

Lilliput

Clinical trials with antiviral drugs against COVID-19: some progress and many shattered hopes

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Summary

Vaccines and drugs are the cornerstones in the fight against the SARS-CoV-2 pandemic. While vaccines were a success story, the development of antiviral drugs against SARS-CoV-2 turned out to be difficult. For an accelerated use of antivirals in the clinic, most SARS-CoV-2 antivirals represented repurposed drugs. The present article summarizes the outcomes of clinical trials with antiviral drugs in COVID-19 patients. Many antiviral drugs failed to demonstrate beneficial effects or showed mixed results. One reason for the low success rate of clinical trials was shortcomings of antiviral tests in cell culture systems and another reason was the abundance of ill-coordinated and underpowered clinical trials. However, large pragmatic clinical trials particularly of the British RECOVERY trial series demonstrated that even under emergency situation drug trials can be conducted in a timely way such that the therapy of COVID-19 patients can be based on evidence basis instead on expert opinion or even worse on political pressure.

Introduction

Apart from public health measure to minimize transmission, infections can be countered with prophylaxis, i.e. protection through vaccination, and treatment, typically with an antimicrobial drug. Prophylaxis reduces the morbidity and mortality burdens, and the socio-economic consequences of these, but generally are not useful for patients already infected or in the days shortly before. The advantage of therapy is that it can arrest an ongoing

infection. In a pandemic, vaccines are needed to prevent infection, and antimicrobials are needed to save those who become infected. Typically, vaccines are highly specific for an infectious agent, so need to be newly developed for each new agent, whereas therapeutics may have much broader efficacy and so can be available (on-the-shelf) for immediate use in new infections. COVID-19 was an announced pandemic and scientists had warned that zoonotic infections particularly with coronaviruses, influenza viruses, alphaviruses and flaviviruses represent an actual pandemic threat. In addition, two coronavirus epidemics (MERS and SARS) have occurred over the last two decades. However, when COVID-19 struck, with the exception of remdesivir, a nucleoside analogue interfering with viral RNA replication, it hit a nearly unprepared drug world. In the first part of this Lilliput piece, I will first summarize the results of clinical trials testing antiviral drugs against COVID-19 and explore in the second part reasons for the frequent negative outcome of these drug trials and the challenges facing antiviral drug developments.

Summary of Clinical Trials with Antivirals

Remdesivir: a too small step into the right direction

Remdesivir is an inhibitor of the viral RNA-dependent RNA polymerase and showed *in vitro* activity against SARS-CoV-2, *in vivo* activity against MERS coronavirus in a primate infection model and was clinically used in Ebola patients. Remdesivir was developed by the Antiviral Drug Discovery and Development Centre (AD3C) of the National Institutes of Health (NIH) in the United States. Since remdesivir is complicated to synthesize and hence expensive and needs intravenous application, AD3C had also developed a second antiviral drug, molnupiravir, which is easier to synthesize and suitable for oral application. A clinical efficacy trial with molnupiravir is currently conducted by Merck (Dolgin, 2021).

Clinical trials with remdesivir showed variable results in COVID-19 patients. An early Chinese trial, which did not reach the planned enrolment of patients due to the rapid

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control of the epidemic in China, demonstrated no difference in time to clinical improvement, or death or duration of viral excretion in 237 Chinese patients hospitalized with severe COVID-19 (Wang *et al.*, 2020).

ACTT-1 trial. In the multi-centre Adaptive COVID-19 Treatment Trial (ACTT)-1 clinical trial, 1062 COVID-19 patients were randomized on remdesivir (10 days treatment) or placebo. Patients receiving remdesivir had overall a significantly shorter time to recovery than placebo recipients: 10 vs. 15 days. However, no significant effect was seen in patients with mild disease (defined as those not needing supplementary oxygen, WHO disease score 4), nor in more severely affected patients in need of high flow oxygen devices (disease score 6) or mechanical ventilation (disease score 7). The remdesivir effect was only significant in patients with disease score 5 (low flow oxygen need). Overall, the odds of improvement in the clinical score were higher in the remdesivir than in the placebo group, but again limited to disease category 5 patients, who represented 40% of the patients. At day 15, mortality was lower in the remdesivir (6.7%) than in the placebo group (11.9%), but the statistical significance was lost when the mortality was compared at day 29 (remdesivir 11.4% and placebo 15.2% mortality). Again, the largest difference was seen in category 5 patients. Remdesivir recipients achieved a one-category clinical improvement 2 days earlier and two-category improvements 3 days earlier than placebo recipients. In subgroup analysis, remdesivir effects were better for white than black patients, for patients younger than 40 years, and in patients with less than 10 days of symptom duration. The clinicians concluded that treatment with remdesivir alone is not sufficient. Current strategies are therefore evaluating remdesivir in combination with modifiers of the immune response (JAK kinase inhibitor, interferon) (Beigel *et al.*, 2020).

Short vs. long treatment. A total of 400 patients with severe COVID-19, but not in need of mechanical ventilation, were attributed to either a 5-day or a 10-day course of remdesivir in an open-label trial. After 14 days, 64% of patients in the 5-day treatment group showed clinical amelioration compared with 54% on the 10-day course. Mortality was 8% and 11%, respectively. Interpretation whether a shorter remdesivir course is better than a longer one is difficult because patients attributed to the 10-day course showed at baseline more severe disease than those on the 5-day course (Goldman *et al.*, 2020).

Gilead, which develops remdesivir as a drug, randomized 600 moderately ill COVID-19 patients not depending on oxygen therapy on a 5-day or a 10-day course of remdesivir or standard treatment. The clinical status was compared after 11 days using a WHO recommended

7-category scale. The 5-day remdesivir, but not the 10-day remdesivir course showed a significantly better clinical score than standard therapy. Death rate was small (1%–2%) and not different between remdesivir and standard treatment (Spinner *et al.*, 2020). A JAMA editorial concluded that there are important knowledge gaps regarding the efficacy of remdesivir, such as the optimal patient population, the duration of therapy, and the clinical importance of remdesivir treatment effects. In view of the cost and production problems, the editorialists asked for more conclusive remdesivir trials before considering its widespread use (McCreary and Angus, 2020).

