The influence of disease-modifying anti-rheumatic drugs and corticosteroids on the association between rheumatoid arthritis and skin cancer: a nationwide retrospective case-control study in Taiwan

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Abstract

Objective

To investigate the influence of corticosteroids and disease-modifying anti-rheumatic drugs (DMARDs, including conventional synthetic and biologic DMARDs) treatment on the association between rheumatoid arthritis (RA) and non-melanoma skin cancer (NMSC).

Methods

This nationwide retrospective case-control study retrieved data from Taiwan National Health Insurance Research Database during 1995–2013. Cases with newly-diagnosed NMSC (n=19,603) were matched with control without NMSC in a 1:1 ratio according to age, sex, and reference date. The aforementioned association was analysed using conditional logistic regression and adjustments for age, sex, residential regions, occupations, and co-morbidities. Causality cannot be inferred by case-control study.

Results

Compared to patients without RA, the patients with RA had a significantly higher association with NMSC (adjusted odds ratio (AOR)=2.23, 95% confidence interval (CI) 1.6-3.1, p<0.001), especially those using cyclosporine (AOR=5.7, 95%CI 2.2-14.86; ≥65 years: AOR=7.28, 95%CI 2.16-24.56), etanercept (AOR=5.27, 95%CI 1.15-24.27; ≥65 years: AOR=8.95, 95%CI 1.12-71.85), and d-penicillamine (AOR=4.79, 95%CI 1.63-14.12; ≥65 years: AOR=3.81, 95%CI 1.26-11.52); those using higher cumulative doses of corticosteroids and methotrexate (corticosteroids: >10g: AOR=2.96, 95%CI 1.67-5.22; >10g and ≥65years: AOR=3.5, 95%CI 1.77-6.92; methotrexate: 1-3g: AOR=2.57, 95%CI 1.13-5.82; >3g: AOR=4.64, 95%CI 1.74-12.4; >3g and ≥65 years: AOR=10.17, 95%CI 2.34-44.26); and those using more kinds of DMARDs (any 3: AOR=3.72, 95%CI 1.67-8.26; any 5: AOR=2.81, 95%CI 1.13-7.04; any 6: AOR=5.23, 95%CI 1.14-24.14; 7-8: AOR=4.06, 95%CI 1.14-14.49).

Conclusion

The patients with RA had significantly increased associations with NMSC, especially those receiving cyclosporine, etanercept, and d-penicillamine; higher cumulative doses of corticosteroids and methotrexate; or more kinds of DMARDs in combination or in sequence. The aforementioned associations were much stronger in the elderly.

Key words

rheumatoid arthritis, non-melanoma skin cancer, disease-modifying anti-rheumatic drugs, retrospective case-control study, Taiwan National Health Insurance Research Database

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Introduction

Rheumatoid arthritis (RA) is the most common chronic autoimmune inflammatory arthritis in adults. It is characterised by inflammatory destruction of the joints and is associated with multiple co-morbidities. The patients with RA have significant functional impairment on the daily activities, lower health-related quality of life, and higher mortality (1, 2). According to the American College of Rheumatology (ACR) guidelines in 2015 (3), the management for RA includes corticosteroids and the disease-modifying anti-rheumatic drugs (DMARDs: conventional synthetic DMARDs (csDMARDs) and biologic DMARDs (bDMARDs).

Several clinical studies have reported that the patients with RA had increasing incidences of malignancies, particularly lymphoma (4-10). The reported risk of site-specific malignancies in patients with RA varies by region. The patients with RA using tumour necrosis factor (TNF) inhibitors and prednisone therapy have been reported to be associated with skin cancer (11).

In Taiwan, non-melanoma skin cancer (NMSC) has been reported to be among the 10 leading types of cancer (12). Several epidemiological studies of RA were reported (8, 13). A cohort study, using Taiwan National Health Insurance Research Database (NHIRD), presented the incidence rate and risk of overall and site-specific malignancies after the diagnosis and DMARDs treatment of RA, and showed that the skin cancer risk was not significantly higher in patients with RA using TNF inhibitor compared with those using csDMARDs therapy (14). The investigation on the association between RA and skin cancer is limited by several factors, such as small numbers of case, relatively lower incidence of malignancies in young patients with RA, and the influence of RA treatment regimen on skin cancer.

The aim of this case-control study, using NHIRD in Taiwan, was to investigate the association between RA and NMSC, and evaluate the influence of treatment of RA (corticosteroids, csDMARDs, and bDMARDs) on NMSC.

