Infection risk of dermatologic therapeutics during the COVID-19 pandemic: an evidence-based recalibration

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Abstract

Recommendations were made recently to limit or stop the use of oral and systemic immunotherapies for skin diseases due to potential risks to the patients during the current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) COVID-19 pandemic. Herein, we attempt to identify potentially safe immunotherapies that may be used in the treatment of cutaneous diseases during the current COVID-19 pandemic. We performed a literature review to approximate the risk of SARS-CoV-2 infection, including available data on the roles of relevant cytokines, cell subsets, and their mediators in eliciting an optimal immune response against respiratory viruses in murine gene deletion models and humans with congenital deficiencies were reviewed for viral infections risk and if possible coronaviruses specifically. Furthermore, reported risk of infections of biologic and non-biologic therapeutics for skin diseases from clinical trials and drug data registries were evaluated. Many of the immunotherapies used in dermatology have data to support their safe use during the COVID-19 pandemic including the biologics that target IgE, IL-4/13, TNF-α, IL-17, IL-12, and IL-23. Furthermore, we provide evidence to show that oral immunosuppressive medications such as methotrexate and cyclosporine do not significantly increase the risk to patients. Most biologic and conventional immunotherapies, based on doses and indications in dermatology, do not appear to increase risk of viral susceptibility and are most likely safe for use during the COVID-19 pandemic. The limitation of this study is availability of data on COVID-19.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also named 2019 novel coronavirus disease COVID-19, is the causative agent of the ongoing pandemic.1 It is not known if patients on immunotherapies for skin disorders are more susceptible to SARS-CoV-2. This uncertainty can result in anxiety for prescribing physicians and treated patients. Several formal and informal recommendations were made to limit or stop immunomodulator therapies in the “COVID-19 era.”2-3 With our knowledge of the immunopathogenesis of coronaviruses and as our understanding of SARS-CoV-2 evolves, it is important to place the emphasis on evidence-based medicine to objectively evaluate SARS-CoV-2 risk in the context of dermatologic indications and doses.

Part 1: Proinflammatory cytokine surge in severe SARS-CoV-2 (COVID-19) infection

The human pathogenic forms of coronaviruses usually cause mild-to-moderate upper respiratory tract illnesses (URTI) with few exceptions with life-threatening implications such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). COVID-19 is marked by symptoms that can include fever, dry cough, fatigue, and shortness of breath. A subset of COVID-19 patients succumb to severe disease with manifestations of acute respiratory distress syndrome (ARDS), cardiac injury, and secondary infections with a high mortality rate.4 It is postulated that a dysregulated immune response to the infection is a consequence of the patients’ comorbidities.5 Dysregulation of the adaptive T-cell-mediated immune response is strongly implicated in pathogenesis of COVID-19.5

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levels of proinflammatory cytokines were shown in patients with severe COVID-19, including plasma levels of tumor necrosis factor α (TNF-α), interleukin (IL)-2, IL-6, G-CSF, IP10, MCP-1, and MIP-1α. This is consistent with the reported elevation of proinflammatory cytokines in SARS-CoV-2 and MERS infections. The massive inflammatory cell infiltration and elevated proinflammatory cytokine/chemokine responses result in acute lung injury and ARDS.4,9,10

**Part 2: Infectious risks associated with biologics:** evaluating cytokine knockout data and reviewing data from randomized controlled trials (RCTs) and biologic treatment registries

**TNF-α**

Infecting TNF-α−/−, TNF receptor 1 (R1)−/−, and TNFR2−/− mice with mouse hepatitis virus-3 (MHV-3, belongs to the coronavirus family) revealed that a deficiency of either TNF-α or TNFR1 reduced morbidity and mortality (Table 1).11 TNF receptors 1/2 knock-out mice infected with SARS-CoV were protected from infection-related morbidity.12 Collectively, TNF-α promotes the deleterious effects of coronavirus infection presumably through excessive inflammation. From clinical trials (Table 2), the relative risk of adalimumab, certolizumab, etanercept, and infliximab for URTI (2.06, 1.54, 2.44, and 0.93) and nasopharyngitis (0.82, 1.5, 1.39, and 0.75), respectively, is elevated compared to placebo, but the absolute risk remains small. Furthermore, in the Psoriasis Longitudinal Assessment and Registry (PSOLAR), biologics that targeted TNF-α had little-to-no increased risk of infections.13 It is important to note that definitions of URTI and nasopharyngitis in dermatology clinical trials are not adjudicated with nasopharyngeal swabs to confirm the presence of rhinovirus or influenza infection and that upper respiratory symptoms due to allergic phenomena could be a confounder. Given the proposed role of TNF-α in acute lung injury and ARDS in COVID-19, TNF-α is a potential target for treating patients with COVID-19.14 Consequently, the efficacy and safety of adalimumab against COVID-19-induced cytokine storm are being evaluated in an ongoing clinical trial.15

