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Considerations for safety in the use of systemic medications for psoriasis and atopic dermatitis during the COVID-19 pandemic

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Abstract

Coronavirus disease 2019 (COVID-19) is responsible for at least 2 546 527 cases and 175 812 deaths as of April 21, 2020. Psoriasis and atopic dermatitis (AD) are common, chronic, inflammatory skin conditions, with immune dysregulation as a shared mechanism; therefore, mainstays of treatment include systemic immunomodulating therapies. It is unknown whether these therapies are associated with increased COVID-19 susceptibility or worse outcomes in infected patients. In this review, we discuss overall infection risks of nonbiologic and biologic systemic medications for psoriasis and AD and provide therapeutic recommendations. In summary, in patients with active infection, systemic conventional medications, the Janus kinase inhibitor tofacitinib, and biologics for psoriasis should be temporarily held until there is more data; in uninfected patients switching to safer alternatives should be considered. Interleukin (IL)-17, IL-12/23, and IL-23 inhibitors are associated with low infection risk, with IL-17 and IL-23 favored over IL-12/23 inhibitors. Pivotal trials and postmarketing data also suggest that IL-17 and IL-23 blockers are safer than tumor necrosis factor alpha blockers. Apremilast, acitretin, and dupilumab have favorable safety data and may be safely initiated and continued in uninfected patients. Without definitive COVID-19 data, these recommendations may be useful in guiding treatment of psoriasis and AD patients during the COVID-19 pandemic.

KEYWORDS

atopic dermatitis, biologics, COVID-19, immunosuppression, psoriasis

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel human coronavirus, with 2 546 527 confirmed cases of coronavirus disease 2019 (COVID-19) and 175 812 deaths worldwide (April 21, 2020).[1] It was declared a pandemic by the World Health Organization. An overall case fatality rate of 3.61% has been reported[2]; however, inaccuracies may exist because those who are asymptomatic or suffer from mild disease may never receive confirmation.

Psoriasis and atopic dermatitis (AD) are common, chronic, inflammatory skin diseases, affecting 2% to 3% of the general population and 7% of adults in the United States, respectively.[3,4] Disease mechanisms are multifactorial, with immune dysregulation important for both conditions, and mainstays of treatment immune-modulation.[5] Systemic therapy is preferred for psoriasis treatment in patients with body surface area >10%, involvement of sensitive areas or topical therapy failure.[6] Systemic treatment is recommended for AD patients

Abbreviations: AD, atopic dermatitis; BADBIR, British Association of Dermatologists Biologic Interventions Register; CI, confidence interval; COVID-19, coronavirus disease 2019; FDA, Food and Drug Administration; HR, hazard ratio; IL, Interleukin; JAK, Janus kinase; RR, relative risk; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF-α, tumor necrosis factor alpha; URI, upper respiratory infection.

with severe disease or recalcitrant to topical therapy.[7] Immunocompromised patients are highly vulnerable to infections, which is particularly concerning in the context of the COVID-19 pandemic.

In this review, we summarize the current literature regarding overall infection risks with systemic immunomodulating agents for psoriasis and AD and provide evidence-based treatment recommendations during the COVID-19 pandemic.

2 | NONBIOLOGIC SYSTEMIC THERAPIES

2.1 | Systemic corticosteroids

Systemic corticosteroids are immunosuppressive medications used to treat AD flares, but very rarely psoriasis. They have been shown to increase infection risk. In a systematic review of 101 studies on AD children (n = 6817) treated with systemic corticosteroids ≥15 days, infection rate was 8.7%, with 21 associated deaths.[8] In a meta-analysis of corticosteroid use in patients with influenza pneumonia (10 studies, n = 6548), compared with placebo, corticosteroids were associated with higher mortality, longer intensive care unit length of stay and a higher rate of secondary infection.[9] Therefore, oral corticosteroids should be avoided, weighing the risks of disease flare vs SARS-CoV-2 infection, to prevent COVID-19 susceptibility. Before discontinuation, dose tapering may be considered to avoid a negative effect on respiratory symptoms.

2.2 | Methotrexate, cyclosporine, and acitretin

Methotrexate and cyclosporine are among the most frequently used systemic medications for psoriasis and AD, with both associated with increased infection rates. There was a 58% higher overall infection risk with cyclosporine vs methotrexate in the BIOBADADERM Registry (Spanish Registry of Adverse Events for Biological Therapy in Dermatological Disease) including 2153 psoriasis patients.[10] In a head-to-head comparison of methotrexate (n = 50) vs cyclosporine (n = 47) in moderate-to-severe AD adults, infections rates were 32% and 24%, respectively.[11] While methotrexate and cyclosporine are associated with decreased infection rates and favored over treatment with systemic corticosteroids,[12] their impact on susceptibility to/severity of COVID-19 is unknown and, if essential, precautions should be taken to avoid infection. Of interest, cyclosporine has anticoronavirus activity *in vitro*, but the effect in humans is unknown.[13]

The systemic retinoid, acitretin, is anti-inflammatory and inhibits cell differentiation; it is Food and Drug Administration (FDA)-approved for psoriasis.[14] It does not suppress the immune system to the extent of the other conventional treatments for psoriasis. In an observational cohort study, there was no increased rate of overall serious infections among acitretin-treated psoriasis patients vs methotrexate; acitretin increased risk of cellulitis compared to methotrexate (propensity score-adjusted hazard ratio [HR], 1.76; 95% confidence interval [CI], 1.11-2.80), possibly due to skin fragility and *Staphylococcus aureus* colonization.[15] Therefore, acitretin has not shown increased viral/respiratory infection risk and can be safely used during the pandemic. Retinoids have been shown to inhibit human herpesvirus eight replication, but their effect on SARS-CoV-2 remains to be established.[16]

2.3 | Azathioprine

Azathioprine is used off-label in the United States for AD treatment in patients recalcitrant or who have contraindications to cyclosporine and methotrexate. In 12 AD children treated with azathioprine, there were no associated infections.[17] In a double-blind, placebo-controlled, crossover study of 37 AD adults treated with azathioprine, there were five cases of upper respiratory infections (URIs) (14%), two cases folliculitis (5%), and one report each impetigo (3%) and sore throat (3%).[18] In a retrospective analysis of 232 611 systemically treated adults with AD (6 months), there were increased risks of serious and opportunistic infections with azathioprine (relative risk (RR) = 1.89) and prednisone (RR = 1.78) compared with methotrexate, with a reduced risk with cyclosporine (RR = 0.87).[12] Therefore, azathioprine may increase susceptibility to infections, and if essential, exposure to COVID-19 should be minimized.

2.4 | Apremilast

Apremilast, an orally administered phosphodiesterase-4 inhibitor is FDA approved for moderate-to-severe plaque psoriasis and has been used off-label for AD.[19-21] Although it does modulate immunologic cascades, this pathway does not seem to significantly increase susceptibility to infection. In a pooled safety analysis of two randomized controlled trials (RCTs) involving psoriasis patients treated with apremilast (n = 1184), URIs and nasopharyngitis occurred in 19.2% and 16.6% of patients, respectively; serious infections (urinary tract infection n = 2; appendicitis n = 3; pneumonia = 2) occurred in 1.4%.[22] Furthermore, in an observational cohort study including systemically treated psoriasis patients, overall serious infections were decreased with apremilast vs methotrexate (HR, 0.50; 95% CI, 0.26-0.94). Thus, apremilast seems to be a safe alternative for uninfected psoriasis patients during the pandemic, but specific COVID-19 data are needed.

