Do Psoriasis Therapies Increase the Risk of Skin Cancer?

Mark Lebwohl, MD
Sol and Clara Kest Professor
And Chairman
Department of Dermatology
The Mount Sinai School of Medicine
• UVB
• Narrowband UVB
• PUVA
• MTX
• Retinoids
• Cyclosporine
• Biologics
• Apremilast
UVB doses in maintenance psoriasis phototherapy versus solar UVB exposure.
Schothorst AA, et al

“The cumulative incidence among patients who received maintenance phototherapy for several decades was calculated to be a factor of 2.5 to 7.5 higher than the incidence among individuals with an outdoor occupation.”
Skin Cancer In Patients With Psoriasis Treated With Coal Tar
A 25-Year follow-up study

Pittelkow MR, Perry HO, Muller SA, Maughan WZ, O'Brien PC.
• Phototherapy is administered in a controlled manner, with slowly increasing increments.

• Typical phototherapy burn is often only a little higher than the MED. Blistering sunburns are often several times the MED.

• Spectrum of phototherapy is not identical to that of sunlight.
The photocarcinogenic risk of narrowband (TL-01) phototherapy: early follow-up data

Man I, Crombie IK, Dawe RS et al.


- 1908 pts
- .04 – 14 years (median 4)
- 1-199 NB treatments (median 23)
- 30-284,415 mJ/cm² (median 13,337)
• No increase SCC or MM
• 10 BCC vs. 4.7 expected, 9 on face
• *Patients under regular dermatological follow-up are more likely to have skin cancers detected.*

Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). The PUVA Follow-Up Study.

Stern RS, Nichols KT, Vakeva LH.


- relative risk 5.4, beginning 15 yrs. after 1st treatment
- ↑risk with ↑number of treatments
Incidence of melanoma and other malignancies among rheumatoid arthritis patients treated with methotrexate.

Buchbinder R et al.


- RA pts started on MTX pre 1986
- State cancer registry (not NMSC)
- 4,145 person-years (avg.9.3 yrs)
MTX associated with:
- 50% ↑ risk of malignancy
- 3-fold ↑ in melanoma
- 5-fold ↑ in nonHodgkins lymphoma
- 3-fold ↑ in lung ca.

Buchbinder R et al.  


- Acitretin 30 mg/d
- 2/19 ➔ 2 SCCs vs 9/19 ➔ 18 SCCs
Chemoprevention of skin cancer in xeroderma pigmentosum.

- 121 BCCs or SCCs in 5 patients 2 years prior to Rx
- Isotretinoin 2 mg/kg/d → 25 tumors over 2 years of Rx

- 18.8%, <5 years
- 24.8%, 5-10 years
- 33.3%, 10-20 years
- 47.1%, >20 years
Skin Cancer in Organ Transplant Patients

Berg and Otley, JAAD 47:1-17, 2002
Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 y cohort study.

- 1252 patients for up to 5 years (average 1.9)
- 6-fold ↑ skin cancer
- No ↑ nonskin cancer
Cutaneous malignant melanoma occurring after cyclosporin A therapy.
Arellano F, Krupp PF.

Cutaneous malignant melanomas occurring under cyclosporin A therapy: a report of two cases.
Mérot Y, et al.
TNF blockers

Key Cells and Mediators in Psoriasis

- **Adaptive immunity**
  - **Ustekinumab**
    - IL-23
    - INF-γ
    - IL-20
  - **Adalimumab**
    - INF-γ
  - **Etanercept**
  - **Infliximab**
  - **Certolizumab**
- **Innate immunity**
  - Keratinocyte
  - Natural killer T cell
  - Myeloid dendritic cell
  - Plasmacytoid dendritic cell
  - Macrophage

**Antimicrobial peptides**
- IL-1β
- IL-6
- TNF-α
- S100
- CXCL8
- CXCL9
- CXCL10
- CXCL11
- CCL20

**Activation**

**Innate immunity**

- **Th1 cell**
  - INF-γ
  - IL-20
  - IL-22
  - IL-17
- **Th22 cell**
  - INF-γ
  - IL-22
  - IL-17A
- **Th17 cell**
  - INF-γ
  - IL-17A
  - IL-17F
  - IL-17R

Rapid onset of cutaneous squamous cell carcinoma in patients with rheumatoid arthritis after starting tumor necrosis factor alpha receptor IgG1-Fc fusion complex therapy.

