Effect of TNF-α blockers on reducing the risk of dementia in rheumatoid arthritis: a nationwide cohort study

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Abstract

Objective

Rheumatoid arthritis (RA) and Alzheimer's disease (AD) share characteristics of chronic inflammation and immune system dysregulation. RA patients are known to have an increased risk of dementia, yet studies on the association between tumour necrosis factor (TNF)-α blocker use and dementia risk in RA patients are lacking. This population-based cohort study aimed to investigate whether TNF-α blocker use is associated with a reduced risk of dementia in RA patients.

Methods

Using Taiwan's National Health Insurance Research Database, we identified RA patients treated with TNF-α blockers (etanercept, adalimumab and golimumab) and matched them 1:4 with RA patients receiving conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). A stratified Cox proportional hazard model was used to compare dementia risk between these groups.

Results

Among 3.987 RA patients using TNF-α blockers and 20,689 RA patients not using TNF-α blockers (comparison group), no significant difference in dementia risk was initially observed. However, upon further analysis stratified by TNF-α blocker exposure, RA patients with long-term (>180 cumulative defined daily dose [cDDD]) TNF-α blocker use had a significantly lower risk of dementia (adjusted hazard ratio [aHR]=0.578, 95% confidence interval [CI]=0.342-0.977), after adjusting for age, sex and comorbidities. Moreover, higher cumulative doses (>1036 cDDD) of TNF-α blockers were associated with a further reduced risk of dementia (aHR=0.387, 95% CI=0.188-0.793).

Conclusion

This nationwide cohort study suggests that long-term and higher cumulative doses of TNF-α blockers may be associated with a lower risk of dementia in patients with RA.

Key words

rheumatoid arthritis, dementia, tumour necrosis factor, chronic inflammation, risk

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterised by joint inflammation leading to irreversible damages and subsequent deformity (1). It affects approximately 0.5%-1% of the general population (2) and often manifests with systemic complications such as cardiovascular disease (3), infection, osteoporosis, peptic ulcer, and malignancy (4, 5). These comorbidities significantly impact patient outcomes (2, 6, 7). The understanding of RA pathogenesis has evolved considerably over time (8), and local and systemic inflammation have been shown to be the core events. Specifically, tumour necrosis factor-α (TNF-α) plays a pivotal role in RA pathophysiology by mediating immune cell activation, endothelial dysfunction, and bone resorption, underscoring its therapeutic relevance in RA management (7, 9, 10). TNF-α blockers have demonstrated substantial efficacy in treating RA through improving disease control, preventing joint damage, and enhancing functional outcomes, especially in combination with methotrexate (MTX) (11). The broad clinical benefits of TNF-α blockade in patients with RA further hint at the possibility that such treatment may influence fatigue and modulate cognitive function, whose effects take place in the central nervous system (10). Though recently more novel approaches have been developed for treating RA (12), TNF-α blockers remain an important therapeutic option.

Dementia encompasses a wide range of cognitive disorders leading to functional impairment, with Alzheimer's disease (AD) being the most prevalent form, accounting for 60%-80% of dementia cases (13, 14). AD is characterised by neuronal degeneration due to beta-amyloid plaques and neurofibrillary tangles accumulation, exacerbated by neuroinflammation mediated by pro-inflammatory cytokines (*e.g.* TNF-α) (15, 16). Elevated serum TNF-α levels in AD correlate with the finding of accelerated cognitive decline (17). Given the dual role of TNF-α in RA pathogenesis and cognitive function, exploring its potential link to dementia in RA patients emerges as a critical issue (13, 17, 18). Chronic systematic inflammation in RA is recognised as a risk factor for incident dementia, with epidemiological studies indicating a higher dementia prevalence in RA patients compared to the general population (19-23). Moreover, RA-related factors such as disease activity and inflammatory burden are inversely associated with the integrity of cognitive function (24).