**CD20**

The B-lymphocyte antigen CD20 is highly expressed on B cells starting at the pre-B-cell stage and on mature B cells, and it is downregulated during terminal differentiation into plasma cells. While the precise function of CD20 is not fully elucidated, IgM expression in immature and mature B cells from CD20-deficient mice was markedly reduced compared to wildtype.16 Furthermore, reduced humoral immunity to adeno-associated viral antigens was demonstrated in CD20-deficient mice.17 A patient who lacked CD20 expression due to homozygous mutations reported intermittent respiratory infections, associated with persistent hypogammaglobulinemia and strong reductions in circulating memory B cells.18 No significant differences in URTI, nasopharyngitis, bronchitis, cough, and sinusitis between rituximab (anti-CD20)19 and placebo were demonstrated in a double-blind RCT for rheumatoid arthritis (RA).20 However, in a prospective, open-label RCT, it was noted that lung infections/pneumonia were higher in the rituximab treatment arm by more than twofold (11% vs. 5% in control, no confidence intervals were presented).21 The role of CD20+ cells in presenting antigen to T cells and in generation of antibodies to protect from new infections remains unclear.

**IL-12/23**

The IL-12/IL-23 common pathway plays a key role in the induction of inflammation in adaptive immune responses, where IL-12 induces a Th1 immune response with a downstream induction of cytokines such as TNF, interferon (IFN)-γ, and IL-23 promotes a Th17 immune response through the induction of inflammatory cytokines such as IL-17 and IL-22. Mice defective in both IL-12/23 (p40−/−) and IL-12 alone (p35−/−) were infected with a murine coronavirus (MHV).22 IL-12 and IL-12/23 knockout mice had similar survival to wild-type animals.23 Therefore, IL-12 does not seem to contribute to antiviral function or survival. Mice deficient in IL-23 alone (p19−/−) were infected with murine coronavirus, and viral control was similar to wild-type mice, demonstrating that IL-23 does not significantly confer protection from infection.24 This was also demonstrated through neutralization of mice using anti-IL-23p19-specific and anti-IL-12/23p40 antibodies, followed by infection of mice with MHV.25 In the absence of IL-12/23 signaling, specific antiviral T-cell response was intact.25 Clinical trials using IL-12/23 or IL-23 inhibitors demonstrated no significant increase in respiratory adverse events (Table 2). Furthermore, the PSOLAR study reported that ustekinumab had no increased risk of serious infections.13 Of note, a recent case study reported COVID-19 in a patient during IL-23 inhibitor (guselkumab) treatment for psoriasis, and the patient had a good outcome.26

**IL-17**

IL-17 is a proinflammatory cytokine with important roles in T-cell activation and neutrophil mobilization and activation.27 IL-17 expression is induced during influenza infection as part of the Th1 immune response that contributes to viral clearance.28 However, a growing body of evidence suggests that IL-17 is also associated with promotion of viral infections and tissue pathology. This is thought to occur through direct suppression of IFN-γ and the pivotal regulators of Th1-cell development T-bet and eomesodermin.29,30 IL-17 in some settings was shown to induce tissue pathology in response to viral infections through neutrophil infiltration. Mouse models developed increased IL-17A-dependent lung pathology upon respiratory syncytial virus (RSV) infection.31 IL-17RA−/− mice challenged with influenza had decreased morbidity and mortality, and this correlated with decreased levels of proinflammatory cytokines.
including TNF-α, IL-1β, and IL-6. In humans, chronic mucocutaneous candidiasis has been attributed to the disruption of Th1 and Th17 pathways. This was illustrated in patients with identified mutations in IL-17RA and STAT1 genes. These patients have no increased risk of viral infections. Clinical trials using IL-17 inhibitors demonstrated no significant increase in respiratory adverse events (Table 2). A recent case report reported a patient receiving therapy with an IL-17 inhibitor (ixekizumab) who was completely asymptomatic but tested positive for COVID-19.

