Review article

Molecular mechanisms and epidemiology of COVID-19 from an allergist's perspective

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The global pandemic caused by the newly described severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused worldwide suffering and death of unimaginable magnitude from coronavirus disease 2019 (COVID-19). The virus is transmitted through aerosol droplets, and causes severe acute respiratory syndrome. SARS-CoV-2 uses the receptor-binding domain of its spike protein S1 to attach to the host angiotensin-converting enzyme 2 receptor in lung and airway cells. Binding requires the help of another host protein, transmembrane protease serine S1 member 2. Several factors likely contribute to the efficient transmission of SARS-CoV-2. The receptor-binding domain of SARS-CoV-2 has a 10- to 20-fold higher receptor-binding capacity compared with previous pandemic coronaviruses. In addition, because asymptomatic persons infected with SARS-CoV-2 have high viral loads in their nasal secretions, they can silently and efficiently spread the disease. PCR-based tests have emerged as the criterion standard for the diagnosis of infection. Caution must be exercised in interpreting antibody-based tests because they have not yet been validated, and may give a false sense of security of being "immune" to SARS-CoV-2. We discuss how the development of some symptoms in allergic rhinitis can serve as clues for new-onset COVID-19. There are mixed reports that asthma is a risk factor for severe COVID-19, possibly due to differences in asthma endotypes. The rapid spread of COVID-19 has focused the efforts of scientists on repurposing existing Food and Drug Administration–approved drugs that inhibit viral entry, endocytosis, genome assembly, translation, and replication. Numerous clinical trials have been launched to identify effective treatments for COVID-19. Initial data from a placebo-controlled study suggest faster time to recovery in patients on remdesivir; it is now being evaluated in additional controlled studies. As discussed in this review, till effective vaccines and treatments emerge, it is important to understand the scientific rationale of pandemic-mitigation strategies such as wearing facemasks and social distancing, and implement them. (J Allergy Clin Immunol 2020;■■■:■■■-■■■.)

Key words: *ACE2, asthma, allergic rhinitis, COVID-19, severe acute respiratory syndrome coronavirus 2, receptor-binding domain, TMPRSS2*

In December 2019, a distinct coronavirus (CoV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the cause of an outbreak of severe acute respiratory syndrome (SARS) associated with atypical pneumonia (coronavirus disease 2019 [COVID-19]).[1,2] The index cases had visited or worked in the Huanan Wholesale Seafood Market in Wuhan, China.[1,2] COVID-19 spread rapidly to mainland China. Outbreaks were subsequently reported in cruise ships such as Diamond Princess, where it infected 712 (19%) of the 3700 passengers and crew.[3] In January 2020, SARS-CoV-2 spread to Europe,[4] with most confirmed cases reported from Italy, Spain, Germany, France, and the United Kingdom. In the United States, the first case was detected in Washington on January 19, 2020,[5] and had a travel history to Wuhan. Genome sequences of SARS-CoV-2 were uploaded from around the globe into the Global Initiative on Sharing All Influenza Data.[6] Genome epidemiologists performed big data analysis of the Global Initiative on Sharing All Influenza Data, and suggested a pattern of spread of the virus from Wuhan to Europe, then the United States and the rest of the world.[7] They determined that COVID-19 spread coast to coast across the United States.[8] On March 11, 2020, the World Health Organization (WHO) declared COVID-19 as a global pandemic. As of June 26, there have been over 2,422,312 confirmed cases in the US and 9.635 million cases worldwide that have contributed to more than 124,415 deaths in the US and 489,922 deaths worldwide (Table I).[3,9-12] The WHO estimates that COVID-19 is fatal in about 3.4% of reported cases.[13] The number of people infected and its associated death toll make the COVID-19 pandemic one of the worst pandemics in recent history, and certainly worse than previous CoV pandemics—SARS and Middle East respiratory syndrome (MERS).[14,15]

Rarely in human history have hospitals, clinicians, epidemiologists, scientists, and pharmaceutical companies worked so rapidly toward a common goal like we are seeing today—to fight the COVID-19 pandemic. This vast scientific and clinical effort has generated a wealth of information at an unbelievable pace. We navigated through this scientific literature, and here we summarize the major developments in this rapidly changing field. We examine the scientific basis and big data aspects of the spread of SARS-CoV-2 and transmission-mitigation strategies such as social distancing and wearing facemasks. We discuss how the development of some symptoms in people suffering from allergic rhinitis can serve as a clue for new-onset COVID-19. We examine how patients with asthma can be at a higher risk for severe

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Abbreviations used

ACE2: Angiotensin-converting enzyme 2
ARDS: Acute respiratory distress syndrome
CDC: Centers for Disease Control and Prevention
CoV: Coronavirus
COVID-19: Coronavirus disease 2019
FDA: Food and Drug Administration
IDO: Indoleamine 2,3-dioxygenase
JAK: Janus kinase
MERS: Middle East respiratory syndrome
MERS-CoV: Middle East respiratory syndrome coronavirus
MMWR: Morbidity and Mortality Weekly Report
MX1: MX dynamin-like GTPase 1
NIH: National Institutes of Health
RBD: Receptor-binding domain
RSV: Respiratory syncytial virus
RV: Rhinovirus
SARS: Severe acute respiratory syndrome
SARS-CoV: Severe acute respiratory syndrome coronavirus
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
S protein: Spike glycoprotein
TMPRSS2: Transmembrane protease serine S1 member 2
WHO: World Health Organization

COVID-19. We review the molecular pathogenesis of COVID-19, and examine how this knowledge has been critical in providing the scientific rationale for identifying novel and Food and Drug Administration (FDA)-approved repurposed therapeutic targets.

