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Review

Infections in psoriatic arthritis: association with treatment

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Athanasios Vassilopoulos, **Konstantinos Thomas** and **Dimitrios Vassilopoulos**

***Abstract*:** Serious infections (SIs) remain one of the most significant comorbidities in patients with inflammatory arthritides including psoriatic arthritis (PsA). Apart from methotrexate (MTX) and biologics such as tumor necrosis factor (TNFi), interleukin-12/23 (IL-12/23i), and IL-17 inhibitors (IL-17i), traditionally used for the treatment of PsA, recently biologics such as IL-23i and targeted synthetic agents like JAK inhibitors (JAKi) have been introduced in the daily clinical practice for the treatment of this disease. Although overall the incidence of SIs in patients with PsA treated with these agents is lower compared to patients with rheumatoid arthritis, still a number of unresolved issues regarding their safety remain. Current evidence is reassuring regarding the safety profile of conventional synthetic disease-modifying anti-rheumatic drugs, such as MTX. The increased risk for reactivation of latent infections, such as tuberculosis and hepatitis B virus (HBV) with the use of TNFi, is well described; nevertheless, it is significantly ameliorated with the appropriate screening and prophylaxis. Regarding IL-12/23i and IL-17i, there are no significant safety signals, except from an increased incidence of usually mild *Candida* infections with the latter class. Newer biologics such as IL-23i and targeted synthetic agents like JAKi have been recently introduced in the daily clinical practice for the treatment of this disease. While IL-23i has not been shown to increase the risk for common or opportunistic infections, a well-established association of JAKi with herpes zoster warrants the attention of rheumatologists. In this narrative review, we summarize the infectious complications of available treatment options by drug class in patients with PsA.

Keywords: biologic therapy, JAK inhibitors, psoriatic arthritis, serious infections

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Correspondence to:
Dimitrios Vassilopoulos
Joint Rheumatology Program, Clinical Immunology–Rheumatology Unit, Second Department of Medicine and Laboratory, National and Kapodistrian University of Athens School of Medicine, General Hospital of Athens Hippokration, 114 Vass. Sophias Avenue, Athens 115 27, Greece
dvassilop@med.uoa.gr

Athanasios Vassilopoulos
Division of Internal Medicine, Rhode Island Hospital, Warren Alpert Medical School of Brown University, Providence, RI, USA

Konstantinos Thomas
Fourth Department of Medicine, National and Kapodistrian University of Athens School of Medicine, Attikon University General Hospital, Athens, Greece

Introduction

The introduction of biologic disease-modifying anti-rheumatic drugs (bDMARDs) and targeted-synthetic DMARDs (tsDMARDs) for the management of rheumatologic diseases, including psoriatic arthritis (PsA), over the last two decades has significantly changed clinical practice leading to improved patient outcomes and quality of life.[1–3] These therapeutic agents have shown high efficacy in patients with inadequate response to conventional synthetic DMARDs (csDMARDs) and simultaneously have been useful as glucocorticoid (GC)-sparing agents in this patient population.[1]

Among patients with PsA, infections contribute significantly to their morbidity and mortality.[4] PsA by itself may increase the risk of infections via the loss of skin barrier integrity (if extensive psoriatic skin lesions are present) as well as immune alterations and particularly increased differentiation of naïve T cells into Th17 cells leading to dysregulation of the interleukin (IL)-23/IL-17 axis.[5] Increased risk for infections could also be explained by the increased prevalence of cardiometabolic comorbidities such as type 2 diabetes mellitus and obesity among patients with PsA.[6,7] In addition, it has been shown that patients with PsA experience a higher rate of infections (more

