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# Use of immunosuppression and subsequent cancer incidence: cohort study

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## ABSTRACT

**Objective** Evaluate the association between cancer incidence and immunosuppressive treatment in patients with ocular inflammatory disease (OID).

**Methods and analysis** We performed a retrospective cohort study of patients from 10 US OID subspecialty practices. Patients with non-infectious OID were included; HIV-infected patients were excluded. Time-dependent exposure to drug classes (ie, antimetabolites, calcineurin inhibitors, alkylating agents, tumour necrosis factor (TNF) inhibitors) and drugs were evaluated. Cancer incidence was ascertained by linkage to 12 state cancer registries from 1996 to 2015. Cancer incidence was analysed using Cox regression survival analysis, using 0-year, 3-year and 5-year lags after immunosuppression began.

**Results** The cancer incidence cohort comprised 10 872 individuals at risk of incident cancer and residing in one of the 12 states covered; 812 primary cancers were identified through cancer incidence tracing with median follow-up time of 10 years. Neither TNF inhibitor, antimetabolite, calcineurin inhibitor nor alkylating agent classes were associated with statistically significant increases in cancer incidence adjusting for covariates. We found statistically significant reduced hazards in the systemic inflammatory disease (SID)-including cohort for adalimumab and chlorambucil, increased hazards for tacrolimus and etanercept in the non-SID cohort and reduced hazards for methotrexate in both. Other immunosuppressive drugs were not associated with overall cancer incidence.

**Conclusions** We found no increased risk of overall or site-specific cancer incidence associated with short-term (non-transplant) therapy with most commonly used immunosuppressive drug classes and many specific drugs. Further research may clarify potentially protective or harmful effects of specific agents that were not consistently associated with reduced or increased cancer incidence.

**Trial registration number** NCT00116090.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Studies have shown conflicting evidence regarding whether the short-term use of immunosuppressive drugs is associated with subsequent cancer development; however, most of those studies have indications-for-treatment bias due to the participants being at risk for cancer because of the disease serving as the indication for immunosuppression.

⇒ This large cohort study examines the incidence of cancer among participants in an eye inflammation cohort, who would not otherwise be at risk for cancer development.

### WHAT THIS STUDY ADDS

⇒ In this retrospective cohort study of 10 872 patients with ocular immune-mediated diseases, there was no increased risk of overall or site-specific cancer incidence associated with the tumour necrosis factor inhibitor, antimetabolite, calcineurin inhibitor and alkylating agent immunosuppressive drug classes and specific drugs most commonly used for inflammatory disease indications.

## INTRODUCTION

Immunosuppressive drugs play a key role in preventing complications of inflammatory diseases while avoiding corticosteroid-induced side effects.[1–8] However, there has been ongoing concern that the use of these

**HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY**

⇒ The lack of increased cancer risk in association with short-term immunosuppression provides reassurance for the large number of patients who require such treatment to control inflammatory diseases.
⇒ Further study of the association between short-term immunosuppressive treatment with cancer incidence is needed for newer drugs.
⇒ Development of a national US Cancer Registry like the National Death Index would greatly advance the study of cancer.

treatments may lead to increased risk of cancer.[9] If even a modest increase in cancer risk were demonstrated, the indications for use of systemic immunosuppression for inflammatory diseases might change. Patients with non-infectious ocular inflammatory diseases (OID), eye-limited, immune-mediated diseases, often receive immunosuppressive treatment; however, they do not have the higher risks for cancer mortality[3 4] common among patients who receive immunosuppressive treatment for other reasons, such as rheumatological and transplant indications. Compared with transplant patients, who are on immunosuppressive therapy for life, patients treated for OID have short-term therapies. Therefore, the OID group is an ideal cohort in which to study the relationship between immunosuppressive therapy use and cancer. In the companion paper (Kempen *et al*[5]), the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study evaluated all eligible patients at academic ocular inflammation practices in the USA. Among the 15 938 subjects, the study found no evidence of increased overall or cancer mortality risk following treatment with the following classes of drugs: tumour necrosis factor (TNF) inhibitors, antimetabolites, T-cell inhibitors and alkylating agents.

However, it is also important to evaluate cancer incidence, as cancer is a significant event even if mortality does not result. Cancer incidence can be identified earlier and accurately due to mandated case reporting to state cancer registries, allowing a robust evaluation in relation to exposure. Here, we evaluated cancer incidence through linkage of SITE Cohort Study data from 10 US OID centres to state cancer registries, providing some of the best evidence to date regarding the safety of immunosuppressive drugs for patients with respect to cancer incidence. The objective of this analysis was to evaluate the incidence of any cancer and of putatively immunosuppression-related cancers after the relatively short-term immunosuppressive treatment given for immune-mediated disease compared with persons unexposed to immunosuppression among our cohort.

## METHODS

### Study cohort

The SITE Cohort Study methods have been described previously.[3 4] For this analysis, the study included all eligible patients seen at six academic ocular inflammation practices and four ancillary centres in the USA between 1 January 1996 and 31 December 2010. Eligible patients were those with non-infectious ocular inflammation: anterior, intermediate, posterior or panuveitis; scleritis; mucous membrane pemphigoid with ocular involvement or other OID. Patients were excluded for any of the following: infectious ocular inflammation, HIV infection or a known cancer diagnosis.