DISTINGUISHING MILD COVID-19 SYMPTOMS FROM THOSE SEEN IN ALLERGIC DISEASES

The median incubation period for COVID-19 has been estimated to be 4 to 5 days,[16,17] and 98% of the subjects develop the symptoms within 12 days of infection.[17] The clinical presentation and current recommendations in the management of COVID-19 are described in considerable detail on the American College of Physicians[18] and National Institutes of Health (NIH)[19] Web sites. There are some differences in symptoms observed in SARS-CoV-2–infected individuals from those observed in seasonal allergies. SARS-CoV-2–infected individuals usually develop symptoms such as dry cough, sore throat, nasal congestion, shortness of breath, myalgia, fatigue, fever,[16,20-24] and rarely (about 1%) conjunctival congestion,[16] and most recover spontaneously. In contrast, seasonal allergies almost universally present with a seasonally reproducible constellation of allergic rhinitis symptoms consisting of runny itchy nose, itchy eyes, sneezing, postnasal drip, and conjunctival congestion.[25-29] From an allergist's perspective, a shift from these allergic rhinitis symptoms to those observed in COVID-19 with fever, cough, and shortness of breath (Table II)[16,22,29] may suggest the possibility of new-onset COVID-19 in allergic individuals. Taste or olfactory dysfunctions such as anosmia and dysgeusia can occur in about 35% to 90% of patients who reported olfactory and gustatory dysfunction,[30,31] which is similar to higher to that seen in allergic rhinitis (taste dysfunction 20%,[32,33] olfactory dysfunction 20%-40%[33,34]). Wheezing, a common feature of asthma exacerbation, rarely occurs in patients hospitalized with COVID-19.[35-39] However, both asthma and COVID-19 are often associated with cough and shortness of breath,[16,20-24,40] and testing for SARS-CoV-2 may be required to exclude the possibility of new-onset COVID-19 in individuals with asthma. The mechanisms underlying the lack of a strong association between asthma and COVID-19 are discussed in greater detail later in this article. Because about a fifth of hospitalized patients with COVID-19 develop cutaneous manifestations such as erythematous rash, urticaria, and chickenpox-like vesicles,[41] if a patient with recurrent urticaria has new-onset urticarial rash together with fever, cough, or shortness of breath, it may suggest new-onset COVID-19. SARS-CoV-2 infection can induce severe Kawasaki-like disease,[42,43] a multisystem vasculitis characterized by persistent fever, conjunctival injection, exanthema, lymphadenopathy, inflammation of the tongue and pharyngeal mucosa, and edema in peripheral extremities.[44] Because its diagnosis is established by the presence of 5 or 6 principal symptoms, Kawasaki disease is not difficult to distinguish from allergic conjunctivitis or skin eruption. Because Kawasaki disease is a risk factor for subsequent allergic diseases,[45,46] children who develop this disease during SARS-CoV-2 infection should be followed longitudinally for the development of allergic diseases.

TABLE I. Confirmed COVID-19 cases and death, and ICU bed availability by country

Country	Total confirmed cases	Total deaths	Total ICU beds per 100,000 capita
World	9,635,935	489,922	NA
United States	2,422,312	124,415	34.7
New York	389,085	24,766	NA
Spain	247,486	28,330	9.7
Italy	239,706	34,678	12.5
France	197,885	29,775	11.6
Germany	193,790	8,962	29.2
United Kingdom	309,456	43,314	6.6

ICU, Intensive care unit; *NA*, not available.
COVID-19 cases and death: data for New York from the New York State Department of Health[9,10]; for others, from Johns Hopkins University.[3]
ICU beds data for the United States are from Wallace et al[11] and for Europe are from Rhodes et al.[12]

TABLE II. Prevalence of clinical symptoms of COVID-19 and AR

Symptom, n (%)	COVID-19*	AR†
Shortness of breath	18.7	0
Fever	88.7	0
Cough	67.8	30
Headache	13.6	54
Conjunctival congestion	0.8	64
Sneezing	NA	64
Rhinorrhea	4‡	64
Nasal congestion	4.8	76

AR, Allergic rhinitis.
*Guan et al.[16]
†Schatz.[29] The 0s for shortness of breath and fever are not real numbers because these symptoms were not discussed in the article, likely because they are not common clinical features of AR.
‡Chen et al.[22]

CLINICAL FEATURES OF SEVERE COVID-19

One of the reasons COVID-19 has developed into such a feared pandemic is that a subset of SARS-CoV-2– infected persons develop severe life-threatening complications such as pulmonary edema, severe pneumonia, and acute respiratory distress

TABLE III. Prevalence of clinical symptoms of COVID-19 reported from China and the United States (New York)

	China*		New York†	
Symptom	Nonsevere	Severe	Noninvasive MV	Invasive MV
Sex: male (%)	58.2	57.8	55.5	70.8
Median age (y)	45	52	61.5	64.5
Cough (%)	67.3	70.5	77.6	83.1
Fever (%)	89.8	91.4	77.2	76.9
Shortness of breath (dyspnea) (%)	15.1	37.6	51.7	66.2
Myalgia, arthralgia, and/or fatigue (%)	14.5	17.3	28.9	23.8
Diarrhea (%)	3.5	5.8	25.1	20.8
Nausea and/or vomiting (%)	4.6	6.9	20.2	16.9

MV, Mechanical ventilation.
*Guan et al.[16]
†Goyal et al.[23]

syndrome (ARDS), heart failure and other organ failures, and septic shock.[15,20-22] A comparison of clinical features of PCR-confirmed patients with COVID-19 hospitalized in China versus those hospitalized in New York suggests that the patients in New York had 4- to 5-fold higher gastrointestinal symptoms such as nausea, vomiting, and diarrhea, and a higher incidence of shortness of breath (Table III).[16,23] These differences could reflect a more severe cohort of patients being included in the report from New York, or suggest racial or other differences.

Risk factors for severe or fatal COVID-19 include age above 60 years, presence of comorbid conditions such as diabetes mellitus, hypertension, chronic obstructive lung disease, asthma, coronary artery disease, cerebrovascular disease, chronic renal disease, history of cigarette smoking, obesity, high Sequential Organ Failure Assessment score, and d-dimer level more than 1 μg/mL.[16,20,37,47] The presence of shortness of breath as an early symptom is associated with more severe COVID-19.[16] Although myocardial injury from SARS-CoV-2 occurs rarely in about 5% of patients hospitalized for COVID-19, its presence has been identified as a risk factor for death.[48,49] The availability of intensive care unit beds to manage patients with severe COVID-19 can be a problem[50,51] because the number of available intensive care unit beds varies widely in the United States[11] or other countries[12] (Table I).

DIAGNOSTIC TESTS FOR DETECTING AND MONITORING COVID-19 AND IMMUNE RESPONSE

The criterion standard test for COVID-19 is a RT-PCR– based test.[52] Nasopharyngeal, oropharyngeal, middle turbinate, anterior nares specimens or swabs collected by health care professionals, and other Centers for Disease Control and Prevention (CDC)-recommended specimens are placed into a virus preservation solution,[53] lysed to extract SARS-CoV-2 genes N, E, S, and RNA-dependent RNA polymerase, and amplified by real-time RT-PCR.[54] COVID-19 point-of-care testing involves qualitative detection of nucleic acid from SARS-CoV-2 in nasopharyngeal swab and/or nasal wash/aspirate specimens. Some in-home testing kits for COVID-19 are now FDA-approved.[55] Virus isolation and culture is not recommended as a routine diagnostic procedure. Seroconversion occurs in 7 days in 50% and 14 days in all patients.[56] Even though many antibody-based tests have flooded the market, it is important to remember that they have not yet been validated, and "positive" test results may give a false sense of security of being "immune" to SARS-CoV-2.[57,58]

