Risk of Cancer in Patients with Psoriasis on Biological Therapies: A Systematic Review

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Risk of Cancer in Patients with Psoriasis on Biologic Therapies: A Systematic Review

Running head: Cancer Risk with Biologic Drugs for Psoriasis

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Conflict of Interest:

KJM received honoraria from Eli Lilly and Janssen. CHS received departmental research funding from Pfizer, Abbvie, Janssen, Novartis. CHS is PI on MRC funded stratified medicine consortium which has a number of industry partners (www.PSORT.org.uk). The other authors state no conflict of interest.

What's already known about this topic?

- The risk of cancer in biologic-exposed psoriasis patients is poorly understood. While the risk is reasonably well-characterized in other chronic autoimmune conditions, these findings cannot be extrapolated to psoriasis patients.

What does this study add?

- This systematic review summarizes the current literature for cancer risk in biologic-exposed psoriasis patients. Signals are emerging that exposure to tumor necrosis factor inhibitors is associated with an increased risk of non-melanoma skin cancers in people with psoriasis, but comparator groups identified were historic and studies lack adjustment for highly relevant confounding factors such as prior phototherapy. Long-term pharmacovigilance is still required to establish whether there is a risk of cancer directly attributable to biologic therapy.

Summary

Biologic therapies are highly effective in psoriasis, but have profound effects on innate and adaptive immune pathways that may negatively impact on cancer immunosurveillance mechanisms. To investigate the risk of cancer in psoriasis patients treated with biologic therapy we searched Medline, Embase, and the Cochrane Library (up to August 2016) for randomized control trials, prospective cohort studies and systematic reviews that reported

cancer incidence in people exposed to biologic therapy for psoriasis compared to a control population. Eight prospective cohort studies met our inclusion criteria. All the evidence reviewed related to tumour necrosis factor inhibitors (TNFi) with the exception of one study on ustekinumab. An increased risk of non-melanoma skin cancer (NMSC), particularly squamous cell carcinoma, was reported with TNFi compared to both a general United States population and a rheumatoid arthritis population treated with TNFi. No evidence for increased risk of cancers (reported as all cancers, lymphoma, melanoma, prostate, colorectal and breast cancer) other than NMSC was identified. There were important limitations to the studies identified including choice of comparator arms, inadequate adjustment for confounding factors and failure to account for latency periods of cancer. There remains a need for ongoing pharmacovigilance in relation to cancer risk and biologic therapy; to determine whether the NMSC signal is specifically attributable to TNFi, further investigation is required using prospectively-collected data with adjustment for known NMSC risk factors.
Systematic review registration number: PROSPERO; 2015:CRD42015017538

Introduction

Biologic agents licensed for the use in psoriasis include tumour necrosis factor inhibitors (TNFi; etanercept, infliximab, and adalimumab), and antagonists of the interleukin (IL)-17 pathway (ustekinumab, secukinumab and ixekizumab) (1). Real-world data accumulated from pharmacovigilance registries show these agents to be generally well-tolerated and effective in clinical practice (2-5). However, biologic therapies have profound effects on innate and adaptive immune pathways that may be relevant to cancer immunosurveillance mechanisms, with the TNFi in particular targeting an established major cytokine in cancer pathways (6).

Prospective cohort studies in other immune-mediated inflammatory diseases (e.g. rheumatoid arthritis (7, 8) and psoriatic arthritis (9)) provide some reassurance regarding risk of cancer following treatment with biologics although these findings may not be generalizable to psoriasis. Increased rates of cancer including non-melanoma skin cancers (NMSC), lymphoma, and colorectal cancers have been reported in psoriasis per se (10) and so establishing risk specifically attributable to biologic therapies is not straightforward. 'Generic' population risk factors, such as demographics (age, ethnicity, family or personal history of cancer), obesity, smoking, or alcohol excess need to be taken into account. Disease-specific factors are also relevant: for example, maladaptive coping mechanisms may be associated with more smoking and alcohol excess (11). Most patients receiving biologic therapies for psoriasis will have had prior exposure to 'non-biologic' systemic immunosuppression, and of relevance to skin cancer, phototherapy, all of which may drive risk (12, 13).

To date, psoriasis treatment guidelines have provided recommendations based on the theoretical concerns about risk of cancer (14, 15). These aim to protect patients but may be limiting access for those who are perceived to be at risk (17). Given that biologic agents have been in use for over 15 years (16, 17) and considering the latency period for developing a cancer, it is reasonable to review the evidence for long-term risk of cancer now. We have therefore performed a systematic review to investigate the risk of cancer in psoriasis patients who have specifically been treated with biologics, focussing on studies with a defined comparator arm and follow-up of at least 6 months. This review informed the updated British Association of Dermatologists guidelines for use of biologic therapies in psoriasis [Br J Dermatol. 2017 May 17. doi: 10.1111/bjd.15665. [Epub ahead of print]

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Materials and methods

The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The review protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO; 2015:CRD42015017538).