| Target | Respiratory virus susceptibility | Coronavirus susceptibility | Interpretation of effect of knockout | References |
|--------|---------------------------------|---------------------------|-------------------------------------|------------|
| TNF-α  |                                | TNF-α−/− mice were less susceptible to MHV-3 and have improved survival | TNF signaling plays an important role in the pathology of coronavirus mouse hepatitis virus. Interruption of this signaling pathway could be useful for clinical therapy | 11         |
| TNF receptor |                        | TNFR1−/− mice were less susceptible to MHV-3 and had improved survival. TNFRs null mutant mice that were infected with SARS-CoV were protected from weight loss associated with infection | Signaling through TNF receptors is implicated in promoting coronaviruses pathogenesis, presumably through excessive inflammation | 11,12      |
| IL-17RA | IL-17RA−/− were less susceptible to influenza virus with decreased morbidity and mortality. IL-17RA knockout protected mice from lung damage | IL-17RA is dispensable for the recruitment of CD8+ T cells specific for influenza. IL-17 signaling in fact plays a key role in promoting a neutrophil response which leads to excessive inflammation in some viral infections | | 32         |
| IL-12   | IL-12 (p35−/−) mice were less susceptible to JHMV. IL-12 (p35−/−) mice had same susceptibility to MHV as WT | IL-12 enhances the magnitude of the inflammatory response in the viral infections after infection, albeit without affecting viral control. MHV-infected mice lacking IL-12 produced a polarized Th1-type cytokine response | | 23,24      |
| IL-12/23 | IL-12 and IL-23 (p40−/−) mice were less susceptible to JHMV | Reduced morbidity in infected IL-12-deficient mice | | 24         |
| IL-23   | IL-23 (p19−/−) mice had similar susceptibility to JHMV as WT | IL-23 appears to be dispensable for the recruitment of specific antiviral immune response | | 24         |
| CD20    | Likely more susceptible. Neutralizing Ab response to adeno-associated virus was significantly reduced in CD20−/− mice | Reduced humoral immunity to adeno-associated viral antigens | | 16,17      |
| IL-1R   | IL-1R1−/− mice had reduced inflammatory lung pathology but more mortality to influenza virus | IL-1R1−/− mice or IL-1R antagonist (IL-1Ra) treated mice show reductions in MHV-3 viral replication, disease progress, and mortality. MyD88−/− mice (defective IL-1 signaling) were more susceptible to SARS-CoV virus | Optimal IL-1R signaling and inflammatory cell recruitment to the lung appear to be required for protection | 36,37,111|
| IL-4    | IL-4−/− or IL-4 overexpressed mice had same susceptibility to RSV as WT. Overexpression of IL-4 delayed viral clearance | Absence of IL-4 signaling does not seem to affect susceptibility to some viruses | | 40         |

TNF, tumor necrosis factor; TNFR1, tumor necrosis factor receptor 1; SARS-CoV, severe acute respiratory syndrome coronavirus 2; IL-17RA, IL-17 receptor antagonist; JHMV, JHM strain of mouse hepatitis virus, a neurotropic coronavirus; MHV, mouse hepatitis virus, a coronavirus; RSV, respiratory syncytial virus; WT, wildtype.
| Drug                        | Type of biologic                                                                 | Trial                                                                 | Serious infections       | URTI                      | Nasopharyngitis           | References |
|-----------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------|-------------------------|---------------------------|---------------------------|------------|
| Adalimumab (TNF inhibitor)  | Fully human recombinant monoclonal antibody                                       | NCT00237887                                                         | 0.6% of 814 pts vs. 1% of 398 controls | 7.2% of 814 pts vs. 3.5% of 398 controls | 5.3% of 814 pts vs. 6.5% of 398 controls | 112        |
| Certolizumab (TNF inhibitor)| Human IgG1 monoclonal antibody                                                   | CIMPASI-1 (NCT02326298) and CIMPASI-2 (NCT02326272)                      | 1.1% of 87 pts vs. 0% of 49 controls | 9.1% of 88 pts vs. 5.9% of 51 controls | 20.5% of 88 pts vs. 13.7% of 51 controls | 113        |
| Etanercept (TNF inhibitor)  | Dimeric fully human fusion protein receptor (TNF type II receptor linked to IgG1 Fc region) | ERASURE and FIXTURE Etanercept Psoriasis Study Group                  | Not reported             | 5.6% of 323 pts vs. 0.9% of 327 controls | 26.6% of 323 pts vs. 8% of 327 controls | 114,115    |
| Infliximab (TNF inhibitor)  | Chimeric (25% mouse; 75% human) monoclonal antibody (IgG)                       | EXPRESS                                                              | Not reported             | 15% of 298 pts vs. 16% of 76 controls | 6% of 298 pts vs. 8% of 76 controls | 116        |
| Ustekinumab (IL-12/23 inhibitor) | Fully human monoclonal antibody against p40 subunit                           | PHOENIX 1                                                           | 0.8% of 255 pts vs. 0.4% of 255 controls | 7.1% of 255 pts vs. 6.3% of 255 controls | 10.2% of 255 pts vs. 8.6% of 255 controls | 117        |
| Brodalumab (IL-17 inhibitor) | Fully human monoclonal antibody (IgG2)                                          | AMAGINE-2 (NCT1708603) and AMAGINE-3 (NCT1708629)                      | 0.3% of 612 pts vs. 0.3% of 309 controls | 5.4% of 612 pts vs. 7.4% of 309 controls | 7.4% of 612 pts vs. 4.5% of 309 controls | 118        |
|Ixekizumab (IL-17 inhibitor) | Humanized monoclonal antibody (IgG4)                                            | UNCOVER-2 and UNCOVER-3                                              | 0.3% of 622 pts vs. 0.6% of 313 controls | 5.3% of 622 pts vs. 5.4% of 313 controls | 5% of 622 pts vs. 7% of 313 controls | 119        |
| Secukinumab (IL-17 inhibitor) | Fully human IgG1 monoclonal antibody                                             | ERASURE and FIXTURE                                                 | 2% of 734 pts vs. 2% of 360 controls | 4% of 734 pts vs. 3% of 360 controls | 8% of 734 pts vs. 8% of 360 controls | 114        |
| Guselkumab (IL-23 inhibitor) | Human immunoglobulin G1 lambda (IgG111) monoclonal antibody                     | VOYAGE 1 (NCT2207231) and VOYAGE 2 (NCT2207244) Phase II and longer-term safety data | 0.12% of 823 pts vs. 0.24% of 422 controls | 5% of 823 pts vs. 4.5% of 422 controls | 7.9% of 823 pts vs. 7.8% of 422 controls | 120,121    |
| Risankizumab (IL-23 inhibitor) | Fully human IgG monoclonal antibody                                               |UltIMMa-1 (NCT02684370) and UltIMMa-2 (NCT02684357)                     | 0.2% of 494 pts vs. 0.4% of 248 controls | 3.2% of 494 pts vs. 4% of 248 controls | 7.1% of 494 pts vs. 6.5% of 248 controls | 122        |
| Tildrakizumab (IL-23 inhibitor) | Humanized, IgG1 x monoclonal antibody                                             | PO5495 (phase II, NCT01225731), reSURFACE 1 (phase III, NCT01722331) and reSURFACE 2 (phase III, NCT01729754) | 0.3% of 708 vs. 0.3% of 355 controls | 3% of 708 vs. 2.8% of 355 controls | 9.3% of 708 vs. 8.2% of 355 controls | 123        |
IL-1

