The virus SARS-CoV-2, first isolated in Wuhan, China and the pathogen responsible for COVID-19, is spreading rapidly across the world. Ever more urgent questions are being asked about vaccines to prevent coronavirus infection and virustatics for effective treatment. Over 80 clinical trials have already been initiated in patients with COVID-19 to resolve the numerous issues around the disease.

Coronaviruses have long been recognized as a cause of respiratory tract infections in humans. The coronavirus genome comprises the longest known plus-strand RNA, around 30,000 bases in length. Its high genetic variability means that new variants are constantly emerging. This family of pathogens first became a focus of public attention when, from 2002 onwards, the zoonosis known as severe acute respiratory syndrome (SARS) spread outwards from China. Ten years later, Middle East respiratory syndrome (MERS) hit the headlines. MERS was first diagnosed in Saudi Arabia in 2012 and was fatal in around one in three patients.

The World Health Organization (WHO) has dubbed the new virus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), and the disease is called COVID-19 (coronavirus disease 2019). Comparisons with other members of the coronavirus family show that the highest correspondence is with a virus from bats; however, direct transmission from bats to humans is considered improbable. A number of factors indicate the existence of an as yet unidentified intermediate host (1–3).

ACE2—a receptor for SARS-CoV-2 and potential target structure for therapeutics

Viruses cannot replicate outside cells. They therefore need access to the cells of a host organism before they can spread. Transmission of a zoonosis to humans implies the existence of a (new) route by which it infiltrates human cells. The SARS virus uses angiotensin-converting enzyme 2 (ACE2), keeping the virus from docking to this receptor is a conceivable treatment approach. Transmembrane protease serine 2 (TMPRSS2) plays a role in the fusion of the virus with cells; inhibitors of this enzyme are known as well. The potential therapeutic efficacy and tolerability of these and other active substances remain to be investigated in clinical trials. At present, more than 80 trials on COVID-19 have already been registered with ClinicalTrials.gov. Some initial findings should already be available in late April 2020.

Conclusion: Clinical trials are now indispensable in order to determine the true clinical benefits and risks of the substances that have been found to be active against SARS-CoV-2 in vitro. There is not yet any recommendation for the therapeutic use of any particular agent beyond standard supportive treatment.

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an anti-inflammatory and vasodilatory action via the MAS receptor.

Genome analysis of the new viruses has shown that—despite a number of mutations—there are structural analogies between the binding sites of the SARS virus and SARS-CoV-2. For the new viruses too, ACE2 serves as receptor and thus as entry point to the human body (3, 4). A crucial part is also played by a serine protease in the host cells: this enzyme, known as transmembrane protease serine 2 (TMPRSS2), enables fusion with the host cell and is thus an important factor in the dissemination of influenza viruses and coronaviruses in the cells of the human body.

Potential candidates for the prevention and treatment of coronavirus infection are therefore peptides or small-molecular substances that block the membrane-associated enzyme ACE2, or alternatively inhibitors of TMPRSS2 (Figure). Camostat, an inhibitor of this protease, is licensed in Japan for treatment of chronic pancreatitis (4), but no clinical trials of camostat in coronavirus infection have yet been conducted. Among the clinical trials initiated to date, one project is investigating the administration of recombinant ACE2 enzyme to treat the infection (Table 1). Soluble ACE2 might slow the spread by competitive binding to the virus. On the other hand, ACE2 antibodies might be a suitable means of blocking the virus’s access to the patient’s cells (5).

According to preliminary reports, the antimalarial drug chloroquine prevents the terminal glycosylation of ACE2. Moreover, chloroquine—or its derivative hydroxychloroquine—increases the pH in the endosomes involved in the uptake of the virus into the cells. In cell cultures, the replication of SARS-CoV-2 was inhibited at a chloroquine concentration (EC50 = concentration with half-maximal effect) of 1.13 μM (6). Several clinical trials are investigating the efficacy and tolerability of chloroquine in the prevention and treatment of COVID-19 (Table 1).

