Risk of malignant melanoma and non-melanoma skin cancer in rheumatoid arthritis patients initiating methotrexate *versus* hydroxychloroquine: a cohort study

H. Lee[1], S.K. Chen[1], N. Gautam[1], S.M. Vine[1], M. He[1], R.J. Desai[1], M.E. Weinblatt[2], R.J. Glynn[1], S.C. Kim[1,2]

[1]Division of Pharmacoepidemiology and Pharmacoeconomics; [2]Division of Rheumatology, Inflammation, and Immunity; Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.

Abstract

Objective

To characterise the incidence rate of skin cancer associated with methotrexate and hydroxychloroquine in older adults with rheumatoid arthritis (RA).

Methods

RA patients aged ≥65 years who initiated methotrexate or hydroxychloroquine as their first disease modifying anti-rheumatic drugs (DMARDs). The primary outcome was new occurrence of any skin cancer (i.e. malignant melanoma or non-melanoma skin cancer; NMSC) based on validated algorithms (positive predictive value >83%). Secondary outcomes were malignant melanoma, NMSC, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC). We estimated the incidence rates (IRs) and hazard ratios (HRs) for each outcome in the 1:1 propensity score (PS)-matched methotrexate and hydroxychloroquine groups.

Results

We included 24,577 PS-matched pairs of methotrexate and hydroxychloroquine initiators. Compared with hydroxychloroquine (IR 25.20/1,000 person-years), methotrexate initiators (IR 26.21/1,000 person-years) had a similar risk of any skin cancer [HR 1.03 -(95%CI 0.92, 1.14)] over a mean follow-up of 388 days. The HR (95%CI) associated with methotrexate was 1.39 (0.87, 2.21) for malignant melanoma, 1.01(0.90, 1.12) for NMSC, 1.37 (1.13, 1.66) for BCC, and 0.79 (0.63, 0.99) for SCC compared with hydroxychloroquine.

Conclusion

In this large cohort of older RA patients initiating methotrexate or hydroxychloroquine as their first DMARD, we found no difference in the risk of skin cancer including malignant melanoma and NMSC. However, for specific components of NMSC, methotrexate initiators had higher risk of BCC but lower risk of SCC compared with hydroxychloroquine initiators.

Key words

rheumatoid arthritis, skin cancer, non-melanoma skin cancer, malignant melanoma, basal cell carcinoma, squamous cell carcinoma, cohort study

Hemin Lee, MD, MPH
*Sarah K. Chen, MD, MPH**
Nileesa Gautam, BS
Seanna M. Vine, MPH
Mengdong He, MHS
Rishi J. Desai, PhD
Michael E. Weinblatt, MD
Robert J. Glynn, ScD, PhD
Seoyoung C. Kim, MD, ScD, MSCE

**Now employed by Gilead.*

Please address correspondence to:
Seoyoung C. Kim,
1620 Tremont Street, Suite 3030,
Boston MA 02120, USA.
E-mail: sykim@bwh.harvard.edu

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Introduction

Malignant melanoma arises from uncontrolled proliferation of melanocytes (1) and can be found in skin, central nervous system, and ocular tract with cutaneous melanoma being the most common form. In 2017, 85,686 new cases of cutaneous melanoma were reported in the U.S (incidence rate 22.7 per 100,000), marking it the sixth most common cancer in the U.S (2). Another class of skin malignancy, non-melanoma skin cancer (NMSC), consists of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) characterised by malignant growth of keratinocytes in epithelial layer. NMSC is the most common type of cancer world-wide, and its incidence is notably increasing partly due to advanced surveillance and aging populations (3). The exact incidence of NMSC is hard to capture as it is not reported to cancer registries; however, the estimated total number of NMSCs treated in the United States was 5,434,193 in 2012 Medicare data – illustrating its high healthcare burden (4).

Malignant melanoma and NMSC can occur de novo in individuals who have risk factors for skin cancer including exposure to ultraviolet radiation, fair skin, atypical nevi, or family history of skin cancer (5). However, they can also arise secondary to immunosuppressed (6) or chronic autoimmune conditions (7) like rheumatoid arthritis (RA) (8). Skin cancers arising in RA are thought to be related to systemic inflammation and dysfunctional immune surveillance combined with adverse effects of medication (9).