WHO SOLIDARITY trial. On 15 October 2020, the WHO SOLIDARITY trial consortium published an interim analysis of four repurposed antiviral drugs against COVID-19, which also included remdesivir (2743 patients, three times the number of all previously published trials). The trial had no placebo group, but each arm was compared with controls receiving standard of care, not containing the four specified drugs, representing 4088 patients. In total, 11 266 adults were randomized from 405 hospitals in 30 countries; 25% had diabetes as risk factor, but only 8% needed ventilation at baseline. The different groups were well balanced and randomization to treatments started 1 day after hospitalization in 62% of patients. With 1253 deaths, the overall 28-day mortality was 11.8%. Death risk depended on several factors, particularly age (20% if ≥ 70 years and 6% if < 50 years) and need of ventilation (39% if ventilated and 10% in non-ventilated patients). Drug compliance was high. The primary end point was mortality. The overall effect of remdesivir was disappointing: no effect on mortality, either overall ($P > 0.10$) or in any subgroup defined by age or ventilation status at entry, other entry characteristics, or geographic region was observed. Death rate ratios (RRs) of remdesivir over control (with 95% confidence interval CI, P -value, and numbers of deaths/enrolled patients in drug vs. control) were $RR = 0.95$ (CI: 0.81–1.11, $P = 0.50$; 301/2743 vs. 303/2708).

Together with a meta-analysis of all published trials on remdesivir and subgroup analysis according to disease severity at baseline, the SOLIDARITY scientists concluded that the data suggest some benefit of remdesivir in low-risk patients and some hazard in high-risk inpatients with the absolute benefit in low-risk patients being smaller than the absolute hazard in high-risk patients (WHO Solidarity Trial Consortium *et al.*, 2021).

The SOLIDARITY authors concluded that narrower confidence intervals would be helpful for remdesivir, but the main need is for better treatments. They admit that the ACTT-1 trial, which showed an earlier hospital discharge in the remdesivir group over the control group (10 vs. 15 days), was placebo-controlled in contrast to

the SOLIDARITY trial. However, at the same time, they noted that the proportion of lower-risk patients (i.e., those not already receiving high-flow oxygen or ventilation) happened to be appreciably greater in the remdesivir group than in the placebo group of the ACTT-1 trial. This chance imbalance might account for some of the differences in time to recovery between ACTT-1 and the SOLIDARITY trial (WHO Solidarity Trial Consortium *et al.*, 2021).

The immunopathology of COVID-19 could explain the disappointing results with remdesivir. An initial phase of intense viral replication progresses into a hyper-inflammatory phase; in the second-phase, viral concentrations are substantially lower than in the first week of illness making an antiviral less useful (Young *et al.*, 2021). One might thus ask whether remdesivir should be reserved for the treatment of patients with lower risk factors, treated early (Harrington *et al.*, 2021). Prominent editorialists spoke with respect to remdesivir of 'A Step in the Right Direction' (Rubin *et al.*, 2020). Since the benefit seems to be small, post-marketing pharmacovigilance will be important to assure the low risk of this intravenously applied antiviral drug particularly with early treatment in low-risk patients. Another comment noted the high price of treatment. Based on an anticipated marginal risk reduction in mortality of 1.6% for patients at low risk, these clinicians calculated that 62-patients need to be treated for preventing one death, causing the very high public health cost of \$146 250 per life saved, which is very high for resource-poor countries (Dal-Ré *et al.*, 2021).

Research on the clinical value of remdesivir continues: a small retrospective effectivity study in 342 hospitalized US COVID-19 patients treated with remdesivir showed clinical improvement by day 28 in 83% of the recipients compared with 75% in 1957 controls. Time to improvement was 5 days in the test and 7 days in the control group. The 28-day mortality was 7.7% in the test and 14% in the control group, but the difference was not statistically significant (Garibaldi *et al.*, 2021).

Hydroxychloroquine: a too large step into the wrong direction

Hydroxychloroquine (HCQ) and chloroquine have been used to treat malaria and rheumatologic conditions and showed *in vitro* inhibition of SARS-CoV-2. A poorly conducted small French clinical trial caused a rapid rush for this drug leading after some inconclusive clinical trials to an emergency use authorization (EUA) by FDA on 15 June 2020, only to be revoked just 11 weeks later. Following media hype and political pressure for HCQ use without sufficient evidence, further confusion was caused by a subsequently retracted *Lancet* article which reported

substantial harm associated with HCQ treatment, an article based on a flawed analysis of a commercial multinational registry compiling treatment modes and clinical outcome for 96 000 COVID-19 patients (Ledford, 2020; Piller and Servick, 2020; Servick and Enserink, 2020). Clarity on the role of HCQ was eventually achieved through a substantial effort of clinical trials and scientific research. But hype from a poor paper, flawed data published in elite medical journals, and undue political pressure eroded trust in science, which is particularly important in an emergency situation of an unfolding pandemic. The *New England Journal of Medicine* – itself victim of retraction of a hastily written report – deplored that media and social forces rather than medical evidence are driving clinical decisions and the global research agenda during the pandemic. This raises a dilemma: at ClinicalTrials.gov not less than 203 COVID-19 trials were listed with HCQ, 60 of which with focus on prophylaxis (Cohen, 2020). This high number is hardly justified and indicated a lack of international coordination and strategy in COVID-19 drug trials.

Treatment trials. Brazilian clinicians conducted a multi-centre trial, involving 500 viral RNA-confirmed patients hospitalized with mild-to-moderate COVID-19, randomized on standard care, HCQ or HCQ plus the antibiotic azithromycin (AZ). After 15 days of treatment, no clinical benefit was associated with HCQ or HCQ/AZ use over standard care. Serious adverse events consisted of prolongation of the QT interval (the interval from ventricular depolarization and repolarization indicating the time during which ventricular contraction and subsequent relaxation occurs) in electrocardiograms, a known adverse effect of HCQ. The authors criticized that the prescription of HCQ had increased by 2000% in the United States after backing by FDA, and that HCQ was formally recommended by the Ministry of Health in Brazil without clinical evidence (Cavalcanti *et al.*, 2020).

