Review

# Pharmacologic Immunomodulation and Cutaneous Malignancy in Rheumatoid Arthritis, Psoriasis, and Psoriatic Arthritis

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***ABSTRACT.*** ***Objective.*** It is unclear if skin cancer risk is affected by the use of immunomodulatory medications in rheumatoid arthritis (RA), psoriasis, and psoriatic arthritis (PsA). The purpose of this study is to evaluate and summarize the available data pertinent to this question.

***Methods.*** The English language literature on PubMed was searched with a combination of phrases, including "malignancy," "skin cancer," "squamous cell carcinoma," "basal cell carcinoma," "melanoma," "psoriasis," "psoriatic arthritis," and "rheumatoid arthritis" in addition to the generic names of a variety of common immunomodulatory drugs. Relevant articles were identified and data were extracted.

***Results.*** In total, 2218 potentially relevant articles were identified through the search process. After further screening, 20 articles relevant to RA were included. An additional 19 articles relevant to either psoriasis or PsA were included as well. RA may be a risk factor for the development of cutaneous malignancy. Treatment with tumor necrosis factor inhibitors increases the rates of non-melanoma skin cancer (NMSC) in RA and psoriasis. This risk doubles when combination methotrexate therapy is used in RA. Methotrexate may increase the risk of malignant melanoma in patients with RA and the risk of NMSC in psoriasis. Cyclosporine and prior phototherapy significantly increase the risk of NMSC.

***Conclusion.*** RA may potentiate the risk of cutaneous malignancy and therefore dermatologic screening in this population should be considered. The use of immunomodulatory therapy in RA, psoriasis, and PsA may further increase the risk of cutaneous malignancy and therefore dermatologic screening examinations are warranted in these groups. More careful recording of skin cancer development during clinical trials and cohort studies is necessary to further delineate the risks of immunomodulatory therapy. (J Rheumatol First Release September 1 2010; doi:10.3899/jrheum.100041)

*Key Indexing Terms:*
RHEUMATOID ARTHRITIS PSORIASIS PSORIATIC ARTHRITIS
MELANOMA SKIN CANCER IMMUNOSUPPRESSION

The societal burden of non-melanoma skin cancer (NMSC) and malignant melanoma (MM) is dramatic with respect to both morbidity and cost. It has been estimated that over 1.2 million cases of NMSC were diagnosed in the US in 2007[1]. In a review of Medicare claims data from 1992 to 1995, NMSC was the fifth most costly cancer despite the relatively low per-patient cost of treatment[2]. MM also places a heavy burden as the fifth most common malignancy in men and the sixth most common malignancy in women in the US in 2009, accounting for an estimated 68,720 new cases and 8,650 deaths[3].

Whereas solar radiation is often cited as the major culprit in skin carcinogenesis, one increasingly important risk factor relates to the host's immune system. The increased risk of both MM and NMSC for solid-organ transplant recipients is well established[4]. These patients are subject to powerful immunosuppressive regimens, often treated simultaneously with multiple agents. Although the nature of treatment is quite different than in transplant recipients, patients with autoimmune and inflammatory disorders are increasingly treated with a variety of immunomodulatory agents. If manipulation of the host immune system can lead to a major increase in skin cancers in transplant recipients, it is plausible, although unknown, that a less dramatic manipulation [as in the treatment of patients with rheumatoid arthritis

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(RA), psoriasis, and psoriatic arthritis (PsA)] can lead to a measurable and important, if small in absolute terms, increase in skin cancer as well.

Immune-modulating drugs including, but not limited to, methotrexate (MTX), mycophenolate mofetil, cyclosporine (CSA), and azathioprine (AZA) have been proven beneficial in RA, psoriasis, PsA, and Crohn's disease[5,6,7,8,9]. The more recent development of the biologics, including alefacept, abatacept, rituximab, the tumor necrosis factor-α (TNF-α) inhibitors, and ustekinumab, has redefined the treatment for RA, juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, PsA, and psoriasis.

Despite the seemingly increased use of these medications, it is unknown whether the immunomodulatory therapy used for many commonly treated inflammatory diseases affects the risk of subsequent cutaneous neoplasia. Numerous large patient registries and clinical trial data have demonstrated the potentially causal role of immunomodulatory therapy in the development of skin cancer. The aim of our study is to assess whether currently available data demonstrate an increased risk of skin cancer in RA, psoriasis, and PsA during treatment with the most commonly prescribed immunomodulatory agents.

