospective and involved no prospective intervention.

Study population and design

We conducted a cohort study using a target trial emulation framework to compare the effectiveness of JAK inhibitors and biologics. The target trial specifications and the emulation details for each component are listed in Supplementary Table S1, available at *Rheumatology* online. We identified patients aged 18 years and above, diagnosed with RA, as indicated by ICD-9-CM codes (714) or ICD-10-CM codes (M05, M06) [20]. Previous studies have validated these codes, showing a positive predictive value of 82% when identifying patients with RA [21, 22]. We included biologics-naïve patients for whom conventional DMARDs had failed, and who initiated JAK inhibitors or biologics between 2010 and 2021, including adalimumab, golimumab, etanercept, certolizumab, abatacept, tocilizumab, tofacitinib or baricitinib. Detailed ATC codes are provided in the Appendix (Supplementary Table S2, available at *Rheumatology* online). We assigned eligible patients into one of three groups based on the medication they initiated (index agent): TNFi biologics (adalimumab, golimumab, etanercept, certolizumab), non-TNFi biologics (abatacept, tocilizumab) or JAK inhibitors (tofacitinib, baricitinib). We defined the index date as the date of treatment initiation. We implemented a 1-year washout period to exclude patients with prior exposure to biologics or JAK inhibitors. We excluded individuals diagnosed with autoimmune diseases such as psoriasis, psoriatic arthritis, ulcerative colitis, Crohn's disease and ankylosing spondylitis within 1 year prior to the index date. In clinical practice, patients were evaluated by a rheumatologist and excluded from taking JAK inhibitors or biologics if they met any of the following criteria: (1) pregnant or breast-feeding women, (2) patients with active tuberculosis or those at high risk of infection, including individuals with chronic leg ulcers and those with incomplete tuberculosis prophylaxis or treatment, (3) patients who had infectious arthritis within the past 12 months, (4) patients with infected prosthetic joints, (5) patients with refractory or recurrent pulmonary infections, (6) patients with malignancies or precancerous conditions and (7) patients with multiple sclerosis. We did not include patients receiving rituximab because National Health Insurance guidelines prescribe rituximab only for those with inadequate response or intolerance to TNFi biologics, and require that it be combined with methotrexate unless contraindicated, indicating different characteristics from patients received other DMARDs.

Outcome definition and follow-up

In the main analyses, we compared the effectiveness of JAK inhibitors with TNFi biologics and non-TNFi biologics, using JAK inhibitors as the reference group. In the secondary analyses, we compared the effectiveness between two JAK inhibitors (tofacitinib and baricitinib), using baricitinib as the reference group. We assessed the drug retention rate by calculating the time to treatment-change (i.e. the duration patients remained on the treatment). The primary outcome was treatment changes, defined as either discontinuation or switching to another treatment. Individual outcomes included discontinuation and switching. Discontinuation was defined as having no refill records within 90 days of the previous prescription's end date. Switching was defined as receiving another biologic or JAK inhibitor, regardless of whether the drug belonged to the same class. We followed up patients from the index date until death, end of the database

(31 December 2021), end of the 2-year follow-up period, or outcome of interest, whichever came first.

Covariates

We captured patients' age, sex, year of index date, income level, RA disease duration, comorbidities and concurrent medications as baseline characteristics (Table 1). The look-back period for comorbidities and co-medications in outpatient and inpatient records was 365 days before the index date. We assessed income level by National Health Insurance determined income-related premium levels (based on the insured's wage), categorized into three groups: low (<15 000 New Taiwan Dollar), medium (15 000–25 000 New Taiwan Dollar) and high (>25 000 New Taiwan Dollar), and this served as a proxy for socioeconomic status [23]. We also included systemic glucocorticoids usage using prednisolone equivalent dose [24]. Detailed ICD-9/10-CM and ATC codes are provided in the Appendix (Supplementary Tables S3 and S4, available at *Rheumatology* online).

Sensitivity and subgroup analysis

We performed a series of sensitivity and subgroup analyses to assess the robustness of the main analysis. First, we examined the potential influence of reimbursement. As tofacitinib received reimbursement approval in December 2014, we selected patients who initiated treatment from 2015 onwards [25]. Second, since patients with RA have widely varying intervals between visits, we redefined the discontinuation period from 90 days to 180 days. Third, since prior medication persistence and administration route may affect physicians' preferences, we examined the potential effect of confounding by prior medication adherence through a subgroup analysis of oral medication adherence levels during the baseline period [26]. We measured oral medication adherence using the medication possession ratio. Those with ratios above 0.8 were considered to have good adherence and were selected for subgroup analysis [27]. Lastly, we evaluated the potential impact of three significant risk factors on effectiveness by conducting subgroup analyses based on age (< 65 *vs* ≥ 65), sex and methotrexate usage [9, 28].

