

Methotrexate Use for Patients with Psoriasis and Risk of Cutaneous Squamous Cell Carcinoma: A Nested Case-control Study

Filippos GIANNOPOULOS^{1,2}, Martin GILLSTEDT^{1,2}, Marta LASKOWSKI^{1,2}, Kasper BRUUN KRISTENSEN³ and Sam POLESIE^{1,2}
¹Department of Dermatology and Venereology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, ²Region Västra Götaland, Sahlgrenska University Hospital, Department of Dermatology and Venereology, Gothenburg, Sweden, and ³Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark

An association between methotrexate use and risk of cutaneous squamous cell carcinoma has been reported in patients with rheumatoid and psoriatic arthritis. A nested case-control study was performed to investigate if methotrexate use among patients with psoriasis was associated with increased risk of cutaneous squamous cell carcinoma. Data were obtained from Swedish registers and included 623 patients with psoriasis and a first cutaneous squamous cell carcinoma from 2010 to 2016. Ten randomly selected patients with psoriasis were matched on age and sex to each case. Among cases, 160 (26%) were ever-users of methotrexate. The corresponding number among the controls was 1,370 (22%), yielding an unadjusted odds ratio (OR) of 1.23 (95% confidence interval (95% CI) 1.02–1.49); $p=0.034$. After adjusting for use of other immunosuppressive drugs the association was close to unity (OR 1.09; 95% CI 0.89–1.34); $p=0.39$. The slightly increased risk of cutaneous squamous cell carcinoma associated with methotrexate-exposure in patients with psoriasis does not seem to be associated with methotrexate, but rather with disease severity, other anti-psoriatic treatments, and ultraviolet exposure.

Key words: adverse effects; epidemiology; methotrexate; pharmacology; psoriasis; squamous cell carcinoma.

Accepted Dec 14, 2020; Epub ahead of print Dec 15, 2020

Acta Derm Venereol 2021; 101: adv00365.

Corr: Sam Polesie, Department of Dermatology and Venereology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gröna stråket 16, SE-413 45 Gothenburg, Sweden. Email: sam.polesie@vregion.se

Immunosuppressive drugs increase the risk of skin cancer, particularly keratinocyte carcinoma (1). Methotrexate (MTX) is an old immunosuppressive and anti-inflammatory drug that has frequently been used for several immune-mediated diseases, including psoriasis, since its introduction more than 70 years ago (2). Use of MTX has been linked with a higher risk of cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma (BCC) among patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsoA) (3). In a cohort of American patients with RA, use of MTX over one year was associated with an enhanced risk of a second non-melanoma skin cancer (NMSC) (4). In another investigation conducted within a cohort of patients with psoriasis, MTX treatment was linked with an increased risk of BCC but not cSCC

SIGNIFICANCE

Squamous cell carcinoma is the second most common type of skin cancer. This study investigated whether use of methotrexate was linked to increased risk of such cancer, using a database of Swedish patients with psoriasis. Among these, patients who developed squamous cell carcinoma were identified and their use of methotrexate compared with cancer-free patients. Patients with squamous cell carcinoma were more likely to be users of methotrexate compared with cancer-free psoriasis controls. However, when the use of other immunosuppressive drugs was taken into account, use of methotrexate was no longer linked to an increased risk of squamous cell carcinoma.

(5). In Swedish investigations, hospitalized patients with psoriasis were more likely to develop NMSC including cSCC, compared with the general population (6, 7). In a meta-analysis the relative risk (RR) for cSCC among individuals with psoriasis compared with population-based controls and cohorts was 2.15 (95% confidence interval (95% CI) 1.32–3.50) (8). In a recent systematic review and meta-analysis patients with psoriasis had an increased risk of keratinocyte carcinoma compared with population controls (RR 2.28, 95% CI 1.73–3.01). This association was not observed in patients with PsoA (RR 1.22, 95% CI 0.89–1.66) (9).

In the Cardiovascular Inflammation Reduction Trial (CIRT) the role of MTX treatment for prevention of a new cardiovascular event in patients with stable atherosclerosis was assessed (10). The trial included 4,786 North American patients (81.2% men, median age 65.7 years) randomized to receive either low-dose MTX ($n=2,391$) or placebo ($n=2,395$). Patients randomized to MTX treatment did not have a lower risk of a subsequent cardiovascular event. However, when the proportion of adverse events in both groups was compared, a significantly increased risk of skin cancer was observed among patients randomized to MTX treatment. For cSCC, 33 cases (1.4%) were reported among the MTX exposed and 10 cases (0.4%) in the placebo group, yielding a hazard ratio (HR) of 3.31 (95% CI 1.63–6.71) (11). Notably, this difference was observed within a median follow-up period of 23 months. Nevertheless, patients with any immune-mediated disease, which is the actual label for MTX, were not included, since any chronic inflammatory condition was listed as an exclusion criterion. Expanding

our knowledge of potential side-effects for old pharmaceuticals is important, particularly those used by millions of patients worldwide, such as MTX. Therefore, the aim of this Swedish nested case-control investigation was to further analyse the association between MTX use among patients with psoriasis and cSCC.