Data were abstracted using a protocol-driven method, including rigorous quality assurance checks.[3 4] Abstracted data included demographics, eye disease clinical characteristics, presence of systemic inflammatory diseases (SID) and medications used at every visit—including immunosuppressive drugs: antimetabolites (primarily methotrexate, azathioprine and mycophenolate mofetil), calcineurin inhibitors (ciclosporin and tacrolimus), alkylating agents (primarily cyclophosphamide and chlorambucil) and TNF inhibitors (primarily infliximab, adalimumab and etanercept).

### Cancer registry tracing

In the USA, cancer registry matching is handled at the state level. We identified states in which study patients lived and applied for permission to match the SITE cohort to the state registry for identification of primary incident cancer cases. Twelve states covered the home residence of 84% of subjects: California, Connecticut, Maryland, Massachusetts, New Jersey, New York, Ohio, Oregon, Pennsylvania, Rhode Island, Virginia and Washington. Because Alabama was not one of the states, the ancillary centre at the University of Alabama Birmingham was not included in the matching as in the mortality linkage. Each centre provided its Institutional Review Board (IRB) approval, investigator human subjects training certificates, protocol, and a signed data use agreement with the cancer registry application. The registries then reviewed and approved the multicentre matching procedures. The complicated process of obtaining approval and matching across the 12 state cancer registries required 5 years' effort, done from 2015 to 2020.

We used as our cancer incidence start date the first date at which all the registries considered their data to be robust, 1 January 1996, and requested all incident cancer cases from 1 January 1996, through 31 December 2015. Variables provided for matching were full name, social security number, date of birth, gender, race, address and place of birth. Registry linkages were done by registry personnel using LinkPlus (https://www.cdc.gov/cancer/npcr/tools/registryplus/lp.htm), a probabilistic linkage programme developed by the CDC, except for Maryland which used its own linkage programme. State cancer registries returned matches which met an agreed on threshold indicating a valid match.

### Statistical analysis

Person-time at risk was calculated from observations between 1 January 1996 and 31 December 2015, the last common date for cancer registry tracing among all state

registries. We counted person-time before exposure to any immunosuppressive drug as unexposed. Person-time following the first exposure to each drug or class of drugs was counted as exposed to the corresponding drug/drug class and was censored at the date of cancer diagnosis, date of death from the National Death Index or 31 December 2015. Patients who reported treatment by a specific drug/drug class were considered exposed from date of cohort entry. Patients who switched treatment were counted as exposed to each treatment drug/drug class. Because 53% of patients were treated with multiple immunosuppressants and individual drugs generally showed no association with increased cancer risk (see below), we made no attempt to examine the many potential combinations of specific drugs.

Descriptive statistics are presented as medians with IQR or count with per cent. There were almost no missing data on age, gender, the year treatment started, Charlson Comorbidity Index and whether inflammation was bilateral, so missingness was not modelled for these variables. Missing race and smoking data were explicitly coded and included as separate categories in the models. We analysed cancer incidence using Cox regression survival analysis, excluding patients with pre-existing cancer. Forward selection using the Wald $\chi^2$ statistic was used to select potential confounders among the covariates found in table 1 ($p \leq 0.05$) for each multiple regression analysis. Separate Cox regression models were generated for every class of immunosuppressants and for every individual immunosuppressant to control for confounding in evaluating the association of treatment exposure with cancer incidence. There were no substantive violations of the proportional hazards assumptions.

We performed all analyses including those with SIDs ('SID-including') and excluding patients with SIDs ('non-SID') to assess indications-for-treatment bias. Additional sensitivity analyses evaluated cumulative dosing, duration on treatment, maximum observed dose by quartile and 3-year and 5-year lags (excluding the first 3 or 5 years of follow-up time after first exposure).

### Additional statements

In this retrospective cohort study where data were obtained from pre-existing records, our IRBs did not