SCIENTIFIC BASIS OF USING SOCIAL DISTANCING, QUARANTINE, AND FACEMASKS TO REDUCE SPREAD OF SARS-CoV-2

SARS-CoV-2 infection is transmitted through aerosol and droplets during coughing.[59] Virus-laden small (<5 μm) aerosolized droplets can remain in the air and travel long distances (>1 m, and sometimes even 4 m),[60,61] thus providing a scientific rationale for the CDC guidelines of social distancing of 6 ft (about 2 m). These droplets can spread and deposit on surfaces, where the virus remains viable for a few days.[62] SARS-CoV-2 is more stable on plastic and stainless steel than on copper and cardboard, and viable virus can be detected up to 72 hours after application to the former surfaces.[63] SARS-CoV-2 remains viable in aerosols for 3 hours, which is similar to that for SARS-CoV.[63] The soles of shoes of medical staff can serve as carriers of SARS-CoV-2.[61] Shedding of SARS-CoV-2 is high even before the onset of symptom,[64] during the first week of symptoms, and continues till the end of symptoms.[56] In one study, fecal samples were positive for SARS-CoV-2 in 52% of hospitalized patients with gastrointestinal symptoms and 39% of the subjects without gastrointestinal symptoms.[65] However, the main mode of transmission appears to be through aerosol, droplets, and contact with surfaces that have deposits of the active virus.[56,63,66]

A big data study of infections in China estimated that 86% of all COVID-19 infections were undocumented.[67] Their modeling studies estimated that because of their greater numbers, undocumented infections were the source for about 80% of infections, and facilitated the rapid dissemination of SARS-CoV2.[67] However, because this report analyzed data from only the first few weeks of January, when local authorities were overwhelmed and underreporting cases, and did not include the data from the huge surge of cases in February, the 86% estimate should be treated with caution. During the previous SARS-CoV pandemic, the importance of social distancing, isolation of patients, contact tracing, and quarantine of exposed persons were identified as effective measures of mitigating the transmission of the virus.[68] These measures were also effective in mitigating the human-to-human transmission of COVID-19 in China.[69] Modeling studies suggest that the travel quarantine of Wuhan delayed the overall epidemic progression by 3 to 5 days in mainland China, but had a more marked effect at the international scale, where case importations were reduced by nearly 80% until mid-February.[70] Recent studies have similarly shown the utility of facemask in mitigating transmission of COVID-19.[71-73] However, some data suggest that surgical or cotton masks may not be enough to filter SARS-CoV-2.[74]

For these reasons, other CDC guidelines such as washing hands, not touching the face, and social distancing should also be followed to reduce the spread of this virus.

CoVs THAT HAVE CAUSED HUMAN DISEASES

CoVs are positive single-strand enveloped RNA viruses that belong to the family Coronoviridae. These viruses are characterized by club-like spikes that project from their surface, a large RNA genome, and a unique replication strategy. Before SARS-CoV-2 appeared, 6 human CoVs have been known to have contributed to human diseases: alpha CoVs HCoV-229E and HCoV-NL63, and beta CoVs HCoV-OC43, HCoV-HKU1, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV).[75] The seasonal CoVs HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1 usually cause mild upper respiratory tract illness.[76-78] However, pandemic CoVs SARS-CoV, SARS-CoV-2, and MERS-CoV behave differently, and have caused staggering illness and death. The lower respiratory tract symptoms such as severe acute respiratory illness, shortness of breath, and chest computed tomography findings of SARS-CoV2 infection are similar to symptoms of SARS-CoV and MERS-CoV infections.[21] Similar to SARS and MERS,[79,80] older age is a risk factor for adverse clinical outcomes in SARS-CoV-2. Although the 3.4% case-fatality rate of SARS-CoV2[13] appears to be lower than that reported for SARS (10%) or MERS (34%),[81] the number of people who tested positive for SARS-CoV-2 (about 9.64 million) is many times greater than the number of people who tested positive for SARS-CoV (about 8500) or MERS-CoV (about 2500).[82] Thus, the overall health effects of COVID-19 have greatly exceeded those observed in previous CoV pandemics.

GENOME SIMILARITIES, RESERVOIR, AND INTERMEDIATE MAMMALIAN HOST OF PANDEMIC CoVs

The genome size of SARS-CoV-2 (29.9 kb) is similar to the genome size of SARS-CoV (27.9 kb) and MERS-CoV (30.1 kb).[83-85] SARS-CoV-2 and SARS-CoV have about 80% genome sequence similarity.[1,86] The SARS-CoV-2 and bat SARS-CoV-like CoVs share approximately 96% sequence similarities.[86] Likewise, CoVs in Malayan pangolins (*Manis javanica*) have a high degree of similarity in all 6 residues of the receptor-binding domain (RBD) site of SARS-CoV-2.[87,88] Because scientific data suggest that civets and camels served as reservoirs for maintenance of SARS-CoV and MERS-CoV,[89] it has been proposed that bat CoV could have been transmitted to humans through pangolin reservoir to cause COVID-19.[88]

RECEPTORS AND LUNG CELLS THAT BIND SARS-CoV-2

Angiotensin-converting enzyme 2 (ACE2) is a well-defined receptor for SARS-CoV.[90] This receptor is expressed in most human respiratory cells,[91,92] explaining its propensity to replicate in these cells. Like SARS-CoV, SARS-CoV-2 binds to the respiratory mucosa through the same ACE2 receptor.[93] The spike glycoprotein (S protein) on SARS-CoV-2 plays a critical role in binding host ACE2 receptor and in membrane fusion.[94,95] Structural studies have elucidated the conformational aspects of the interaction of the RBD of S protein with ACE2 (Fig 1, *A*).[37,94-97] This binding induces conformational changes in amino acids that help create salt bridges, increase van der Waals interactions, and facilitate binding with ACE2 with much greater affinity than SARS-CoV.[98] The S protein contains subunit S1 with the RBD that binds ACE2, the membrane-fusion subunit S2, the transmembrane anchor, and the intracellular tail (Fig 1, *B*). Attachment of the RBD of S1 to host ACE2 receptor requires the help of the cellular transmembrane protease serine S1 member 2 (TMPRSS2)[99] to cleave S2 protein from S1, and help in membrane fusion[100,101] (Fig 1, *B*). Some unique features of the S1 protein of SARS-CoV-2[14,56] account for its 10- to 20-fold higher receptor-binding capacity compared with SARS-CoV and MERS-CoV.[99] Structural analysis also suggests that some variations of ACE2 can strengthen the interactions between the RBD of SARS-CoV-2 and ACE2.[98] A neutralizing antibody CR3022 that recognizes the conserved epitope RBD of SARS-CoV[102] also targets the RBD of SARS-CoV-2[103] only when 2 RBDs on the trimeric S protein are changed to the "up" position conformationally.[104] A careful study of this conformationally dependent interaction of this neutralizing antibody with RBD of SARS-CoV-2 may provide critical information required for developing additional high-potency neutralizing antibodies.

