Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Public Health 197 (2021) 48–55

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Commentary

COVID-19, corticosteroids and public health: a reappraisal

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ARTICLE INFO

Article history:
Received 16 October 2020
Received in revised form
4 May 2021
Accepted 25 May 2021
Available online 7 June 2021

Keywords:
COVID-19
RECOVERY trial
WHO meta-analysis
Variants
Immunity
Public health

ABSTRACT

Objectives: To assess whether regulatory guidance on the use of dexamethasone in hospitalised COVID-19 patients is applicable to the larger population of COVID-19 cases. The surge in worldwide demand for dexamethasone suggests that the guidance, although correct, has not emphasised the danger of its wider use.
Study design: Data from the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial and the World Health Organisation (WHO) prospective meta-analysis have been deconstructed and analysed.
Methods: To provide context, relevant publications were identified in PubMed using the following keywords: COVID-19, RECOVERY trial, WHO meta-analysis, variants, immunity, public health.
Results: The WHO guidance 'Corticosteroids for COVID-19' was based on their prospective meta-analysis. This meta-analysis was weighted by data from the RECOVERY trial.
Conclusions: In terms of COVID-19, dexamethasone has value in a narrow indication, namely, in hospitalised patients requiring respiratory support. The media blitz likely resulted in the wider use of dexamethasone in outpatients and as a preventive medication. This is reflected in the surge in worldwide demand for dexamethasone. We ask whether the use of steroids, beyond regulatory indications, may be responsible for the recent increase in mortality and especially the emergence of mucormycosis? From the public health standpoint, the current guidance for use of dexamethasone in COVID-19 could benefit from clarification and the addition of a cautionary note.

Introduction

There is no evidence that specific interventions can decrease mortality in acute respiratory distress syndrome (ARDS); therefore, the preliminary results of the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, announced in June 2020, were both surprising and welcomed.[1–4] This trial was conducted in hospitalised COVID-19 patients and explored the effect of dexamethasone in the following three severity-based categories: (i) individuals receiving invasive mechanical ventilation (IMV); (ii) individuals receiving oxygen only; and (iii) individuals receiving no oxygen. The organisation and implementation of the RECOVERY trial was phenomenal[5] and upon completion, regulatory and policy action was prompt. In September 2020, the World Health Organisation (WHO), based on results from the RECOVERY trial[2] and its sponsored prospective meta-analysis[6] updated their guidance on the use of corticosteroid drugs in patients with COVID-19.[7]

Here, we analyse the RECOVERY trial within the broader context of the natural history of COVID-19 disease and comment on whether the preliminary results are sufficient to formulate global policy. We identify several gaps in the evidence and suggest that policy formulation is deferred until the protocol-specified 180-day follow-up report is published. This would allow for efficacy to be assessed against adverse events in all population categories, especially the elderly, those with relevant comorbidities and those with a weakened immune system; A 180-day safety report would represent an index of sustained benefit. In this commentary, we do not question the results of these trials, but focus on the interpretation of the analyses and the communication of a consistent message relative to global public health.

Methods

Data source and analysis

Relevant publications were identified in PubMed using the following keywords: COVID-19, RECOVERY trial, WHO meta-analysis, variants, steroids, mucormycosis, public health. To allow

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https://doi.org/10.1016/j.puhe.2021.05.028
0033-3506/

for comparisons between RECOVERY and the WHO meta-analysis, published tables were deconstructed and analysed. Simple, comprehensive, and uniform risk measures[8–10] were calculated to allow for an understanding of, and comparisons between, the trials.

RECOVERY trial

In this randomised trial of 6425 patients, 2104 received dexamethasone 6 mg once per day for 10 days and 4321 received usual care. The 28-day mortality was calculated for the total study group, as well as subgroups of individuals who required IMV ($n = 1007$), oxygen only ($n = 3883$) and in those who did not require respiratory support ($n = 1535$). Overall, 482 patients (23%) in the dexamethasone group and 1110 patients (26%) in the usual care group died within 28 days after randomisation (odds ratio [OR]: 0.86; 95% confidence interval [CI]: 0.75 to 0.97; $P = 0.017$) [refer Table 1].