In the UK RECOVERY trials, 1561 COVID-19 patients were assigned to receive HCQ and 3155 received usual care (RECOVERY Collaborative Group, 2021). Overall, 60% of the patients needed supplementary oxygen, 17% even invasive mechanical ventilation. The primary outcome was death at 28 days which was 27% in HCQ recipients and 25% in usual care recipients. Consistent results were seen over all predefined subgroups, showing overall a non-significant trend for usual care patients faring better than HCQ recipients. The slight mortality increase in the HCQ group over the usual care group was due to a 0.4% greater risk of death from cardiac causes, a major toxic effect of HCQ. The RECOVERY trial showed that HCQ was not an effective treatment and ruled out any reasonable possibility of a meaningful mortality benefit from HCQ treatment. HCQ was used at the

upper end of HCQ dosing scheme in rheumatoid arthritis (RA), excluding a too low concentration as reason for the lack of efficacy. As secondary outcomes, the HCQ group had a longer duration of hospitalization (16 days vs. 13 days) and a somewhat lower probability of discharge alive within 28 days (60% vs. 63%). The results were consistent across subgroups sorted by age, sex, race, and time since illness onset, level of respiratory support, and baseline-predicted risk (RECOVERY Collaborative Group *et al.*, 2020).

In the HCQ arm of the WHO SOLIDARITY trial, death occurred in 104 of 947 COVID-19 patients receiving HCQ and in 84 of 906 controls (WHO Solidarity Trial Consortium *et al.*, 2021). Death RR of HCQ over controls was $RR = 1.19$ (CI: 0.89–1.59, $P = 0.23$). Subgroup analysis by age or ventilation status at entry or other entry characteristics, or geographic region, also failed to reveal a benefit. For HCQ, the confidence interval excluded any material benefit from this drug in hospitalized patients. The statistical analysis is compatible with some hazard but does not prove hazard. No significant difference for time to discharge was seen between HCQ and the control group or new initiation of ventilation. Recruitment to the HCQ arm was therefore stopped.

Prevention trials. A total of 821 US subjects exposed to COVID-19 patients were within 4 days randomized on high-dose HCQ or placebo; 11.8% and 14.3%, respectively, developed an illness. The authors concluded that HCQ has no effect in post-exposure prophylaxis of COVID-19 (Boulware *et al.*, 2020). The study has limitations since the infection status 14 days after exposure was only defined clinically and not by viral RNA detection.

HCQ is an approved treatment for patients with rheumatoid arthritis (RA). In England, 31 000 of the 195 000 registered RA patients received HCQ. In a population-based cohort study using national primary care data and linked death registrations in the OpenSAFELY platform, there were 547 COVID-19 deaths in the RA population during the spring 2020 epidemic. Cumulative COVID-19 mortality was 0.23% among HCQ users and 0.22% among non-users. After accounting for age, sex, ethnicity, use of other immunosuppressive drugs, no association of HCQ with COVID-19 mortality was observed (Rentsch *et al.*, 2021).

For 672 COVID-19 index cases from Spain, 2525 contacts were randomized on HCQ given at therapeutic doses or no treatment (Mitja *et al.*, 2021). During the 14-day follow-up, 6.0% had a PCR-confirmed, symptomatic COVID-19 episode with no difference between HCQ-treated (5.7%) and untreated contacts (6.2%) (primary outcome). Of the 2000 contacts who tested PCR negative at baseline, 18.2% either became PCR-positive or

developed symptoms, again with no difference between HCQ (18.7%) and the control group (17.8%) (secondary outcome).

Brazilian clinicians reasoned that pharmaceutical interventions that showed no clinical benefits in hospitalized settings may still show effects in outpatients who are in an earlier disease stage. They randomized 214 COVID-19 outpatients to HCQ, 244 to lopinavir-ritonavir, and 227 to placebo. The primary outcomes were COVID-19-associated hospitalization and death assessed at 90 days after randomization. No significant difference was seen for the rate of hospitalization or mortality between the three groups, nor were there differences in viral clearance through day 14 (Reis *et al.*, 2021).

Lopinavir: failure of a repurposed drug

Lopinavir is a human immunodeficiency virus (HIV)-1 protease inhibitor, which is combined with ritonavir to increase its plasma half-life. Lopinavir has *in vitro* inhibitory activity against SARS-CoV-2 and reduced clinical symptoms of SARS-CoV-2 in a ferret model.

China trials. Chinese clinicians randomized 199 patients hospitalized with severe COVID-19 to receive lopinavir-ritonavir (L-R) or standard care in an open-label trial. No significant treatment effect was seen for the primary end point, the time to clinical improvement (16 days), or mortality at 28 day (19% vs. 25%). The percentage of patients with detectable viral RNA at various time points were similar. In a modified intention-to-treat analysis, treated patients showed a modest 1-day and 2-days shorter time to improvement or to hospital discharge, respectively (Cao *et al.*, 2020). A subsequent smaller Chinese trial enrolling COVID-19 patients with mild/moderate disease likewise failed to demonstrate an effect of L-R on positive-to-negative conversion for viral RNA shedding in the throat or clinical improvement (Li *et al.*, 2020a).

RECOVERY trial. In the UK RECOVERY trial 374 (23%) of 1616 hospitalized COVID-19 patients allocated to L-R and 767 (22%) of 3424 COVID-19 patients allocated to usual care died within 28 days. A lack of difference was consistent across all pre-specified subgroups of patients. The researchers observed no significant difference in time until discharge alive from hospital (median 11 days in both groups) or the proportion of patients discharged from hospital alive within 28 days. Among patients not on invasive mechanical ventilation at baseline, there was no significant difference in the proportion who met the composite end point of transition to invasive mechanical ventilation or death. The UK clinicians concluded that L-R is not an effective treatment for COVID-19 since the

size of the trial rules out any reasonable possibility of a meaningful mortality benefit (RECOVERY Collaborative Group, 2020).