Statistical analysis

We described continuous variables using mean with standard deviation and categorical variables by numbers with proportions. The analysis of variance (ANOVA) and chi-squared tests were used to compare the differences between groups. We used Kaplan–Meier survival curves to demonstrate the time to treatment-change within each group. We estimated absolute risk of effectiveness by calculating the incidence rate of time to treatment-change. We used multivariable Cox regression models to estimate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for treatment change to compare the effectiveness of JAK inhibitors *vs* biologics, using JAK inhibitors as the reference group. We adjusted our models using all baseline covariates mentioned above. All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

Results

Description of study population

We identified 24 196 patients with RA receiving either biologics or JAK inhibitors. A total of 16 212 biologics-naïve patients were eligible for the analysis, with a mean age of 56.48 ± 13.16 years, of whom 79.27% were female. In total, 2654 (16.37%) patients received JAK inhibitors, 10 080 (62.18%) patients received TNFi biologics and 3478 (21.45%) patients received non-TNFi biologics (Table 1). Fig. 1 depicted the flowchart for study cohort composition.

Time to treatment-change

The average length of treatment in the cohort was 1.54 years, and incidence rates for treatment-change were 11.81, 17.08 and 12.74 per 100 person-years for JAK inhibitors, TNFi biologics and non-TNFi biologics, respectively. As regards individual outcomes, the incidence rates for discontinuation were 4.30, 6.63 and 5.68 per 100 person-years for JAK inhibitors, TNFi biologics and non-TNFi biologics, respectively. The incidence rates for switching were 7.51, 10.45 and 7.06 per 100 person-years for JAK inhibitors, TNFi biologics and non-TNFi biologics, respectively (Table 2). Fig. 2 presented Kaplan–Meier survival curves comparing the outcomes of treatment-change, discontinuation and switching among the three groups over time. After a 1-year observation period, 80% of our study population remained on their respective index agents. After a 2-year observation period, 80% of JAK inhibitor- and non-TNFi biologics users remained on the index agents, while only 70% of TNFi biologics users remained on the index agents.

Relative risk of treatment change

We observed that TNFi biologics were associated with a higher risk of treatment change than JAK inhibitors (HR: 1.38; 95% CI: 1.25–1.53) after adjusting for patient demographics, baseline comorbidities and medications. The risk of treatment change was similar for non-TNFi biologics and JAK inhibitors (HR: 1.03; 95% CI: 0.91–1.16) (Table 2).

The incidence rates in several subgroups and sensitivity analyses were similar to those in the main analysis, except for patients not using methotrexate during the baseline period and in the sensitivity analysis defined by a 180-day grace period. Patients not using methotrexate had a higher incidence rate of treatment change, compared with the main findings (Supplement Table S5, available at *Rheumatology* online). The HRs of the sensitivity- and subgroup analyses were consistent with the main analysis (Fig. 3). In intra-class comparison of JAK inhibitors, the risk of treatment change was comparable between tofacitinib and baricitinib (HR: 1.04; 95% CI: 0.76–1.43). The risk of switching and discontinuation also showed a similar trend (Supplement Table S6, available at *Rheumatology* online).

Discussion

JAK inhibitors are a new class of RA treatment, characterized by small-molecule drugs that are considered safer and that improve patient adherence due to their oral administration. Our study extended current knowledge and assessed the effectiveness of JAK inhibitors in real-life patients with RA using target trial emulation. We specifically chose biologics-naïve patients who directly switched to JAK inhibitors or biologics, in order to reduce bias from confounding by indication. We assessed the effectiveness of the treatment by measuring drug retention rates, an approach that offers a comprehensive evaluation from both clinicians' and patients' perspectives, encompassing efficacy, side effects and

Table 1. Baseline characteristics of TNFi biologics, non-TNFi biologics and JAK inhibitors

