Serious infections among a large cohort of subjects with systemically treated psoriasis

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Background: Biologic therapy is effective for treatment of moderate-to-severe psoriasis but may be associated with an increased risk for serious infection.

Objective: To estimate the serious infection rate among patients with psoriasis treated with biologic as compared with nonbiologic systemic agents within a community-based health care delivery setting.

Methods: We identified 5889 adult Kaiser Permanente Northern California health plan members with psoriasis who had ever been treated with systemic therapies and calculated the incidence rates and 95% confidence intervals (CIs) for serious infections over 29,717 person-years of follow-up. Adjusted hazard ratios (aHRs) were calculated using Cox regression.

Results: Adjusting for age, sex, race or ethnicity, and comorbidities revealed a significantly increased risk for overall serious infection among patients treated with biologics as compared with those treated with nonbiologics (aHR, 1.31; 95% CI, 1.02-1.68). More specifically, there was a significantly elevated risk for skin and soft tissue infection (aHR, 1.75; 95% CI, 1.19-2.56) and meningitis (aHR, 9.22; 95% CI, 1.77-48.10) during periods of active biologic use.

Limitations: Risk associated with individual drugs was not examined.

Conclusion: We found an increased rate of skin and soft tissue infections among patients with psoriasis treated with biologic agents. There also was a signal suggesting increased risk for meningitis. Clinicians should be aware of these potential adverse events when prescribing biologic agents. (J Am Acad Dermatol 2017;77:838-44.)

Key words: biologics; epidemiology; psoriasis; serious adverse infections; soft tissue infections; TNF-α.

Psoriasis is a chronic, immune-mediated skin disease associated with considerable morbidity that afflicts 2% to 3% of the general population.[1-3] Patients with moderate-to-severe psoriasis have traditionally been treated with systemic antiproliferative or immunosuppressive agents. More recently, biologic agents, including tumor necrosis factor-α (TNF-α) inhibitors, interleukin

Abbreviations used:

aHRs:	adjusted hazard ratios
CI:	confidence interval
IL:	interleukin
IR:	incidence rate
KPNC:	Kaiser Permanente Northern California
SSTI:	skin and soft tissue infection
TNF-α:	tumor necrosis factor alpha

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(IL) 12/IL-23 inhibitors, and IL-17 inhibitors[4-6] targeting key components of the dysregulated inflammatory response, have increased therapeutic options for psoriasis. Despite the efficacy of biologic agents, their effects on immune function may increase risk for adverse events, including infections.

Serious infection, defined as an infection that that requires hospitalization and treatment with systemic antibiotics, can cause substantial morbidity and mortality. Although there is an established association between serious infections and use of biologics in patients with other autoimmune conditions, evidence of this relationship in patients with psoriasis who are using biologics has been disputed.[7-10] A recent meta-analysis revealed no increased risk for serious infection, whereas a prospective cohort study observed a significantly increased risk for serious infection with specific biologic agents.[11,12] The contradictory results may be a result of data aggregation from multiple locations, inadequate follow-up time and sample size, variable exclusion criteria, and inconsistent definitions of serious infection. To address these concerns, we analyzed these events in patients with newly diagnosed psoriasis in a real-world, integrated practice setting with the longest follow-up time to date of any study, together allowing for greater accuracy in data capture and increased likelihood of recording these rare, but serious events. Using data from a large cohort of patients with moderate-to-severe psoriasis treated systemically within an integrated community-based health care system, we have estimated the serious adverse infectious event incidence rate (IR) and adjusted hazard ratio (aHR) among subjects during periods of treatment with a biologic agent, treatment with a nonbiologic agent, and no active systemic treatment.

CAPSULE SUMMARY

- Biologic agents used for psoriasis affect the immune system, potentially increasing serious infection risk.
- We demonstrate increased risk for skin and soft tissue infections and a signal suggesting increased risk for meningitis among systemically treated patients with psoriasis who are undergoing biologic therapy.
- Increased awareness of these serious infection risks may be warranted.

METHODS

Study setting and population

Kaiser Permanente Northern California (KPNC) is a prepaid, comprehensive, integrated care delivery system that maintains computerized data of all visits, procedures, pharmacy-dispensed medications, and other medical goods and services to its 3.9 million members, representing 35% of the insured population in Northern California.[13] The study population included all KPNC health plan members 18 years or older with a diagnosis of psoriasis (defined as having an outpatient dermatologist-rendered visit coded with the *International Classification of Diseases, Ninth Revision,* diagnosis code 696.1) between January 1, 1998, and December 31, 2011, and treated with a systemic agent for psoriasis after diagnosis during the study period. For each subject, the index date was defined as the date on which the member filled a prescription for a systemic agent used to treat psoriasis. At least 12 months of health plan enrollment before the index date was required for study inclusion. Members with the following disease codes in the 365 days before their index dates were excluded: solid organ or autologous bone marrow transplantation, HIV infection, advanced kidney or liver disease, or prior cancer diagnoses (excluding nonmelanoma skin cancer). Patients were followed from their index date until the first occurrence of (1) serious infection; (2) loss of health plan membership; (3) newly diagnosed advanced kidney or liver disease, cancer (excluding nonmelanoma skin cancer), or HIV; (4) solid organ or autologous bone marrow transplant; (5) death; or (6) end of the study period (December 31, 2012). The study was approved by the Kaiser Foundation Research Institute institutional review board.

Data sources

Medication data included the date of the dispensed medication or infusion, route, dose, quantity dispensed, and number of days supplied. Infusions of infliximab were considered equivalent to a 56-day supply, rituximab to a 180-day supply, and other injected or infused drugs to a 30-day supply.

Definition of psoriasis treatment episode

For each individual, we extracted data on all dispensed medications and infusions for oral, intravenous, and intramuscular biologic and nonbiologic agents during the study period. The following agents were classified as biologic treatments: adalimumab, etanercept, infliximab, ustekinumab, golimumab, certolizumab, tocilizumab, abatacept, anakinra, and rituximab. The following