Data regarding infection risks of nonbiological therapies for psoriasis and AD are summarized in Table 1.

2.5 | Biologic medications and Janus kinase inhibitor

Biologic medications are widely used for psoriasis and AD patients, with limited data regarding infection risk. Since biologics inhibit immune-mediated pathways involving specific cytokines, there is at least theoretical risk of increased susceptibility to and severity of infection. A common reason for discontinuation of biologics is infection.[29] Among the targeted cytokines for these biologics, tumor necrosis

TABLE 1 Studies on infection risk of nonbiological systemic therapies for psoriasis and atopic dermatitis

Study, year/ medication	Patient demographics	Medication, dosage	Indication	Outcome/type of infection, n (%)
Cyclosporine				
Garritsen et al[23]	n = 267 Mean age = 35.50 y Male = 146 (55%)	Mean maximum dose = 4.23 mg/kg/d	Atopic dermatitis	Infection leading to discontinuation: recurrent viral infection with herpes simplex: 1 (0%)
Schmitt et al[24]	n = 17 Mean age = 30.1 y Female = 7 (41%)	2.7-4.0 mg/kg/d for 6 wk	Atopic dermatitis	Common cold: 4 (24.0%), infection of the skin: 4 (24.0%)
Goujon et al[11]	n = 47 Mean age = 33 y Male = 31 (66%)	2.5-5 mg/kg divided in two doses daily	Atopic dermatitis	Nonskin infection: 10 (21.3%), skin infection: 5 (10.6%)
Methotrexate				
Garritsen et al[23]	n = 37 Mean age = 43.89 y Male = 19 (51%)	Mean maximum dose = 20.90 mg/wk	Atopic dermatitis	Infection leading to discontinuation: none reported
Goujon et al[11]	n = 50 Mean age = 32 y Male = 28 (57%)	15-25 mg/wk	Atopic dermatitis	Nonskin infection: 6, skin infection: 6
Baranauskaite et al[25]	n = 54 Mean age = 42.3 y Male = 33 (61.1%)	15-20 mg/wk, for 16 wk	Psoriatic arthritis	Infection leading to discontinuation: none reported
Saurat et al[26]	n = 110 Mean age = 41.6 y Male = 66.4%	7.5 mg, increased as needed and as tolerated to 25 mg weekly	Psoriasis	Serious infection: 0, nonserious infection: 46 (41.8%), nasopharyngitis: 26 (23.6%), viral infection: 6 (5.5%)
Corticosteroids				
Garritsen et al[23]	n = 24 Male = 14 (58%) Prednisone Mean age = 43.89 y Celestone Mean age = 36.40	Mean maximum dose: Prednisone: 23.0 mg/d Celestone: 1.50 mg/d	Atopic dermatitis	Infection leading to discontinuation: unknown
Aljebab et al[8]	n = 6817 Age range = 28 d to 18 y	Prednisolone, dexamethasone, budesonide, methylprednisolone, deflazacort, betamethasone. For ≥15 d	Atopic dermatitis	Incidence rate: all infections: 8.7%, resulting in 21 deaths
Aljebab et al[27]	n = 3200 Age range = 28 d to 18 y	Prednisolone, dexamethasone, or betamethasone	Atopic dermatitis	Incidence rate: all infections: 0.9%, resulting in 1 death
Schmitt et al[24]	n = 21 Mean age = 28.8 y Female = 10 (48%)	Prednisolone: 0.5-0.8 mg/kg/d for 2 wk	Atopic dermatitis	Skin infection: 1 (4.0%)

(Continues)

TABLE 1 (Continued)

Study, year/ medication	Patient demographics	Medication, dosage	Indication	Outcome/type of infection, n (%)
Azathioprine				
Garritsen et al[23]	n = 46 Mean age = 40.24 y Male = 22 (48%)	Mean maximum dose = 121.56 mg/d	Atopic dermatitis	Infection leading to discontinuation: flu-like symptoms: 1 (4.0%)
Caufield et al[17]	n = 12 Mean age = 9.0 y Male = 4 (33%)	1.25-3.4 mg/kg/d	Atopic dermatitis	No infection reported
Berth-Jones et al[18]	n = 37 Mean age = 38 y Male = 25 (68%)	2.5 mg/kg/d	Atopic dermatitis	URI: 5 (14.0%), folliculitis: 2 (5.0%), impetigo: 1 (3.0%), sore throat: 1 (3.0%)
Apremilast				
Crowley et al[22]	n = 1184 Mean age = 45.9 y Male = 805 (68.0%)	30 mg twice a day	Psoriasis	URI: 227 (19.2%), nasopharyngitis: 196 (16.6%), urinary infection: 2 (0%), serious infection: 17 (1.4%), serious opportunistic infection: 0
Kavanaugh et al[28]	n = 168 Mean age = 48.7 y Female = 83 (49.4%)	20 mg daily	Psoriatic arthritis	URI: 10 (6.0%)
Kavanaugh et al[28]	n = 168 Mean age = 51.4 y Female = 92 (54.8%)	30 mg daily	Psoriatic arthritis	URI: 7 (4.2%)
Dommasch et al[15]	n = 1623 Mean age = 51.37 y Male = 820 (50.5%)	Unknown	Psoriasis	Rate of overall serious infections compared with methotrexate: hazard ratio, 0.50; 95% CI, 0.26-0.94
Simpson et al[20]	n = 82	30 mg twice daily	Atopic dermatitis	Nasopharyngitis: 8 (9.8%), URI: 8 (9.8%), cellulitis 0
Simpson et al[20]	n = 86	40 mg twice daily	Atopic dermatitis	Nasopharyngitis: 14 (16.3%), URI: 6 (7.0%), cellulitis 7 (7.0%)
Samrao et al[21]	n = 6 Mean age = 38 y Male: female ratio = 5:1	20 mg twice daily	Atopic dermatitis	URI: 2 (33.3%), other infection: 2 (33.3%)
Samrao et al[21]	n = 10 Mean age = 45 y Male: female ratio = 5:5	30 mg twice daily	Atopic dermatitis	URI: 3 (30.0%), other infection: 3 (30.0%)
Acitretin				
Dommasch et al[15]	n = 2726 Mean age = 52.31 y Male = 1582 (58%)	Unknown	Psoriasis	Rate compared with methotrexate, hazard ratio (HR): overall serious infection: HR, 1.09; 95% CI, 0.83-1.44, bacteremia/ sepsis: HR, 0.93, 95% CI, 0.51-1.70, cellulitis/soft-tissue infection: HR, 1.76, 95% CI, 1.11–2.80, pneumonia: HR, 0.85, 95% (0.54-1.35)

Abbreviations: CI, confidence interval; HR, hazard ratio; URI, upper respiratory infection.

factor alpha (TNF-α) plays a crucial role in the immune response against intracellular pathogens and formation of granulomas,[30] and interleukin (IL)-12 and IL-23 are involved in cell-mediated immunity by inducing interferon-γ.[31] IL-23 also induces T-helper 17 cell differentiation and IL-17 secretion, fundamental in providing immunity against bacteria, viruses, fungi, and parasites.[32,33] IL-4 and IL-13 play key roles in the immune response against helminth infections.[34]

Five classes of biologic therapies are used for psoriasis or AD: TNF-α inhibitors (Table 2), IL-17 inhibitors, an IL-12/23 inhibitor, IL-23 inhibitors, an IL-4/13 inhibitor, and a Janus kinase (JAK) inhibitor (Table 3).