While some previous studies have shown elevated risk of skin cancer in RA patients treated with tumor necrosis factor inhibitor (TNFi) (10, 11), others have found no difference in the NMSC risk specific to RA treatments (12, 13). Similarly, the link between conventional disease modifying anti-rheumatic drugs (DMARDs) and skin cancer is unclear. A previous study reported a greater risk of melanoma among patients with RA treated with methotrexate compared to the general population (14); however, another study in patients with psoriasis found no association between methotrexate and the risk of cutaneous malignancy (15). With hydroxychloroquine, a case-control study reported an increased risk for NMSC associated with high cumulative dose of hydroxychloroquine among patients with systemic lupus erythematosus and primary Sjögren's syndrome (16), but no clear association with skin cancer risk in RA has been reported.

Recently, interest in the risk of skin cancer in RA patients related to use of DMARDs increased after a placebo-controlled randomised controlled trial of methotrexate (Cardiovascular Inflammation Reduction Trial, CIRT) (17, 18) and observational cohort studies (19, 20) reported elevated risk of NMSC in methotrexate users. However, it remains unclear how methotrexate risk compares to other commonly used conventional DMARDs. Ideally, a randomised controlled trial comparing RA drugs on the outcome of safety endpoints could provide us guidance on the risk of cancer in methotrexate *versus* other DMARDs, but there has been no adequately powered head-to-head comparison of conventional DMARDs on the risk of skin cancer in patients with RA.

We aimed to compare the rate of any skin cancer including malignant melanoma and NMSC after treatment initiation with methotrexate v*ersus* another commonly used non-biologic DMARD, hydroxychloroquine, among older patients with RA.

Methods

Data source

We conducted a new user, active comparator cohort study using Medicare fee-for-service claims data between January 1, 2006 and December 31, 2017. Medicare is a federally funded insurance programme that covers legal residents in the United States who are 65 years and older or those who have certain disabilities. The database contains longitudinal information on demographics, insurance enrollment, and diagnosis or procedures claims in inpatient setting (Part A), outpatient clinics (part B), and outpatient pharmacy dispensing (Part D). This study was approved by the institutional review board of the Brigham and Women's Hospital,

Boston, Massachusetts (2011P002580-177). Personal identifiers were removed from the data to protect patient confidentiality, and therefore, the requirement for patients' informed consent was waived. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study design and population

Cohort formation began with identification of the first prescription claim for methotrexate or hydroxychloroquine through Medicare on or after January 1, 2006 (Supplementary Fig. S1). Patients were required to have at least 365 days of continuous enrolment in Medicare Parts A, B, and D prior to cohort entry. Using a previously validated claims-based algorithm for RA with positive predictive value (PPV) of 87% (21), all patients were required to have at least 1 inpatient or 2 outpatient RA diagnosis codes using International Classification of Diseases, 9th Revision (ICD-9) or 10th revision (ICD-10), separated by 7 to 365 days during the 365-day baseline period.

We excluded patients aged less than 65 years old and those with any previous dispensing for other immunosuppressants, TNFi, other biologics, or chloroquine. Patients with history of malignancy including NMSC, radiation therapy, end-stage renal disease or renal dialysis, HIV/AIDS, or psoriatic arthritis were also excluded. Additionally, we excluded those with missing age, gender, or race, no follow-up, and nursing home residents.

Study outcomes

The primary outcome of interest was new occurrence of any skin cancer consisting of malignant melanoma or NMSC including carcinoma in situ of skin. The secondary outcomes were individual components of the primary outcome: malignant melanoma, NMSC including BCC, and SCC. Carcinoma in situ of skin was included as part of the primary outcome of any skin cancer and secondary outcome of NMSC but it was not assessed separately. Positive control outcome was prespecified as an occurrence of an ophthalmologic exam under the rationale that eye exams are routinely performed with hydroxychloroquine prescription to monitor retinal toxicity.

Outcome validation

For our outcome ascertainment, we conducted a separate validation study of claims-based algorithms (Suppl. Table S1) for cutaneous malignant melanoma and NMSC with chart review using longitudinal Medicare claims data linked to the Partners' Research Patient Data Registry (RPDR) for the period between January 1, 2008 and September 30, 2015. The details of RPDR are described elsewhere (22). Following algorithms were selected based on their high performance:

1) malignant melanoma was identified with 2 ICD-9 or ICD-10 diagnosis codes separated by 1 to 60 days (PPV 82%);

2) NMSC including carcinoma *in situ* was identified based on at least 1 ICD-9 or ICD-10 diagnosis code followed by Healthcare Common Procedure Coding System (HCPCS) codes for NMSC treatment occurring within 60 days (PPV 84%) (Suppl. Table S2).

