Importance The efficacy of treatment for psoriasis must be balanced against potential adverse events.

Objective To determine the effect of treatment on the risk of serious infections in patients with psoriasis.

Design, Setting, and Participants A multicenter, longitudinal, disease-based registry (Psoriasis Longitudinal Assessment and Registry [PSOLAR]) at dermatology centers. Participants were adult patients with psoriasis who were receiving or were eligible to receive conventional systemic or biologic agents. The registry opened on June 20, 2007, and data included herein were collected through August 23, 2013.

Exposures Patients were prescribed psoriasis therapies as in standard clinical practice. Patients will be followed for up to 8 years. Data were collected and serious adverse events (including serious infections) were assessed at regular intervals.

Main Outcomes and Measures Cohort characteristics are described based on evaluation at entry into the registry. The cumulative incidence rates of serious infections are reported across treatment cohorts, including ustekinumab, infliximab, adalimumab, etanercept, and nonbiologics (with or without methotrexate). A multivariate analysis using a Cox proportional hazards regression model was used to identify predictors of the time to the first serious infection using the nonmethotrexate/nonbiologics cohort as the reference.

Results Data were analyzed from 11,466 patients with psoriasis (22,311 patient-years). Differences in patient characteristics were found between the biologics and nonmethotrexate/nonbiologics cohorts (eg, age, sex, body mass index, and disease characteristics), as well as among the individual biologic groups (eg, a higher prevalence of psoriatic arthritis in the infliximab cohort). The cumulative incidence rate of serious infections was 1.45 per 100 patient-years (n = 323) across treatment cohorts, and the rates were 0.83, 1.47, 1.97, and 2.49 per 100 patient-years in the ustekinumab, etanercept, adalimumab, and infliximab cohorts, respectively, and 1.05 and 1.28 per 100 patient-years in the nonmethotrexate/nonbiologics and methotrexate/nonbiologics cohorts, respectively. The most commonly reported types of serious infections across the registry were pneumonia and cellulitis. Increasing age, diabetes mellitus, smoking, significant infection history, infliximab exposure, and adalimumab exposure were each associated with an increased risk of serious infection.

Conclusions and Relevance Results from PSOLAR suggest a higher risk of serious infections with adalimumab and infliximab compared with nonmethotrexate and nonbiologic therapies. No increased risk was observed with ustekinumab or etanercept.

Trial Registration clinicaltrials.gov Identifier: NCT00508547

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Psoriasis is a chronic immune-mediated disorder that often requires long-term treatment, including conventional systemic therapy (eg, methotrexate) and biologic therapies (eg, tumor necrosis factor [TNF] and interleukin 12/23 antagonists). Although biologic therapy offers new treatment options with high levels of efficacy and convenience, these treatments (along with conventional systemic therapies) have immunomodulatory or immunosuppressive effects that may predispose patients to potential adverse events. Therefore, understanding the long-term safety profile of such therapy, particularly with regard to events such as serious infections, is crucial.

Biologic and conventional systemic agents used for treating psoriasis may be associated with an increased risk of serious infection; however, these treatments may confer different degrees of risk. Much of the available data regarding susceptibility to infection with biologic therapy derives from studies in inflammatory diseases other than psoriasis, such as rheumatoid arthritis and Crohn's disease. However, these patients may have a higher incidence of infection compared with patients with psoriasis due to differences in the underlying disease state. In addition, the approach for treating psoriasis may differ from that for other inflammatory diseases because patients with rheumatoid arthritis or Crohn's disease may be more commonly treated with higher doses of concomitant immunomodulating therapies (eg, systemic corticosteroids, methotrexate, or other systemic therapies), which may increase the risk of infection.

The Psoriasis Longitudinal Assessment and Registry (PSOLAR) is a large intercontinental, prospective, psoriasis-based registry and is designed to capture adverse events (including serious infections) across the spectrum of therapies commonly used to treat psoriasis. This study evaluates the incidence of serious infections among patients with psoriasis exposed to different biologic therapies in a real-world setting and compares the risk with these individual therapies to the risk with nonbiologic treatments. Based on the standard definition promulgated by the US Food and Drug Administration, a serious infection was defined as any infection that results in death, is life threatening, requires inpatient hospitalization or prolonged existing hospitalization, causes persistent or significant disability or incapacitation, or may jeopardize the patient or require intervention to prevent one of these outcomes. The cumulative rates of serious infections across treatment cohorts and the most frequently reported types of infections are summarized, and potential predictors of the time to the first serious infection are evaluated in a multivariate analysis.