Medications with anti-inflammatory properties, including non-steroid anti-inflammatory drugs (NSAIDs) (25-27) and MTX (28, 29), have been suggested to mitigate dementia risk in patients with RA. Biologic disease-modifying anti-rheumatic drugs (DMARDs) such as TNF-α blockers, despite limited blood-brain barrier penetration, may influence dementia risk through modulation of systemic inflammation (28, 30). However, this topic is seldom addressed in the existing literature, and the associated findings remain inconclusive. Therefore, our study aimed to assess the cumulative impact of TNF-α blocker exposure (including etanercept, adalimumab, and golimumab) on the probability of dementia development in patients with RA, utilising data from Taiwan National Health Insurance (NHI) programme. Understanding the potential benefits of long-term TNF-α blocker use in mitigating RA-related comorbidities like dementia can be crucial for optimising treatment strategies and evaluating healthcare cost-effectiveness in affected individuals.

Materials and methods

Study design

This retrospective nationwide population-based study used a claim-based dataset from 2006 to 2015 in Taiwan, to investigate whether TNF-α blockers reduced the risk of dementia in patients with RA.

Data sources

The NHI programme started in 1995, aiming to reimburse healthcare for all citizens in Taiwan. This universal, obligatory, and single-payer health care system covers >99% of the population in Taiwan. The National Health Research Institute maintains the NHI claim-based database for the purpose

of research, including registration files and claims data, such as diagnoses, medications and examinations. Diagnoses were coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) system. In the NHI programme, patients who fulfilled the American Rheumatism Association 1987 revised criteria for the classification RA (31) or 2010 RA classification criteria (32) were eligible to apply for a catastrophic illness certificate, which were reviewed by a dedicated committee for the eligibility of registration in the Catastrophic Illness Registry. This made the diagnosis of RA recorded in NHI very reliable. The research protocol was approved by the Taipei Medical University-Joint Institutional Review Board (N201908055) and was performed in accordance with the approved guidelines. Informed patient consent was waived because the dataset consisted of deidentified secondary data released for the purpose of research only.

Study population and design

We used the Catastrophic Illness Registry and included all Taiwanese patients diagnosed with RA from 2006 to 2015. Patients who received TNF-α blockers were defined as the case group, and others who did not use any TNF-α blocker served as controls. Exclusion criteria were as follows: (1) unknown birthdate or sex, (2) <18 years old, (3) a history of malignancy, and (4) a history of dementia before enrolment. Patients who had received rituximab, tocilizumab or abatacept were excluded. The date of the first TNF-α blocker prescription was designated as the index date in the case group. Patients receiving conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) but without using any biologics were selected as controls based on the same exclusion criteria. We then applied a 1:4 age and sex-matching approach to identify controls. The csDMARDs included in the matching process consisted of hydroxychloroquine, sulfasalazine, methotrexate and leflunomide. The index date of the control group was defined as the date csDMARDs were initiated (Fig. 1 and Table I).