Follow-up time

In the primary as-treated analysis, follow-up time started on day after cohort entry and continued until the earliest of the following events: occurrence of the study outcome, end of insurance enrollment, end of study period, death, switch to a comparator drug, discontinuation of index drug, or initiation of biologics/targeted therapies. A patient could contribute to multiple events for secondary outcome analyses (*i.e.* a patient who had BCC could also contribute to SCC). For primary outcome, occurrence of earliest skin cancer was counted as an outcome. We allowed additional 60 days of supply to methotrexate and hydroxychloroquine prescriptions after end of day supply from the most recent prescription ("grace" period).

Covariates

We measured a total of 62 prespecified covariates (see Table I for the full list of covariates) during the baseline period of 365 days before the initiation of study drug. The covariates included demographics, evaluation of health status [combined comorbidity score (23), claims-based frailty index (24)], use of other drugs, RA or skin cancer-related risk factors, and healthcare utilisation.

Statistical analysis

We first compared the baseline characteristics of the methotrexate and the hydroxychloroquine groups. For confounding control, we used multivariable logistic regression to estimate the propensity score (PS) which is the probability of starting methotrexate *versus* hydroxychloroquine in this study population with model that included the 62 predefined baseline covariates (25). Using the nearest-neighbour matching algorithm (maximum caliper width of 0.01 on the PS scale), methotrexate initiators were PS-matched to hydroxychloroquine initiators with a 1:1 ratio. After matching, we assessed covariate balance using the standardised mean differences: variables with a standardised mean difference <0.10 were determined as having acceptable imbalance (26).

For the primary and secondary outcomes, we estimated the incidence rates (IR) and incidence rate differences (RD) with 95% confidence intervals (CI) in the PS matched groups. Cox proportional hazards regression models estimated hazard ratios (HR) comparing the risk for each outcome among methotrexate *versus* hydroxychloroquine initiators. The Kaplan-Meier curves were generated to assess the risk of the primary outcome in PS-matched groups over time. Prespecified subgroup analyses were conducted within strata defined by sex, race, baseline steroid use, and baseline NSAID use. We performed a sensitivity analysis with a 90-day latency period by starting the follow-up for outcomes 90 days after the cohort entry date. In addition, we calculated the number of events and incidence rates stratified by follow-up time (*i.e.* 0–365 days, 366–730 days, and 731+ days) to assess the risk of skin cancer related to the treatment duration. All analyses were conducted using the Aetion Evidence Platform® (2020). Software for real-world data analysis. Aetion, Inc. http://aetion.com and R (v. 3.31; R Foundation for Statistical Computing).

Results

Baseline characteristics of the study population

After applying the inclusion and exclusion criteria (Fig. 1), our study cohort consisted of 38,842 new users of methotrexate (75.6% female; age (mean±SD) 73.59±6.27 years) and 25,291 new users of hydroxychloroquine (79.9% female; age (mean±SD) 73.75±6.46 years). Before PS matching (Supplementary Table S3), methotrexate users had a higher proportion of recent oral steroid use (58.7% *vs*. 48.8%), while hydroxychloroquine users had more history of skin cancer procedures (7.2% *vs*. 8.6%) and dermatologist visit (11.0% *vs*. 13.9%).

After 1:1 PS matching, we had 24,577 pairs of methotrexate and hydroxychloroquine initiators with the mean±SD age of 73.8±6.4 years in the methotrexate group and 73.7±6.5 years in the hydroxychloroquine group. Nearly 80% were female and 84% white. All measured baseline characteristics were adequately balanced with standardised differences <10% (Table I).

Risk of malignant melanoma and NMSC

During a mean follow-up of 388.96 days in the PS-matched cohort (412.57 days for methotrexate, 365.35 days for hydroxychloroquine), 728 methotrexate initiators (IR 26.21 per 1,000 person-years) and 620 hydroxychloroquine initiators (IR 25.20 per 1,000 person-years) developed the primary outcome, *i.e*. any skin cancer including malignant melanoma, BCC, SCC, or carcinoma in situ of skin (Table II). The RD between methotrexate and hydroxychloroquine was 1.00 (95% CI -1.75, 3.75) per 1,000 person-years. The HR for any skin cancer associated with methotrexate was 1.03 (95% CI 0.92, 1.14) compared with hydroxychloroquine. The Kaplan-Meier curve of any skin cancer also showed no difference in the risk between the two groups (Fig. 2).

