

Risk of malignancy with systemic psoriasis treatment in the Psoriasis Longitudinal Assessment Registry

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Background: The effect of systemic therapy on malignancy risk among patients with psoriasis is not fully understood.

Objective: Evaluate the impact of systemic treatment on malignancy risk among patients with psoriasis in the Psoriasis Longitudinal Assessment and Registry (PSOLAR).

Methods: Nested case-control analyses were performed among patients with no history of malignancy. Cases were defined as first malignancy (other than nonmelanoma skin cancer) in the Psoriasis Longitudinal Assessment and Registry, and controls were matched by age, sex, geographic region, and time on registry. Study therapies included methotrexate, ustekinumab, and tumor necrosis factor- α (TNF- α) inhibitors. Exposure was defined as 1 or more doses of study therapy within 12 months of malignancy onset and further stratified by duration of therapy. Multivariate conditional logistic regression, adjusted for potential confounders, was used to estimate odds ratios of malignancies associated with therapy.

Results: Among 12,090 patients, 252 malignancy cases were identified and 1008 controls were matched. Treatment with methotrexate or ustekinumab for more than 0 months to less than 3 months, 3 months to less than 12 months, or 12 months or longer was not associated with increased malignancy risk versus no exposure. Longer-term (≥ 12 months) (odds ratio, 1.54; 95% confidence interval, 1.10-2.15; $P = .01$), but not shorter-term treatment, with a TNF- α inhibitor was associated with increased malignancy risk.

Limitations: Cases and controls could belong to 1 or more therapy categories.

Conclusions: Long-term (≥ 12 months) treatment with a TNF- α inhibitor, but not methotrexate and ustekinumab, may increase risk for malignancy in patients with psoriasis. (J Am Acad Dermatol <http://dx.doi.org/10.1016/j.jaad.2017.07.013>.)

Key words: biologic; conventional systemic; malignancy; methotrexate; psoriasis; PSOLAR; tumor necrosis factor- α inhibitors; TNF- α inhibitors; ustekinumab.

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Psoriasis is a chronic, immune-mediated, inflammatory disease that affects the skin and has important systemic manifestations.^{1,2} In the United States, psoriasis affects nearly 7 million adults age 20 years or older.³ Results of observational studies and a large meta-analysis have indicated that patients with psoriasis have an increased risk for development of malignancies, including lymphoma and nonmelanoma skin cancer (NMSC), compared with those without psoriasis.⁴⁻¹⁰

Understanding whether the risk for malignancy is attributable to the disease state itself or to immunosuppressive systemic therapy is a key consideration for providers and patients. Data quantifying the effect of treatment on malignancy development on the basis of long-term extensions of clinical trials in psoriasis have not demonstrated increased risk for malignancy with tumor necrosis factor- α (TNF- α) inhibitors (etanercept, adalimumab, infliximab) or the anti-interleukin 12/23 antibody, ustekinumab.¹¹⁻¹⁵ Although studies regarding the risk for malignancy with other systemic treatments (eg, methotrexate) are limited in psoriasis, data regarding malignancy risk with long-term exposure to a TNF- α inhibitor in rheumatoid arthritis and across immune-related diseases (including psoriatic arthritis and Crohn's disease) have led to mixed conclusions, with a few studies indicating increased risk.¹⁶⁻²²

The current study was conducted using data from the large, disease-based Psoriasis Longitudinal Assessment and Registry (PSOLAR) of patients with psoriasis. Previous PSOLAR analyses using safety surveillance methodologies and safety data from smaller registries, including Biobadaderm and PsoBEST, suggest no association between use of conventional systemic therapies or biologic agents and malignancy.²³⁻²⁶ This comprehensive case-control analysis assessed whether exposure to commonly used systemic psoriasis therapies and biologic agents is associated with an increased risk for malignancy (excluding NMSC).

PATIENTS AND METHODS

Data source and study population

The study design and methodology of PSOLAR have been detailed elsewhere.^{27,28} Briefly, the registry (established in 2007) comprises a long-term,

prospective, observational cohort of patients with moderate-to-severe psoriasis (aged ≥ 18 years) who were receiving, or were candidates to receive, systemic therapy (including phototherapy) at clinics across North and South America and Europe. Information related to demographic characteristics, disease activity and severity, comorbidities, and

psoriasis medication use is collected every 6 months. Planned follow-up for each patient is at least 8 years from registry enrollment. Governing ethical bodies approved the registry protocol, and all patients provided written informed consent. As of the registry cutoff date for this analysis (August 23, 2015), 12,090 registry participants had been followed for a median of 4.17 years, with a maximum follow-up of 8.2 years (total patient-

years [PYs], 48,870).

To calculate risk associated with study therapy, a nested case-control analysis was performed. Cases consisted of patients with newly diagnosed malignancy (other than NMSC) during PSOLAR participation; malignancies in those with a history of malignancy (other than NMSC) were excluded. The date of first malignancy diagnosis is referred to as the index date. Four randomly chosen control patients were matched with each case by age at index date (± 6 months), sex, geographic region, and enrollment date (± 1 year). The duration of follow-up for each case was the difference between index date and enrollment date. The index date for the matched control was imputed as the enrollment date for that control plus the index duration of follow-up for the matched case. Matched controls were selected without replacement.

Exposure assessment

For the primary analysis, exposure was defined as having received a dose of study therapy within 1 year of the index date. Exposure was further stratified by duration of therapy into 3 discreet categories for each study therapy: more than 0 months to less than 3 months, 3 months to less than 12 months, and 12 or more months. No exposure (ie, no dose of study therapy within 1 year of the index date) was referred to as 0 months. Exposure to multiple therapies was allowed; patients in each category could have been exposed to other study or nonstudy therapies.

CAPSULE SUMMARY

- Systemic therapy may alter the risk for malignancy in patients with psoriasis.
- Long-term (≥ 12 months) treatment with TNF- α inhibitor therapy, but not ustekinumab or methotrexate, may increase risk for malignancy.
- Consideration of malignancy risk associated with individual treatments will help clinicians make informed therapeutic decisions.

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