**Table 1** Cohort characteristics, excluding patients with systemic inflammatory diseases*

| Characteristics | Category | None | TNF inhibitors | Antimetabolites | Alkylating agents | Calcineurin inhibitors |
|---|---|---|---|---|---|---|
| Patients | Sum | 8607 | 1061 | 3454 | 469 | 995 |
| Age | Median (IQR) | 44.9 (32.2–56.7) | 36.9 (18.4–50.7) | 42.8 (26.1–55.1) | 49.3 (36.8–61.7) | 39.4 (25.2–52.2) |
| Gender | Male | 3050 (35.4%) | 354 (33.4%) | 1105 (32.0%) | 163 (34.8%) | 370 (37.2%) |
| | Female | 5557 (64.6%) | 707 (66.6%) | 2349 (68.0%) | 306 (65.2%) | 625 (62.8%) |
| Race | White | 5366 (62.3%) | 662 (62.4%) | 2162 (62.6%) | 329 (70.1%) | 647 (65.0%) |
| | Black/African-American | 1371 (15.9%) | 108 (10.2%) | 431 (12.5%) | 40 (8.5%) | 114 (11.5%) |
| | Hispanic | 351 (4.1%) | 63 (5.9%) | 177 (5.1%) | 29 (6.2%) | 62 (6.2%) |
| | Other | 485 (5.6%) | 55 (5.2%) | 184 (5.3%) | 18 (3.8%) | 61 (6.1%) |
| | Missing | 1034 (12.0%) | 173 (16.3%) | 500 (14.5%) | 53 (11.3%) | 111 (11.2%) |
| Year start | 1996–2000 | 2452 (28.5%) | 43 (4.1%) | 597 (17.3%) | 138 (29.4%) | 243 (24.4%) |
| | 2001–2005 | 2973 (34.5%) | 313 (29.5%) | 1257 (36.4%) | 178 (38.0%) | 373 (37.5%) |
| | 2006–2010 | 3166 (36.8%) | 696 (65.6%) | 1579 (45.7%) | 153 (32.6%) | 375 (37.7%) |
| | 2011+ | 16 (0.2%) | 9 (0.8%) | 21 (0.6%) | 0 (0%) | 4 (0.4%) |
| Smoking | Never | 5605 (65.1%) | 789 (74.4%) | 2421 (70.1%) | 308 (65.7%) | 680 (68.3%) |
| | Former | 1042 (12.1%) | 94 (8.9%) | 345 (10.0%) | 54 (11.5%) | 74 (7.4%) |
| | Current | 1401 (16.3%) | 125 (11.8%) | 497 (14.4%) | 85 (18.1%) | 144 (14.5%) |
| | Missing | 559 (6.5%) | 53 (5.0%) | 191 (5.5%) | 22 (4.7%) | 97 (9.7%) |
| Charlson Comorbidity Index score | 0 | 5260 (61.1%) | 350 (33.0%) | 1505 (43.6%) | 152 (32.4%) | 508 (51.1%) |
| | 1 | 2141 (24.9%) | 465 (43.9%) | 1200 (34.7%) | 154 (32.8%) | 288 (29.0%) |
| | 2 or more | 1201 (14.0%) | 245 (23.1%) | 749 (21.7%) | 163 (34.8%) | 198 (19.9%) |
| Bilateral ocular inflammation | Yes | 5600 (65.1%) | 859 (81.0%) | 2796 (80.9%) | 382 (81.4%) | 878 (88.2%) |

*Patients on multiple treatments contributed to more than one category.
TNF, tumour necrosis factor.

authorise contacting the participants, so patients were not personally involved in the study execution. Study Principal Investigator and author JHK 'affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained' (quoted from https://www.bmj.com/about-bmj/resources-authors/article-types, accessed on 18 October 2022). None of the funding organisations had any role in the conduct or reporting of the study. As per our study agreements at the outset of the study in 2004, we do not plan to share the data reported here. The other IRBs at each participating centre are included in the online supplemental roster.

## RESULTS

The cancer incidence cohort comprised 10 872 individuals (7853 in the non-SID group) who resided in one of the 12 states covered and who were alive and at risk of incident cancer between 1996 and 2015. Over 122 966 person-years, 812 primary cancers were identified through cancer incidence tracing. Overall, 28.0% of patients had a SID associated with their ocular inflammation (607 cancers were identified over 88 653 person-years in the non-SID group).

Table 1 shows patient characteristics by class of immunosuppressive treatment received. Patients on TNF inhibitors were the youngest, while those on alkylating agents were the oldest. The majority of patients were female, white and never smokers; >70% of patients had a Charlson Comorbidity Index score[10] of 1 or greater. The distribution of covariates was similar for the cohort with and without SIDs (online supplemental table 1); the count of those treated with TNF inhibitors (n=1061) and alkylating agents (n=469) was larger among SID-associated cases. Online supplemental table 2 shows the median dosage and dosing frequency by drug, which showed typical doses were used for the drugs of interest. Online supplemental table 3 includes the number of patients with each type of SID by treatment group.

Table 2 shows summary information for each drug class in the non-SID cohort. The median follow-up time for most classes was approximately 10 years except for TNF inhibitors, which was 7.5 years. There were 109 cancer events among 1945 patients who received antimetabolites. Median years on immunosuppressive therapy ranged from 0.54 years for corticosteroids to 1.47 years for antimetabolites.

The crude overall cancer incidence was 6.85 (95% CI 6.32 to 7.41) and 6.60 (95% CI 6.16 to 7.07) per 1000 person-years in the non-SID and SID-including analyses, respectively. Table 3 shows results by treatment exposure. Most adjusted HRs (aHRs) were <1 for immunosuppressant exposure in both non-SID and SID-including analyses. Overall, no immunosuppressant class (TNF inhibitor, antimetabolite, calcineurin inhibitor or alkylating agent) was associated with statistically significantly increases in cancer incidence; etanercept and tacrolimus had statistically significant elevations when excluding those with SID, but not including SID (figure 1). aHRs in the SID-including analysis tended to be lower than the non-SID analysis. For most drugs/drug classes, adjustment attenuated the unadjusted HR to near 1.0.