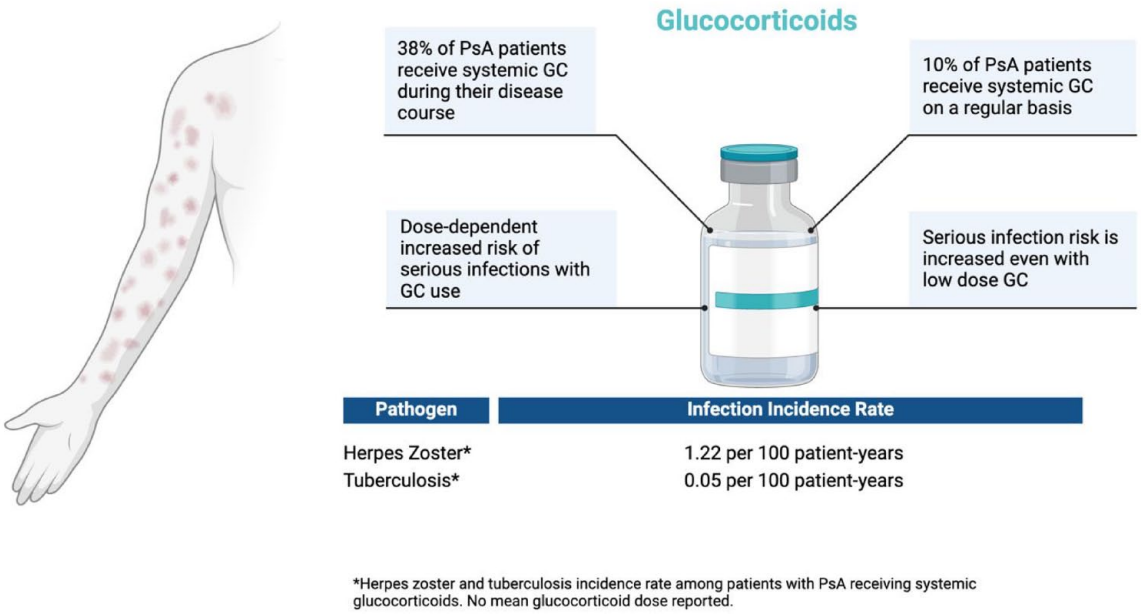

Figure 1. Systemic glucocorticoid use and serious infection risk among patients with psoriatic arthritis.
GC, glucocorticoid; PsA, psoriatic arthritis.

than 50%) compared to patients with psoriasis (PsO) alone.[8] Most frequently, serious infections (SIs) reported in patients with PsA are lower respiratory tract infections due to common bacterial or viral pathogens.[4] Opportunistic infections (OIs) and especially tuberculosis (TB), herpes zoster (HZ), and *Candida* infections can also affect patients on DMARDs and/or systemic GCs.[9,10]

The incidence and risk of each specific infection differs among available treatment options and rheumatologists need to remain informed on the safety profile of each specific agent. In this review, we aimed to evaluate the infectious complications of available treatment options in PsA as presented in randomized controlled trials (RCTs), their long-term extension (LTE) periods, and real-world studies.

Materials and methods

Search strategy

In this review, we searched the PubMed and EMBASE databases for RCTs, LTEs, and observational studies or registries, with the last access on March 15, 2024. For our literature search, we used the following combination of keywords: "psoriatic arthritis," "methotrexate," "glucocorticoids," "bDMARD," "tumor necrosis factor inhibitor," "interleukin-12/23 inhibitor," "IL-17 inhibitor," "IL-23 inhibitor," "tsDMARD," "JAK inhibitor," and "infection." An additional manual search of reference lists for eligible studies complemented our initial search.

Infection rate of available therapeutic options by drug class

Non-biologic options

Glucocorticoids. The use of systemic GCs is not usually recommended in treatment guidelines for PsA.[3] Previous reports of increased risk for PSO flare with high-dose GC administration, further limited GC prescription but data regarding their true risk remain unknown.[11] Systemic GCs, however, are still prescribed in disease flares or as bridging therapy, pending the full effect of DMARDs followed by their gradual withdrawal. A recent meta-analysis showed that 38% of patients with PsA have been treated with systemic GCs during their disease course[12] while a most recent nationwide cross-sectional study of 924 patients with PsA showed that approximately 10% of patients were receiving systemic GCs regularly (Figure 1).[13]

GCs have multiple effects explaining their anti-inflammatory and immunosuppressive properties.[14] They exert their action in different immune cells including neutrophils, macrophages, B and

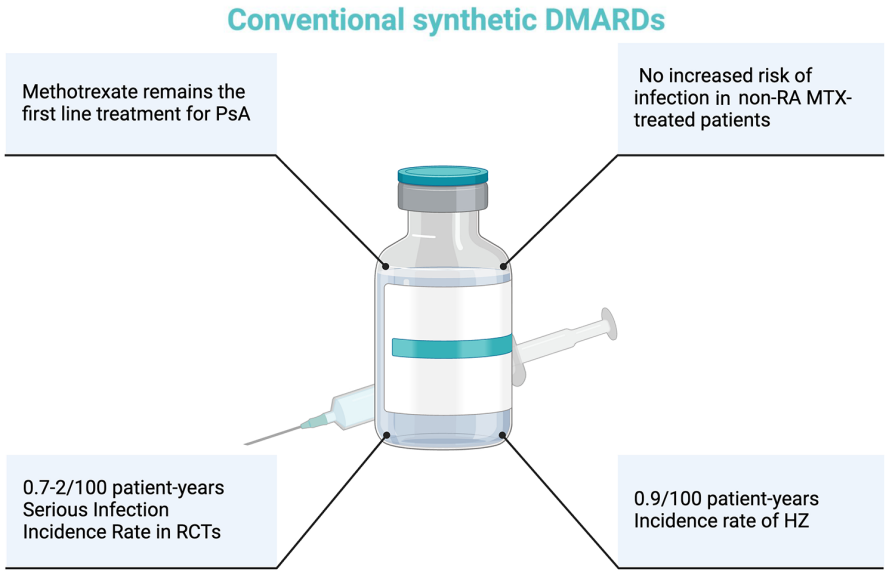

Figure 2. Conventional synthetic DMARDs and infection.
DMARD, disease-modifying anti-rheumatic drugs; HZ, herpes zoster; MTX, methotrexate; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCT, randomized controlled trial.

