IN-DEPTH REVIEWS

Psoriasis therapies and the risk of cutaneous malignancy

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ABSTRACT

Background: Systemic therapies for moderate-to-severe psoriasis target the dysregulated inflammatory response. However, their immunomodulatory properties may also contribute to carcinogenesis, leading to an increased risk of cutaneous malignancy in patients exposed to systemic agents.

Objective: A review of the literature was performed to evaluate the risk of cutaneous malignancy associated with the following therapies for moderate-to-severe psoriasis: Psoralen and ultraviolet A (PUVA), ultraviolet B (UVB), cyclosporine, methotrexate, retinoids, TNF-α inhibitors, IL-12/23 inhibitors, and IL-17 inhibitors.

Results: Rates of non-melanoma skin cancer (NMSC), most notably squamous cell carcinoma (SCC), increase linearly with the number of PUVA exposures. UVB radiation, both narrowband and broadband, has no clear association with skin cancer. There is a well-characterized association between cyclosporine and NMSC, particularly SCCs, although it is less clear whether cyclosporine predisposes to malignant melanoma. Methotrexate appears to increase the risk of melanoma and NMSC in a dose-dependent fashion. Retinoids, on the other hand, have chemopreventative properties and may decrease the risk of NMSC in patients with psoriasis. A large body of evidence supports an increased risk of NMSC, particularly SCC, in TNF-α inhibitors, but an association with melanoma is less clear. The newly-developed agents, IL-12/23 and IL-17 inhibitors, do not clearly show an increased carcinogenic risk, but their long-term safety profiles are still under investigation.

Conclusions: Many systemic psoriasis therapies, including PUVA, cyclosporine, methotrexate, and TNF-α inhibitors, appear to increase the risk of cutaneous malignancy. When prescribing these agents, physicians must weigh the benefit of treatment with their carcinogenic potential. Additional post-marketing surveillance is required to better understand the long-term risks of the newer biologic agents.

INTRODUCTION

Psoriasis is a complex inflammatory disease that affects approximately 3.2% of US adults[1]. Chronic inflammation associated with psoriasis is a risk factor for multiple medical comorbidities, including malignancy. Several studies have revealed an increased

incidence of skin, lymphohematopoietic, and solid cancers in this population[2]. This risk arises independently of exposure to systemic agents. In a cohort of 186,076 patients with mild psoriasis (defined as never receiving systemic therapy), there was a small but significant increase in non-melanoma skin cancer (NMSC) [adjusted hazard ratio (aHR) 1.09, 95% confidence interval (CI) 1.05-1.13] and all other cancers (aHR 1.06, 95% CI 1.02-1.09) compared to age- and gender-matched controls[3]. An increased risk of NMSC was also recently observed in large cohorts of psoriasis patients in the United States and Taiwan[4,5].

In addition to the intrinsic risk of malignancy associated with the psoriasis disease state, patients with psoriasis are also exposed to several therapies with carcinogenic potential. Approximately 25% of psoriasis patients have moderate (3-10%) to severe (>10%) body surface area involvement, often requiring systemic therapy. Treatment options include phototherapy (ultraviolet B radiation and psoralen and ultraviolet A), systemic non-biologic immunosuppressants (cyclosporine, methotrexate, and retinoids), and biologic agents that inhibit specific targets of the inflammatory pathway (TNF-α, IL-12/23, and IL-17 inhibitors). These immunomodulatory therapies target the dysregulated inflammatory response in psoriasis, but also may contribute to carcinogenesis. A review of the literature was performed to evaluate the risk of malignancy associated with the above systemic agents.

PSORALEN AND ULTRAVIOLET A (PUVA)

The long-term safety profile of PUVA has been studied most comprehensively by Stern *et al*. through the PUVA Follow-up Study, which prospectively followed 1,380 patients with moderate-to-severe psoriasis. Three decades of follow-up have revealed an increased risk of NMSC, particularly squamous cell carcinoma (SCC), in PUVA-treated patients[6]. 351 participants (25%) developed a total of 2,973 SCCs, corresponding to a 32 times greater incidence (95% CI 30.8-33.1) of SCC compared to age- and gender-matched controls. SCC risk increases linearly with the number of exposures, most notably after 150 treatments. Basal cell carcinoma (BCC) risk is less pronounced than SCC risk but still 4.7 times higher (95% CI 4.5-4.9) than the general population. NMSC risk is further amplified with prior or concomitant exposure to other carcinogens, including methotrexate and cyclosporine, and decreased with active oral retinoid use[6-8]. SCC risk does not significantly decrease even 15 years after discontinuation of therapy[9].