Patients and methods

Data sources

The NHIRD in Taiwan was the primary data source for this study. The National Health Insurance (NHI) program has provided compulsory, single-payer and universal health insurance for Taiwan residents since 1995, and covers approximately 98% of the total population. All insurance claims data in the NHIRD include birth dates, sex, residential regions, occupation, diagnostic codes, surgery or procedures performed, medications prescribed, hospitalisation, and expenditure. The diagnosis codes were according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

The Longitudinal Health Insurance Database (LHID) 2010 contains the original claims data of 1,000,000 beneficiaries who were enrolled and randomly sampled from all beneficiaries of the NHIRD in the year 2010, and were also followed from 1995 to 2013. The Taiwan catastrophic illness certificates database (TCICD) contains data of all patients with a catastrophic illness certificate (CIC), whose original claims data were extracted from the NHIRD from 1995 to 2013. Each CIC were reviewed by two specialists on the basis of clinical presentation, laboratory data, pathological reports, and imaging studies. Patients with RA or cancer are eligible for obtaining a CIC, and those with RA must fulfill the diagnostic criteria of the American College of Rheumatology classification. TCICD covers approximately 99% of all eligible patients because copayment is waived for patients with a CIC. To protect privacy, patient identification numbers were encrypted in NHIRD; therefore, informed consent was waived for this study. The Institutional Review Board of Kaohsiung Veterans General Hospital approved this study (VGHKS15-EM10-02), and followed the principles of the Declaration of Helsinki.

Study design

This retrospective nationwide population-based case-control study included two study groups: a case group with NMSC and a control group without

NMSC. The case group included the patients with newly-diagnosed NMSC (n=19,603) between January 1, 2000, and December 31, 2013 as identified from the TCICD. NMSC (ICD-9-CM code 173) includes basal cell carcinoma, squamous cell carcinoma, and malignant neoplasm of sebaceous and sweat glands, but no specified skin cancer type. The reference date for each patient in the case group was the date of their first diagnosis of NMSC in the TCICD. The control group was matched to the case group in a 1:1 ratio considering age, sex, and the reference date by propensity score (15) and was selected from the LHID2010 in the period of 1995–2013 after excluding patients with malignancies (ICD-9-CM codes 140-208, including skin cancer). The patients with NMSC as outcome were collected first for recruiting sufficient number, and then the patients with RA (ICD-9-CM code 714.0, 714.30~714.33, excluding juvenile rheumatoid arthritis) and co-morbidities were identified before the reference date of the case and control group retrospectively in the TCICD from 1995–2013.

The patients with other co-morbidities, namely coronary artery disease (CAD; ICD-9-CM code 410-414, A270, and A279), diabetes mellitus (DM; 250), hypertension (HT; 401-405), chronic kidney disease (CKD; 585), chronic obstructive pulmonary disease (COPD; 490-496, a surrogate for smoking), obesity (278, 278.00, 278.01, and V778), and any organ transplant (OT, V42.0-V42.9) were identified before the reference date of the case and control group from 1995–2013. The diagnoses were based on at least two outpatient visits and an admission event. Figure 1 shows the patient selection flowchart.

The exclusion criteria were an age of <18 years (case: n=162; control: n=248,696), incomplete NHIRD information (case: n=3, control: n=4), and diagnosis of any cancer, including skin cancer, before the reference date of the control group (n=54,645). Patients with skin cancer identified before the first diagnosis of RA and co-morbidities were excluded.

Residential regions were classified into three categories: (1) urban, (2) suburban, and (3) rural area. Occupations were classified into three categories as (1) government or company employee, teachers, workers spending most of their time indoors, (2) soldier, farmer, fisherman, labourers (working in forestry, animal husbandry, and construction), and workers with outdoor jobs with chronic sun exposure, (3) very low income households.

The Anatomical Therapeutic Chemical (ATC) code and defined daily dose (DDD) of the medication was defined from the web site of the Collaborating Centre for Drug Statistics Methodology of World Health Organization. Medication included corticosteroids (methylprednisolone (ATC code H02AB04, DDD 20mg) and prednisolone (H02AB06, DDD 10 mg)), and DMARDs. The csDMARDS included hydroxychloroquine (ATC code P01BA02, DDD 516 mg), sulfasalazine (A07EC01, DDD 2g), d-penicillamine (M01CC01, DDD 500 mg), cyclosporine (L04AD01 DDD 250mg), leflunomide (L04AA13, DDD 20mg), azathioprine (L04AX01, DDD 150 mg), cyclophosphamide (L01AA01), methotrexate (L01BA01). Biologics DMARDs includes TNF-α inhibitors