Vaccination strategies

Although vaccination strategies were developed in the context of previous epidemics, such as SARS and MERS, no vaccine for coronavirus infections is yet available. Potential vaccines are directed against the viral proteins. The spike (S) protein is of particular interest as a possible antigen for vaccination, because of its crucial role in viral dissemination. Different types of vaccines can be distinguished: For instance, they can contain inactivated viruses, which induce neutralizing antibodies. A plausible alternative is administration of RNA- or DNA-based vaccines, with nucleic acids coding for the S protein. In these cases, the human organism produces the protein by which an immune response is induced. Subunit vaccines contain the S protein or another viral protein, without carrier virus. However, the immunogenicity is relatively low, so an adjuvant is needed. Vector-based vaccines comprise a protein, e.g., the S protein, that is coupled to non-replicating carrier virus particles. This concept was pursued in the development of a vaccine for MERS, but no finished vaccine for this coronavirus infection ever became available. In any case, it will take some time until we have a vaccine for COVID-19. It goes without saying that the safety of a vaccine is extremely important (7, 8).

Potential antiviral treatments

No specific treatment for COVID-19 is yet known, but the search for a suitable drug is well under way. On 11 March 2020, 84 trials were listed on www.clinicaltrials.gov under the keyword “COVID-19.” The substances under investigation range from immunomodulatory approaches with immunoglobulins, interferon, thalidomide, and glucocorticoids to treatment with virustatics such as oseltamivir, darunavir, and umifenovir, which was developed in Russia for the treatment of influenza (Table 1). In view of the possibility of resistance developing, it would certainly be desirable to have more than one option for treatment. On the basis of experience with antiviral therapeutics to date, it is to be expected that evolutionary mutations of the viral genome will endow SARS-CoV-2 with new properties, including resistance to certain substances.

Glucocorticoid treatment was tried two decades ago in patients with SARS, but turned out not to be beneficial because it delayed elimination of the virus. Treatment with corticosteroids is also not recommended for COVID-19 (9–11). The nucleoside analog ribavirin was used at the beginning of the SARS epidemic in 2002. This substance can be administered to treat infections with respiratory syncytial (RS) viruses or chronic hepatitis C. In patients with SARS it was usually given in combination with glucocorticoids. Clinically and also radiologically confirmed successful treatment was reported, but none of the studies included a control group, so it remains uncertain whether the medications took effect or whether recovery was spontaneous. The situation is similar for the administration of some antiretrovirals, such as lopinavir and nelfinavir, that were developed for the treatment of HIV infection.

The protease inhibitor lopinavir has been used—together with a small booster dose of ritonavir—to treat patients with COVID-19 in the current pandemic. Five of 18 patients with worsening clinical symptoms received this medication in a Singapore hospital. Improvement was seen in three patients, but not in the other two. Details of the disease course were published, but yielded no clear evidence for the potential efficacy of lopinavir (12). In Wuhan, 41 (21%) of 181 patients were treated with lopinavir/ritonavir, but no decrease in virus excretion was seen (13).

A detailed report of the treatment of a 35-year-old man with COVID-19 in the USA was published on 5 March 2020 (14). This was the first instance of treatment with the as yet unlicensed nucleoside analog remdesivir. The otherwise healthy patient first a cough and fever, followed by vomiting and diarrhea. Four days after onset of the symptoms he was...
admitted to the hospital. The initial treatment was unspecific, with antipyretics such as ibuprofen and paracetamol. Chest radiography then indicated pneumonia, upon which the antibiotics vancomycin and cefepime were given. They were discontinued a day later, however, because the suspicion of bacterial pneumonia was not confirmed. Remdesivir was infused on the evening of day 11. The patient was no longer febrile the next day and could be discharged a few days later. Whether the recovery was effected by remdesivir or occurred spontaneously is unknown. Efficacy can be determined only in randomized controlled clinical trials. Large clinical studies of remdesivir were initiated in February 2020, and the first results can be expected in a few weeks.

Unresolved issues in antiviral treatment

No specific treatment has yet been developed for coronavirus infections, despite the enormous advances in antiviral drug therapy in recent years. Chronic diseases such as infections with HIV or hepatitis B virus can now be treated with virustatics. These substances bring about long-term suppression of viral replication—and in the case of chronic hepatitis C, cure. Drugs are also available for acute viral infections. Treatment with aciclovir can save the life of a patient with herpes encephalitis. Nucleoside analogs may shorten the course of a herpes simplex infection, but the effect tends to be minor in patients with an intact immune system. The course of influenza can be slightly abbreviated by neuraminidase inhibitors such as oseltamivir, but only if treatment is initiated very early. As a number of placebo-controlled studies have shown, no additional benefit is achieved—in a patient with functioning immune defenses—when administration of the drug is delayed to even just a few days after onset of infection.