Exposure	TNFi biologics	Non-TNFi biologics	JAK inhibitors	*P*-value for difference
Number of patients	10 080	3478	2654	
Age (mean, SD)	55.66 (13.07)	58.30 (13.32)	57.19 (12.99)	<0.0001
18–55 years	4439 (44.04)	1272 (36.57)	1044 (39.34)	
55–65 years	3061 (30.37)	1040 (29.90)	819 (30.86)	
65–85 years	2534 (25.14)	1126 (32.37)	769 (28.98)	
>85 years	46 (0.46)	40 (1.15)	22 (0.83)	
Female proportion (*n*, %)	7999 (79.36)	2701 (77.66)	2151 (81.05)	0.0049
RA duration (median, Q1–Q3)	30 (15–58)	44 (16–75)	59 (17–93)	<0.0001
Less 6 months	199 (1.97)	63 (1.81)	38 (1.43)	
6 months–2 years	4009 (39.77)	1062 (30.53)	774 (29.16)	
2–10 years	5521 (54.77)	2145 (61.67)	1592 (59.98)	
Over 2 years	351 (3.48)	208 (5.98)	250 (9.42)	
Monthly insurance premium (New Taiwan Dollar) (median, Q1–Q3)	24 000 (21 900–38 200)	24 000 (21 009–38 200)	24 000 (22 800–38 200)	0.0613
Missing	41 (0.41)	12 (0.35)	9 (0.34)	
>25 000	4278 (42.44)	1461 (42.01)	1154 (43.48)	
15 000–25 000	3911 (38.80)	1297 (37.29)	957 (36.06)	
<15 000	1850 (18.35)	708 (20.36)	534 (20.12)	
Prednisone equivalent dose (mg/day)	6 (3–10)	6 (3–10)	5 (2–8)	<0.0001
>7.5 mg per day	3791 (37.61)	1367 (39.30)	771 (29.05)	
2.5–7.5 mg per day	3816 (37.86)	1269 (36.49)	1126 (42.43)	
<2.5 mg per day	2473 (24.53)	842 (24.21)	757 (28.52)	
Comorbidities (*n*, %)				
Asthma	377 (3.74)	152 (4.37)	100 (3.77)	0.2392
Atrial fibrillation	55 (0.55)	42 (1.21)	17 (0.64)	0.0003
Chronic kidney disease	370 (3.67)	207 (5.95)	109 (4.11)	<0.0001
Chronic obstructive pulmonary disease	301 (2.99)	125 (3.59)	57 (2.15)	0.0043
Coronary artery disease	546 (5.42)	220 (6.33)	121 (4.56)	0.0099
Fracture	410 (4.07)	168 (4.83)	133 (5.01)	0.0378
Heart failure	125 (1.24)	68 (1.96)	39 (1.47)	0.0091
Hyperlipidaemia	1244 (12.34)	467 (13.43)	345 (13.00)	0.2184
Hypertension	2680 (26.59)	1051 (30.22)	684 (25.77)	<0.0001
Liver disease	857 (8.50)	334 (9.60)	236 (8.89)	0.1396
Peripheral vascular disease	87 (0.86)	15 (0.43)	5 (0.19)	0.0001
Renal dialysis	31 (0.31)	23 (0.66)	n<3	0.0003
Stroke	193 (1.91)	101 (2.90)	68 (2.56)	0.0014
Type 2 diabetes mellitus	1032 (10.24)	425 (12.22)	270 (10.17)	0.0033
Conventional DMARDs (*n*, %)				
Azathioprine	275 (2.73)	97 (2.79)	53 (2.00)	0.0869
Ciclosporin	662 (6.57)	84 (2.42)	n<3	<0.0001
Hydroxychloroquine	7519 (74.59)	2655 (76.34)	2022 (76.19)	0.0555
Leflunomide	2946 (29.23)	982 (28.23)	697 (26.26)	0.0099
Methotrexate	8478 (84.11)	2802 (80.56)	2247 (84.66)	<0.0001
Sulfasalazine	6117 (60.68)	1905 (54.77)	1426 (53.73)	<0.0001
Analgesics (*n*, %)				
COX-2 inhibitors	8070 (80.06)	2776 (79.82)	2149 (80.97)	0.4909
NSAIDs	7316 (72.58)	2488 (71.54)	1775 (66.88)	<0.0001
Opioids	2684 (26.63)	901 (25.91)	559 (21.06)	<0.0001
Antibiotics (*n*, %)				
Aminoglycosides	175 (1.74)	68 (1.96)	32 (1.21)	0.0698
First-generation cephalosporins	1736 (17.22)	648 (18.63)	403 (15.18)	0.0019
Second-generation cephalosporins	285 (2.83)	111 (3.19)	64 (2.41)	0.1890
Third-generation cephalosporins	191 (1.89)	103 (2.96)	51 (1.92)	0.0006
Fourth-generation cephalosporins	10 (0.10)	12 (0.35)	5 (0.19)	0.0087
Fluroquinolone	448 (4.44)	238 (6.84)	96 (3.62)	<0.0001
Macrolides	603 (5.98)	242 (6.96)	136 (5.12)	0.0104
Penicillins	1836 (18.21)	734 (21.1)	461 (17.37)	0.0001
Tetracyclines	269 (2.67)	114 (3.28)	77 (2.90)	0.1715
Trimethoprim/sulfamethoxazole	183 (1.82)	69 (1.98)	32 (1.21)	0.0517
Co-medications (*n*, %)				
Insulins	211 (2.09)	92 (2.65)	47 (1.77)	0.0500
Non-insulin antidiabetic drugs	885 (8.78)	364 (10.47)	247 (9.31)	0.0123
Statins	1000 (9.92)	454 (13.05)	296 (11.15)	<0.0001
Non-statin lipid-lowering drugs	94 (0.93)	34 (0.98)	20 (0.75)	0.6223
ACE inhibitors	280 (2.78)	95 (2.73)	50 (1.88)	0.0336
ARBs	1899 (18.84)	811 (23.32)	523 (19.71)	<0.0001

