Current Rheumatology Reports (2019) 21: 36
https://doi.org/10.1007/s11926-019-0832-y

INFECTION AND ARTHRITIS (KEVIN WINTHROP, SECTION EDITOR)

In the Real World: Infections Associated with Biologic and Small Molecule Therapies in Psoriatic Arthritis and Psoriasis

Sarah A. R. Siegel[1] · Kevin L. Winthrop[1,2]

Published online: 6 June 2019

Abstract

Purpose of Review To summarize our most current understanding of the real world risk of infections associated with biologic and small molecule therapies in the setting of psoriatic disease.

Recent Findings Patients with psoriasis or psoriatic arthritis are at increased risk for infection from both their disease and some of their therapies. There is little real world data for biologic and small molecule therapies; however, ustekinumab and biologics inhibiting IL-17 or IL-23 appear to have reduced risk estimates compared to anti-TNF therapies. Apremilast seems to have little infectious signal with limited real world data, and for JAK inhibitors, limited real world data suggest a higher risk of herpes zoster.

Summary Recently approved targeted and small molecule therapies for psoriasis carry infectious risks for patients, although they appear to vary across mechanism of action. As these treatments become more widespread, and additional therapies are approved, it will be imperative to evaluate their safety in the context of real world data.

Keywords PsA · PsO · Opportunistic infection · Biologics · Serious infections

Introduction

Psoriasis is a chronic, inflammatory disease that affects roughly 7.5 million Americans, with psoriatic arthritis affecting an estimated 17.1–22.1% of these individuals [1–4]. Psoriatic disease is associated with substantial morbidity, increased mortality, and overall decreases in patient-reported quality of life [5–9]. In particular, individuals with psoriatic disease are more likely to experience serious infections [10], as compared to the general population, due to disruptions of their immune systems and the therapies used to treat them.

Psoriatic disease is associated with dysregulation of the immune system, with recent focus on the cytokines involved in the IL-23/Th17 pathway [11, 12]. In recent years, biologic and small molecule therapies targeting this or related pathways have been developed and are now widely used. While these therapies have been shown to be effective in clearing cutaneous plaques, and in some cases, in ameliorating joint disease, their adverse event profiles frequently include infection.

The risk of serious infections (i.e., hospitalized infections) and opportunistic infections (OIs) have been reported to be elevated with some of these compounds, but not in all studies. However, most of these risk estimates come from clinical trial data, and there is limited understanding of the incidence of these infections in patients in the real world. In this review, we will summarize our most current understanding of the real world risk of infections associated with these compounds in the setting of psoriatic disease.

Infection Risk and Psoriasis

Psoriatic disease, like other autoimmune diseases, seems to predispose individuals to infection independent of immunosuppressive treatment. A 2011 Dutch study found that individuals with psoriasis have twice the risk of serious infections leading to hospitalization (aHR 1.58 [95% CI 1.48, 1.68]), compared to individuals without psoriasis. The risk of infection was similar for individuals with psoriasis being treated

This article is part of the Topical Collection on *Infection and Arthritis*

✉ Sarah A. R. Siegel
siegels@ohsu.edu

[1] School of Public Health, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, GH 104, Portland, OR 97239, USA

[2] Division of Infectious Diseases, Oregon Health & Science University, Portland, OR, USA

with topical therapy only (aHR 1.54 [95% CI 1.44, 1.65)], but increased for patients who were prescribed phototherapy, systemic drugs, or inpatient treatment (aHR 1.851 [95% CI 1.57, 2.08]) [10].

A more recent Taiwanese study from 2014 found a similarly increased incidence of pneumonia for those with psoriasis compared to those without psoriasis (HR 1.50 [95% CI 1.21, 1.86]). Kao et al. utilized the Taiwan Longitudinal Health Insurance Database 2000 to review the medical records of individuals with psoriasis and then match them to non-psoriasis individuals who utilized ambulatory care within the same time period. These individuals were followed for 3 years and tracked for admission due to pneumonia. Both patients with mild and moderate-to-severe psoriasis had increased risks of hospitalization due to pneumonia (aHR 1.36 [95% CI 1.09, 1.70] and HR 1.68 [95% CI 1.12, 2.52], respectively) compared to individuals without psoriasis [13].

The University of Toronto Psoriasis Cohort was used to prospectively identify and observe individuals diagnosed with psoriasis and psoriatic arthritis. Of the 695 patients with psoriatic arthritis, 264 (40.0%) patients developed an infection, compared to 62 (12.2%) of those with cutaneous disease alone [14]. Correspondingly, when looking at the numbers of patients who experienced multiple infections in this cohort, those with psoriatic arthritis experienced a higher burden of infection than those with psoriasis. This study found that 27.7% of those with psoriatic arthritis had 3 or more infections compared to 3.2% of those with psoriasis alone who had two or more infections [14]. Infections were self-reported and included all infections individuals experienced after the baseline visit including both serious and non-serious infections.

Similarly, a cross-sectional study of the Nationwide Inpatient Sample data from 2002 to 2012 was reviewed to determine rates of infection in the psoriasis population [15]. This study tracked admitted patients with a diagnosis of psoriasis over time and found that the rates of serious infections increased when compared to a similar group of patients lacking psoriasis, specifically methicillin-resistant *Staphylococcus aureus* (OR 1.76 [95% CI 1.52, 2.03]), cellulitis (OR 3.21 [95% CI 3.12, 3.30]), herpes simplex virus infection (OR 2.21 [95% CI 1.70, 2.89]), infectious arthritis (OR 1.82, [95% CI 1.58 2.09]), osteomyelitis (OR 1.31 [95% CI 1.18, 1.46]), meningitis (OR 1.31, [95% CI 1.16, 1.47]), encephalitis (OR 1.22 [95% CI 1.02, 1.47]), and tuberculosis (OR 1.34 [95% CI 1.20, 1.49]) [15]. The authors were unable to evaluate the impact of disease-modifying therapies in this analysis, and some of the reported risk differences could have been attributable to such therapies.