SOLIDARITY trial. This conclusion was confirmed by the outcome of the WHO SOLIDARITY trial (WHO Solidarity Trial Consortium *et al.*, 2021) treating 1339 hospitalized COVID-19 patients with L-R who were compared to 1372 controls receiving standard care. The primary end point was mortality. Death occurred in 148 treated and 146 control patients. The death RR (with confidence interval CI and *P* value) was RR = 1.00 (CI: 0.79–1.25, *P* = 0.97). No significant difference for time to discharge was seen compared to controls. No evidence of benefit or of hazard was detected in any subgroup.

Outpatient trial. In a Brazilian trial, 244 COVID-19 outpatients were treated with L-R and compared with 277 controls. No significant difference was seen for transition to COVID-19-associated hospitalization and death assessed at 90 days after randomization between the groups, indicating that an earlier treatment with L-R also failed to achieve beneficial effects (Reis *et al.*, 2021).

Convalescent plasma: mixed results with a classical concept

Passive immunity with purified human immunoglobulins is a classical approach for treating and preventing infectious diseases. It was thus logical to explore the clinical value of convalescent plasma (CP) transfusions from recovered COVID-19 patients for the treatment of COVID-19 patients. Prior experience had demonstrated the efficacy of this approach against influenza and SARS (Cheng *et al.*, 2005).

China. An early exploratory trial in five severe COVID-19 patients showed that CP transfusion was associated with a significantly higher viral clearance compared to 11 controls (Zeng *et al.*, 2020).

In a subsequent Chinese trial (Li *et al.*, 2020b), 52 patients received CP and showed a 2 day reduced time to improvement compared to 51 controls. CP-treated patients had large reductions in their viral load and most were virus negative 3 days after infusion; 91% of severely affected COVID-19 patients treated with CP had improved, compared with 68% in the control group; mortality was 16% and 24%, respectively, but the difference was statistically not significant.

United States. In a New York hospital, clinicians evaluated a retrospective case–control study of CP treatment in 39 patients with severe or life-threatening COVID-19 compared with 120 score-matched controls (Liu

et al., 2020). Oxygen status worsened in 18% of CP recipients versus 28% in controls. Death rate was 12.8% in CP and 24.4% in the control group. The difference remained significant after adjusting for covariates. Donor plasma was screened for neutralizing antibody; titers ranged from 40 to 300, but no correlation between titre and survival was observed.

Emergency Use Authorization (EUA) has been issued by FDA for the use of CP on 23 August 2020 without clear data on efficacy nor transparency of the approval process. At the moment of this decision, the only published data showed the relative safety of plasma transfer in 5000 people with severe COVID-19. Transfusion was associated with a mortality rate of 0.3% in the first 4 h after intervention. NIH warned that there was insufficient data to recommend either for or against the use of CP in the treatment of COVID-19. An editorial stressed that, in a time when science is being manipulated and disregarded, it is critical that the FDA uphold its standards and its objectivity, free from political interference in the approval process (Baden *et al.*, 2020).

Subsequently more than 80 000 US Americans with COVID-19 have been treated with CP provided by the Biomedical Advanced Research and Development Authority (BARDA). Of them 36 226 patients with severe disease (52% in intensive care, 28% on mechanical ventilation) from nearly 2000 hospitals entered an open label trial without controls. The clinicians deduced efficacy of CP treatment from two observations. First, the 30-day mortality rate was 22.2% in patients transfused within 3 days of COVID-19 diagnosis but 29.5% in patients transfused 4 or more days after diagnosis. Second, a gradient of mortality was seen in relation to SARS-CoV-2 IgG antibody levels in the transfused plasma as determined in a subsample of 3000 patients. The 30-day mortality was 22.3%, 27.4% and 29.6% in patients receiving plasma with high, medium and low antiviral antibody titers, respectively. Subgroup analysis showed that the effect of high titre CP on mortality was limited to patients who were not on mechanical ventilation (Joyner *et al.*, 2021).

India. A trial from India with 464 moderately ill COVID-19 patients randomized to CP or standard care showed progression to severe disease or death within a month in 19% of CP treated and 18% of control patients; 15% of plasma treated and 14% control patients died. A higher proportion of patients in the intervention arm showed resolution of shortness of breath and fatigue at day 7 and a higher rate of return to a negative viral RNA test result. A limitation of the study was that for safety reasons plasma from young patients with mild COVID-19 were used that showed only a neutralization titre of 20 (Agarwal *et al.*, 2020).

Argentina. In a trial from Argentina, 334 adult patients with severe COVID-19 pneumonia were randomized on CP or placebo infusion 8 days after symptom onset. A 500 ml of plasma with a neutralizing antibody titre of 300 was infused. Serum antibody titers were higher in the CP group at day 2 after infusion compared to controls, but not at 7 days. At day 30, no significant difference was noted between the groups for clinical outcomes or mortality (11%). Intensive care admission was 54% and 60% and invasive ventilatory support requirements were 27% and 23% in the CP and control group, respectively (Simonovich *et al.*, 2021).

Argentinian clinicians then reasoned that antibodies might be more effective when administered earlier in the course of illness. They treated 160 outpatients within 72 h after the onset of mild COVID-19 symptoms either with CP or with placebo. Severe respiratory disease developed in 16% of CP compared with 31% of placebo recipients. Risk reduction was even greater when patients received CP with neutralizing titers of 3000. 5% of CP and 12% placebo recipients had a life-threatening respiratory disease. The treatment was safe and with \$190 per patient cheap (Libster *et al.*, 2021).

UK RECOVERY trial. In the RECOVERY trial 11'500 hospitalized COVID-19 patients were randomized on CP or usual care; 87% of the patients received oxygen, 5% were on mechanical ventilation. Corticosteroids were given to 92% of the patients from both groups. A mean time of 9 days passed from symptom onset to randomization. The first unit of CP was given within 36 h from randomization. No significant difference was seen for day 28 mortality which was 24% in both groups; mortality was higher in patients who were seronegative at randomization, but CP made here again no difference with a 32% vs. 34% mortality in the two groups. In patients who were seropositive at baseline, mortality was lower, but again not affected by transfusion of CP: 19% vs. 18% mortality in the treatment vs. controls, respectively. The median time to discharge was comparable (12 vs 11 days) and progression to mechanical ventilation was identical between both groups (29%). The clinicians excluded two reasons for the negative trial outcome: the antibody titre used in the RECOVERY trial was substantially higher than that used in high titre sera from the United States as set by FDA standards. No difference in trial results was seen before and after the alpha variant became dominant in United Kingdom, excluding a mismatch between CP antibodies and variant virus as a reason for the negative outcome (RECOVERY Collaborative Group, 2021).