Several retrospective studies of the Dutch, Swedish, and Finnish Cancer Registries also demonstrate a dose-dependent increased risk of NMSC, primarily SCC, in PUVA-exposed patients, although reported risks were not as high as described in the United States cohort[10-12].

PUVA also stimulates melanocyte hyperplasia, predisposing to atypical pigmented lesions. There is a small but significant increased risk of melanoma in PUVA-treated patients compared to age- and sex-adjusted controls (RR = 2.3, 95% CI 1.1-4.1)[13]. This risk is amplified in patients at least 15 years from their first PUVA treatment (IRR = 5.9, 95% CI 2.2-15.9) and in those who received at least 200 PUVA treatments (IRR = 2.0, 95% CI 0.9-9.5), although the latter result was not statistically significant[14]. However, the association between malignant melanoma and PUVA is not as clear as that described for NMSC,

and all of the major retrospective European studies reported no increased risk of malignant melanoma in PUVA- treated patients[10-12].

ULTRAVIOLET B (UVB)

UVB phototherapy includes broadband (280-320 nm) and narrowband (311-313 nm) radiation. Narrowband UVB (NB-UVB) was developed after studies demonstrated that wavelengths below 300 nm are more likely to produce burns, while wavelengths above 313 nm are not effective in clearing psoriasis. The optimized anti-psoriatic to erythemogenic ratio in NB-UVB promotes more rapid clearance and longer remission than broadband UVB (BB-UVB)[15].

Although natural sunlight is a known carcinogen, several studies suggest that BB-UVB therapy does not appreciably increase carcinogenesis in patients with psoriasis. A systematic review of 11 studies involving 3,400 patients revealed no increased risk of NMSC or melanoma in BB-UVB-treated patients[16]. The PUVA Follow-up Study initially demonstrated no association between NMSC and long-term exposure to UVB or topical tar. However, a later study published after an additional 14 years of data collection suggested that high UVB exposure, defined as greater than 300 treatments, was associated with a small but significant increased risk of SCC (adjusted IRR = 1.37, 95% CI 1.03-1.83) and BCC (adjusted IRR = 3.00, 95% CI 1.30-6.91) in PUVA-treated patients[17]. Of note, an increased risk of genital tumors has also been observed in men treated with PUVA or UVB without genital shielding[18], which has subsequently become standard practice. BB-UVB may be used alone or in combination with topical tar with no appreciable increase in skin cancer risk[19].

NB-UVB therapy also does not appear to increase the incidence of NMSC or melanoma. In the largest study to date of 3,867 patients treated with NB-UVB in Scotland, half of whom had psoriasis, no significant association with SCC, BCC, or melanoma was detected[20].

CYCLOSPORINE

The carcinogenic potential of cyclosporine has been well characterized in post-transplant patients on immunosuppressive regimens. The risk of NMSC, particularly SCC, rises proportionally with duration of treatment and is as high as 47.1% after 20 years of immunosuppressive therapy[21]. Interestingly, the risk of NMSC appears higher on sun-exposed skin, suggesting that immunosuppression may promote UV radiation-mediated carcinogenesis[22]. Murine experimental models also suggest that cyclosporine promotes tumor growth independently of its effect on host immunity through several direct cellular mechanisms, including promoting invasiveness of non-transformed cells[23].

An increased risk of NMSC is evident in psoriasis patients on cyclosporine as well. A cohort of 1,252 patients with severe psoriasis demonstrated a 6-fold higher incidence of cutaneous malignancies, mostly SCC, in patients treated with cyclosporine compared to the general population after 5 years (SIR = 6.2, 95% CI 3.8-9.5)[24]. Patients treated with cyclosporine for more than 2 years showed an elevated risk of NMSC over those treated for shorter periods (RR = 3.3, 95% CI 1.3-8.4). Prior exposure to PUVA, methotrexate, or immunosuppressants also significantly amplified risk of NMSC.

Several case reports suggest an association between cyclosporine and malignant

melanoma[25,26]. However, this observation has not been substantiated in larger studies[24].

METHOTREXATE

Methotrexate appears to increase the risk of NMSC in a dose-dependent manner. In a recently-published study of 405 patients with rheumatoid arthritis or psoriatic arthritis, patients who received methotrexate doses above 8,000 mg developed NMSC at a rate almost 5-times that of patients never exposed to methotrexate (SIR 4.81, 95% CI 3.60-6.29). This risk drops to 2-fold in patients with cumulative doses less than 5,000 mg (SIR 2.31, 95% CI 1.58-2.36). In the PUVA Follow-Up Study, exposure to at least two years of methotrexate increased SCC risk by an additional 2.4-fold (95% CI 2.13-2.79). However, some studies have shown no association between methotrexate exposure and NMSC[27].