The RECOVERY trial[2] showed that, overall, 482 of 2104 patients (22.9%) receiving dexamethasone died compared with 1110 of 4321 patients (25.7%) receiving usual care; a difference of 3%. In the no-oxygen subgroup, 89 of 501 patients (17.8%) in the dexamethasone group died compared with 145 of 1034 patients (14.0%) receiving usual care; a difference of 4%.

In the oxygen-only subgroup, 298 of 1279 patients (23.3%) in the dexamethasone group died compared with 682 of 2604 patients (26.2%) receiving usual care; a difference of 3%. And, in the IMV subgroup, 95 of 324 patients (29.3%) in the dexamethasone group died compared with 1110 of 4321 patients (41.4%) receiving usual care; a difference of 12%.

The organisation and implementation of the RECOVERY trial was phenomenal[5] and upon completion, regulatory and policy action was prompt. The results were communicated enthusiastically in the media and positioned as a breakthrough: dexamethasone is the first drug shown to save lives.[3] On 2 September 2020, and based on the preliminary report on the RECOVERY trial and related meta-analyses, the WHO endorsed the use of corticosteroids in cases of severe and critical COVID-19.[7] Dexamethasone reduced deaths by one-third in ventilated patients and by one-fifth in patients receiving oxygen only. However, there was a trend to harm in patients who did not require oxygen. Based on these results, one death could be prevented by dexamethasone treatment of around eight ventilated patients or around 25 patients requiring oxygen alone.[1] Chief investigator Martin Landray, in an interview with *Science* stated, 'It's very, very rare that you announce results at lunchtime, and it becomes policy and practice by tea time, and probably starts to save lives by the weekend'.[11]

RECOVERY trial: advantages and limitations of a platform design

RECOVERY, a platform trial, involved the following two interventions in hospitalised COVID-19 patients: (i) dexamethasone to all patients and (ii) additional IMV in patients with severe disease. Platform trials that randomise patients with a homogenous and stable disease to a variety of single treatments are a valid and efficient method to explore benefit under uncertainty.[12] However, in an intensive care unit (ICU) setting, the rapid dynamics of disease may require a severe subgroup to be exposed to more than one intervention. Accordingly, implementation of a platform trial in an ICU can evolve into a treatment trial. Here, interpretation of results is problematic on account of interactions between interventions: can outcomes be assigned to a single intervention − dexamethasone, IMV or more prudently to the combination?[13] It is impossible to design a trial in human volunteers to assess a possible beneficial effect of dexamethasone in alleviating the adverse effects of IMV. However, Reis et al.[14] have demonstrated a beneficial effect of pretreatment with dexamethasone in ventilator-induced lung injury (VILI) in Wistar rats.

The objective of a platform trial is to attribute outcomes to distinct and discrete interventions. This is a relevant concern since IMV can be complicated by a cytokine-related, hyper-inflammatory lung injury (termed VILI) that is similar to COVID ARDS. In RECOVERY, both interventions relate to the trial end point, which is mortality via multiple organ dysfunction syndrome (MODS).[15,16] Therefore, it is possible that the beneficial effect of dexamethasone in the severe IMV subgroup was related to its dampening impact on the effects on both viral and mechanical ventilation-induced inflammation, rather than the sole inhibition of a COVID-19 specific mechanism. In RECOVERY, dexamethasone did not show beneficial effects in hospitalised patients who did not require oxygen with or without respiratory support.[2]

Steroids, IMV and COVID-19

The literature on this topic is both controversial and confusing. In ARDS, the administration of steroids within the first 72 h of mechanical ventilation is directed to dampen the hyper-inflammatory response, as evidenced by an increase in ventilator-free days and lower mortality. Several studies have experienced confounding from the likely presence of VILI, and steroids may have shown beneficial effects by minimising the ongoing inflammation caused by non-protective ventilator settings.[17] In patients receiving IMV, Zhang et al.[18] concluded that corticosteroids did not decrease mortality. However, Meduri et al.[19] have shown that steroids decrease the adverse effects of mechanical ventilation and reduce mortality in patients with non-COVID ARDS. VILI occurs when mechanical ventilation exacerbates lung injury in critically ill patients. In ARDS, iatrogenic injury caused by VILI contributes to their high mortality via a systemic inflammatory response that drives MODS.[20–24]