(continued)

Table 1. (continued)

Exposure	TNFi biologics	Non-TNFi biologics	JAK inhibitors	*P*-value for difference
Beta-blockers	1673 (16.60)	639 (18.37)	405 (15.26)	0.0042
Calcium channel blockers	1788 (17.74)	718 (20.64)	408 (15.37)	<0.0001
Diuretics	924 (9.17)	375 (10.78)	195 (7.35)	<0.0001
Nitrates	258 (2.56)	92 (2.65)	65 (2.45)	0.8905
Antidepressants	544 (5.40)	223 (6.41)	122 (4.60)	0.0069
Antipsychotics	630 (6.25)	264 (7.59)	164 (6.18)	<0.0001
Benzodiazepines	3333 (33.07)	1246 (35.83)	763 (28.75)	0.0162

ARBs: angiotensin receptor blockers; ACE: angiotensin-converting enzyme; NSAID: non-steroidal anti-inflammatory drugs; COX-2: cyclooxygenase-2; TNFi: TNF inhibitor; JAK: Janus kinase; n<3: exact numbers are not reported due to data privacy restrictions.

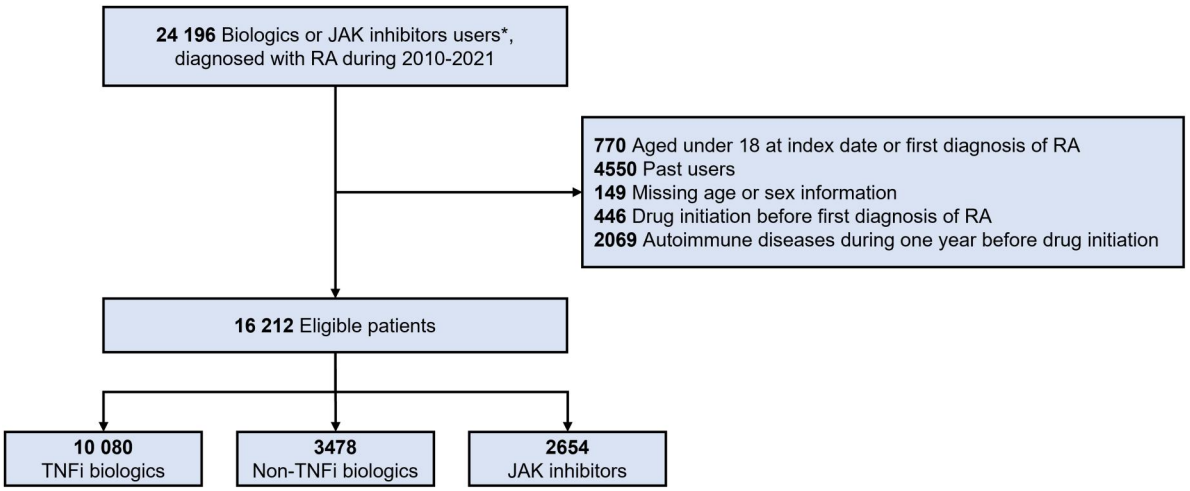

Figure 1. Flowchart for identification of eligible patients. *The exclusion criteria that required checking by rheumatologists included: (1) pregnant or breastfeeding women, (2) patients with active tuberculosis or those at high risk of infection, including individuals with chronic leg ulcers and those with incomplete tuberculosis prophylaxis or treatment, (3) patients who had infectious arthritis within the past 12 months, (4) patients with infected prosthetic joints, (5) patients with refractory or recurrent pulmonary infections, (6) patients with malignancies or precancerous conditions and (7) patients with multiple sclerosis. RA: rheumatoid arthritis; TNFi: TNF inhibitor; JAK: Janus kinase

Table 2. Assessment of treatment change among TNFi biologics, non-TNFi biologics and JAK inhibitors