Predefined search strategy and selection criteria

An *a priori* protocol was established as follows (complete protocol in Supplementary material, S1):

The objective was to determine the risk of cancer in people with psoriasis (all phenotypes) exposed to biologic therapies. The outcome of interest was incidence of any cancer in studies with follow-up of ≥6 months using the initiation of biologic treatment or a reference starting time-point. Data for different cancers were summarised separately (NMSC, melanoma, lymphoma, and solid cancer).

The primary population included all patients with psoriasis treated with biologics. Only studies with a comparator arm were included. Analysis by strata (cancers and psoriatic arthritis) and confounding factors considered for sub-group analysis are described in Supplementary material, S1.

Systematic reviews, randomized controlled trials (RCTs), open-label extension (OLE) studies, and prospective cohort studies on any biologic were included. Studies with indirect populations were excluded; populations where the proportion being treated primarily for psoriatic arthritis was greater that 50% were considered indirect.

Search and Study Selection

The systematic literature search was performed in Medline, Embase, and the Cochrane Library from inception until August 2016, with the results de-duplicated, titles reviewed and irrelevant studies excluded by an information scientist (LE). The search strategy and search terms are available in Supplements S2.1-2.3. Studies reported in languages other than English were excluded.

The abstracts were screened by two assessors (LE and EP), and disagreements resolved by a third (CS). The full-text articles were obtained and checked against the protocol and those that did not meet the criteria were excluded (LE, CS and EP). Reference lists of systematic reviews and meta-analyses were screened for additional papers (LE and EP).

Data Extraction and Quality Assessment

Data extraction and appraisal was performed using a standardized template (EP) and repeated by a second researcher (LE) and differences were resolved by a third independent assessor (CS). Data collected included: study details (study type, data source, setting, duration of study, funding sources), population details (disease severity, subgroup analysis, number of groups/participants, selection criteria, age, gender, ethnicity, exposure to previous phototherapy, previous immunosuppression, comorbidities including smoking and alcohol, psoriatic arthritis, body weight, previous cancers, family history of cancers), interventions, and results (type and number of cancers, when these developed).

The methodological quality was assessed for individual studies using the Cochrane Collaboration's tool for assessing risk of bias (18). Adjustment for or consideration of potential confounders was also evaluated.

Data Analysis

Where possible, meta-analyses were planned. If not appropriate, descriptive statistics were used to summarize the data.

Results

The systematic literature search yielded 4566 results after duplicates were removed (Figure 1). Of these, 245 abstracts were screened, and 63 full-text articles were assessed for eligibility. Seventeen additional papers were identified through hand-searching reference lists of systematic reviews. Data were extracted from eight prospective cohort studies that met the inclusion criteria. The studies and reasons for exclusion are listed in Supplement S3. In summary, reasons for study exclusion were lack of a comparator arm (n=26), duplicate publication (n=20), follow-up less than 6 months (n=7), no extractable data (n=10), indirect populations (n=4), retrospective design (n=1), out of scope (n=3, one study was on tildrakizumab, two did not look at biologics), or study was withdrawn (n=1).

[Fig.1]

Risk of bias

Using the Cochrane Collaboration's tool for assessing risk of bias, the overall risk of bias for all of the studies was rated as very high (Table 1) (18). Risk of selection bias was low in 7/8 (88%) studies; it was graded high in van Lumig as data collected from hospital registries risks missing some events due to misclassification and there is a potential risk of surveillance bias (19). Given that the outcome is objective, the risk of performance bias was low in all studies. The risk of attrition bias was high for all studies.

Risk of detection or measurement bias was high in 7/8 studies. Research was funded by pharmaceutical companies (n=7) or it was not reported (n=1). The outcome was defined as patients with cancer (n=3) (20-22), as cancers (n=2) (23, 24), or both (n=3) (19, 25, 26). The quality of the evidence across all studies was very low, due to the high risk of bias.

The studies could not be pooled for a meta-analysis due to differences in the biologic therapies investigated, variable exposure lengths, variable outcome definitions, incomplete data and no adequate control for key confounding factors, other than age and sex. The data were therefore summarized using descriptive statistics.

Confounding factors

Confounding factors were either poorly reported or not reported. No studies reported skin type. In the 6 studies that reported ethnicity, over 80% of patients were Caucasian (range 81.1%-96.4%; Table 2) (20-22, 24-26).

Sex- and age-matched comparison cohorts were used in 7/8 studies; adjustment for age or sex, or for other confounders, were not reported in Pariser et al. (Table 2) (26). van Lumig et al. adjusted for multiple confounders (19), but it is unclear whether the remaining six studies adjusted for the confounding factors (Table 2).