T lymphocytes but also in tissue cells including fibroblasts and adipose cells.[14] Following GC administration, their impact on several types of immune cells is rapidly observed, with CD4 lymphopenia being the most profound. GC use is also associated with reduced phagocytosis, decreased T-cell activity, and delayed healing of wounds.[15] A daily dose of 10 mg of prednisone equivalent (PEQ) is considered a threshold of increased risk for infections; however, specific OIs may require higher (i.e. *Pneumocystis jirovecii* pneumonia) or lower (i.e. HZ) PEQ doses.[15] Mean daily dose is not the only determinant since cumulative GC dose and treatment duration also contribute to the overall infectious risk.[15]

Available data regarding systemic GC use and the risk of infection among patients with PsA are limited given their less frequent use than in rheumatoid arthritis (RA). However, studies directly evaluating the safety of systemic GCs in patients with psoriatic disease indicate that although the risk for SIs is dose dependent, SIs can occur even with low-dose GCs.[16] A recent real-world study evaluating the incidence of specific OIs, namely TB and HZ, showed an incidence rate of 0.05 and 1.22 per 100 patient-years, respectively, in patients receiving only GCs.[17]

Conventional synthetic DMARDs. Still considered to be first-line treatment for PsA, csDMARDs, mainly methotrexate (MTX), but also leflunomide, do not appear to have a substantial infection risk.[18] The majority of available safety data among patients with PsA treated with MTX are gathered from control groups of RCTs evaluating b- and ts-DMARDs. In control groups of RCTs, at least 50% of patients were receiving MTX, the rate of SIs ranged from 0.7% to 2%, while OIs were limited during the short follow-up period of 12–24 weeks[19,20] (Figure 2). Similarly, a meta-analysis evaluating the risk of infection in inflammatory rheumatic diseases corroborated that there is no increased risk of infection and SIs in non-RA patients[21] treated with MTX. Of note, it has also been reported that there is no increased risk for pneumonia in such MTX-treated patients.[22]

As for OIs and more specifically HZ, a retrospective cohort study found that the incidence rate of HZ was 0.9 per 100 patient-years among patients with PsA receiving csDMARDs, mainly MTX.[23] This finding did not translate to an increased risk for HZ with csDMARD treatment alone.[23]

Biologic DMARDs

Tumor necrosis factor inhibitors. Tumor necrosis factor inhibitors (TNFis) were the first bDMARDs

approved for PsA and have been proven highly efficacious.[20,24–37] The immunomodulatory effect of TNFis and their infection risk has been thoroughly studied especially among patients with RA. The mechanism of action of TNFi raised, from early on, concerns the risk of latent *Mycobacterium tuberculosis* infection (LTBI) and hepatitis B virus (HBV) reactivation.[38–40] Therefore, screening for the aforementioned pathogens has been successfully implemented before treatment initiation in the past decades. Currently, TNFis that are available for PsA include adalimumab, certolizumab, etanercept, golimumab, and infliximab.

The rate of SIs among patients with PsA reported in RCTs and their LTEs ranged from 0% to 2.8%[20,24–37] and from 0.9 to 3.3/100 patient-years in up to 5 years of follow-up,[40–47] respectively (Table 1). The highest incidence rate during LTEs was reported among patients receiving certolizumab.[41,42] Furthermore, there is currently a plethora of real-world evidence regarding SIs in TNFi-treated patients with PsA. Of note, their incidence rate was similar to those found during RCT and LTE studies (0.9–3.9/100 patient-years), with the highest being reported among patients receiving infliximab.[48–52] Even though it has been previously reported that etanercept, a soluble decoy TNF receptor,[51] had lower SI risk, the incidence rates that we present herein are similar across all TNFis. It should be noted however that direct head-to-head comparisons cannot be performed from these data (Figure 3).

Overall, the risk of SIs among PsA patients treated with TNFi was approximately 40% lower compared to RA patients (hazard ratio (HR): 0.59, 95% confidence interval (CI): 0.41–0.85) treated with the same agents.[53] The most common SIs among patients with PsA treated with TNFi include pneumonia and cellulitis with an incidence rate of 0.54 and 0.41/100 patient-years, respectively.[52] It is also important to remain vigilant for other intracellular pathogens in TNFi-treated patients.[54] For instance, the incidence rate of listeriosis for patients with PsA on TNFi enrolled in a Spanish Registry was 0.7/1000 patient-years.[55] Even though the absolute risk is low, this is significantly higher (~75%) compared to the general population.[55,56]

Taking into consideration the effect of TNFi in suppressing the formation and/or maintenance of granulomas, LTBI reactivation, or acquiring TB while being on chronic TNFi treatment is still a concern, especially in areas with moderate to high TB prevalence. As previously mentioned, extensive screening as part of current clinical practice has greatly decreased the incidence of TB in this patient population. Notably, the rate of TB in RCTs and their LTE periods has been <0.4/100 patient-years which confirms the rigorousness of screening in RCT protocols.[20,24–37,40–47]