Methods

Patients and Study Design
The study design and the inclusion and exclusion criteria for study enrollment have been presented elsewhere. Briefly, eligible adult patients had an established diagnosis of psoriasis for which they were actively receiving (or were eligible to receive) systemic therapies, including biologic agents. Physicians prescribed treatments based on usual clinical practice and standard of care. The use of commercially available medications was not restricted. The planned duration of observation for each patient is 8 years, which permits the capture of long-term exposure outcomes over the course of registry participation. A total of 93 institutional review boards or ethics committees (ie, 41 in North America, 37 in Europe and the Middle East, and 15 in Latin America) approved the registry protocol, and all patients provided written informed consent before study procedures were initiated. The registry opened on June 20, 2007, and data included herein were collected through August 23, 2013.

Data Collection
Data were collected at entry into the registry and approximately every 6 months thereafter, whereas serious adverse events were submitted and evaluated on a real-time basis. All adverse event reports were reviewed. When provided by the investigative site, hospital records were assessed by the study physician to verify reported events. Events were identified as infections if they were coded to terms in the “Infections and Infestations” System organ class of the Medical Dictionary for Regulatory Activities (version 16.0). Per the study protocol, infections were defined as serious if they were associated with 1 or more of the following: (1) death, (2) a life-threatening condition, (3) persistent or significant disability or incapacity, (4) a cause or prolongation of hospitalization, or (5) another medically important condition. Medically important conditions included infections that, based solely on the clinical judgment of the study investigator, may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or require intervention to prevent one of the other conditions included in the definition of serious infections. For this analysis, serious infections were summarized as specific types of infection for further categorization, where relevant. For example, pneumonia pneumococcal and pneumonia staphylococcal were combined into the infection type of pneumonia, whereas nonspecific terms, such as localized infection, were not categorized.

Study Populations and Treatment Cohorts
Patients receiving each biologic (ie, infliximab, adalimumab, ustekinumab, and etanercept) were included in separate cohorts. As in all observational studies, treatment dosing was determined by the treating physician. The sample sizes for other biologics that were either not indicated in major markets for psoriasis currently (eg, golimumab, abatacept, and certolizumab pegol), no longer commercially available (eg, efalizumab, alefacept), or investigational in nature (eg, briakinumab, secukinumab, and brodalumab) were not large enough to allow for feasible statistical analyses at this time. Consequently, results for the other biologics cohort were not included in these analyses (but are reflected in the overall population). Nonbiologic therapies included (but were not limited to) methotrexate, systemic retinoids, psoralen plus UV-A, and UV-B, which may also impact infection risk in different ways and to different degrees. The incidences of serious infections in the biologic cohorts were compared with the incidence in a standard reference group (the subset of patients exposed to only therapies other than methotrexate and biologics), as well
as a sensitivity analysis comparison with those exposed to methotrexate, which is the most commonly prescribed nonbiologic systemic therapy for psoriasis. Patients receiving cyclosporine were not included in the nonbiologics cohort so that biologic therapies could be directly compared with the nonmethotrexate/nonbiologics and methotrexate/nonbiologics cohorts in the absence of any contribution of risk from cyclosporine. Data are presented for the following biologic treatment cohorts: ustekinumab, infliximab, adalimumab, and etanercept. These biologic cohorts did not exclude methotrexate or cyclosporine use. Data are also presented for the 2 nonbiologics cohorts of nonmethotrexate/nonbiologics and methotrexate/nonbiologics (excluding cyclosporine).

