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Review

The role of interleukin 13 and the type 2 immune pathway in COVID-19: A review

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Key Messages

- In vitro studies reveal that interleukin (IL)-13 leads to down-regulation of the severe acute respiratory syndrome coronavirus 2 receptor angiotensin-converting enzyme 2, which is inconsistent with in vivo studies that reveal similar severe acute respiratory syndrome coronavirus 2 viral loads in those receiving IL-13 blockade compared with control groups.
- Elevated type 2 biomarkers are associated with worse outcomes in acute moderate-to-critical coronavirus disease 2019 (COVID-19).
- IL-13 inhibition, reduction in downstream HA molecules, and inhibition of HA receptor CD44 is associated with clinical improvement and survival in COVID-19 mouse models, suggesting a mechanistic plausibility for downstream influence of IL-13 on post–COVID-19 conditions.
- Large COVID-19 patient databases reveal improved COVID-19 outcomes for patients on dupilumab, a monoclonal antibody that blocks IL-4Rα, compared with those not on dupilumab.
- In a 40-patient randomized clinical trial, those who received dupilumab had a higher 60-day survival compared with placebo (secondary outcome).

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ABSTRACT

Although much has been learned about severe acute respiratory syndrome coronavirus 2 since December 2019, uneven global vaccine distribution, rapid viral spread, and variant evasion of preventative measures have led to its persistence in the population for the foreseeable future. Additional therapies are needed to support patients through their acute, immune-mediated disease process that continues to lead to considerable morbidity and mortality. Data revealing the involvement of type 2 immune pathway in acute coronavirus disease 2019 and post-recovery conditions represent a potential additional area for intervention. Herein, we review the current understanding of interleukin 13 in acute severe acute respiratory syndrome coronavirus 2 infection, the clinical outcomes associated with type 2 immune processes, and the impact of type 2 blockade on acute and long-term coronavirus disease 2019 conditions.

Introduction

Although overall there are improved clinical outcomes since December of 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to persist in the population at constant numbers with perpetual hospitalizations and deaths.[1] As there is now substantial preexisting immunity in the population because of either natural infection or vaccination, those requiring hospital admission for their disease are more likely to have failed outpatient antiviral management and/or had ineffective adaptive immune response to SARS-CoV-2. Therefore, coronavirus disease 2019 (COVID-19) inpatients have likely progressed to a host-mediated hyperinflammatory state that is less influenced by direct viral-mediated tissue damage.[2]

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It is this stage of disease that there remains a substantial need for additional therapeutics as current therapies were found to have variable or modest benefit.[3-5] Although there have been numerous immune pathways posited as responsible for critical COVID-19, there are now substantial data revealing that interleukin (IL)-13, a potent inducer of type 2 immune pathway and regularly implicated in atopic disease,[6] is a significant component of the process.

IL-13 primarily co-recognizes the receptor IL4Rα along with IL-4, which induces intracellular Janus kinases (JAK1, JAK2, JAK 3) and downstream phosphorylation of signal transducer and activator 6 (STAT-6). Although thought to be in part a decoy receptor, additional alternative signaling has been found to occur through IL-13Rα2, with subsequent intracellular signal-regulated protein kinase (ERK) 1/2 phosphorylation and dimerization of activator protein (AP)-1 transcription factor.[6,7] On stimulation by allergens, pollutants, and/or microbial antigens, epithelial cells release thymic stromal lymphopoietin, IL-33 and IL-25, which induce IL-13 production by various cell types, notably group 2 innate lymphoid cells (ILC2s) and T helper (T_H) cells.[7] Downstream impact of IL-13 includes B cell induction of immunoglobulin E (IgE) class switching, M2 polarization of macrophages, smooth muscle cell proliferation, eosinophil stimulation and trafficking, fibroblast proliferation, and goblet cell hyperplasia[7] (Fig 1).