MATERIALS AND METHODS

Cohort

The specific Swedish psoriasis cohort definition and detailed information about the registries used have been described previously (12). Briefly, the cohort consists of 81,738 patients with psoriasis. To allow for an adequate exposure assessment window (the drug prescription registry was initiated in July 2005), patients with an incident cSCC (including cutaneous squamous cell carcinoma *in situ* (cSCCis)) during the period 2010 to 2016 were selected (cases). Prior to the date of the cSCC diagnosis, the cases needed to be cancer-free with the exception of BCC. All cSCC were identified through combining International Classification of Diseases, Tenth Revision (ICD-10) and the morphology codes for International Classification of Diseases for Oncology, third edition (ICD-O/3). The exact definitions are available in the supplementary material (Table S1¹).

The date of the cSCC diagnosis was used as the matching date for the controls (index date). Eligible controls needed to be alive and cancer-free on the index date and were matched for age (same birth year) and sex. Risk set sampling was used as the matching strategy (13). All patients needed to reside continuously in Sweden from July 2005 to the index date. Patients with any International Classification of Diseases (ICD) code indicating a previous organ transplant surgery and/or HIV were discarded if the diagnosis antedated the index date. Ethical approval was obtained from the Swedish Ethical Review Authority (approval number 2020-01839).

Exposure

Exposure to MTX was based on filled prescriptions recorded in the Swedish Prescription Registry. The main exposure of interest was defined as ever-use of MTX, while cumulative doses were analysed in supplementary analyses to assess dose response. Exposure to MTX was assessed from data availability (July 2005) until the index date. Accumulated MTX doses to the index date (in g) were obtained.

Covariates

The Charlson Comorbidity Index was obtained for all patients to adjust for comorbidity at large (14). Furthermore, conditions that are considered prior to MTX prescription and other formal indications for MTX were obtained. Specifically, alcohol-associated conditions, diabetes, liver diseases, renal diseases, peptic and duodenal ulcers, smoking-associated conditions, actinic keratosis, Crohn's disease, RA and PsoA were included as covariates (Table S1¹).

Primary analysis

In the main analysis, association between ever-use of MTX and cSCC was examined with conditional logistic regression models, adjusting for relevant comorbidities and immunosuppressive drugs.

Secondary analyses

(i) The filled MTX doses used before the index date were summarized and per oral and subcutaneous doses, as well as totally accumulated doses, were assessed as a continuous variable. Moreover, totally accumulated MTX doses were analysed separately as a categorical variable.

(ii) Analyses of the association between cSCC and ever-use of ciclosporin, acitretin, azathioprine, tumour necrosis factor α inhibitors (TNFis) and interleukin pathway-inhibitors (ILis).

(iii) Mortality analyses, investigating overall mortality between cases and controls and MTX-exposed and MTX-unexposed within the case group.

Sensitivity analysis

Three sensitivity analyses were conducted. First, to examine the potential for reverse causation or protopathic bias, different lag periods (period before the index date that is disregarded with respect to filled MTX prescriptions) were introduced. In the second analysis, the case group only included patients with an invasive cSCC and their respective controls. In the final sensitivity analysis, the study inclusion criteria for cases and controls were changed. In this analysis prevalent cancers (other than cSCC or cSCCis) were permitted prior to the index date. For the 2 last sensitivity analyses, the primary and all secondary analyses were repeated.

Post hoc analysis

To examine the impact of potential confounding by UV exposure, a *post hoc* analysis restricted to individuals without a history of actinic keratosis was conducted. To this end, an updated risk set sampling was used, in which only cases and controls without a previous history of actinic keratosis before the index date were included, and the primary and secondary analyses were repeated in this population.