## MATERIALS AND METHODS

PubMed was searched using the following phrases (number of articles obtained per search): "rheumatoid arthritis" and "squamous cell carcinoma" (86), "basal cell carcinoma" (18), "melanoma" (134), "malignancy and adalimumab (32) or infliximab (63) or etanercept (64) or methotrexate (not lymphoma) (133) or azathioprine (82) or cyclosporine (32) or prednisone (129) or rituximab (66) or abatacept (12) or leflunomide (12)"; "psoriasis" and "squamous cell carcinoma" (412), "basal cell carcinoma" (270), "melanoma" (289), "malignancy and adalimumab (15) or infliximab (24) or etanercept (40) or methotrexate (140) or cyclosporine (63) or ustekinumab (2) or alefacept (13) or efalizumab (17)"; "psoriatic arthritis" and "squamous cell carcinoma" (4), "basal cell carcinoma" (4), "melanoma" (5), and "malignancy and adalimumab (3) or infliximab (7) or etanercept (15) or methotrexate (14) or cyclosporine (4) or ustekinumab (0) or alefacept (4) or efalizumab (1)". Titles and abstracts were searched for references pertinent to cutaneous malignancy. Titles before 1975 date and case reports were excluded from analysis. Only English language literature was included in study data. Data were extracted from relevant articles, reviewed, and summarized.

The data included in this study are collected from a variety of national cohort registries as well as clinical trial databases. Because the methods of data collection and analysis vary among the national registry data, these will be briefly summarized. The National Data Bank for Rheumatic Diseases (NDB) pools data collected through patient-reported outcomes from an open cohort of RA and osteoarthritis patients in the US[10]. The patients are initially recruited from the practices of 908 US rheumatologists. If a NMSC was reported in the patient questionnaire, an outcomes assessor contacted the patient to ensure the diagnosis was correct and novel. Patients' reports were not confirmed by assessment of the pathology report. The Swedish registry data are collected from the following 3 data sources: Swedish Inpatient Register, the Swedish Outpatient Register, and the Swedish Early RA Register[11]. The inpatient register collects data (dates, diagnoses, etc.) on any patient admitted to the hospital since 1964. The outpatient register collects data from the majority of nongeneral practitioner visits since 2001. Importantly, basal cell carcinoma was not reported to the Swedish national registry during the study periods included in the articles included in this report. The Swedish Early RA Register collects data from the nationwide incident cases of RA starting in 1995. Starting in 1998, all patients older than 16 years starting treatment with a TNF antagonist were entered into the Anti-Rheumatic Therapy in Sweden (ARTIS) registry. Physician-recorded outcomes questionnaires in addition to patient clinical data (medications, etc.) are continuously updated in the registry. The Australian Victorian State Cancer Registry collects data on all malignancies, except for NMSC, which occur in the Australian state of Victoria[12]. Registry data are collected via mandatory reporting of new malignancies from pathology laboratories, hospital medical records departments, and the screening of death certificates. The RA cohort in the Buchbinder study[12] was assembled from 6 community-based rheumatology practices in Melbourne, Australia. Establishment of melanoma diagnosis was made through retrospective review of hospital records. Because the Swedish registry follows all patients older than 16 years who start anti-TNF therapy, the quality of the data from this registry can be considered more robust than the NDB data, for example. The latter relies on patient-reported outcomes, which may provide less accurate data than systematic reviews of medical charts and thoroughly developed national registry data.

## RESULTS

*Rheumatoid arthritis*. For RA, a total of 863 articles were evaluated for relevance. Six cohort studies, 7 metaanalyses, and 4 controlled trials were identified for analysis (Table 1).

Of the cohort studies, 2 were from the Swedish registry data[11,13], 2 from the US National Data Bank for Rheumatic Diseases (NDB)[10,14], one from the Australian Victorian State Cancer Registry[12], and one from a nonregistry-derived cohort from the United Kingdom[15]. Five of 6 cohort studies assessed the rates of malignancy in either anti-TNF agents or MTX, whereas the UK data assessed azathioprine's role in malignancy.

*Baseline risk*. Data in the "control" groups from the Swedish Registry and NDB indicate that RA patients at baseline (in particular those not treated with TNF inhibitors) may be at an increased risk of NMSC. Since the non-TNF-treated groups likely were receiving other therapy, these data likely do not represent a true "baseline" risk. Nonetheless, the rate of NMSC in the RA cohort versus a population with osteoarthritis in the NDB was increased [hazard ratio (HR) 1.19, 95% CI 1.01–1.41], raising the possibility that RA in and of itself may increase risk for cutaneous malignancy. This question is difficult to sort out because of the difficulty in controlling for background immunomodulatory therapy. Similarly, in the Swedish Registry, rates of squamous cell carcinoma (SCC) and MM were increased comparing the inpatient RA cohort and the general population [SCC standardized incidence ratio (SIR) 1.66, 95% CI 1.50–1.84)] and MM (SIR 1.19, 95% CI 1.01–1.41)[10,13].