The SIREN trial. The Strategies to Innovate Emergency Care Clinical Trials Network (SIREN) used CP with a neutralization titre of 600 in 511 outpatients with at least

one risk factor for severe Covid-19. The outpatients were randomized on CP or placebo. The primary outcome was disease progression within 15 days, which occurred in 30% of CP and 31.9% of placebo recipients, respectively. Five patients in the CP and one patient in the placebo group died. Hospital-free days were similar in the two groups. The authors of this US study concluded that CP did not prevent disease progression (Korley *et al.*, 2021).

A meta-analysis concluded that CP treatment was not significantly associated with a decrease in all-cause mortality or with any benefit for other clinical outcomes (Janiaud *et al.*, 2021).

The authors of the CP trials with negative outcome mentioned some reasons for the failure of CP treatment. This included too low neutralizing antibody titers in the CP and mismatch between antibody specificity and circulating virus. Overall, the approach failed both in inpatients and outpatients – the possibility remains that CP treatment might protect still uninfected contacts of COVID-19 patients from contracting infection and disease, but this remains to be proven. Since the temporal relationship between virus-induced and immunity-induced pathology is not entirely settled, intervention with CP in both outpatients and inpatients with SARS-CoV-2 infection might come too late. Since CP is a treatment modality that is available early in a novel epidemic, before the nature of the infectious agent is characterized, it is a sad observation that this classical approach did not work with COVID-19. CP treatment has a rational basis, but CP treatment of COVID-19 illustrates that even in an emergency situation, no rational reasoning should replace evidence-based medical treatments based on randomized controlled clinical trials powered to provide sound data. Only this type of evidence, and not 'expert opinion' can spare patients useless or even potentially harmful treatments, and pave the way for efficacious interventions during later infection waves.

Neutralizing monoclonal antibodies for contact protection?

BLAZE-1. The neutralizing monoclonal antibody (mab) LY-CoV555 (also called: bamlanivimab) developed by Eli Lilly binds with high affinity to the receptor-binding domain of the SARS-CoV-2 spike protein. This mab was tested in the Blocking Viral Attachment and Cell Entry (BLAZE)-1 trial at 0.7 g, 2.8 g, or 7 g intravenously infused doses in 317 subjects who had only mild symptoms but showed high viral titers, while 150 patients received a placebo. Only a small effect of mab was seen on viral load at day 11 after treatment when compared to placebo and was only observed with the 2.8 g dose. At day 29, 1.6% of the antibody-treated patients were

hospitalized compared to 6.3% of the placebo-recipients (Chen *et al.*, 2021).

BLAZE-2. The BLAZE-2 trial enrolled 588 study participants who received 4.2 g of mab LY-CoV555 and 587 participants who received placebo. A total of 300 participants were residents of US skilled nursing homes and 666 were staff; all residents and 41% of the staff had risk factors for developing severe COVID-19. By day 57, 8.8% vs. 22.5% of the residents treated with intravenous mab or controls, respectively, had developed symptomatic COVID-19. Among the staff 8.4% vs. 12.2% developed COVID-19, a non-significant difference. Five COVID-related deaths occurred in the study, all were observed in the placebo group. Among the residents, antibody infusion was associated with significantly lower incidence of SARS-CoV-2 infection compared with placebo (15% vs. 32%), but not among the staff (19% vs. 20%). Viral load was 10-fold lower in antibody-treated infected subjects and fewer treated patients developed natural antibodies against infection than controls (3% vs. 15%) (Cohen *et al.*, 2021). While the BLAZE trials showed some effect of passive immunity with mab LY-CoV555, this effect was not confirmed in the next trial leading first to approval and then to revocation of this treatment mode by the FDA.

TICO. In the TICO trial, 314 hospitalized COVID-19 patients from the United States, Denmark and Singapore were randomized on treatment with mab LY-CoV555 or placebo before they developed organ dysfunction. TICO (Therapeutics for Inpatients with COVID-19) is a master protocol to evaluate the safety and efficacy of multiple investigational agents aimed at modifying the host immune response to SARS-CoV-2 infection or at enhancing viral control in order to limit disease progression. Overall 95% of the enrolled patients were in addition treated with remdesivir, 50% with glucocorticoids, and 50% with anticoagulants as standard care. Five days after treatment no difference in pulmonary ordinal outcome was seen, and at day 28 hospital discharge occurred in 88% and 90% of treatment and control patients, respectively. Fourteen patients died: nine in the treatment and five in the placebo group; 12 of the deaths were attributed to worsening of COVID-19. The trial was stopped at interim analysis for futility (ACTIV-3/TICO LY-CoV555 Study Group *et al.*, 2021).

Bamlanivimab and etesevimab trial. The FDA granted emergency use authorization for bamlanivimab monotherapy in November 2020, but this authorization was later revoked. Therefore, Eli Lilly developed a cocktail containing two neutralizing monoclonal antibodies, bamlanivimab and etesevimab, isolated from a

convalescent United States and a Chinese COVID-19 patient, respectively. The cocktail containing 5.6 g mab or placebo were infused 4 days after the onset of symptoms into 1035 outpatients, 77% of whom had mild COVID-19. The patients were at risk of developing severe symptoms since they showed a BMI > 34. 2% of the mab-treated compared to 7% of the controls experienced a hospitalization for COVID-19. By day 29, nine placebo recipients died from COVID-19 while no death was observed in the mab-treated group. High viral loads at day 7 were observed in 30% of placebo and 10% of mab recipients, mab-treated patients had a 16-fold lower viral titre and no viral escape mutants were observed in the treatment group (Dougan *et al.*, 2021).

