

Treatment of Coronavirus Disease 2019: Shooting in the Dark

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Abstract

The identification of effective interventions against the coronavirus disease 2019 (COVID-19) pandemic has become a health priority. The rational treatment of a disease is based on the knowledge of its pathophysiology, the identification of a therapeutic target and the confirmation of the efficacy and safety of the selected therapeutic intervention in randomised controlled trials. However, we are facing the COVID-19 pandemic without a clear understanding of the pathophysiology of the disease. As we are fighting against a viral infection, drugs previously developed or approved to treat other viral infections or that exhibit a broad-spectrum antiviral activity, anti-inflammatory drugs and drugs against cytokine storm are currently being tested. Unfortunately, the efficacy and safety of these medications remain uncertain, and some may increase the risk of cardiovascular complications in patients with COVID-19. Thus, at the present time, due to the lack of solid scientific data to support a therapeutic strategy, we truly are shooting in the dark with the treatment of COVID-19. We must wait for the results of ongoing randomised, controlled studies before the widespread adoption of these drugs. In the meantime, investigational anti-COVID-19 drugs should be used in hospitals or as part of clinical trials.

Keywords

COVID-19, SARS-CoV-2, coronavirus, pandemic, pharmacology

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"When the cause of the sickness is unknown, only a miracle can cure it." Don Quixote, Miguel de Cervantes, 1605.

The coronavirus 2019 (COVID-19) pandemic was caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).^{1,2} COVID-19 rapidly spread from China to most countries around the world, and on 11 March 2020 the WHO declared a global pandemic. The COVID-19 pandemic has already had a major negative impact on global health systems and the economy.³ From a pharmacological point of view, the rational treatment of a disease is based on the knowledge of its pathophysiology, the identification of a therapeutic target and trial confirmation of the effectiveness of the intervention. Indeed, under normal circumstances, well-designed randomised controlled trials (RCTs) are key to confirm that a pharmacological intervention directed at a selected target is effective and safe. However, these are not normal times and we find ourselves facing a pandemic caused by a virus of which we know very little, and for which there is no clear understanding of the pathogenesis or pathophysiology of the diseases triggered by COVID-19. Moreover, little is known regarding the short- and long-term clinical consequences of the disease and why different individuals respond so differently to the aggression of the virus. Without specific effective therapies for COVID-19 we are facing a very large death toll and the collapse of many health services worldwide.

As a result of the severity of the problem, in the past few months numerous drugs have been proposed that might be effective in the treatment of

COVID-19 (Table 1). However, due to the lack of true scientific data to support a therapeutic strategy for COVID-19, it has become apparent that we truly are shooting in the dark. This article aims to convey my reflections on the current situation from a clinical pharmacologist's viewpoint. Several issues have attracted my attention since the initial reports emerged from China at the time of rapid death progression in that country.

The Ibuprofen Story

On 14 March 2020 the French Health Minister, Olivier Véran, claimed on Twitter that anti-inflammatory drugs such as ibuprofen or cortisone could be an aggravating factor in people with COVID-19.⁴ A few days later, on 18 March, the WHO recommended using paracetamol instead of ibuprofen. On 19 March, the WHO updated its advice on the official Twitter account: "Based on currently available information, WHO does not recommend against the use of ibuprofen".⁵ Finally, on 14 April, the Commission on Human Medicines Expert Working Group on COVID-19 concluded that there is currently insufficient evidence to link ibuprofen or other non-steroidal anti-inflammatory drugs, with a susceptibility to contracting COVID-19 or the worsening of its symptoms.⁶

Use of Renin-Angiotensin-Aldosterone System Inhibitors in COVID-19 Patients

The angiotensin-converting enzyme 2 (ACE2) is the receptor responsible for SARS-CoV entry into cells, and because ACE2 expression increases in patients treated with ACE inhibitors (ACEIs) and angiotensin II type 1 receptor blockers (ARBs), it was hypothesised in a letter published in