*Tumor necrosis factor agents*. Three cohort studies identify an increased risk of NMSC with use of anti-TNF agents in RA. The Swedish cohort analysis identified an increased risk of SCC in the anti-TNF-α agent group (infliximab, adalimumab, etanercept; SIR 3.6, 95% CI 1.8–6.5)[13]. The NDB data (published 2007) demonstrate an odds ratio of 1.5 (95% CI 1.2–1.8) for NMSC in the anti-TNF agent-treated cohort. Although the background rate of use of disease-mod-

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*Table 1.* Rheumatoid arthritis and risk of cutaneous malignancy per immunomodulatory agent.

| Medication | Case-Control/Cohort Study | Metaanalysis Data | Clinical Trials Data |
|---|---|---|---|
| Baseline (broad inclusion of RA patients, unspecified medication) | Review of open prospective cohort of osteoarthritis (OA) and RA patients in the US National Data Bank for Rheumatic Diseases (NDB), n = 15,789 RA and 3,639 OA patients. RA vs OA, NMSC multivariate HR 1.19, 95% CI 1.01–1.41[10]<br>Swedish cohort analysis, n = 4160 RA patients treated with anti-TNF (infliximab, adalimumab, etanercept), mean 2.3 yrs followup; SCC (BCC not reported to Cancer Registry): inpatient RA cohort NMSC HR 1.66, 95% CI 1.50–1.84; MM HR 1.19, 95% CI 0.99–1.42[13] | Danish hospital discharge registry, n = 20,699, average 7-yr followup, RA vs general population 1977–87, NMSC RR 1.3, 95% CI 1.1–1.4[43] | |
| TNF-α inhibitors | Swedish cohort analysis, n = 4160 RA patients treated with anti-TNF (infliximab, adalimumab, etanercept), mean 2.3 yrs followup; SCC (BCC not reported to Cancer Registry); inpatient RA cohort SIR 1.66, 95% CI 1.5–1.84; early arthritis RA cohort SIR 0.7, 95% CI 0.2–1.6, TNF antagonist cohort SIR 3.6, 95% CI 1.8–6.5. Melanoma: inpatient RA cohort SIR 1.19, 95% CI 0.99–1.42, early arthritis RA cohort SIR 0.9, 95% CI 0.2–2.2, TNF antagonist cohort 0.3, 95% CI 0.0–0.18[13]<br>Swedish cohort analysis, n = 6604 RA patients treated with anti-TNF (infliximab, adalimumab, etanercept), median 3.6 yrs followup (BCC not reported to Cancer Registry): no increased risk of solid malignancy[11]<br>Review of open prospective cohort of patients in NDB, n = 15,789 RA and 3639 OA patients: NMSC in TNF inhibitor (infliximab, adalimumab, etanercept) without MTX, HR 1.24, 95% CI 0.97–1.58, with MTX, HR 1.97, 95% CI 1.51–2.58[10]<br>Review of NDB, n = 13,001, comparison RA patients treated with anti-TNF agents (infliximab, etanercept, adalimumab) compared with non-biologic treated RA patients: melanoma, OR 2.3, 95% CI 0.9–5.4, NMSC, OR, 1.5 95% CI 1.2–1.8; infliximab alone, NMSC, OR 1.7, 95% CI 1.3–2.2[14] | RA clinical trials database reviewed, n = 1442, mean etanercept exposure 3.7 yrs; no increased incidence of SCC in etanercept treated patients[16]<br>Combined RCT data of etanercept in RA, 9 trials, n = 3316. Etanercept treated n = 2244, 8 BCC, 1 SCC, 1 MM; control group n = 1072, 2BCC, 1 NMSC, 0 MM[18]<br>Combined data from 9 RCT of RA patients treated with infliximab or adalimumab, n = 5014; exposed group n = 3493: 7 BCC, 3 BCC, 0 SCC, 0 MM[17]<br>Combined data from 36 global clinical trials of RA, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, psoriasis, juvenile idiopathic arthritis, n = 19,041 patients treated with adalimumab; comparing with national Cancer Institute dataset for controls, in RA SIR for BCC 1.24, 95% CI 1.01–1.51, and SCC 1.97, 95% CI 1.34–2.80[19]<br>Combined clinical trial data of etanercept use in multiple disease indications (RA, juvenile idiopathic arthritis, PsA, ankylosing spondylitis, psoriasis), n = 13,977. Rate ratio in RA, NMSC 1.05, 95% CI 0.31–4.50 (Gottlieb AB, Giannini EH, Mease PJ, Li J, Chi E, et al. Malignancies from patients receiving etanercept across approved indications [abstract]. Ann Rheum Dis 2008; 67 Suppl II:322. | Open-label multicenter study, etanercept 25 mg twice weekly in RA, n = 549; 2 BCC, 0 SCC, 0 MM[21] |