Given that TNFis have been available for more than 20 years, the most pertinent data are found in real-world studies or registries with large patient populations followed for prolonged periods of time. The incidence rates in such studies range from 0 to 1.62/100 patient-years,[51,57–59] depending on their respective baseline TB prevalence in the studied general populations.[51,58,60] Interestingly, the incidence rate of TB that was reported from MarketScan data in the United States was only 0.04/100 patient-years during 255,451 patient-years of follow-up, a percentage much lower than those previously mentioned. Consequently, it is evident that awareness among rheumatologists regarding TB and risk with TNFi usage has greatly increased over the years and proper screening protocols are being widely implemented. Increased caution is required in geographic locations with high TB prevalence since some patients may still be at risk of being infected after screening. Rheumatologists should also be aware of the prevalence of resistance to antitubercular drugs in their areas since this could lead to failure of the prescribed LTBI treatment.

Other OIs of special interest among TNFi-treated patients include HZ, HBV, and HCV reactivation. Regarding HZ, it has been shown that its risk increases with a longer treatment duration.[61] There were few HZ cases during RCTs[20,24–37] with the incidence rate increasing up to 0.5% in their LTEs (up to 4 years of follow-up)[42,46,47] and subsequently up to 2% in real-world studies.[17,48,49,51,57,62] Interestingly, a retrospective study has shown that the time to HZ development is shorter among PsA patients receiving TNFi compared to those receiving csDMARDs.[23]

For HBV reactivation, there are limited data in RCTs or their LTEs while data are sparse in observational cohorts or registries. A recent meta-analysis estimated the prevalence of HBV reactivation among patients with PsO treated with bDMARDs at 0.04%.[63] In a sub-analysis, it was also highlighted that the prevalence was higher in studies conducted in Asia compared to Europe,

Table 1. Serious infection incidence rate by therapeutic category.

Study type	RCT		LTE		Real-world studies	
SI incidence	**IR range (/100 PY)**	**Duration (wks or PY)**	**IR range (/100 PY)**	**Duration (years)**	**IR range (/100 PY)**	**Duration (years or PY)**
Therapeutic category						
TNFi (overall)	**0.00–2.80**	**12–24 wks**	**0.90–3.29**	**0.5–5 years**	**0.90–3.90**	**0.5–3 years**
Adalimumab	0.00–2.00	12–24 wks	1.30–2.50	0.5–3.5 years	1.10–3.05	>0.5 years
Certolizumab	1.40–1.50	24 wks	1.64–2.00	4 years	1.83–1.99	765–905 PY
Etanercept	0.00–2.80	12–48 wks	0.90	4 years	1.13–2.19	>0.5 years
Golimumab	0.00–2.60	417 PY	1.16–3.29	1–5 years	1.06–2.90	202–1696 PY
Infliximab	1.80	16 wks	2.50	2 years	0.95–3.90	364–5139 PY
IL17i (overall)	**0.16–2.70**	**12–48 wks**	**0.70–2.00**	**3 years**	**0.70–4.80**	**1–5 years**
Bimekizumab	0.2–1.70	16–48 wks	0.70	3 years	NA	NA
Brodalumab	0.16–2.00	12–16 wks	NA	NA	NA	NA
Ixekizumab	1.00–1.44	24 wks	0.70–1.20	3 years	0.83–2.06	436–727 PY
Secukinumab	1.80–2.70	24 wks	1.60–2.00	2–5 years	0.70–4.80	1–5 years
IL12/23i (Ustekinumab)	**0.00**	**16 wks**	**0.82–1.50**	**1–3 years**	**0.84–2.00**	**1.2–3 years**
IL23i (overall)	**0.00–1.00**	**24 wks**	**1.10–1.90**	**1–4 years**	**0.00**	**2 years**
Guselkumab	0.00–0.80	24 wks	1.10–1.90	1–4 years	0.00	2 years
Risankizumab	0.90–1.00	24 wks	1.40	1 year	NA	NA
Tildrakizumab	0.30	24 wks	NA	NA	NA	NA
CTLA4-Ig (Abatacept)	**0.50–2.30**	**24 wks**	**NA**	**NA**	**NA**	**NA**
JAKi (overall)	**0.00–2.80**	**12–24 wks**	**1.20–5.40**	**1–3 years**	**0.70–2.12**	**0.5–9 years**
Tofacitinib	0.0–2.00	12–24 wks	1.20–1.40	1–3 years	2.12	1–9 years
Upadacitinib	0.50–2.80	24 wks	2.30–5.40	1–3 years	0.70	0.5 years
Filgotinib	2.00	16 wks	NA	NA	NA	NA
Deucravacitinib	0.00	16 wks	NA	NA	NA	NA

IL, interleukin; IR, incidence rate; JAK, Janus activated kinase; LTE, long-term extension; PY, patient-years; RCT, randomized controlled trial; SI, serious infection; TNF, tumor necrosis factor. In bold the cumulative data for each therapeutic category are shown.

reflecting the differences in HBV prevalence in the respective general populations. In this meta-analysis, the prevalence of human immunodeficiency virus (HIV) infection was also calculated to be 0.12%, a percentage similar to baseline global prevalence.[63,64]

Interleukin-17 inhibitors. Another class of bDMARDs frequently used in PsA is IL-17 inhibitors (IL-17i) which are highly efficacious and preferred for patients with extensive skin PsO.[3] By suppressing the IL-17 pathway, the risk of fungal infections, and especially *Candida*, is increased in IL-17i-treated patients. Approved IL-17i for PsA include ixekizumab, secukinumab, and bimekizumab. These inhibitors exert their effects in different forms of IL-17 and its receptors (e.g., IL-17A, IL-17F).