In a 2018 study, Takeshita et al. utilized The Health Improvement Network (THIN), which is an electronic medical records database that includes a large cohort of the general UK population, to ascertain the risk of infection in a large cohort of individuals with psoriasis [16••]. In this cohort, the risk of serious infection for all individuals with psoriasis was significant (aHR 1.21 [95% CI 1.18, 1.23]), as compared to those without psoriasis, and the risk was even higher for those with moderate-to-severe psoriasis (aHR 1.63 [95% CI 1.52, 1.75]). A similar, albeit weaker, signal was seen for risk of herpes zoster infection in the mild and moderate-to-severe psoriasis groups (aHR 1.07 [95% CI 1.05, 1.10] and aHR 1.17 [95% CI 1.06, 1.30], respectively), compared to the healthy population. Interestingly, the increased risk of opportunistic infection was only seen in the moderate-to-severe psoriasis group (aHR 1.57 [95% CI 1.06, 2.34]) as compared to those without psoriasis. It should be noted that in the overall cohort, the moderate-to-severe psoriasis group was not defined by body surface area (BSA), but instead by receiving either phototherapy or systemic therapy [16••]. However, disease severity was defined by treatment, preventing separation of disease effect from treatment effect. The authors addressed this limitation by utilizing a nested cohort within the THIN network, which included clinical data such as BSA. The results of this sub-analysis found an elevated risk of serious infection for those with any psoriasis (aHR 1.21 [95% CI 11.09, 1.35]) and those with moderate to severe psoriasis (aHR 1.27 [1.10, 1.47]), compared to a set of randomly selected patients who were matched on age category, were still alive, were registered at the same practice, and who did not have psoriasis [16••]. Importantly, this analysis suggests that increased disease severity is a predictor for an increased risk of serious infection.

The Influence of Psoriasis Therapy upon the Risk of Serious Infection

The evaluation of real world infection risk associated with biologic or other psoriasis therapy is complicated by the influence of disease severity. Administrative databases frequently used in "Real World" analyses do not contain disease severity measures, and it is difficult to control for the effect of severity upon infection risk. Some variables proxy for more advanced disease, and these can be used in modeling of infectious risk, including treatment utilization patterns (e.g., initiation of medication) [10, 17] and the number of hospital visits or procedures over a certain time-period [18]. However, these methods are indirect and still allow for potential residual confounding and channeling bias. Some studies using registry data have overcome this, as there was access to disease severity measures. It would be useful to develop and validate a claims-based algorithm for psoriasis disease severity within administrative databases, but to date this has yet to be done. Selected results are shown in Fig. 1.

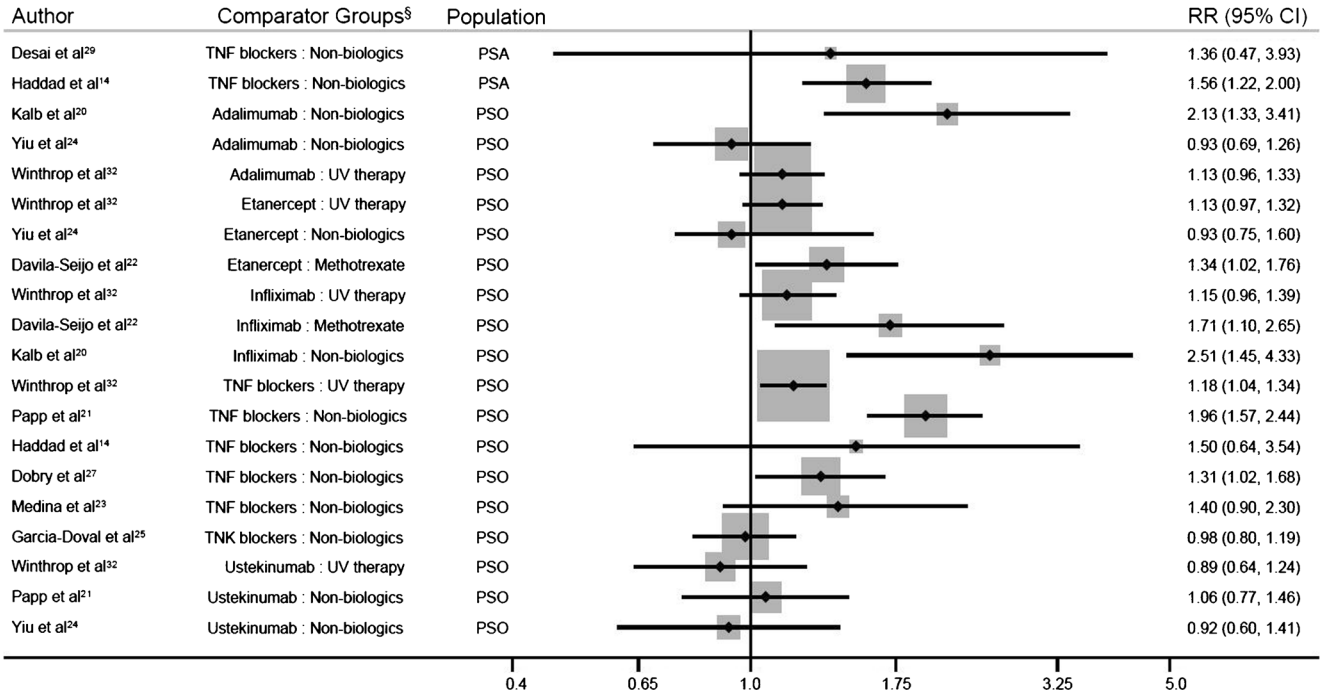

Fig. 1 Recent studies *showing* risk of serious infection and biological therapy. Comparator groups show the active therapy first, and the comparison group second