Table 1: Drugs Under Development for the Treatment of COVID-19

Family	Drugs
Antibiotics	Azithromycin plus chloroquine
Antifibrotic drugs	Defibrotide, pirfenidone
Anthelmintic drugs	Ivermectin, niclosamide, nitazoxanide
Anti-inflammatory drugs	Glucocorticoids, NSAIDs
Antimalarial drugs	Chloroquine, hydrochloroquine
Antiviral drugs	Anti-influenza compounds: baloxavir, DAS181, [†] favipiravir, [†] laninamivir, [†] oseltamivir, peramivir, rintatolimod, zanamivir HIV protease inhibitors: ASC09/ritonavir, darunavir/cobicistat, lopinavir/ritonavir Other antivirals: Azvudine, [†] galidesivir, [†] merimepodib, [†] remdesivir, [†] ribavirin, umifenovir
Cytokine therapy (inhibit cytokine storm)	IL-6 inhibitors: sarilumab, tozilizumab Interferons Monoclonal antibodies: bevacizumab, camrelizumab, [†] eculizumab, emapalumab, IFX-1, [†] leronlimab [†]
Immunosuppressants	Baricitinib, fingolimod
Neurokinin 1 receptor antagonists	Tradipitant [†]
Pathway-targeted therapies	Ruxolitinib
Recombinant fusion proteins	CD24Fc [†]

[†]Experimental drugs. Ongoing trials with these and other drugs in patients with coronavirus disease 2019 (COVID-19) can be consulted on ClinicalTrials.gov (<https://clinicaltrials.gov>), National Institutes of Health COVID-19 page (<https://www.nih.gov/health-information/coronavirus>) and Chinese Clinical Trials (<http://www.chictr.org.cn/enindex.aspx>). IL = interleukin; NSAID = non-steroidal anti-inflammatory drug.

The *Lancet Respiratory Medicine* that patients treated with agents capable of increasing ACE2 availability/density such as ACEIs, ARBs, and ibuprofen could be at higher risk of developing severe and fatal COVID-19 infection.⁷⁻⁹ Furthermore, the authors added that ACEIs can modify the adaptive immune response and suggested that long-term use of ACEIs might suppress the adaptive immune response in individuals affected by COVID-19. The article caused great consternation among patients and physicians alike. Although it was somewhat 'reasonable' on theoretical grounds, there is no clinical or scientific evidence to indicate that treatment with these important medications should be abandoned or discontinued in patients affected by SARS-CoV-2 infection.^{10,11}

The above examples are of concern, given that they led to confusing and contradictory recommendations, created uncertainty among prescribers and increased mistrust in medical decisions among the general public. They may also fuel the proliferation of false information or imaginative uses for medications or substances that may not only be ineffective but also extremely dangerous and life-threatening.

As expected, scientists all over the world are assessing whether drugs that inhibit SARS-CoV-2 *in vitro* (even when their effects *in vivo* may remain uncertain), agents with broad-spectrum antiviral actions, previously developed and approved for the treatment of other viral infections (particularly RNA viruses, i.e. influenza and HIV) or drugs approved for other clinical indications that exhibit potent broad-spectrum antiviral effects (i.e. chloroquine, hydrochloroquine, ivermectin) might also be effective against SARS-CoV-2 (Table 1). Azithromycin was also tested in this context because its early use is known to reduce the likelihood of recurrent severe episodes of lower respiratory tract illness.¹² The race to find an effective medication is progressing at high speed, but the risk is that the quality of the research could be compromised by the anxiety driving some of the research projects.

Severe pneumonia caused by human coronavirus is often associated with massive inflammatory cell infiltration, increased plasma concentration of inflammatory cytokines/chemokines and multiorgan failure, resulting in acute lung injury and acute respiratory distress

syndrome.^{13,14} Indeed, high virus titres and deregulated cytokine/chemokine responses cause a cytokine storm, which results in high morbidity and mortality due to immunopathology.^{1,14,15} Furthermore, a recent meta-analysis found that measurement of circulating interleukin-6 (IL-6) may predict disease progression in COVID-19 patients.¹⁶ This suggests that besides controlling viral load, novel strategies directed at attenuating the cytokine storm (e.g. IL-6 receptor antagonists, immunosuppressants, interferons, fingolimod) may possibly improve clinical outcome, although these medications can increase the risk of secondary infection.

Table 2 summarises the mechanisms of action, the main adverse effects and potential interactions with other cardiovascular drugs, of drugs currently under clinical investigation for the treatment of COVID-19.