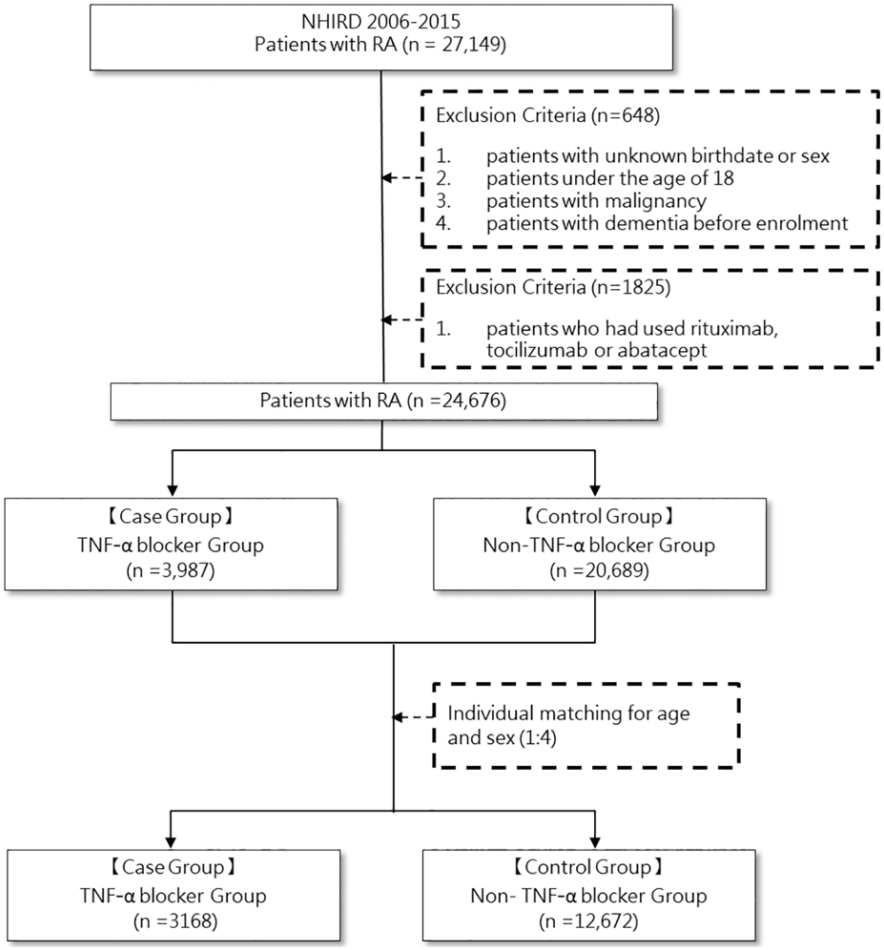


Fig. 1. Patient selection flow-chart of the current study.
NHIRD: National Health Insurance Research Database; RA: rheumatoid arthritis; TNF: tumour necrosis factor.

Biologic DMARD in NHI

Reimbursement for most biologic DMARDs (bDMARDs) for RA was sequentially approved and offered by the NHI, including etanercept (since 2003), adalimumab (since 2004), tocilizumab (since 2012), golimumab (since 2012), rituximab (since 2008), tofacitinib (since 2014), and abatacept (since 2015). In patients with poor responses to sufficient csDMARD (definition provided below), biologics can be prescribed after pre-authorisation based on chart review and are reimbursed by the NHI programme. Sufficient csDMARD should include at least two DMARDs used continuously for more than 6 months, during which MTX should be used if tolerable and without contraindications to MTX. During the pre-authorisation period (6 months), the full dose of MTX (15 mg/week) in combination with another DMARD should be used for more than 2 months. In those who are refractory to the above "sufficient csDMARD" regimen and still exhibit a high RA disease activity (disease activity score-28 (DAS-28) over 5.1), biologics will be reimbursed by the NHI programme.

TNF-α blocker exposure

TNF-α blockers identified in this study included etanercept, adalimumab and golimumab (ATC code: L04AB01, L04AB04 and L04AB06, respectively). The defined daily dose (DDD), established by the World Health Organisation as the average maintenance dose per day for a drug used for its main indication, was used to determine TNF-α blocker dosage. We defined short- and long-term use of TNF-α blockers based on prescriptions indicating a DDD of ≤180 and >180 days during the inclusion period, respectively. Exposure to

Table I. Baseline characteristics of patients with rheumatoid arthritis.