Registry Studies

The PSOLAR cohort is a multicenter, longitudinal, disease-based registry consisting of dermatology centers across the USA [19]. An analysis of PSOLAR data published by Kalb et al. found a higher risk of serious infections in the psoriasis population for those individuals treated with adalimumab and infliximab, when compared to non-biologic therapies (HR 2.13 [95% CI 1.33, 3.41] and HR 2.51 [95% CI 1.45, 4.33], respectively). Interestingly, the presence of psoriatic arthritis was not associated with serious infection when compared to individuals with psoriasis who started non-biologic therapies (HR 1.14 [95% CI 0.88, 1.49]) [20]. The authors included both prevalent and incident therapy users in their analysis and observed a similar association when restricting to only incident therapy users of adalimumab (HR 2.52 [95% CI 1.47, 4.34]) compared to non-biologic users. When the analysis was further restricted to bionaïve therapy users, elevated risk between therapy and serious infection (HR 2.10 [95% CI 0.93, 4.75]) when compared to non-biologic therapy users was observed; however, it was not statistically significant.

Papp et al. performed additional analyses utilizing the PSOLAR database and found similar results as Kalb et al. In the population of individuals with psoriasis, those who were on other biologics (infliximab, adalimumab, or etanercept) had a significant increased risk of serious infections as compared to those who were on non-biologic therapy (aHR 1.96 [95% CI 1.57, 2.44]). For those individuals who were on ustekinumab, there was no association between risk of serious infection and starting therapy, as compared to those on non-biologic therapies (1.06 [95% CI 0.77, 1.46]) [21].

Three additional studies in recent years have found significant associations between serious infection and biologic use in the psoriasis population. The 2016 Haddad et al. study found that when biologic therapy-use was considered a time-dependent covariate, the psoriatic arthritis group taking biologic therapy had nearly twice as many serious infections as those taking non-biologic therapy (HR 1.56 [95% CI 1.22, 2.0]). The study, however, did not identify a statistically significant association in the population of patients with psoriasis who lacked psoriatic arthritis (HR 1.50 [95% CI 0.64, 3.54]) [14]. Patients self-reported the occurrence of infection, which included serious infections as defined by infections that required hospitalization or intravenous antibiotics, potentially introducing bias into the results, but this was likely to be non-differential in nature. In 2017, Dávila-Seijo et al. also found an increased risk of infection associated with biologic therapy in a Spanish dermatological registry. In this group of individuals with psoriasis, infection risk was increased for individuals treated with infliximab or etanercept compared to those treated with methotrexate (aRR 1.71 [95% CI 1.1, 2.65] and aRR 1.34 [95% CI 1.02–1.76], respectively) [22]. Curiously, a similar risk for infection was seen when biologic therapy was prescribed with systemic therapy, such as methotrexate, as compared to biologic alone. There was elevated risk for individuals taking adalimumab with methotrexate, or

ustekinumab with methotrexate, compared to methotrexate as a monotherapy (aRR 2.13 [95% CI 1.2, 3.7] and aRR 1.56 [95% CI 1.08, 2.25]) [22].

Some patient registry data have failed to find associations between biologic therapy and serious infection. The BIOBADADERM database, the Spanish Registry of Adverse Events from Biological Therapy in psoriasis, prospectively enrolls patients with psoriasis who are starting new therapy. Medina et al. compared the risk of infection for initiating biologic therapy as compared to non-biologic therapy found no significant association for adverse events and serious adverse events, both including infection (HR 0.7 [95% CI 0.6, 0.7] and HR 1.4 [95% CI 0.9, 2.3], respectively) [23]. One limitation of this observational study was that the authors only controlled for age, which may explain the lack of observed association due to potential confounding. The British Association of Dermatologists Biologic Interventions Register (BADBIR) also found no significant increase in risk of infection for etanercept (aHR 1.10 [95% CI 0.75, 1.60]), adalimumab (aHR 0.93 [95% CI 0.69, 1.26]), or ustekinumab (aHR 0.92 [95% CI 0.60, 1.41]), compared to non-biologics [24•]. Similar risks were found when comparing biologic therapy use to methotrexate use alone (aHR 1.47 [95% CI 0.95, 2.28], aHR 1.26 [95% CI 0.86, 1.84], aHR 1.22 [0.75, 1.99] for etanercept, adalimumab, and ustekinumab, respectively). This particular analysis adjusted for a wide range of variables, including demographics, disease severity, comorbidities, and immunodeficiency syndromes [24•].

Data from the BIOBADADERM and BADBIR registries were pooled with those from the PsoCare database, an Italian registry of psoriasis patients who newly prescribed either systemic or biologic therapy. The results of this prospective meta-analysis found that there was no significant association between biologic therapy (infliximab, adalimumab, and etanercept) use and serious infection, compared to non-biologic (acitretin, methotrexate, or cyclosporine) therapies (aHR 0.98 [95% CI 0.80, 1.19] pooled from all 3 registries) [25]. Analysis by Garcia-Doval et al. found that the variation across countries, including prescribing trends, did not contribute to the lack of association [26].