Some Pharmacological Reflections

COVID-19 is a new pandemic and to date, no specific drug (or vaccine) has been found to be effective. Therefore, there is no solid evidence at this point in time that allows treating physicians to use COVID-19-specific treatments, thus management should include the prompt implementation of proven infection prevention and control measures and supportive care, ranging from symptomatic outpatient management to full intensive care support.¹⁷ At the onset of the COVID-19 outbreak and in view of the lack of specific treatment for this new coronavirus, SARS-CoV-2, antiviral screening programs identified many antiviral agents that showed *in vitro* activity against SARS-CoV-2. These drugs are presently being tested in ongoing clinical trials. Several issues have emerged in relation to the strategies that are currently being implemented.

The first is whether the antiviral effects reported *in vitro* could also be achieved *in vivo*. Sometimes the concentrations at which these agents inhibit SARS-CoV *in vitro* are much higher ('supratherapeutic') than the therapeutic plasma levels reached at the recommended doses. Thus, it is possible that plasma levels with meaningful activity against SARS-CoV *in vitro* would not be achieved *in vivo* without potentially adverse effects. This may be the case for ivermectin and ribavirin.¹⁸ Furthermore,

Table 2: Main Pharmacological Characteristics of Some Proposed Drugs for Treating COVID-19

Drug	Target	Adverse Effects	Drug Interactions/Cautions
Baricitinib	Reversible inhibitor of JAK1 and 2	Hyperlipidaemia, deep vein thrombosis, pulmonary embolism, ALT/AST elevations	Avoid in pregnancy
Bevacizumab	Inhibits the binding of VEGF to its receptors VEGFR-1 and VEGFR-2	Hypertension, venous thromboembolism, deep vein thrombosis, congestive heart failure, supraventricular tachycardia, pulmonary embolism	Avoid in pregnancy
Camostat mesylate	Inhibits transmembrane serine protease TMPRSS2	Not published	Not published
CD24Fc	CD24 extracellular domain-IgG1 Fc domain recombinant fusion protein	Not published	Not published
Chloroquine(CQ)/ hydroxychloroquine (HCQ)	Interfere with ACE2 receptor glycosylation; block virus infection by increasing the endosomal pH required for virus/cell fusion; reduce the production of pro-inflammatory cytokines. Inhibit SARS-CoV-2 <i>in vitro</i> (HCQ > CQ)	Inhibit Na ⁺ , L-type Ca ²⁺ and several cardiac K ⁺ channels Hypotension, hypoglycaemia, ECG changes (inversion or depression of the T-wave, QT, PR and/or QRS prolongation), conduction disorders (AV block, bundle branch block), torsade de pointes, ventricular tachycardia, ventricular fibrillation. Cardiomyopathy, which may result in cardiac failure and in some cases a fatal outcome	Inhibit CYP2D6, increasing the exposure of carvedilol, digoxin, metoprolol, propranolol; decrease effectiveness of prodrugs reliant on CYP2D6 for activation (codeine, tramadol). Avoid in patients treated with QT-prolonging drugs or with electrolyte abnormalities. Concomitant use with amiodarone contraindicated. CQ/HCQ are recommended for COVID-19 infection when prescribed in the hospital or as part of a clinical trial. May be used in pregnancy
HCQ + azithromycin		No evidence of the efficacy of this combination	These drugs prolong the QT interval and their combination is contraindicated
Corticosteroids	Anti-inflammatory and immunosuppressive drugs	Oedema, electrolyte abnormalities, hypertension, risk of secondary infection	Reduce the dose of warfarin and monitor the INR
Darunavir/cobicistat	HIV protease inhibitor/CYP3A4 inhibitor. Darunavir is not active against SARS-CoV-2	Dyslipidaemia, hepatotoxicity (AST/ALT elevations, jaundice), severe skin reactions	Both inhibited CYP3A and CYP2D6. Avoid coadministration with amiodarone, dabigatran, dronedarone, ivabradine, lovastatin, quinidine, PDE5 inhibitors, ranolazine, simvastatin, ticagrelor. Avoid during pregnancy
DAS181 [†]	Sialidase catalytic domain/amphiregulin glycosaminoglycan binding sequence fusion protein	Unknown	Unknown
Eculizumab (NCT04288713)	Humanised mAb that specifically binds to the complement protein C5 preventing the generation of the terminal complement complex C5b-9	Muscle and back pain, headache, nasopharyngitis, hypertension. Increases the risk of fatal meningococcal infections	Caution with any systemic infections
Emapalumab	Human mAb that binds to and neutralises IFN-gamma	Hypertension, hypokalaemia, tachycardia, oedema	Increases the risk of serious infections. Emapalumab may normalise CYP450 activities and reduce the efficacy of drugs that are CYP450 substrates
Favipiravir (investigational)	Inhibits RNA polymerase. No effect against SARS-CoV-2 <i>in vitro</i>	No significant differences were observed in the severe or severe and moderate (combined) arms Hyperuricemia, AST/ALT elevations, neutropenia	Contraindicated during pregnancy and breastfeeding
Fingolimod	Sphingosine 1-phosphate receptor modulator	Hypertension, bradycardia, AV block, ALT/AST elevations	Contraindicated in patients with: recent (>6 months) MI, unstable angina, stroke/transient ischemic attacks, NYHA Class III/IV heart failure; cardiac arrhythmias treated with Class Ia or III anti-arrhythmic drugs; second- or third-degree AV block, or sick-sinus syndrome without a pacemaker; baseline QTc interval ≥500 ms. Avoid with bradycardic agents (Class Ia, III and IV anti-arrhythmics, ivabradine, digoxin)
IFX-1	Anti-human complement factor C5a mAb	Unknown	Unknown
IFN-alpha and IFN-beta	Activate cytoplasmic enzymes affecting viral mRNA translation and protein synthesis	Hypertension, palpitations, tachycardia	Not recommended to treat SARS-CoV-2