Overall and site-specific cancer incidence results are presented in table 3; results regarding specific a priori cancers of interest are given in table 4. In summary:

- *TNF inhibitors*: as shown in table 3, patients treated with TNF inhibitors had relatively few events with no statistically significant associations. TNF inhibitors had a lower hazard of cancer when including patients with SIDs (aHR 0.78 (95% CI 0.53 to 1.16)). Adalimumab was associated with a statistically significantly reduced aHR in the SID-including cohort (aHR 0.36 (95% CI 0.13 to 0.97)) but the aHR was not statistically significantly reduced in the non-SID cohort. Infliximab had no statistically significant aHRs <1.0. Etanercept had a statistically significantly increased aHR in the non-SID analysis (four events, aHR 2.90 (95% CI 1.07 to 7.84)), but in the SID-inclusive analysis the aHR was <1.0 (0.79 (95% CI 0.43 to 1.45)). As shown in table 4, there were very few events in

**Table 2** Follow-up, person-years and number of incident cases by drug class excluding patients with systemic inflammatory diseases

| Group | Number | Median years IMT (IQR) | Median years of incidence FU (IQR) | Person-years | Cancer events |
|---|---|---|---|---|---|
| Pre-IMT/No IMT* | 6756 | | 9.45 (5.64–13.67) | 63 261 | 414 |
| TNF inhibitors | 330 | 0.97 (0.43–2.16) | 7.48 (5.81–9.52) | 2635 | 17 |
| Antimetabolites | 1945 | 1.47 (0.59–2.97) | 9.68 (7.11–12.52) | 19 530 | 109 |
| Alkylating agents | 248 | 0.62 (0.32–1.26) | 9.91 (7.43–13.12) | 2483 | 27 |
| Calcineurin inhibitors | 668 | 1.11 (0.39–2.38) | 10.34 (7.37–13.68) | 7103 | 44 |
| Corticosteroids | 2413 | 0.54 (0.19–1.55) | 10.04 (7.28–13.84) | 25 526 | 165 |

*Person time for those never receiving or before the start of immunosuppressive therapy or corticosteroids.
FU, Follow-up; IMT, immunosuppressive therapy; TNF, tumour necrosis factor.

**Table 3** Incidence rates and HRs by drug and drug class for all cancers, excluding (first row) and *including (second row)* patients with systemic inflammatory diseases*

| Drug | Patients | Follow-up years | Cancer events | Crude incidence rate/1000 person-years | Unadjusted HR | Adjusted HR† |
|---|---|---|---|---|---|---|
| None | 6756 | 63 261 | 414 | 6.54 (5.94–7.21) | | |
| | *8607* | *78 472* | *514* | *6.55 (6.01–7.14)* | | |
| TNF inhibitor | 330 | *2635* | 17 | 6.45 (4.01–10.38) | 0.98 (0.60–1.59) | 1.28 (0.73–2.24) |
| | *1061* | *9084* | *38* | *4.18 (3.04–5.75)* | *0.64 (0.46–0.90)* | *0.78 (0.53–1.16)* |
| Adalimumab | 110 | 447 | 2 | 4.47 (1.12–17.87) | 0.74 (0.18–2.97) | 0.88 (0.22–3.54) |
| | *400* | *3014* | *7* | *2.32 (1.11–4.87)* | *0.36 (0.17–0.75)* | ***0.36 (0.13–0.97)*** |
| Etanercept | 37 | 342 | 4 | 11.69 (4.39–31.14) | 1.80 (0.67–4.81) | **2.90 (1.07–7.84)** |
| | *339* | *3204* | *15* | *4.68 (2.82–7.77)* | *0.72 (0.43–1.20)* | *0.79 (0.43–1.45)* |
| Infliximab | 231 | 1902 | 10 | 5.26 (2.83–9.77) | 0.80 (0.43–1.50) | 0.94 (0.44–2.00) |
| | 653 | *5552* | 22 | *3.96 (2.61–6.02)* | *0.61 (0.40–0.94)* | *0.74 (0.44–1.23)* |
| Antimetabolites | 1945 | 19 530 | 109 | 5.58 (4.63–6.73) | 0.86 (0.69–1.06) | 0.83 (0.65–1.05) |
| | *3454* | *34 842* | *181* | *5.19 (4.49–6.01)* | *0.80 (0.67–0.94)* | *0.83 (0.69–1.01)* |
| Azathioprine | 359 | 3764 | 23 | 6.11 (4.06–9.19) | 0.94 (0.61–1.42) | 0.94 (0.60–1.46) |
| | *629* | *6575* | *42* | *6.39 (4.72–8.64)* | *0.98 (0.71–1.34)* | *1.01 (0.73–1.41)* |
| Methotrexate | 1209 | 12 339 | 60 | 4.86 (3.78–6.26) | 0.75 (0.57–0.98) | 0.73 (0.53–1.002) |
| | *2429* | *24 752* | *113* | *4.57 (3.80–5.49)* | *0.70 (0.57–0.86)* | ***0.77 (0.61–0.98)*** |
| Mycophenolate mofetil | 936 | 8627 | 50 | 5.80 (4.39–7.65) | 0.89 (0.66–1.19) | 0.90 (0.66–1.24) |
| | *1364* | *12 663* | *66* | *5.21 (4.09–6.63)* | *0.80 (0.62–1.04)* | *0.85 (0.64–1.13)* |
| Alkylating agents | 248 | 2483 | 27 | 10.87 (7.46–15.85) | 1.67 (1.13–2.46) | 1.18 (0.78–1.78) |
| | *469* | *4823* | *46* | *9.54 (7.14–12.73)* | *1.46 (1.08–1.97)* | *1.18 (0.85–1.63)* |
| Cyclophosphamide | 190 | 1840 | 27 | 14.67 (10.06–21.40) | 2.25 (1.52–3.32) | 1.30 (0.86–1.96) |
| | *369* | *3687* | *45* | *12.21 (9.11–16.35)* | *1.87 (1.38–2.54)* | *1.28 (0.92–1.77)* |
| Chlorambucil | 76 | 814 | 0 | 0.00 (0.00–0.00) | 0.00 (0.00–0.36) | **0.00 (0.00–0.56)** |
| | *128* | *1423* | *1* | *0.70 (0.10–4.99)* | *0.11 (0.02–0.76)* | *0.18 (0.03–1.30)* |
| Calcineurin inhibitors | 668 | 7103 | 44 | 6.19 (4.61–8.32) | 0.95 (0.70–1.30) | 1.17 (0.83–1.65) |
| | *995* | *10 845* | *57* | *5.26 (4.05–6.81)* | *0.81 (0.61–1.06)* | *1.04 (0.77–1.42)* |
| Ciclosporin | 615 | 6629 | 39 | 5.88 (4.30–8.05) | 0.91 (0.65–1.26) | 1.13 (0.78–1.62) |
| | *920* | *10 158* | *52* | *5.12 (3.90–6.72)* | *0.79 (0.59–1.05)* | *1.04 (0.75–1.43)* |
| Tacrolimus | 31 | 256 | 5 | 19.51 (8.12–46.87) | 2.96 (1.23–7.16) | **3.03 (1.13–8.15)** |
| | *45* | *363* | *5* | *13.78 (5.73–33.10)* | *2.10 (0.87–5.08)* | *2.11 (0.79–5.67)* |
| Intravenous immunoglobulin | 46 | 399 | 6 | 15.05 (6.76–33.49) | 2.30 (1.03–5.15) | 1.41 (0.58–3.43) |
| | *83* | *819* | *8* | *9.77 (4.88–19.53)* | *1.49 (0.74–3.00)* | *1.04 (0.46–2.35)* |
| Corticosteroids | 2413 | 25 526 | 165 | 6.46 (5.55–7.53) | 0.98 (0.82–1.18) | 1.08 (0.88–1.31) |
| | 3815 | 40 494 | *239* | *5.90 (5.20–6.70)* | *0.90 (0.77–1.05)* | *0.93 (0.79–1.10)* |