Population-Based Health Plan or Administrative Database Studies

Most recently in 2017 among a large cohort of individuals with psoriasis, an association between serious infection and biologic therapy was identified in a large real world population-based health plan [27]. Dobry et al. utilized the Kaiser Permanente system of Northern California and found that after controlling for age, sex, race, and ethnicity, as well as comorbidities, those individuals with psoriasis who were prescribed biologic therapy were more likely to develop serious infections, as compared to individuals with psoriasis treated with non-biologic therapy (aHR 1.31 [95% CI 1.02, 1.68]). Both skin and soft tissue infection, as well as meningitis, had strong significant associations (aHR 1.75 [95% CI 1.19, 2.56] and aHR 9.22 [95% CI 1.77, 48.10], respectively) [27]. While this signal was strong, this study was unable to determine associations for specific therapies most likely due to small numbers for each therapy, and instead grouped all biologic therapies together in comparison to non-biologic therapies. Conversely, a 2011 study by Grijalva et al. found that among patients on anti-TNF therapy for psoriasis, psoriatic arthritis, or ankylosing spondylitis, the rate of serious infections was not significantly higher than those taking non-biologic DMARDs (HR 1.05 [95% CI 0.76, 1.45]) [17]. This study also noted a dose-dependent increase in the risk of serious infection and glucocorticoid steroid use (HR 2.01 [95% CI 1.08, 3.73] and HR 2.77 [95% CI 1.44, 5.32] for 5-10 mg/day and > 10 mg/day use of glucocorticoid steroid use, respectively), which has previously been reported in the rheumatoid arthritis population [28]. One limitation to this study was that psoriasis, psoriatic arthritis, and ankylosing spondylitis patients were lumped together, all of which are related conditions; however, the risk of infection could potentially differ between these populations.

A 2017 study by Desai et al. used administrative healthcare databases (Medicaid and Optum Clinformatics) to investigate an association between risk of serious infections and therapy in a cohort of pregnant women with inflammatory disease, including rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, psoriatic arthritis, and inflammatory bowel disease [29]. The analysis found that there was no increased risk for serious infection in this population for the following pairwise comparisons: non-biologic systemic therapy vs. steroid monotherapy (HR 0.81 [95% CI 0.48, 1.37]), TNF inhibitors vs. steroid monotherapy (HR 0.91 [95% CI 0.36, 2.26]), and TNF inhibitors vs. non-biologic systemic therapy (HR 1.36 [95% CI 0.47, 3.93]) [29]. The authors controlled for a wide variety of confounders including demographics, comorbidities, presence of infections prior to the start of the observation period, and both prescription and illicit drug use, as well as hospital admissions and outpatient visits. This study did not address disease severity, potentially confounding the results, as well as lumped together several inflammatory diseases making a measurement of the effect of therapy type on psoriatic arthritis [29]. Even though there was no risk of serious infection based on therapy type, the authors reported a dose-response trend with increase steroid use. Similar to other studies [30, 31], an increased risk of serious infections in the population of pregnant women with inflammatory disease was associated with higher steroid dose ($p = 0.02$) [29].

Winthrop et al. analyzed Medicare data and failed to find a statistically significant risk of serious infection and initiation of any single biologic therapy, as compared to UV therapy in the population of individuals with psoriasis (aHR 1.13 [95%

CI 0.96, 1.33], aHR 1.13 [95% CI 0.97, 1.32], aHR 1.15 [95% CI 0.96, 1.39], aHR 0.89 [95% CI 0.64, 1.24] for adalimumab, etanercept, infliximab, and ustekinumab, respectively) [32]. The lack of association was potentially due to the lack of power associated with a small sample size with regard to some of the drug-exposure groups. To further support this hypothesis, when all TNF blockers were pooled together, there was an increased risk of serious infection (HR 1.18 [95% CI 1.04, 1.34]) [32]. The authors hypothesized that this signal was observed in the pooled therapies group as an artifact of being unable to account directly for psoriatic disease severity.

Opportunistic Infection Risk and Psoriasis Therapy

There have been few studies investigating the risk of OIs by therapy type in the psoriasis population (selected results in Fig. 2). A 2014 study by Baddley and Winthrop et al. found that in a combined cohort of patients with psoriasis, psoriatic arthritis, and ankylosing spondylitis starting anti-TNF therapy, the risk of non-viral opportunistic infections was elevated compared to those patients who started non-biological therapies (aHR 1.4 [95% CI 0.3, 6.4]), although this finding was not statistically significant and overall few infections were identified [18]. Similarly, a 2016 Medicare-based study found a lack of statistically significant association between OIs and biologic therapies, with adjusted hazard ratios for each compound as compared to UV therapy (aHR 1.32 [95% CI 0.88, 1.98], aHR 1.18 [95% CI 0.78, 1.79], aHR 1.03 [95% CI 0.67, 1.59], aHR 1.19 [95% CI 0.54, 2.60] for adalimumab, etanercept, infliximab, and ustekinumab respectively) [32]. Potential for residual confounding due to indirect measurements of psoriatic disease severity was a concern for this study. The Baddley study also found a significant association between baseline glucocorticoid steroid use and increased risk of OIs (aHR 4.7 [95% CI 1.2, 19.6]) [18]. These findings were similar to those from rheumatoid arthritis and other settings where low-dose glucocorticoid use is associated with an increased risk of OIs [28, 31].