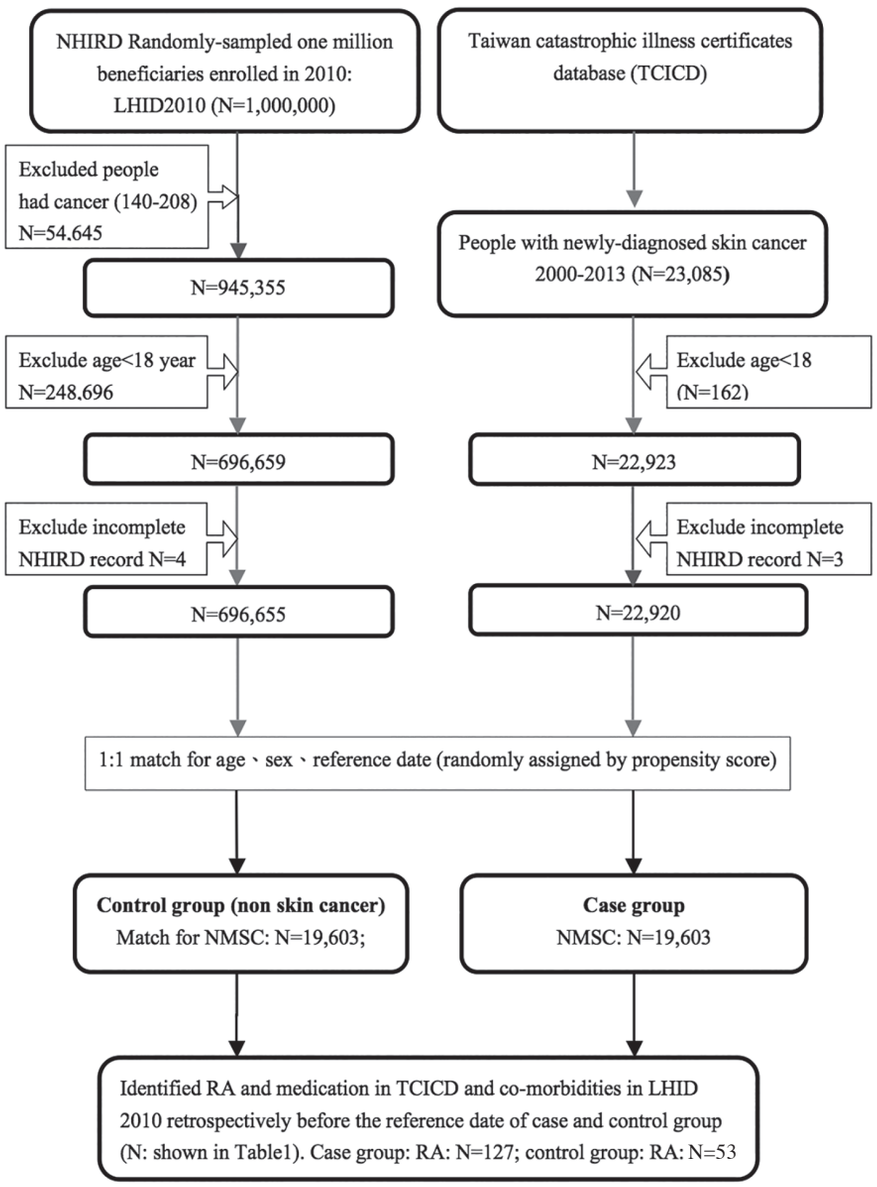

Fig. 1. Study design and flowchart of patient selection of this case-control study.
NHIRD: National Health Insurance Research Database; NMSC: non-melanoma skin cancer; RA: rheumatoid arthritis; LHID: Longitudinal Health Insurance Database; Taiwan catastrophic illness certificates database (TCICD); N: number.

(etanercept (L04AB01, DDD 7mg), adalimumab (L04AB04, DDD 2.9mg), and golimumab (L04AB06, DDD 1.66mg)), abatacept (L04AA24, DDD 27mg), tofacitinib (L04AA29, DDD 10mg), tocilizumab (L04AC07, DDD 20mg), and rituximab (L01XC02). Information on medications was retrieved from the pharmacy prescription database. Reliability of the retrieved information was independently verified by two statisticians.

Under the NHI regulation, hydroxychloroquine, azathioprine, d-penicillamine, methotrexate, cyclosporine, and cyclophophamide had been used since 1995. Etanercept, adalimumab, and leflunomide were approved since 2003 and 2004, respectively. Rituximab had been used since 2008 as a second line therapy when the patients had inadequate treatment response or were contraindicated to TNF inhibitor therapy (patient number in case/control groups: rituximab: 1/1). Golimumab, tocilizumab, and abatacept were not covered until 2012. Tofacitinib was approved in 2013. Therefore, none of the patients included in this study were treated with golimumab, tofacitinib, tocilizumab or abatacept. Under the NHI regulation, RA patients can apply for reimbursement for cyclosporine or bDMARDs if they have continuous and active disease and if they failed to respond to treatment with more than two csDMARDs for at least 3 or 6 months. TNF inhibitors are used as combination therapy with methotrexate. Patients with prior histories of pre-malignant or malignant diseases in the past 10 years or those with active infections are not eligible for biologics (14).

Statistical Analysis

Conditional logistic regression analysis was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between RA (exposure) and NMSC (outcome) and the influence of the use of corticosteroids or DMARDs (exposure), with adjustment for age, sex, residential regions, occupations, and co-morbidities; and stratification analysis in age subgroup.

NHIRD data were extracted using SAS v. 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical analyses were performed using IBM SPSS v. 20 (IBM Institute Inc, NY, USA). A 2-tailed *p*-value of <0.05 was considered to be statistically significant.