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*Table 1.* Continued.

| Medication | Case-Control/Cohort Study | Metaanalysis Data | Clinical Trials Data |
|---|---|---|---|
| Abatacept | | Abatacept multicenter trials database, n = 4134 abatacept treated patients; NMSC excluded from analysis; MM not specifically evaluated[25] | Open-label, washout (prior anti-TNF therapy) study evaluating abatacept for RA (ARRIVE trial), n = 1046; NMSC excluded from analysis[22]<br>Open-label, longterm extension of ATTAIN trial, evaluating abatacept in RA, n = 317; 2-yr followup; 3 BCC, 2 SCC, 0 MM[23]<br>1-year RCT, double-blind, placebo-controlled to evaluate safety and efficacy of abatacept in RA, n = 1795; BCC and SCC most common solid malignancy, but specific rates/data not presented[24] |
| Methotrexate | Retrospective review, RA patients, n = 458, average followup 9.3 yrs; melanoma, SIR 3.0, 95% CI 1.2–6.2 (control = Victorian State Cancer Registry, Australia/general population representation); NMSC not in VSCR registry[12]<br>Review of open prospective cohort of patients in the NDB, n = 15,789 RA and 3639 OA patients: NMSC in TNF inhibitor (infliximab, adalimumab, etanercept), MTX without TNF, HR 1.15, 95% CI 0.81–1.64[10] | | |
| Azathioprine | Prospective cohort study, a mix of RA, lupus, IBD, and other nontransplant patients treated with azathioprine (68%) or cyclophosphamide (28%), n = 1634 patients; increase in expected number of SCC and BCC vs "general population" of controls (undefined)[15] | | |
| Prednisone | | | |
| Rituximab | | Clinical trials pooled safety data, 9 trials, n = 2578 (501.3 pt-yrs), NMSC excluded from study data[26] | |

NMSC: non-melanoma skin cancer; HR: hazard ratio; TNF: tumor necrosis factor; SCC: squamous cell carcinomas; BCC: basal cell carcinoma; MM: malignant melanoma; SIR: standardized incidence ratio; IBD: inflammatory bowel disease; RCT: randomized controlled trial.



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ifying antirheumatic drugs (DMARD) in conjunction with anti-TNF therapy is not clearly defined in this study, the collective study population's background rate of MTX use was 56.9%. Out of the 3 agents (infliximab, etanercept, adalimumab), only infliximab use was shown to correlate independently with the risk of NMSC (OR 1.7, 95% CI 1.3–2.2)[14]. A third cohort study (also from the NDB, published 2005) demonstrated an increased risk of NMSC in anti-TNF agent use as well (HR 1.24, 95% CI 0.97–1.58 and HR 1.97, 95% CI 1.51–2.58, for MTX-free and MTX-exposed groups, respectively)[10]. With respect to melanoma and anti-TNF agent use, only the more recent 2007 NDB cohort study shows a trend toward increased risk (OR 2.3, 95% CI 0.9–5.4)[14]. Notably, the Swedish registry does not show an increased risk of melanoma with anti-TNF agent use[13].

Five metaanalyses assess the risk of NMSC in patients with RA. In a study of 1,442 RA patients by Lebwohl, *et al*, no increased risk of SCC in etanercept-treated patients was identified after an average followup of 3.7 years[16]. Two other studies identify absolute numbers of basal cell carcinoma (BCC) or SCC or MM in patients treated with anti-TNF agents, but the odds ratios are not calculated[17,18]. One of these evaluated 3,493 patients treated with either infliximab or adalimumab [identified in 9 randomized controlled trials (RCT) of patients with RA] compared to 1,512 untreated controls. Ten of 3,493 (0.286%) but only 3 of 1,512 (0.198%) of the anti-TNF agent-treated and untreated groups, respectively, were identified with either BCC or SCC. In the third study, the data for 9 etanercept trials were evaluated for risk of malignancy[18]. Nine of 2,244 (0.401%) patients and 3 of 1,072 (0.280%) patients of the etanercept-treated and untreated groups, respectively, were identified having either BCC or SCC.