It is important to note that neither of these studies evaluated the risk of combination methotrexate and TNF-α therapy, as opposed to TNF-α therapy alone. An Israeli study focusing on the risk of herpes zoster infection associated with initiation of new therapy found increased risk of herpes zoster in those using combination anti-TNF therapy and methotrexate as compared to individuals with psoriasis on no treatment (RR 1.66 [95% CI 1.08, 2.57]) [33]. The authors found no association between the risk of herpes zoster and monotherapy, specifically methotrexate monotherapy (aRR 0.98 [95% CI 0.78 1.23]) or biologic monotherapy, neither TNF inhibitors nor IL-12/23 blockers, (aRR 2.67 [95% CI 0.69, 10.3]), compared to no treatment [33]. Shalom et al. controlled for confounders including demographic characteristics, Charlson comorbidity index, steroid exposure, filled drug prescriptions, and previous herpes zoster episodes. As with nearly every study discussed, the authors were unable to directly account for psoriatic disease severity, leaving the potential for confounding. A second study by Shalom et al. utilizing the PSOLAR database focused on risk of herpes zoster by prevalent and incident therapy users, and a sub-analysis evaluating risk in only incident users [34]. While elevated hazard ratios were observed when lumping incident and prevalent users, a statistically significant association was not observed for either TNF inhibitor (aHR 2.22 [95% CI 0.82, 5.97]) or ustekinumab (aHR 2.73 [95% CI 0.98, 7.58]) users, as compared to a reference group (combined phototherapy, systemic steroids, topical treatment, and non-methotrexate immunosuppressant therapies) [34]. An incident user sub-analysis within this study, however, found a significant association between new users of TNF inhibitors and herpes zoster infection (aHR 3.66 [1.15, 11.63]), but did not see the same association when looking at new users of ustekinumab (aHR 2.69 [0.76, 9.58]), as compared to the same referent group [34]. The lack of association with serious or opportunistic infection and ustekinumab has been seen in multiple studies [21, 24•, 32, 34] suggesting the likelihood

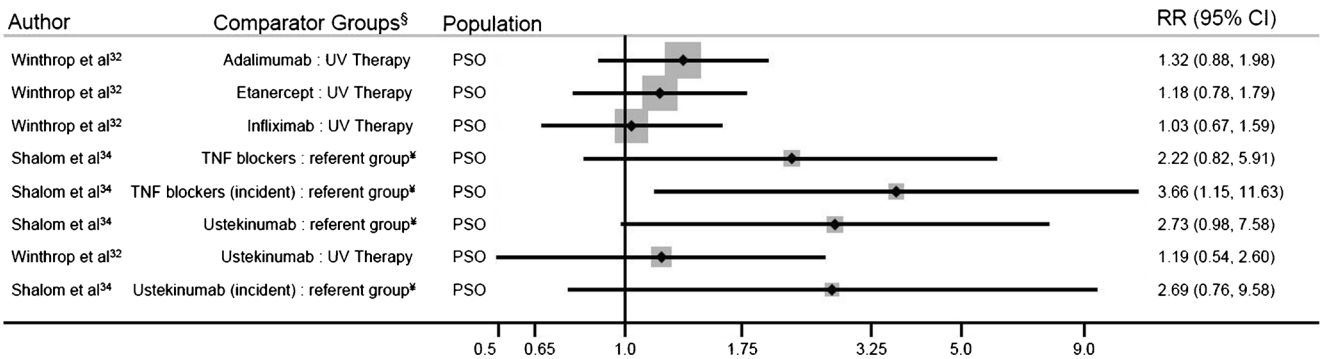

Fig. 2 Recent studies *showing* risk of opportunistic infection and biological therapy. Comparator groups show the active therapy first, and the comparison group second. Referent group refers to individuals taking either phototherapy, systematic steroids, topical treatment, or non-methotrexate immunosuppressant therapies

that ustekinumab has a lower risk of infection than the TNF inhibitors.

Newer Biologic and Small Molecule Therapies for Psoriasis

Given the limited experience post-marketing with these therapies, there is little or no real world data yet evaluating their infection risk in psoriasis and psoriatic arthritis. For now, our understanding of their infectious risk results from evaluation of phase 3 and long-term extension data from the various therapeutic development programs.

IL-17 Blockers

Non-invasive cutaneous fungal infections emerged as an important signal in anti-IL-17 therapy trials in both psoriasis and psoriatic arthritis trials for secukinumab, an IL-17A inhibitor, infections including *candida*, were more common in the secukinumab arm as compared to placebo [35, 36]. An observational institutional-based cohort study of individuals with psoriasis found that 13% of patients experienced at least one episode of fungal infection while on secukinumab [37]. Phase 3 clinical trials of ixekizumab found upper respiratory tract infections were more common in the ixekizumab arm than the placebo arm for both individuals with psoriasis and psoriatic arthritis [38, 39]. The proportion of psoriasis patients with *candida* infections on ixekizumab were 1.8% and 0.8%, for every 2 weeks and every 4 weeks respectively, as compared to 0.5% for placebo, all of which were mild to moderate in severity [39]. For brodalumab, *Candida* infection was also more common in the active arm than the placebo arm (2.3%, 0.5%, and 1.4% for 210 mg brodalumab, 140 mg brodalumab, and placebo, respectively), though none of these infections were serious [40].

IL-23 Blockers

4Limited published data exists examining the infectious risk of these compounds relative to others. Several therapy blocking IL-23 through targeting the p19 have either been recently approved or remain in the developmental pipeline [41]. These therapies are thought likely to be safer as the targeting mechanism is downstream, and therefore more selective, compared to TNF inhibiters. There are currently no real-world data; however, results of phase 2 and 3 clinical trials in the population of individuals with moderate-to-severe psoriasis suggested that rates of infection were similar between the guselkumab, adalimumab, and placebo arms (20%, 12%, and 14%, respectively) [42]. A phase 2 trial for psoriatic arthritis found similar results with infection being the most frequent adverse event and rates of infection were similar between the guselkumab and placebo arms (16% and 20%, respectively) [43]. In a pivotal phase III trial of guselkumab, the proportion of patients with serious infections was similarly low between guselkumab and adalimumab. In the first 16 weeks of treatment, subjects randomized to guselkumab experienced 0 serious infections compared to those randomized to adalimumab with 2 (0.6%) of serious infections. These numbers were more matched between treatment arms after 48 weeks of treatment (0.6% vs. 0.9%, for guselkumab and adalimumab, respectively) [44].