	No. of events (*n*)	No. of patients (*n*)	Follow-up year (mean)	Incidence rate (per 100 patient-years)	Crude HR	Adjusted HR
Treatment change						
TNFi biologics	2679	10 080	1.56	17.08 (16.44–17.74)	**1.45 (1.31–1.60)**	**1.38 (1.25–1.53)**
Non-TNFi biologics	684	3478	1.54	12.74 (11.80–13.73)	1.08 (0.96–1.21)	1.03 (0.91–1.16)
JAK inhibitors	459	2654	1.46	11.81 (10.75–12.94)	Ref.	Ref.
Switching						
TNFi biologics	1639	10 080	1.56	10.45 (9.95–10.97)	**1.39 (1.23–1.58)**	**1.34 (1.18–1.52)**
Non-TNFi biologics	379	3478	1.54	7.06 (6.36–7.80)	0.94 (0.81–1.10)	0.90 (0.77–1.05)
JAK inhibitors	292	2654	1.46	7.51 (6.67–8.42)	Ref.	Ref.
Discontinuation						
TNFi biologics	1040	10 080	1.56	6.63 (6.23–7.05)	**1.54 (1.31–1.82)**	**1.47 (1.24–1.74)**
Non-TNFi biologics	305	3478	1.54	5.68 (5.06–6.35)	**1.32 (1.09–1.59)**	**1.25 (1.04–1.51)**
JAK inhibitors	167	2654	1.46	4.30 (3.67–5.00)	Ref.	Ref.

Bold indicates statistical significant. TNFi: TNF inhibitor; JAK: Janus kinase; HR: hazard ratio.

tolerability [13, 16, 29]. We found that patients receiving JAK inhibitors were associated with a reduced risk of treatment change, compared with TNFi biologics, while the risk was similar for non-TNFi biologics. Additionally, we found no difference in the risk of treatment change between the two individual JAK inhibitors. These findings provided evidence that JAK inhibitors may offer effectiveness comparable to non-TNFi biologics, but better than TNFi biologics in real-world practice. Our findings supported the use of JAK inhibitors for RA patients for whom conventional DMARDs have failed.

Measuring effectiveness based on the duration for which patients continue treatment takes into account therapeutic