Multiple biologics have been developed for treatment of allergic diseases through blockade of the type 2 immune pathway.[8] Among the therapies that target IL-13, including tralokinumab and lebrikizumab, dupilumab, a monoclonal antibody that blocks IL4Rα, has been studied in a COVID-19 randomized clinical trial based on robust prior data suggesting therapeutic benefit in this population.[9] Dupilumab was originally Food and Drug Administration (FDA) approved for treatment of moderate-to-severe atopic dermatitis in 2017, with subsequent approval for asthma, chronic rhinosinusitis with nasal polyps (CRSwNPs), and eosinophilic esophagitis (EoE).[10] Studies investigating its use in these patients found successful ability to reduce downstream type 2 biomarkers, including eotaxin-3, periostin, and thymus, and activation-regulated chemokine (TARC).[11] In addition, post hoc analysis of asthma and/or chronic CRSwNP phase III studies found reduced incidence of investigator-reported respiratory infections with dupilumab use, which is thought, in part, to be due to type 1 antiviral immune activation in response to a diminished type 2 immune pathway.[12]

Interleukin 13 and Other Type 2 Biomarkers Are Associated With Poor Outcomes in Coronavirus Disease 2019

Immune analyses of patients requiring hospitalization for acute COVID-19 reveal that those with high IL-13 levels and associated type 2 cytokines are associated with worse clinical outcomes, with sustained elevation for weeks after symptom onset. Serum analysis of patients with acute COVID-19 revealed that patients in the highest IL-13 quantile were 2.7 times as likely to require mechanical ventilation for their illness compared with those in the lowest quantile when adjusting for age, sex, and comorbidities.[13] Gibellini et al[14] also found that elevated levels of type 2 cytokines, including IL-13, IL-4, and IL-33, were predictive of life-threatening COVID-19 when analyzing serum from those patients admitted to the hospital with COVID-19. This is further supported by Carapito et al[15] who revealed that plasma IL-4 level (IL-13 levels were not measured) was elevated in