No account of pharmacotherapy for viral infections would be complete without a mention of the numerous setbacks that have occurred. Right at the beginning of the “nucleoside era,” in the 1970s, it was recognized that cytarabine could not be used as a virustatic in disseminated herpes despite its high antiviral activity. Dissemination of the virus persisted for longer in the treatment group than in the placebo group (15). Decades later, the nucleosides fialuridine and clevudine were tested for possible use against hepatitis B. In both cases, the treatment had to be discontinued owing to toxicity with long-term intake, and research was abandoned (16, 17). Trials of various combinations for HIV infection were also discontinued because the treatments were insufficiently effective or poorly tolerated.

Some pharmacological substances are known to possess high activity against coronaviruses in vitro, but their efficacy and tolerability remain to be explored. Since most cases of COVID-19 run a mild course, it has to be clarified whether administration of virustatics would be advisable in such cases and whether early initiation of treatment would be essential. This requires careful consideration of the
| Substance                  | Brief description of trial                                                                 | Number of participants | Institution/sponsor               | Country                      | Planned completion |
|----------------------------|--------------------------------------------------------------------------------------------|------------------------|-----------------------------------|------------------------------|--------------------|
| Chloroquine                | Prevention, placebo-controlled trial (1:1 randomization) Participants: Employees in a health care facility or other persons at high risk of infection, e.g., relatives of patients with COVID-19 Treatment: Placebo or 10 mg chloroquine base/kg, thereafter 250 mg chloroquine phosphate daily for 3 months | 10 000                | University of Oxford             | UK                           | May 2022           |
| Chloroquine plus darunavir/cobicistat | Open trial Participants: Patients with positive COVID-19 test result Treatment: 800 mg darunavir (plus 150 mg cobicistat as booster) for 7 days together with chloroquine; contacts receive 1 g chloroquine phosphate on days 1 and 2, 0.5 g on day 3 | 2900                 | Lihir Medical Center            | Spain (Catalonia) Department of Health, Generalitat de Catalunya | July 2020           |
| Hydroxychloroquine         | Open trial, pilot study Participants: Patients with pneumonia from SARS-CoV-2 Treatment: 400 mg hydroxychloroquine daily for 5 days | 30                    | Shanghai Public Health Clinical Center | China                       | August 2020        |
| Remdesivir                 | Placebo-controlled double-blind trial (1:1 randomization) Participants: Moderately to severely ill patients with PCR-confirmed COVID-19, max. 12 days since disease onset, oxygen saturation SaO2/SpO2 ≤ 94% at time of admission Treatment: 200 mg remdesivir i.v. on day 1, then 100 mg daily for a total of 9 days Comment: A similar trial is being carried out simultaneously in 308 patients with mild symptoms | 453                  | Capital Medical University Peking | China                       | April 2020         |
| Remdesivir                 | Open trial, comparison with standard treatment Participants: Severely ill patients with PCR-confirmed COVID-19 (max. 4 days since diagnosis); oxygen saturation SaO2/SpO2 ≤ 94% at time of admission; radiological demonstration of pulmonary infiltrates Treatment: 200 mg remdesivir i.v. on day 1, then 100 mg daily for a total of 5 or 10 days Comment: A similar trial is being carried out simultaneously in 600 patients with moderate symptoms (SpO2 >94%) | 400                | Gilead Sciences                 | USA                          | May 2020           |
benefits versus the risks. In most cases of COVID-19 it first becomes clear after a few days whether the infection is spreading to the lower respiratory tract, i.e., whether pneumonia will ensue. Trials are therefore necessary to determine whether efficacy can be demonstrated also when treatment is commenced later.

The in-vitro activity of different substances

The first data on inhibition of SARS-CoV-2 by various substances in cell culture were published online on 4 February 2020 (Table 2). Seven different pharmaceuticals were investigated in Vero-E6 cells, a renal cell line from primates. The concentration that evoked a half-maximal response (EC50) varied between <1 µM and >100 µM. As shown in Table 2, the nucleoside analog penciclovir had a relatively weak effect (EC50: 96 µM). Favipiravir, licensed for the treatment of influenza in Japan, exhibited moderate activity, as did nafamostat. A striking finding was the relatively high in vitro activity of nitazoxanide, a drug that was developed mainly for the treatment of protozoal infections but also acts against some bacteria and viruses. The highest activity under the experimental conditions described in this publication was displayed by remdesivir, with an EC50 of 0.77 µM and an EC90 of 1.76 µM (1 µM = 0.6 mg/L) (6).