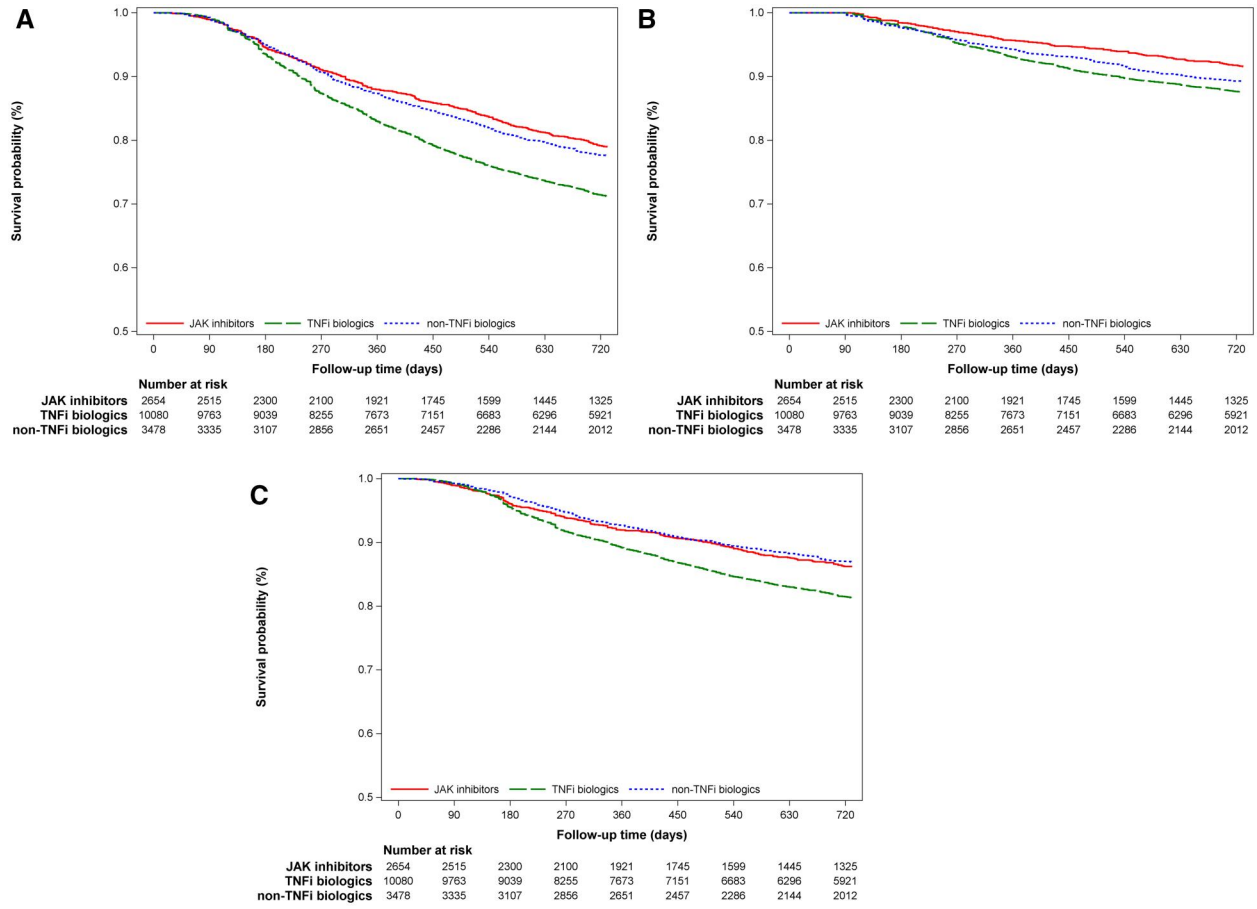

Figure 2. Survival curves for (A) treatment change, (B) discontinuation, (C) switching over time (in days). TNFi: TNF inhibitors; JAK: Janus kinase

effect, adverse events and remission [30, 31]. We observed that TNFi biologics were associated with a higher risk of treatment change, compared with JAK inhibitors, with no significant difference between non-TNFi biologics and JAK inhibitors. Observational studies from Australia, Sweden and Japan have reported similar trends [9, 12, 32]. However, the overall drug-survival time in our study population was longer than that reported in previous studies. In our study, nearly 90% of JAK inhibitors and non-TNFi biologics users continued their treatment over a 1-year observation period. By contrast, in studies by Gilbert *et al.* and Scheepers *et al.*, <70% of JAK inhibitor users and 60% of biologics users remained on treatment [12, 32]. This discrepancy may be attributed to varying reimbursement criteria for biologics first-use across countries. Biologics-naïve patients in Taiwan were required to have treatment failure with at least two conventional DMARDs, and a minimum 6-month disease duration [33]. In comparison, biologics-naïve patients in Sweden had no such requirements regarding disease duration or failed conventional DMARDs treatments [34, 35]. Although they were all categorized as biologics-naïve patients, their disease severity may not be similar. Therefore, reimbursement policies for biologics treatment should be considered when comparing outcomes across study populations from different countries.

The primary reason for switching might have been inefficacy, followed by adverse events and other factors such as financial issues or personal preferences [36, 37]. Therefore, switching can serve as a proxy for effectiveness, as physicians tend to change the regimen if RA remained active and progressive [31]. In previous studies, outcomes were defined by discontinuation and switching, but no studies specifically reported the results for switching [12, 32, 38, 39]. We observed that TNFi biologics were associated with a higher risk of switching, compared with JAK inhibitors, but we found no significant difference between non-TNFi biologics and JAK inhibitors. These findings were consistent with our main results and further supported the use of JAK inhibitors in biologics-naïve patients.

The primary reason for discontinuing TNFi biologics might have been loss of efficacy [9, 32, 40]. Despite an initially good response, the effectiveness diminishes over time, primarily due to the formation of ADA [40]. These antibodies generally bind to an idiotope of monoclonal antibodies, such as adalimumab and golimumab. By comparison, etanercept, as a receptor, does not express an idiotype, which explains its lower ADA concentration compared with other TNFi biologics [41]. Other non-TNFi biologics, including abatacept and tocilizumab, have also shown lower ADA formation in phase II/III clinical trials, compared with TNFi biologics [42]. Therefore, the time to secondary failure may explain why JAK inhibitors and non-TNFi biologics had better effectiveness than TNFi biologics. Another potential reason may be related to pain relief [4]. Results from the RA-BEAM study indicate that baricitinib results in greater improvement in pain relief, compared with both placebo and adalimumab [5], suggesting that baricitinib users experience faster