Regeneron. Regeneron pharmaceuticals developed a cocktail of two neutralizing monoclonal antibodies, REGN10933 and REGN10987, targeting distinct structural epitopes of the receptor binding domain from the viral spike protein in order to prevent escape of the virus from antibody neutralization by a single mutation event. Two hundred sixty-nine symptomatic COVID-19 outpatients were randomized on placebo or 2.4 g or 8.0 g of this antibody cocktail. Overall 3% of the mab and 6% of the placebo recipients reached the pre-specified key clinical end point with a medically attended visit through day 29 for COVID-19 (the definition given in the publication). At baseline, 123 patients were seropositive and 113 were seronegative. In the seronegative subgroup, 15% of the placebo recipients and 6% of antibody recipients reached this clinical end point. Antibody treatment was associated with a modest decrease in viral load only in subjects seronegative at baseline. No significant effect of treatment was seen on viral load in subjects seropositive at baseline (Weinreich *et al.*, 2021). The efficacy of the Regeneron antibody cocktail for treatment of hospitalized COVID-19 patients is currently being tested in a RECOVERY trial.

Subsequently, the Regeneron antibody cocktail was subcutaneously injected with a 1.2 g dose in 753 seronegative household contacts of COVID-19 index patients while 752 contacts received a placebo. Symptomatic SARS-CoV-2 infection developed in 1.5% of mab-treated and in 7.8% of placebo recipients, corresponding to an 81% risk reduction. Asymptomatic infections occurred in 3.3% of the mab- and 6.4% of the placebo-treated contacts. Participants who became infected despite antibody treatment had a lower peak viral load and a 2-week shorter duration of symptoms than placebo recipients (O'Brien *et al.*, 2021).

In view of the disappointing results with passive immunity by convalescent sera, the value of passive immunity with monoclonal neutralizing antibodies needs to be

substantiated in large controlled clinical trials with both inpatients and outpatients. The available data seem to suggest a protective effect in uninfected contacts of COVID-19 patients.

Interferons: mixed results

During viral infections, pattern recognition receptors detect viral nucleic acids, inducing the production of interferons (IFN). Severely and critically ill patients in contrast to mild and moderately affected COVID-19 patients showed an impaired type I IFN response with no detectable INF- β and low INF- α production. Type I IFNs orchestrate a coordinated antiviral programme. Low INF- α level preceded clinical deterioration in COVID-19 patients and transfer to intensive care (Hadjadj *et al.*, 2020). Based on these research data, some hope was put on interferon treatment approaches.

Combination therapy. Eighty-six hospitalized COVID-19 patients were attributed to a combination treatment consisting of the protease inhibitor lopinavir, the nucleotide analogue ribavirin and interferon beta-1b, while the control group was only treated with lopinavir. The combination group showed with 7 days a significantly reduced time to disappearance of virus in the nasopharynx compared to 12 days in the control group and also showed significant clinical improvement over the control and a shorter hospital stay. Due to a post hoc subgroup analysis, the clinicians attributed the beneficial effect to interferon and not ribavirin (Hung *et al.*, 2020).

Inhaled INF. A small UK trial randomized 98 COVID-19 patients on inhaled nebulized interferon beta-1a or placebo. Over the 14-day treatment period, patients in the interferon group were more than twice as likely to recover than controls. Three deaths occurred in the placebo and none in the interferon group (Monk *et al.*, 2021).

Pegylated INF. Canadian clinicians randomly assigned 60 subjects to a single subcutaneous injection of pegylated INF lambda or placebo; treatment was within 7 days of symptom onset. Pegylation was used to increase the in vivo half-life of INF. The decline in SARS-CoV-2 RNA was significantly greater in INF-treated than in placebo recipients with a 100-fold difference in viral copies at day 7 (Feld *et al.*, 2021).

SOLIDARITY and INF. The WHO SOLIDARITY trial treated 2050 hospitalized COVID-19 patients with INF- β 1a, mostly by subcutaneous application. The primary end point was mortality which occurred in 243 of 2050 INF-treated patients and 216 of 2050 control patients. The relative risk ratio was 1.16 indicating a non-

significant ($P = 0.11$) increased risk of death with INF treatment (WHO Solidarity Trial Consortium 2021). Interferon given later in the infection process might have negative effects since IFN- λ has been reported to impair lung epithelial cell proliferation during recovery from viral pneumonia (Grajales-Raya and Colonna, 2020).

Critical evaluation of the antiviral clinical trials

Drug approaches without a rational basis: the case of doxycycline and ivermectin

Doxycycline is a widely available, inexpensive antibiotic. Community prescribing data from the United States and the United Kingdom showed an increased use of doxycycline during the COVID-19 pandemic while an antiviral effect was only shown in a single cell culture study.

PRINCIPLE trial. The Oxford University-led PRINCIPLE trial is an open-label, multi-arm, adaptive platform randomized trial of interventions against COVID-19 in elderly outpatients across primary care centres in the United Kingdom (Macleod and Norrie, 2021). PRINCIPLE tested doxycycline in older patients and those with comorbidity and compared it with standard care. End points were time to self-reported recovery, hospitalization or death related to COVID-19 over 28 days after start of treatment. A total of 2689 participants were enrolled: mean time to recovery was 9.6 days in the treatment and 10.1 days in the control group; hospitalization occurred in 5.3% and 4.5% of the enrolled outpatients; death in 5 and 2 subjects (Butler *et al.*, 2021). The authors acknowledged the challenge of designing trials with relatively little information early in a new pandemic but urged for controlled trials of repurposed drugs to prevent inefficient or even harmful drug use. Doxycycline has no meaningful benefit since COVID-19 pneumonia is not known to be exacerbated by bacterial infection but increases antibiotic resistance if widely used. Overall, drug treatments not based on sound preclinical test results and subsequently tested in large carefully controlled clinical trials have led nowhere in the COVID-19 pandemic.

Ivermectin. The drug situation is complicated by unwise governmental support for some unproven repurposed drugs. This was the case for ivermectin in Latin America, a cheap, over-the-counter drug for the treatment of parasitic worms. Ivermectin is now notorious for the retraction of two papers reporting mortality reduction in flawed clinical data analysis (Rodriguez Mega, 2020; Reardon, 2021) A large Brazilian study with ivermectin is ongoing and it is hoped that by the end of 2021 one will know whether ivermectin has a benefit or not.