IL-1 is a key player in the regulation of inflammation. IL-1 signaling may enhance or attenuate viral replication depending on the setting. Mice deficient in MyD88, an adapter protein that mediates Toll-like receptor (TLR), IL-1R, and IL-18R signaling, are more susceptible to SARS-CoV infection.36 On the other hand, mice that were infected with MHV-3 had high levels of IL-1

\[ \text{IL-1} \]

in the serum and liver. 37 IL-1

\[ \text{IL-1}\beta \]

receptor-I deficient (IL-1R1

\[ \text{IL-1R1}^-\]

) or IL-1R antagonist (IL-1Ra)-treated mice infected with MHV-3 showed attenuation in viral replication and mortality, demonstrating that IL-1 may contribute to the pathogenesis of coronavirus in mice.37 Patients with unopposed activation of IL-1 due to recessive mutations in IL1RN, the gene encoding IL-1–receptor antagonist, had elevated levels of proinflammatory cytokines TNF-\( \alpha \), IL-6, and IL-17, and some of these patients presented with respiratory distress.38 Treatment of these patients with IL-1 receptor antagonist decreased mortality.38 The use of anakinra in clinical trials was associated with a slightly higher frequency of serious infectious episodes, primarily pneumonia (2.1% vs. 0.4%, comparative risk 5.25), than the placebo group.39 It appears that normal IL-1 expression/function is required to mount an optimal antiviral immune response.

IL-4

IL-4 is a key regulator in humoral and Th2 adaptive immunity. Mouse models demonstrated that the constitutive overexpression of IL-4 prior to RSV infection delayed viral clearance, increased the density of the lymphocytic infiltrate in the lungs, and diminished induction of primary cytotoxic T lymphocyte responses.40 Conversely, IL-4

\[ \text{IL-4}^-\]

mice cleared RSV readily after primary infection, with minimal pathology.40 A pooled analysis of two phase III RCTs demonstrated safety of dupilumab, where URTIs, nasopharyngitis, and severe infection rates were comparable to the placebo group.41 Recently, several case reports demonstrated no evidence of increased risk for COVID-19 infection in patients treated with dupilumab.42-45

**Anti-immunoglobulin E**

Anti-IgE biologics (e.g., omalizumab) block IgE molecule binding to receptors on mast cells and basophils and are approved for urticaria. Omalizumab was shown in multiple trials to be a safe biological therapy with no significant increase in adverse respiratory events.46-48