Three populations (ie, overall, incident, and bionaive) within the registry were evaluated to assess the risk of serious infections. The overall population is the broadest group and includes patients who started receiving a biologic agent before (prevalent population), at the time of, or after (incident population) enrolling in the registry. The incident population represents the subset of patients who initiated a biologic agent at the time of or after enrolling in the registry but may have been exposed to a different biologic previously. The bionaive population is the subset of incident patients who received their first biologic agent at the time of or after enrolling in the registry and had never had any prior biologic exposure. The primary analysis was focused on the incidence of serious infections in patients in the overall population, including incident and prevalent biologic users, and sensitivity analyses were performed for the narrower incident and bionaive populations. The following 2 nonbiologics cohorts included all patients who had never been exposed to any biologic: (1) those who had not received methotrexate (nonmethotrexate/nonbiologics) (primary comparison) and (2) those who had received methotrexate (methotrexate/nonbiologics). Exposure for each biologic group started at exposure to the first biologic therapy in the registry. For prevalent users, exposure began at the registry start date; however, exposure began at the first dose in the registry for incident and bionaive users. End of exposure for all groups occurred at the earlier of (1) 90 days after discontinuation of that treatment, (2) the initiation of a different biologic, (3) discontinuation from the study, or (4) the data cutoff date (August 23, 2013). Infections that occurred before the start of exposure to the first biologic or after that exposure ended were not included in this analysis. All cohorts within each population analysis were mutually exclusive.

Statistical Analysis
Demographic, disease, and social characteristics, as well as medical history and prior treatments, were summarized using descriptive statistics. To detect differences between combined biologics (ustekinumab, infliximab, etanercept, and adalimumab) and the reference (nonmethotrexate/nonbiologics) cohort and differences across biologic cohorts, corresponding P values were calculated based on the overall F test from an analysis of variance for continuous variables or a χ² test for categorical variables. For statistically significant differences (P ≤ .05) across biologics, pairwise comparisons were conducted between individual biologics using Bonferroni multiplicity adjustment for multiple comparisons. For comparisons of the number of prior biologics used, the 2 nonbiologics cohorts were excluded. The numbers of serious infection were summarized by type, and the rate per 100 patient-years and 95% CIs were calculated for each treatment cohort.

A multivariate analysis using a Cox proportional hazards regression model was performed to identify risk factors for serious infection. The distribution of continuous baseline variables was rescaled to facilitate clinical interpretation (eg, age and duration of disease were transformed to age divided by 10 and duration of disease divided by 5). Adjusted hazard ratios (HRs), 95% CIs, and corresponding P values (Wald χ² test) were calculated for each clinical characteristic compared with a defined reference group. Missing values for covariates in the Cox proportional hazards regression model were imputed (ie, means for continuous factors and medians for categorical factors). Covariates (predefined based on clinical relevance by the coauthors) included the following: age, sex, race/ethnicity, body mass index (calculated as weight in kilograms divided by height in meters squared), duration of psoriasis, diagnosis of psoriatic arthritis, diagnosis of diabetes mellitus, history of immunomodulator use, number of biologic therapies used historically, history of significant infection (defined as infections requiring treatment within 3 years before registry enrollment), Physician’s Global Assessment score at baseline, smoking status at enrollment, and alcohol use status at enrollment. In addition, individual use of ustekinumab, infliximab, adalimumab, and etanercept was included in the model, and the reference group for comparison was the nonmethotrexate/nonbiologics cohort. As a sensitivity analysis, the multivariate analysis was also performed using the methotrexate/nonbiologics cohort as the reference group.