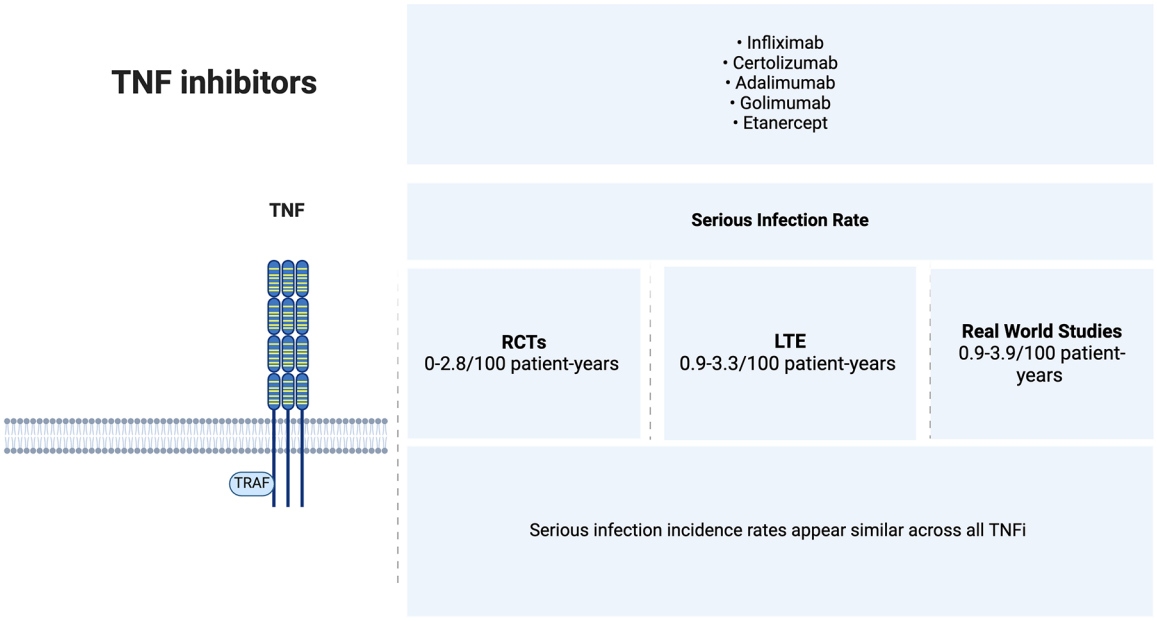

Figure 3. TNF inhibitors and infection in psoriatic arthritis.
LTE, long-term extension; RCT, randomized controlled trial; TNFi: Tumor necrosis factor inhibitors.

Compared to TNFi, a recent real-world study showed that the risk of SIs among IL-17i-treated PsA patients was slightly lower (adjusted HR: 0.89, 95% CI: 0.48–1.66)[50] (Figure 4). Among different IL-17i, the incidence of SIs in RCTs studying ixekizumab and secukinumab ranged from 1% to 2.7% (24–52 weeks of follow-up)[65–71] with similar rates being identified during the LTE periods (0.7–2%, with up to 5 years of follow-up, Table 1).[72–74] Of note, recent RCTs on the newer IL-17i, bimekizumab did not identify any new safety concerns with the rates of SIs being 0.2%–1.7%.[75–77] Similarly, LTE on bimekizumab showed an incidence rate of 0.7/100 patient-years with 3 years of follow-up.[78]

Finally, available data from real-world studies that evaluated patients receiving ixekizumab or secukinumab showed an SI incidence rate of 0.83–2.06/100 patient-years for ixekizumab and 0.7–4.8/100 patient-years for secukinumab.[48,72,79,80] Based on the above data, it appears that the occurrence of SIs is similar among patients treated with either ixekizumab or secukinumab.