One metaanalysis pools the combined worldwide clinical data from 36 global trials of adalimumab in RA, PsA, Crohn's disease, psoriasis, and juvenile idiopathic arthritis (n = 19,041). Rates of malignancy are compared to 3 control populations (National Cancer Institute, Arizona Registry, and Minnesota Registry) — all vary somewhat in baseline risk of developing NMSC (likely due to variable sun exposure levels and historical skin cancer trends)[19]. For RA, the SIR for BCC (1.24, 95% CI 1.01–1.51) and SCC (1.97, 95% CI 1.34–2.80) are elevated with respect to the National Cancer Institute data. Nonetheless, the elevated risk does not persist when rates are compared to either the Arizona or Minnesota registry data.

A metaanalysis of the combined safety data from 49 global trials of etanercept in RA, juvenile idiopathic arthritis, psoriasis, PsA, and ankylosing spondylitis has recently been completed[20]. At least 13,977 subjects treated with etanercept were included in the study. In contrast to the data above, this analysis depicts a rate ratio of only 1.05 (95% CI 0.31–4.50) for NMSC in RA.

An open-label study of etanercept for RA (n = 549) notes discovery of 2 BCC but no SCC or MM during the study[21].

*Methotrexate*. Two cohort studies address the risk of cutaneous malignancy with use of MTX in RA. The Australian registry study (which does not collect data on NMSC) identified an SIR of 3.0 (95% CI 1.2–6.2) for MM in a cohort of RA patients[12]. Despite the reported 2-fold increase in the risk of NMSC in the anti-TNF agent plus MTX group seen in the NDB study, MTX administered on its own does not seem to elevate the risk for NMSC (OR 1.15, 95% CI 0.81–1.64)[10].

*Abatacept*. The ARRIVE trial, which evaluated the use of abatacept, a T cell modulator, in RA, excluded NMSC from safety analysis[22]. In the ATTAIN trial (n = 317), another study evaluating longterm efficacy and safety of abatacept in RA, 3 BCC, 2 SCC, and no MM were identified during the 2-year study period[23]. BCC and SCC were identified as the most common solid malignancies in a year-long double-blind, placebo-controlled RCT evaluating the efficacy and safety of abatacept in RA; specific data regarding rates of NMSC in treated patients versus controls were unfortunately not presented[24]. A metaanalysis (n = 4,134) addressed the safety of abatacept in patients with RA pooled from the clinical trial database[25]. Unfortunately, NMSC data were not included in the database and rates of melanoma were not specifically characterized. The study notes that there was no pooling of risk for any given malignancy category (when excluding NMSC).

*Azathioprine*. The risk of NMSC in patients treated with either AZA or cyclophosphamide was evaluated in a mixed cohort of patients with a variety of nontransplant indications (RA, lupus, inflammatory bowel disease, undefined cutaneous disease, etc.)[15]. The data from this study are unreliable in that the control population is undefined. Further, the statistical analysis is limited given the low number of incident malignancies (2 SCC and 2 BCC in the AZA-treated group) and the heterogeneous treatment group.

*Rituximab*. The pooled clinical trial safety database (n = 2,578) from 9 trials involving the use of rituximab in RA did not include rates of NMSC[26]. No case of melanoma was specifically mentioned in the study. Malignancies were reported not to cluster around any specific type.

*Psoriasis and psoriatic arthritis*. A total of 1,294 and 61 articles were identified as relevant to psoriasis and PsA, respectively. Eleven cohort studies, 2 metaanalyses, and 9 studies summarizing clinical trial safety data were included in the analysis (Table 2). No study specifically addressed the risk of cutaneous malignancy in PsA.

*Baseline risk*. As with the RA literature, several studies attempt to define the baseline risk of NMSC and MM in psoriasis and PsA. A single survey study from Saskatchewan, Canada, addresses the risk of BCC in psoriasis. No difference in the prevalence of psoriasis was noted between the

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*Table 2.* Psoriasis, psoriatic arthritis, and risk of cutaneous malignancy per immunomodulatory agent.