The cells in the lungs and airways that are likely to be infected by SARS-CoV-2 have been investigated by single-nuclei and single-cell RNAseq analysis of human lung tissues. ACE2 and TMPRSS2 are expressed in transient secretory cells in the segmental bronchial branches and cells derived from lung tissues.[105] Because SARS-CoV-2 has a furin-cleavage site in its S protein, a feature missing in SARS-CoV, it can use the serine endoprotease furin in host cells to streamline its internalization.[94,105] The binding of SARS-CoV-2 to ACE2 increases the expression of ACE2, which further damages the alveolar cells. After fusion with the host cell, the viral genome RNA is released into the cytoplasm. The uncoated RNA translates the replicase-transcriptase polyproteins pp1a and pp1ab encoded in open-reading frame 1a and 1ab located at the 5'-terminus of the genome, and the replication-transcription complex[106] replicates RNA for assembly and virus release.[107-109]

RESPIRATORY VIRUSES, CoVs, SARS-CoV-2, AND ASTHMA

Many respiratory viruses have been associated with asthma exacerbations, including respiratory syncytial virus (RSV), rhinoviruses (RVs), influenza virus, CoV, enterovirus, parainfluenza, adenovirus, bocavirus, and metapneumovirus.[77,110-116] Atopy and asthma are risk factors for lower respiratory tract infection, more severe virus-induced wheezing, and asthma exacerbation.[117-119] The contribution of RV or RSV to the initiation of asthma and asthma exacerbation has been investigated for many years. Positive family history of asthma, history of atopy, and wheezing are risk factors for RSV-induced lower respiratory tract infection,[118] and hospitalizations due to RV infection.[119] RSV-induced bronchiolitis is the most common cough, wheezing, and respiratory distress, and requires hospitalization in infants.[120] Many prospective long-term follow-up studies demonstrated that the history of wheezing illnesses caused by RV or RSV infections is a predictor of the subsequent development of asthma.[113,121-125] From these studies, 2 hypotheses have emerged; RSV- or

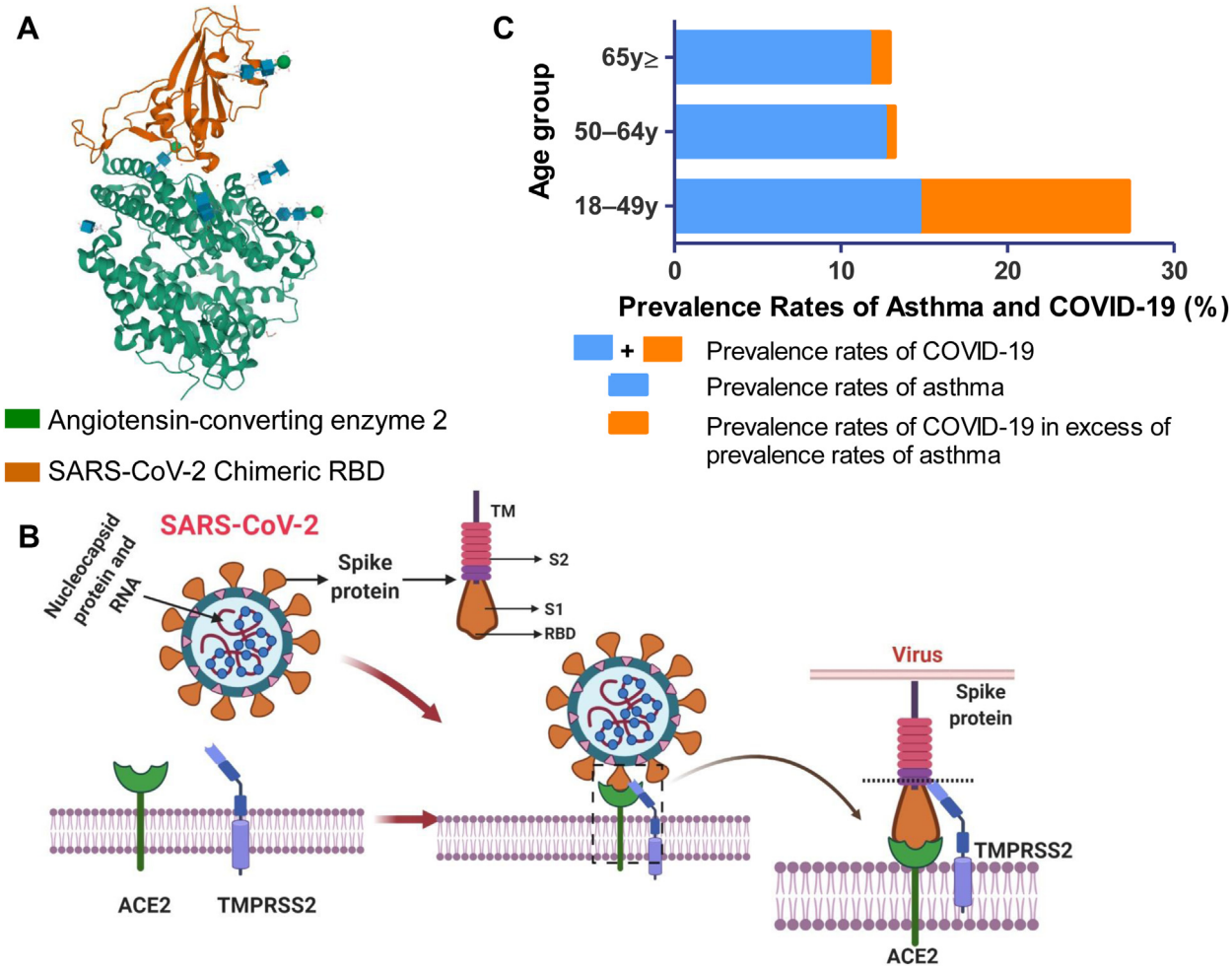

FIG 1. A, Structure of RBD of spike protein S1 of SARS-CoV-2 bound to ACE2. Structure of ACE2 bound to the RBD of the S1 spike protein of SARS-CoV-2.[94-96] The chimeric RBD is in orange, and human ACE2 is in green. The figure was created with Research Collaboratory for Structural Bioinformatics Protein Data Bank (https://www.rcsb.org/). *RBD*, RBD of S1 spike protein of SARS-CoV-2. **B,** Cartoon showing how SARS-CoV-2 binds to the lung epithelial cells. SARS-CoV-2 has a spike protein with transmembrane (TM), S1 and S2 part. S1 part has an RBD. The virion uses the spike protein S1 to attach with RBD of the host ACE2 receptor on the cell membrane with the help of the cellular TMPRSS2. Following attachment of S1 to ACE2, the host serine protease TMPRSS2 cleaves the S2 protein from S1, and plays a role in membrane fusion of CoVs. The figure was created using BioRender (https://biorender.com/). **C,** The prevalence of asthma in patients hospitalized for COVID-19 in United States. Data were extracted from April 8, 2020, MMWR report[37] and Centers for Disease Control and Prevention.[97] The total length of each bar represents the prevalence rates of COVID-19 in each age group. The length of the blue part of this bar is the expected prevalence rate of asthma in each age group. The orange part represents the prevalence rate of COVID-19 in excess of the expected prevalence rate of asthma in each age group.