Cell culture traps

Reasons for HCQ failure. German virologists provided crucial insights why HCQ could not work. Chloroquine and HCQ elevate endosomal pH and inhibit viruses that depend on low pH in the endosome for viral uncoating. However, SARS-CoV-2 virus can employ pH-dependent and pH-independent pathways for entry into cells. While HCQ does inhibit the viral entry into Vero cells, a standard cell culture system, it does not inhibit viral entry into cells which express the pH-independent, plasma membrane resident serine protease TMPRSS2, which is present in human lung cells. The virologists stressed the importance of using relevant cell lines for drug testing against SARS-CoV-2 and criticized that an obviously ineffective drug in human lung cells was tested in worldwide more than 80 registered clinical trials (Hoffmann *et al.*, 2020).

French virologists also failed to demonstrate an inhibitory effect of HCQ in macaques. HCQ-treated animals showed no effect on viral titers nor clinical efficacy, regardless whether HCQ was given before infection as pre-exposure prophylaxis, or early after infection (before viral replication peak) or late after infection (after the peak of viral replication) to assess antiviral and immunomodulatory activities of HCQ separately (Maisonasse *et al.*, 2020). Doubts on the usefulness of HCQ were already expressed early during the COVID-19 pandemic since in influenza or dengue virus infections, clinical trials likewise failed to demonstrate efficacy of chloroquine or HCQ (Touret and de Lamballerie, 2020).

HCQ use was nevertheless recommended in China, France, Italy, the Netherlands, and South Korea. After EUA by FDA, 60% of COVID-19 patients in New York were treated with HCQ during the spring peak of the epidemic. Unqualified political and regulatory support combined with media hype for an inefficient drug has not only provided no benefit but has become a hindrance for COVID-19 drug development by an unjustified concentration of research resources.

Phospholipidosis artefacts. When the pandemic struck the health systems, a widely shared view was that the emergency situation needed a quick drug answer and repurposed approved drugs or drug candidates already in clinical tests seemed the quickest solution. Some drug candidates were chosen based on supposed known mechanisms for antiviral activities in cell culture, HCQ is an example. Further antiviral candidates were identified in hypothesis-free screens of pharmaceutical compounds for virus inhibitory activity in cell culture. When cell biologists identified host proteins that interact with SARS-CoV-2 viral proteins (Gordon *et al.*, 2021), inhibitors for these host proteins were searched that displayed antiviral

activity in cell culture. With these approaches nearly 2000 drugs and investigational drugs were reported to have inhibitory activity against SARS-CoV-2 in cell culture assays. When US pharmacologists investigated inhibitors against a specific host protein, the human sigma receptor, they noted that the selected antiviral drugs were all cationic at physiological pH and relatively hydrophobic and they found no correlation between the potency with which the drugs inhibited the host protein and their antiviral activity (Tummino *et al.*, 2021). They observed that many of these in vitro active antivirals, several of which were and are in clinical trials against COVID-19, induced 'phospholipidosis'. Phospholipidosis is the formation of vesicle-like structures or 'foamy' or 'whorled' membranes in the cell which are induced by an altered lipid metabolism that also interferes with intracellular viral replication. They realized that many, perhaps most, of the identified repurposed antivirals act through this mechanism, including chloroquine and HCQ. Unfortunately, this activity did not translate into in vivo antiviral activity. What was planned as a shortcut to COVID-19 drugs turned out to be a dead end, explaining the low success rate of clinical trials with antiviral drugs against COVID-19. According to the DrugBank COVID-19 dashboard, 316 phase 1 to phase 3 clinical trials against COVID-19 were conducted with antivirals that induce phospholipidosis (more than half of these registered trials tested chloroquine or HCQ!). In addition, 136 trials were conducted with 33 other predicted or known phospholipidosis inducers. This caused expenses in clinical trials of estimated US\$6 billion resulting from possible artefacts in cell culture tests. This not only led to an unnecessary waste of money, but a diversion of resources from more promising drug development programmes. In the rush for drugs in a pandemic, the experience of medicinal chemists was neglected. Drug researchers use early counter screens and insist – in hindsight with a lot of justification – on time-consuming controls such as systematic correlations of structural changes of the compounds with biological activity. Such approaches necessitate the synthesis of multiple chemical compounds but might avoid the high rate of failed clinical trials as unfortunately seen with COVID-19 antivirals (Edwards and Hartung, 2021).

Challenges

Despite the roll-out of highly efficient vaccines, developing efficient drugs remains a priority since widely shared vaccine hesitancy will result in coverage rates that are insufficient to achieve herd immunity against viral variants with high transmission capacity. Since large numbers of people will still get infected, even when only a low percentage will develop a serious disease, this will

nevertheless translate into very high numbers of hospitalized patients for whom therapeutic drugs are needed. Antivirals active against coronaviruses and other viruses with pandemic potential will also be needed as part of pandemic preparedness programmes.

Challenges for industry. Challenges exist to create industry-government coalitions during medical emergencies. A recent viewpoint in *The Lancet* explored the ethical obligations of pharmaceutical companies in a global health emergency (Emanuel *et al.*, 2021). The question was raised in the context of vaccine development, its distribution and pricing, but these considerations also apply to drug development since some major pharma companies stepped out of both the vaccine and antibiotic business due to concerns about return of investments. While in a market economy, pharmaceutical companies have the freedom to choose what treatments to research and develop, in a pandemic emergency situation, pharma industry with its knowledge in the biomedical field cannot simply stay on the sideline. This double responsibility of pharmaceutical industry towards their shareholders and the public (their consumers) creates an economic and ethical dilemma. Commerce must engage in low return partnerships with government and academia in joint drug discovery environments as part of a new ethical-social responsibility corporate culture.

Challenges for governments. In this new culture, governments with their public health obligations for their populations have to create the financial incentives (and markets) for industry to develop antiviral drugs against the current pandemic and new antimicrobials against the projected antibiotic crisis predicted to cause 10 million annual deaths by 2050 (Kwon and Powderly, 2021). The governmental investments in vaccine development against COVID-19 have demonstrated that such approaches can work, even work very efficiently under emergency situations. Since the failure of many clinical trials testing antivirals against COVID-19 were in retrospective based on false assumptions in cell biology and physiology, it is essential that also academic research with the help of appropriate grant calls join the concerted effort of the government-industry coalition for developing antiviral drugs.