Statistical analysis

Conditional logistic regression models were used, with cSCC as the dependent variable and MTX as the independent variable. Cox proportional hazards regression models were adjusted for age group (≤ 40 , $> 40 - \leq 50$, $> 50 - \leq 60$, $> 60 - \leq 70$ and > 70 years) and sex. Kaplan–Meier survival plots were performed as mortality analyses. In all models, drugs and comorbidities refers to registered events before index date. Fisher's exact test and Wilcoxon's rank sum test were used for comparing proportions and 2-sample tests, respectively. All tests were 2-sided and $p < 0.05$ was considered as statistically significant. All data were analysed using R version 3.5.3 (<https://www.r-project.org/>).

RESULTS

In total, 623 patients with psoriasis (52.2% women) with a first cSCC, including cSCCis ($n = 314$) were identified (cases) during 2010 to 2016. A total of 6,230 patients with psoriasis were sampled as controls (Fig. S1¹). The majority (95.0%) were born in any of the Nordic countries. Except for renal diseases and actinic keratosis, which were more prevalent in the case group ($p = 0.050$ and $p < 0.0001$), comorbid conditions were distributed similarly among cases and controls. The cases had more visits to a dermatology clinic ($p < 0.0001$), visits related to psoriasis ($p = 0.0007$) and outpatient visits ($p < 0.0001$)

¹<https://www.medicaljournals.se/acta/content/abstract/10.2340/00015555-3725>

Table I. Demographic data

	Cases (n = 623)	Controls (n = 6,230)
Sex, n (%)		
Men	298 (48)	2,980 (48)
Women	325 (52)	3,250 (52)
Age, median, (IQR)	74 (68–80)	74 (68–80)
< 50 years	14 (2)	140 (2)
50–59 years	33 (5)	330 (5)
60–69 years	150 (24)	1,500 (24)
70–79 years	273 (44)	2,730 (44)
≥ 80 years	153 (25)	1,530 (25)
Diagnoses, n (%)		
Alcohol-associated conditions	22 (4)	257 (4)
Diabetes	124 (20)	1,338 (21)
Liver disease	86 (14)	944 (15)
Renal disease	30 (5)	205 (3)
Peptic ulcer	19 (3)	183 (3)
Smoking-associated conditions	73 (12)	744 (12)
Actinic keratosis	301 (48)	766 (12)
Crohn's disease	8 (1)	56 (1)
Rheumatoid arthritis	33 (5)	314 (5)
Psoriatic arthritis	126 (20)	1,286 (21)
Charlson Index ^a , n (%)		
CCI 0	306 (49)	3,014 (48)
CCI 1	167 (27)	1,740 (28)
CCI 2+	150 (24)	1,476 (24)
Educational level ^b , n (%)		
Low	180 (29)	1,892 (30)
Middle	241 (39)	2,287 (37)
High	136 (22)	1,311 (21)
Missing data	66 (11)	740 (12)
Dermatology visits, median (IQR) ^c	7 (4–15)	4 (2–9)
Psoriasis visits, median (IQR) ^d	4 (2–11)	4 (2–8)
Outpatient visits, median (IQR) ^e	32 (17–55)	22 (12–38)
Hospitalizations, median (IQR) ^f	5 (2–9)	4 (2–9)

^aCharlson Comorbidity Index (CCI) 0, no comorbidity; CCI 1 low level of comorbidity; CCI 2+, moderate to severe level of comorbidity. ^bEducational levels: low, compulsory school (<10 years); middle, upper secondary school (10–12 years); high, higher education (>12 years). ^cNumber of outpatient visits at a dermatological clinic prior to index date in the period 2001 to 2016. ^dNumber of outpatient visits (not including primary healthcare) prior to index date in the period 2001 to 2016 with any psoriasis diagnosis. ^eNumber of all outpatient visits (not including primary healthcare) prior to index date in the period 2001 to 2016. ^fNumber of hospitalizations prior to index date in the period 1962 to 2016. IQR: interquartile range.

compared with controls (**Table I**). The median time (interquartile range (IQR)) from the first available diagnosis of psoriasis to the index date among the cases was 7.7 years (3.7–10.7 years). The corresponding time for the controls was 7.4 years (3.8–10.5 years; $p=0.43$).

When investigating all filled MTX prescriptions among cases and controls, 45%, 31%, 9%, 6% and 9% were prescribed by dermatologists, rheumatologists,

internists, general practitioners and other physicians, respectively. Fig. S2¹ illustrates the summarized MTX doses for MTX-exposed cases and controls. The time from first to last filled prescription of MTX was 3.0 years for both groups combined and did not differ significantly between the groups. The median time (IQR) from a first prescription of MTX to the index date was 5.8 years (3.2–8.2) for the cases and 5.5 years (2.9–7.8) for the MTX-exposed controls ($p=0.28$).