Remdesivir is a nucleotide analog that is intracellularly metabolized to triphosphate (18). As well as ebolaviruses, remdesivir inhibits coronaviruses and a range of other viruses (19). It was developed as a substance to treat Ebola infection. It was effective in an experiment on non-human primates, but the results of a clinical trial in patients with Ebola were not convincing. After a preliminary analysis revealed that monoclonal antibodies offered better protection from a fatal outcome, no further patients were treated with remdesivir. The reasons for remdesivir's poor efficacy against Ebola in this clinical trial remain unexplained (20).

Clinical trials on COVID-19

In the past few weeks a number of clinical trials have been initiated to investigate the efficacy of remdesivir, chloroquine, and other substances against COVID-19 (Table 1). Since no specific treatment for this infection has yet been established, and in the light of previous experience, some of these trials are planned as placebo-controlled double-blind studies. They differ with regard to their inclusion criteria, e.g., severity of disease and time from diagnosis to randomization. The first trials are expected to reach completion by the end of April 2020. Details of all these studies can be found at www.clinicaltrials.gov.

None of the medications mentioned in this article is yet licensed for the treatment of COVID-19. Any administration of drugs approved for other indications constituted off-label use in an individual attempt to achieve cure that deviates from standard medical practice. It is not yet known whether any of the the substances currently undergoing clinical testing will prove to be beneficial and have no adverse effects.
The outbreak of infection with a novel coronavirus is the latest reminder of the dangers associated with zoonoses. Several drugs are known to inhibit the new coronavirus SARS-CoV-2 in vitro. Since no treatment has yet proved efficacious, the strengths and weaknesses of the new substances must be established in clinical trials. Until an effective therapy is developed, the spread of SARS-CoV-2 must be restricted as far as possible and patients with severe COVID-19 must be treated with the means at our disposal.

Conflict of interest statement
The authors declare that non conflict of interest exists.

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### TABLE 2

| Substance | Brief description | EC50 (µM) |
|-----------|------------------|-----------|
| Remdesivir | Nucleotide analog (base with adenine-like structure) inhibits viral polymerase, developed as a substance to combat ebolaviruses, several clinical trials in COVID-19 | 0.77 |
| Chloroquine | 4-Aminoquinoline derivative: prevention and treatment of malaria, also in rheumatoid arthritis; antiviral action due to elevated pH in endosomes (similar activity is known for hydroxychloroquine) | 1.1 |
| Nitazoxanide | Nitrothiazole derivative, deacetylated in vivo to tizoxanide, acts against protozoa such as Cryptosporidium parvum and some species of bacteria; additional antiviral action, clinical trials in influenza and other virus infections | 2.1 |
| Nafamostat | Serine protease inhibitor, anticoagulant, inhibits membrane fusion, showed action against MERS-CoV in vitro | 22 |
| Favipiravir | Pyrazine carboxamide, inhibits viral RNA-dependent RNA polymerase, licensed for treatment of influenza in Japan | 62 |
| Penciclovir | Nucleoside analog, guanosine derivative, inhibits viral DNA polymerase; its prodrug famciclovir is licensed for treatment of herpes zoster | 96 |
| Ribavirin | Nucleoside analog, guanosine derivative, inhibits inosine monophosphate dehydrogenase and inhibits DNA and RNA viruses; also has an immunomodulatory action; licensed for treatment of chronic hepatitis C | 109 |

EC50 = Concentration with half-maximal effect
(modified from Wang et al., 2020 [6])
A 44-year-old Bavarian woman with allergic asthma consulted a community medical practice at the end of February 2020 with a febrile airway infection and breathing difficulties after visiting a carnival-related event. She was first assumed to have seasonal influenza and treated symptomatically with antipyretics, and on day 4 empirical antimicrobial treatment was initiated on the assumption of community-acquired pneumonia. Six days after the onset of her symptoms, nucleic acid amplification of material from a nasopharyngeal swab demonstrated the new coronavirus SARS-CoV-2. At the time of hospital admission on day 7, the patient had marked dyspnea at rest (respiration rate: 30 breaths per minute; oxygen saturation: 90% in ambient air) and a chest radiograph showed atypical infiltration of both lungs (Figure 1A). Thoracic computed tomography revealed peripheral ground-glass opacities in both lungs, compatible with COVID-19 pneumonia (Figure 1B). After the occurrence of COVID-19-associated hepatitis on day 12, the clinical and laboratory findings gradually improved with antipyretic and antimicrobial treatment of a bacterial superinfection.