Study characteristics

The main study characteristics are summarised in Table 3, including: RCTs or OLEs (n=6); a post-marketing surveillance registry (n=1); and prospective registries from medical centres (n=1). The studies included between 280 to 4410 patients located in North America (n=2), Europe (n=1), or internationally (n=5). Patients in the intervention groups received etanercept (n=3 studies), infliximab (n=1), adalimumab (n=2), multiple TNFi **class** (n=1), or

ustekinumab (n=1). Studies included patients with plaque-type psoriasis only (n=6), or it was not reported (n=2), and disease severity was moderate-to-severe on the Physician Global Assessment scale in most studies. The majority of patients were male (52.4% to 68.5%), and the mean age ranged from 44 to 47 years.

A variety of comparator arms were used. Six studies investigating any cancers excluding NMSC used the United States (US) National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) database; four studies used data recorded between 1992-2003 (23-26), and two studies did not report the time period used (Table 3) (21, 22). In order to investigate the risk of NMSCs specifically, four of these studies obtained incidence rates from the 1977-1978 NCI Survey (23, 24) and the South-eastern Arizona Skin Cancer Registry and Rochester Epidemiology Project in Minnesota (25, 26) as comparator arms (Table 3). One study used US patients who received methotrexate and/or ciclosporin for other unspecified inflammatory conditions identified through insurance claims databases as the comparator arm for all outcomes; in van Lumig et al., the intervention (psoriasis patients) and comparator arms (rheumatoid arthritis) exposed to TNFi were identified from two hospital registries (19) (Table 3).

All of the studies included a biologic cohort of psoriasis patients with mixed prior exposure to biologics, conventional systemics and/or phototherapy; none of the studies included a biologic-naïve comparator arm of psoriasis patients.

Risk of cancers

(i) Any Cancers

Compared to the general US population, standardized incidence ratios (SIRs) show no increased risk in psoriasis patients of 'any cancers excluding NMSC' with TNFi therapies or ustekinumab (Table 4). There was no increased risk with etanercept compared to patients on non-biological systemic therapies for other inflammatory conditions (conditions not reported).

(ii) Skin Cancers

Four studies investigated the risk of NMSC in psoriasis patients on TNFi therapies (Table 4). In the two studies reporting data on adalimumab, there was an increased risk of NMSC compared to the general US population (SIR 1.76, 95% confidence interval (CI) 1.26-2.39 and SIR 1.51, 95% CI 1.04-2.11) (23, 24). We believe there is considerable overlap in the data presented in these studies based on the number of trials and patients reported, despite marginal differences in the reported results. Consistent with the previous findings, an increased risk of NMSC was reported in patients receiving TNFi for psoriasis compared to those with rheumatoid arthritis (adjusted hazard ratio 6.0, 95% CI 1.6–22.4 and adjusted risk ratio 5.5, 95% CI 2.2-13.4) (19). This risk may be driven by an increase in SCC with increases reported with both etanercept (SIR 1.78, 95% CI 1.11-2.69 and SIR 4.28, 95% CI 2.68,-6.47) and adalimumab (SIR 3.84, 95% CI 1.54-7.92) compared to a general US population (24, 26). Only one study specifically evaluated the risk of melanoma in those receiving ustekinumab, and found no increased incidence compared to a general US population (Table 4).

(iii) Solid cancers and Lymphoma

SIRs showed no increased incidence of prostate, colorectal or breast cancer for ustekinumab compared to the general US population. SIRs for lymphoma demonstrated no increased risk; however, fewer than 5 events were reported for psoriasis patients exposed to etanercept (20), adalimumab (23) and ustekinumab (22). The median follow-up for studies evaluating risk of lymphoma was only 0.5 years for adalimumab, and 5-7 years for etanercept and ustekinumab (Table 4). The incidence of lymphoma was 0.11 and 0.13 per 1000 person years for etanercept and ustekinumab, respectively.

Discussion

This systematic review provides an up-to-date synthesis of the published evidence regarding the risk of cancer with biologic therapies in psoriasis patients and is the first to specifically address the long-term incidence of cancer in this population. The most significant finding in this review is the increased risk of NMSC, associated with exposure to TNFi. This risk appears to be driven by an increase in SCC, which is consistent with findings observed with non-biologic 'immunosuppression' (12, 13). However, there are important limitations to the design and reporting of the included studies that make it difficult to be certain that this signal is specifically attributable to biologic therapy.

Firstly, the comparator arms are problematic. As psoriasis patients who were exposed to non-biologic therapies were not included in any comparator arms, it is impossible to determine whether the incidence rates of cancer were further elevated following exposure to biologics (10). For NMSC incidence, studies included the 1977-8 NCI-SEER survey (23, 24), and the 1985-1996 Arizona and 1984-1992 Minnesota registries (25, 26). Not only do these general population cohorts fail to account for confounders present in the psoriasis population (including phototherapy and conventional systemic therapies), but these cohorts are also not

contemporaneous with the cohorts of biologic-exposed psoriasis patients. NMSC incidence has significantly increased over time, as demonstrated by incidence rates in Germany more than doubling between 1998 (43/100,000 population) and 2010 (105/100,000 population) (27). Comparing NMSC risks at distinct time points may lead to inflated risk estimates.