Primary analysis

Among the cases and controls, 160 patients (26%) and 1,370 (22%) had filled any MTX prescription. A univariate conditional logistic regression model, using ever exposure of MTX, yielded an OR of 1.23 (95% CI 1.02–1.49; $p=0.034$) for ever use of MTX associated with cSCC. When adjusting for TNFis and immunosuppressants other than MTX, the confidence intervals overlapped 1; however, the point estimates were similar to the above result. In univariate analyses for the covariates associated with cSCC, actinic keratosis was strongly associated with cSCC (OR 7.77, 95% CI 6.43–9.41; $p<0.0001$) (**Fig. 1**). In a complementary analysis, the effect on the OR for MTX associated with cSCC after adjusting for each covariate separately are shown (**Table II**).

Secondary analyses

(i) A trend for an increased risk of cSCC with increasing doses of accumulated MTX was observed. When modelling dose as a continuous variable, the risk of cSCC increased significantly with per oral and total dose of MTX (**Table III**).

(ii) Filled immunosuppressive drugs other than MTX, azathioprine and TNFis were more frequent among cases compared with controls. The distribution of ever-use of drugs and drug classes are shown in **Table IV**.

(iii) There were no differences in mortality rates between cases and controls (adjusted HR 1.0, (95% CI 0.7–1.2); $p=0.71$). When MTX-exposed and MTX-unexposed cases were compared no difference in mortality was observed (Fig. S3¹).

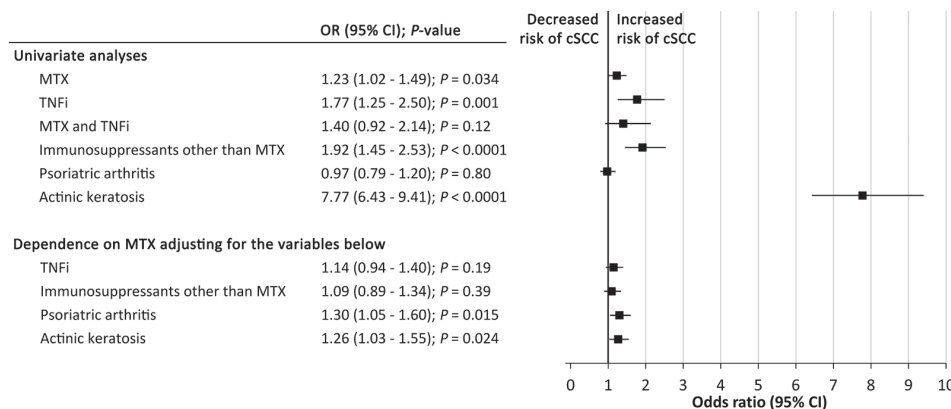


Fig. 1. Odds ratios. 95% CI: 95% confidence interval; cSCC: cutaneous squamous cell carcinoma *in situ*; MTX: methotrexate; OR: odds ratio; PsoA: psoriatic arthritis; TNFi: tumour necrosis factor α inhibitor.

Table II. Confounding analysis

	OR (95% CI) ^f	p-value
No adjustment	1.23 (1.02–1.49)	0.034
Comorbidities		
Alcohol-associated comorbidity	1.23 (1.02–1.49)	0.034
Crohn's disease	1.23 (1.02–1.49)	0.035
Diabetes	1.23 (1.02–1.49)	0.032
Liver disease	1.23 (1.02–1.49)	0.032
Peptic ulcer (gastric and duodenal ulcer)	1.23 (1.02–1.49)	0.034
Smoking-associated conditions	1.23 (1.02–1.49)	0.033
Actinic keratosis	1.26 (1.03–1.55)	0.024
Kidney-associated disease	1.23 (1.02–1.49)	0.033
Rheumatoid arthritis	1.24 (1.02–1.51)	0.034
Psoriatic arthritis	1.30 (1.05–1.60)	0.015
Drugs		
Acitretin	1.22 (1.00–1.47)	0.046
Ciclosporin	1.22 (1.01–1.48)	0.042
Azathioprine	1.23 (1.02–1.49)	0.033
Tumour necrosis factor α inhibitor	1.14 (0.94–1.40)	0.19
Interleukin pathway-inhibitor	1.24 (1.02–1.50)	0.031
Immunosuppressants excluding MTX ^a	1.09 (0.89–1.34)	0.39
Other variables		
Charlson comorbidity index ^b	1.24 (1.02–1.50)	0.031
Civic status ^c	1.23 (1.02–1.49)	0.034
Education ^d	1.23 (1.02–1.50)	0.031
Income ^e	1.25 (1.03–1.51)	0.025

The different drugs were defined as ever-exposure, implying ≥ 1 filled prescription(s) of the respective drug/drug class.