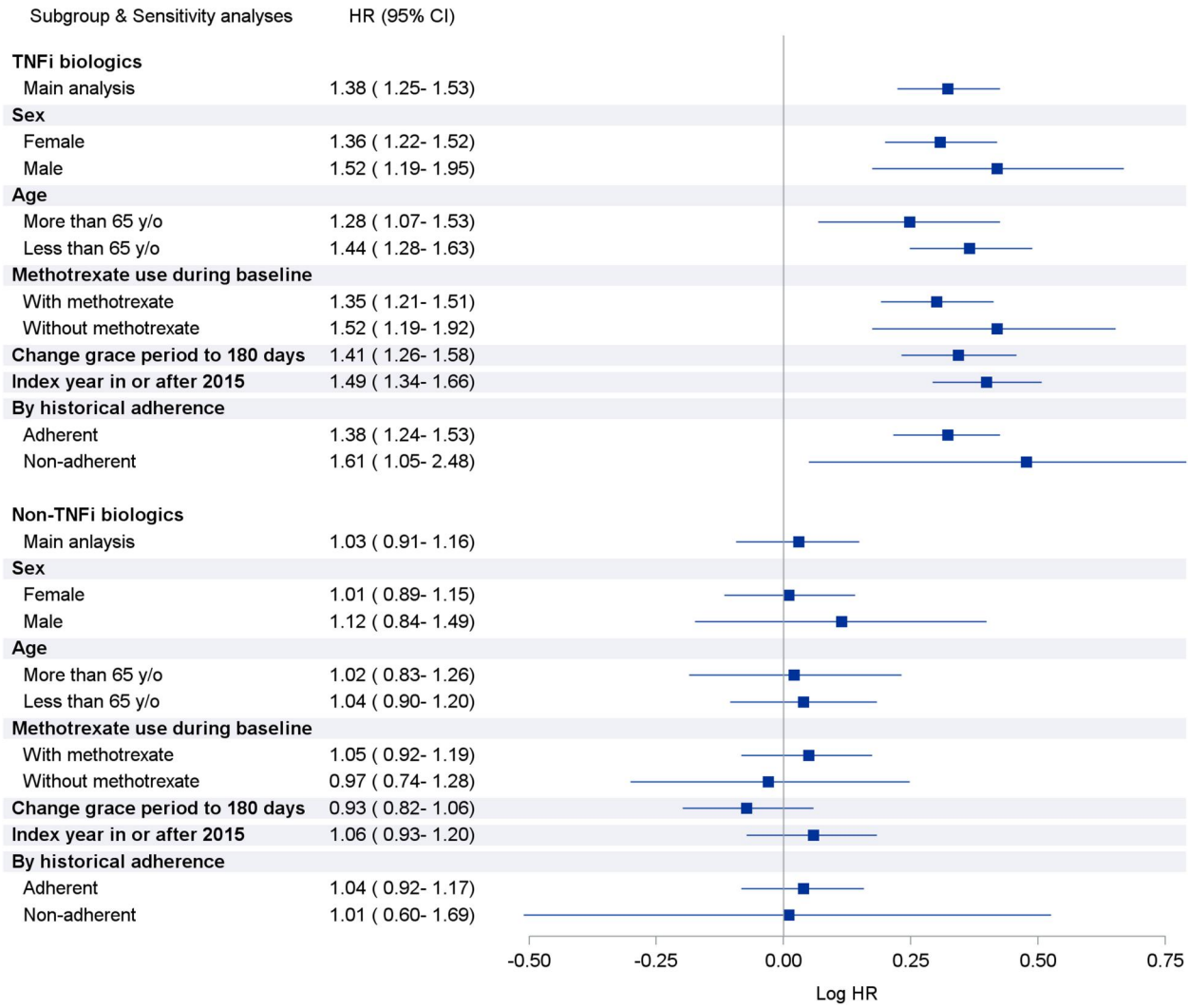

Figure 3. Forest plot of results using subgroup and sensitivity analysis. TNFi: TNF inhibitor; y/o: years old; HR: hazard ratio; CI: confidence interval

improvements in quality of life and work productivity, enabling them to better adhere to the regimen.

Several uncontrolled factors may explain the difference between our study and previous studies [8, 13, 26], including line of therapy and confounding by indication. In previous studies, biologics were mainly used as second-line agents, whereas JAK inhibitors were employed as third-line or later treatments [8, 13]. This difference reflected the severity of the patients' disease and their tolerance to biologics, representing a significant confounder in estimating effectiveness. This could bias the results in favour of JAK inhibitors, as the likelihood of switching among JAK inhibitor users may be reduced, given that most of these patients could not tolerate biologics or experienced ineffectiveness with biologics. To decrease the chance of confounding by indication, our study included new users of JAK inhibitors or biologics among biologics-naïve patients, who were more homogeneous than in previous studies in terms of disease severity and duration. According to the National Health Insurance guidelines in Taiwan, JAK inhibitors are in the same line of therapy as TNFi biologics, and all eligible patients must have an intolerance or an inadequate response to at least two kinds of conventional DMARDs. In addition, before treatment initiation, the disease severity should be assessed for all patients, based on the American College of Rheumatology and DAS-28 (disease activity score by 28 joints) criteria and validated by rheumatologists [43]. All in all, our findings provided a more precise estimation of effectiveness, since we minimized confounding by indication.

JAK inhibitors target the JAK/STAT pathway and offer the convenience of oral administration over parenteral use. Although both tofacitinib and baricitinib are pan-JAK inhibitors, they have distinct therapeutic targets [5, 44, 45]. Previous observational studies have shown inconsistent results for the effectiveness of baricitinib and tofacitinib, possibly due to varying sample sizes and population heterogeneity. One observational study, which included over 1400 baricitinib patients with a disease duration of over 10 years, demonstrated higher drug survival for baricitinib compared with tofacitinib [13]. In contrast, our study population primarily had a disease duration of 2–5 years, with smaller sample sizes and shorter follow-up times for baricitinib patients. These differences may affect outcome estimation. Therefore, further investigation is required with sufficient baricitinib sample sizes.