Despite a rationale for the prolonged use of steroids in COVID-19,[25] the general experience is that they are ineffective in virus-induced ARDS.[26–28] Furthermore, steroids enhance viral replication,[29] delay viral clearance[30–33] and may increase mortality.[34] For good reason, its use during active infection is generally discouraged. Li et al.[32] performed a meta-analysis to determine safety and efficacy of corticosteroids in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), SARS-CoV and Middle East respiratory syndrome coronavirus infections. The use of corticosteroids

Table 1
Effect of dexamethasone on 28-day mortality according to respiratory support.[2]

Subgroup	Dexamethasone 28-day mortality [n/N (%)]	Usual care 28-day mortality [n/N (%)]	OR (95% CI); *P*-value	Risk difference (%)	Risk ratio
No oxygen	89/501 (17.8%)	145/1034 (14%)	1.32 (0.99–1.77); $P = 0.067$	−3.8	1.27 = 27%
Oxygen only	298/1279 (23.3%)	682/2604 (26.2%)	0.86 (0.73–1.0); $P = 0.06$	+2.9	1.12 = 12%
IMV	95/324 (29.3%)	283/683 (41.4%)	0.59 (0.44–0.78); $P = 0.0003$	+12	1.41 = 41%
TOTAL	482/2104 (22.9%)	1110/4321 (25.7%)	0.86 (0.75–0.97); $P = 0.017$	+2.8	1.12 = 12%

CI, confidence interval; IMV, invasive mechanical ventilation; OR, odds ratio.

delayed viral clearance and did not improve survival but did reduce duration of hospital stay, ICU admission rate and/or use of IMV. Liu et al.[33] at the Shanghai Jiao Tong University School of Medicine, Shanghai, China, analysed the outcome of corticosteroid treatment, mainly methyl prednisolone, in severe COVID-19 patients with ARDS ($n = 409$) compared with standard care ($n = 365$). The end point was 28-day all-cause mortality. For patients receiving standard care, mortality was 31% (113 of 365 patients) and for those receiving steroids, mortality was 44% (181 of 409 patients). The increase in mortality in patients receiving steroids was 13% (OR: 1.77; 95% CI: 1.31 to 2.38; $P = 0.0002$). Patients with moderate-to-severe COVID-19 pneumonia are likely to benefit from moderate-dose corticosteroid treatment when administered relatively late in the disease course.[34] Before the RECOVERY trial, clinical evidence did not show any beneficial effects of corticosteroid treatment for COVID-19 lung disease.[35,36] In viral pneumonia, there is a tendency for steroids to delay viral clearance and thereby increase residence time but this is controversial.[28,37–39]

Framework for research and development: natural history of COVID-19

COVID-19 is a progressive disease that primarily affects the lungs. About 85% of COVID-19 cases are asymptomatic, and it is estimated that 15% require hospitalisation and a smaller fraction need IMV. It is not possible to predict possible progression or lack thereof in individual COVID-19 cases. In those with serious progressive disease, hospitalisation is indicated and management is predicated on the need for oxygen or IMV. Although subgroups facilitate analysis, they are not distinct or stable. It should be noted that progression of the disease is a continuum and ranges from 'no oxygen required' to 'oxygen only' and 'IMV'.

COVID-19 variants, steroids, ageing and the adaptive immune system – Dr Jekyll and Mr Hyde

Similar to *The Strange Case of Dr Jekyll and Mr Hyde*, steroids show contrasting clinical outcomes in viral infections – both benefit and harm (refer Fig. 1). The chemistry and effects of steroids are intriguing; they have anti-inflammatory, immunosuppressive effects and accelerate the replication of viruses. Increased replications favour mutations and increase the viral load. According to Javier Ramirez at the Departamento de Química Orgánica, Universidad de Buenos Aires, Buenos Aires, Argentina, the clinical outcome of the use of steroids in viral diseases is still controversial.[40] Upon encountering a pathogenic virus, the host senses the invasion and triggers complex and sequential innate and adaptive immune responses resulting in inflammation. Steroids are effective in controlling hyper-inflammation, but they also have the potential to cause deleterious effects.