RV-induced wheezing initiates the development of asthma, or, these viruses trigger wheezing and exacerbation of asthma. The validity of these 2 schools of thought has been debated for decades.

Like other respiratory viruses that infect the airway epithelial cells and pneumocytes through their receptors and induce asthma exacerbations,[110,111,126-131] seasonal human CoVs HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1 can also cause common cold and induce asthma exacerbations.[110,131-133] Inoculation of SARS-CoV-2 or MERS-CoV pandemic CoVs into cynomolgus macaques infects airway cells with subtle differences.[134] SARS-CoV-2 infects type I and II pneumocytes in ciliated airway mucosal epithelial cells and damages alveolar cells, whereas MERS-CoV infects predominantly type II pneumocytes, and causes less lung damage.[134] Investigators have proposed a hypothesis to explain the mechanism by which respiratory viruses trigger asthma exacerbations—patients with asthma have an attenuated IFN-I and IFN-III response to these infections, and the resultant unopposed T_H2 responses contribute to asthma exacerbation.[135-137] Because infection of lung and airway cells with SARS-CoV-2 induces an attenuated IFN-I and INF-III signature[138,139] similar to that observed in patients with asthma, COVID-19 would be expected to frequently trigger asthma exacerbations. Furthermore, the high levels of proinflammatory cytokines and their receptors such as CXCL1, CXCL2, CXCL8, CXCL17, CCL2, CCL3, CCL4, CCR1, CXCR2, IL5RA, IL-6,

IL-1β, and IL-1R2 observed in the bronchoalveolar lavage and lungs of patients with COVID-19[138,139] also suggests that SARS-CoV-2 infection should frequently induce asthma exacerbations. Yet, quite surprisingly, in the April 8, 2020, Morbidity and Mortality Weekly Report (MMWR)[37] report of 1482 patients hospitalized for COVID-19 in the United States in March 2020, it was mentioned that wheezing was present in only about 7% of the 178 patients in whom data were available on underlying conditions, which is less than the prevalence rate of about 10% of asthma in the general population.[140] These reports suggest that SARS-CoV-2 rarely induces asthma exacerbations during hospitalization for COVID-19.[37,140]

Could host immune-response factors contribute to the reduced ability of SARS-CoV-2–infected airway and lung cells from inducing asthma exacerbations? SARS-CoV-2 entry–associated genes ACE2 and TMPRSS2 are highly expressed in human nasal and lower airway epithelial cells, and cells that express these genes often coexpress innate immune genes such as indoleamine 2,3-dioxygenase (IDO) 1 and MX dynamin-like GTPase 1 (MX1).[141] IDO is a rate-limiting enzyme in tryptophan catabolism that increases the synthesis of tryptophan metabolites such as kynurenine, 3-hydroxykynurenine, and xanthurenic acid that induce immune tolerance and suppress experimental allergic inflammation.[142,143] Thus, increased expression of IDO in ACE2 and TMPRSS2-expressing cells could reduce asthma exacerbations in COVID-19. MX1 is an IFN-inducible GTPase with antiviral activities against a broad range of RNA viruses.[144] The data from the Childhood Origins of Asthma study and Copenhagen Prospective Study on Asthma in Childhood suggest that polymorphisms of the MX1 gene are associated with asthma exacerbations.[145] Thus, similar to IDO, increased expression of MX1 in ACE2 and TMPRSS2-expressing cells could reduce asthma exacerbations in COVID-19. IL-33, an alarmin that normally resides dormant exclusively in the nucleus, becomes a proallergic cytokine when it is secreted extracellularly and induces allergic inflammation and contributes to asthma exacerbation.[146-148] Infection with respiratory viruses that trigger asthma exacerbation, such as influenza and rhinovirus, induce IL-33 secretion from bronchial epithelial cells and alveolar cells in the airways.[146,148,149] Yet, our search of databases such as PubMed and Google Scholar did not find peer-reviewed publications that show that SARS-CoV-2 induces IL-33 secretion in the airways. Taken together, the unique host immune response to SARS-CoV-2 could explain why it does not frequently trigger asthma exacerbations.

If SARS-CoV-2 does not induce asthma exacerbations, can asthma be a risk factor for severe COVID-19 infection as suggested on the CDC Web site[150]? The comorbid diseases data in the April 8, 2020, MMWR report show that in 18- to 49-year-old patients hospitalized for COVID-19, 27% had a history of asthma.[37] The COVID-19 task force of the American Academy of Allergy, Asthma & Immunology suggests that given the 10% prevalence of asthma in the United States, the higher 27% of patients with COVID-19 who were hospitalized in this age group suggests that they may be at increased risk of hospitalization due to COVID-19 (Fig 1, *C*).[37,151] The same MMWR report suggests that African Americans have a disproportionally higher hospitalization for COVID-19, accounting for 33% of the US hospitalizations,[37] just as they have a higher propensity for severe asthma.[152-154] In contrast to these MMWR data, a retrospective analysis of 140 hospitalized patients with COVID-19 in China with confirmed results of SARS-CoV-2 viral infection reported that none of them had asthma.[35] Another study performed in China involving 548 patients with COVID-19 revealed that 0.9% of patients with COVID-19 had asthma, which is lower than the prevalence rate of asthma in the general population in China.[36] The discrepancy between the US MMWR report and these studies from China could reflect racial differences in the role of asthma in the severity of COVID-19.[35,37,151] However, in a very large study of 5700 patients in New York City hospitalized for COVID-19, only 9% of the patients had underlying asthma,[155] similar to the prevalence rates of asthma in the general population. That presence of asthma does not contribute to the severity of COVID-19 is also evident from another study performed in New York City that showed no increase in asthma in invasive compared with noninvasive mechanically ventilated patients with COVID-19.[23]

What could be the explanation for the paucity of patients with asthma in patients with COVID-19 in studies performed in China?[35,36] Because the expression of airway levels of ACE2 is lower in atopic subjects compared with nonatopic subjects,[156] T_H2-high endotype of asthma may be at a lower risk for severe COVID-19 because their airways would have fewer receptors for entry of SARS-CoV-2. Likewise, because exposure of the airways of allergic patients with asthma to environmental allergens reduces ACE2 expression levels,[156] seasonal exposure to aeroallergens may protect them from COVID-19. As discussed later, ciclesonide and formoterol are commonly used inhalers in asthma, and their antiviral properties could protect patients with asthma from COVID-19.