Results from early RCTs[65–71] and a recent meta-analysis have shown an increased incidence rate of *Candida* infections among patients receiving IL-17i compared to patients receiving placebo and/or csDMARDs (2.27 times higher).[10] Similar results have been reported in real-world studies (incidence rate: 1.5–2.9/100 patient-years).[72,74,79,81] Nevertheless, the severity of *Candida* infection is mild to moderate, usually resolving with topical treatments while disseminated candidiasis is rare.[82] Of note, bimekizumab is associated with an increased incidence of mild to moderate candidiasis during the first 16 weeks of treatment among patients with moderate to severe plaque PsO according to pooled data of RCTs.[83]

Regarding TB, pooled data from five phase III clinical trials evaluating secukinumab showed that this was an extremely rare event with only one patient developing LTBI (incidence rate: 0.02/100 patient-years).[84]

Interleukin-12/23 inhibitors. Ustekinumab is a monoclonal antibody targeting the p40 subunit of IL-12 and IL-23. It has been found to have significant efficacy in the treatment of patients with PsA due to its effect on Th17 cell proliferation.[1–3]

The SI incidence rate in RCTs and LTE periods ranged from 0.82 to 1.5/100 patient-years during up to 3 years of follow-up (Table 1)[85–89] with a similar rate (0.84–1.2/100 patient-years) in real-world studies with up to 13,121 patient-years of follow up.[48,49,52,90]

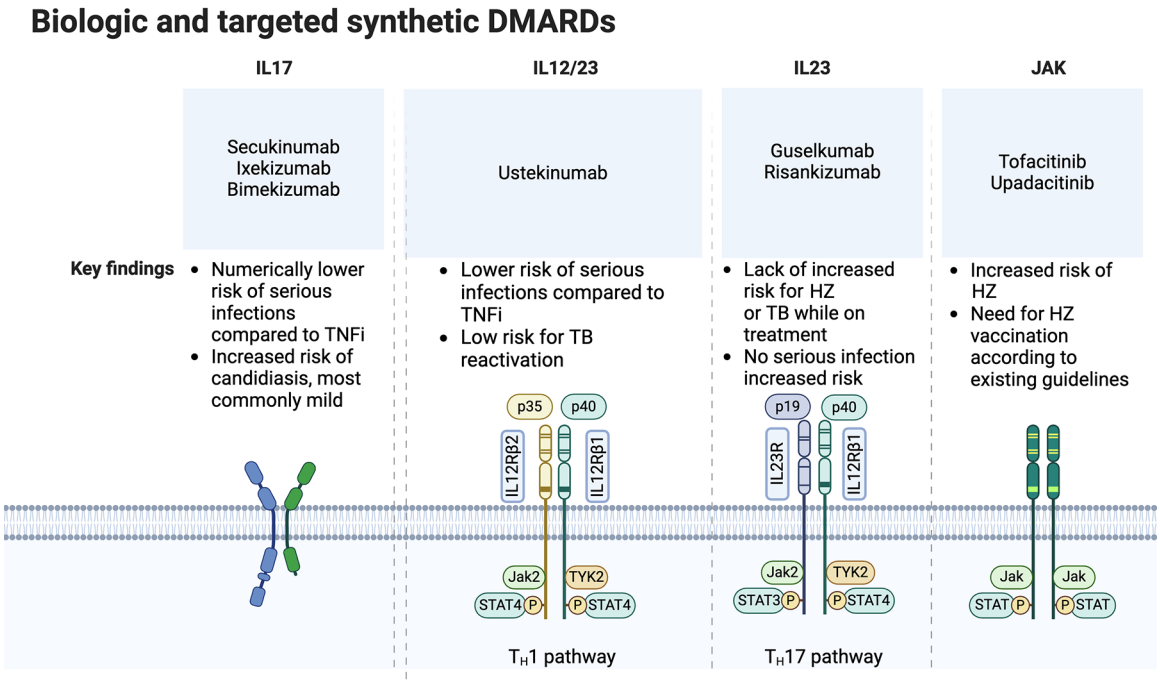

Figure 4. Other DMARDs and infection in psoriatic arthritis.
DMARD, disease-modifying anti-rheumatic drugs; HZ, herpes zoster; IL, interleukin; JAK, Janus activated kinase; TB, Tuberculosis; TNFi: Tumor necrosis factor inhibitors.

The overall SI risk in TNFi-treated patients with PsA is higher compared to ustekinumab-treated patients (×1.1–3 times)[48] (Figure 4) while a similar trend is observed in patients with IBD.[91]

There have not been any safety signals raised for TB among patients receiving ustekinumab. Of note, it has been reported that even with long-term use of ustekinumab, there is no increased risk for OIs compared to placebo with an incidence numerically close to zero.[92] In RCTs and their LTE periods of up to 3 years, there was no TB case reported.[85–89] Furthermore, in a real-world setting, the conversion rate, of annually performed interferon-gamma release assays (Quantiferon-QFT) in patients with PsO treated with ustekinumab, was only 7.3% without any cases of TB.[93] Accordingly, data from the Korean National Health Insurance Service showed that there is no increased risk of TB development among patients with PsA receiving ustekinumab when compared to the general population, even in a high endemicity area.[94]

Interleukin-23 inhibitors. After the successful use of ustekinumab in patients with PsA, therapies directly targeting only IL-23 have been evaluated. Guselkumab, risankizumab, and tildrakizumab are IL-23i evaluated for PsA treatment in RCTs, with guselkumab and risankizumab approved by the FDA and EMA.[19,95–102]

The infectious safety profile of IL-23i is reassuring in RCTs with an SI rate of 0–1% with up to 24 weeks of follow-up. Equivalent rates were identified during LTE periods of guselkumab and risankizumab (Table 1),[103–105] while real-world data available for guselkumab with a maximum of 2 years of follow-up have not shown any increase in the rate.[106,107]

As with ustekinumab, OIs are not a major concern for IL-23i-treated patients with PsA.[10,108] Even with a special focus on TB or HZ, the findings are promising showing a lack of an increased risk in IL-23i-treated patients and also confirming that there was no reactivation among patients with LTBI continuing treatment with IL-23i[107,109] (Figure 4).