Results

The patients with NMSC (n=19,603) had a mean age (±standard deviation, range) of 68.11 (±15.87, 18–103) years with a male to female ratio 1.23. In the case and control groups, 127 and 53 patients had RA, with female to male ratios of 1.9 and 3.8; and median follow-up periods of 7.8 and 7.1 from the diagnosis date of RA to the reference date, respectively. The mean age in the case and control groups was 64.5 and 65.5 after excluding data from the first year that NHIRD was launched (1995).

The associations between RA, residential regions, occupations, co-morbidities and NMSC using conditional logistic regression analysis were shown in Table I. The patients with RA had a statistically significantly higher association with NMSC (adjusted odds ratio (AOR)=2.24, 95% CI 1.62–3.11, $p<0.001$). The patients with each co-morbidity, including DM, HT, CAD, CKD, COPD, and organ transplant, also had significantly higher associations with NMSC.

Regarding residential regions, those living in suburban or rural areas had a significantly higher association with NMSC than those in urban areas (suburban: AOR=1.23, 95%CI 1.16–1.3, $p<0.001$; rural: AOR=1.49, 95%CI 1.4–1.58, $p<0.001$). Regarding occupations, the patients with outdoor occupations (category 2) had a significantly higher association with NMSC than those in category 1 (AOR=1.22, 95%CI 1.16–1.29, $p<0.001$); whereas those with a very low income had a significantly lower association with NMSC (AOR=0.79, 95%CI 0.75–0.84, $p<0.001$).

The case group had much higher maximum and median cumulative doses of each DMARD and corticosteroids than the control group (Table II).

None of the patients with RA in the control group used azathioprine and cyclophosphamide (numbers in case/control groups: azathioprine: 12/0; cyclophosphamide: 8/0). So the ORs for azathioprine and cyclophosphamide between the two groups cannot be calculated. However, this was an important clinical finding.

The influence of corticosteroids and DMARDs received on the associations between the patients with RA and NMSC using conditional logistic regression analysis were shown in Table III. First, the patients with RA who had ever used a DMARD were compared with those without RA. Second, the patients with RA who had ever used TNF inhibitors were compared with those who had ever used csDMARDs.

Compared to patients without RA, the patients with RA receiving DMARDs or corticosteroids had a significantly higher association with NMSC, especially with cyclosporine (AOR=5.7, 95%CI 2.2–14.86, $p<0.001$), etanercept (AOR=5.27, 95%CI 1.15–24.27, $p=0.03$), d-penicillamine (AOR=4.78, 95%CI 1.62–14.1, $p=0.005$), hydroxychloroquine (AOR=2.29, 95%CI 1.58–3.32, $p<.001$), sulfasalazine (AOR=2.26, 95%CI 1.54–3.33, $p<0.001$) and corticosteroids (AOR= 2.32, 95%CI 1.64–3.3, $p<0.001$); and this especially pronounced in patients aged ≥65 years (cyclosporine AOR=7.28, 95%CI 2.16–24.56, $p=0.001$; etanercept AOR=8.95, 95%CI 1.12–71.85, $p=0.04$; d-penicillamine AOR=3.81, 95%CI: 1.26-11.52, $p=0.02$, hydroxychloroquine AOR=2.49, 95%CI 1.63–3.8, $p<0.001$; sulfasalazine AOR=2.43, 95%CI 1.54–3.81, $p<0.001$; and corticosteroids AOR= 2.43, 95%CI 1.61–3.65, $p<0.001$).

The patients with RA using TNF inhibitors (etanercept or adalimumab) had significantly higher association with NMSC than those without RA in the patients aged ≥65 years (AOR=5.45, 95%CI 1.18–25.11, $p=0.03$). The patients with RA using csDMARDs had significantly higher association with NMSC than those without RA (AOR=2.12, 95%CI 1.5–3.01, $p<0.001$). The patients with RA using TNF inhibitors had no significantly higher association with NMSC than those using csDMARDs (etanercept and adalimumab: AOR=1.15, $p=0.8$; etanercept: AOR=2.6, $p=0.23$). Leflunomide and adalimumab were not significant associated with NMSC, respectively.

Table I. The crude and adjusted odds ratio of rheumatoid arthritis or co-morbidities associated with non-melanoma skin cancer (n=19603) by conditional logistic regression analyses.