Small Molecule Therapies

There is very little real world data regarding the risk of infections in the population of individuals with psoriatic disease who are taking small molecule therapies. Apremilast is a phosphodiesterase 4 inhibitor, and regulates pro-inflammatory signaling [45]. Clinical trials in the psoriasis and psoriatic arthritis population found that respiratory tract infections were one of the most common adverse events (7.1% and 6.0%, respectively) but were typically mild or moderate [46, 47]. Similar rates for serious adverse events were seen in psoriatic arthritis patients treated with placebo and apremilast (2.8% vs. 1.1%, respectively) in the first 24 weeks of treatment. After 52 weeks of therapy, there were 22 patients who reported serious adverse events with 3 of these being serious infections and none were opportunistic: one event was a chronic tonsillitis, one was a gallbladder empyema, and one an acute pyelonephritis [47]. A clinical trial for the use of apremilast in individuals with plaque psoriasis found that rates of serious adverse events between apremilast and placebo were low (2.0% vs. 0%, respectively) with only 1 serious infection being reported [48]. A 2018 retrospective study by Kishimoto et al. found no association between apremilast and any type of infection [49]. This study was small in nature with fewer than 50 individuals enrolled; however, these exploratory results indicate that apremilast may be safe with regard to associated infections in this psoriatic population.

Tofacitinib, or other janus kinase (JAK) inhibitors, has few or no real world data regarding the risk of infections in individuals with psoriatic disease [50]. One such study in rheumatoid arthritis, however, utilized two administrative databases (Medicare and Marketscan) and found that for rheumatoid arthritis patients the risk of herpes zoster was approximately double for those on tofacitinib as compared to those on biologics [51]. A review of phase 2, phase 3, and long-term extension data within the tofacitinib psoriasis developmental program found that the risk of herpes zoster was increased for those treated with tofacitinib, as compared to placebo [52]. This risk was found to be dose-dependent with higher incidence at higher doses (aHR for 10 mg bid versus 5 mg bid dosage 1.72 [95% CI 1.01, 2.94]), and higher incidence noted among patients within Asia [52]. Similar data were reported within the developmental program of tofacitinib

for psoriatic arthritis, a condition for which the drug is FDA-approved. The FDA Advisory Committee report for psoriatic arthritis found that incidence of serious infections was 3.69/100 person-year for those in the tofacitinib arm, which was elevated compared to the placebo arm (0 serious infections/year) [53]. Further real world studies are needed to better understand the risk of herpes zoster and opportunistic infections in this setting.

Conclusion

Patients with psoriasis are at increased risk for infection from both their disease and at least some of their therapies. Glucocorticoids have consistently been associated with higher infectious risk in real world studies, and the majority of studies evaluating the risks of anti-TNF therapies also reveal elevated risk estimates. Although fewer real world data exist for ustekinumab and more recently approved biologics like those inhibiting IL-17 or IL-23, the emerging picture is that their ability to cause serious and opportunistic infections is diminished compared to anti-TNF therapies. Small molecule therapies such as apremilast appear to have little infectious signal with limited real world data, and for JAK inhibitors, very little data exists in the real world but extrapolation from clinical trials and other indications like rheumatoid arthritis suggest a higher risk of herpes zoster. As more post-marketing data accumulates of these newly approved agents, the opportunity will exist to compare their real-world infectious risks, although challenges will remain particularly with the need to control for psoriasis disease severity within these studies.