Secondly, two of the studies compared the overall incidence of cancer in the intervention group (ie: multiple cancers per patient), to the incidence of first-time diagnosis of cancer in the comparison cohort (23, 24). Therefore the increased SIRs for NMSCs may be related to overestimating incidence by counting the number of cancers.

Thirdly, the studies did not adequately control for key confounders other than age and sex (including previous phototherapy, prior exposure to immunosuppression, and previous NMSCs) (13, 28). Outcomes were not separately reported for patients who had a history of cancer, and only one study corrected for history of previous NMSC (19). Clinical trials have historically excluded patients with history of cancer; six studies present data from RCTs and open-label studies, and at least one excluded patients with history of cancer as above (19), while the other studies do not report full exclusion criteria. In van Lumig, although the authors correct for confounders, they do not correct for UV exposure (Table 2). This could partly explain the high adjusted hazard ratio and risk ratio for NMSC (29).

Whilst the data on the risk of cancers other than NMSC in the present review are reassuring, the studies are likely to be underpowered to ascertain the risk of other solid cancers, and particularly the risk of lymphoma following exposure to TNFi. In common with the data on NMSC, most studies used the general population as a comparison cohort, and adjustment for confounding factors was inadequate.

A number of other aspects make interpretation of findings difficult. Confounding by indication (prognostic factors that may bias prescribing) is problematic for two of the eight studies identified (19, 20); excess alcohol and current smoking are factors that may influence

clinician choice of which treatment to prescribe a patient. Also, the psoriasis patients included in the identified studies were recruited from diverse geographical areas, which potentially influences baseline risk of cancer, the likelihood of seeking treatment, how events are reported, and how patients are treated. These factors, alone or in combination, further complicate interpretation of risk estimates: in relation to NMSC for example, there is regional variation in use of PUVA and natural sun exposure as a treatment for psoriasis.

Latency periods were not investigated in any of the included studies. Most cancers develop over a long period of time and so it is unlikely that biologic therapy initiated close to a diagnosis of cancer is causally related. The 8 studies identified include all cancers since the initiation of treatment with only three studies providing information on when the cancers developed (19, 20, 26). None of the included studies summarised the length of time between a previous cancer and initiating biologic therapy. Follow-up time, which may have an effect on the incidence of cancers reported, is highly variable among and within studies. Patients often did not complete the planned duration of treatment or follow up, and three studies only included cancers that developed during treatment and up to 30-70 days after treatment was discontinued (23, 24, 26).

In conclusion, studies show an increased risk of NMSC, especially SCC, with the TNFi therapies etanercept and adalimumab, compared to the general US population. The evidence to date suggests that there is no increased risk of cancers other than NMSC. There is however no 'real world' evidence and there are significant limitations to the studies identified with the data largely from relatively short-term RCT and OLE studies, making it difficult to extrapolate to real-world practice. There is therefore a continuing need for pharmacovigilance.

Based on an estimated cancer frequency of 1 in 500 in patients only exposed to conventional systemic therapies and a recruitment rate of 2:1 (biologic-exposed : biologic-naïve), 18,250 and 9,125 person years of follow-up, respectively, would be needed to detect a two-fold increase in the risk of cancer (30); if the cancer frequency is rarer (1 in 1000), the person years of follow-up would increase to 36,550 for biologic-exposed and 18,275 for biologic-naïve patients. The detail and scale of the data capture within ongoing pharmacovigilance registries, such as the British Association of Dermatologists Biologic Interventions Register (BADBIR) (30) as well as collaborative efforts through Psonet (4), offer the opportunity to investigate cancer risk; specifically, the risk attributable to biologic therapy compared with patients only exposed to conventional systemic therapies and phototherapies. In order to determine whether there is a real increased risk of NMSC with biologic therapies, analyses need to take into account key confounders prevalent in the population (including excess alcohol and smoking) and the timing of events in relation to starting biologic therapies, and should report outcomes both as events and patients with events.