	Case n (%)	Control n (%)	COR (95% CI)	*p*-value	AOR[a] (95% CI)	*p*-value
Age >65	12651 (64.5)	12565 (64.1)	1.24 (1.08-1.42)	**0.002**	1.08 (.94-1.25)	0.29
Sex (men)	10803 (55.1)	10821 (55.2)	0.99 (0.95-1.05)	0.82	1.08 (1.03-1.14)	**0.004**
RA	127 (0.64)	53 (0.27)	2.4 (1.74-3.3)	**<0.001**	2.23 (1.6-3.1)	**<0.001**
Residential regions						
1	3832 (19.5)	5131 (26.2)	reference	-	-	-
2	7721 (39.4)	8132 (41.5)	1.28 (1.21-1.35)	**<0.001**	1.23 (1.16-1.3)	**<0.001**
3	8050 (41.1)	6340 (32.3)	1.73 (1.63-1.82)	**<0.001**	1.49 (1.4-1.58)	**<0.001**
Occupation						
1	5688 (29)	6344 (32.4)	reference	-	-	-
2	10011 (51.1)	8046 (41)	1.39 (1.33-1.46)	**<0.001**	1.22 (1.16-1.29)	**<0.001**
3	3904 (19.9)	5213 (26.6)	0.84 (0.79-0.89)	**<0.001**	0.79 (0.75-0.84)	**<0.001**
Co-morbidities						
DM	11222 (57.2)	10119 (51.6)	1.34 (1.28-1.4)	**<0.001**	1.23 (1.17-1.29)	**<0.001**
HT	5353 (27.3)	4349 (22.2)	1.34 (1.28-1.4)	**<0.001**	1.17 (1.11-1.23)	**<0.001**
CAD	7222 (36.8)	6287 (32.1)	1.27 (1.22-1.33)	**<0.001**	1.12 (1.06-1.18)	**<0.001**
COPD	7602 (38.8)	6580 (33.6)	1.28 (1.23-1.34)	**<0.001**	1.18 (1.12-1.23)	**<0.001**
CKD	1400 (7.1)	762 (3.9)	1.91 (1.75-2.1)	**<0.001**	1.67 (1.51-1.83)	**<0.001**
OT	70 (0.36)	24 (0.12)	2.92 (1.84-4.64)	**<0.001**	2.54 (1.57-4.09)	**<0.001**
Obesity	123 (0.6)	127 (0.6)	0.97 (0.76-1.24)	0.80	0.87 (0.67-1.12)	0.27

RA: rheumatoid arthritis; DM: diabetes mellitus; HT: hypertension; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; OT: organ transplant; N: number; Residential region: (1) urban, (2) suburban, and (3) rural area. Occupations: (1) government or company employee, teachers, workers spending majority of their time indoors, (2) soldier, farmer, fisherman, labourers (working in forestry, animal husbandry, construction sites), workers with outdoor jobs under chronic sun exposure; (3) Very low income households. COR: crude odds ratio, AOR: adjusted odds ratio: a: adjusted covariate: residential regions, occupation, DM, CAD, HT, COPD, CKD, OT, obesity, Age 65, and sex. *p*-value <0.05: two-tailed statistical significance.

Some DMARDs and corticosteroids showed higher associations with NMSC, and higher cumulative doses of these medication resulted in much higher significantly association with NMSC than lower cumulative doses after adjustment, especially for the patients aged ≥65years. (corticosteroids: ≤10g: AOR=1.97, 95%CI 1.26–3.1, *p*=0.003, >10g: AOR=2.96, 95%CI 1.67–5.22, *p*<0.001, >10g and ≥65years: AOR=3.5, 95%CI 1.77–6.92, *p*<0.001; methotrexate: ≤1g: AOR=1.27, 95% CI 0.73–2.19 *p*=0.4, 1–3g, AOR=2.57, 95%CI 1.13–5.82, *p*=0.02, >3g: AOR=4.64, 95%CI 1.74–12.4, *p*=0.002, >3g and ≥65 years: AOR=10.17, 95%CI 2.34–44.26, *p*=0.002; hydroxychloroquine: 1–500TDDD: AOR=1.68, 95%CI 0.99–2.87, *p*=0.06, >500TDDD: AOR=2.99, 95%CI 1.78-5.06, *p*<0.001, >500TDDD and ≥65 years: AOR=3.25, 95%CI 1.78–5.96, *p*<0.001). Other DMARDs could not be analysed for such trend due to the limited number of patients for evaluating their effect.

During the follow-up periods, more than 50 kinds of DMARDs in combinations or in sequence were used, and thus it was difficult to categorise the specific combinations of DMARDs to evaluate their effects. The patients with higher diseases severity usually need more kinds of DMARDs in combination or in sequence with higher cumulative doses. The association between the cumulative number of all DMARDs and corticosteroids used in combination or in sequence during the follow-up period and NMSC were present in Table IV.

Table II. the characteristics of the patients with RA and cumulative doses of treatment.

	Case group	Control group
RA (n%)	127 (0.64)	53 (0.27)
Men/ women (n)	44 / 83	11 / 42
Age ≥65 / <65 (n)	102 / 25	41 / 12
Age at onset[a], mean ± SD (range)	64.5±10.4 (37.4-89.6)	65.5±11.3 (41.3-86.8)
Duration[b], year, mean ± SD (range)	7.8 ±4.6 (0-17.1)	7.1 ±4.2 (0.5-15.3)
Cumulative dose of medication of RA (mg or TDDD)	median, maximum	median, maximum
Corticosteroids (mg)	9184, 489760	6602.4, 99109
Methotrexate (mg)	1431.2, 7212.5	780, 4682.5
Hydroxychloroquine (TDDD)	733.7, 3923.3	469.2, 2930.6
Sulfasalazine (TDDD)	536, 3988	283.4, 3305.5
D-penicillamine (TDDD)	196, 1258.6	388.2, 846
Leflunomide (TDDD)	220, 1875.5	133, 1046.5
Ciclosporine (TDDD)	216, 2498	520, 1121.6
Azathioprine (mg)	60.7, 1243	—,—
Cyclophophamide (mg)	3350, 22200	—,—
Entanercept (TDDD)	257.14 , 1503.6	435.5, 617.4
Adalimumab (TDDD)	241.4, 579.3	137.9, 413.8
Rituximab (mg)	—, 1000	—, 5000