In the secondary outcome analysis (Table II), methotrexate was not associated with a higher RD or HR for malignant melanoma or NMSC. However, methotrexate had a higher IR of BCC compared with hydroxychloro-

Table I. Selected patient characteristics in 365 days prior to cohort entry after 1:1 PS matching.

Patient characteristics	Methotrexate (n=24,577)	Hydroxychloroquine (n=24,577)	Abs. Std. Diff.
Demographic			
Age, years, mean (SD)	73.80 (6.36)	73.73 (6.45)	0.011
Female	19,502 (79.4%)	19,528 (79.5%)	0.003
Region			0.01
Northeast	4,190 (17.0%)	4,189 (17.0%)	
South	10,739 (43.7%)	10,628 (43.2%)	
North central	6,002 (24.4%)	6,058 (24.6%)	
West	3,608 (14.7%)	3,663 (14.9%)	
Unknown	38 (0.2%)	39 (0.2%)	
Race			0.008
White	20,656 (84.0%)	20,663 (84.1%)	
Black	2,577 (10.5%)	2,536 (10.3%)	
Asian	446 (1.8%)	461 (1.9%)	
Hispanic	721 (2.9%)	733 (3.0%)	
Native American	177 (0.7%)	184 (0.7%)	
Comorbidities			
Actinic keratosis	1,646 (6.7%)	1,660 (6.8%)	0.002
Atopic dermatitis/contact dermatitis	74 (0.3%)	80 (0.3%)	0.004
Psoriasis	60 (0.2%)	65 (0.3%)	0.004
Alopecia areata	26 (0.1%)	30 (0.1%)	0.005
Vitiligo	38 (0.2%)	38 (0.2%)	0
Hypertension	19,668 (80.0%)	19,628 (79.9%)	0.004
Hyperlipidaemia	17,411 (70.8%)	17,510 (71.2%)	0.009
Diabetes	7,287 (29.6%)	7,256 (29.5%)	0.003
Combined comorbidity score, mean (SD)	1.21 (2.08)	1.21 (2.09)	0.001
Claims-based frailty index, mean (SD)	0.15 (0.05)	0.15 (0.05)	0.002
Medications			
Amiodarone	263 (1.1%)	271 (1.1%)	0.003
First-generation macrolide	433 (1.8%)	418 (1.7%)	0.005
Second-generation macrolide	5,350 (21.8%)	5,374 (21.9%)	0.002
Tetracycline	2,236 (9.1%)	2,249 (9.2%)	0.002
Antiplatelet agents	2,251 (9.2%)	2,234 (9.1%)	0.002
Anticoagulant	2,268 (9.2%)	2,264 (9.2%)	0.001
NSAIDs and Coxibs	11,423 (46.5 %)	11,424 (46.5%)	0
ACE inhibitor	7,973 (32.4%)	7,922 (32.2%)	0.004
ARBs	5,619 (22.9%)	5,566 (22.6%)	0.005
Beta blockers	9,739 (39.6%)	9,672 (39.4%)	0.006
Calcium channel blocker	7,306 (29.7%)	7,319 (29.8%)	0.001
Loop diuretics	4,761 (19.4%)	4,733 (19.3%)	0.003
Thiazides	8,396 (34.2%)	8,314 (33.8%)	0.007
Insulin	1,466 (6.0%)	1,448 (5.9%)	0.003
Non-insulin diabetes medications	4,451 (18.1%)	4,420 (18.0%)	0.003
Statins	11,899 (48.4%)	11,867 (48.3%)	0.003
Antidepressants	7,951 (32.4%)	7,917 (32.2%)	0.003
Opioids	15,648 (63.7%)	15,623 (63.6%)	0.002
Antipsychotics	604 (2.5%)	579 (2.4%)	0.007
Anticonvulsants	5,184 (21.1%)	5,146 (20.9%)	0.004
Any oral steroid use	15,872 (64.6%)	15,877 (64.6%)	0
Recent oral steroid use*	12,267 (49.9%)	12,269 (49.9%)	0
Cumulative prednisone-equivalent milligrams, mean (SD)	518.98 (1,065.81)	462.40 (826.25)	0.059
Procedures/Healthcare utilisation			
Procedures on benign/premalignant lesions	2,039 (8.3%)	2,045 (8.3%)	0.001
Skin biopsy	303 (1.2%)	313 (1.3%)	0.004
Dermatologist visit	3,256 (13.2%)	3,262 (13.3%)	0.001
Rheumatologist visit	19,359 (78.8%)	19,394 (78.9%)	0.003
Emergency room visit	8,260 (33.6%)	8,329 (33.9%)	0.006
Recent hospitalisation*	1,034 (4.2%)	1,047 (4.3%)	0.003

*Recent: 60 days prior to (including) the index date.