**Intravenous immunoglobulin**

Intravenous immunoglobulin (IVIG) is used for several dermatological diseases. IVIG has been shown to have a good safety profile with no significant increase in the rates of nasopharyngitis and URTI.49,50 Of note, a clinical trial on IVIG and pemphigus demonstrated that the incidence of adverse drug reactions was 6/21 (28.6%) in the 400 mg/kg/day group and 7/20 (35.0%) in
### Table 3: Trial data on systemic medications and the risk of infection

| Trial                      | Trial Type                                    | Type of infectious risk assessed                                                                 | Number                                                      |
|----------------------------|-----------------------------------------------|--------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| Cyclosporine               | Grattan et al.124                            | URTI                                                                                             | 10% of 20 vs. not reported/10 placebo                       |
|                            | Randomized, double-blind, placebo controlled  | Flu-like symptoms                                                                                | 15% of 20 vs. not reported/10 placebo                       |
|                            |                                               | Infections                                                                                       | 3.2% of 62 vs. 8.6% of 35                                   |
|                            | Vena et al.125                               | URTI                                                                                             | 3.5% CsA of 57 vs. 10.3% of 58 ADA                         |
|                            | Randomized, double-blind, placebo controlled  | Flu-like symptoms                                                                                | 0% of 57 CsA vs. 1.7% of 58 ADA                             |
|                            |                                               | Any infection                                                                                     |                                                             |
|                            | Karanikolas et al.126                        | Any serious infection                                                                            |                                                             |
|                            | Non-randomized, unblinded, ADA vs. CsA       | URTI                                                                                             | 1.8% of 57 CsA vs. 8.6% of 58 ADA                          |
|                            |                                               | Infections (UTI)                                                                                 | 5.6% of 18 vs. 0% of 18 placebo                            |
|                            | Lai et al.127                                | URTI                                                                                             |                                                             |
|                            | Randomized, double-blind, placebo controlled  | Infections (UTI)                                                                                 |                                                             |
|                            |                                               |                                                                                                 |                                                             |
| Mycophenolate mofetil      | Beissert et al.128                           | Grade 3 Infections (severe)                                                                      | 11% of 35 Methylpred + MMF vs. 0% of 38 Methylpred + AZA    |
|                            | Randomized, non-blinded, methylpred + MMF vs. | Methylpred + AZA                                                                                  |                                                             |
|                            | methylpred + AZA                             | Grade 4 Infections (life threatening)                                                            | 0% of 35 Methylpred + MMF vs. 3% of 38 Methylpred + AZA    |
|                            | Beissert et al.62                            | Nasopharyngitis                                                                                  | 12% of 58 Pred + MMF vs. 0% of 36 Pred                    |
|                            | Randomized non-blinded,Prednisone (Pred) + MMF | URTI                                                                                             | 10% of 58 Pred + MMF vs. 3% of 36 Pred                    |
|                            | Pred vs. MMF                                 | Influenza viral                                                                                   | 0% of 58 Pred + MMF vs. 3% of 36 Pred                    |
|                            |                                               | LRTI                                                                                             | 3% of 58 Pred + MMF vs. 0% of 36 Pred                    |
|                            |                                               | Overall Infections                                                                               | 59% of 58 Pred + MMF vs. 36% of 36 Pred                   |
|                            | Akhyani et al.129                           | Infectionsd                                                                                      | 0% of 20 vs. 0% of 18 MTX                                  |
|                            | Randomized, open-label MMF vs. MTX            |                                                                                                |                                                             |
|                            | Ioannides et al.130                          | Internal Infection                                                                               | 8% of 24 Methylpred + MMF vs. 4% of 23 Methylpred (P = 1.0000) |
|                            | Randomized, non-blinded, methylpred vs.       |                                                                                                |                                                             |
|                            | methylpred + MMF                             |                                                                                                |                                                             |
|                            | Zhou et al.131                               | Infection                                                                                       | 0% of 23                                                   |
|                            | Open-label                                   | URTI                                                                                             | 5% of 41 vs. 0% of 20                                       |
|                            | Meggitt et al.58                             |                                               | 5% of 41 vs. 5% of 20                                      |
|                            | Randomized, double-blind, placebo controlled  | URTI                                                                                             | 20% of 25 vs. 8% of 25                                     |
|                            | Berth-Jones et al.87                         | URTI                                                                                             |                                                             |
|                            | Double blind, randomized, placebo crossover   | URTI                                                                                             |                                                             |
|                            | Schram et al.69                              | Infection                                                                                       | 36% of 22 vs. 25% of 20 MTX                                 |
|                            | Randomized, single blind compared to methotrexate | Moderate intensity infection                                                                   |                                                             |
|                            |                                               |                                                                                                 |                                                             |
| Azathioprine               | METOP73                                       | Any infection                                                                                     | 44% of 91 weeks 0–16 and 41% of 76 weeks                   |
|                            | Randomized, double-blind, placebo-controlled  | 16–52 vs. 45% of 29 weeks 0–16 placebo                                                           |
|                            |                                               | Serious infection                                                                                 | 0% of 91 vs. 3% of 29 placebo                               |
|                            | Pasnoor et al.74                             | Infection                                                                                       | 16% of 175 vs. 11% of 161 placebo                           |
|                            | Randomized, double-blind, placebo-controlled  |                                                                                                 |                                                             |
|                            | Kingsley et al.75                            | Respiratory tract infection                                                                      | 28% of 109 vs. 22% of 112 placebo                           |
|                            | Randomized, double-blind, placebo-controlled  |                                                                                                |                                                             |
| Methotrexate               | UNVEIL84                                      | Nasopharyngitis                                                                                  | 10% of 211 vs. N/A placebo                                  |
|                            | Double-blind, placebo-controlled, 52 weeks   | URTI                                                                                             | 7% of 211 vs. N/A placebo                                   |
|                            |                                               |                                                                                                 |                                                             |
|                            | LIBERATE85                                    | URTI                                                                                             | 7% of 74 vs. 7% of 73 placebo/Aprem                        |
|                            | Randomized, double-blind, Aprem vs. Enbrel vs. placebo with Aprem extensiona | Nasopharyngitis                                                                                  | 3% of 74 vs. 6% of 73 placebo/Aprem                        |
|                            |                                               | URTI                                                                                             | 5% of 74 vs. 1% of 73 placebo/Aprem                        |
|                            | Bissonette et al.96                          | Bronchitis                                                                                       | 26% of 53 vs. 14% of 50 placeboa                           |
|                            | Randomized, double-blind, placebo-controlled  | URTI                                                                                             | 6% of 50 vs. 0% of 50 placebo                               |
|                            |                                               |                                               | 10% of 560                                                  |
|                            | ESTEEM 187                                    | URTI                                                                                             | EAIR/100 py = 37.6 vs. 7% of 282 EAIR/100 py = 27.3 placebo |
|                            | Randomized, double-blind, placebo-controlled  | Nasopharyngitis                                                                                  | 7% of 560                                                   |
|                            |                                               |                                               | EAIR/100 py = 26.6 vs. 8% of 282 EAIR/100 py = 30.1                             |
|                            | ESTEEM 288                                    | URTI                                                                                             | 5% of 272 EAIR/100 py = 17.3 vs. 4% of 136 EAIR/100 py = 16.7 |