2.6 | TNF-α inhibitors (adalimumab, etanercept, infliximab, certolizumab)

Anti-TNF-α therapies inhibit a crucial immunological pathway, therefore an immunosuppressive effect and increased infection risk are expected. There is an FDA-required black box warning of infection susceptibility.[59] However, assessing infection risk is challenging because RCTs are often not adequately powered to detect rare events and ineligibility criteria may exclude up to 30% of real-world patients.[60] Real-world, postmarketing surveillance studies may be more helpful in evaluating infection rates. In a 10-year cohort study of 422 infliximab-treated psoriasis patients from the British Association of Dermatologists Biologic Interventions Register (BADBIR), there was increased infection risk compared to nonbiologic treated patients (adjusted HR, 1.95, 95% CI 1.01-3.75) and methotrexate only (adjusted HR 3.49, 95% CI 1.14-10.70).[44] Using real-world data from the Psoriasis Longitudinal Assessment and Registry involving 11 466 psoriasis patients (n = 9154 biologics, n = 490 methotrexate or other nonbiologics [excluding cyclosporine], n = 1610 with other than biologics or methotrexate), cumulative incidence rates of serious infections were 0.83, 1.47, 1.97, and 2.49 per 100 patient-years in ustekinumab, etanercept, adalimumab, and infliximab cohorts, respectively, and 1.28 and 1.05 per 100 patient-years in methotrexate or other nonbiologics, and nonbiologics without methotrexate cohorts, respectively.[37] Cellulitis and pneumonia were the two most common serious infections.[37] In another BADBIR study of etanercept (n = 1352), adalimumab (n = 3271), and ustekinumab (n = 994)-treated psoriasis patients, there were no increased risk of serious infections with etanercept (HR = 1.10, 95% CI = 0.75-1.60), adalimumab (HR = 0.93, 95% CI = 0.69-1.26), or ustekinumab (HR = 0.92, 95% CI = 0.60-1.41) compared with nonbiologic systemic therapies or methotrexate-only (etanercept: HR = 1.47, 95% CI = 0.95-2.28; adalimumab: HR = 1.26, 95% CI = 0.86-1.84; ustekinumab: HR = 1.22, 95% CI = 0.75-1.99).[35] Nonetheless, a 7% increased risk of all infections with adalimumab compared with placebo was reported based on pivotal trials, with no increased risk for etanercept.[59] Certolizumab increased risks of all infections, URIs, and nasopharyngitis by 5%, 2% and 2%, respectively.[59] Additionally, anti-TNF-α therapy is associated with latent tuberculosis reactivation, even with chemoprophylaxis; infliximab is associated with increased risk of herpes zoster.[61,62] Therefore, based on available data, anti-TNF-α biologics should be held during active infection; in asymptomatic/healthy patients, safer and more effective alternatives should be considered. TNF-α inhibitors have been hypothesized to treat SARS-CoV-2-related cytokine storm.[63]

2.7 | IL-17 inhibitors (secukinumab, ixekizumab, brodalumab)

Secukinumab selectively targets IL-17A, a downstream product of Th17 cells, and does not interfere with other essential Th17 functions, including IL-22 and TNF release; therefore, lower infection risk compared with anti-TNF-α therapies is expected.[64] Since anti-IL-17 therapies are relatively new medications, long-term "real-world" studies are sparse and estimation of infection risk is primarily based on RCTs. In a pooled analysis of 10 phase 2/3 studies assessing long-term safety of secukinumab (150 or 300 mg) and etanercept, there were increased infection rates for all treatments compared to placebo during the first 12 weeks.[43] The risks of serious infections were 1.47 and 1.37 per 100 subject-years in the secukinumab and etanercept groups, respectively.[43] No cases of tuberculosis reactivation were reported, and patients with latent tuberculosis were not excluded.[43] Similarly, in two phase 3 studies involving 3712 psoriasis patients randomized to treatment with brodalumab (n = 2475), ustekinumab or placebo, rates of serious infections were 1.0 (AMAGINE-2) and 1.3 (AMAGINE-3) per 100 patient-year exposure to brodalumab, and *Candida* infections were more frequent with brodalumab vs ustekinumab or placebo.[53] Similarly, an 11% increased risk in overall infections with secukinumab was reported based on pivotal trials, with most attributable to yeast infections; URIs were increased slightly for secukinumab, but not for ixekizumab or brodalumab.[59] Since IL-17 plays an important role in immunological response against *Candida* infections, there is a theoretical increased risk of yeast infections with anti-IL17 therapies.[65] In a pooled analysis from 10 phase 2 and phase 3 clinical studies on 3430 psoriasis patients treated with secukinumab 300 mg (n = 11 410), 150 mg (n = 1395), and etanercept (n = 323), *Candida* infections were reported in 2.9%, 1.5%, and 1.2% of subjects, respectively.[66] All infections were mild, resolved spontaneously, or responded to standard treatment, without causing treatment discontinuation.[66] Overall, increased infection risk has been shown with IL-17 inhibitors, but yeast infections may constitute a large proportion of that increase; URIs are particularly uncommon. Therefore, IL-17 inhibitors may be safely prescribed and continued, unless the patient is symptomatic or positive for SARS-CoV-2.

2.8 | IL-12/23 inhibitors (ustekinumab)

Ustekinumab inhibits IL-12 and IL-23, with IL-12 playing an important role in protection against viral infections.[59,67,68] However, no increased susceptibility to infection with ustekinumab has been reported. In a pooled analysis of four phase 2/3 studies of 3117 ustekinumab-treated psoriasis patients, there were similar rates of all infections amongst placebo (121.0), ustekinumab 45-mg (145.7), and ustekinumab 90-mg

TABLE 2 Studies on infection risk of tumor necrosis factor alpha inhibitors for psoriasis