a: age at onset: delete the information of patients in the first year that NHIRD was launched (1995). Number of RA in case /control: 106/47. b: duration: diagnosis date of RA to reference date of NMSC. Corticosteroids: cumulative approximate equivalent dose (mg) of methylprednisolone and prednisolone. n: number; SD: standard deviation; TDDD: total daily defined dose; mg: milligram.

Table III. The adjusted odds ratio of rheumatoid arthritis associated with non-melanoma skin cancer in each DMARDs and in subgroup age ≥65 years by conditional logistic regression analyses.

	Overall				Age ≥65 years			
	case	control	Case / control		case	control	Case / control	
	n (%)	n (%)	AOR (95% CI)	*p*-value	(n %)	(n %)	AOR (95% CI)	*p*-value
Non-RA	Reference group							
Corticosteroids								
Ever use	117 (0.6)	46 (0.2)	2.32 (1.64-3.3)	**<0.001**	96 (0.76)	35 (0.28)	2.43 (1.61-3.65)	**<0.001**
1-10(g)	61 (0.31)	30 (0.15)	1.97 (1.26-3.1)	**0.003**	47 (0.37)	24 (0.19)	1.9 (1.13-3.2)	**0.02**
>10(g)	56 (0.29)	16 (0.08)	2.96 (1.67-5.22)	**<0.001**	49 (0.39)	11 (0.09)	3.5 (1.77-6.92)	**<0.001**
Methotrexate								
Ever use	82 (0.42)	36 (0.18)	2.01 (1.35-3.01)	**0.001**	69 (0.55)	26 (0.21)	2.19 (1.35-3.55)	**0.001**
<1(g)	33 (0.17)	23 (0.12)	1.27 (0.73-2.19)	0.4	25 (0.2)	16 (0.13)	1.07 (0.54-2.13)	0.84
1-3(g)	25 (0.13)	8 (0.04)	2.57 (1.13-5.82)	**0.02**	22 (0.17)	7 (0.056)	2.57 (1.06-6.23)	**0.04**
>3(g)	24 (0.12)	5 (0.03)	4.64 (1.74-12.4)	**0.002**	22 (0.17)	3 (0.02)	10.17 (2.34-44.26)	**0.002**
Hydroxychloroquine								
Ever use	103 (0.53)	42 (0.21)	2.29 (1.58-3.32)	**<0.001**	88 (0.7)	32 (0.26)	2.49 (1.63-3.83)	**<0.001**
1-500(TDDD)	40 (0.2)	23 (0.12)	1.68 (0.99-2.87)	0.06	34 (0.27)	17 (0.14)	1.83 (0.99-3.4)	0.06
>500(TDDD)	63 (0.32)	19 (0.1)	2.99 (1.78-5.06)	**<0.001**	54 (0.43)	15 (0.12)	3.25 (1.78-5.96)	**<0.001**
Sulfasalazine								
Ever use	93 (0.47)	38 (0.19)	2.26 (1.54-3.33)	**<0.001**	79 (0.62)	29 (0.23)	2.43 (1.54-3.81)	**<0.001**
1-500(TDDD)	45 (0.23)	22 (0.11)	2.04 (1.21-3.46)	**0.008**	37 (0.29)	16 (0.13)	2.27 (1.22-4.21)	**0.009**
>500(TDDD)	48 (0.24)	16 (0.08)	2.55 (1.43-4.54)	**0.002**	42 (0.33)	13 (0.1)	2.62 (1.35-5.09)	**0.005**
d-penicillamine	21 (0.11)	4 (0.02)	4.78 (1.62-14.1)	**0.005**	18 (0.14)	4 (0.03)	3.81 (1.26-11.52)	**0.02**
Cyclosporine	31 (0.16)	5 (0.03)	5.7 (2.2-14.86)	**<0.001**	27 (0.21)	3 (0.02)	7.28 (2.16-24.56)	**0.001**
Leflunomide	18 (0.09)	10 (0.05)	1.53 (0.69-3.4)	0.3	15 (0.12)	6 (0.5)	2.24 (0.78-6.49)	0.14
Etanercept	11 (0.06)	2 (0.01)	5.27 (1.15-24.27)	**0.03**	11 (0.09)	1 (0.008)	8.95 (1.12-71.85)	**0.04**
Adalimumab	4 (0.02)	3 (0.015)	0.86 (0.18-4.13)	0.85	4 (0.03)	2 (0.016)	2.49 (0.25-25.23)	0.44
TNF inhibitor	14 (0.07)	5 (0.025)	2.44 (0.86-6.99)	0.1	14 (0.11)	3 (0.02)	5.45 (1.18-25.11)	**0.03**
csDMARD	109 (0.55)	48 (0.24)	2.12 (1.5-3.01)	**<0.001**	86 (0.68)	38 (0.3)	1.98 (1.33-2.95)	**0.001**
TNF inhibitor *vs*. csDMARD			1.15 (0.38-3.49)	0.8			2.76 (0.57-13.37)	0.9
Etanercept *vs*. csDMARD			2.6 (0.54-12.42)	0.23			4.53 (0.54-37.74)	0.16