	Case group (n=3168) n (%)	Comparison group (non-users) (n=12672) n (%)	*p*-value
Gender			1.0000
Female	2484 (78.41%)	9936 (78.41%)	
Male	684 (21.59%)	2736 (21.59%)	
Age (Index date)			0.9986
00–30	76 (2.40%)	315 (2.49%)	
31–40	314 (9.91%)	1244 (9.82%)	
41–50	656 (20.71%)	2580 (20.36%)	
51–60	1087 (34.31%)	4387 (34.62%)	
61–70	655 (20.68%)	2613 (20.62%)	
71–80	341 (10.76%)	1368 (10.80%)	
>80	39 (1.23%)	165 (1.30%)	
Mean (SD)	55.33 (12.23)	55.34 (12.22)	0.9640
Median (IQR)	56 (16)	56 (16)	0.9704
Comorbidities			
Diabetes mellitus	3.11 (9.82%)	1291 (10.19%)	0.5357
Hyperlipidaemia	360 (11.36%)	1553 (12.26%)	0.1683
Hypertension	790 (24.94%)	3022 (23.85%)	0.1997
Heart failure	31 (0.98%)	199 (1.57%)	0.0127
Cardiovascular disease	442 (13.95%)	1965 (15.51%)	0.0292
Stroke	71 (2.24%)	361 (2.85%)	0.0604
Psychosis	66 (2.08%)	327 (2.58%)	0.1076
Traumatic brain injury	10 (0.32%)	60 (0.47%)	0.2310
Follow-up duration			
Mean (SD)	3.41 (2.26)	3.37 (2.27)	0.2961
Median (IQR)	3.04 (3.44)	2.98 (3.45)	0.2368
Medication			
Methotrexate			<0.0001
No use	380 (11.99%)	2701 (21.31%)	
Use	2788 (88.01%)	9971 (78.69%)	
Average weekly dose (mg)			<0.0001
0	380 (11.99%)	2701 (21.31%)	
0.01–7.5	658 (20.77%)	5536 (43.69%)	
>7.5	2130 (67.23%)	4435 (35.00%)	
Steroid			<0.0001
No use	132 (4.17%)	1210 (9.55%)	
Use	3036 (95.83%)	11462 (90.45%)	
NSAIDs			0.0927
No use	10 (0.32%)	70 (0.55%)	
Use	3158 (99.68%)	12602 (99.45%)	
Aspirin			0.7799
No use	2548 (80.43%)	10164 (80.21%)	
Use	620 (19.57%)	2508 (19.79%)	
Statin			0.3254
No use	2571 (81.16%)	10186 (80.38%)	
Use	597 (18.84%)	2486 (19.62%)	
Incident dementia			0.6175
No	3131 (98.83%)	12510 (98.72%)	
Yes	37 (1.17%)	162 (1.28%)	

NSAIDs: non-steroidal anti-inflammatory drugs: TNF: tumour necrosis factor.

TNF-α blockers (cumulative dose during follow-up) was evaluated based on adding the daily prescribed dose, and the results were grouped into different cumulative defined daily doses (cDDDs), to assess dose-response effects using hazard ratios (HRs) for determining the effects on the risk of dementia. cDDDs were estimated during the study period based on the sum of the daily prescribed dose. Patients were classified into four subgroups stratified by cDDDs, including non-users, low (1-483), medium (484-1036), and high (>1036) DDDs. We combined the DDDs of different TNF-α blockers within each patient for analysis.

Endpoint and comorbidities

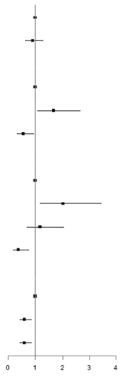
The primary endpoint was the diagnosis of dementia by a neurologist during at least two outpatient department visits or during at least one hospitalisation. The ICD-9-CM codes for dementia included AD (code 331.0), arteriosclerotic dementia (code 290.4), and unspecified dementia (codes 290.0-290.3, 294.1, 331.1-331.2, and 331.82). Patients were followed up until death, withdrawal from the NHI programme, or end of the study period. Comorbidities were defined as having at least two diagnoses of a certain disease within 180 days before and after being enrolled in our study based on corresponding ICD-9-CM diagnosis codes for major comorbidities. These comorbidities included diabetes (code 250), hyperlipidaemia (code 272), hypertension (codes 401-405), heart failure (codes 428, I50.2, and I50.3), cardiovascular disease (codes 393-398, 410-414, 420-429, 440-449, and 451-459), stroke (codes 430-438), major psychosis or a substance-related disorder (codes 291-299 and 303-305), and traumatic brain injury (codes 801-804 and 850-854). They were considered as covariates.