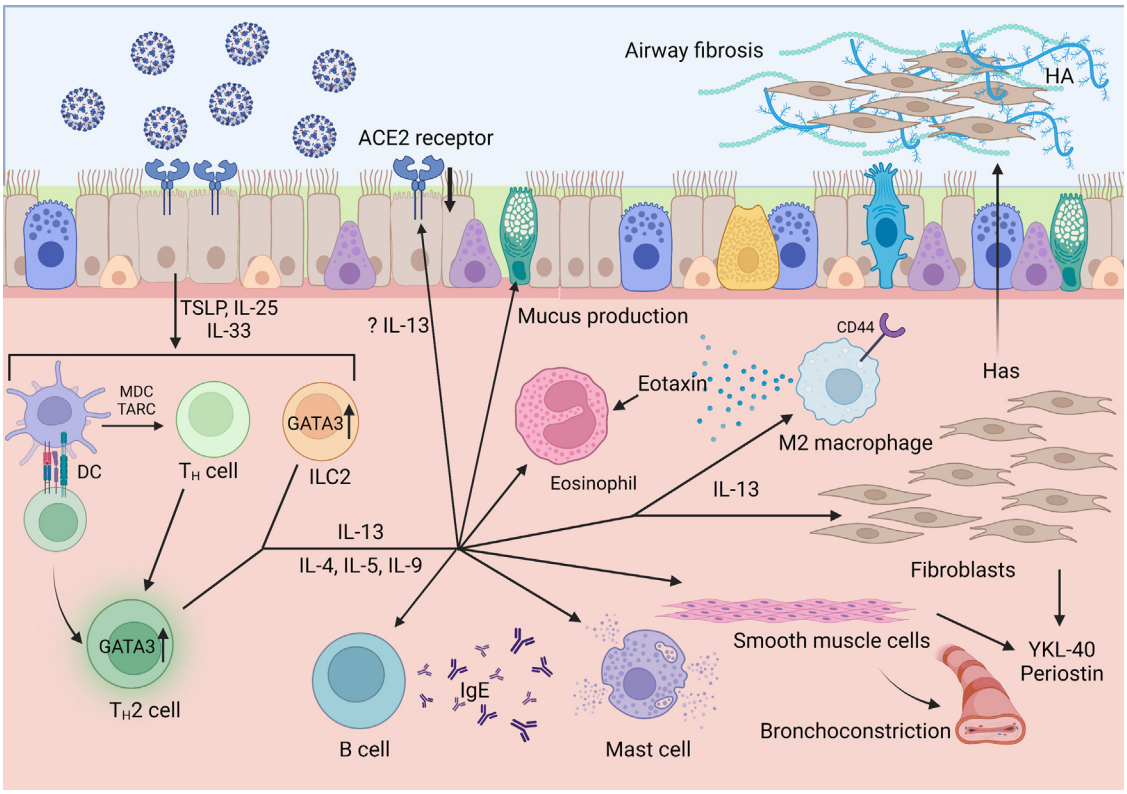

Figure 1. IL-13–mediated type 2 immune pathway in the setting of acute COVID-19 infection. On stimulation by viral antigens, airway epithelial cells secrete type 2 mediators, among which are IL-33, which stimulates various cells, notably ILC2, T_H2, and DCs. Through up-regulation of the transcription factor GATA3, these cells secrete type 2 markers including MDC, TARC, IL-13, IL-4, IL-5, and IL-9. Type 2 cytokines cause B cell induction of IgE class switching, M2 polarization of macrophages, smooth muscle cell proliferation, eosinophil stimulation and trafficking, fibroblast proliferation, and goblet cell hyperplasia. IL-13 may cause down-regulation of SARS-CoV-2 receptor ACE2 on epithelial cells. IL-13–stimulated fibroblasts produce CHI3L1 or YKL-40 and periostin and cause up-regulation of Has with extracellular production of HA, all of which mediate airway fibrosis. Adapted from BioRender.com templates (2022). Retrieved from https://app.biorender.com/biorender-templates. ACE2, angiotensin-converting enzyme 2; CHI3L1, chitinase 3-like protein 1; COVID-19, coronavirus disease 2019; DC, dendritic cell; HA, hyaluronan; Has, hyaluronan synthase; IgE, immunoglobulin E; IL, interleukin; ILC2, group 2 innate lymphoid cell; MDC, macrophage-derived chemokine; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TARC, thymus and activation regulated chemokine; T_H2, type 2 T-helper cells;

patients with COVID-19 on intensive care unit (ICU) relative to non-ICU patients when broadly analyzing serum from younger (age < 50 years) patients without comorbidities and varying COVID-19 disease severities. When looking at longitudinal (out to 25 days) samples of patients admitted to the hospital with moderate-to-severe COVID-19, Lucas et al[16] found increasing levels of IL-13 and IL-5 over the disease course in those with severe infection compared with those with moderate infection. They further saw increasing levels of eosinophils and eotaxin-2 over time in patients with severe disease.

Reanalysis of data sets derived from bulk ribonucleic acid (RNA) sequencing of blood samples comparing COVID-19–positive with COVID-19–negative patients revealed elevation of the IL-4/IL-13 signaling pathway with significant association with disease severity.[17,18] Single-cell RNA sequencing of autopsied lung also revealed enrichment of the IL-4/IL-13 signaling pathway in macrophages and neutrophils within the lung tissue.[19]

Through single-cell RNA sequencing of peripheral blood mononuclear cells collected from patients with severe COVID-19, Zhang et al[20] found phenotypically exhaustive CD4+ cells, a subset of which exhibited a type 2 phenotype with up-regulation of GATA3, an important transcription factor involved in type 2 differentiation.[21] Gomez-Cadena et al[22] observed a significant increase in IL-33 levels in patients with COVID-19 and, through multiparametric flow cytometry-based immune monitoring of circulating ILCs, saw an increase in ILC2 subpopulation in severely ill patients. Zeng et al[23] identified up-regulated type 2 biomarkers, chitinase 3-like 1 (or YKL-40) and periostin, in bronchoalveolar lavage fluid of critical patients with COVID-19 compared with healthy controls. When comparing with autopsied lung tissue from control and H1N1 samples, Vaz de Paula et al[24] discovered significantly elevated expression of IL-4 and sphingosine-1, a marker of M2 macrophages, in those who died from COVID-19.