Results
The overall population consisted of 11 466 patients (22 311 patient-years): 9154 had received a biologic agent, 490 had received methotrexate (and possibly other nonbiologics), and 1610 had received therapy other than methotrexate and biologics during the registry (Table 1 and Figure). The incident population included approximately half of the patients in the overall population (5609 patients [10 560 patient-years]), and the bionaive population comprised more than half of the incident population (3274 patients [6858 patient-years]). Most patients in PSOLAR were enrolled in North America (74.3% in the United States and 15.7% in Canada). Just over half of the PSOLAR population was male (6321 patients [55.1%]), and the mean age at enrollment was 48.5 years (Table 2). Of 11 466 patients in the overall population, 8192 (71.4%) had received at least 1 biologic agent before entering the registry. Notable differences in patient and disease characteristics at entry into the registry (Table 3) were found between the biologics groups and the nonmethotrexate/nonbiologics cohort, as expected. Some potentially clinically relevant findings were also observed in statistical comparisons between biologic groups. Body mass index was significantly higher and medical comorbidities (eg, psoriatic arthritis, cardiovascular disease) and history of sig-
**Table 1. Number of Patients and Patient-years of Follow-up by Population and Treatment Cohort Among Patients Enrolled in PSOLAR**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ustekinumab</th>
<th>Infliximab</th>
<th>Etanercept</th>
<th>Adalimumab</th>
<th>Nonmethotrexate/Nonbiologics</th>
<th>Methotrexate/Nonbiologics</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>3474</td>
<td>1151</td>
<td>1854</td>
<td>2675</td>
<td>1610</td>
<td>490</td>
<td>11466</td>
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<tr>
<td>Patient-years</td>
<td>5923</td>
<td>2253</td>
<td>3750</td>
<td>5173</td>
<td>3800</td>
<td>1246</td>
<td>22311</td>
</tr>
<tr>
<td>Duration of follow-up, median, y</td>
<td>1.60</td>
<td>1.62</td>
<td>1.82</td>
<td>1.72</td>
<td>2.27</td>
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<td><strong>Incident Population</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>1519</td>
<td>246</td>
<td>461</td>
<td>1157</td>
<td>1610</td>
<td>490</td>
<td>5609</td>
</tr>
<tr>
<td>Patient-years</td>
<td>2489</td>
<td>324</td>
<td>715</td>
<td>1887</td>
<td>3800</td>
<td>1246</td>
<td>10560</td>
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<tr>
<td>Duration of follow-up, median, y</td>
<td>1.42</td>
<td>0.93</td>
<td>1.10</td>
<td>1.26</td>
<td>2.27</td>
<td>2.52</td>
<td>1.65</td>
</tr>
<tr>
<td><strong>Bionaive Population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>376</td>
<td>64</td>
<td>298</td>
<td>412</td>
<td>1610</td>
<td>490</td>
<td>3274</td>
</tr>
<tr>
<td>Patient-years</td>
<td>585</td>
<td>97</td>
<td>501</td>
<td>614</td>
<td>3800</td>
<td>1246</td>
<td>6858</td>
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<tr>
<td>Duration of follow-up, median, y</td>
<td>1.37</td>
<td>1.21</td>
<td>1.22</td>
<td>1.21</td>
<td>2.27</td>
<td>2.52</td>
<td>1.91</td>
</tr>
</tbody>
</table>

Abbreviation: PSOLAR, Psoriasis Longitudinal Assessment and Registry.  
* The nonmethotrexate/nonbiologics cohort includes patients who have never received a biologic or methotrexate, while the methotrexate/nonbiologics cohort includes those who have never received a biologic but have received methotrexate. Nonbiologic therapies included systemic retinoids, psoralen plus UV-A, and UV-B.

**Figure. Cumulative Incidence Rates of Serious Infections of Interest per 100 Patient-years**

Findings for the incident and bionaive populations were generally similar to those reported for the overall population.

In the overall population, 323 serious infections were reported during the registry follow-up period. For 287 events (88.9%), the study investigator considered the infection to be serious because it caused or prolonged hospitalization. The cumulative unadjusted incidence rate of serious infections was 1.45 per 100 patient-years (Table 4). The rates in the incident and bionaive populations were 1.35 and 1.12 per 100 patient-years, respectively. In the overall population, the rates of serious infection were 0.83, 1.47, 1.97, and 2.49 per 100 patient-years in the ustekinumab, etanercept, adalimumab, and infliximab cohorts, respectively, and 1.05 and 1.28 per 100 patient-years in the nonmethotrexate/nonbiologics and methotrexate/nonbiologics cohorts, respectively (Figure and Table 4). Compared with the overall population, the trend was similar across the 4 biologic cohorts in the incident and bionaive populations (ie, lowest rates for the ustekinumab or etanercept cohorts, followed by either the infliximab or adalimumab cohort) (Figure). The most commonly reported types of serious infections across the registry were pneumonia and cellulitis (Table 4). The single most frequently reported serious infection was cellulitis. There were isolated reports of necrotizing fasciitis (n = 4), tuberculosis (n = 2), histoplasmosis (n = 2), hepatitis C (n = 1), and Salmonella bacteremia (n = 1). In the overall population, 6 patients (0.1% [0.03 per 100 patient-years]) had serious infections that resulted in death.