Compliance with Ethical Standards

Conflict of Interest Sarah Siegel has no conflicts of interest. Dr. Winthrop reports grants and personal fees from Pfizer, grants and personal fees from BMS, personal fees from AbbVie, personal fees from UCB, personal fees from Lilly, personal fees from Galapagos, personal fees from GSK, personal fees from Roche, and personal fees from Gilead, outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Helmick CG, Sacks JJ, Gelfand JM, Bebo B Jr, Lee-Han H, Baird T, et al. Psoriasis and psoriatic arthritis: a public health agenda. Am J Prev Med. 2013;44(4):424–6.
2. Kurd SK, Gelfand JM. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: results from NHANES 2003-2004. J Am Acad Dermatol. 2009;60(2):218–24.
3. Gelfand JM, Gladman DD, Mease PJ, Smith N, Margolis DJ, Nijsten T, et al. Epidemiology of psoriatic arthritis in the population of the United States. J Am Acad Dermatol. 2005;53(4):573.
4. Alinaghi F, Calov M, Kristensen LE, et al. Prevalence of psoriatic arthritis in patients with psoriasis: a systematic review and meta-analysis of observational and clinical studies. J Am Acad Dermatol. 2018.
5. Armstrong AW, Gelfand JM, Boehncke WH, Armstrong EJ. Cardiovascular comorbidities of psoriasis and psoriatic arthritis: a report from the GRAPPA 2012 annual meeting. J Rheumatol. 2013;40(8):1434–7.
6. Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and obesity: a systematic review and meta-analysis of observational studies. Nutr Diabetes. 2012;2:e54.
7. Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and hypertension: a systematic review and meta-analysis of observational studies. J Hypertens. 2013;31(3):433–42 discussion 442-433.
8. Armstrong EJ, Harskamp CT, Armstrong AW. Psoriasis and major adverse cardiovascular events: a systematic review and meta-analysis of observational studies. J Am Heart Assoc. 2013;2(2):e000062.
9. Ma C, Harskamp CT, Armstrong EJ, Armstrong AW. The association between psoriasis and dyslipidaemia: a systematic review. Br J Dermatol. 2013;168(3):486–95.
10. Wakkee M, de Vries E, van den Haak P, Nijsten T. Increased risk of infectious disease requiring hospitalization among patients with psoriasis: a population-based cohort. J Am Acad Dermatol. 2011;65(6):1135–44.
11. Blauvelt A. New concepts in the pathogenesis and treatment of psoriasis: key roles for IL-23, IL-17A and TGF-β1. Expert Rev Dermatol. 2007;2:69–78.
12. Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med. 2009;361(5):496–509.
13. Kao LT, Lee CZ, Liu SP, Tsai MC, Lin HC. Psoriasis and the risk of pneumonia: a population-based study. PLoS One. 2014;9(12):e116077.
14. Haddad A, Li S, Thavaneswaran A, Cook RJ, Chandran V, Gladman DD. The incidence and predictors of infection in psoriasis and psoriatic arthritis: results from longitudinal observational cohorts. J Rheumatol. 2016;43(2):362–6.
15. Hsu DY, Gordon K, Silverberg JI. Serious infections in hospitalized patients with psoriasis in the United States. J Am Acad Dermatol. 2016;75(2):287–96.
16. •• Takeshita J, Shin DB, Ogdie A, Gelfand JM. Risk of serious infection, opportunistic infection, and herpes zoster among patients with psoriasis in the United Kingdom. J Invest Dermatol. 2018;138(8):1726–35 **This is one of the first studies that identifies psoriasis severity, as measured by BSA, as contributing to risk of serious infection independent of other risk factors associated with psoriasis**.
17. Grijalva CG, Chen L, Delzell E, Baddley JW, Beukelman T, Winthrop KL, et al. Initiation of tumor necrosis factor-alpha antagonists and the risk of hospitalization for infection in patients with autoimmune diseases. JAMA. 2011;306(21):2331–9.
18. Baddley JW, Winthrop KL, Chen L, Liu L, Grijalva CG, Delzell E, et al. Non-viral opportunistic infections in new users of tumour necrosis factor inhibitor therapy: results of the SAfety Assessment of Biologic ThERapy (SABER) study. Ann Rheum Dis. 2014;73(11):1942–8.
19. Papp KA, Strober B, Augustin M, Calabro S, Londhe A, Chevrier M, et al. PSOLAR: design, utility, and preliminary results of a prospective, international, disease-based registry of patients with