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*UTI*: upper respiratory tract infection. *LRTI*: lower respiratory tract infection. *MTX*: methotrexate. *Aprem*: apremilast. *MMF*: mycophenolate mofetil. *AZA*: azathioprine.
Table 3 Continued

| Trial                  | Trial Type                        | Type of infectious risk assessed | Number  |
|------------------------|-----------------------------------|----------------------------------|---------|
| Vossen et al.88        | Randomized, double-blind, placebo-controlled | Nasopharyngitis                  | 7% of 272 |
|                        |                                    | EAIR/100 py − 27.3 vs. 4% of 136 EAIR/100 py − 16.9 placebo |
| Thalidomide            | Droitcourt et al.132               | Any type of infection            | 25% vs. 21% placebo |
|                        | Kaur et al.133                     | Common cold                      | 26% of 15 vs. 20% of 5 placebo |
|                        | Lazzerini et al.134                | Cough and fever                  | 5% of 20 vs. 0% of 19 placebo |
|                        | Hamuryudan et al.135               | Infectiond,e                     | 0% of 30 vs. 0% of 30 prednisolone |
|                        |                                    | Infectiond                        | 0% of 12 vs. 0% of 31 placebo |
|                        |                                    | Infectiond                        | 0% of 63 vs. 0% of 32 placebo |

URTI, upper respiratory infection; ADA, adalimumab; CsA, Cyclosporine; UTI, urinary tract infection; MEP, methylprednisolone; MMF, mycophenolate mofetil; AZA, azathioprine; Pred, prednisone; LRTI, lower respiratory infection; MTX, methotrexate; Aprem, apremilast; EAIR, exposure-adjusted incidence rate; py, patient years. 

ªUrinary tract infection.

Three infections were URTIs; one infection was recurrent HSV.

No patients withdrew due to infection.

No infections reported in paper.

One patient had amoebic dysentery within 2 weeks of initiation of study and stopped therapy.

the 200 mg group including one URTI vs. 5/20(25.0%) in the placebo group.51

Parts 3: Non-biologic systemic agents and risk of infection

Cyclosporine

Cyclosporine is a calcineurin inhibitor that blocks IL-2 signaling and T-cell proliferation.62,53 The most common infectious side effects from cyclosporine were flu-like symptoms seen in 15% of patients enrolled in an RCT for chronic idiopathic urticaria.54 Psoriasis registries examining cyclosporine reported infection rates of 8.1–17.7 infections per 100 patient-years65-57 with severe or serious infection rates of 1.4 and 2.0 per 100 patient-years, slightly higher than comparators.56,57 Of note, cyclosporine has been shown to inhibit the replication of diverse coronaviruses including SARS as demonstrated by in vitro experiments.58,59