Results of the multivariate analysis for the overall population showed that increasing age (HR, 1.37; 95% CI, 1.24-1.52; P < .001), presence of diabetes mellitus (HR, 1.70; 95% CI, 1.25-2.32; P < .001), and history of significant infections before registry entry (HR, 1.67; 95% CI, 1.28-2.18; P < .001) were each found to be a significant predictor of serious infection (eTable in the Supplement). The presence of psoriatic arthritis was not associated with serious infection (HR, 1.14; 95% CI, 0.88-
1.49; \( P = .33 \). Current smoking status (HR, 1.43; 95% CI, 1.08-1.88; \( P = .01 \)) was associated with an increased risk of serious infection; however, patients who reported current alcohol use were less likely to develop serious infection compared with those who never used alcohol (HR, 0.68; 95% CI, 0.51-0.93; \( P = .01 \)). In addition, exposure to infliximab (HR, 2.51; 95% CI, 1.45-4.33; \( P < .001 \)) and exposure to adalimumab (HR, 2.13; 95% CI, 1.33-3.41; \( P = .002 \)) during the registry were independently associated with the risk of serious infection, whereas treatment with ustekinumab or etanercept was not associated with serious infection. Predictors for the incident population were similar to those for the overall population, except that only adalimumab (and not infliximab) was significantly associated with the risk of serious infection. In the bionaire population, increasing age was found to be associated with an elevated risk of serious infection, while alcohol use was associated with a lower risk. No other significant associations were observed, although the number of patients was low in this subpopulation. Results of the sensitivity multivariate analysis using the methotrexate/nonbiologics cohort as the reference group were similar to those obtained using the nonmethotrexate/nonbiologics cohort as the reference group.

### Discussion

Our findings from the prospective, disease-based PSOLAR (in which more than 11,000 patients were enrolled) better char-
patients enrolled in clinical trials and other registries. 1-4,16,17 The association between TNF inhibitor use and serious infection risk in the treatment of psoriasis and other inflammatory diseases has been well documented in the literature. 6,8-9,18 Multivariate analyses of PSOLAR data confirmed that the use of adalimumab and infliximab was associated with serious infection compared with nonbiologic therapy (with and without methotrexate) for the overall patient population. This finding was replicated for adalimumab (but not for infliximab) in the patients initiating biologic therapy at the time of or after entry into the registry; however, neither treatment was associated with an increased risk of serious infection in the smaller subset of bionaive patients. Adalimumab and infliximab are monoclonal antibodies that share a similar mechanism of action. 19 In contrast, etanercept (a TNF receptor fusion protein) was not associated with the risk of serious infections for any of the evaluated populations. This finding is consistent with observations of a difference in infection risk between patients with rheumatoid arthritis exposed to etanercept and those treated with other anti-TNF agents. 19 Analyses of all 3 populations showed that the use of ustekinumab (an interleukin 12/23 antagonist) was not associated with an increased risk of serious infection compared with the use of nonbiologic therapies (with and without methotrexate).

As expected, increasing age, diabetes mellitus, history of significant infection, and the use of tobacco were also significantly associated with serious infections in the modeled analysis for the overall population. All of these variables have been identified previously as risk factors for serious infection in the population with psoriasis. 20 Concurrent psoriatic arthritis was not associated with serious infections. The use of alcohol reported at registry entry appeared to be associated with a lower likelihood of developing a serious infection. However, the reasons underlying this finding are unclear, and details on the quantity of intake were not captured.