^aImmunosuppressive drugs other than methotrexate (MTX) were defined as a drug with ATC code starting with L04A other than L04AX03 (i.e. the Anatomical Therapeutic Chemical (ATC)-code for MTX). ^bCharlson Comorbidity Index (CCI): CCI 0, no comorbidity; CCI 1 low level of comorbidity; CCI 2+, moderate to severe level of comorbidity. ^cCivic status: married, unmarried or missing data. ^dEducational levels: low, compulsory school (<10 years); middle, upper secondary school (10–12 years); high, higher education (>12 years). ^eIncome quartiles are calculated using the source population (i.e. the psoriasis cohort consisting of 81,738 patients). ^fOdds ratios (ORs) represent ever-use of MTX associated with cutaneous squamous cell carcinoma adjusted for each potential confounder individually. CI: confidence interval.

Sensitivity analyses

Altering the lag periods had no impact for the main analysis (Table SII¹). When the case group was restricted to those patients with invasive cSCC ($n=309$) and their respective controls ($n=3,090$) previous associations were preserved (Tables SIII and SIV¹). In the final sensitivity analysis, the case and control group included patients who also could have had previous malignancies (other than

cSCC or cSCCis) prior to index date. For this separate investigation, a new risk set sampling was performed and this analysis included 878 cases (47.5% men) and 8,780 controls. The results of the primary and secondary analyses echoed in this separate investigation (Tables SV and SVI¹).

Post hoc analysis

In the *post hoc* analysis including patients without a history of actinic keratosis, 28.6% (92 of 322) and 22.5% (726 of 3,220) of cases and controls had any MTX use, which yielded a crude OR of 1.38 (95% CI 1.07–1.78; $p=0.014$). The results of the primary and secondary analyses were preserved in this analysis (Tables SVII and SVIII¹).

DISCUSSION

This Swedish nested case-control study, demonstrated an association between use of MTX among patients with psoriasis and cSCC. Moreover, a trend for a dose-response association was seen. However, the association was no longer significant when adjusting for ever-use of TNFis or immunosuppressants other than MTX.

The results from the current study may support the findings in the CIRT, which showed an enhanced risk of cSCC among patients exposed to MTX (10, 11). Even though this randomized and double-blinded prospective trial had optimal design to investigate whether MTX reduced the risk of cardiovascular events, it was not devised to detect differences in adverse events specifically skin cancer. Therefore, it is interesting that the authors were able to detect a significantly higher risk of cSCC among those patients randomized to MTX treatment compared with those randomized to placebo. While the results are important to the scientific community at large, it is essential to underline that no patients with inflammatory diseases were included in the CIRT. This raises the ques-

Table III. Methotrexate (MTX) doses among cases and controls and dose-response analysis

	Cases ($n=623$)	Controls ($n=6,230$)	OR (95% CI)	p-value
MTX exposure, n (%)				
Never	463 (74)	4,860 (78)	1 [Reference]	
Ever	160 (26)	1,370 (22)	1.23 (1.02–1.49)	0.034
MTX dose intervals (g), n (%)				
None	463 (74)	4,860 (78)	1 [Reference]	
(0, 2.5)	90 (14)	866 (14)	1.10 (0.86–1.39)	0.45
(2.5, 5)	41 (7)	307 (5)	1.40 (1.00–1.97)	0.049
(5, 7.5)	21 (3)	145 (2)	1.54 (0.96–2.47)	0.073
>7.5	8 (1)	52 (1)	1.64 (0.77–3.49)	0.20
Per oral MTX dose (g) ^a , median (range)*	1.75 (0.08,8.73) $n=147$	1.50 (0.08,13.58) $n=1,316$	1.06 (1.00–1.12) ^d	0.047
Subcutaneous MTX dose (g) ^b , median (range)*	1.02 (0.04,10.63) $n=33$	0.90 (0.01,12.15) $n=238$	1.09 (0.97–1.23) ^d	0.14
Total MTX dose (g) ^c , median (range)*	2.06 (0.04,10.63) $n=160$	1.73 (0.01,13.58) $n=1,370$	1.06 (1.01–1.12) ^d	0.014

Filled prescriptions of MTX was available in the period July 2005 to 2016. The accumulated MTX doses was calculated up to the index date, which was in the period 2010 to 2016.