Multiple squamous cell carcinomas in the setting of psoriasis treated with etanercept: A report of four cases and review of the literature.

Brewer JD, et al.

The rapid onset of multiple squamous cell carcinomas during etanercept treatment for psoriasis.

Ly L, et al.

Rapid onset and fatal outcome of two squamous cell carcinomas of the genitalia in a patient treated with etanercept for cutaneous psoriasis.

Comte C, et al.

Multiple and fulminant cutaneous squamous cell carcinomas in a Crohn's disease patient treated with immunosuppressants and adalimumab.

Nancey S, et al.

Inflamm Bowel Dis. 2011;17(4):1060-1.
Kowalzick L et al.
Metastatic melanoma in a young woman treated with TNF-α inhibitor for psoriatic arthritis: a case report.

Marasini B, et al.

Eruptive latent metastatic melanomas after initiation of antitumor necrosis factor therapies.

Fulchiero GJ Jr, et al.

Cutaneous melanoma in patients in treatment with biological therapy: review of the literature and case report.

Manganoni AM, et al.

Development of two primary malignant melanomas after treatment with adalimumab: a case report and review of the possible link between biological therapy with TNF-alpha antagonists and melanocytic proliferation.
Melanoma at a dysplastic nevus excision site in a patient on etanercept.

Hacard F, et al.

Primary cutaneous melanoma: a complication of infliximab treatment?

Khan I, et al.

Multiple basal cell carcinomas after etanercept treatment for psoriasis.

Maire C, et al.

Merkel cell carcinoma in a patient treated with adalimumab: case report.

Krishna SM, et al.

Malignancy rates in a large cohort of patients with systemically treated psoriasis in a managed care population.
Maryam M. Asgari, et al. 
JAAD. Available online 3 February 2017 (In press).

age, gender, race & comorbidity adjusted HR

- Any cancer (except NMSC) 0.86 (0.66-1.13)
- cSCC 1.81 (1.23-2.67)
- BCC 1.23 (0.91-1.66)
- MM 1.57 (0.61-4.09)
- Lymphoma 1.01 (0.38-2.70)
Cumulative Rates of NMSC Through 5 Years of Follow-up

- 47 patients reported NMSCs (3 patients reported both SCC and BCC)
  - 40 had BCC (21 on 45 mg and 19 on 90 mg)
  - 10 had SCC (5 on 45 mg and 5 on 90 mg)

**Controlled Period**

<table>
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<th>UST 45 mg</th>
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<td>Rate per 100 PY (95% CI)</td>
<td>1.13 (0.14, 4.09)</td>
<td>0.49 (0.01, 2.75)</td>
<td>0.98 (0.12, 3.55)</td>
<td>0.74 (0.15, 2.16)</td>
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<td>n</td>
<td>732</td>
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<td>792</td>
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**2010 Analyses**

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<tr>
<td>Rate per 100 PY (95% CI)</td>
<td>0.70 (0.43, 1.09)</td>
<td>0.53 (0.33, 0.82)</td>
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**2011 Analyses**

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<td>Rate per 100 PY (95% CI)</td>
<td>0.64 (0.41, 0.95)</td>
<td>0.44 (0.28, 0.66)</td>
<td>0.52 (0.39, 0.70)</td>
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BCC:SCC = 3:1

BCC:SCC = 4:1

ACCEPT data were not included in the Controlled Period rates since it did not include a placebo comparator.
For PHOENIX 2, patients who were dose adjusted from 45 mg to 90 mg were switched to the corresponding column following dose adjustment.
Rates of NMSC by Year Through 5 Years of Follow-up

PHOENIX 2 patients who were dose adjusted from 45 mg to 90 mg were switched to the corresponding column following dose adjustment.
Inborn errors of human IL-17 immunity underlie chronic mucocutaneous candidiasis.
Puel A, et al.  
IL-17 Mediated Inflammation Promotes Tumor Growth and Progression in the Skin

D. He, et al

IL-23 $\rightarrow$ ↑IL-17 $\rightarrow$ ↑tumor growth

Could blocking IL-17 be protective against cancer?
Pubmed search→ no cases of malignancy
Association with Skin Cancer

• Sunlight – strong association
• PUVA – strong association
• Cyclosporine – strong association
• Phototherapy UVB, narrowband UVB – No clear association
• Methotrexate – association
• Retinoids – protective
• TNF blockers – association
• Ustekinumab – no association
• IL-17 blockers – no association – too new
• Apremilast – no association – too new