Table 2: Cont.

Drug	Target	Adverse Effects	Drug Interactions/Cautions
Ivermectin	Inhibits replication of SARS-CoV-2 <i>in vitro</i>	Hypotension, oedema, tachycardia, ALT/AST increases.	
Leronlimab (experimental)	Humanized mAb against CC chemokine receptor 5 (CCR5)	Unknown	Unknown
Lopinavir/ritonavir (±IFN-beta)	Inhibits the enzyme 3-CL protease crucial in processing the viral RNA. Lopinavir inhibits SARS-CoV-2 replication <i>in vitro</i>	There is no strong evidence to recommend the use of lopinavir/ritonavir for COVID-19 Hypertension, AV block, QTc prolongation, high-degree AV block, PR and QT prolongation, torsades de pointes. Elevated ALT/AST, hepatotoxicity, hyperlipidaemia, new-onset diabetes, pancreatitis	They are potent inhibitors of CYP3A4 and should not be administered with CYP3A4 substrates: amiodarone, apixaban, atorvastatin, bosentan, calcium channel blockers, clarithromycin, cyclosporin, dronedarone, digoxin, edoxaban, flecainide, lovastatin, PDE5 inhibitors, propafenone, ranolazine, riociguat, rosuvastatin, simvastatin, tacrolimus, ticagrelor, warfarin. Decrease the exposure to clopidogrel and prasugrel. Avoid QT-prolonging drugs. Can be used in pregnancy
Merimepodib	Inosine-5'-monophosphate dehydrogenase inhibitor. Inhibits SARS-CoV-2 replication	Unknown	Unknown
Nicosamide	Prevents viral entry by altering endosomal pH and prevents viral replication	No longer approved for use in the US as an antihelminthic drug	
Nitazoxanide	Increases phosphorylated factor 2-alpha required for protein synthesis	Adverse effects are rare	Unknown
NSAIDs	Anti-inflammatory drugs		Acetaminophen is recommended
Oseltamivir	Inhibits influenza A and B neuraminidases. No apparent effect against SARS-CoV-2 <i>in vitro</i>	ALT/AST elevations, hepatotoxicity, angioneurotic oedema	No role in the management of COVID-19 once influenza has been excluded
Pirfenidone	Inhibits the release of pro-inflammatory cytokines (TNF-alpha, IL-1beta)	Hot flush, ALT/AST elevations	Unknown
Remdesivir [†]	Inhibits RNA polymerase to stop viral replication. Antiviral activity against SARS-CoV-2	Approved by the FDA (emergency use authorisation) and EMA (conditional marketing authorisation). Infusion-related reaction (hypotension, nausea, vomiting, sweating and shivering), ALT/AST elevations, renal impairment, multiorgan failure	Not reported
Rintatolimod [†]	TLR3 agonist	Unknown	Unknown
Ribavirin	Inhibits viral RNA-dependent RNA polymerase. No antiviral effect against SARS-CoV-2 <i>in vitro</i>	Palpitations, tachycardia, hypotension, hypertriglyceridemia, hyperuricemia, ALT/AST elevations. Haemolytic anaemia, which may result in worsening of cardiac disease and lead to MI	Inconclusive results in the treatment of SARS. Contraindicated if pre-existing cardiac disease, including unstable or uncontrolled cardiac disease, during pregnancy and breastfeeding
Ruxolitinib	JAK1 and JAK2 inhibitor	Hypertension, increases in ALT/AST and lipid parameters, infections	Strong CYP3A4 inhibitors increase ruxolitinib exposure: reduce the dose by 50%. Ruxolitinib increases the exposure to dabigatran etexilate, cyclosporin, rosuvastatin and digoxin
Sarilumab	Human mAb that specifically binds to IL-6 receptors	Hyperlipidaemia, upper respiratory tract infection, ALT/AST elevations	Increases the expression/activity of CYP450 enzymes (1A2, 2B6, 2C9, 2C19, 2D6 and 3A4) decreasing the plasma levels of drugs that are substrates of these enzymes
Tocilizumab	Recombinant humanised anti-human IL-6 receptor mAb	Hypertension, upper respiratory tract infections, hyperlipidaemia, ALT/AST elevations, hepatotoxicity, gastrointestinal perforations. Increased severe and sometimes fatal infections. Serious allergic reactions, including death	Increases the expression/activity of CYP450 enzymes (1A2, 2B6, 2C9, 2C19, 2D6 and 3A4), decreasing the plasma levels of drugs that are substrates of these enzymes. Caution in patients with neutropenia or thrombocytopenia. May cause foetal harm
Tradipitant	Neurokinin-1 receptor antagonist	Unknown	Unknown
Umifenovir	S protein/ACE2 membrane fusion inhibitor that prevents viral entry to the target cell	GI upset, ALT/AST elevations, allergic reactions	Caution with potent CYP3A4 inhibitors/inducers