Statistical analysis

Baseline characteristics were compared between the case and control groups using tests described below. The chi-square test was used to compare categorical data and the paired *t*-test was used to compare continuous data. We used the incidence rate (IR) of dementia, its incidence rate ratio (IRR), and 95% confidence intervals (CIs) to estimate the risk of dementia. The Kaplan-Meier curves depicted the cumulative incidence of dementia in specific groups, and we compared the event-free curves between groups using the log-rank test. Multivariate Cox proportional hazard models were used to evaluate HRs and 95% CIs for dementia risk associated with the variables of interest. A p-value of <0.05 was considered statistically significant. All results were calculated by SAS v. 9.4.

Table II. Incidence rate of dementia in patients with rheumatoid arthritis with or without TNF-α blocker use.

	Event	Person Years	Incidence rate	IRR	95% CI
TNF-α blocker					
No use	162	42663.80	379.71	Ref.	
Use	37	10814.91	342.12	0.90	(0.63–1.29)
Type of user					
No use	162	42663.80	379.71	Ref.	
Short-term	21	3276.88	640.85	1.69*	(1.07–2.66)
Long-term	16	7538.03	212.26	0.56*	(0.33–0.93)
Cumulative DDD					
No use	162	42663.80	379.71	Ref.	
Low	15	1951.06	768.81	2.02**	(1.19–3.44)
Medium	14	3123.24	448.25	1.18	(0.68–2.04)
High	8	5740.62	139.36	0.37**	(0.18–0.75)
Weekly dose of MTX (mg)					
0	59	10779.96	547.31	Ref.	
0.01–7.50	73	22211.83	328.65	0.60**	(0.43–0.85)
>7.50	67	20486.92	327.04	0.60**	(0.42–0.85)



TNF: tumour necrosis factor; DDD: defined daily dose; MTX: methotrexate; CI: confidence interval. * 0.01 ≤ *p*-value <0.05, ** 0.0001 ≤ *p*-value <0.01, *** *p*-value <0.0001