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Figures

Figure 1- Flow chart of the selection of articles using the 2009 PRISMA statement format

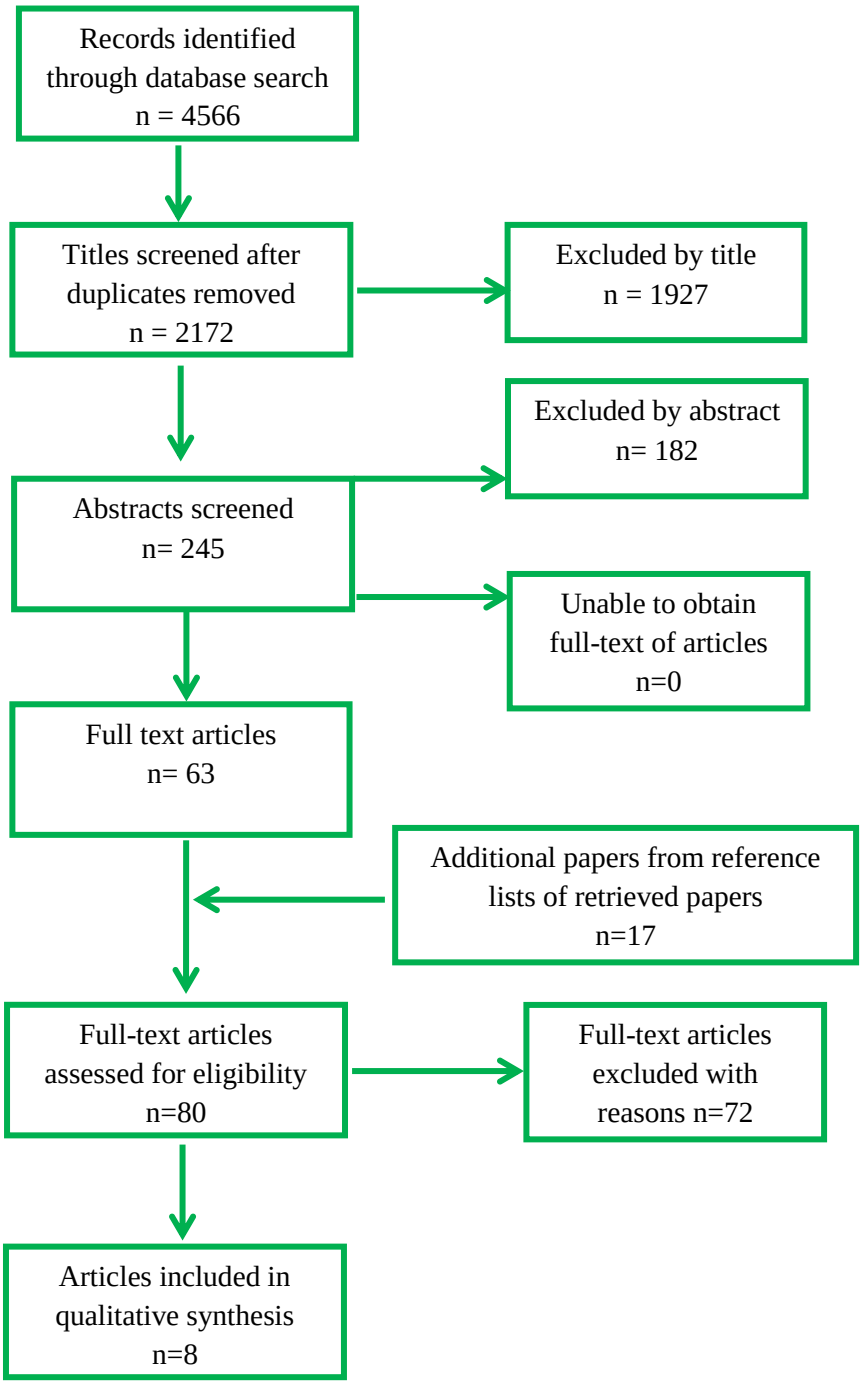

Table 1: Risk of bias

Study	Treatment	Overall risk of bias	Risk of selection bias	Risk of performance bias	Risk of attrition bias	Risk of detection / measurement bias
Burmester et al. (23)	adalimumab	High	Low	Low	High	High
Kimball et al. (20)	etanercept	High	Low	Low	Very high	High
Leonardi et al. (24)	adalimumab	High	Low	Low	High	High
Menter et al. (21)	infliximab	High	Low	Low	Very high	Low
Papp et al. (25)	etanercept	High	Low	Low	Very high	High
Papp et al. (22)	ustekinumab	High	Low	Low	High	High
Pariser et al. (26)	etanercept	High	Low	Low	High	High
van Lumig et al. (19)	TNFi	High	High	Low	High	High

TNFi: tumor necrosis factor inhibitor.

Table 2: Confounding factors included in analysis of cancer risk

	All cancers						Skin cancers		Solid tumours and Lymphoma	
Study	**Age**	**Sex**	**Previous cancers**	**Previous systemic tx**	**Previous biologic tx**	**BMI or obesity**	**Previous phototherapy**	**Skin type/ ethnicity**	**Smoking**	**Alcohol excess**
Burmester et al. (23)	✓	✓	**X**	**X**	**?**	**X**	**?**	**X**	**X**	**X**
Kimball et al. (20)	✓	✓	**X**	**X**	**?**	**X**	**X**	**X**	**X**	**X**
Leonardi et al. (24)	✓	✓	**X**	**X**	**X**	**X**	**?**	**X**	**X**	**X**
Menter et al. (21)	✓	✓	✓ excluded	**X**	**X**	**X**	**N/A[2]**	**N/A[2]**	**X**	**X**
Papp et al. (22)	✓	✓	**X**	**X**	**X**	**X**	**X**	✓	**X**	**X**
Papp et al. (25)	✓	✓	**X**	**X**	**?**	**X**	**X**	**X**	**X**	**X**
Pariser et al. (26)	**?**	**?**	**X**	**X**	**?**	**X**	**X**	**X**	**X**	**X**
van Lumig et al. (19)	✓	✓	✓	✓[3]	✓	**X**	**X**	**Partly[4]**	**X**	**X**

✓ included; **X** not included; **?** unclear whether included.