[†]Experimental drugs. 3-CL = 3-chymotrypsin-like; ACE2 = angiotensin-converting enzyme 2; ALT/AST = alanine/aspartate aminotransferase; AV = atrioventricular; CYP = cytochrome P450; FDA = Food and Drug Administration; GI = gastrointestinal; IFN = interferon; IL = interleukin; INR, international normalised ratio; JAK = Janus-associated kinase; mAb = monoclonal antibody; NYHA = New York Heart Association; PDE5 = phosphodiesterase type 5; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TLR = Toll-like receptors; TMPRSS2 = transmembrane protease, serine 2; TNF = tumour necrosis factor; VEGF = vascular endothelial growth factor.

several drugs under development or already approved for other indications, exhibiting a broad-spectrum antiviral activity, are now being tested in COVID-19 patients even when their efficacy and safety in *in vivo* models or in patients is uncertain. Some antivirals (favipiravir, baloxavir) show no activity against SARS-CoV-2 *in vitro* at concentrations under 100 µmol/l, but they are, however, being tested in ongoing trials.¹⁹ It would not be surprising if the results were disappointing.

The second is how the pharmacokinetic properties of many of the currently investigated drugs, which were studied in healthy volunteers or in patients affected with the disease for which the drug was initially approved, behave in COVID-19 patients.

In the rush to find a treatment, several ongoing trials are being conducted with drugs that were developed but not approved as yet, or were approved to treat other non-COVID-19 diseases (repurposed agents). However, the half maximum effective concentrations and the recommended doses of these drugs against different viruses are quite different and are based on the particular type of infectious disease. Therefore, the question is how will the most effective and safer dose be calculated in patients with COVID-19? In fact, doses of a given drug may differ in different trials. For example, the dose of chloroquine used to treat COVID-19 varies from 500 mg orally twice daily for 5–10 days to a loading dose of 400 mg twice daily for 1 day followed by 200 mg twice daily for 4 days.^{20–22} Thus, studies are needed to determine the optimal dose range for the drugs used in the treatment of COVID-19 patients.