Study, year/medication	Patient demographics	Medication, dosage	Indication	Outcome/ type of infection, n (%)
TNF-α inhibitors				
Adalimumab				
Yiu et al[35]	n = 3271 Mean age = 44.7 y Female = 1323 (40.4%)	Unknown	Psoriasis	N (incidence rate per 1000 person-years): all serious infection: 108 (13.78), lower respiratory infection: 31 (3.96), skin and soft tissue infection: 19 (2.42)
Menter et al[36]	n = 814 Mean age = 44.1 y Male = 546 (67.1%)	80 mg at week 0, followed by 40 mg every other week	Psoriasis	All infections: 235 (62.2%), serious infection: 5 (0.6%), URI: 59 (7.2%), opportunistic infection (excluding tuberculosis): 1, tuberculosis: 1
Kalb et al[37]	n = 2675 Mean age = 47.6 y Male = 1505 (56.3%)	Unknown	Psoriasis	Incidence rate per 100 patient-years: serious infection: 1.97
Dommasch et al[15]	n = 7181 Mean age = 46.10 y Male = 4061 (56.6%)	Unknown	Psoriasis	Rate compared with methotrexate, HR: overall serious infection: HR, 1.08; 95% CI, 0.88-1.33, bacteremia/ sepsis: HR, 1.06; 95% CI, 0.66-1.68, cellulitis/soft-tissue infection: HR, 1.34; 95% CI, 0.95-1.89, Meningitis/ encephalitis: HR, 0.78; 95% CI, 0.10-6.28, pneumonia: HR, 0.94; 95% CI, 0.68-1.31, pyelonephritis: HR, 1.11; 95% CI, 0.27-4.51, septic arthritis/osteomyelitis: HR, 0.78; 95% CI, 0.25-2.19
Mease et al[38]	n = 106 Mean age = 47.4 y Female = 50 (47%)	40 mg every 2 wk	Psoriatic arthritis	Nasopharyngitis: 10.0%, URI: 8.0%, serious infection (herpes simplex and streptococcal pyoderma): 1.0%
Reich et al[39]	n = 248 Mean age = 43.2 y Male = 170 (68.5%)	80 mg at week 0, then 40 mg at week 1, and every 2 wk through week 23	Psoriasis	Nasopharyngitis: 34 (13.7%), URI: 10 (4.0%), all infections: 87 (35.1%), requiring treatment: 29 (11.7%), serious infection: 3 (1.2%)
Blauvelt et al[40]	n = 334 Mean age = 42.9 y Male = 249 (74.6%)	80 mg week 0, 40 mg week 1, then 40 mg every 2 wk through week 46	Psoriasis	Nasopharyngitis: 74 (22.2%), URI: 42 (12.6%), all infections: 167 (50.2%), infections requiring treatment: 60 (18.0%), serious infection: 3 (0.9%)
Saurat et al[26]	n = 108 Mean age = 42.9 y Male = 64.8%	80 mg at week 0, then 40 mg every other week	Psoriasis	Serious infection: 0, nonserious infection: 51 (47.7%), nasopharyngitis: 30 (28.0%), viral infection: 0
Etanercept				
Yiu et al[35]	n = 1325 Mean age = 45.5 y Female = 565 (41.8%)	Unknown	Psoriasis	N (incidence rate per 1000 person-years): serious infection: 50 (14.2), lower respiratory infection: 10 (5.5), skin and soft tissue infection: 18 (5.5)

TABLE 2 (Continued)

Study, year/medication	Patient demographics	Medication, dosage	Indication	Outcome/ type of infection, n (%)
Mease et al[41]	n = 30 Median age = 46.0 y Age range = 30-70 y Male = 16 (53%)	25 mg twice weekly	Psoriasis/psoriatic arthritis	URI: 8 (27%), pharyngitis: 8 (27%), sinusitis: 3 (10%), influenza syndrome: 0
Kalb et al[37]	n = 1854 Mean age = 48.7 y Male = 1038 (56.0%)	Unknown	Psoriasis	Incidence rate per 100 patient-years: serious infection: 1.47
Langley et al (FIXTURE)[42]	n = 326 Mean age = 43.8 y Male = 232 (71.2%)	50 mg twice weekly for 12 wk, then once weekly	Psoriasis	N (incidence rate per 100 subject-years): Infections and infestations: 170 (91.4), nasopharyngitis: 86 (35.7), URI 18 (6.4)
Van de Kerkhof et al[43]	n = 323 Mean age = 43.8 y Male = 229 (70.9%)	Unknown	Psoriasis	Exposure-adjusted incidence rates per 100 subject-years of all infections: 93.7
Dommasch et al[15]	n = 7102 Mean age = 45.45 Male = 3903 (55.0%)	Unknown	Psoriasis	Rate compared with methotrexate, HR: overall serious infection: HR, 0.75; 95% CI, 0.61-0.93, bacteremia/ sepsis: HR, 0.51; 95% CI, 0.32-0.82, cellulitis/soft-tissue infection: HR, 1.16; 95% CI, 0.82-1.65, pneumonia: HR, 0.94; 95% CI, 0.68-1.31, pyelonephritis: HR, 0.68; 95% CI, 0.20-2.34, septic arthritis/osteomyelitis: HR, 1.61; 95% CI, 0.36-7.16
Infliximab				
Yiu et al[44]	n = 422 Mean age = 46.6 y Male = 159 (37.7%)	Unknown	Psoriasis	Rate per 1000 person-years of all serious infections: 47.82, lower respiratory infection: 11.69
Gottlieb et al[45]	n = 33 Age range = 21-69 y	3 groups: placebo or 5 mg/kg or 10 mg/kg at weeks 0, 2 and 6	Psoriasis	All infections (excluding URI): 7 patients (21%)
Reich et al[46]	n = 301 Mean age = 42.6 y Female = 94 (31%)	5 mg/kg at weeks 0, 2, 6, and 14	Psoriasis	All infections: 125 (42.0%), URI: 46 (15.0%), serious infection: 3 (1.0%)
Menter et al[47]	n = 313 Mean age 43.4 y Male = 65.8%	3 mg/kg at weeks 0, 2, and 6	Psoriasis	Patients with ≥1 infection: 106 (33.9%), URI: 50 (16%)
Menter et al[47]	n = 314 Mean age = 65.8 y Male = 65%	5 mg/kg at weeks 0, 2, 6, and 14	Psoriasis	Patients with ≥1 infection: 97 (30.9%), URI: 42 (13.4%)

(Continues)

TABLE 2 (Continued)

Study, year/medication	Patient demographics	Medication, dosage	Indication	Outcome/ type of infection, n (%)
Kalb et al[37]	n = 1151 Mean age = 48.5 y Male = 655 (56.9%)	Unknown	Psoriasis	Incidence rate of serious infection per 100 patient-years: 2.49
Dommasch et al[15]	n = 408 Mean age = 50.20 y Male = 202 (49.5%)	Unknown	Psoriasis	Rate compared with methotrexate, HR: overall serious infection: HR, 1.47; 95% CI, 0.75-2.87, bacteremia/sepsis: HR, 1.30; 95% CI, 0.19-8.63, cellulitis/soft-tissue infection: HR, 1.76; 95% CI, 0.55-5.63, pneumonia: HR, 0.80; 95% CI, 0.29-2.24, pyelonephritis: HR, 0.68; 95% CI, 0.20-2.34
Certolizumab				
Blauvelt et al[48]	n = 351 Mean age = 46.1 y Male = 238 (67.8%)	200 mg every 2 wk	Psoriasis	[Incidence rate]: Infections and infestations: 108 (30.9) [121.6], serious infections: 0
Blauvelt et al[48]	n = 342 Mean age = 45.2 y Male = 210 (61.4%)	400 mg every 2 wk	Psoriasis	[Incidence rate]: Infections and infestations: 124 (36.3) [146.6], serious infections: 2 (0.6) [1.9]

Abbreviations: CI, confidence interval; HR, hazard ratio; URI, upper respiratory infection.