On the basis of MMWR data,[37] if one assumes that asthma is a risk factor for severe COVID-19 particularly in the 18- to 49-year age group (Fig 1, *C*), what could be the mechanisms of this increased propensity toward severity of COVID-19? Because obesity is a known risk factor for severe COVID-19,[37] obesity-related endotype of asthma[157,158] could be a higher risk for severe COVID-19. The expression of ACE2 and TMPRSS2 in sputum cells is higher in males, in African Americans, and in patients with asthma with a history of diabetes, all risk factors for severe COVID-19.[159] Persons with ACE D/D genotypes have higher immunoreactive ACE concentration in serum and a higher risk of asthma than those with other genotypes.[160-162] Because SARS-CoV-2 uses ACE2 to infect cells, future studies should evaluate whether the ACE D/D genotype is a risk factor for COVID-19. TMPRSS2 is expressed in human airway epithelium[163] and thought to contribute to the severity of SARS-CoV and MERS-CoV lung infection.[164] Because subjects with atopic asthma have higher nasal levels of TMPRSS2 compared with healthy volunteers,[165] these increased levels could be a risk factor for the severity of COVID-19 in asthma. Treatment of mice with ACE2 activator or angiotensin (1-7) reduces airway inflammation in experimental asthma.[166,167] In addition, loss of ACE2 in the animal model study has been shown to aggravate severe acute lung injury, and the administration of recombinant human ACE2 alleviates lung injury.[168] Taken together, these studies suggest that signaling through ACE2 provides protection against both allergic airway inflammation and acute lung injury. Because attachment of S1 part of the S protein to ACE2 can stimulate splicing of ACE2 by TMPRSS2,[169] it is possible that this spliced ACE2 is less effective in providing protection against acute lung injury

and asthma. Future studies will have to determine whether the administration of human recombinant ACE2 could be a treatment option for COVID-19 in patients with asthma.

SCIENTIFIC STRATEGIES BEHIND MAJOR CLINICAL TRIALS FOR COVID-19

Many clinical trials such as seen in NIH ClinicalTrials.gov[170] or EU Clinical Trials Register[171] are being performed worldwide for COVID-19 (Table IV),[172-176] but as of today there are no proven effective treatments. On March 20, 2020, WHO announced the launch of SOLIDARITY,[177] an unprecedented, coordinated push to collect robust scientific data rapidly during a pandemic.[178] Properly designed large clinical trials are required for assessing drugs in each category of the following mechanistic categories (Fig 2), and are being performed.

Inhibiting viral entry: Decoy receptor, mAbs, convalescent plasma, camostat

Some data suggest that this strategy may be effective in COVID-19 (Fig 2, *A*). Acting as a decoy, human recombinant soluble ACE2 treatments dramatically inhibited the growth of SARS-CoV-2–infected Vero cells by more than 1000-fold,[179] and suppressed SARS-CoV-2 infection with engineered human blood vessel and kidney organoids.[179] These results suggest that human recombinant soluble ACE2 could block early stages of SARS-CoV-2 infections, and is a potential drug for use in COVID-19. In another study, transfusion of convalescent plasma containing neutralizing antibodies collected from the donors who had recovered from SARS-CoV-2 infection to 5 patients with COVID-19 and ARDS receiving mechanical ventilation improved their clinical status.[180] Likewise, the administration of convalescent plasma had a beneficial effect on 10 patients with severe COVID-19.[181] Human neutralizing mAbs from convalescent patients with COVID-19, B38 and H4, inhibit the binding of SARS-CoV-2 S protein RBD to ACE2[182] (Fig 2, *A*). These antibodies reduced virus titers in the lungs and ameliorated the lung inflammation in an animal model developed to test the efficacy of drugs—human ACE transgenic mice infected with SARS-CoV-2.[182] Treatment with serine protease inhibitor camostat inhibited entry of SARS-S and SARS-2-S protein into primary human lung cells.[100] Likewise, nafamostat inhibits membrane fusion of S protein of MERS-CoV[183] and SARS-2-S.[184] Well-designed clinical trials are required to assess the role of human recombinant soluble ACE2, mAbs, convalescent sera, and camostat in COVID-19.

Inhibiting endocytosis and initial assembly of the virus genome

Chloroquine and hydroxychloroquine may inhibit SARS-CoV-2 by inhibiting pH-dependent viral fusion/replication and prevention of viral envelope glycoprotein as well as host receptor protein glycosylation, and virion assembly in endoplasmic reticulum-Golgi intermediate compartment–like structures[185] (Fig 2, *B*). In addition to its suppressive effects on viral replication, hydroxychloroquine inhibits Toll-like receptor 7/9–dependent inflammatory responses.[186] In a small study, azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination than hydroxychloroquine alone or either drug given orally.[175] The low cost and vast availability of chloroquine and hydroxychloroquine is one of the reasons it is being evaluated as part of SOLIDARITY trials. However, a parallel, double-masked, randomized clinical trial in hospitalized patients with COVID-19 revealed that the mortality rate until day 13 was higher in the high-dosage chloroquine diphosphate group than in the low-dosage group.[187] The high-dosage group of chloroquine showed more often increased QTc interval than the low-dosage group.[187] Likewise, another report suggests that neither hydroxychloroquine alone nor in combination with azithromycin had beneficial clinical effects in hospitalized patients with COVID-19.[188,189] Furthermore, the administration of hydroxychloroquine may contribute to increased mortality[180] and prolongation of QTc interval in electrocardiogram.[19] These studies suggest that chloroquine and hydroxychloroquine may not have significant efficacy in COVID-19, and their excessive use may contribute to electrocardiogram changes and even death.

Inhibiting translation of the viral genome and replication of virus

Lopinavir-ritonavir is a boosted protease inhibitor used for treating HIV type 1 infection that had favorable effects on SARS[190] and MERS[191] in small studies. However, a randomized trial of lopinavir-ritonavir treatment demonstrated no beneficial effect in hospitalized adult patients with severe COVID-19.[184] Remdesivir is an adenosine analog that incorporates into nascent viral RNA chains, and causes its early termination[192] (Fig 2, *B*). In a case report, treatment with intravenous remdesivir was initiated on the evening of day 7 in a patient hospitalized for severe COVID-19, and on hospital day 8, the patient's clinical condition improved.[5] The administration of remdesivir on a compassionate-use basis to patients hospitalized with COVID-19 showed a beneficial effect in about 70% of patients.[193] The preliminary results from the Adaptive COVID-19 Treatment Trial indicate that patients who received remdesivir had a 31% faster time (11 days) to recovery than those who received placebo (15 days; $P < .001$).[194] However, a randomized, double-blind, placebo-controlled, multicenter trial from China demonstrated that remedesivir has no beneficial impact on hospitalized patients with COVID-19 compared with the placebo group.[195] A study comparing the effect of favipiravir and umifenovir in the patients with moderate COVID-19 showed statistical superiority of favipiravir over umifenovir.[173]