*Italicised rows include patients with systemic disease. Bolded row headings represent classes of immunosuppressive drugs including those lists below without bolding.
†Model includes adjustment for age, sex, smoking and Charlson Comorbidity Index score. Statistically significant associations in this column are bolded (not adjusted for multiple comparisons).
TNF, tumour necrosis factor.

specific cancer categories of interest, with no statistically significant associations.

- *Antimetabolites*: as shown in table 3, among patients treated with antimetabolites, there were 109 and 181 cancer events excluding and including those with SID, respectively. All drug-specific HRs were near or below 1. The most commonly used immunosuppressant, methotrexate, was associated with a statistically significantly reduced aHR in the SID-including cohort (aHR 0.77 (95% CI 0.61 to 0.98), although the CI included

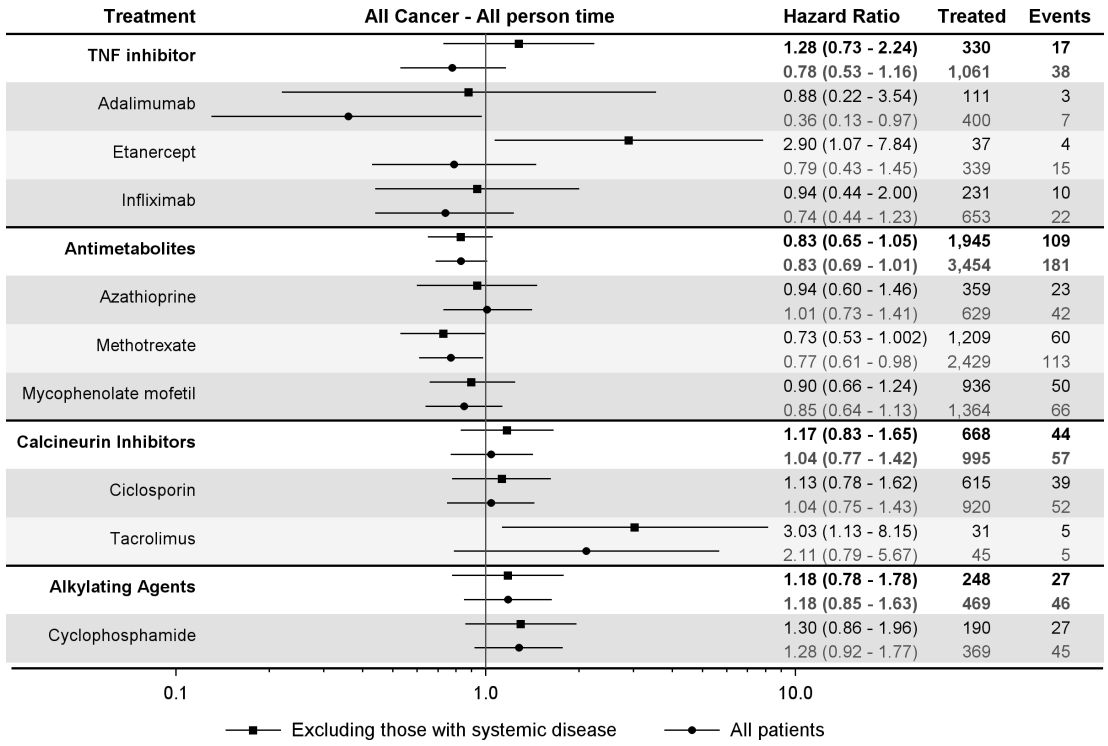


**Figure 1** Forest Plot of All Cancer Hazards, Including and Excluding Patients with Systemic Disease. TNF, tumour necrosis factor.