AOR: adjusted odds ratio; a: adjusted covariate: residential regions, occupation, DM, CAD, HT, COPD, CKD, OT, Age65, and sex.
RA: rheumatoid arthritis; TNF: tumour necrosis factor; csDMARD: conventional synthetic disease-modifying anti-rheumatic drugs; n: number; CI: confidence interval; TDDD: total defined daily dose; g: gram. *p*-value <0.05: two-tailed statistical significance. Corticosteroids cumulative approximate equivalent dose of methylprednisolone and prednisolone.

Table IV. The adjusted odds ratios of cumulative effect of ever-used DMARDs and corticosteroids in combination or in sequence associated with non-melanoma skin cancer during follow-up period.

	Overall (n=19603)				age ≥65 year			
	Case	Control			Case	Control		
Combination*	n (%)	n (%)	AOR 95% CI	*p*-value	n (%)	n (%)	AOR 95% CI	*p*-value
0–1	10 (0.05)	3 (0.02)	2.91 (0.78-10.81)	0.11	6 (0.05)	3 (0.02)	1.86 (0.45-7.6)	0.39
2	17 (0.09)	13 (0.07)	1.29 (0.61-2.72)	0.47	10 (0.08)	11 (0.09)	0.76 (0.31-1.89)	0.55
3	28 (0.14)	8 (0.04)	3.72 (1.67-8.26)	0.001	23 (0.18)	4 (0.03)	5.92 (2.01-17.49)	**0.001**
4	25 (0.13)	18 (0.09)	1.28 (0.68-2.39)	0.45	20 (0.16)	16 (0.13)	1.09 (0.54-2.2)	0.82
5	22 (0.11)	6 (0.03)	2.81 (1.13-7.04)	0.03	21 (0.17)	4 (0.03)	3.99 (1.34-11.89)	**0.01**
6	11 (0.06)	2 (0.01)	5.23 (1.14-24.14)	0.03	10 (0.08)	2 (0.015)	7.83 (0.96-63.78)	0.054
7–8	14 (0.07)	3 (0.015)	4.06 (1.14-14.49)	0.03	12 (0.09)	1 (0.008)	9.15 (1.15-72.99)	**0.04**

Note:* Number of ever-used DMARDs and corticosteroids in combination or in sequence during follow-up period.
AOR: adjusted odds ratio; a: adjusted covariate: residential regions, occupation, DM, CAD, HT, COPD, CKD, OT, Age65, and sex.
Case: patients with non-melanoma skin cancer. n: number; OR: odds ratio; CI: confidence interval. *p*-value <0.05: two-tailed statistical significance.

Using the patients without RA as the reference group, the patient with RA who used any 3, 5, 6 or 7–8 kinds of DMARDs and corticosteroids had significantly higher AORs of NMSC. (any 3: AOR=3.72, 95%CI 1.67–8.26, *p*=0.001; any 5: AOR=2.81, 95%CI 1.13–7.04, *p*=0.03; any 6: AOR=5.23, 95%CI 1.14–24.14, *p*=0.03; 7-8: AOR=4.06, 95%CI 1.14–14.49, *p*=0.03), and this especially pronounced in the patients aged ≥65 years (any 3: AOR=5.92, 95%CI 2.01–17.48, *p*=0.001; any 5: AOR=3.99, 95%CI 1.34–11.89, *p*=0.01; any 6: AOR=7.83, 95%CI 0.96–63.78,

p=0.054; 7-8: AOR=9.15, 95%CI 1.42–72.99, *p*=0.04).

Discussion

In this study, the patients with RA had a significantly higher association with NMSC. Certain DMARDs were significantly higher associated with NMSC, in particular cyclosporine, etanercept, and d-penicillamine. The higher cumulative doses of corticosteroids, methotrexate, and hydroxychloroquine were much higher associated with NMSC than lower cumulative doses significantly. The patients with RA receiving more kinds of DMARDs in combination or in sequence during the follow-up period had much stronger positive associations with NMSC. Furthermore, the aforementioned associations were markedly higher in the elderly with RA (age ≥65 years). The patients with RA using TNF inhibitors had no significantly higher association with NMSC than those using csDMARDs.

The median age of NMSC was around 70 years according to Taiwan cancer registry annual reports (16). RA can occur at any age, particularly between the ages of 50 and 75. Kuo *et al*. reported that the mean age at diagnosis of RA was 53.7±14.0 years during 2002–2007 in Taiwan. The incidence of RA was low in younger patients, and increased gradually to a peak at 60–69 years (13). In this study, the mean age of the patients with RA was 65 years, which is higher than that reported by Kuo *et al*., but in the range of peak incidence (60-69 years). The elderly with RA using DMARDs tended to have a higher risk of skin cancer.