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is an antimetabolite that blocks B-cell and T-cell maturation.60,61 Most reported trials examined MMF with an oral corticosteroid or other steroid-sparing agent. Trials that combined MMF with corticosteroids had significantly higher rates of infections, up to 59%.62 MMF is reported to increase patients’ susceptibility to viral infections,63 and an increase in nasopharyngitis and URTIs was noted comparing prednisone plus MMF to prednisone monotherapy in pemphigus vulgaris.62 Of note, MMF was used to treat eight patients with MERS with a 100% survival rate; however, when analyzing the severity of illness and treatment, MMF was given to less severely ill patients.64

Azathioprine

Azathioprine inhibits purine synthesis and downregulates B-cell and T-cell function.65,66 Documented types of infection with use of azathioprine include lower respiratory tract infections (LRTI) and URTI, which had rates of 5% and 5–20%, respectively.67,68 Thirty-six percent of patients in one study had infections of moderate intensity.69 There were no registries evaluating the prevalence of infections during azathioprine therapy for dermatologic uses. One systematic review evaluating the off-label use of azathioprine found mild infections reported in 0.36% of patients and severe infections in only 0.30% of patients70 (Table 3).

Methotrexate

The use of methotrexate (MTX),71 a folic acid antagonist that inhibits nucleotide synthesis,72 had slightly increased risk of infections ranging from 16 to 44% vs. 3 to 45% compared to placebo in three RCTs.73-75 A large cardiovascular trial using 15–20 mg doses of methotrexate showed rates of serious
infection were similar to the placebo group. A review of infectious risks in rheumatoid arthritis (RA) patients indicated that although MTX has previously been implicated not only with increased risk of infection but also increased severity, the evidence was not clear. The review concluded that MTX appears to be associated with minimal, if any, increased infection risk in the RA population.

**Hydroxychloroquine**

Hydroxychloroquine is an antimalarial medication that inhibits lysosomal functions and interferes with a myriad of immune pathways. Its exact mechanism in many dermatologic processes has never been fully elucidated. Hydroxychloroquine has been shown to have a favorable side effect profile in terms of infection risk in many clinical trials. It is currently under investigation in numerous phase 2 clinical trials as treatment for COVID-19 as it may inhibit viral fusion to the host cell and inhibit viral assembly and release.

**Apremilast**

Apremilast is a phosphodiesterase 4 (PDE4) inhibitor with side effects including nasopharyngitis and URTI. The incidence of URTI in the apremilast-treated groups is comparable to placebo ranging from 4.8 to 26.0% and 4.4 to 14.0%, with higher rates being accounted for from one study examining apremilast in palmoplantar psoriasis (Table 3). Overall, rates of infection were not increased in patients treated with apremilast.

A recent case was reported of a patient with erythrodermic psoriasis, with contraindication to most treatments due to a recurrent brain oligodendroglioma who had psoriasis.

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**Table 4 Registry, databases, systematic reviews, and meta-analyses on systemic medications and the risk of infection**

| Medication          | Registry/Database | Level of evidence | Type of infectious risk assessed | Outcome |
|---------------------|-------------------|-------------------|---------------------------------|---------|
| Cyclosporine        | Biobadaderm Registry | 55 2019 | Infections and infestations     | Incidence per 1,000 py = 177 (136–231) |
|                     | Biobadaderm Registry | 57 2017 | Serious and deadly infections   | Rate/1,000 py = 20 (8.3–47.9) |
|                     | PsoBest Registry   | 56      | Infections (non-severe*)        | Rate/100 py = 8.1 [95% CI 5–13] |
|                     | Schmitt et al.136  | Meta-analysis    | Infections (severe*)            | Rate/100 py = 1.4 [95% CI 0.25–4] |
| Mycophenolate mofetil | Sparse data       | Azathioprine     | Flu-like illness                 | 13/255 (5%) |
|                     | Sood et al.137Prospective database |              | Mild infection                   | 36/1,128 (0.36%) |
|                     | Schram et al.70Systematic review |             | Severe infection                 | 3/1,128 (0.3%) |
| Methotrexate        | Biobadaderm Registry | 55 2019 | Infections and infestations     | Incidence per 1,000 patient years = 112 (98–129) |
|                     | Biobadaderm Registry | 128 2017 | Infection                       | Rate/1,000 py = 113.1 (95.2–134.3) |
|                     | SDNTT Registry138 |                  | Serious and fatal infection      | Rate/1,000 py = 9.6 (5.3–17.3) |
|                     | PsoBest Registry   | 56      | Infections                      | 0/86 (0%) |
| Apremilast          | Biobadaderm Registry | 55      | Infections and infestations     | Incidence per 1,000 patient years = 105 (95% CI 64–175) |
|                     | Papadavid et al.139Prospective observational |       | Infection                       | 3/50 (6.0) |
| Thalidomide         | Sparse data        | Systemic Corticosteroids | Infections | 9% AE/100 py = 12 (95% CI 8–16) |
|                     | Hoes et al.98Meta-analysis | (low- to medium-dose oral glucocorticoids) |           |       |
| Non-biologic Systemics | Biobadaderm Registry | 140 | All infections                  | Rate/1,000 py (95% CI) |
|                     | Clalit Database140 |                  | Serious infections               | 88.35 (75.19–103.15) |
|                     | Psocare Registry140 |                  | Serious infections               | 9.80 (5.90–15.31) |
|                     |                   |                  | All infections                   | 48.14 (42.50–54.32) |
|                     |                   |                  | Serious infections               | 32.6 (28.00–37.67) |
|                     |                   |                  | All infections                   | 21.77 (17.00–37.46) |
|                     |                   |                  | Serious infections               | 12.21 (8.73–16.63) |

py, patient years; CI, confidence interval; AE, adverse event.