1 in the non-SID cohort (aHR 0.73 (95% CI 0.53 to 1.00)). As shown in table 4, cause-specific cancer HRs were similar, except for squamous cell cancers which had no statistically significantly elevated aHRs (7 events, aHR 1.34 (95% CI 0.52 to 3.46) and 13 events, aHR 1.40 (95% CI 0.66 to 2.97), respectively). None of the cause-specific aHRs were statistically significant.

- *Alkylating agents*: as shown in table 3, all cause and cause-specific crude HRs were elevated for the (older) alkylating agent-treated patients, but adjustment attenuated the aHRs, none of which were statistically significant. There was only one event among patients with SID treated with chlorambucil and none in patients without SID. As shown in table 4, among specific cancers of interest, bladder cancer (aHR 3.21 (95% CI 0.64 to 16.0)) and squamous cell cancers (aHR 2.75 (95% CI 0.76 to 9.95)) tended to be higher, but not statistically significantly associated.
- *Calcineurin inhibitors*: as shown in table 3, there were 44 and 57 events among those without and with SID, respectively, in those treated with calcineurin inhibitors, resulting in aHRs near 1. Most person-time and events were for patients treated with ciclosporin (39 events, aHR 1.13 (95% CI 0.78 to 1.62) and 52 events, aHR 1.04 (95% CI 0.75 to 1.43), respectively). The aHR for tacrolimus was statistically significantly elevated in both non-SID unadjusted and adjusted models based on five events (aHR 3.03 (95% CI 1.13 to 8.15) with no statistically significant association in the SID-including cohort (aHR 2.11 (95% CI 0.79 to 5.67)). As shown in table 4, while there were only three bladder cancer events, the aHRs were statistically significantly elevated among patients without and with SID (HR 4.58 (95% CI 1.15 to 18.21); HR 4.31 (95% CI 1.12 to 16.49), respectively). aHRs for haematological cancers and melanoma were not statistically significantly elevated. The aHR for squamous cell cancers was not statistically significantly elevated in patients with SID based on three events.

In our sensitivity analyses evaluating quartiles of maximum dose, cumulative time on a treatment and 3-year and 5-year lags after exposure, we found similar measures of association to those shown in tables 3 and 4. There was no pattern of increased risk withincreased exposure (within the relatively short overall duration of treatment used for non-transplant indications (data not shown)).

## DISCUSSION

This analysis of cancer incidence risk among a large cohort of patients treated with relatively short-term immunosuppressive for OID found no evidence of excess risk by drug treatment or type of cancer for the most commonly used immunosuppressant classes and for most individual drugs. Median time on treatment during the study was approximately 1 year for each drug/drug class. While we did not find clear associations with higher dose or longer duration of our cohort's relatively short-term therapy, these results do not apply to lifelong (eg, transplant) immunosuppressive therapy. The lack of increased risk for most drugs/drug classes in our cohort

Table 4 Cancer incidence results among treatment-exposed patients (compared with unexposed patients) by type of cancer excluding and including patients with systemic disease