Data from these studies reveal that IL-13 along with multiple components in the type 2 immune pathway are associated with moderate-to-critical COVID-19 (Fig 1). Further investigation is needed to determine interactions with non-type 2 immune mediators (ie, IL-6, interferon gamma), which have also been found to contribute to poor COVID-19 outcomes. Nevertheless, there is significant evidence for both peripheral and pulmonary IL-13–mediated inflammatory activation in this stage of acute COVID-19 infection.

Type 2 Immune Processes Have Been Associated With Post–Coronavirus Disease 2019 Conditions

Prior data implicating IL-13 and the type 2 immune pathway in non-COVID-19–related fibrotic lung disease and disruption of differentiation of type 2 alveolar epithelial cells (AECs) suggest a potential role in postrecovery pulmonary dysfunction and post–COVID-19 conditions.[7,25,26] Flow cytometry analysis of peripheral T lymphocyte populations of patients with persistent symptoms over 1 year after COVID-19 infection revealed specific elevation of IL-4 CD4+ T cells, suggesting persistent inflammatory activation postrecovery rather than acute injury.[27] In addition, standard BALB/c laboratory mice infected with SARS-CoV-2 mouse adapted strain (MA10) observed out to 120 days postinfection were found to have persistently elevated IL-33 in the lungs of older (1 year) mice compared with younger (10 weeks) mice.[28] These studies suggest an association between the type 2 immune pathway, persistent pulmonary immune activation, and post–COVID-19 conditions.

K18-hACE2 C57Bl/6J mice infected with SARS-CoV-2 who received anti–IL-13 antibody had reduced clinical score, weight loss, and mortality compared with those who received immunoglobulin G (IgG) isotype control.[13] RNA-seq analysis of whole lung tissue taken from infected mice who underwent IL-13 neutralization revealed the most down-regulated gene to be Has1, which encodes a synthase responsible for hyaluronan (HA) production, a polysaccharide apart of the extracellular matrix that has previously been implicated in other inflammatory pulmonary disease.[29] This was mechanistically further supported by an increase in HA deposition in mouse lung with SARS-CoV-2 infection and improved mouse survival with neutralization of the HA receptor CD44.[13] Diffuse HA deposition has also been identified in fatal COVID-19 through staining of human lung tissue obtained from autopsies.[30,31] As HA has been proposed previously in asthma as a potential culprit in airway remodeling, this led to the hypothesis that HA, as a downstream effector of IL-13, may be involved in pulmonary dysfunction postrecovery from COVID-19 (Fig 2).[32]

Type 2 Immune Blockade and Acute Coronavirus Disease 2019 Clinical Outcomes

Using the TriNetX electronic medical record (EMR) database comprising data from 11 countries, patients who were prescribed dupilumab (n = 2523) had a lower risk of death compared with propensity score-matched controls without a dupilumab prescription.[33] This was validated using the National COVID Cohort Collaborative (N3C) database, a large COVID-19 patient database in the United States, where patients prescribed dupilumab and subsequently diagnosed with having COVID-19 within 61 days (n = 220) had significantly fewer deaths than control patients diagnosed with having COVID-19 matched for age, sex, race, ethnicity, site, and asthma diagnosis (n = 1100).[33] In a cohort of 1237 patients with moderate-to-severe atopic dermatitis, Ungar et al[34] found that dupilumab-treated patients had reduced COVID-19 symptoms and disease severity compared with those on other systemics and not on active treatment when controlled for age, sex, body mass index (BMI), asthma, and other comorbidities. Retrospective analysis of the World Health Organization (WHO) global pharmacovigilance database revealed that those on dupilumab had reduced severity of disease from COVID-19 infection.[35] Last, through analysis of Surveillance Epidemiology of Coronavirus Under Research Exclusion for Atopic Dermatitis (SECURE-AD) registry, a global physician registry of patients with atopic dermatitis, Musters et al[36] found that those who were receiving topical therapies for their disease had significantly higher odds of hospitalization from COVID-19 compared with those receiving dupilumab after adjusting for age, sex, ethnicity, and comorbidity score. Keeping in mind the inherent limitations of retrospective studies, these findings suggest improved COVID-19 clinical outcomes with IL4Rα blockade for those patients with allergic conditions for which dupilumab would be prescribed.