BMI: body mass index; N/A: not applicable; tx: treatment. [1]Including broad-band ultraviolet B (UVB), narrow-band UVB, and systemic and topical psoralen and ultraviolet A (PUVA); [2]Study adjusted for race, but it did not look at incidence of skin cancers; [3]Including ciclosporin, methotrexate, and corticosteroids; [4]The intervention and comparison groups are from the same area (Netherlands) and same time period. The authors also expect that background degree of sun exposure related to latitude and skin cancer trends are similar for both groups.

Table 3: Study Characteristics

Study; design	Intervention group	Baseline characteristics and exposures	Comparison	Follow-up
Burmester et al. (23); RCTs & OLE	Data from 13 international adalimumab trials (including RCTs, open-label trials and long-term extension studies) Inclusion: Criteria varied per study Exclusion: Criteria varied per study	n= 3010 Prior exposure to standard systemic or phototherapy: not specified Prior exposure to biologic therapy: not specified Age mean 44.7years Caucasian not specified Weight mean not specified Psoriatic arthritis: none (analyzed separately) Previous cancers: not specified Exposure: median 0.7 years, maximum 5.7 years (40.8% had > 2years exposure, 2.9% had > 5years)	General US population For all cancers exc NMSC: 5-year age-specific incidence rates from the NCI SEER database, 1993–2001; age-and sex-matched For NMSC: 10-year age-specific incidence rates from 1977-1978 NCI survey	variable, up to 5.7 years; median exposure 0.7 years; adverse events included follow-up for 70 days after last dose
Kimball et al. (20); prospective cohort	Postmarketing safety surveillance registry of psoriasis patients on etanercept in USA/Canada (OBSERVE-5); starting May 2006 Inclusion: Patients with plaque-type psoriasis for whom etanercept therapy was indicated Exclusion: Initially, patients were etanercept-naïve but later protocol amendment allowed patients with prior etanercept treatment to enrol. Previous	n=2510 Prior exposure to standard systemic or phototherapy: not specified Prior exposure to biologic therapy: 664 (26%) had prior etanercept exposure Age mean 46.3 years Caucasian 81.8% Weight mean not specified Psoriatic arthritis 18.5% Previous cancers: not specified Exposure: mean(SD) was 1.7(1.1) years and 1.6(1.1) years in the prior etanercept and etanercept-naive groups, respectively	US patients who received non-biologic systemic therapies (methotrexate, cyclosporine) for other inflammatory conditions in 2006 From medical and drug insurance claims databases; using incidence rates based on person-time of observation; age- and sex-matched	7 years (8 years for some outcomes)

	treatment with any other TNFi therapies.			
Leonardi et al. (24); RCTs & OLE	Data from 13 international adalimumab RCTs and their OLE studies (BELIEVE, PRIDE, M10-238, M10-405, M02-528, M02-529, M02-538, M03-596, M03-658, M04-688, M04-702, REVEAL, CHAMPION); data pooled up to Nov 2009 Inclusion: adults with moderate-to-severe plaque-type psoriasis. Exact criteria varied per study. Exclusion: prior exposure to any TNFi therapy, except in extension trials (of adalimumab RCTs), and in M10-238 and PRIDE (all prior TNFi therapy was permitted).	n= 3010 Prior exposure to standard systemic or phototherapy: not specified Prior exposure to biologic therapy: not specified Age mean 44.7 years (SD 12.7) Caucasian 87.5% Weight mean 89.0kg (SD 22) Psoriatic arthritis 28.6% (out of 2034) Previous cancers: not specified Exposure: varied per study	General US population For all cancers exc NMSC: rates from the NCI SEER database for 1993–2001; age- and sex-matched For NMSC: rates from the 1977–8 NCI Survey.	varied from 12 weeks to >5years (adverse events that occurred up to 70 days after the final dose of adalimumab were analysed)
Menter et al. (21); RCTs	Data from three international infliximab RCTs (SPIRIT, EXPRESS, EXPRESS II); published 2004-2007 Inclusion: Adults (≥18 years) with moderate-to-severe plaque psoriasis, with PASI >12 and BSA at least 10% Exclusion: nonplaque forms of psoriasis, recent or recurrent serious infections;	n= 1373 (and 334 placebo); baseline data below is from 1462 patients Prior exposure to standard systemic or phototherapy: UVB 54.3%, PUVA 34.8%, methotrexate 39.3%, acitrecin 19.9%, cyclosporin 19.7% Prior exposure to biologic therapy: 18.1% Age mean 43.8 years (SD 12.5) Caucasian 92.9% Weight mean 90.8 (SD 22.3kg)	General US population For all cancers exc NMSC: NCI SEER database; age-, race-, sex-matched	30 weeks (N=248) and 50 weeks (N=1209)