Some limitations inherent to observational studies should be considered when interpreting these data, including treatment selection and patient participation biases due to the lack of randomization. Treatments are chosen solely by the prescriber, and only patients with access to participating sites were represented. Patients were enrolled based on broad enrollment criteria, and participation was voluntary. It may some-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ustekinumab (n = 3474)</th>
<th>Infliximab (n = 1151)</th>
<th>Etanercept (n = 1854)</th>
<th>Adalimumab (n = 2675)</th>
<th>Nonmethotrexate/Nonbiologics (n = 1610)*</th>
<th>Methotrexate/Nonbiologics (n = 490)*</th>
<th>Total (N = 11 466)*,d</th>
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<tr>
<td>Duration of disease, y</td>
<td>19.4 (12.8)</td>
<td>18.4 (12.7)</td>
<td>17.4 (13.35)</td>
<td>17.2 (13.1)</td>
<td>14.3 (14.6)</td>
<td>&lt;.001</td>
<td>14.3 (14.8)</td>
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<td>Prior Treatment, No./Total No. (%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Systemic corticosteroids</td>
<td>735/3470 (21.2)</td>
<td>346/1148 (30.1)</td>
<td>408/1848 (22.3)</td>
<td>666/2670 (24.9)</td>
<td>307/1606 (19.1)</td>
<td>&lt;.001</td>
<td>121 (24.7)</td>
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<tr>
<td>Immunomodulators</td>
<td>1969/3470 (56.7)</td>
<td>795/1148 (69.3)</td>
<td>813/1848 (44.0)</td>
<td>1254/2670 (47.0)</td>
<td>132/1606 (8.2)</td>
<td>&lt;.001</td>
<td>384 (78.4)</td>
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<td>Cyclosporine</td>
<td>831/3470 (23.9)</td>
<td>288/1148 (25.1)</td>
<td>204/1848 (11.0)</td>
<td>379/2670 (14.2)</td>
<td>16/1606 (1.0)</td>
<td>&lt;.001</td>
<td>10 (2.0)</td>
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<td>Methotrexate</td>
<td>1652/3470 (47.6)</td>
<td>682/1148 (59.4)</td>
<td>712/1848 (38.5)</td>
<td>1077/2670 (40.3)</td>
<td>101/1606 (6.3)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0 376/3470 (10.8)</td>
<td>64/1148 (5.6)</td>
<td>298/1848 (16.1)</td>
<td>412/2670 (15.4)</td>
<td>1610 (100)</td>
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<td>490 (100)</td>
<td>3274/11 444 (29.6)</td>
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<td>1 1262/3470 (36.3)</td>
<td>484/1148 (42.1)</td>
<td>1204/1848 (64.9)</td>
<td>1313/2670 (49.1)</td>
<td>0/1606</td>
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<td>0</td>
<td>4352/11 444 (38.0)</td>
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<td>2-3 1546/3470 (44.5)</td>
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<td>338/1848 (18.2)</td>
<td>907/2670 (33.9)</td>
<td>0/1606</td>
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<td>0</td>
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<td>4-7 290/3470 (8.3)</td>
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<td>43/2670 (1.6)</td>
<td>0/1606</td>
<td>NA</td>
<td>0</td>
<td>441/11 444 (3.8)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not applicable.

*a The total number is defined in the Table 1 footnotes. The number of patients for selected parameters varied across treatment cohorts based on data availability.

*b The number of patients for selected parameters varied somewhat across treatment cohorts based on data availability; differences are noted.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ustekinumab (n = 3474)</th>
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<th>Methotrexate/Nonbiologics (n = 490)*</th>
<th>Total (N = 11 466)*,d</th>
</tr>
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<tr>
<td>Disease Characteristics, Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Physician’s Global Assessment score</td>
<td>2.0 (1.3)</td>
<td>1.8 (1.2)</td>
<td>1.9 (1.1)</td>
<td>1.9 (1.2)</td>
<td>2.3 (1.1)</td>
<td>&lt;.001</td>
<td>2.1 (1.2)</td>
</tr>
</tbody>
</table>

The total number of identified risk factors for serious infection in the overall population was 0.83, 1.47, 1.97, and 2.49 per 100 patient-years for the ustekinumab, etanercept, adalimumab, and infliximab cohorts, respectively, and 1.05 and 1.28 per 100 patient-years in the 2 nonbiologics cohorts (without methotrexate and with methotrexate, respectively). The most common types of serious infection in the overall population were pneumonia and cellulitis, as is typical of hospitalized patients in general and patients enrolled based on broad enrollment criteria. Patients were enrolled based on broad enrollment criteria, and participation was voluntary. It may some-
times be impossible to validate diagnoses and outcomes. In this analysis, the use of methotrexate (which carries its own risk of infection) was not excluded from the biologic comparator cohorts, which may have affected some outcomes. Finally, based on statistical testing, some differences were noted in patient characteristics across biologic cohorts at entry into the registry. However, due to the large sample sizes, the statistical tests were sensitive enough to detect small differences between groups, even in cases in which numerical differences were not apparent. Therefore, statistical significance may not necessarily connote clinical relevance. Nonetheless, because such variables would be expected to differ in an observational study given the lack of randomization of patients to treatment groups, clinical characteristics were included in the Cox proportional hazards regression modeling analyses of PSOLAR data.