This raises the question as to the clinical impact of SARS-COV-2 in those with a hyperactive type 2 immune response as found in patients with atopic conditions. Retrospective studies and meta-analyses investigating COVID-19 outcomes in patients with asthma have found mixed results, likely owing to the heterogeneous nature of the disease entity in itself (severity and subtype) and of the patient populations that data are collected from.[37,38] That said, there is likely an increased risk of poor COVID-19 outcomes in those with severe and/or uncontrolled asthma requiring recent systemic corticosteroids.[39,40] When comparing patients with allergic asthma with those with non-allergic asthma using a large US-based EHR database, patients with allergic asthma were found to have a lower risk of hospitalization and death from COVID-19 when propensity score matched (n = 1578) for age, sex, ethnicity, geographic region, index month, asthma severity status, and medications (excluding biologics) suggesting a potential protective role of type 2 immunity.[41] However, it should be noted that a significantly higher number of patients in the allergic asthma group were maintained on biologics, making it difficult to discern

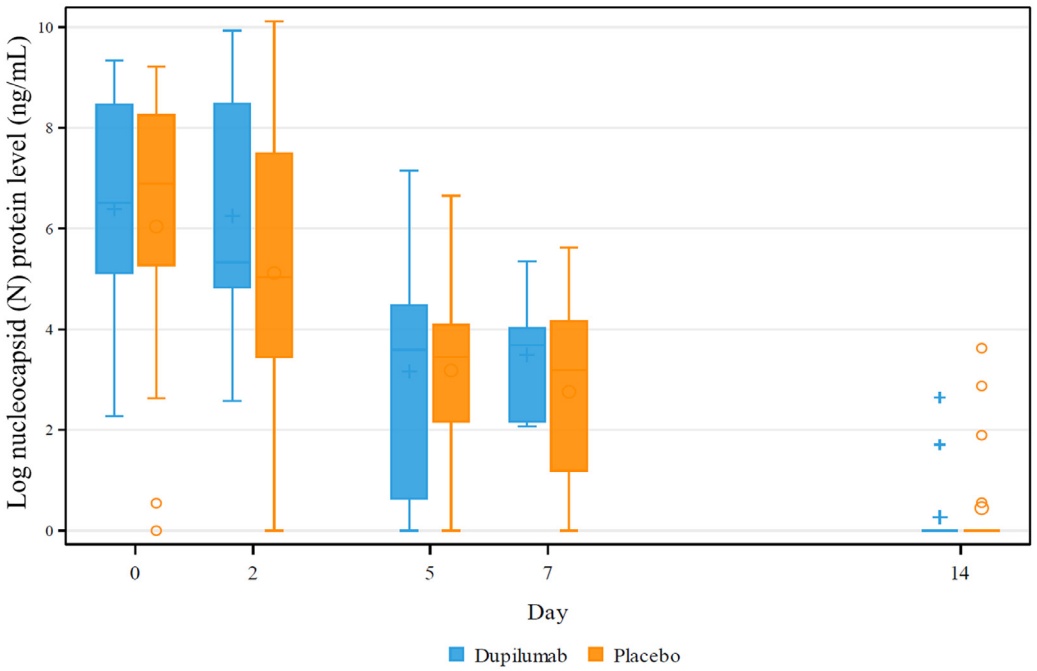

Figure 2. N-protein levels over time between those receiving dupilumab vs those receiving placebo.[9] Box plot depicting N-protein levels on days 0, 2, 5, 7, and 14 after enrollment in a randomized, double-blind, placebo-controlled trial which investigated the use of dupilumab, a monoclonal antibody that blocks IL-13 and IL-4 signaling, for those hospitalized with COVID-19. Patients received either dupilumab (blue boxes) or placebo (orange boxes) in addition to standard-of-care COVID-19 therapies on day 0. There was a similar rate of decline of N-protein levels over the 14 days after the study drug was received. Outliers are represented by orange open circles for the placebo group and blue crosses for the dupilumab group. COVID-19, coronavirus disease 2019; IL, interleukin; N, nucleocapsid.

between inherent immunophenotype (asthma subtype) and type 2 immune inhibitor influence as a cause for the different outcomes observed between the 2 groups.

Currently, there is no evidence of increased COVID-19 severity or mortality in patients receiving type 2 biologics for their allergic conditions. Hudes et al[42] found that among 128 patients with moderate-to-severe asthma in New York City, those receiving omalizumab (an anti-IgE monoclonal antibody), mepolizumab (an anti–IL-5 monoclonal antibody), or dupilumab had statistically similar rates of COVID-19 outcomes compared with patients with moderate-to-severe asthma not receiving these therapies. In a multicenter retrospective cohort study of 545 adult patients in Spain with severe asthma, those treated with biologics including omalizumab, mepolizumab, benralizumab (an anti–IL-5 receptor monoclonal antibody), reslizumab (an anti–IL-5 monoclonal antibody), and dupilumab did not have differences in COVID-19 severity, mortality, and ICU admissions compared with patients with asthma of different severity and those not on biologics, with no difference found in baseline comorbidities between all 3 groups.