| Medication | Case-Control/Cohort Study | Metaanalysis Data | Clinical Trials Data |
|---|---|---|---|
| Baseline evaluation | Survey study, n = 538 patients with BCC, n = 738 age, sex, and location matched controls; no association between psoriasis and BCC[27]<br>Danish cohort study of n = 6910 psoriasis patients mean followup 9.3 yrs, prior PUVA exposure unknown. SIR SCC men 3.86 ($p < 0.05$), women 4.7 ($p < 0.05$); SIR BCC men 2.16 ($p < 0.05$), women 2.33 ($p < 0.05$); melanoma men and women SIR 1.3, 95% CI 0.8–2.1[29]<br>Case-control study, Western Canada Melanoma Study, n = 651 cases, 651 age and sex matched controls; RR of psoriasis (in melanoma cohort) 1.22, 95% CI 0.76–1.94; UV light exposure was not significantly different, although minimal in both cases and controls[28] | | |
| TNF-α inhibitors | Retrospective cohort study, n = 77 patients with severe psoriasis, treated with etanercept; total followup 48 wks; 0 BCC, 0 cutaneous SCC (1 mucosal SCC), 0 MM reported[31] | Combined data from 36 global clinical trials of RA, PsA, ankylosing spondylitis, Crohn's disease, psoriasis, juvenile idiopathic arthritis, n = 19,041 patients treated with adalimumab; comparing with National Cancer Institute dataset for controls, SIR for SCC in psoriasis 3.84, 95% CI 1.54–7.92; no longer significant when compared with either Arizona or Minnesota data as controls[19]<br>Combined clinical trial data of etanercept use in multiple disease indications (RA, juvenile idiopathic arthritis, PsA, ankylosing spondylitis, psoriasis), n = 13,977. Rate ratio NMSC in psoriasis 2.77, 95% CI 0.59–25.97. 70% SCC patients with history phototherapy (Gottlieb AB, Giannini EH, Mease PJ, Li J, Chi E, et al. Malignancies from patients receiving etanercept across approved indications [abstract]. Ann Rheum Dis 2008;67 Suppl II:322. | Randomized, double-blind trial, infliximab for psoriasis administered as intermittent or continuous dosing, n = 835, 50-wk followup. 9 BCC, 1 SCC, 0 MM. All patients with BCC or SCC with prior exposure to nbUVB (8 subjects, PUVA (2), or both (2); placebo group 0 BCC, 0 SCC, 0 MM identified[30] |
| Cyclosporine | Multicenter observational prospective 5-yr cohort study in severe psoriasis patients, n = 1252, controls from general population cancer registries in anticipating areas; 47% patients w/prior PUVA therapy; mean duration 1.9 yrs exposure, initial average dose 2.7–3.0 mg/kg. Overall SIR BCC 1.8, 95% CI 0.6–4.1, SCC 24.6, 95% CI 13.8–40.7, MM 4.7, 95% CI 0.6–17.0[32]<br>Nested cohort crossover PUVA followup study, n = 28; with prior PUVA (> 200 sessions) and MTX use, incident rate ratio 3.1, 95% CI 2.6–3.7[33]<br>Retrospective cohort study, n = 272 (n = 63 psoriatics) of cyclosporine in skin disease; 0 BCC, 0 SCC, 0 MM. Powered to exclude 2× increase in cancer risk w/power 90%, at paired 0.05 significance level; median followup 10.9 yrs, median treatment 8 mo; half of patients with prior "phototherapy" exposure[34] | | Multicenter study in severe psoriasis patients, treatment 6 to 30 mo with 3 mo post-treatment observation, n = 217; 2 BCC[44]<br>Combined data from 3 clinical trials of cyclosporine in psoriasis, n = 122; median treatment 21.5 mo. 1 metastatic SCC of neck noted after treatment in followup; > 70% with prior PUVA exposure[45] |



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*Table 2.* Continued.

| Medication | Case-Control/Cohort Study | Metaanalysis Data | Clinical Trials Data |
|---|---|---|---|
| Methotrexate | Cohort study, n = 248 psoriatic, dose 5–25 mg, median followup 7 yrs; 1 SCC noted[46]<br>Nested case-control study of Finnish hospitalized psoriasis patients, n = 67 cases; RR MTX exposure 0.4, 95% CI 0.1–1.9; elevated rate of SCC in cohort likely associated with prior PUVA use[47]<br>Initial assessment, PUVA followup study, n = 1380, evaluate history of MTX use and NMSC; no association between MTX and NMSC in either PUVA-naive or treated patients[48]<br>PUVA followup cohort study, average followup 13.2 yrs, n = 1380, MTX exposure > 4 yrs, average at least 3 g (independent of PUVA exposure) RR SCC 2.0, 95% CI 1.4–2.8[35] | | |
| Alefacept | | | Open-label trial of alefacept (up to 3 courses) in parallel with other chronic psoriasis thrapy (MTX, retinoids, UVB, cyclosporine, prednisone, topicals), n = 449; 4 BCC, 4 SCC, 0 MM[37]<br>Combined data from 13 trials in the alefacept clinical trial program, n = 1869; 39% with prior PUVA exposure. 36% of malignancies in trial were BCC or SCC; no specifics provided[38] |
| Ustekinumab | | | Double-blind, placebo-controlled RCT in psoriasis, n = 146, 52-wk followup; 1 BCC, 0 SCC, 0 MM[39]<br>PHOENIX 1: Double-blind, place bo controlled RCT in psoriasis, n = 766 76-wk followup; 2 BCC, 0 SCC, 0 MM[40]<br>PHOENIX 2: Double-blind, placebo controlled RCT in psoriasis, n = 1230, 52-wk followup; 0 BCC, 0 SCC, 0 MM[41]<br>Randomized trial ustekinumab vs etanercept in moderate to severe psoriasis, n = 903, 64-wk followup; 6 BCC, 1 SCC, 2 patients with BCC + SCC; no case of NMSC in etanercept-only group[42] |

Abbreviations as in Table 1. PUVA: psoralen ultraviolet A; nbUVB: narrow-band ultraviolet B.