^aThe oral MTX doses are the accumulated doses of oral MTX among cases and controls. For this specific odds ratio (OR), conditional logistic regression controlling for the subcutaneous dose was used. ^bThe subcutaneous MTX doses are the accumulated doses of subcutaneous MTX among cases and controls. For this specific OR, conditional logistic regression controlling for the oral dose was used. ^cConditional logistic regression was used with only the total dose as the independent variable. ^dORs indicating the increase in risk of cutaneous squamous cell carcinoma per 1 g increment in MTX dose.

*Dose among exposed.

95% CI: 95% confidence interval.

Table IV. Ever-use of drugs and drug classes among cases and controls

	Cases (n = 623) n (%)	Controls (n = 6,230) n (%)	OR (95% CI) ^b	p-value
Ever-exposure to:				
Immunosuppressants other than MTX ^a	66 (10.6)	367 (5.9)	1.92 (1.45–2.53)	<0.0001
Ciclosporin	9 (1.4)	68 (1.1)	1.33 (0.66–2.67)	0.43
Acitretin	56 (9.0)	467 (7.5)	1.22 (0.91–1.63)	0.18
Azathioprine	10 (1.6)	50 (0.8)	2.01 (1.02–3.96)	0.045
TNFi	41 (6.6)	241 (3.9)	1.77 (1.25–2.50)	0.001
ILi	2 (0.3)	25 (0.4)	1.25 (0.31–10.9)	1

^aImmunosuppressive drugs other than methotrexate (MTX) were defined as a drug with Anatomical Therapeutic Chemical code starting with L04A other than L04AX03 (i.e. the ATC-code for MTX).

^bUnadjusted crude odds ratios (ORs).

CI: confidence interval; ILi: interleukin pathway-inhibitor; TNFi: tumour necrosis factor α inhibitor.

tion as to whether the results are generalizable to patients in whom MTX is used clinically (15). Furthermore, the accumulated doses for the case group were not presented in the CIRT and the study mainly included men (81.7%), compared with the current investigation, in which the sex distribution was equal (47.8% men). Moreover, the patients included were younger at inclusion compared with our investigation (median age 65.7 vs 73.7 years). The present study had a median follow-up time of 5.6 years. While this can be considered short, in the CIRT an increased risk of cSCC was observed within a median time of less than 2 years (23 months).

To address the results from the recent systematic review and meta-analysis by Vaengebjerg et al. (9), the current study adjusted for PsoA in the primary analysis. Adjustment for PsoA did not influence the OR of cSCC with respect to MTX. The association between MTX and cSCC was no longer statistically significant when the analysis was adjusted for use of TNFis. Previous studies show conflicting results on the impact of biologic agents on incident cSCC. In a Swedish cohort investigation consisting of patients with RA (n = 12,558), use of TNFis was associated with an increased risk of cSCC (including cSCCis) compared with biologics-naïve patients (adjusted HR 1.43, 95% CI 1.22–1.69) (16). In the meta-analysis by Vaengebjerg et al. (9), including 13 investigations, biologic agents did not increase the risk of keratinocyte carcinoma compared with treatment with conventional therapies in patients with psoriasis (RR 0.91, 95% CI 0.64–1.30).

In the case definition for the primary and secondary analyses, the current study included cSCCis. Experienced dermatologists can often identify these lesions clinically and therefore these tumours are not always sent for pathology report. Therefore, it is expected that the number of cSCCis is underestimated in both groups. Moreover, among patients with psoriasis, it may be challenging to distinguish cSCCis from psoriasis plaques. In this context it is also worth mentioning that patients treated with MTX might have clearer skin, which, intrinsically, may facilitate detection of cSCC. Using that line of argument, MTX use *per se* could result in detection bias and possibly an exaggerated OR. Nonetheless, our results were

robust when we only restricted the case group to those with invasive cSCC, which are typically more conspicuous lesions and thus more easily detected both by the patient and physician, regardless of the presence or absence of psoriatic plaques. Allowing any prevalent cancer, other than cSCC, prior to the index date among cases and controls did not impact the results.

This investigation has some limitations.