CTLA4-Ig (Abatacept). Abatacept is a bDMARD that has shown promising findings in recent RCTs, especially in patients with PsA and inadequate response to TNFi.[110] It is a selective T-cell co-stimulation modulator (CTLA4-Ig) that exerts its effects by inhibiting the interaction between CD80/

CD86 and CD28 and therefore limiting T-cell activation by antigen-presenting cells.[111] The extent of abatacept use among patients with PsA is limited, given that other b- or ts-DMARDs are used as first- or second-line options. Therefore, safety data are mostly derived from the published RCTs on PsA or indirectly from RA studies.

In RA, it has been demonstrated that the risk of SIs is lower among patients receiving abatacept compared to TNFi-treated patients (HR: 0.78).[112] Among patients with PsA treated with abatacept, the SI rate in RCTs ranged from 0.5% to 2.3% during 24 weeks of follow-up (Table 1).[110,113] Less than 0.5% of patients developed OIs during the same time frame and no cases of TB or HZ were observed.[110,113]

Targeted-synthetic DMARDs

JAK inhibitors. Among the most recent additions in the arsenal of DMARD options for patients with PsA are JAK inhibitors (JAKi), such as tofacitinib and upadacitinib, a class of ts-DMARDs that inhibit the downstream effect of JAK/STAT pathways leading to the generation of pro-inflammatory cytokines that play a significant role in psoriatic disease pathogenesis.[3] Available JAKi have varying JAK selectivity.[114] For instance, tofacitinib inhibits JAK1 and JAK3 while upadacitinib inhibits mainly JAK1.[115–121] Filgotinib (a selective JAK1 inhibitor) and deucravacitinib (a TYK2 inhibitor) have shown promising results in early studies but have not been approved yet for PsA.[122,123] Overall, the main concern for JAKi is their increased risk of VZV reactivation and therefore HZ infection via their action on VZV-specific T cells.[124]

Regarding SIs, their rate during the placebo-controlled period of RCTs was up to 2% among all JAKi evaluated during 12–24 weeks of follow-up after excluding patients in the 30 mg upadacitinib arms (Table 1).[115–123] The respective SI incidence was up to 2.8/100 patient-years.[116,117,119,120] Similar trends are also identified in LTE and real-world studies evaluating tofacitinib and upadacitinib. More specifically, the SI incidence rate was up to 1.4 in LTE and 2.12 in real-world studies per 100 patient-years among tofacitinib-treated patients[62,125,126] and 2.3/100 patient-years for patients receiving 15 mg/day of upadacitinib in LTE, respectively.[127] Reassuringly, no new safety signals were raised in the first published cohort study of upadacitinib treatment for PsA.[128]

Regarding the HZ risk in LTEs, the incidence rate was 2.1 for tofacitinib and 3.8 per 100 patient-years for upadacitinib (15 mg/day), respectively.[125–127] In real-world settings, a large study evaluating tofacitinib for 9 years showed a lower incidence rate of 0.41/100 patient-years.[129] Of note, HZ severity appears to be mild to moderate in the majority of cases with a very high percentage of resolution.[129] The introduction of the recombinant VZV vaccine has shown very promising findings in studies among patients with autoimmune diseases prior to initiating immunomodulating therapies.[130] Reassuringly, the most recent data also suggest that the recombinant VZV vaccine is serologically immunogenic in RA patients even while being treated with JAKi.[131] However, it appears that the percentage of vaccinated patients with rheumatic diseases remains very low, less than 20%[132] (Figure 4).

Finally, data on filgotinib and deucravacitinib are currently limited but have been highly promising, especially for deucravacitinib.[122,123] Its mechanism of action differs from previously available JAKi as it acts on tyrosine kinase 2, which could potentially have a more targeted action with less effect on VZV reactivation.[133]

Comparative infectious risk from head-to-head studies in PsA

So far, there have been four head-to-head randomized studies comparing different classes of b- and ts-DMARDs in patients with PsA.

McInnes et al.[134] in a double-blind, parallel-group, randomized, active-controlled study compared a TNFi (adalimumab) to an IL-17i (secukinumab) given for 52 weeks in biologic-naïve patients with PsA who were intolerant or had an inadequate response to csDMARDs. There was no difference in the incidence of SIs between the two groups (secukinumab: 7/426, 2% vs adalimumab: 6/427, 1%) while there was a slightly higher incidence of *Candida* infections in the secukinumab group (16/426, 4% vs 7/427, 2%).