### Conclusions

Among 9154 patients treated with biologic agents in PSOLAR, our results indicate that the risk of serious infection varies across treatments. Specifically, adalimumab and infliximab appear to carry a higher risk of serious infection compared with nonmethotrexate and nonbiologic therapies, whereas etanercept and ustekinumab do not. Continued follow-up of PSOLAR patients will provide increasingly robust data and may allow for assessment of the risk of infection in other treatment cohorts, such as those treated with combination or sequential therapy. The risk of serious infection associated with TNF inhibitors is noted in current international guidelines for treating patients with psoriasis, but the risk is not differentiated across individual biologic therapies.21-23 The

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**Table 4. Cumulative Incidence of Serious Infections per 100 Patient-years and Number of Patients by Type of Infection Among the Overall Population**

<table>
<thead>
<tr>
<th>Infection or Infection</th>
<th>No. (%) [95% CI]</th>
<th>Overall</th>
<th>Pneumonia</th>
<th>Cellulitis</th>
<th>Sepsis</th>
<th>Diverticulitis</th>
<th>Urinary tract infection</th>
<th>Abscess</th>
<th>Skin</th>
<th>Bronchitis</th>
<th>Pyelonephritis</th>
<th>Colitis</th>
<th>Gastroenteritis</th>
<th>Appendicitis</th>
<th>Osteomyelitis</th>
<th>Wound infection</th>
<th>Influenza</th>
<th>Meningitis</th>
<th>Necrotizing fasciitis</th>
<th>Viral</th>
<th>Herpes zoster</th>
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<tbody>
<tr>
<td>Ustekinumab</td>
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<tr>
<td>(5923 Patient-years)</td>
<td></td>
<td>49 (0.83) [0.61-1.09]</td>
<td>56 (2.49) [1.88-3.23]</td>
<td>55 (1.47) [1.10-1.91]</td>
<td>102 (1.97) [1.61-2.39]</td>
<td>40 (1.05) [0.75-1.43]</td>
<td>16 (1.28) [0.73-2.09]</td>
<td>323 (1.45) [1.29-1.61]</td>
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<tr>
<td>Infliximab</td>
<td></td>
<td>2253 Patient-years</td>
<td>10 (0.44) [0.21-0.82]</td>
<td>10 (0.27) [0.13-0.49]</td>
<td>20 (0.39) [0.24-0.60]</td>
<td>8 (0.21) [0.09-0.41]</td>
<td>2 (0.16) [0.02-0.58]</td>
<td>61 (0.27) [0.21-0.35]</td>
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<tr>
<td>Etanercept</td>
<td>(3730 Patient-years)</td>
<td>11 (0.19) [0.09-0.33]</td>
<td>9 (0.40) [0.18-0.76]</td>
<td>14 (0.37) [0.20-0.63]</td>
<td>10 (0.19) [0.09-0.36]</td>
<td>5 (0.13) [0.04-0.31]</td>
<td>3 (0.24) [0.05-0.70]</td>
<td>53 (0.24) [0.18-0.31]</td>
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<td>Adalimumab</td>
<td>(5173 Patient-years)</td>
<td>11 (0.19) [0.09-0.33]</td>
<td>9 (0.40) [0.18-0.76]</td>
<td>14 (0.37) [0.20-0.63]</td>
<td>10 (0.19) [0.09-0.36]</td>
<td>5 (0.13) [0.04-0.31]</td>
<td>3 (0.24) [0.05-0.70]</td>
<td>53 (0.24) [0.18-0.31]</td>
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<tr>
<td>Nonmethotrexate/Nonbiologics</td>
<td>(3800 Patient-years)</td>
<td>11 (0.19) [0.09-0.33]</td>
<td>9 (0.40) [0.18-0.76]</td>
<td>14 (0.37) [0.20-0.63]</td>
<td>10 (0.19) [0.09-0.36]</td>
<td>5 (0.13) [0.04-0.31]</td>
<td>3 (0.24) [0.05-0.70]</td>
<td>53 (0.24) [0.18-0.31]</td>
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<tr>
<td>Methotrexate/Nonbiologics</td>
<td>(1246 Patient-years)</td>
<td>11 (0.19) [0.09-0.33]</td>
<td>9 (0.40) [0.18-0.76]</td>
<td>14 (0.37) [0.20-0.63]</td>
<td>10 (0.19) [0.09-0.36]</td>
<td>5 (0.13) [0.04-0.31]</td>
<td>3 (0.24) [0.05-0.70]</td>
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</table>