(132.2) groups; also similar rates of serious infections between placebo (1.70) and 90-mg (1.97) groups, and a lower rate in the 45-mg group (0.49).[54] No cases of tuberculosis reactivation were reported.[54] In one observational cohort study of 107 707 systemically treated psoriasis patients, ustekinumab (HR: 0.65; 95% CI, 0.47-0.89), apremilast (HR: 0.50; 95% CI, 0.26-0.94) and etanercept (HR: 0.75; 95% CI, 0.61-0.93) had decreased risks of overall serious infections compared with methotrexate.[15] Similar risks of infection between ustekinumab and placebo were reported by Lebwohl et al.[59] Thus, treatment with ustekinumab may be considered relatively safe during the COVID-19 pandemic; however, switching to specific IL-23 inhibitors may be prudent. Notably, ustekinumab may positively affect SARS-CoV-2-related cytokine storm.[63]

2.9 | IL-23 inhibitors (guselkumab, tildralkizumab, risankizumab)

Contrary to IL-12/23 inhibitors, anti-IL-23 therapies do not target IL-12, and IL-12 plays a key role fighting viral infections.[59,69] Reduced risks of *Salmonella*, *Candida*, and *Mycobacterium* infections were seen in IL-23p19-targeted vs IL-12/23p40-targeted animal models.[56,70-72] Nonetheless, RCTs on IL-23 inhibitors have shown conflicting results regarding infection risks. In a phase 3, double-blinded, placebo-controlled study on 837 psoriasis patients randomized to treatment with guselkumab, adalimumab, or placebo, overall, *Candida*, and serious infections, occurred at comparable rates across treatment groups.[40] In 798 risankizumab-treated psoriasis patients, there was increased overall infection risk in two phase 3 studies.[55] The most common infections were URIs, urinary tract infections, and influenza.[55] Two cases of latent tuberculosis were reported in the risankizumab group; both patients tested negative at baseline.[55] Data assessing infection risk with tildrakizumab are sparse. Lebwohl et al reported an increase in nasopharyngitis (4%) with tildrakizumab compared with placebo.[59] Risk, however, is low and comparable to placebo. Therefore, based on available data, IL-23 inhibitors may be continued/initiated, unless the patient is symptomatic or positive for SARS-CoV-2.

2.10 | JAK inhibitor (tofacitinib)

Tofacitinib is a small molecule inhibitor of tyrosine kinases of the Janus family, preferentially JAK1 and JAK3, downregulating cytokines crucial for lymphocyte development; therefore, there is potential for increased risks of intracellular bacterial and viral infections.[73] It has been hypothesized, nonetheless, that fluctuations in plasma levels of JAK inhibitors throughout the day may preserve immunogenicity against infectious pathogens.[74] Tofacitinib carries an FDA-required black box warning for serious infections. In one placebo-controlled phase 3 trial of 422 patients with psoriatic arthritis, randomized to treatment with 5-mg or 10-mg tofacitinib, adalimumab, or placebo, nasopharyngitis (in 7%, 12% and 10%, respectively) and URIs (in 9%, 11%, and 8%, respectively) were the most common adverse events.[38]

TABLE 3 Studies on infection risk of interleukin-17, 12/23, and 23 inhibitors, tofacitinib and dupilumab for psoriasis or atopic dermatitis

Study, year	Patient demographicsand clinical characteristics	Medication, dosage	Indication	Outcome/ type of infection, n (%)
IL-17 inhibitors				
Secukinumab				
Langley et al (ERASURE)[42]	n = 245 Mean age = 44.9 y Male = 169 (69%)	300 mg once weekly for 5 wk, then every 4 wk	Psoriasis	N (incidence rate per 100 subject-years): infections and infestations: 193 (100.0), nasopharyngitis: 57 (20.9), URI: 32 (11.1), influenza-like illness: 14 (4.7)
Langley et al (ERASURE)[42]	n = 245 Mean age = 44.9 y Male = 168 (68.6%)	150 mg once weekly for 5 wk, then every 4 wk	Psoriasis	N (incidence rate per 100 subject-years): infections and infestations: 185 (95.4), nasopharyngitis: 69 (26.2), URI: 36 (12.7), influenza-like illness: 17 (5.8)
Langley et al (FIXTURE)[42]	n = 327 Mean age = 44.5 y Male = 224 (68.5%)	300 mg once weekly for 5 wk, then every 4 wk	Psoriasis	N (incidence rate per 100 subject-years): infections and infestations: 269 (105.4), nasopharyngitis: 122 (35.2), URI: 26 (6.6)
Langley et al (FIXTURE)[42]	n = 327 Mean age = 45.4 y Male = 236 (72.2%)	150 mg once weekly for 5 wk, then every 4 wk	Psoriasis	N (incidence rate per 100 subject-years): infections and infestations: 240 (91.9), nasopharyngitis: 108 (31.4), URI: 26 (6.6)
Van de Kerkhof et al[43]	n = 3430	150 or 300 mg	Psoriasis	Exposure-adjusted incidence rates per 100 subject-years of all infections 150 mg: 85.3; 300 mg: 91.1
Reich et al[49]	n = 514 Mean age = 45.3 y Male = 342 (67%)	300 mg at weeks 0, 1, 2, 3, and 4, and then every 4 wk	Psoriasis	All infections: 331 (65.0%), infections requiring treatment: 147 (29.0%), serious infection: 5 (1.0%), *Candida* infection: 29 (6.0%), tinea infection: 23 (5.0%) nasopharyngitis: 125 (24.0%), URI: 92 (18.0%)
Ixekizumab				
Langley et al[50]	n = 5689	160 mg at week 0, followed by 80 mg every 4 or 2 wk	Psoriasis	Proportion of patients with any infection: 60.8%, mild: 25.4%, moderate: 32.4% and severe: 3% infections. N (%): of nasopharyngitis: 1302 (22.9%), URI: 769 (13.5%); the incidence risk (95% CI) of *Candida* infection: 0.9 (0.8, 1.1)
Armstrong et al[51]	n = 5898 Mean age = 45.8 y Male = 4000 (67.8%)	160 mg at week 0, followed by 80 mg every 4 or 2 wk	Psoriasis	N (%) [incidence rate per 100 patient-years]: ≥1 infection: 3859 (65.4%) [22.7], nasopharyngitis: 1515 (25.7) [8.9], bronchitis: 398 (6.7%) [2.3], sinusitis: 369 (6.3%),[2] urinary infection: 333 (5.6) [2.0], influenza: 307 (5.2) [1.8], pharyngitis: 278 (4.7) [1.6], gastroenteritis: 237 (4.0) [1.4], patients with ≥1 serious infection/infestation: 223 (3.8) [1.3], cellulitis: 40 (0.7) [0.2], pneumonia: 25 (0.4) [0.1], appendicitis: 11(0.2) [0.1], erysipelas: 9 (0.2) [0.1]

(Continues)

TABLE 3 (Continued)