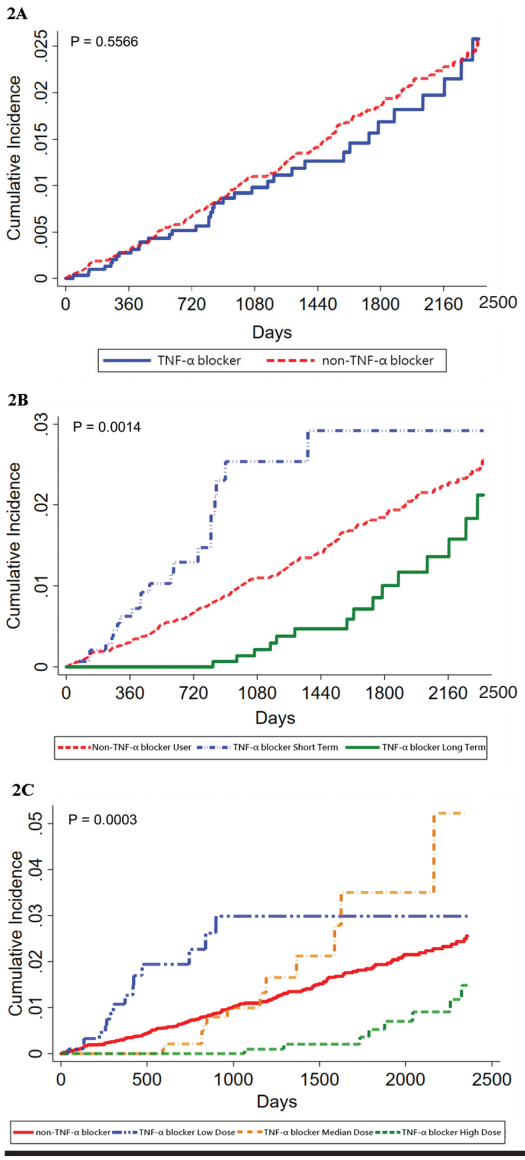


Fig. 2. Kaplan-Meier plots of the cumulative incidence of dementia among patients with rheumatoid arthritis (**A**) receiving and non-receiving TNF-α blocker; (**B**) with different durations of TNF-α blocker use; (**C**) with different cumulative doses of TNF-α blocker use.
TNF: tumour necrosis factor.

Results

Baseline characteristics of the study population

Initially, 27.149 patients with confirmed RA were identified from January 1, 2006, to December 31, 2015. A total of 24,676 patients with RA were finally included after excluding those according to the exclusion criteria (Fig. 1). In the TNF-α blocker users and non-users, 67.0% of patients were older than 50 years while 78.4% were women (Table I). Both groups had a similar mean age of 55 years. The mean duration of RA before TNF-α blocker treatment was 3.41±2.26 years. Significantly fewer patients with heart failure and cardiovascular disease were found in the TNF-α blocker users than non-users (the former *vs*. the latter, 0.98% *vs*. 1.57% and 13.95% *vs*. 15.51%, respectively). Significantly more patients with MTX and steroid use were found in the TNF-α blocker users than non-users (88.01% *vs*. 78.69% and 95.83% *vs*. 90.45%, respectively). There was no significant difference regarding the incidence of dementia between the TNF-α blocker users and non-users (1.17% *vs*. 1.28%; 37 of 3.168 *vs*. 162 of 12.672, respectively).

Incidence rate, ratio, and adjusted HR (aHR) of dementia in TNF blocker user and non-user group

Table II presents the IR and IRR of dementia in the TNF-α blocker users and non-users. The IR of dementia in the TNF-α blocker users and non-users was 342.12 and 379.71 per 100.000 person years, respectively. Patients with short-term use in the user group (IRR=1.69, 95% CI=1.07–2.66) had a higher IRR of dementia than that in the non-user group (the reference). In contrast, patients with long-term use in the user group (IRR=0.56; 95% CI=0.33-0.93) had a lower IRR of dementia than that in the non-user group (the reference). Furthermore, patients using a low cumulative dose (1-483 cDDD) (IRR=2.02, 95% CI=1.19–3.44) had a higher IRR of dementia than that in the non-user group (the reference). In contrast, patients using a high cumulative dose (>1036 cDDD) (IRR=0.37, 95%

Table III. The hazard rate of dementia in patients with rheumatoid arthritis with or without TNF-α blocker use.