| | Excluding systemic disease | | | Including systemic disease | | |
|---|---|---|---|---|---|---|
| Type of cancer | Events | Unadjusted HR | Adjusted HR* | Events | Unadjusted HR | Adjusted HR* |
| TNF inhibitor | n=330 | | | n=1061 | | |
| All | 17 | 0.98 (0.60 to 1.59) | 1.28 (0.73 to 2.24) | 38 | 0.64 (0.46 to 0.90) | 0.78 (0.53 to 1.16) |
| Bladder | 0 | 0.00 (0.00 to 4.97) | 0.00 (0.00 to 13.43) | 0 | 0.00 (0.00 to 1.52) | 0.00 (0.00 to 3.61) |
| Haematological | 3 | 1.18 (0.37 to 3.79) | 0.76 (0.10 to 5.60) | 3 | 0.33 (0.10 to 1.05) | 0.20 (0.03 to 1.46) |
| Melanoma | 0 | 0.00 (0.00 to 2.32) | 0.00 (0.00 to 3.25) | 3 | 1.16 (0.34 to 3.90) | 0.52 (0.07 to 4.08) |
| Squamous cell | 0 | 0.00 (0.00 to 2.71) | 0.00 (0.00 to 4.87) | 2 | 0.82 (0.19 to 3.51) | 1.14 (0.25 to 5.18) |
| Antimetabolites | n=1945 | | | n=3454 | | |
| All | 109 | 0.86 (0.69 to 1.06) | 0.83 (0.65 to 1.05) | 181 | 0.80 (0.67 to 0.94) | 0.83 (0.69 to 1.01) |
| Bladder | 3 | 0.88 (0.24 to 3.15) | 1.09 (0.29 to 4.15) | 4 | 0.72 (0.23 to 2.20) | 1.01 (0.31 to 3.25) |
| Haematological | 14 | 0.79 (0.44 to 1.41) | 0.76 (0.39 to 1.47) | 21 | 0.62 (0.38 to 1.00) | 0.71 (0.42 to 1.21) |
| Melanoma | 6 | 0.94 (0.38 to 2.35) | 0.77 (0.25 to 2.34) | 9 | 0.90 (0.42 to 1.95) | 0.75 (0.29 to 1.94) |
| Squamous cell | 7 | 1.23 (0.52 to 2.93) | 1.34 (0.52 to 3.46) | 13 | 1.30 (0.66 to 2.56) | 1.40 (0.66 to 2.97) |
| Alkylating agents | n=248 | | | n=469 | | |
| All | 27 | 1.67 (1.13 to 2.46) | 1.18 (0.78 to 1.78) | 46 | 1.46 (1.08 to 1.97) | 1.18 (0.85 to 1.63) |
| Bladder | 2 | 4.71 (1.04 to 21.25) | 3.21 (0.64 to 16.01) | 3 | 3.87 (1.10 to 13.60) | 3.68 (0.96 to 14.03) |
| Haematological | 4 | 1.76 (0.64 to 4.86) | 1.20 (0.43 to 3.38) | 11 | 2.34 (1.24 to 4.39) | 1.78 (0.90 to 3.52) |
| Melanoma | 2 | 2.43 (0.57 to 10.37) | 0.95 (0.12 to 7.35) | 2 | 1.42 (0.34 to 6.04) | 0.66 (0.09 to 5.03) |
| Squamous cell | 3 | 3.98 (1.18 to 13.42) | 2.75 (0.76 to 9.95) | 4 | 2.73 (0.95 to 7.87) | 2.27 (0.74 to 6.91) |
| Calcineurin inhibitors | n=668 | | | n=995 | | |
| All | 44 | 0.95 (0.70 to 1.30) | 1.17 (0.83 to 1.65) | 57 | 0.81 (0.61 to 1.06) | 1.04 (0.77 to 1.42) |
| Bladder | 3 | 2.39 (0.67 to 8.58) | 4.58 (1.15 to 18.21) | 3 | 1.67 (0.48 to 5.86) | **4.31 (1.12 to 16.49)** |
| Haematological | 7 | 1.09 (0.50 to 2.39) | 1.46 (0.62 to 3.44) | 9 | 0.86 (0.43 to 1.71) | 1.12 (0.51 to 2.47) |
| Melanoma | 3 | 1.28 (0.38 to 4.29) | 1.85 (0.53 to 6.48) | 5 | 1.58 (0.60 to 4.17) | 2.35 (0.85 to 6.53) |
| Squamous cell | 1 | 0.46 (0.06 to 3.46) | 0.72 (0.09 to 5.52) | 3 | 0.92 (0.28 to 3.05) | 1.45 (0.42 to 5.00) |

Bold value signifies p<0.05.
*Model includes adjustment for age, sex, smoking and Charlson Comorbidity Index score.
TNF, tumour necrosis factor.

might reflect a reversal of risk after immune suppression therapy ends, which has been shown among transplant patients.[11] However, in contrast to that study, few of the cancers identified in this study were considered to be infectious in origin.

Median follow-up time after exposure was approximately 10 years for all drug groups examined except TNF inhibitors (7 years), which likely was adequate for most but not all events. The HRs for alkylating agents, and cyclophosphamide in particular—both with an older population distribution—were statistically significant in unadjusted models, but models adjusted for age, sex, smoking and Charlson Comorbidity Index led to not statistically significant HRs of 1.07 and 1.18, respectively, suggesting the higher crude incidence related mostly to differences in age and other factors. Chlorambucil only had one cancer event; however, we know from our analysis of mortality in the same cohort that there were four cancer deaths among those treated with chlorambucil in our cohort (Kempen *et al*, 2022) that were not included as incident cases in our cancer incidence analysis which had a smaller range of dates at risk.

Antimetabolites as a class were not associated with higher cancer incidence. In fact, the popular and commonly used immunosuppressant, methotrexate, was associated with lower cancer incidence in the SID cohort and the non-SID cohort, the latter at the threshold of non-significance. These observations make it very unlikely that the incidence of overall cancer is increased by methotrexate, azathioprine or mycophenolate mofetil therapy in a setting such as this one, which includes a wide range of inflammatory disease treatment settings but is not a transplant setting. These findings mostly align with a large case-control study examining autoimmune diseases.[12] We

found a similar lack of associations for methotrexate and mycophenolate mofetil, but did not find an increased risk with azathioprine as noted by Ertz-Archambault *et al*.