psoriasis who are receiving, or are candidates for, conventional systemic treatments or biologic agents. J Drugs Dermatol. 2012;11(10):1210–7.
20. Kalb RE, Fiorentino DF, Lebwohl MG, Toole J, Poulin Y, Cohen AD, et al. Risk of serious infection with biologic and systemic treatment of psoriasis: results from the psoriasis longitudinal assessment and registry (PSOLAR). JAMA Dermatol. 2015;151:961–9.
21. Papp K, Gottlieb AB, Naldi L, Pariser D, Ho V, Goyal K, et al. Safety surveillance for ustekinumab and other psoriasis treatments from the psoriasis longitudinal assessment and registry (PSOLAR). J Drugs Dermatol. 2015;14(7):706–14.
22. Davila-Seijo P, Dauden E, Descalzo MA, et al. Infections in moderate to severe psoriasis patients treated with biological drugs compared to classic systemic drugs: findings from the BIOBADADERM registry. J Invest Dermatol. 2017;137(2):313–21.
23. Medina C, Carretero G, Ferrandiz C, Dauden E, Vanaclocha F, Gómez-García FJ, et al. Safety of classic and biologic systemic therapies for the treatment of psoriasis in elderly: an observational study from national BIOBADADERM registry. J Eur Acad Dermatol Venereol. 2015;29(5):858–64.
24.• Yiu ZZN, Smith CH, Ashcroft DM, et al. Risk of serious infection in patients with psoriasis receiving biologic therapies: a prospective cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). J Invest Dermatol. 2018;138(3):534–41 **This study is one of the best examples from a pharmacoepidemiology standpoint for exploring robust methods to reduce confounding between disparate groups**.
25. Garcia-Doval I, Cohen AD, Cazzaniga S, Feldhamer I, Addis A, Carretero G, et al. Risk of serious infections, cutaneous bacterial infections, and granulomatous infections in patients with psoriasis treated with anti-tumor necrosis factor agents versus classic therapies: prospective meta-analysis of Psonet registries. J Am Acad Dermatol. 2017;76(2):299–308 e216.
26. Garcia-Doval I, Rustenbach SJ, Stern R, Dam TN, Cohen AD, Baker C, et al. Systemic psoriasis therapy shows high between-country variation: a sign of unwarranted variation? Cross-sectional analysis of baseline data from the PSONET registries. Br J Dermatol. 2013;169(3):710–4.
27. Dobry AS, Quesenberry CP, Ray GT, Geier JL, Asgari MM. Serious infections among a large cohort of subjects with systemically treated psoriasis. J Am Acad Dermatol. 2017;77(5):838–44.
28. Winthrop KL, Furst DE. Rheumatoid arthritis and herpes zoster: risk and prevention in those treated with anti-tumour necrosis factor therapy. Ann Rheum Dis. 2010;69(10):1735–7.
29. Desai RJ, Bateman BT, Huybrechts KF, et al. Risk of serious infections associated with use of immunosuppressive agents in pregnant women with autoimmune inflammatory conditions: cohort study. BMJ. 2017;356:j895.
30. Abuabara K, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Cause-specific mortality in patients with severe psoriasis: a population-based cohort study in the U.K. Br J Dermatol. 2010;163(3):586–92.
31. Strangfeld A, Eveslage M, Schneider M, Bergerhausen HJ, Klopsch T, Zink A, et al. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? Ann Rheum Dis. 2011;70(11):1914–20.
32. WInthrop KL, Siegel SAR, Chen L, et al. Comparative infectious risk of immunosuppressive therapies used in psoriasis. J Psoriasis Psoriatic Arthritis. 2016;2(1):7.
33. Shalom G, Zisman D, Bitterman H, Harman-Boehm I, Greenberg-Dotan S, Dreiher J, et al. Systemic therapy for psoriasis and the risk of herpes zoster: a 500000 person-year study. JAMA Dermatol. 2015;151(5):533–8.
34. Shalom G, Naldi L, Lebwohl M, Nikkels A, de Jong EMGJ, Fakharzadeh S, et al. Biological treatment for psoriasis and the risk of herpes zoster: results from the psoriasis longitudinal assessment and registry (PSOLAR). J Dermatolog Treat. 2018:1–20.
35. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, et al. Secukinumab in plaque psoriasis–results of two phase 3 trials. N Engl J Med. 2014;371(4):326–38.
36. Mease PJ, McInnes IB, Kirkham B, Kavanaugh A, Rahman P, van der Heijde D, et al. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. N Engl J Med. 2015;373(14):1329–39.
37. van den Reek J, van Vugt LJ, van Doorn MBA, et al. Initial results of secukinumab drug survival in patients with psoriasis: a multicentre daily practice cohort study. Acta Derm Venereol. 2018;98(7):648–54.
38. van der Heijde D, Gladman DD, Kishimoto M, Okada M, Rathmann SS, Moriarty SR, et al. Efficacy and safety of ixekizumab in patients with active psoriatic arthritis: 52-week results from a phase III study (SPIRIT-P1). J Rheumatol. 2018;45(3):367–77.
39. Farahnik B, Beroukhim K, Zhu TH, Abrouk M, Nakamura M, Singh R, et al. Ixekizumab for the treatment of psoriasis: a review of phase III trials. Dermatol Ther (Heidelb). 2016;6(1):25–37.
40. Papp KA, Barber K, Bissonnette R, Bourcier M, Lynde CW, Poulin Y, et al. A Randomized, blinded assessor study to Evaluate the efFIcacy and safety of etanercept 50 mg once weekly plus as Needed topical agent vs. Etanercept 50 mg twice weekly in patients with moderate to severe plaque psoriasis (REFINE). J Eur Acad Dermatol Venereol. 2015;29(2):361–6.
41. Gordon KB, Duffin KC, Bissonnette R, Prinz JC, Wasfi Y, Li S, et al. A phase 2 trial of guselkumab versus adalimumab for plaque psoriasis. N Engl J Med. 2015;373(2):136–44.
42. Howell ST, Cardwell LA, Feldman SR. Treating moderate-to-severe plaque psoriasis with guselkumab: a review of phase II and phase III trials. Ann Pharmacother. 2018;52(4):380–7.
43. Deodhar A, Gottlieb AB, Boehncke WH, Dong B, Wang Y, Zhuang Y, et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study. Lancet. 2018;391(10136):2213–24.
44. Blauvelt A, Papp KA, Griffiths CE, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. J Am Acad Dermatol. 2017;76(3):405–17.
45. Keating GM. Apremilast: a review in psoriasis and psoriatic arthritis. Drugs. 2017;77(4):459–72.
46. Stein Gold L, Bagel J, Lebwohl M, Jackson JM, Chen R, Goncalves J, et al. Efficacy and safety of apremilast in systemic- and biologic-naive patients with moderate plaque psoriasis: 52-week results of UNVEIL. J Drugs Dermatol. 2018;17(2):221–8.
47. Wells AF, Edwards CJ, Kivitz AJ, Bird P, Nguyen D, Paris M, et al. Apremilast monotherapy in DMARD-naive psoriatic arthritis patients: results of the randomized, placebo-controlled PALACE 4 trial. Rheumatology (Oxford). 2018;57:1253–63.
48. Strober B, Bagel J, Lebwohl M, Stein Gold L, Jackson JM, Chen R, et al. Efficacy and safety of apremilast in patients with moderate plaque psoriasis with lower BSA: week 16 results from the UNVEIL study. J Drugs Dermatol. 2017;16(8):801–8.

49. Kishimoto M, Komine M, Hioki T, Kamiya K, Sugai J, Ohtsuki M. Real-world use of apremilast for patients with psoriasis in Japan. J Dermatol. 2018;45:1345–8.
50. Elyoussfi S, Thomas BJ, Ciurtin C. Tailored treatment options for patients with psoriatic arthritis and psoriasis: review of established and new biologic and small molecule therapies. Rheumatol Int. 2016;36:603–12.
51. Curtis JR, Xie F, Yun H, Bernatsky S, Winthrop KL. Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. Ann Rheum Dis. 2016;75(10):1843–7.
52. Winthrop KL, Lebwohl M, Cohen AD, Weinberg JM, Tyring SK, Rottinghaus ST, et al. Herpes zoster in psoriasis patients treated with tofacitinib. J Am Acad Dermatol. 2017;77(2):302–9.
53. FDA. FDA Briefing Document: Arthritis Advisory Committee Meeting. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM569317.pdf. Published 2017. Accessed February 18, 2019.