Previous studies have reported inconsistent associations between RA and skin cancer, and most have focused on the effect of TNF inhibitors, rather than csDMARDs (17, 18). Mellemkjaer *et al*. reported an increased risk of NMSC in patients with RA (19). Increased incidence of cutaneous squamous cell carcinoma has been shown in patients with autoimmune inflammatory rheumatic diseases after long-term azathioprine treatment (17). Lange *et al*. reported that the patients with inflammatory arthritis using methotrexate, concurrent methotrexate with cyclosporine or d-penicillamine, were associated with an increased risk of NMSC. Those using leflunomide had no increased risk of NMSC (18). Buchbinder *et al*. reported that methotrexate-treated RA patients have an increased incidence of melanoma compared with the general population (20). Amari *et al*. reported that TNF-α inhibitor therapy in veterans with RA may be associated with an increased risk of NMSC, compared with csDMARDs therapy (21). Raaschou *et al*. reported that a small increased risk of basal cell carcinoma was seen in biologics-naive patients with RA, but not increased in those receiving TNF inhibitors treatment, whereas increased risks of squamous cell carcinoma were found in both groups (22). Mercer *et al*. reported that a higher incidence of skin cancer among patients with RA receiving TNF inhibitors and no evidence that this treatment increased the risk of basal cell carcinoma or squamous cell carcinoma (23). Furthermore, a large European collaborative project did not find an overall increased risk of melanoma following exposure to TNF inhibitors in 2017 (24).

In this study, it was difficult to postulate that the carcinogenic effect was caused by any single DMARD because the patients with RA usually have used several kinds of DMARDs in combinations or in sequence during their disease courses.

Disease severity for RA fluctuated during the patients' lifetime. Many kinds of DMARDs in combinations or in sequence for RA were recorded in the follow-up period. The effect of the cumulative dose of each DMARDs and the cumulative number of DMARDs in combination, instead of the average daily dose, could be used to summarise the patients' disease severity and status of immunocompromisation in follow-up period. Higher average daily dose usually means higher disease activity during the period of this treatment. In fact, the patient may not always use the same drug or same combination due to changing disease activity. Higher cumulative doses might imply higher daily dose or longer duration of treatment. Higher number of DMARDs in combinations or in sequence suggested probably poor treatment response, higher disease activity, and cumulative effect for immunocompromisation. In addition, the cyclosporine and bDMARDs prescribed indicates higher disease severity of RA that has been refractory to at least two DMARDs in combinations according to the NHI Bureau regulation in Taiwan. These situations can be associated with a markedly higher risk of NMSC.

Patients with co-morbidities, including DM, CAD, or COPD, had been reported to have higher risks of skin cancer (25-28). Patients with CKD have status of immunocompromisation because of the accumulation of uremic toxins and oxidative stress (29), and patients on chronic haemodialysis have been reported to have a higher risk of NMSC (30). Hypertension has also been positively associated with total incident cancer, including NMSC and melanoma in men (31).

The strengths of this study include the population-based large sample size of patients with skin cancer, minimal misclassification and diagnosis bias because NMSC and RA were recorded in the TCICD. In addition, the case-control study design is advantageous because it is suitable for rare diseases, for diseases with a long latency period between exposure and outcome disease manifestation, and for studying dynamic populations in whom follow-up is difficult (32, 33).

Several limitations were especially with regards to the NHIRD. Personal histories were unavailable in NHIRD, including actual intensity of sun exposure, amount of smoking and alcohol consumption, body mass index, laboratory data, and actual disease severity. However, the occupations and residential regions probably have been representative the extent of sun exposure in this study and they were adjusted as confounder. The cumulative doses and cumulative numbers of ever-used DMARDs may be considered to represent disease severity. Some patients may have used self-paid biologics but been classified into the never-user group because self-paid medication are not recorded in NHIRD. This misclassification may have led to an under-

estimation of the association between bDMARDs and NMSC. The incidence rates of RA and skin cancer were relatively low and this may have affected statistical power. The small number of ever-users of certain DMARD may be due to the short follow-up period. Finally, the results should be carefully applied to other ethnic group because of differences in the population rates of NMSC due to skin colour, latitude, climate, ozone levels, and culture (34), and the characteristics of the case group was not similar to general population. The disadvantages of a case-control study design are that the incidence cannot be calculated, selection or observation bias may affect exposure information, it is inefficient for rare exposures, and causality cannot be inferred.

In conclusion, the residents of suburban and rural areas, and those with outdoor occupations had higher risks of NMSC. The patients with RA had significantly higher associations with NMSC, especially those using cyclosporine, etanercept, and d-penicillamine; those using higher cumulative doses of corticosteroids and methotrexate, or those using more kinds of DMARDs combinations or in sequence. The aforementioned associations were much stronger in the elderly with RA.

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