Abs. Std. Diff.: absolute standardised difference; ACE: angiotensin converting enzyme; ARBs: angiotensin II receptor blockers; Coxibs: selective cyclooxygenase 2 inhibitors; HCQ: hydroxychloroquine; n: number; NSAIDs: non-steroidal anti-inflammatory drugs; NUVB: narrow-band ultraviolet B; PDT: photodynamic therapy; PS: propensity score; SD: standard deviation; TIA: transient ischaemic attack.

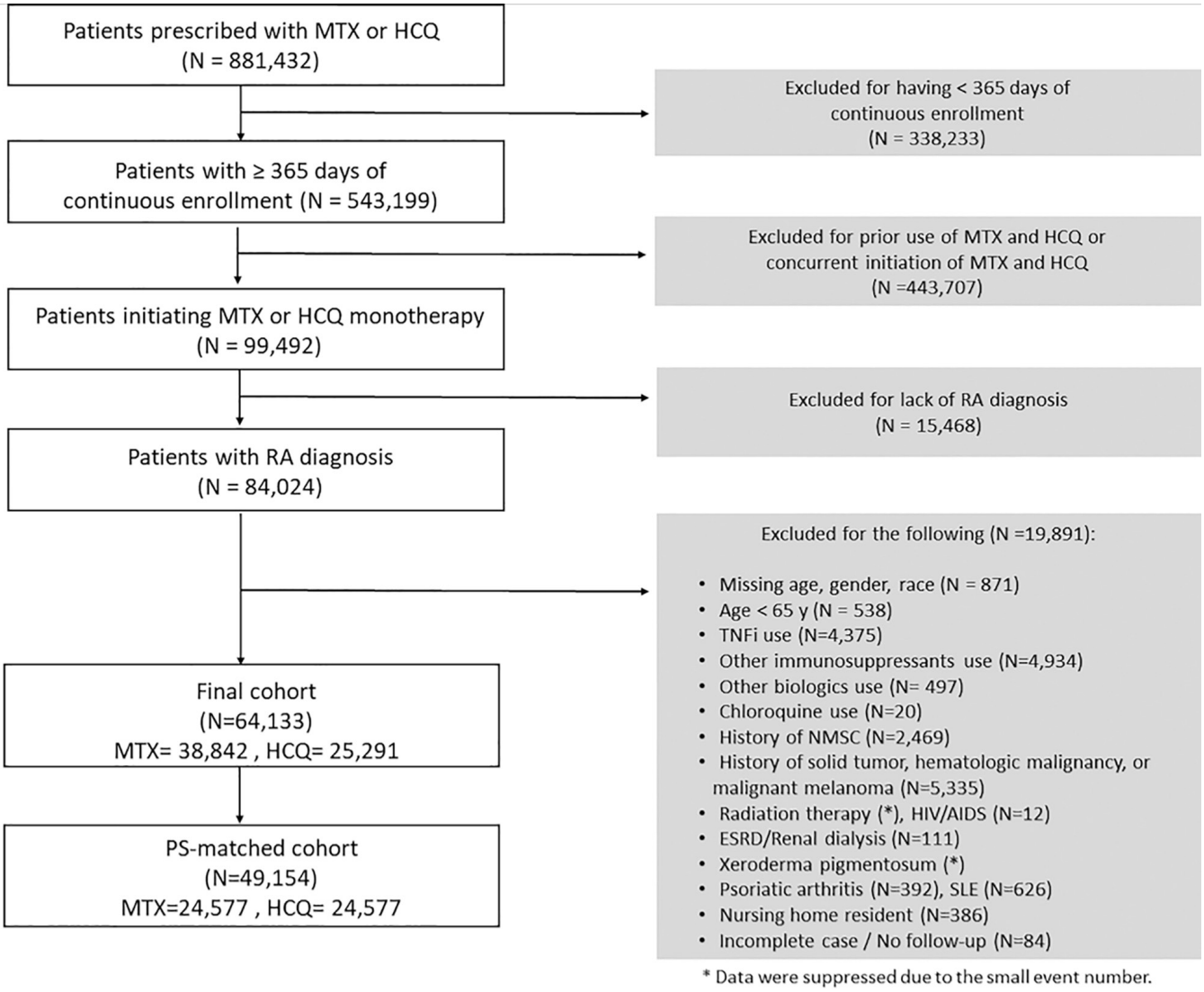

Fig. 1. Flowchart of study cohort selection for the methotrexate *versus* hydroxychloroquine comparison.
AIDS: acquired immunodeficiency syndrome; ESRD: end stage renal disease; HCQ: hydroxychloroquine; HIV: human immunodeficiency virus; MTX: methotrexate; N: number; NMSC: non-melanoma skin cancer; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; TNFi: tumour necrosis factor-alpha inhibitor.