Study, year	Patient demographicsand clinical characteristics	Medication, dosage	Indication	Outcome/ type of infection, n (%)
Brodalumab				
Papp et al[52]	n = 441 Mean age = 46 y Male = 323 (73%)	140 mg or 210 mg every 2 wk	Psoriasis	Serious infectious episode: 4 (1.8%), suspected *Candida* infections: 18 (3.5%)
Lebwohl et al (AMAGINE-2)[53]	Total n = 1222 140 = mg group: n = 610 Mean age = 45 y Male = 413 (68%) 210-mg group: n = 612 Mean age = 45 y Male = 421 (69%)	140 mg or 210 mg every 2 wk	Psoriasis	Serious infections and infestations: 13 (1.0%), *Candida* infection: 71 (5.2%)
Lebwohl et al (AMAGINE-3)[53]	Total n = 1253 140-mg group: n = 629 Mean age = 45 y Male = 437 (70%) 210-mg group: n = 624 Mean age = 45 y Male = 431 (69%)	140 or 210 mg every 2 wk	Psoriasis	Serious infections and infestations: 18 (1.3%), *Candida* infections: 80 (5.7%)
IL-12/23 inhibitor (ustekinumab)				
Yiu et al[35]	n = 994 Mean age = 45.9 y Female = 377 (37.9%)	Unknown	Psoriasis	N (incidence rate per 1000 person-years): all serious infections: 34 (15.07), lower respiratory infection: 12 (5.32), 8 (3.55), skin and soft tissue infection: 8 (3.55)
Kalb et al[37]	n = 3474 Mean age = 47.2 y Male = 1999 (57.5%)	Unknown	Psoriasis	Incidence rate of serious infections per 100 patient-years: 0.83
Gordon et al[54]	n = 3219 Mean age = 45.6 y Male = 2206 (68.5%)	45 or 90 mg	Psoriasis	Rate per 100 patient-years during placebo-controlled: rate of overall infection: 45 mg (145.7), 90 mg (132.2), and during controlled and uncontrolled period: 45 mg (113.7), 90 mg (111.2); rates of serious infections during placebo-controlled period: 45 mg (0.49), 90 mg (1.97), and controlled and uncontrolled period: 45 mg (0.82), 90 mg (1.50)

TABLE 3 (Continued)

Study, year	Patient demographicsand clinical characteristics	Medication, dosage	Indication	Outcome/ type of infection, n (%)
Dommasch et al[15]	n = 4085 Mean age = 46.50 y Male = 2302 (56.4%)	Unknown	Psoriasis	Rate compared with methotrexate, hazard ratio (HR): overall serious infection: HR, 0.65; 95% CI, 0.47-0.89, bacteremia/sepsis: HR, 0.83; 95% CI, 0.39-1.73, cellulitis/soft-tissue infection: HR, 0.87; 95% CI, 0.51-1.48, pneumonia: HR, 0.53; 95% CI, 0.32-0.88, pyelonephritis: HR, 1,32; 95% CI, 0.20-8.78, septic arthritis/osteomyelitis: HR, 0.51; 95% CI, 0.08-3.52
Gordon et al (ULtIMMA-1)[55]	n = 100 Mean age = 46.5 y Male = 70 (70%)	45 or 90 mg	Psoriasis	All infections: 20 (20.0%), serious infections: 3 (3.0%), active tuberculosis: 0, latent tuberculosis: 0
Gordon et al (ULtIMMA-2)[55]	n = 99 Mean age = 48.6 y Male = 66 (67%)	45 or 90 mg	Psoriasis	All infections: 20 (20.2%), serious infections: 1 (1.0%), active tuberculosis: 0, latent tuberculosis: 0
Lebwohl et al (AMAGINE-2)[53]	n = 300 Mean age = 45 y Male = 205 (68%)	45 mg for patients with a body weight ≤ 100 kg and 90 mg for patients >100 kg	Psoriasis	Serious infections and infestations: 2 (0.8%), candida infections: 10 (4.1%)
Lebwohl et al (AMAGINE-3)[53]	n = 313 Mean age = 45 y Male = 212 (68%)	45 mg for patients with a body weight ≤ 100 kg and 90 mg for patients >100 kg	Psoriasis	Serious infections and infestations: 3 (1.2%), candida infections: 4 (1.6%)
IL-23 inhibitors				
Guzselkumab				
Reich et al[39]	n = 496 Mean age = 43.7 y Male = 349 (70.4%)	100 mg at weeks 0, 4, then every 8 wk	Psoriasis	Nasopharyngitis: 51 (10.3%), URI: 25 (5.1%), all infections: 153 (31%), infections requiring treatment: 58 (11.7%), serious infections: 3 (0.6%)
Reich et al[39]	n = 248 Mean age = 43.4 y Male = 173 (69.8%)	Placebo to guselkumab 100 mg at weeks (0, 4 and 12 then guselkumab at weeks 16 and 20)	Psoriasis	Nasopharyngitis: 12 (6.2%), URI: 5 (2.1%), all infections: 153 (31%), infections requiring treatment: 41 (17.6%), serious infections: 1 (0.4%)
Blauvelt et al[40]	n = 329 Mean age = 43.9 y Male = 240 (72.9%)	100 mg at weeks 0, 4, then every 8 wk	Psoriasis	Nasopharyngitis: 83 (25.2%), URI: 46 (14.3%), all infections: 172 (62.3%), infections requiring treatment: 54 (16.4%), serious infections: 2 (0.6%)
Blauvelt et al[40]	n = 174 Mean age = 44.9 y Male = 119 (68.4%)	Placebo to guselkumab 100 mg at weeks (0, 4 and 12 then guselkumab at weeks 16 and 20)	Psoriasis	Nasopharyngitis: 34 (20.6%), URI: 17 (10.3%), all infections: 76 (46.1%), infections requiring treatment: 25 (15.2%), serious infections: 1 (0.6%)
Reich et al[49]	n = 534 Mean age = 46.3 y Male = 365 (68%)	100 mg at weeks 0, 4, then every 8 wk	Psoriasis	Overall infections: 313 (59.0%), infections requiring treatment: 118 (22.0%), serious infections: 6 (1.0%), candida infections: 12 (2.0%), tinea infections: 9 (2.0%) nasopharyngitis: 118 (22.0%), URI: 83 (16.0%)

(Continues)

TABLE 3 (Continued)