Due to the retrospective design, important risk factors for cSCC including detailed data on sun exposure and UV radiation could not be obtained. Light therapies, including narrow-band UVB (nbUVB) and psoralen plus UVA, both of which have been associated with an enhanced risk of cSCC, in both American and European investigations (17–20), are not included in the Swedish healthcare registries. Nevertheless, in a Swedish cross-sectional investigation, the skin cancer risk of patients with psoriasis treated with nbUVB was not higher than the general population (21). While there is only a limited number of investigations conducted, nbUVB therapy for patients with psoriasis does not seem to increase the risk of cSCC (22–25). Having said that, confounding by UV-radiation, both due to lifestyle factors and light therapy, cannot be excluded. The presence of actinic keratosis is generally considered as an indicator of chronically sun-damaged skin and, hence, cumulative sun exposure. In a recent Swedish cohort investigation including 2,983 patients with actinic keratosis and 14,668 age- and sex-matched patients without such a disease, a HR of 7.7 (95% CI 6.7–8.8) for cSCC was observed (26). In a *post hoc* analysis, we examined whether the findings persisted after excluding patients with actinic keratosis. The findings from this separate analysis were in line with the primary and secondary analyses, indicating that confounding due to UV exposure may be limited. Of note, since BCC is not included in the Swedish cancer registry, it was not included in our analysis. Therefore, future investigations including both cSCC and BCC are encouraged.

All data in the Swedish registers are prospectively added. Consequently, we acknowledge that other study designs addressing this specific question could have been chosen. An alternative approach would be the active comparator design (i.e. patients with psoriasis who fill prescriptions of MTX could be compared with those who receive another systemic treatment, such as ciclosporin, TNFis or acitretin). This design would allow comparison of different drugs and would position MTX to other drugs with respect to the risk of cSCC. On the other hand, in Sweden, ciclosporin is rarely selected as an anti-psoriatic treatment, and patients dispensed with biological treatments in Sweden most often have a history of MTX use, making it difficult to exclude an additive effect. Finally, since acitretin might lower the risk of

cSCC (27, 28), the active comparator design would also have intrinsic weaknesses.

Strengths of this investigation are that it includes cSCCs, which is infrequently included in observational investigations. Since inclusion of *in situ* carcinomas in national cancer registries is a rare event, it is important to underline that the results were robust when only considering those patients with invasive cSCC as cases. Moreover, the study is conducted within a cohort of patients with psoriasis, which minimizes the risk of confounding by indication. Furthermore, dermatological follow-up for patients with psoriasis includes a total-body examination, meaning that the risk of surveillance bias is diminished. However, even after nesting the cohort in patients with psoriasis, we observed that cases had more visits to a dermatology clinic, visits related to psoriasis and outpatient visits compared with controls. Thus, arguably the cases most likely had higher disease severity and were examined more frequently than controls.

In conclusion, while the results of the current study suggest an increased risk of cSCC associated with use of MTX among patients with psoriasis in a dose-response pattern, it is important to underline that, when the current analysis was adjusted for TNFis or other immunosuppressants, the association was no longer significant. Thus, the key message to practicing dermatologists is that the slightly increased risk of cSCC associated with MTX may be due to confounding by disease severity, other anti-psoriatic treatments, and UV exposure. While a theoretical increase in risk cannot be excluded, it is probably not significant for the dermatologist in everyday clinical practice.

The authors have no conflicts of interest to declare.