In an open-label, head-to-head, blinded assessor clinical trial, Mease et al.[135] compared adalimumab (TNFi) to a different IL-17i (ixekizumab) in bDMARD-naïve, csDMARD-inadequate-responder patients with PsA for 52 weeks. The incidence of SIs was slightly higher in adalimumab (8/283, 2.8%) compared to ixekizumab

(4/283, 1.4%)-treated patients while *Candida* infections were more common in the ixekizumab group (7/283, 2.5% vs 2/283, 0.7%).

In a third randomized, double-blind, placebo-controlled, active reference trial, adalimumab (TNFi) was compared to bimekizumab (an IL-17A and F inhibitor) in biologic-naïve patients with PsA for 24 weeks.[136] The SI incidence was similar between the two groups (bimekizumab: 3/431, 1% vs adalimumab: 2/140, 1%) while there were more fungal infections in the bimekizumab compared to the adalimumab group (33/431, 8% vs 1/140, 1%). These fungal infections observed in the bimekizumab group were mainly *Candida* infections, none of them was serious, leading to drug discontinuation in only one patient.

In a more recent trial, a TNFi (adalimumab) was compared to upadacitinib (JAKi) for 24 weeks in patients with PsA with an inadequate response to non-biologic DMARDs.[116] There was no difference in the incidence of SIs in the upadacitinib (15 mg/day, 5/429, 1.2%) compared to the adalimumab (3/429, 0.7%) group while there were four cases of mild to moderate HZ in the upadacitinib group compared to 0 in the adalimumab group.

Overall, these head-to-head trials that compared a TNFi (adalimumab) to three different IL-17i (secukinumab, ixekizumab, bimekizumab) and a JAKi (upadacitinib) revealed no significant differences in the incidence of SIs between these agents while they showed a slightly higher incidence of *Candida* infections in the IL-17i and HZ in the JAKi groups, respectively. These results though should be interpreted with caution since the duration of follow-up was rather short (6–12 months).

Conclusion

Biologic and more recently tsDMARDs have transformed the therapeutic landscape in patients with PsA. These treatments have been proven highly efficacious in preventing joint and bone damage and clearing skin PsO while, more importantly, improving the quality of patients' daily lives. Although initially there have been concerns about their infectious safety profile, a cumulative experience that has been gathered from RCTs and their LTEs and more importantly from real-world studies has shown that overall, these agents are safe and can be given for prolonged periods of time without any new safety signals. In this narrative review we provide insight into the infectious risk of various therapeutic options in patients with PsA with the limitation that our review was not a systematic one.

There is a slightly increased infection risk in patients with PsA compared to the general population, with this risk being shaped by a combination of disease characteristics (loss of skin barrier integrity), coexisting comorbidities (obesity), and disease-modifying treatment. Overall though the risk for SIs appears to be lower compared to patients with RA, owing probably in part and to the younger age of patients with PsA.

Biologic and more recently tsDMARDs have been proven highly efficacious in preventing joint and bone damage and clearing skin PsO while, more importantly, improving the quality of patients' lives. A cumulative experience that has been gathered from RCTs and their LTEs and more importantly from real-world studies has shown that overall, these agents are safe and can be administered for prolonged periods of time with very low safety issues.

Between the different classes of b- and ts-DMARDs, it appears, mainly from real-world data, that IL-12/23i and IL-23i have the most favorable infectious risk profile with no significant differences in the SI risk between TNFi and IL-17i or JAKi revealed in head-to-head randomized controlled studies. Rheumatologists should be aware of the slightly higher risk for fungal, mainly *Candida*, infections in patients treated with IL-17i; however, these infections are usually mild, easily managed, and do not require permanent treatment discontinuation. JAKi confers an increased risk for VZV reactivation and JAKi-treated patients could benefit from vaccination with the highly efficacious adjuvanted vaccine against HZ.

In conclusion, the currently available therapies in PsA appear to be safe, whereas implementation of the appropriate screening (TB, HBV) and preventive (vaccinations) strategies as well as close long-term monitoring of these patients are crucial in further decreasing this infectious risk.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Athanasios Vassilopoulos: Conceptualization; Formal analysis; Writing – original draft; Writing – review & editing.

Konstantinos Thomas: Conceptualization; Formal analysis; Writing – original draft; Writing – review & editing.

Dimitrios Vassilopoulos: Conceptualization; Formal analysis; Writing – original draft; Writing – review & editing.

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ORCID iDs
Athanasios Vassilopoulos https://orcid.org/0000-0001-6486-608X

Konstantinos Thomas https://orcid.org/0000-0002-7489-7776

Dimitrios Vassilopoulos https://orcid.org/0000-0003-2288-3863

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Appendix

Abbreviations

DMARD	disease-modifying anti-rheumatic drugs
GC	glucocorticoid
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HZ	herpes zoster
IL	interleukin
JAK	Janus activated kinase
LTBI	latent *Mycobacterium tuberculosis* infection
LTE	long-term extension
MTX	methotrexate
PsA	psoriatic arthritis
PsO	psoriasis
RA	rheumatoid arthritis
RCT	randomized controlled trial
SI	serious infection
TB	tuberculosis
TNF	tumor necrosis factor