Deborah Shoemark et al.[41] at the University of Bristol and the Max Planck Bristol Centre for Minimal Biology, UK, suggest that in COVID-19, dexamethasone binds to the spike protein and thus interferes with infection by changing its interaction with the host cell. It is possible that dexamethasone acts directly at the molecular level and indirectly by modulating the immune system. This may explain, in part, the complex response to corticosteroids. A discrete intervention, as with steroids, can elicit opposite clinical outcomes which is likely to be a result of the evolution of the virus in adapting to differing states and changes in the immune environment – the dynamic host response to infection.

Sandra Amor and colleagues at the VU University Medical Center, Amsterdam, The Netherlands, explain that the virus subverts the initial immune response, leading to respiratory and vascular damage.[42] Alex Sette and Shane Crotty at the La Jolla Institute for Immunology and the University of California, San Diego La Jolla Center for Immunology, US, present a comprehensive analysis of the components and functions of the adaptive response to SARS-CoV-2 and COVID-19.[43] The adaptive immune system consists of three cell types: B cells, $CD4^+$ T cells and $CD8^+$ T cells. B cells produce neutralising antibodies, $CD4^+$ T cells generate helper and effector functionalities, and $CD8^+$ T cells kill infected cells. When the host response includes the sequential involvement of all three elements, patients, in general, do well. Progression to severe disease usually follows an uncoordinated adaptive immune response. The advanced phase is marked by high levels of cytokines, antibodies and virus load, together with a low T-cell count. Since host responses are important for the control and clearance of viral infection, and immune memory is central to the success of vaccines, it is important to understand the phasic immune responses to SARS-CoV-2[43–45] (refer Fig. 2).

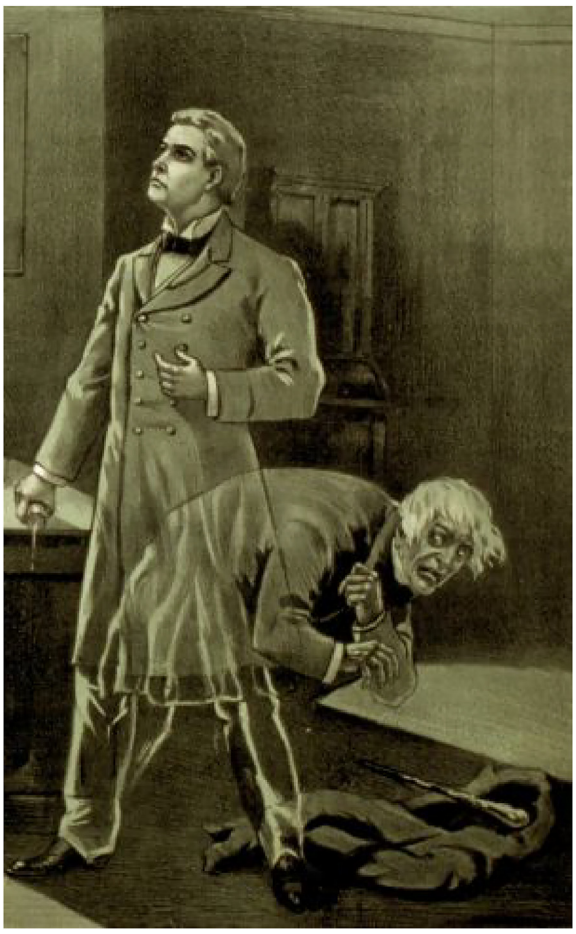

Fig. 1. In viral infection, the administration of steroids can result in contrasting clinical outcomes. (The Strange Case of Dr Jekyll and Mr Hyde. By, Robert Louis Stevenson. London; Longmans, Green and Company, 1886).