quine [RD 2.61 (95% CI 1.11, 4.11) per 1,000 person-years; HR 1.37 (95% CI 1.13, 1.66)]. In addition, methotrexate initiators had a lower IR of SCC *versus* hydroxychloroquine [RD -1.14 (95% CI -2.39, 0.11) per 1,000 person-years; HR 0.79 (95% CI 0.63, 0.99)]. In the analysis using the receipt of ophthalmic examination as a positive control for hydroxychloroquine use, the occurrence of eye exams in the methotrexate users was lower than hydroxychloroquine users as expected [HR 0.39 (95% CI 0.38, 0.41)].

Subgroup and sensitivity analyses

There was no difference in the risk of any skin cancer stratified by baseline use of steroids or NSAIDs, gender, or race (Suppl. Table S4). For both MTX and HCQ groups, the incidence rate of any skin cancer was higher in males (43.38 per 1,000 PYs for methotrexate, 41.36 per 1,000 PYs for hydroxychloroquine) than in females (22.18 per 1,000 PYs for methotrexate, 20.36 per 1,000 PYs for hydroxychloroquine) and greater in whites (29.38 per 1,000 PYs for methotrexate, 28.16 per 1,000 PYs for hydroxychloroquine) than in non-whites (1.91 per 1,000 PYs for methotrexate, 1.94 per 1,000 PYs for hydroxychloroquine). In the sensitivity analysis with a 90-day latency period, there was no difference in the risk of any skin cancer [HR 1.03 (95% CI 0.92, 1.16)] (Suppl. Table S5). When patients were stratified according to their time of follow-up, the distribution of patients for each follow-up time tier was as follows: 72.64% for methotrexate and 68.15% for hydroxychloroquine between 0–365 days ; 13.29% for methotrexate and 15.27% for hydroxychloquine between 366–730 days; 14.07% for methotrexate and 16.58% for hydroxychloroquine beyond 731 days (Suppl. Table S6). In the follow-up time stratified analysis, the incidence rate was highest during the first year of follow-up (46.20 per 1,000 PYs for methotrexate, 41.48 per 1,000 PYs for hydroxychloroquine) and decreased as follow-up time lengthened

Table II. Incidence rates and hazard ratios (95% CI) for primary and secondary outcomes in the 1:1 PS matched cohort.

	Methotrexate (n=24,577)					Hydroxychloroquine (n=24,577)				
	number of events	PY	IR/1,000 PY	RD/1,000 PY (95% CI)	HR (95% CI)	number of events	PY	IR/1,000 PY	RD/1,000 PY (95% CI)	HR (95% CI)
Primary outcome										
Any skin cancer*	728	27,780	26.21	1.00 (-1.75, 3.75)	1.03 (0.92, 1.14)	620	24,600	25.20	Ref	Ref
Secondary outcomes										
Malignant melanoma	46	28,938	1.59	0.45 (-0.16, 1.07)	1.39 (0.87, 2.21)	29	25,540	1.14	Ref	Ref
NMSC	700	27,819	25.16	0.54 (-2.16, 3.25)	1.01 (0.90, 1.12)	606	24,616	24.62	Ref	Ref
BCC	264	28,543	9.25	2.61 (1.11, 4.11)	1.37 (1.13, 1.66)	168	25,301	6.64	Ref	Ref
SCC	140	28,741	4.87	-1.14 (-2.39, 0.11)	0.79 (0.63, 0.99)	152	25,307	6.01	Ref	Ref
Control outcome										
Ophthalmologic exam	4,342	23,263	186.64	-362.38(-375.51, -349.26)	0.39 (0.38, 0.41)	8,181	14,901	549.03	Ref	Ref

* Includes malignant melanoma, non-melanoma skin cancer and carcinoma *in situ* of skin.
BCC: basal cell carcinoma; CI: confidence interval; HR: hazard ratio; IR: incidence rate; n: number; NMSC: non-melanoma skin cancer; PS: propensity score; PY: person-years; RD: rate difference; SCC: squamous cell carcinom.