	lymphoproliferative disease; cancer or history of cancer within 5 years of screening (other than previously excised, nonrecurrent BCC); severe systemic disease; congestive heart failure, SLE, demyelinating disease; active or latent TB.	Psoriatic arthritis 28.9% Previous cancers: not specified Exposure: varied per study		
Papp et al. (25) RCTs & OLE	Data from two Canadian etanercept trials (starting May 2002 and June 2003) and their OLEs. Inclusion: Patients with plaque-type psoriasis. Specific criteria varied per study. Exclusion: Criteria varied per study.	n= 506 Prior exposure to standard systemic or phototherapy: 71.9% phototherapy Prior exposure to biologic therapy: not specified Age mean 46.0, SD 11.7 Caucasian 96.4% Weight mean 90.1kg, SD 20.6 Psoriatic arthritis not specified Previous cancers: not specified Exposure: varied per study	General US population For all cancers exc NMSC: rates from the NCI SEER database for 1992-2002; age-and sex- matched For NMSC: Minnesota and Arizona databases; age- and sex-matched	Up to 54 months [449 (88.7%) patients treated for at least 12 months, 398 (78.7%) at least 24 months, 144 (28.5%) at least 36 months, and 108 (21.3%) at least 48 months; 60 patients remained on study after 48 months, up to an additional 6 months]
Papp et al. (22) RCTs	Long-term safety data from 4 RCTs using ustekinumab (phase II, PHOENIX 1, PHOENIX2, ACCEPT); published between 2007-2010 Inclusion: adults (≥18 years) with moderate-to-severe psoriasis. Exact criteria varied per study. Exclusion: Criteria varied per study.	n=3117 Prior exposure to standard systemic or phototherapy: PUVA 27.4%, UVB 56.1%, ciclosporin 13.7%, methotrexate 35.3% Prior exposure to biologic therapy: 26.3% etanercept/infliximab/ adalimumab Age mean 45.6 years (SD 12.3) Caucasian 92.2% Weight: 47.8% BMI ≥30, 33.0% BMI	General US population For all cancers exc NMSC: rates from the NCI SEER database; age-and sex- and race-matched	5 years

		≥25-30, 19.1% BMI <25 Psoriatic arthritis 27.5% Previous cancers: not specified Exposure: varied per study; at least 4 years in 1482 patients		
Pariser et al. (26); RCT	Analysis of 7 international etanercept psoriasis trials and extension studies (160032, 160039, 160042, 20030117, 20030115, 20030190, 20040216); published between 2003-2010 Inclusion: : Adults (≥18 years) with moderate-to-severe plaque-type psoriasis and >10% BSA Exclusion: Criteria varied per study.	n=4410 Prior exposure to standard systemic or phototherapy: not specified Prior exposure to biologic therapy: not specified Age mean 45.4 years Caucasian 86.6% Weight mean 90.7kg Psoriatic arthritis not specified Previous cancers: not specified Exposure: varied per study	General US population For all cancers exc NMSC: NCI SEER database for 1992-2003 For NMSC: Minnesota and Arizona databases	12 weeks to 144 weeks Events occurring between the first dose and within 30 days after the last dose of etanercept were included.
van Lumig et al. (19); prospective cohort	Patients on etanercept, adalimumab and/or infliximab at two medical centers in the Netherlands; during February 2005 to November 2011 Inclusion: patients with plaque psoriasis initiated on etanercept, adalimumab and/or infliximab at 2 hospitals, with a follow-up of at least 1 year after the start of TNFi therapy and enrolled in their respective registries	n= 280 Prior exposure to standard systemic or phototherapy: phototherapy 99% (of 279), UVB 92% (of 276), PUVA 58% (of 275), methotrexate 96%, ciclosporin 78%, prednisolone 9%, azathioprine 1% Prior exposure to biologic therapy: not specified Age mean 46.8 years (SD 11.9) Caucasian not specified Weight mean not specified Psoriatic arthritis 28% Previous cancers: 2.1% NMSC (and	All rheumatoid arthritis patients from same region treated with the same TNFi agents; between 2001 and November 2011	median 4.8 years (range 1.0–9.3)

	Exclusion: not specified	1.1% in RA group, p =0.4) Exposure: median 4.1 (0.1-14.9)		

BCC: basal cell carcinoma; BSA: body surface area; kg: kilogram; OLE: open-label extension; n: number of patients; NCI: National Cancer Institute; NMSC: non-melanoma skin cancer; PASI: Psoriasis Area Severity Index; PUVA: psoralen and ultraviolet A; RA: rheumatoid arthritis; RCTs: randomized controlled trials; SD: standard deviation; SEER: Surveillance, Epidemiology, and End Results database; SLE: systemic lupus erythematosus; TB: tuberculosis; TNFi: tumor necrosis factor inhibitor; US: United States; UVB: ultraviolet B.