	Model 1		Model 2		Model 3	
	aHR	95% CI	aHR	95% CI	aHR	95% CI
TNF-α blocker						
No use (ref.)	1.000					
Use	0.903	(0.619-1.318)				
Use type						
No use (ref.)			1.000			
Short-term			1.529	(0.953-2.453)		
Long-term			0.578*	(0.342-0.977)		
Cumulative DDD						
No use (ref.)					1.000	
Low					1.716	(0.995–2.960)
Medium					1.164	(0.658–2.061)
High					0.387**	(0.188–0.793)
MTX, weekly dose (mg)						
0 (ref.)	1.000		1.000		1.000	
0.01–7.50	0.849	(0.619–1.318)	0.844	(0.603–1.182)	0.836	(0.596–1.173)
>7.50	0.947	(0.606–1.189)	0.966	(0.669–1.396)	0.970	(0.672–1.401)
Gender						
Female (ref.)	1.000		1.000		1.000	
Male	0.868	(0.633–1.191)	0.867	(0.633–1.187)	0.869	(0.634–1.190)
Index age						
Age	1.139***	(1.123–1.154)	1.138***	(1.122–1.154)	1.138***	(1.122–1.153)
Comorbidities						
Diabetes mellitus	1.380	(0.962–1.978)	1.369	(0.954–1.964)	1.393	(0.969–2.002)
Hyperlipidaemia	1.057	(0.702–1.590)	1.050	(0.697–1.583)	1.055	(0.701–1.588)
Hypertension	1.185	(0.853–1.646)	1.191	(0.857–1.654)	1.172	(0.843–1.630)
Heart failure	1.364	(0.671–2.774)	1.390	(0.690–2.801)	1.325	(0.646–2.719)
Cardiovascular disease	1.022	(0.729–1.433)	1.023	(0.729–1.435)	1.029	(0.734–1.442)
Stroke	1.674*	(1.058–2.650)	1.681*	(1.061–2.664)	1.696*	(1.068–2.694)
Psychosis	0.904	(0.357–2.287)	0.871	(0.345–2.202)	0.876	(0.345–2.221)
Traumatic brain injury	4.273*	(1.302–14.02)	4.583*	(1.436–14.62)	4.060*	(1.175–14.03)
Steroid						
No (ref.)	1.000		1.000		1.000	
Yes	0.714	(0.409–1.246)	0.716	(0.409–1.252)	0.714	(0.409–1.246)
Aspirin						
No (ref.)	1.000		1.000		1.000	
Yes	1.472*	(1.079–2.007)	1.475*	(1.080–2.014)	1.478*	(1.081–2.020)
Statin						
No (ref.)	1.000		1.000		1.000	
Yes	0.779	(0.548–1.107)	0.792	(0.557–1.127)	0.782	(0.550–1.113)

aHR: adjusted hazard rate; TNF: tumour necrosis factor; ref.: reference; DDD: defined daily dose; MTX: * 0.01 ≤ *p*-value <0.05, ** 0.0001 ≤ *p*-value <0.01, *** *p*-value <0.0001

CI=0.18–0.75) had a lower IRR of dementia than that in the non-user group (the reference).

Table III provides the aHR for dementia in the TNF-α user and non-user groups stratified by sex, age, medication, and comorbidities. A lower aHR of dementia was observed in patients with the long-term use or a high cumulative dose of TNF-α blockers (Model 2, aHR=0.578, 95% CI=0.342–0.977; Model 3, aHR=0.387, 95% CI=0.188–0.793) than that in non-user group (the reference). After adjustment for sex, age, and comorbidities, patients with RA, stroke and traumatic brain injury had a higher risk of dementia (aHR=1.696, 95% CI=1.068–2.694, and aHR=4.060, 95% CI=1.175–14.03, respectively) than those without any comorbidity (the reference).

Kaplan-Meier analysis of dementia in TNF blocker user and non-user groups

Kaplan-Meier analysis showed that there was no significant difference between the cumulative incidence of dementia for patients with RA with or without TNF-α blocker use (Fig. 2A). Patients with long-term use of TNF-α blockers had a significantly lower risk of dementia than those who were non-users or users with short-term use of TNF-α blocker (Fig. 2B, p=0.0014). In addition, patients with a high cumulative dose of TNF-α blockers had a significantly lower risk of dementia than non-users or users with low to medium cumulative dose use of TNF-α blocker (Fig. 2C, p=0.0003).

Discussion

In this population-based cohort study, we initially did not find a significant difference in the risk of dementia between RA patients who were or were not TNF-α blocker users, which may be attributed to several factors.

First, higher frequencies of MTX and steroid use in the TNF-α blocker users suggest their potentially higher RA disease activity and inflammation levels compared to nin-users. Additionally, fewer incidences of heart failure and cardiovascular disease in the TNF-α blocker users could influence their dementia risk, since cardiovascular morbidities are known to elevate dementia risk in patients with RA (33).