Study, year	Patient demographicsand clinical characteristics	Medication, dosage	Indication	Outcome/ type of infection, n (%)
Tildrakizumab				
Papp et al[56]	n = 42 Mean years = 43.2 y Male = 31 (74%)	5 mg at week 0, 4 and every 12 wk until week 52	Psoriasis	Weeks 0-16: all infections: 0 Weeks 16-52: all infections: 0
Papp et al[56]	n = 92 Mean age = 46.3 y Male = 60 (65%)	25 mg at week 0, 4 and every 12 wk until week 52	Psoriasis	Weeks 0-16: serious infections: 0, bacterial arthritis: 1 (1.0%) Weeks 16-52: serious infections: 1 (1.0%), sinusitis 1 (1.0%)
Papp, 2015[56]	n = 89Mean age = 45.5Male = 76 (85%)	100 mg at week 0, 4 andevery 12 weeks until week 52	Psoriasis	Weeks 0-16: serious infections: 1 (1.0%)Weeks 16-52: serious infections: 1 (1.0%), appendicitis: 1 (1.0%), epiglottitis: 1 (1.0%), sinusitis: 1 (1.0%)
Papp et al[56]	n = 86 Mean age = 43.2 y Male = 65 (76%)	200 mg at week 0, 4 and every 12 wk until week 52	Psoriasis	Weeks 0-16: all infections: 0 Weeks 16-52: serious infections: 1 (1.0%), postoperative wound infection: 1 (1.0%), bursitis: 1 (1.0%)
Risankizumab				
Gordon et al (ULtIMMA-1)[55]	Risankizumab: n = 304 Mean age = 48.3 y Male = 212 (70%) Placebo to risankizumab: n = 102 Mean age = 49.3 Male = 79 (77%)	150 mg	Psoriasis	Risankizumab group: all infections: 75 (24.7%), serious infection: 1 (0.3%), active tuberculosis: 0 Placebo to risankizumab group: all infections: 17 (16.7%), serious infections: 0, active tuberculosis: 0, latent tuberculosis: 0
Gordon et al (ULtIMMA-2)[55]	Risankizumab: n = 294 Mean age = 46.2 y Male = 203 (69%) Placebo to risankizumab: n = 98 Mean age = 46.3 Male = 67 (68%)	150 mg	Psoriasis	Risankizumab group: all infections: 56 (19.0%), serious infections: 3 (1.0%), active tuberculosis: 0 Placebo to risankizumab group: all infections: 9 (9.2%), serious infections: 0, active tuberculosis: 0, latent tuberculosis: 0
Janus kinase 1/3 inhibitor (tofacitinib)				
Mease et al[38]	n = 159	5 mg twice daily	Psoriatic arthritis	Nasopharyngitis: 7.0%, URI: 9.0%, serious infections: 4.0%, herpes zoster: 2.0%
Mease et al[38]	n = 157	10 mg twice daily	Psoriatic arthritis	Nasopharyngitis: 12.0%, URI: 11.0%, serious infections: 1.0%, herpes zoster: 2.0%
Papp et al[57]	Total n = 745 OPT Pivotal 1: n = 363 Mean age = 46 (range = 18-78) y Male = 261 (71.9%) OPT Pivotal 2: n = 382 Mean age = 47 (range = 19-79) Male = 268 (70.2%)	5 mg twice daily	Psoriasis	Serious infection: 3 (pneumonia, herpes zoster and erysipelas), herpes zoster: 6, herpes simplex: 2

TABLE 3 (Continued)

Study, year	Patient demographicsand clinical characteristics	Medication, dosage	Indication	Outcome/ type of infection, n (%)
Papp et al[57]	Total n = 741 OPT Pivotal 1: n = 360 Mean age = 46 (range = 18-79) y Male = 261 (72.5%) OPT Pivotal 2: n = 381 Mean age = 44 (range = 18-82) y Male = 257 (67.5%)	10 mg twice daily	Psoriasis	Serious infection: 2 (appendicitis; pneumonia and pyelonephritis), herpes zoster: 6, herpes simplex: 3
IL 4/13 inhibitor (dupilumab)				
Eichenfield et al[58]	n = 1095	300 mg weekly	Atopic dermatitis	N (number of patients per 100 patients-years): all infections: 452 (126.49), infection leading to treatment discontinuation: 2 (0.38), serious infection: 7 (2.40)
Eichenfield et al[58]	n = 746	300 mg every 2 wk	Atopic dermatitis	N (number of patients per 100 patients-years): all infections: 287 (133.59), infection leading to treatment discontinuation: 1 (0.37), serious infection: 7 (2.39)

Abbreviations: CI, confidence interval; HR, hazard ratio; URI, upper respiratory infection.

There were three cases of serious infections (influenza, appendicitis and pneumonia) and four cases of herpes zoster in the tofacitinib-treated group.[38]

Similarly, in 2 randomized, placebo-controlled studies of 745 and 741 psoriasis patients treated with tofacitinib 5-mg and 10-mg, respectively, nasopharyngitis and URIs were the most common infections, and 5 serious infections (pneumonia, herpes zoster and erysipelas in the 5-mg group; and appendicitis, pneumonia, and pyelonephritis in the 10-mg group) were reported in tofacitinib-treated patients.[57] Furthermore, herpes zoster was reported in 12 tofacitinib-treated patients vs none in the placebo groups.[57] Thus, tofacitinib has an association with increased infection risk in psoriasis/psoriatic arthritis patients. Tofacitinib-treated patients may be more susceptible to COVID-19, strict protective measures are recommended to minimize viral exposure.

2.11 | Dupilumab

Dupilumab targets IL-4 and IL-13, elements of the type 2 immune response.[58] As type 1 and type 2 immune responses crossregulate each other, suppression of type 1 immunity can potentially facilitate uncontrolled or persistent viral and bacterial infections.[75] Nonetheless, dupilumab has been associated with a reduced infection rate in AD patients. A pooled analysis of seven RCTs on dupilumab-treated AD adults showed a decreased risk of serious infections, skin infections, and herpes infections (eczema herpeticum or herpes zoster) in the dupilumab groups compared with placebo. Furthermore, by also treating asthma, dupilumab may theoretically decrease risk for COVID-19-infected patients for severe respiratory disease.[58] Therefore, current evidence suggests continuing and initiating dupilumab treatment in AD patients during the COVID-19 pandemic.

3 | CONCLUSIONS

It is difficult to make definitive conclusions about susceptibility to SARS-CoV-2 infection in psoriasis or AD patients on systemic treatments, solely based on general infection risk data. Furthermore, the majority of studies included patients with mean age of approximately 40 years; therefore, these recommendations may not be applicable to older individuals, who on average have higher COVID-19 associated mortality. There is also a potential role for some of these medications as treatments of COVID-19 but this remains largely unknown. In conclusion, in patients with active infection, systemic conventional medications, the JAK inhibitor tofacitinib, and biologics for psoriasis should be temporarily held until there is more data. Otherwise, conventional systemic immunosuppressive medications (corticosteroids, methotrexate, cyclosporine, and azathioprine) are associated with increased infection risk and therefore warrant strict measures to minimize exposure. Tofacitinib and TNF-α inhibitors may also increase infection risk and safer alternatives may be considered. IL-17/12/23 inhibitors seem to be among the safer medications (IL-17, IL-12/23 > IL-23), but exact infection risks have not been fully characterized. Finally,