Type I and III interferons, the body's first line of antiviral defence, are cytokines that are secreted by host cells in response to viral infection and which block virus replication at several levels.[46,47] In COVID-19, this response may be dampened by the early administration of glucocorticoids.[48–50] This, in part, may explain the role of a weakened and uncoordinated immune system in both the recent surge in mortality and the generation of variants.[51,52] A weakened immune system is clinically relevant to the management of infection in elderly patients and those who are immunosuppressed, in addition to its importance in vaccination programmes.

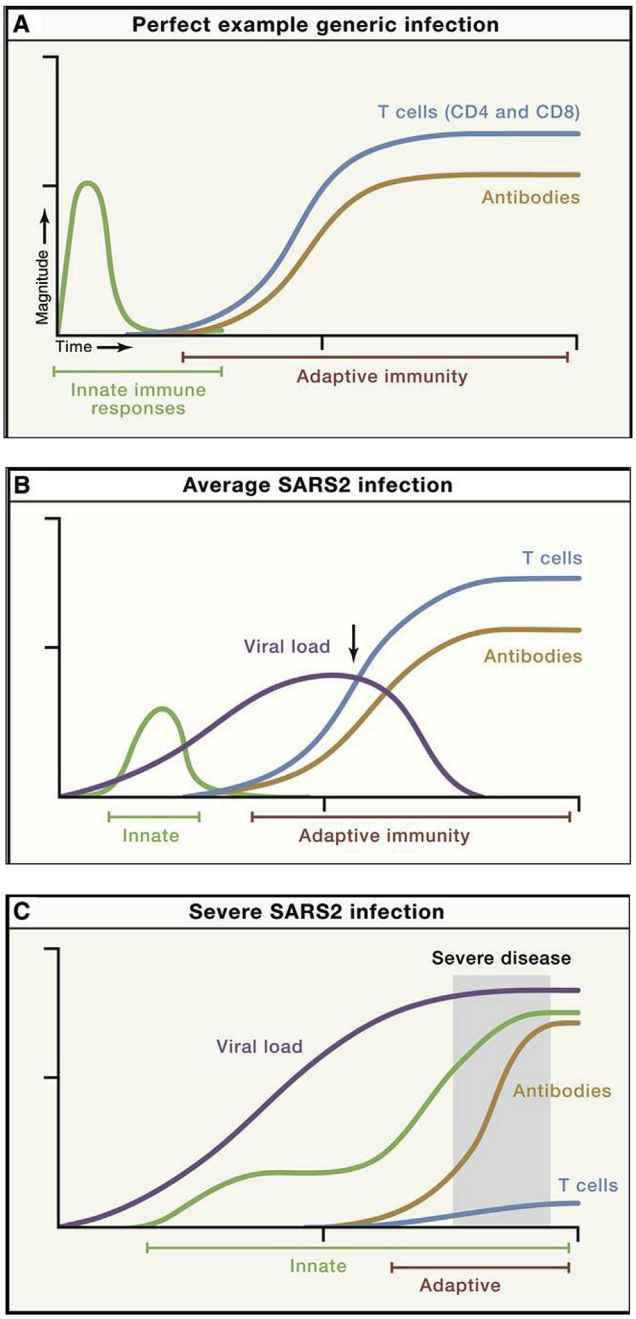

Fig. 2. Innate and adaptive immune response trajectories in COVID-19 (reproduced from Sette and Crotty,[43] with permission). (A) Generic viral infection. (B) Usual SARS-CoV-2 infection. (C) Severe SARS-CoV-2 infection. The initial innate immune response is depicted in green while the later adaptive response consists of antibodies (orange) and T cells (blue). In the usual infection, the coordinated response results in a decrease in the viral load (purple). An uncoordinated and delayed immune response results in an increased and sustained viral load. The latter is likely related to a weak T-cell response. The period of severe COVID-19 clinical disease is shaded grey. Note: T cells refer to virus-specific CD4+ and CD8+ T cells and antibodies refer to virus-specific neutralising antibodies. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