We must keep in mind that patients with COVID-19 and pre-existing cardiovascular disease have an increased risk of developing severe symptoms and death, and COVID-19 itself is associated with several cardiovascular complications, including acute myocardial injury, myocarditis, arrhythmias and venous thromboembolism.^{8,23} Some drugs tested in ongoing trials produce serious cardiovascular and non-cardiovascular adverse effects (hepatotoxicity, neutropenia and increased risk of infection), which clearly represents a clinical challenge (Table 2). It is also recommended to avoid the coadministration of drugs that prolong the QT interval (azithromycin with chloroquine/hydroxychloroquine) and to prescribe chloroquine/hydroxychloroquine, which can produce serious cardiovascular events, only in-hospital or as part of a clinical trial, in patients with COVID-19.

Although corticosteroids were not initially recommended for COVID-19 patients because of the lack of proven benefit and potential harm with these drugs, the RECOVERY Collaborative Group has very recently shown that in hospitalised patients with COVID-19, the use of dexamethasone for up to 10 days resulted in lower 28-day mortality than usual care among those who were receiving either invasive mechanical ventilation or oxygen alone at randomisation.²⁴

Interestingly, the safety profile of drugs not already approved by the Food and Drug Administration (FDA) or the European Medicines Agency is based on limited published evidence, so that their safety profile remains uncertain and we must await the results of ongoing prospective, randomised, controlled studies before the widespread adoption of these drugs.²⁵ Additionally, some drugs (HIV protease inhibitors, IL-6 receptor antagonists) inhibit or induce the activity of some cytochrome P450 3A4 enzymes and

increase or decrease, respectively, the exposure of multiple drugs that are substrates of such isoforms (Table 2). Therefore, investigational anti-COVID-19 therapeutics should be used only in approved, RCTs.

Almost on a daily basis, case reports, observational or small retrospective, non-randomised studies are published in major journals and non peer-reviewed journals. Albeit describing interesting cases and findings, many of these articles suffer from serious methodological problems, including lack of blinding, small sample size (<50 patients per group) and marked variations in the inclusion/exclusion criteria, presence of background therapy and varied treatment regimens (different doses, different duration of therapy and different routes of administration), which makes it difficult to ascertain the true treatment effect. Furthermore, the effects of current treatments on quality of life and drug safety are underreported. This variability can explain why even studies performed in the same country with the combination of hydroxychloroquine and azithromycin may lead to contradictory results.^{26,27} Additionally, the non-standardised collection of clinical data limits the conclusions from retrospective analysis. As an example, one trial recruiting 21 patients concluded that 91% of patients were discharged on average 13.5 days after the treatment with tocilizumab (400 mg IV), with most patients receiving only one dose; however, the lack of a comparator group limits the interpretation of these results.²⁸

Furthermore, sometimes the preliminary exciting results of one study are not confirmed in other trials. This may indeed be the case of remdesivir. In 53 patients hospitalised for severe COVID-19 who were treated with compassionate-use remdesivir, clinical improvement was observed in 68% of patients.²⁹ These promising results led to a Phase III trial in China. Surprisingly, on 23 April 2020, the WHO reported the preliminary results of a Phase III Chinese trial but this report was quickly withdrawn, suggesting that remdesivir did not have beneficial effects in COVID-19 patients or that it was not able to reduce the virus in the bloodstream. Interestingly, the researchers responsible for the study indicated that they had not approved its posting. This is a good example of how rushing to obtain results can lead to speculation and unhelpful rumours about the effectiveness of drugs. Nevertheless, on 1 May 2020, the FDA issued an Emergency Use Authorisation for emergency use of remdesivir for the treatment of hospitalised COVID-19 patients.³⁰ Ongoing clinical trials will define which patients will best benefit from remdesivir treatment.

Conclusion

COVID-19 is a new pandemic and, to date, no specific drug has been found to be effective. The identification of effective interventions against COVID-19 (including vaccines) has become a public health priority. Scientists and physicians are facing the challenge to better understand the characteristics of this new virus and the pathophysiology of the disease that it causes, in order to identify possible therapeutic targets and effective therapeutic drugs and vaccines. Despite these efforts, at the present time, we are still shooting in the dark for the reasons mentioned here. Adequately powered randomised clinical trials are needed to establish the efficacy and safety of therapeutic agents prior to the widespread adoption of these therapies. Attempts should be made to develop suitable treatment protocols and to standardise datasets that could facilitate meaningful analysis of treatment effects and clinical outcomes. ■

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