[43] Through multivariate analysis of 8242 adult patients with asthma in Israel who tested positive for COVID-19, biologic use was not associated with a significantly increased risk of moderate-to-severe COVID-19 or all-cause mortality within 90 days when adjusting for age, sex, ethnicity, diabetes, hypertension, ischemic heart disease, obesity, smoking, and steroid use.[40]

A phase IIa, randomized, double-blind, placebo-controlled trial was done to evaluate the safety and efficacy of dupilumab plus standard of care vs placebo plus standard of care in mitigating respiratory failure and death in those hospitalized with COVID-19.[9] Although the primary end point of 28-day ventilator free survival was not reached, subjects randomized to dupilumab had a higher 60-day survival rate: 89.5% of subjects in the dupilumab group were alive compared with 76.2% in the placebo group. There was also a trend toward reduction in ICU admission in the dupilumab group compared with the placebo group. Of note, 20% of the total patient population studied had preexisting asthma and/or other atopic conditions, which were evenly split between the treatment groups.[9]

Interleukin 13 and Type 2 Immune Impact on Severe Acute Respiratory Syndrome Coronavirus 2 Viral Load

Although in vitro studies have suggested a role for IL-13 in decreasing viral cell entry, in vivo studies have not revealed an impact on SARS-CoV-2 viral load during acute infection. SARS-CoV-2 enters the cells through angiotensin-converting enzyme 2 (ACE2) receptor engagement with Spike1 (S1) virion surface protein (S protein cleaved into S1 and S2 subunits after biosynthesis in infected cells) and subsequent exposure of S2 for cleavage by transmembrane protease serine 2 (TMPRSS2) allowing for fusion pore formation.[44] Using in vitro endobronchial-protected brushings obtained from patients with and without type 2 asthma, Kimura et al revealed that IL-13 significantly reduces ACE2 and increases TMPRSS2 expression in airway epithelial cells.[45] Jackson et al[46] further revealed IL-13 modification of ACE2 expression using nasal and bronchial epithelial samples of adults and children with atopy. Bonser et al[47] also revealed that cultured human bronchial epithelial cells stimulated with IL-13 reduced viral RNA recovered from SARS-CoV-2–infected cells and decreased markers of viral replication. These data together suggest a role for IL-13 in reducing SARS-CoV-2 viral cell entry and replication.