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cases and controls[27]. A case-control study from Western Canada from the 1980s showed no association between psoriasis and MM[28]. Ultraviolet light [likely psoralen ultraviolet A (PUVA) at the time] was controlled for; however, the number of exposed individuals in both cases and controls was quite low. On the other hand, a Danish cohort study of 6,910 psoriatic patients identified an SIR of 3.86–4.7 for SCC and 2.16–2.33 for BCC[29]. The rates of melanoma were similar in psoriasis patients and the general population. Prior PUVA exposure was not accounted for in the latter, which may explain the discrepancy in NMSC risk between these studies.

*Tumor necrosis factor agents*. Four studies examined the role of anti-TNF agents in the development of cutaneous malignancy in psoriasis. Analyzing the combined data from 36 global trials of adalimumab, the SIR for SCC was 3.84 (95% CI 1.54–7.92)[19]. Similar to the RA data, the elevated risk of SCC was only significant when the National Cancer Institute dataset, but neither the Arizona nor Minnesota datasets, was used as the control population. A trend for increased risk of NMSC in psoriasis patients was noted during the analysis of 49 global trials (n = 13,977) of etanercept in RA, juvenile idiopathic arthritis, psoriasis, PsA, and ankylosing spondylitis (rate ratio 2.77, 95% CI 0.59–25.97)[20]. This elevated risk of NMSC is seen when the rate of NMSC in etanercept-treated psoriatic patients is compared to 2 general population cohorts representing 2 different sun-exposure climates, Arizona and Minnesota. Nine BCC and one SCC were identified during an RCT investigating continuous versus intermittent dosing in infliximab[30]. All of these subjects had been exposed to either PUVA or narrow-band ultraviolet B (nbUVB). No malignancies were identified in the placebo group. One retrospective study of 77 psoriatic patients treated with etanercept (most completed 6 months of treatment, a small number were treated up to 2 years) did not identify any new malignancies[31]. Mean followup was not reported in this study.

*Cyclosporine*. Several studies assess the risk of NMSC and MM in psoriatic patients treated with cyclosporine. The level of phototherapy exposure ranges from as low as half to 100% of patients in each of 4 cohort studies. Two cohort studies identify an increased rate of SCC in cyclosporine-treated patients. The largest study is a multicenter observational prospective 5-year cohort study of 1252 patients[32]. While the rates of BCC and MM were not elevated, the SIR for SCC was 24.6. When low exposure (< 2 years) versus high exposure (> 2 years) groups were compared, the risk of NMSC was 3.3 times greater in the latter group even after controlling for PUVA, MTX, and other immunomodulatory exposures. The other positive study is a nested cohort study from the larger PUVA followup dataset[33]. In contrast, one retrospective cohort study shows no increased risk of either NMSC or MM with cyclosporine use in psoriatic patients[34]. Nonetheless, a relatively small number of psoriatic patients were included in this current study (the mixed dataset included patients with psoriasis, atopic dermatitis, palmoplantar pustulosis, and hand eczema), thus limiting the study's power.

*Methotrexate*. Four cohort studies assessed the risk of cutaneous malignancy in psoriatic patients treated with MTX. The only study that links MTX use in psoriasis to cutaneous malignancy is from the Photochemotherapy Follow-up Study[35]. Assessment of 1,380 patients treated with an average MTX exposure > 4 years and followup of 13.2 years demonstrated a relative risk of 2.0 (95% CI 1.4–2.8) for SCC, after controlling for prior PUVA therapy. This result is particularly intriguing because the prior analysis of this study population showed no correlation between MTX use in psoriasis when patients were followed up after only 1 to 3 years[36].

*Alefacept*. The risk of cutaneous malignancy with alefacept in psoriasis is addressed in 2 studies. The first simply characterizes the number of cutaneous malignancies noted during an open-label trial[37]; a total of 8 cases of NMSC were noted in 449 subjects. Without a control group, however, this information is difficult to interpret. A second study reviews the combined clinical trial data of 13 studies in the alefacept clinical trial program[38]. Examining the malignancies in 1,869 subjects exposed to alefacept, the authors note that 63% of all malignancies discovered (total number not provided) were either SCC or BCC. Unfortunately, further details characterizing these malignancies were not provided. Again, how this compares to the expected number is difficult to determine.