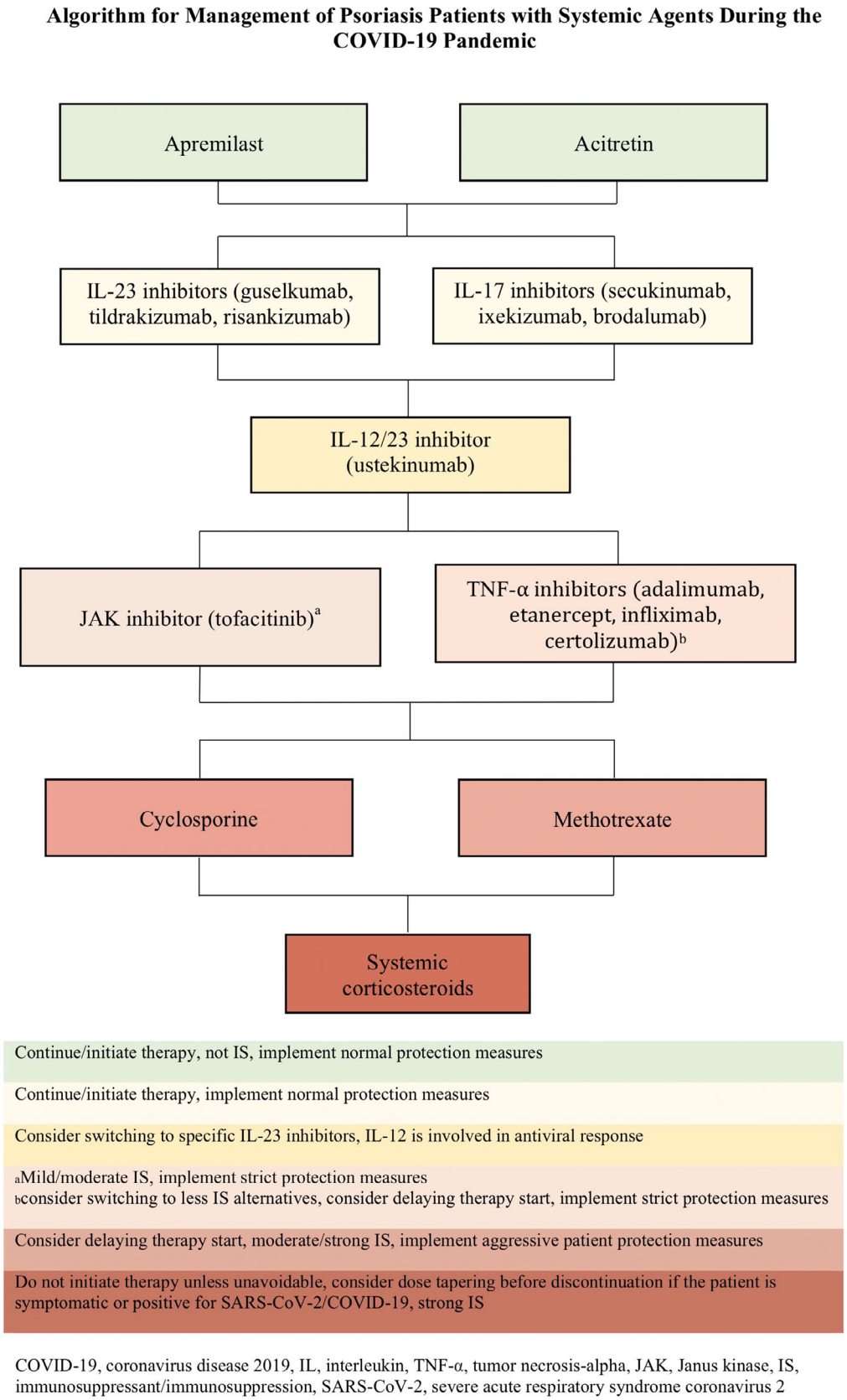

FIGURE 1 Proposed treatment algorithm of systemically treated psoriasis patients during the COVID-19 pandemic. In case the patient is positive or symptomatic for SARS-CoV-2/COVID-19, all immunomodulating medications must be discontinued. COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

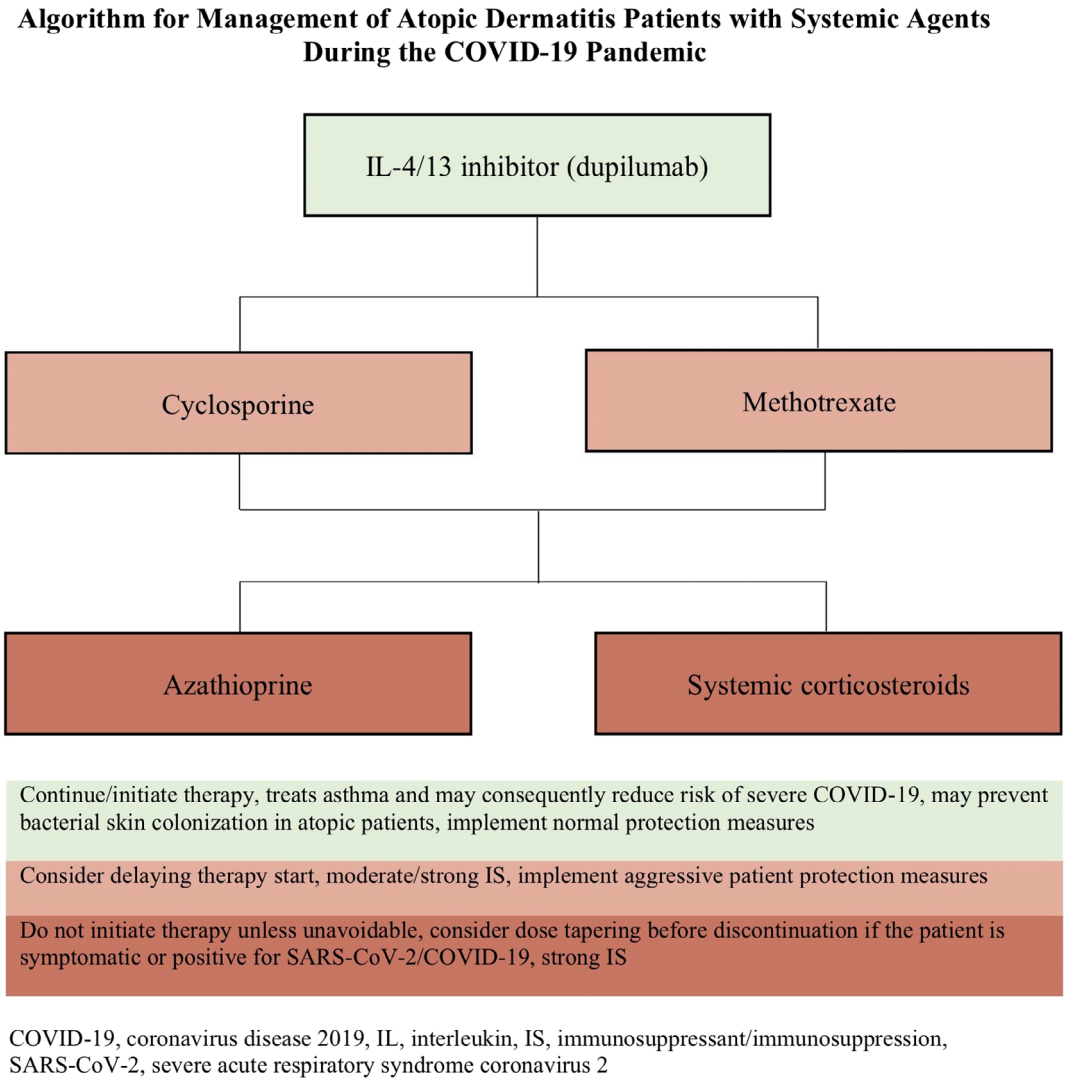

FIGURE 2 Proposed treatment algorithm of systemically treated atopic dermatitis patients during the COVID-19 pandemic. In case the patient is positive or symptomatic for SARS-CoV-2/COVID-19, all immunomodulating medications must be discontinued. COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

apremilast, dupilumab, and acitretin are not associated with increased infection risks and appear to have favorable safety profiles. We suggest the following algorithms for treatment of psoriasis and AD during the COVID-19 pandemic (Figures 1 and 2).

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