*Serious infections displayed here are those that occurred at least 4 times across treatment cohorts.

*The nonmethotrexate/nonbiologics and methotrexate/nonbiologics cohorts are described in the Table 1 footnotes.*

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findings reported herein, and in other safety analyses of PSOLAR data,²⁴,²⁵ provide real-world evidence of serious infection risk with specific biologic treatments, thereby providing physicians with important guidance regarding the potential for serious infections when choosing treatment for patients with psoriasis.

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Author Contributions: Drs Kalb and Goyal had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Kalb, Poulin, Cohen, Goyal, Falckarzadeh, Langhoff.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Langhoff, You.
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Study supervision: Goyal, Falckarzadeh, Calabro, Chevrier.
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NOTABLE NOTES

19th Century Dermatologic Atlases in the Early Age of Photography

Emily C. Milam, BA; Sarika Ramachandran, MD

Medical photography is now ubiquitous, particularly among the visually oriented fields like dermatology. While dermatology’s descriptive language allows for clear oral communication, the benefit of a visual guide is inarguable.

Dermatologic atlases originated as hand-drawn or painted illustrations, relying on the skill and interpretation of artists. Photography was not incorporated into medicine until the mid-19th century, soon after Louis Daguerre introduced the daguerreotype in 1839.1 The daguerreotype was the first image process with permanence and was heralded for its fidelity, lifelikeness, and objectivity. It was excitedly applied to medicine, with its first use in 1844 by Alfred Donné, who published 86 daguerreotypes of micrographic images in Cours de Microscopie, a cytology atlas. The first medical portrait of a patient—depicting a woman with a sizeable goiter—followed circa 1847.

Nearly 20 years elapsed before the first known photography atlas of dermatologic disease emerged. Photographs (Colored From Life) of the Diseases of the Skin was published in 1865 by Alexander Balmano Squire, a British physician. His highly acclaimed atlas included 12 albumen prints that were hand-colored and displayed alongside case descriptions. Subsequently, Parisian physician Alfred Hardy and his student, A. de Montméja, published the second known dermatology atlas, titled Clinique Photographique de l’Hôpital Saint Louis, in 1867.

Inspired by the work abroad, American physician Howard F. Damon published Photographs of Disease of the Skin, Taken From Life Under the Superintendence of Howard F. Damon in 1868.2 Damon’s inaugural series included oval photographs of chronic eczema, herpes zoster, impetigo, ecthyma, and rupia. The photographs were initially sold as monthly installments for 50 cents, intended to complete the study of dermatology “at a cost not exceeding the means of the student.”2

George Henry Fox, a New York dermatology professor, published the next set of dermatology atlases, most notably Photographic Illustrations of Skin Diseases: Forty-Eight Plates From life, Colored by Hand around 1879. Fox’s atlases were distinct from his predecessors’ because he used the cheaper, larger, and more efficient method of image production, ar- totype (or, collotype). The atlases could be published in greater numbers and at lower costs, encouraging their dissemination. Fox’s success was also thanks to Oscar G. Mason, one of America’s first medical photography experts, and Dr Joseph Gaertner, who meticulously colored the photographs. At the time, Fox contended that “the study of Skin Disease without cases or colored plates is like the study of osteology without bones, or the study of geography without maps.”3

Early photographic atlases undoubtedly helped dermatology advance to a recognized specialty in the late 19th century. Their importance for clinical diagnosis and education persists to this day. Since medical photography’s humble beginnings, it has grown to include multitudes of atlases, even with themes specific to single diagnoses.

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