* Non-severe infections: all other.

* Severe infections: requiring antibiotics, inpatient stay or life-threatening.

* Estimated from a bar graph.

* Serious infections: resulted in death, life-threatening, required prolonged hospitalization, caused persistent disability.
partially controlled on apremilast. The patient contracted COVID-19 while on apremilast treatment and has fully recovered despite being at high risk of complications from COVID-19 (obesity, recent chemotherapy, and active malignancy); his apremilast treatment was not interrupted.90

Thalidomide

Thalidomide,91 an immunomodulatory drug with a range of activity that is not fully characterized,92 is effective for various refractory dermatoses, but its side effect profile is unfavorable, and risks of teratogenicity and neuropathy often preclude its use.91 Table 3 highlights four RCTs where there was no increased risk of infection in thalidomide compared to placebo.

Oral corticosteroids

Prolonged use of oral corticosteroids is generally avoided due to side effects.93 None of the following studies reported infection as an adverse reaction.94-97 A meta-analysis including 2,382 patients from 28 studies showed a rate of infectious adverse events of 9% in all patients (AE/100 py = 12, 95% CI: 8–16).98 Pooled data from 71 RCTs for steroids vs. no steroids found the relative risk of infections was increased by 60% (95% CI 30–90) for those receiving steroids (Table 4).99 In a large cohort of patients with inflammatory bowel disease that was collected through an international registry, the outcomes of the use of high-dose corticosteroids, among other immunosuppressives, in COVID-19-positive patients was evaluated.100 The study demonstrated a strong positive association between systemic corticosteroid use and increased mortality/ICU admission of COVID-19 patients. The study also indicated that TNF antagonist, methotrexate, and IL-12/23 inhibitors do not appear to be associated with severe COVID-19.100 We note that the effects of low-dose dexamethasone against COVID-19 are currently being evaluated in the RECOVERY trial.101

Part 4: Non-biologic agents in transplant recipients with coronavirus

It is known that transplant patients are at higher risk of severe infections, including more severe and complicated influenza.102 However, coronaviruses have not been shown to cause more severe disease in transplant recipients compared to other common viruses such as adenovirus and rhinovirus.103

COVID-19 in transplant recipients

Immunosuppression is not a comorbidity that is commonly reported in COVID-19 patients despite it commonly being referred to as a risk factor.104 The limited data do not suggest increased risk of severe complications compared to the general population. Lei et al.105 reported two heart transplant patients in China who survived COVID-19 infections. Two reported renal transplant patients who contracted COVID-19 and succumbed to the illness had similar clinical courses compared to non-transplant patients.106 Transplant recipients may practice more stringent physical distancing practices compared to the general population, resulting in falsely low numbers.

SARS in transplant recipients

The literature surrounding SARS and transplant recipients is sparse. Risk factors for severe SARS included hypertension, diabetes, coronary heart disease, hepatitis, and pregnancy with a mortality rate with ≥1 risk factor compared to none of 54.5% vs. 7.5%; P < 0.01.107 There is no evidence that suggests transplant recipients had poorer outcome in the SARS epidemic.

MERS in transplant recipients

A retrospective cohort study of a MERS outbreak in Korea revealed that the number of affected immunosuppressed patients was low and did not identify any transplant patients.108 Immunosuppression was not identified as a poor prognostic factor in MERS infection.109

Closing remarks

Immunomodulatory regimens have revolutionized the treatment of dermatological diseases. With the current COVID-19 pandemic, it is imperative to examine the evidence and conduct a risk–benefit analysis for each patient. There may be patients who require more or less treatment, for instance some patients with existing comorbidities may require a more conservative

Figure 1 A pictorial representation of COVID-19 risk assessment of dermatologic treatments where green represents "safe" and red represents "higher risk"
approach.\textsuperscript{110} The greatest risk of infections in biologics appear to occur with CD20 inhibition (Fig. 1). For non-biologic immunotherapies, the greatest risk of infection appears to occur with the use of high doses of oral corticosteroids. A slight increased infection risk is seen with cyclosporine, although cyclosporine has been shown to inhibit coronavirus replication and did not increase susceptibility in transplant patients.

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