REFERENCES

- Grosse Y, Baan R, Straif K, Secretan B, El Ghissassi F, Bouvard V, et al. A review of human carcinogens – Part A: pharmaceuticals. *Lancet Oncol* 2009; 10: 13–14.
- Kalish RE, Strober B, Weinstein G, Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. *J Am Acad Dermatol* 2009; 60: 824–837.
- Lange E, Blizzard L, Venn A, Francis H, Jones G. Disease-modifying anti-rheumatic drugs and non-melanoma skin cancer in inflammatory arthritis patients: a retrospective cohort study. *Rheumatology (Oxford)* 2016; 55: 1594–1600.
- Scott FI, Mamtani R, Brensinger CM, Haynes K, Chiesa-Fuxench ZC, Zhang J, et al. Risk of nonmelanoma skin cancer associated with the use of immunosuppressant and biologic agents in patients with a history of autoimmune disease and nonmelanoma skin cancer. *JAMA Dermatol* 2016; 152: 164–172.
- deShazo R, Soltani-Arabshahi R, Krishnasamy S, Langley RG, Kalia S, Stahle M, et al. Non-melanoma skin cancer risk among patients in the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *J Drugs Dermatol* 2019; 18: 1059–1060.
- Boffetta P, Gridley G, Lindelof B. Cancer risk in a population-based cohort of patients hospitalized for psoriasis in Sweden. *J Invest Dermatol* 2001; 117: 1531–1537.
- Ji J, Shu X, Sundquist K, Sundquist J, Hemminki K. Cancer risk in hospitalised psoriasis patients: a follow-up study in Sweden. *Br J Cancer* 2009; 100: 1499–1502.
- Trafford AM, Parisi R, Kontopantelis E, Griffiths CEM, Ashcroft DM. Association of psoriasis with the risk of developing or dying of cancer: a systematic review and meta-analysis. *JAMA Dermatol* 2019; 155: 1390–1403.
- Vaengebjerg S, Skov L, Egeberg A, Loft ND. Prevalence, incidence, and risk of cancer in patients with psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *JAMA Dermatol* 2020; 156: 421–429.
- Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, et al. Low-dose methotrexate for the prevention of atherosclerotic events. *N Engl J Med* 2019; 380: 752–762.
- Solomon DH, Glynn RJ, Karlson EW, Lu F, Corrigan C, Colls J, et al. Adverse effects of low-dose methotrexate: a randomized trial. *Ann Intern Med* 2020; 172: 369–380.
- Polesie S, Gillstedt M, Paoli J, Osmancevic A. Methotrexate treatment for patients with psoriasis and risk of cutaneous melanoma: a nested case-control study. *Br J Dermatol* 2020; 183: 684–691.
- Rothman KJ, Greenland S, Lash TL. *Modern epidemiology*. Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia, PA, US, 2008.
- Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373–383.
- Bykerk VP. A Call to Systematically monitor for adverse events in users of low-dose methotrexate therapy. *Ann Intern Med* 2020; 172: 425–426.
- Raaschou P, Simard JF, Asker Hagelberg C, Askling J. Rheumatoid arthritis, anti-tumour necrosis factor treatment, and risk of squamous cell and basal cell skin cancer: cohort study based on nationwide prospectively recorded data from Sweden. *BMJ* 2016; 352: i262.
- Archier E, Devaux S, Castela E, Gallini A, Aubin F, Le Maitre M, et al. Carcinogenic risks of psoralen UV-A therapy and narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. *J Eur Acad Dermatol Venereol* 2012; 26: 22–31.
- Lim JL, Stern RS. High levels of ultraviolet B exposure increase the risk of non-melanoma skin cancer in psoralen and ultraviolet A-treated patients. *J Invest Dermatol* 2005; 124: 505–513.
- Lindelof B, Sigurgeirsson B, Tegner E, Larko O, Johannesson A, Berne B, et al. PUVA and cancer risk: the Swedish follow-up study. *Br J Dermatol* 1999; 141: 108–112.
- Stern RS. The risk of squamous cell and basal cell cancer associated with psoralen and ultraviolet A therapy: a 30-year prospective study. *J Am Acad Dermatol* 2012; 66: 553–562.
- Osmancevic A, Gillstedt M, Wennberg AM, Larko O. The risk of skin cancer in psoriasis patients treated with UVB therapy. *Acta Derm Venereol* 2014; 94: 425–430.
- Black RJ, Gavin AT. Photocarcinogenic risk of narrowband ultraviolet B (TL-01) phototherapy: early follow-up data. *Br J Dermatol* 2006; 154: 566–567.
- Hearn RM, Kerr AC, Rahim KF, Ferguson J, Dawe RS. Incidence of skin cancers in 3867 patients treated with narrow-band ultraviolet B phototherapy. *Br J Dermatol* 2008; 159: 931–935.
- Man I, Crombie IK, Dawe RS, Ibbotson SH, Ferguson J. The photocarcinogenic risk of narrowband UVB (TL-01) phototherapy: early follow-up data. *Br J Dermatol* 2005; 152: 755–757.
- Weischer M, Blum A, Eberhard F, Rocken M, Berneburg M. No evidence for increased skin cancer risk in psoriasis patients treated with broadband or narrowband UVB phototherapy: a first retrospective study. *Acta Derm Venereol* 2004; 84: 370–374.
- Georgis G, Anderson CD, Lyth J, Falk M. Actinic keratosis diagnosis and increased risk of developing skin cancer: a 10-year cohort study of 17,651 patients in Sweden. *Acta Derm Venereol* 2020; 100: adv00128.
- George R, Weightman W, Russ GR, Bannister KM, Mathew TH. Acitretin for chemoprevention of non-melanoma skin cancers in renal transplant recipients. *Australas J Dermatol* 2002; 43: 269–273.
- Harwood CA, Leedham-Green M, Leigh IM, Proby CM. Low-dose retinoids in the prevention of cutaneous squamous cell carcinomas in organ transplant recipients: a 16-year retrospective study. *Arch Dermatol* 2005; 141: 456–464.