Methotrexate may also increase melanoma risk. In a cohort of 459 rheumatoid arthritis patients receiving methotrexate, a 3-fold (SIR = 3.0, 95% CI 1.2-6.2) increased risk of melanoma was observed compared to the general population after an average follow up of 9.3 years[28]. Recently, a small but significant increased risk of cutaneous melanoma was detected in patients to whom methotrexate was dispensed from Swedish pharmacies when compared to age- and sex-matched controls (HR 1.17, 95% CI 1.08-1.26)[29].

RETINOIDS

Retinoids have been studied extensively for their chemopreventive properties. They protect against malignant transformation by limiting cell cycle progression, promoting apoptosis of cancer cells, and downregulating proto-oncogenes[30]. Systemic retinoids have demonstrated efficacy in preventing NMSC formation in high risk populations like organ transplant recipients or patients with genodermatoses such as xeroderma pigmentosum or basal cell nevus syndrome[31,32]. In a randomized controlled trial of 44 renal transplant recipients, 11% of patients treated with 30 mg/day of acitretin for 6 months developed two new SCCs, while 47% of patients receiving placebo developed 18 new SCCs[32].

The chemoprotective benefit of systemic retinoids seems to apply only for the duration of therapy. Five patients with xeroderma pigmentosum showed 63% (p=0.019) reduction of cutaneous tumor burden during two years of high-dose oral isotretinoin therapy, from 121 tumors in the two years proceeding therapy to 25 tumors during treatment. However, during one year of continued observation after discontinuation of isotretinoin, the tumor burden increased 8.5-fold (p=0.007) over that observed during the treatment period, returning to pre-treatment levels[31].

Low-dose systemic retinoid regimens were developed in an attempt to limit side effects but appear less effective overall[33]. However, one study did demonstrate a significant chemoprotective effect of low-dose (0.3 mg/kg) daily acitretin in renal transplant patients for up to 4 years of treatment[34]. Topical regimens also do not appear efficacious in preventing malignancy. Recently, a randomized controlled trial of 1,131 patients from the Veterans Affairs system with a 5-year history of 2 or more NMSCs showed no statistically significant benefit of 0.1% topical tretinoin in precluding development of invasive NMSC or actinic keratosis[35].

TNF-a INHIBITORS

TNF-α inhibitors are effective therapies for a variety of immune-mediated diseases, but TNF-α also facilitates the immune response against tumor cells via dendritic cell activation and tumor cell apoptosis. In murine tumor cells, transduction with the human TNF-α gene promotes tumor regression, an effect that is reversed following treatment with anti-TNF-α antibody[36].

The carcinogenic potential of TNF-α inhibitors has been studied most extensively in rheumatoid arthritis patients. A large meta-analysis of 74 randomized controlled trails of the TNF-α inhibitors adalimumab, etanercept, and infliximab revealed a 2.02 relative risk (95% CI 1.11-3.95) of NMSC in 15,418 pooled patients on TNF-α inhibitors compared to 7,486 comparators at a median duration of <6 months[37]. A systematic review and meta-analysis of four studies encompassing over 29,000 patients revealed a 45% increased risk of NMSC in patients treated with TNF-α inhibitors compared to those receiving non-biologic therapy (relative risk = 1.45, 95% CI 1.15-1.76)[38].

A recently-published study of 5,889 patients within the Kaiser Permanente Northern California health plan assessed malignancy rates among patients receiving systemic therapy for psoriasis[39]. The cohort was subdivided into those treated with at least one biologic and those treated exclusively with non-biologic systemic agents. SCC rates were increased 81% among biologic users (aHR 1.81, 95% CI 1.23-2.675), 97% of whom were treated with TNF-α inhibitors. Conversely, BCC and melanoma rates were comparable among biologic and non-biologic users (BCC aHR = 1.23, 95% CI 0.91-1.66; melanoma aHR = 1.57, 95% CI 0.61-4.09).

Larger studies have consistently failed to show a significantly increased risk of melanoma in patients treated with TNF-α inhibitors[38,40].