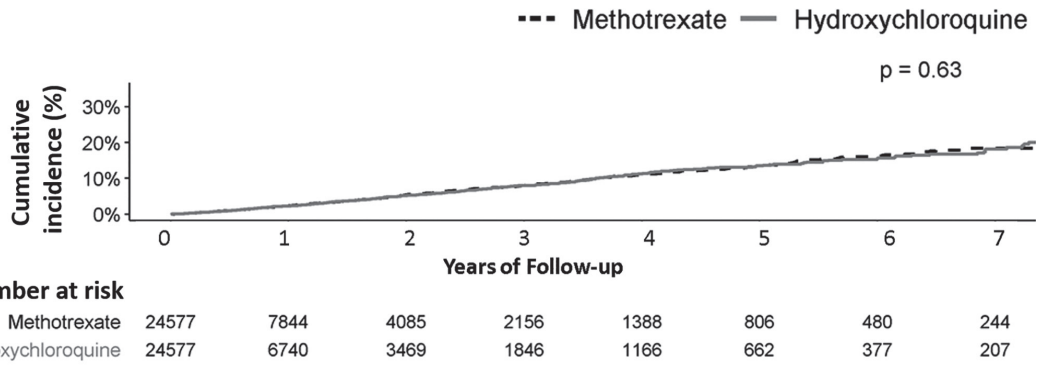

Fig. 2. Cumulative incidence of any skin cancer in the 1:1 propensity score-matched cohort.

(Suppl. Table S6). HR for all three time intervals were similar to the primary outcome [HR 1.07 (95% CI 0.91,1.25) for follow-up between 0–365 days; HR 1.03 (95% CI 0.83, 1.28) for follow-up between 366–730 days; HR 1.03 (95% CI 0.84, 1.25) for follow-up beyond 731 days. (Suppl. Table S6).

Discussion

In this observational cohort of 49,154 older RA patients, 2.74% of patients developed any skin cancer during a mean follow-up of 388 days after initiating methotrexate or hydroxychloroquine. We observed no difference in the risk of any skin cancer consisting of malignant melanoma and NMSC (BCC, SCC, and carcinoma in situ) between methotrexate and hydroxychloroquine initiators. The results for individual subsets of skin cancer were different, however, with a 37% increased risk for BCC and a 21% lower risk for SCC in the methotrexate group. The risk for malignant melanoma did not differ.

In a previous study based on self-reported questionnaires in RA patients, the risk of NMSC was not elevated in patients on methotrexate without TNFi (HR 1.15; 95% CI 0.81–1.64).(11) Yet in a recent randomised placebo-controlled trial, CIRT, patients without RA or any systemic inflammatory disease who received low dose methotrexate had a 2-fold increase in the risk of skin cancer compared to placebo (HR 2.04; 95% CI 1.28–3.26) (17, 18). The CIRT result was largely driven by the increased risk for SCC (HR 3.31; 95% CI 1.63–6.71) , but the risk for BCC (HR 1.35; 95% CI 0.68–2.68) and melanoma (HR 2.33; 95% CI 0.60–9.04) were also numerically increased. Our study did not observe elevated risk of composite skin cancer with methotrexate (HR 1.03; 95% CI 0.92–1.14), and the risk of SCC was lower in the methotrexate users than in hydroxychloroquine users (HR 0.79; 95% CI 0.63, 0.99).

Studies which compared methotrexate against other DMARDs as a group also showed different findings. Analysing RA patients in Medicare, the risk of recurrent NMSC was higher when methotrexate was used in combination with other DMARDs (HR 1.49; 95% CI 1.08–2.37) (19). Also, in a Consortium of Rheumatology Researchers of North America (CORRONA) registry based study, the risk of NMSC was lower in conventional DMARDs than in methotrexate (HR 0.11; 95% CI 0.01–0.91) (20).

To better understand our results, key differences in the study design and population should be reiterated. First, unlike CIRT which compared methotrexate against placebo in patients with no systemic inflammatory disease, our study compared methotrexate with an active comparator, hydroxychloroquine, among older patients with RA. To our knowledge, no studies have directly compared methotrexate against a single conventional DMARD agent, and studies on the effect of methotrexate and hydroxychloroquine on keratinocytes are limited. Both drugs exert immunosuppressive actions which can lead to increased susceptibility to malignancy. However, the relative risk

of skin cancer when two drugs are directly compared is unknown. There is a growing body of literatures on hydroxychloroquine's antitumour activity in non-small cell lung cancer (27) and bladder cancer (28) through its effects on inhibiting autophagy (29), but the limited evidence provides so far only modest support for a relative benefit of hydroxychloroquine *versus* methotrexate on malignancy risk.