INHIBITION OF THE CYTOKINE STORM

SARS-CoV-2 triggers a cytokine storm with secretion of IL-6 and other proinflammatory cytokines that has been suggested as one of the mechanisms for organ damage and ARDS.[21,196,197] A meta-analysis of 6 studies suggested that the mean IL-6 concentrations were about 3-fold higher in patients with complicated COVID-19 compared with uncomplicated disease.[198] IL-6 binds to the IL-6 receptor on the cell surface and Janus kinase (JAK) is phosphorylated and the subsequent inflammatory cascade initiates.[199] Inhibitor for IL-6 signaling and JAK1/2 are being evaluated to suppress the cytokine storm in COVID-19.[197] Compared with patients with COVID-19 without ARDS, patients with COVID-19 with ARDS had increased level of IL-6 in serum,

TABLE IV. Clinical trials completed or are being performed worldwide for COVID-19 (listed in clinicaltrials.gov)

Intervention	Category	Suggested mechanism of action	Design of trial	Status	Key outcome	Reference or ID
Lopinavir-ritonavir	Anti-HIV drug	Inhibition of protease	Open-label, randomized, and controlled trial	Completed	No benefit on the hospitalized adult patients with severe COVID-19	172
Favipiravir vs umifenovir	Anti-influenza virus drug	Inhibition of viral RNA polymerase	Open-label randomized	Completed	Preferred clinical outcome in the favipiravir group than in the umifenovir group	173
Chloroquine	Immunosuppressive drug and antiparasite drug	Inhibition of virus entry	Clinical study	NA	Beneficial effect, but details have not been published	174
Hydroxychloroquine-azithromycin	Antimalarial drug, antibiotics	Inhibition of virus entry	Open-label nonrandomized	Completed	Combination drug reduced viral load in nasopharyngeal swabs	175
Hydroxychloroquine vs azithromycin	Antimalarial drug, antibiotics	Inhibition of virus entry	Open-label randomized	Recruiting Phase 2	NA	clinicaltrials.gov (NCT04329832)
Lopinavir/ritonavir, ribavirin and IFN-β combination	Antivirus drug	Prodrug metabolized into nucleoside analogs that blocks and caps viral RNA	Open-label randomized	Completed	Preferred clinical outcome in the triple antiviral therapy group than in the lopinavir-ritonavir group	176
IFN-A2B	Antivirus drug	Activate multiple immunomodulatory and antiviral proteins	Open-label randomized, blank-controlled	Not yet recruiting Early phase 1	NA	clinicaltrials.gov (NCT04293887)
Remdesivir	Antiebola drug	Inhibition of viral RNA polymerase	Open-label, randomized	Recruiting Phase 3	NA	clinicaltrials.gov (NCT04292899)
Tocilizumab	Anti–IL-6 receptor antibody	Anti-inflammation	Open-label, single-group assignment	Recruiting Phase 2	NA	clinicaltrials.gov (NCT04317092)
Ciclesonide vs ciclesonide plus hydroxychloroquine, vs no intervention	Inhaled corticosteroids	Anti-inflammation	Open-label randomized	Not yet recruiting Phase 2	NA	clinicaltrials.gov (NCT04330586)
Camostat mesilate	Antiproteinuric drug	Serine protease inhibitors	Randomized placebo-controlled	Recruiting Phases 1 and 2	NA	clinicaltrials.gov (NCT04321096)
Recombinant human ACE2	Monocarboxypeptidase that leads to degradation of angiotensin II	Antihypertensive	Double-blind randomized	Not yet recruiting Phase 2	NA	clinicaltrials.gov (NCT04335136)

NA, Not applicable/available.

and the serum levels of IL-6 in patients with COVID-19 with ARDS who died were higher compared with levels in patients with COVID-19 with ARDS who survived.[47] Thus, suppression of the IL-6 signaling pathway could be a therapeutic strategy against COVID-19. The FDA-approved drug tocilizumab is prescribed by rheumatologists, and has been administered to patients with COVID-19. A systematic review and meta-analysis of IL-6 and COVID-19 revealed that serum level of IL-6 was elevated among patients with COVID-19 with adverse clinical outcomes, and the administration of humanized monoclonal anti–IL-6 receptor antibody tocilizumab to these patients was efficacious and safe.[198] Baricitinib is an oral JAK1/JAK2 inhibitor that binds to AP2-associated protein kinase 1,[200] and has been used for the treatment of rheumatoid arthritis. Because AP2-associated protein kinase 1 is a regulator of endocytosis,[201] baricitinib may inhibit SARS-CoV-2 replication and suppress IFN-controlled gene expression.[202] A recent small study suggested that baricitinib therapy combined with lopinavir-ritonavir in moderate COVID-19 pneumonia is clinically more effective than the control treatment (lopinavir-ritonavir plus hydroxychloroquine) (intensive care unit transfer 0% vs 33%, discharge at week 2 8% vs 58%, respectively).[203] Additional well-designed large-scale clinical trials are being performed to assess the role of tocilizumab and baricitinib in COVID-19.

INHALED CICLESONIDE STEROID AND LONG-ACTING β-ADRENERGIC RECEPTOR FORMOTEROL

Ciclesonide is prescribed by allergists as an intranasal or inhaled corticosteroid for treating allergic rhinitis and asthma, but recent studies suggest that it has antiviral properties (Fig 2, *B*). In one study, 48 FDA-approved drugs were screened for their antiviral properties against SARS-CoV2 using Vero cells.[204] From this screening, ciclesonide was identified as one of the very few drugs that had significant antiviral properties against SARS-CoV-2, but had no toxicity.[204] Likewise, in another study that