Our results also support safety for the most commonly used TNF inhibitors for all cancers or specific subtypes of cancer potentially associated with immunosuppression, with no evidence of increased risk for adalimumab and infliximab. Etanercept was associated softly with increased cancer incidence in the non-SID cohort (based on 4 cases over 342 person-years, with multiple comparisons conducted) but lower aHRs in the SID-inclusive cohort based on nearly 10-fold more person-time, suggesting the first observation might be a random association. Similar results were observed in our analysis about overall and cancer mortality (Kempen *et al*, 2022). These results also are consistent with those from a large population-based cohort study of patients with inflammatory bowel disease, rheumatoid arthritis or psoriasis treated with TNF inhibitors, which found an HR of 0.82 when comparing the TNF inhibitor treatment group with a control group.[13] These observations combined make a strong case that the popular TNF inhibitors adalimumab and infliximab do not increase the risk of cancer to a degree that would constrain clinical use for short-term (non-transplant) indications.

Calcineurin inhibitors, and tacrolimus specifically, have been implicated in the development of solid tumour cancers.[14] However, in vitro evidence has also been found that tacrolimus may inhibit urothelial tumourigenesis.[15] We did not find an increase in the incidence of overall cancers with ciclosporin. We did find a statistically significantly elevated all cancer HR for tacrolimus based on five events and for bladder cancer among all calcineurin inhibitors based on three events, consistent with prior information.[14] Considering the limited number of cases and person-time for these specific cancers, further research is warranted. While HRs for other specific types of cancers (haematological, melanoma and squamous cell) were slightly elevated, none were statistically significant and were based on small numbers of events.

While this study had numerous strengths, it also had some limitations. Cancer incidence studies in the USA remain exceptionally difficult. Each state has its own registry with its own procedures for approval and linkage. However, state cancer registry accuracy and completeness have improved dramatically in the past 20 years.[16] Each state cancer registry involved in linkages in this study has achieved Gold status from the North American Association of Central Cancer Registries, except Massachusetts, which has achieved Silver status (https://www.naaccr.org/certified-registries/). Gold status indicates that registries have 95% case ascertainment and are 100% error-free in variables used to develop cancer incidence statistics (data variables used to create incidence statistics by cancer type, sex, race, age and county) while silver status indicates 90% completeness and 97% error-free records for those variables. Additionally, the LinkPlus software has been extensively validated by the Centers for Disease Control and Prevention for vital statistics linkages. This multicentre, multistate cohort required thousands of hours to obtain permissions from state cancer registries and state IRBs over a period of 5 years. Registry staffs are small, and the process can take months to years due to lack of resources. Our study was limited to the approximately 84% of cohort members covered by the 12 registries accessed so as to avoid including cohort members not 'at risk'. We were unable to perform linkages in some states due to excessive fees for the matching, temporary closure of the registry to research or due to restrictions with data sharing that precluded linkage. A national cancer registry similar to the National Death Index would overcome these difficulties and would be a valuable epidemiological resource making it more feasible to assess cancer risk in clinical cohorts, such as providing long-term follow-up of clinical trial cohorts to assure safety of new drugs (among other applications).

Absolute risk of cancer is probably somewhat underestimated in our study because people may have moved out of state; however, loss of events in these patients is likely to be distributed approximately evenly across exposure groups (non-differential misclassification), so is unlikely to have qualitatively altered our immunosuppression association results. In addition, despite the large cohort size, there were small numbers of cancer incidence events for some specific drugs and drug classes, as well as for specific types of cancer. Findings should be interpreted with caution until replicated with a larger number of events. This cohort provided a unique opportunity to evaluate associations in patients whose immunosuppression use is often short/limited. This is a strength but may also be construed as a weakness. We did not assess competing risks in this analysis. However, the risk of mortality is relatively low in this younger cohort. A minority of deaths were from cancer, and, therefore, it is unlikely that losses to mortality would differentially affect the HRs of primary interest. Data were abstracted from electronic health records and data on comorbidities, in particular, may underestimate those conditions. However, we do not anticipate that would be unbalanced between the groups. Because this was a retrospective study using existing records, we did not have patient or public input into the study design.

Our analysis included all patients ever treated with a drug/drug class, allowing patients to be counted in more than one treatment exposure group. However, within the group excluding those with systemic disease, 67% of our cancer events were only on one treatment class. It is unlikely that interactions between drugs are carcinogenic when individual drugs are unassociated with overall cancer risk. Immunosuppressants were taken when indicated and patterns of prescribing were by best medical judgement, generally following a consensus statement led by several of the SITE clinic founders.[17] It is unlikely that differences in healthcare utilisation affected the likelihood of outcome detection through registries. The patients in the cohort accessed tertiary care, so may have had similar utilisation.

In summary, our results suggest that the overall risk of cancer is not increased over a median period of approximately 10 years after relatively short-term (compared with the transplant scenario) exposure to TNF inhibitors, antimetabolites, ciclosporin and cyclophosphamide, providing reassuring news for the large number of patients who require such treatments to control inflammatory disease to avoid inflammatory death, disability and/or other complications. Within this relatively short-term treatment period, dose and duration of therapy were not associated with increased, although they are associated with increased risk in lifelong (transplant) therapy. This cohort consists of patients for whom it was unlikely that the indication for treatment was associated with the cancer incidence outcome, in contrast to most SID cohorts, providing an extra layer of reassurance. While these results cover a large amount of the period in which cancer incidence is likely to have occurred, long-term study would be reassuring, especially if a national cancer registry became available. Further study of newer TNF inhibitors, biosimilars, and the small molecule immunosuppressants, tacrolimus and chlorambucil, is needed because our study was limited for evaluating their effects on cancer.

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