Secondly, our study highlighted the potential impact of duration and cumulative dosage of TNF-α blocker use on dementia risk. Adjustment for comorbidities and considering TNF-α blocker exposure durations and cumulative dosages further yielded notable findings. Specifically, long-term TNF-α blocker use (>180 days) was associated with a nearly halved risk of dementia (aHR=0.578). Moreover, a high cumulative dose (>1036 DDDs) of TNF-α blockers was associated with a substantially lower dementia risk (aHR=0.387).

These findings support a potential protective role of TNF-α blockers against dementia development in patients with RA following prolonged use.

Comparative studies within Taiwan's NHIRD have shown contrasting risks of dementia between patients with RA using csDMARDs and bDMARDs. A

case-control study reported a higher dementia risk with csDMARDs but not with bDMARD use (22). Furthermore, patients with RA overall were found less likely to develop dementia compared to non-RA individuals, with a protective association observed particularly among csDMARD users (34). These findings support the notion that DMARDs, including TNF-α blockers, may confer benefits regarding dementia risk reductions in patients with RA (35). Further prospective interventional trials are needed to validate this phenomenon.

Consistent with the established dementia risk factors, our study identified associations between stroke, traumatic brain injury, and an increased dementia risk in patients with RA. Vascular dementia, often resulting from cerebrovascular events, and traumatic brain injury, which disrupts normal brain function and predisposes affected individuals to neurodegenerative diseases, uncover additional risk features in this population (36).

The economic implications of bDMARD use, including TNF-α blockers, warrant consideration despite their higher cost relative to csDMARDs. Studies like that of Joensuu *et al*. (37) suggest comparable effectiveness between csDMARDs and bDMARDs, but have not extensively explored their impact on RA-related comorbidities such as cardiovascular disease and dementia. Given the systemic inflammatory nature of RA, bDMARDs hold promise in mitigating these risks (38, 39). A prior study using national data from the USA addressed similar issues; Sattui *et al*. assembled a large group of older adults (median age, 67 years) and examined their risk of incident dementia according to csDMARD or bDMARD use, over a shorter period (mean, 1.1 years) than ours (40). They showed that bDMARD users had significantly lower dementia risk than csDMARD users, without differences between types of bDMARDs. However, unlike their their findings, we showed that TNF-α blockers only exhibited a protective effect for high-dose and long-term users, which extends the existing knowledge on this issue.

Although the mechanistic link between RA and dementia, both involving TNF-α production, remains largely unexplored, chronic inflammation in RA may promote reactive amyloidosis. This process results from the deposition of amyloid A fibrils in tissues and linked to TNF-α, interleukin-1 (IL-1), and IL-6-potentially influencing dementia pathogenesis (41, 42). Amyloid A is derived from the circulating precursor serum amyloid A (SAA), an acute-phase reactant participating in chemotaxis, cellular adhesion, cytokine production, and metalloproteinase secretion. SAA is involved in various inflammatory disorders including atherosclerotic plaques, rheumatoid synovitis and also in brain tissues affected by AD (41-43). SAA is an independent risk factor in patients with vascular dementia (44). Therefore, control of inflammation and SAA normalisation may assist in ameliorating amyloidosis in RA (41) and potentially dementia as well.

Strengths of our study include the robustness of Taiwan NHIRD, providing a large representative sample of patients with RA out of nearly 22 million citizens of Taiwan (5). Importantly, the characteristics of patients with RA identified using similar approaches to ours are consistent with those reported by others, with a strong female predominance and middle-aged individuals (4, 5, 45, 46). However, limitations include the absence of detailed laboratory data, which precluded analysis of RA disease activity or elevated inflammatory markers impact on dementia. Unmeasured confounders such as lifestyle factors (*e.g*. body mass index, smoking, alcohol consumption) and medication adherence might also have influenced our findings.

In conclusion, our findings suggest that long-term use and high cumulative doses of TNF-α blockers may reduce dementia risk in patients with RA. Further research is warranted to elucidate the role of TNF-α in the pathogenesis of dementia and explore potential therapeutic avenues.

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