Under target trial emulation framework, we concluded that biologics-naïve patients initiating JAK inhibitors

remained on their regimen longer than those initiating TNFi biologics. This finding underscored the difference in time to treatment-change between JAK inhibitors and TNFi biologics for those directly switching to second-line therapy after failing conventional DMARDs. Despite recent concerns regarding the cardiovascular risks of tofacitinib, observational and long-term extension studies have supported the better effectiveness of JAK inhibitors compared with TNFi biologics [3, 12, 13, 32, 46]. Additionally, the risks associated with tofacitinib were considered to affect only individuals with cardiovascular risk factors [47]. Therefore, in the absence of specific risk factors, physicians should consider the convenience and pain relief offered by JAK inhibitors for biologics-naïve patients. Since adhering to the treatment regimen could reduce the likelihood of flare-ups, prevent loss of efficacy, and alleviate the disease burden among RA patients, it is advisable to choose medications with better effectiveness and adherence, such as JAK inhibitors.

Strengths and limitations

The strength of our study lay in the inclusion of the entire RA population in Taiwan. Both biologics and JAK inhibitors were reimbursed under Taiwan's National Health Insurance, ensuring that all patients using these treatments were recorded in the NHIRD. Due to the comprehensive National Health Insurance coverage, the costs of these medications were not a concern for patients, allowing treatment continuation to be based on clinical rather than financial considerations.

Our study had some limitations. First, the NHIRD contains no data on the reasons for discontinuing or switching JAK inhibitors or biologics. Determining effectiveness by discontinuation may lead to misclassification, as one reason for discontinuation could be remission, which differs significantly from loss of efficacy or intolerance to the medication. However, in cases of discontinuation due to remission, physicians stopped the regimen only if patients were in remission after 2 years of the regimen. In our study, patients were censored after 2 years of observation, which reduced the likelihood of including cases of discontinuation due to remission. Second, the NHIRD lacks laboratory and radiographic data on disease severity in the RA population. However, according to National Health Insurance guidelines, RA patients who initiated biologics or JAK inhibitors had to have been evaluated by a rheumatologist to confirm disease conditions and conventional DMARD usage. The reimbursement guidelines in Taiwan required that claims for all JAK inhibitors, TNFi biologics or non-TNFi biologics be reviewed by experts to ensure that the claimants' DAS-28 scores were at least 5.1. Therefore, the impact of disease severity on our effectiveness measure should be limited. Third, because biologics and JAK inhibitors have different administration routes, patients' preferences for these routes may influence the time to treatment-change. Medication adherence can be influenced by various factors, including the preferences of both patients and prescribers, and can therefore serve as a surrogate to estimate the potential effects of patients' preferences. Since the database did not include information on patient preferences, we conducted a subgroup analysis based on historical medication adherence and obtained results consistent with the main findings [26]. Fourth, the difference in dosing intervals between JAK inhibitors and biologics may have influenced discontinuation rates. We evaluated the proportion of patients who were re-prescribed the same medication after discontinuation and found a similar proportion of re-prescribing among the groups (71%, 72% and 60% for JAK inhibitors, non-TNFi biologics and TNFi biologics, respectively.). We also conducted a sensitivity analysis which extended the grace period from 90 to 180 days and the results remained consistent with the main analysis. These findings suggested that dosing intervals may not be the primary factor influencing treatment discontinuation.

Conclusion

Our study provided evidence regarding biologics-naïve patients who directly switched to biologics or JAK inhibitors after conventional DMARDs regimens had failed. We found that JAK inhibitors carried a reduced risk of treatment change, compared with TNFi biologics, while the risks were similar between JAK inhibitors and non-TNFi biologics. Additionally, we found no difference in the risk of treatment change between the two individual JAK inhibitors available in Taiwan, tofacitinib and baricitinib. We concluded that biologics-naïve patients who initiated JAK inhibitors had a longer persistence on the regimen, indicating better effectiveness of JAK inhibitors, compared with TNFi biologics. Our findings supported the use of JAK inhibitors for RA patients for whom conventional DMARDs have failed.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The authors were unable to share data. All data were from the data centre of the Ministry of Health and Welfare in Taiwan. Researchers interested in accessing this dataset can submit a formal application to the Taiwan Ministry of Health and Welfare to request access (No 488, Sect. 6, Zhongxiao E Rd, Nangang District, Taipei 115, Taiwan; website: https://dep.mohw.gov.tw/DOS/cp-2516-59203-113.html).

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