Table 4: Summary of evidence

Outcome	Intervention	Comparison	No of Participants, N; Follow-up[a]	Patients with events, N; [number of events, N]	Relative effect (95% CI)
Any cancers					
Any cancers excluding NMSC	adalimumab (23)	general US population	3010; 0.5 years (median), 5.5 years (max)	[9][b]	SIR 0.96 (0.65-1.36)[c]
	adalimumab (24)	general US population	3010; >0.5 years (median), >5 years (max)	[35]	SIR 0.90 (0.60-1.29)[c]
	etanercept (20)	Patients on methotrexate or ciclosporin	2510; 7 years (all patients)	59	SIR 0.78 (0.59-1.00)
	etanercept (25)	general US population	506; 2-3 years (median), 4.5 years (max)	6 [7]	SIR 0.91 (0.37-1.88)
	etanercept (26)	general US population	4410; 3 years (max)	[30]	SIR 1.15 (0.78-1.64)
	infliximab (21)	general US population	1373; 1 year (median), 0.5-1 years (range)	2	SIR 0.39 (0.05-1.42)
	ustekinumab (22)	general US population	3117; 5 years (all patients)	54	SIR 0.98 (0.74–1.29)
Skin cancers					
NMSC	adalimumab (23)	general US population	3010; 0.5 years (median), 5.5 years (max)	[40]	**SIR 1.76 (1.26-2.39)** [c,d]
	adalimumab (24)	general US population	3010; >0.5 years (median), >5 years (max)	[34]	**SIR 1.51 (1.04-2.11)** [c,d]
	TNFi (19)	Rheumatoid Arthritis patients on TNFi	280; 5 years (median) 1-9.5 (range)	11 [38]	**HR 6.0 (1.6–22.4) RR 5.5 (2.2-13.4)**
	etanercept (20)	general US population on MTX or ciclosporin	2510; 7 years (all patients)	66	SIR 0.54 (0.42-0.69)
BCC	etanercept (25)	general US population	506; 2-3 years (median), 4.5 years (max)	9 [12]	SIR 0.52 (0.23-1.03) [e]
	etanercept (26)	general US population	4410; 3 years (max)	28 [31]	SIR 0.55 (0.37-0.80) [e]
SCC	adalimumab (24)	general US population	3010; >0.5 years (median),	[14]	**SIR 3.84 (1.54-**

			>5 years (max)		**7.92)**[c,d,f]
	etanercept (25)	general US population	506; 2-3 years (median), 4.5 years (max)	4	SIR 1.08 (0.29-2.76) [e] SIR 2.68 (0.72-6.87) [g]
	etanercept (26)	general US population	4410; 3 years (max)	22 [25]	**SIR 1.78 (1.11-2.69) [e] SIR 4.28 (2.68-6.47) [g]**
Melanoma	ustekinumab (22)	general US population	3117; 5 years (all patients)	6	SIR 1.42 (0.52–3.09)
Solid Cancers and Lymphoma					
Prostate Colorectal Breast	ustekinumab (22)	general US population	3117; 5 years (all patients)	14 5 4	SIR 1.21 (0.66–2.04) SIR 0.99 (0.32–2.31) SIR 0.62 (0.17–1.58)
Lymphoma	adalimumab (23)	general US population	3010; median 0.5 years, max 5.5 years	1	SIR 0.63 (0.01-3.49)
	etanercept (20)	general US population on MTX or ciclosporin	2510; 7 years (all patients)	2	SIR 0.26 (0.03-0.95)
	ustekinumab (22)	general US population	3117; 5 years (all patients)	2	SIR 0.80 (0.10–2.91)

BCC: basal cell carcinoma; CI: confidence interval; HR: hazard ratio; max: maximum length; NMSC: non-melanoma skin cancer; N: number of patients; RR: risk ratio; SCC: squamous cell carcinoma; SIR: standardized incidence ratio; TNFi: tumor necrosis factor inhibitor; US: United States. [a] Estimated to the nearest half-year. [b]Not clear from paper whether solid cancers were counted (the 9 cancers were only lymphoma and melanoma). [c]Based on incidence of cancers, not patients with event; [d] Using the 1977–8 National Cancer Institute study database; [e] Using the Arizona registry; [f] Not significant if Arizona or Minnesota registries are used. [g] Using the Minnesota registry.