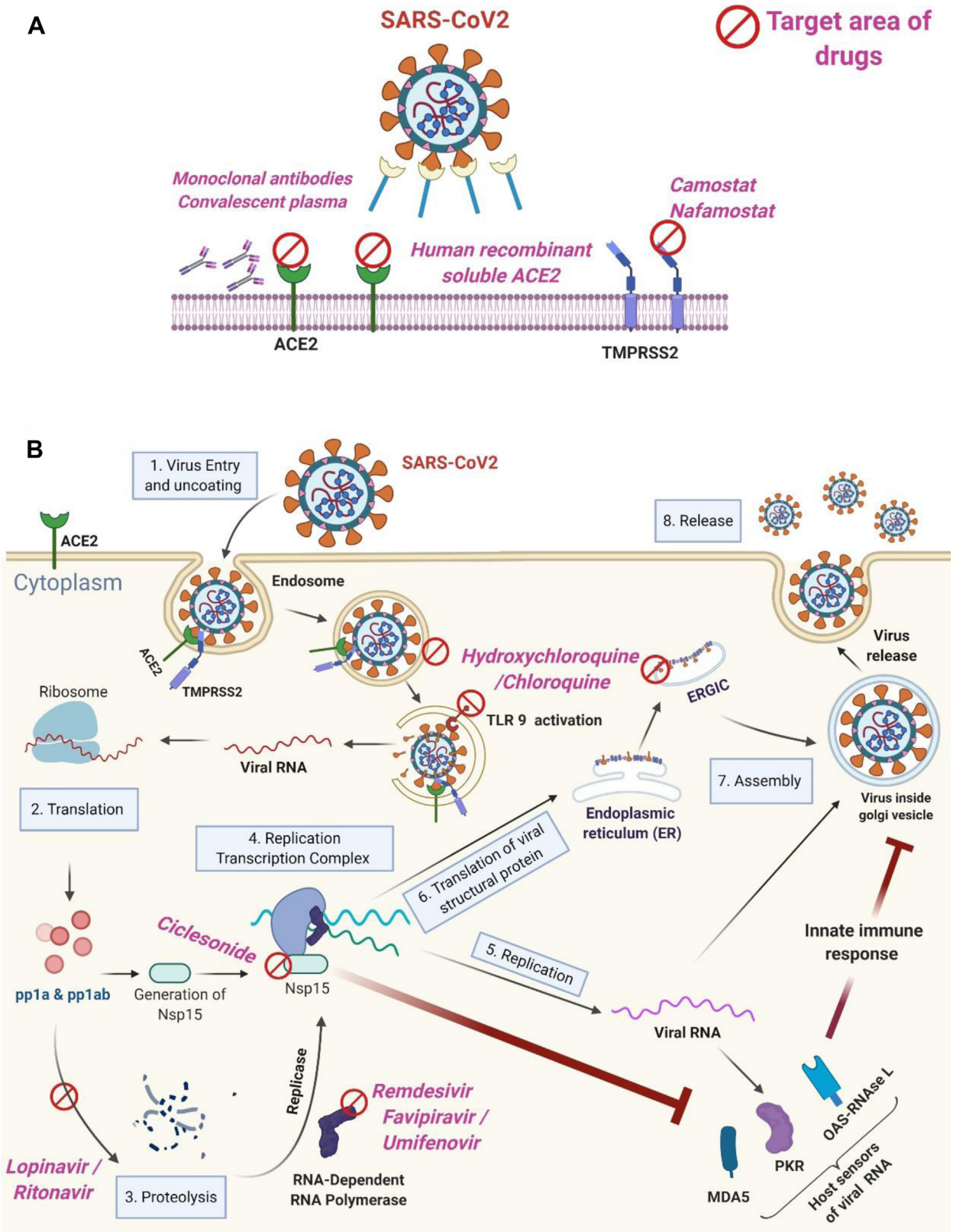

FIG 2. Treatment strategies for COVID-19. **A,** Drugs that are designed to block entry of SARS-CoV into the cells. **B,** Drugs that act at different steps of virus replication inside the cell. The figure shows 8 steps from viral entry to virus release in airway epithelial cells. After fusion to the host cell, the viral genome RNA is released into the cytoplasm. The uncoated RNA translates pp1a and pp1ab polyproteins, and the replication-transcription complex replicates RNA for assembly and virus release. The figure was created using BioRender (https://biorender.com/). *ERGIC*, Reticulum-Golgi intermediate compartment; *MDA5*, melanoma differentiation-associated protein 5; *NSP*, nonstructural protein; *OAS*, 2′-5′ oligoadenylate synthetase; *PKR*, protein kinase R; *pp1a*, polyprotein1a; *pp1ab*, polyprotein1ab; *TLR9*, Toll-like receptor 9.

involved screening of FDA-approved drugs for their antiviral properties, ciclesonide demonstrated antiviral effects against MERS-CoV.[205] Nonstructural protein 15 produced by CoVs impair the ability of retinoic acid–inducible gene–I–like receptors such as retinoic acid–inducible gene–I and melanoma differentiation–associated protein (MDA-5) to detect viral RNA in the cytosol, thereby facilitating replication of the virus in host macrophages.[206] Ciclesonide targets nonstructural protein 15 (Fig 2, *B*), thereby facilitating retinoic acid–inducible gene–I and MDA-5–mediated inhibition of MERS-CoV and SARS-CoV-2 replication.[206,207] Lung imaging studies have shown that the small particle size of ciclesonide (1 μm) facilitates widespread lung deposition, including small airways.[208,209] Thus, inhaled ciclesonide should be able to penetrate deep into the lungs and suppress SARS-CoV-2 infection. Indeed, inhaled ciclesonide clinically improved 3 patients with pneumonia caused by SARS-CoV-2 who required oxygen support.[210] Likewise, formoterol, a long-acting selective β-adrenergic receptor agonist that is often prescribed by allergists as a combination drug for treatment of patients with persistent asthma, can suppress replication of HCoV-229E.[211] Thus, well-designed large-scale clinical trials are required to assess the role of intranasal/nebulized ciclesonide and inhaled beta-adrenergic receptor agonists in treatment or prevention of COVID-19.

STRUCTURE-ASSISTED DRUG SCREENING FOR COMPOUNDS THAT INHIBIT SARS-CoV-2 MAIN PROTEASE ACTIVITY

The SARS-CoV-2 main protease mediates viral replication and transcription.[212] A study using structure-assisted drug design, virtual drug screening, and high-throughput screening identified 6 compounds, disulfiram, carmofur, ebselen, shikonin, tideglusib, and PX-12, that inhibited main protease activity.[212] Additional studies will be required to assess the clinical efficacy of these compounds in COVID-19.

VACCINES TO PREVENT COVID-19

The NIH launched a clinical trial of investigational vaccine for NIH-funded candidate mRNA vaccines for COVID-19 on March 16, 2020.[213,214] Several clinical trials are in progress, and the WHO announced and updated a DRAFT landscape of COVID-19 candidate vaccines.[215] As of today, there is no clinically available vaccine against SARS-CoV-2.

Conclusions

COVID-19 has become a feared pandemic because it has infected more than 200-fold greater number of people in the population than SARS-CoV or MERS-CoV pandemic, has spread at an unbelievable pace, and caused severe life-threatening complications in a significant subset of these infected persons. Here, we reviewed the molecular pathogenesis of COVID-19, and examined how this knowledge has been critical in providing the scientific rationale for identifying novel and FDA-approved repurposed therapeutic targets. From an allergists' perspective, we discussed how the development of some symptoms in allergic rhinitis may serve as a clue for new-onset COVID-19 in subjects with allergy, and examined how asthma could be a risk factor for severe COVID-19. Till effective vaccines or treatments emerge, it is important to understand the scientific rationale discussed in this article that underlie pandemic-mitigation strategies such as wearing facemasks and social distancing. The knowledge gained from this review will give the readers a broad-based knowledge required to understand and correctly interpret current and future publications and developments in this rapidly changing field of COVID-19 pandemic.

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