*Ustekinumab*. No studies directly evaluated the risk of cutaneous malignancy during ustekinumab therapy. Three placebo-controlled randomized clinical trials identified only one BCC in 2,048 subjects with 52- to 76-week followup[39,40,41]. However, in a recent trial (n = 903) of ustekinumab versus etanercept in moderate to severe psoriasis, the following numbers of patients with NMSC were identified after 64-week followup: 6 BCC, one SCC, 2 BCC and SCC[42]. No patients in the etanercept-only treatment group were described. No case of MM was identified in any of the treatment subgroups.

## DISCUSSION

Baseline risk for cutaneous malignancy appears to be increased in patients with RA. Determining whether patients receiving immunomodulatory therapy for RA, psoriasis, and PsA are at further increased risk for cutaneous malignancy with the data currently available is challenging. The number and quality of available data are limited for most of the immunomodulatory agents. In comparison to some of the older, established medications, the data are more plentiful for the biologics. Further, the RA data are more robust than

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the psoriasis and PsA data. This is not surprising, given the relatively higher number of RA patients treated with systemic immunomodulatory agents compared to psoriasis and PsA. Despite the relative dearth of data in psoriasis and PsA, generalizing the RA data to either of these patient populations should be done with caution.

The most robust data presented in this review demonstrate that TNF inhibitors are likely to increase the risk of NMSC. Two separate cohorts (from the Swedish registry and the National Data Bank for Rheumatic Diseases) show 1.2-fold to 6.5-fold increase in NMSC in anti-TNF-treated patients with RA. Another important feature of the 2005 NDB study is the almost 2-fold increase in NMSC in TNF-treated RA patients treated with MTX. Although the randomized clinical trial data do not support these associations, this is likely because the length of followup during the clinical trials is quite limited in comparison to the cohort analyses. The exception to this short followup is the etanercept in RA study by Lebwohl, *et al*, in which the mean drug exposure was 3.7 years[16]. SCC may have been underreported during the postmarketing surveillance of etanercept, thus underestimating the risk of NMSC.

A trend for an increase in MM in TNF-treated RA patients was noted in both the Swedish registry and the NDB. Despite the lack of statistical significance, such trends raise a cautionary flag and should be evaluated further with longterm prospective studies. The increase noted in MTX monotherapy in RA patients seen in the Australian registry is concerning. Although this is only one study characterizing increased risk, clinicians may find it most prudent and cautious to ensure regular skin screening examinations for these patients.

In contrast to RA, there are no well established psoriasis cohorts that can provide adequate length of followup data to assess the risk of cutaneous malignancy during immunomodulatory therapy. Prospective cohorts established in conjunction with postmarketing surveillance could help clarify these risks, especially with respect to the introduction of new medications on the market. Such cohorts, properly designed, could help reduce the phototherapy bias found in the current psoriasis data.

The noted increase in SCC with cyclosporine in PUVA-treated psoriatic patients is not surprising. Caution is advised in treating patients with any history of PUVA therapy with cyclosporine.

There are a number of limitations in these studies. The difficulty in assessing risk of NMSC for newer medications is mostly due to lack of data collection and exclusion of NMSC data from study registries. Exclusion of these data is unfortunate and does not allow more thorough safety analysis of these medications. Because only the studies discovered during the search algorithm were included in analysis, it is possible that the data for one or more relevant studies are not presented. Inclusion of studies not identified during the search algorithm may have led to biased data collection.

Given the relative ease of skin examination and knowledge that early detection is the best treatment for cutaneous melanoma, our recommendations are relatively conservative. We propose that patients receiving MTX monotherapy or TNF inhibition (particularly with combination MTX) should undergo regular skin examination by a dermatologist. Further, any patient (in particular those with psoriasis or psoriatic arthritis) with a history of PUVA exposure undergoing therapy with any of the immunomodulatory agents mentioned (especially cyclosporine) should also undergo regular skin examination. Clinical judgment may also determine that all patients with RA should undergo regular screening given the possible increased risk of NSMC. Lastly, as the existing data are so sparse for many immunomodulators (MTX, rituximab, ustekinumab, azathioprine, abatacept, alefacept), it may be prudent for some of these patients to undergo regular skin examination as well. It is important to remember that the absence of data does not indicate a lack of association; conservative management, particularly in those with a prominent history of sun exposure, may be in the patient's best interest.

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