However, in vivo studies suggest that the IL-13 blockade has no impact on SARS-CoV-2 viral load. K18-hACE2 C57Bl/6J mice infected with SARS-CoV-2 and given either anti–IL-13 or IgG isotype control had no difference in viral burden in lungs tissue when measured on day 5 postinfection.[13] In addition, in the randomized controlled trial evaluating the use of dupilumab for treatment of those hospitalized with COVID-19, there was no difference in the rate of decline of measured nucleocapsid (N)-protein (a marker of viral load[48]) between those receiving dupilumab and those receiving placebo (Fig 2).

Furthermore, those subjects with a high initial N-protein had reduced 60-day mortality when receiving dupilumab compared with those with high initial N-protein who received placebo.[9] Although these data suggest minimal impact of IL-13 blockade on viral load, it is noted that IL4Rα blockade was given postinfection in these studies. This, along with the potential impact of IL-13 on ACE-2 receptor availability, suggests a potential influence of type 2 blockade on initial infection susceptibility.

Nevertheless, this has not been consistently found in retrospective studies evaluating COVID-19 infection risk in those on type 2 biologics. One study did find an increased risk for contracting COVID-19 in those receiving dupilumab using a global pharmacovigilance database for drug monitoring in more than 140 countries, where 127 drug reports concerned COVID-19.[35] However, a population-based cohort study evaluating 78,073 patients with atopic dermatitis on dupilumab found no increased risk for SARS-CoV-2 infection compared with those on systemic steroids, undergoing phototherapy and on other systemic immunosuppressive agents.[49] In addition, in a cohort of 80,602 patients with asthma from an Israeli health care system, there was no increased risk of COVID-19 infection found in those on type 2 inhibitor therapies.[40]

Conclusion

In vitro studies have revealed IL-13 induced suppression of the SARS-CoV-2 receptor, ACE2, suggesting its role in prohibiting viral entry with initial infection. This suggests a need for thoughtful consideration of the timing of IL-13 blockade in patients with COVID-19 with emphasis on delivery later in the disease process, which is inherent to its proposed use for treatment already. That said, in vivo studies reveal similar SARS-CoV-2 viral loads with IL-13 blockade compared with control groups. Furthermore, studies involving patients already on dupilumab or other type 2 biologics have not consistently found an increased risk of COVID-19 infection. All of these combined with the hypothesis that type 2 blockade may enhance viral clearance consequently through a diminished type 1 antiviral response[50] suggest that although IL-13 may be a component of the process that controls ACE-2 receptor availability, there are likely additional factors that contribute to COVID-19 susceptibility and ultimately SARS-CoV-2 viral load.

Studies investigating COVID-19–induced hyperinflammation reveal an association of high IL-13 levels and other type 2 immune biomarkers with poor outcomes. Large database retrospective studies and a randomized controlled trial investigating dupilumab use in acute COVID-19 have found improved outcomes, with no increased risk of disease severity with those on type 2 biologics in general. These findings suggest that the type 2 immune pathway may be a significant piece of the process that leads to ineffective viral clearance and immune-mediated pulmonary destruction in acute COVID-19 infection (Fig 1).

Data further suggest that IL-13 and type 2 immune mediators can remain persistently elevated for weeks after symptom onset, with mechanistic and biologic plausibility to support its impact on post–COVID-19 conditions. Larger randomized studies are needed to validate the use of dupilumab for treatment of acute immune-mediated COVID-19, with identification of subpopulations for which dupilumab's therapeutic effect will be optimized. As there are currently multiple hypotheses as to the pathogenesis of post–COVID-19 conditions and the relative contribution of immune-, viral-, or autoantibody-induced damage, there needs to be further investigation into the longevity and postrecovery impact of COVID-19–induced type 2 immunity.

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