IL-12/23 INHIBITORS

IL-12 and IL-23 are inflammatory cytokines that contribute to the aberrant immune response in psoriasis. IL-12 promotes Th1-helper cell differentiation and the production of interferon by natural killer cells. IL-23 stimulates Th17 cells, whose effector cytokines are thought to promote keratinocyte proliferation. Pre-clinical models have produced conflicting data on whether IL-12 and IL-23 promote or protect against tumor development.

Ustekinumab, a fully human monoclonal antibody that inhibits the p40 subunit of IL-12 and IL-23, was approved in September 2009 for the treatment of moderate-to-severe plaque psoriasis. In short-term, placebo-controlled clinical trials of ustekinumab, rates of NMSC were comparable among patients receiving placebo (1.13/100 patient-years, 95% CI 0.14-4.09), 45 mg ustekinumab doses (0.49/100 patient-years, 95% CI 0.01-2.75), and 90 mg ustekinumab doses (0.98/100 patient-years, 95% CI 0.12-3.55) through 3 years[41]. Safety data pooled from four studies of 3,117 psoriasis patients found the rate of NMSC was 0.64 (0.41-0.95) and 0.44 (0.28-0.66) per 100 patient-years for 45 mg and 90 mg doses of ustekinumab, respectively, after up to 5 years of follow-up[42]. These rates are comparable to but lower than those reported for TNF-α inhibitors, which range from 0.7 to 1.17 per 100 patient-years. However, the IL-12/23

inhibitors are too new to make conclusive statements regarding their safety profile.

IL-17 INHIBITORS

IL-17 inhibitors are the newest biologics used to treat moderate-to-severe plaque psoriasis. Th17 cells produce IL-17 upon activation by IL-23 from dendritic cells. Some studies suggest that IL-17 promotes inflammation-mediated tumor growth[43], in which case inhibiting expression of IL-17 or its upstream regulatory cytokine, IL-23, could theoretically protect against carcinogenesis. However, other studies have described a protective role of IL-17 in tumor immunity[44].

Secukinumab is a fully human monoclonal antibody that was approved in January 2015. In data pooled from 10 phase II/III secukinumab psoriasis trials involving 3,993 subjects, the incidence of NMSC was comparable in the first 12 weeks among patients receiving placebo (0.4, 95% CI 0.1-1.2), 150 mg secukinumab doses (0.17, 95% CI 0.03-0.68), or 300 secukinumab doses (0.09, 95% CI 0-0.55)[45]. Four cases of melanoma were identified, all of which occurred in patients at increased risk based on medical history or prior exposure to immunosuppressive agents.

Ixekizumab was recently approved in March 2016 and brodalumab in February 2017. Long-term safety data is not yet available for these agents, and additional follow up is required to more accurately assess their risk of NMSC and melanoma.

CONCLUSIONS

Patients with psoriasis have an increased risk of several malignancies, which is amplified by exposure to certain systemic therapies. PUVA-treated patients exhibit higher rates of NMSC, most notably SCC, which increase linearly with the number of exposures. Melanoma risk is amplified in patients at least 15 years from their first PUVA treatment and in those who received at least 200 PUVA treatments. UVB radiation, both narrowband and broadband, has no clear association with skin cancer. There is a well-characterized association between cyclosporine and NMSC, particularly SCCs, although it is less clear whether cyclosporine predisposes to malignant melanoma. Methotrexate appears to increase the risk of melanoma and NMSC in a dose-dependent fashion. Retinoids, on the other hand, have chemopreventative properties and may decrease the risk of NMSC in patients with psoriasis.

Biologic agents, including TNF-α, IL-12/23, and IL-17 inhibitors, target specific components of the inflammatory pathway. These agents have proven very effective in treating psoriasis, so much so that psoriasis area severity index (PASI) 90 scores are now achievable targets in newer clinical trials. A large body of evidence supports an increased risk of NMSC, particularly SCC, in TNF-α inhibitors, but an association with melanoma is less clear.

The newly-developed agents, IL-12/23 and IL-17 inhibitors, do not clearly show an increased carcinogenic risk, but their long-term safety profiles are still under investigation. Interestingly, the ratio of BCC to SCC observed thus far in these agents approximates that of the general population (4:1). In contrast, a SCC predominance has historically been observed in patients on immunosuppressive therapy, like cyclosporine and TNF-α inhibitors. It is possible that this observation may reflect a

lower degree of immunosuppression and lower malignancy risk in patients treated with IL-12/23 or IL-17 inhibitors. However, additional post- marketing surveillance is required to better understand their long-term risks. Until more comprehensive data are available, physicians must weigh the benefit of treatment with the possibly underestimated carcinogenic potential of these newer agents.

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