While governments have supported vaccine development with US\$ 90 billion, governments failed to do the same for antiviral drugs, with the exception of remdesivir. The Corona Accelerated R&D in Europe project received €75-million for drug development and the Rapidly Emerging Antiviral Drug Development Initiative hopes for US\$ 500 million (Anonymous, 2021). These sums are still small when compared with investments in vaccine development.

Challenges for clinicians. Challenges also exist for the medical professionals. In the early phase of the pandemic, doctors were confronted with the dilemma of using treatment methods and drugs against a new disease for which no evidence-based therapy was available. This led to treatments based on expert opinions and the use of repurposed drugs, some of them with questionable claims of efficacy, where political and media support replaced scientific evidence. A large number of clinical drug trials were started, but many were in the initial phase not coordinated leading to many underpowered studies or flawed designs such that no conclusions could be drawn from them (Bauchner and Fontanarosa, 2020). This led to EUA for treatment modes based on plausibility, but without clinical proof which later turned out to be inefficient (e.g. CP in the United States) and the revocation of approvals. Centralized and rapid coordination of large clinical trials under the authority of the World Health Organization (WHO) – an institution undermined by the previous US government – should become a priority during a pandemic. Thanks to large trials from WHO ('SOLIDARITY') and those conducted by the UK National Health System (NHS) ('RECOVERY'), definitive data on drug efficacy or, disappointingly, mostly their inefficacy were obtained demonstrating that such trials can be organized under emergency situations delivering timely results.

Need for innovation. There is a postulate that new drug developments cost billions of dollars and take years of work. The work of a crowd-sourced consortium of academic researchers has shown that this is not necessarily so at least for the early steps of drug development (von Delft *et al.*, 2021). The prevailing postulate of a costly and lengthy drug development led to the strategy to use repurposed drugs for many clinical trials instead of developing new drugs specifically targeted to the SARS-CoV-2 infection. This is understandable from the viewpoint of the clinician confronted with the problem to care for seriously ill patients. This strategy led to a conservative approach trying out what worked for other infections while it could be anticipated that the success rate of clinical trials using drugs not tailored to COVID-19 would be low. The fact that the new mRNA vaccines were authorized within a year and hit the market indicate that the repurposed drug approach might have been unnecessarily conservative. However, we have decades of experience of vaccine development, but each new drug is different and needs a palette of tests to be carried out before use. Repurposing approved drugs that avoids all these tests therefore makes sense as part of a dual strategy (parallel to the search for new disease-specific drugs), so long as their (in)efficacy is rigorously assessed.

Challenges for researchers. COVID-19 was after SARS and MERS the third or according to circumstantial clinical and virological evidence (Brüssow and Brüssow, 2021) perhaps the fourth coronavirus epidemic with pandemic potential. It is thus likely that further coronavirus epidemics will occur. To achieve a better pandemic preparedness than was realized when COVID-19 struck, it is desirable that antivirals are not only developed that act against SARS-CoV-2 but also antivirals that show pan-coronavirus inhibitory activity. It will be important that this broad antiviral activity is not only observed in cell culture tests, but is also exhibited in relevant animal models of coronavirus disease. Exploring this option will be a challenge for researchers, but the first steps in this direction were already made with promising results for the anti-leprosy drug clofazimine (Yuan *et al.*, 2021).

Outlook

It would be inappropriate to end this overview of COVID-19 antiviral drugs with a pessimistic note. Even if we do not yet have the efficient antiviral drug we wish, a major learning lesson in the COVID-19 pandemic was that clinical drug trials can be conducted efficiently and in a timely way even under emergency conditions. The UK Randomized Evaluation of COVID-19 Therapy (RECOVERY) trials are here a shining example. The simple, pragmatic protocol looking for a single clinically relevant end point (mortality, later also time to hospital discharge), conducted under strong leadership of the UK Chief Medical Officers favoured the recruitment of 60% of eligible patients with COVID-19 into clinical trials. The participating 178 NHS hospitals enrolled 15% of all COVID-19 patients from United Kingdom into controlled trials and thus assured a maximal gain of clinical knowledge for a new disease that will profit future patients. RECOVERY recruited 12 000 patients from 176 sites in just over a 3 months period. With this number of patients, the RECOVERY trial was powered to provide a 90% chance of picking up a reduction in deaths of about 18%. Key features were a just 20 pages long protocol that allowed stressed clinicians to conduct these trials with minimal administrative burden, which allowed trial arms to be halted or added and amendments to receive ethical and regulatory approval in just 9 days. The evaluation was supported by a data system implemented in the UK National Health System (NHS) which was backed by IBM, the University of Oxford and Microsoft. Trust from patients and public was achieved by great transparency (documents were available on a public website, results were released by press releases, data were shared with WHO and published as full report preprints and then submitted to leading medical journals for peer review). In this way, RECOVERY quickly sorted out what worked and

what did not work against COVID-19 in hospitalized patients, setting an example for evidence-based treatments in a pandemic which was quickly adopted by the clinicians as current standard care (Kupferschmidt, 2020; Mullard, 2021).

RECOVERY was not the only one of these trend-setting large trial formats. The WHO, for example, organized the SOLIDARITY trial that is a useful complement to the UK RECOVERY trial by its international scope which allows conclusions for patients with different genetic backgrounds, but suffered from the burden to get authorizations from dozens of countries, which took sometimes so long that the trial had to follow the pandemic for patient enrolment as the epidemic evolved geographically in the participating countries. SOLIDARITY also generated data on viral levels and blood parameters, which will allow mechanistic insights into drug action. Trial formats have also been developed for testing drugs in outpatients in order to identify treatments that general practitioners can prescribe to prevent disease deterioration and hospitalization (PRINCIPLE trial) (Macleod and Norrie, 2021). There is thus confidence that when appropriate drug candidates are identified, these tested trial formats will quickly identify efficient treatment modes or discard useless drug candidates.

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