Second, the differences in the study population and outcome definition can impact the results. The outcome definitions in the previous Medicare RA cohort study by Scott *et al*. (19), and our work were similarly based on ICD diagnosis and procedures codes. However, Scott *et al*. included only patients who already had an incident NMSC event, and the follow-up for the cohort began 1 year after the first NMSC study to assess the outcome of the second NMSC. Consequently, the population captured in Scott *et al*. study are patients with a history of prior skin cancer who are inevitably at a higher risk of NMSC than our cohort who were malignancy-naïve during the covariate assessment period (30).

Our subgroup analyses found no significant modification of the overall effect across several prespecified clinical factors. Glucocorticoids possess immunosuppressive effects which could increase the risk of skin cancer (30-32), and NSAIDs are linked with a lower risk of malignancy by inhibiting the production of COX-2 (33, 34). However, some NSAIDs are not captured completely in insurance claims datab due to the availability of over-the-counter NSAIDs, and a single claims-based history of steroid use may not accurately represent patients who are at increased risk of skin cancer due to prolonged exposure. On the other hand, increased risk of skin cancer in males and whites has been observed consistently throughout past studies (35-37). Our study reaffirmed these findings which can be attributed to differential surveillance in addition to other genetic or pathophysiological factors.

In a case-control study using Taiwan National Health Insurance Research Database, RA patients had a higher risk of NMSC (odds ratio=2.23) compared to those without RA, and the risk was even higher in those with higher cumulative doses of corticosteroids and methotrexate (38). We also assessed the potential association between the duration of the treatment and risk of skin cancer by conducting a follow-up time (*i.e*. time on treatment) stratified analysis. Most outcomes (NMSC and malignant melanoma) occurred during the first year of the follow-up, and the incidence rate decreased as follow-up time lengthened although the hazard ratios remained similar in all three time intervals.

We also conducted a sensitivity analysis by applying a 90-day latency period based on the rationale that cutaneous malignancy will take time to develop after the initiation of drugs. The results did not differ between our main analysis and the 90-day latency period analysis.

Our study is subject to several limitations. First, we are unable to distinguish whether an apparent difference in risk is due to greater hazard of one treatment or a protective effect of the other. However, we purposefully designed our study as an active comparator, new user design without a non-user comparator group because non-user comparator designs in observational studies are prone to critical methodological flaws such as confounding by indication, immortal time bias, and healthy user bias (39).

Second, we could not assess RA disease activity and duration which might impact risk for malignancy. Inability to fully control for these factors could lead to confounding by indication (*i.e*. less severe RA patients may be assigned to hydroxychloroquine which may lead to a outcome rate) (40). However, as noted, we utilised a new user, active comparator design (41) and PS matching (42) to minimise potential bias and balance covariates between treatment groups. In addition to RA disease activity and duration, risk factors for skin cancer (*e.g*. family history, smoking, amount of UV exposure) were not measurable in claims data. As a proxy for extreme UV exposure, we looked at the proportion of people with ICD diagnosis codes for sunburn which was well-balanced. However, we could not determine the characteristic of sun exposure that can confound an individual's risk for skin cancer. For example, intermittent overexposure is associated with development of melanoma and BCC, and cumulative sun exposure is associated with SCC (43).

Third, our outcome definition of skin cancer is subject to misclassification with its reliance on claims-based diagnosis and procedure codes. However, our evaluation of these definitions yielded PPVs of 82% for malignant melanoma and 84% for NMSC.

In conclusion, in our large population-based cohort of older RA patients, 2.74% of patients developed any skin cancer during the follow-up. The risk for overall skin cancer did not differ between methotrexate and hydroxychloroquine. However, the secondary outcome analysis showed 37% higher risk of BCC and 21% lower risk of SCC in the methotrexate group than the hydroxychloroquine group. We could not distinguish whether observed differences indicated enhanced risk of one treatment or protective effects of the alternative. Nevertheless, differences in the risk of skin cancer subtypes signify a need to monitor development of cutaneous malignancy in patients who are initiating non-biologic DMARDs for treatment of RA.

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