The terms mutation, variant and strain are often used interchangeably, but the distinctions are important.[53] Mutation refers to a change in the sequence of amino acids. Viral mutants are termed variants. Strains are variants that have a different phenotype resulting in differences in antigenicity, transmissibility or virulence. Steven Kemp and colleagues at the University of Cambridge, UK, reported on a real-time mutation of the coronavirus in a single patient.[54] It is likely that at some point, the virus infects an individual with a weak immune system; this allows time for adaptation and evolution prior to transmission. The virus accumulates mutations every time it replicates and the effect of steroids in accelerating replication should be kept in mind. In an excellent editorial in *Virulence*, van Oosterhout et al.[55] at the School of Environmental Sciences, University of East Anglia, Norwich, UK, warn that novel variants show an improved interaction with host-cell receptors, such as ACE2 on epithelial cells. This enables the virus to better establish and propagate infections, resulting in higher levels of virus in the host and an increased rate of transmission. Neutralising antibodies bind to spike proteins and can block the ability of the virus to infect new cells. SARS-CoV-2 can mutate its spike proteins to evade these antibodies. There is a need to ensure that interventions are designed to activate the strongest possible immune response, especially in the elderly, against more than one target region on the spike protein and thereby prevent the development of variants.[56,57]

At this time, about a dozen COVID-19 variants have been identified and three are now spreading globally: the UK/Kent variant (B.1.1.7), the South Africa/Nelson Mandela Bay variant (B.1.1351) and the Brazilian/Manaus variant (B.1.1.28.1/P.1).[58] The recent surge in India may be related to a 'double mutant' B.1.617 (mutations in E484Q and L452R). The B.1.617 variant is associated with increased infectivity and immune evasion from antibodies. According to Vaughn Cooper at the University of Pittsburgh's Center for Evolutionary Biology and Medicine, US, the generation of variants is consistent with convergent evolution, where a few mutations (e.g. in the spike protein) in different independent lineages occur as they adapt to similar environments.[59] All three variants have mutations in the spike protein (E484K), and this is the main driver of immune evasion. Steroids have dual and opposing clinical effects in COVID-19 disease – Dr Jekyll and Mr Hyde. This is likely due to the presence or absence of inflammation. In an advanced hyper-inflammatory state it provides benefit, while in the earlier, paucisymptomatic and non-inflammatory state, its use is associated with harm.[51] The newly recognized association of virus variants in people with weakened immune systems should prompt concern in the use of steroids in milder and the early stages of the disease, and in those with autoimmune disease. These variants have a high transmission potential (i.e. are very contagious) and interference with mRNA vaccines is a concern.[60]

Public health and policy considerations

The RECOVERY trial demonstrated that dexamethasone decreased 28-day mortality in about one-third of hospitalised patients receiving IMV. Dexamethasone is about 25 times more potent than hydrocortisone. Steroids accelerate viral replication, delay viral clearance and predispose individuals to nosocomial infection. For good reason, its use during active infection is generally discouraged. Accordingly, a careful distinction should be made between early intervention in progressive disease and mass prevention, especially with an agent with a known safety liability. Dexamethasone is risky in mild cases.[61]

The recent epidemic of Mucormycosis in India has been attributed to the rampant use of steroids in non-hospitalised individuals, uncontrolled diabetes, and exposure to the fungal spores found in the soil and decaying organic matter. Infection is via inhalation of spores and spread occurs via the sinuses, orbit and the brain. The mortality rate exceeds 50%. Management is based on antifungal medicines and advanced disease requires exentration – removal of the eye and surrounding tissue. At last count, in June 2021, over 30

000 cases have been reported. This may be the first instance of an iatrogenic epidemic complicating a pandemic.

Unfortunately, these concerns have not received attention. Both the statement of the chief investigator, Peter Horby, 'this treatment can be given to pretty much anyone'[3] and the guidance offered to primary care physicians to consider dexamethasone for home treatment[62] do not appear appropriate. This is important since the preliminary report on the RECOVERY trial, and the media blitz that followed, may have prompted a worldwide surge in demand for dexamethasone for outpatient use.[63–66] After the RECOVERY announcement, US drug suppliers struggled to keep up with the demand for dexamethasone. Group drug purchaser VIZIENT, which supplies medicines to about half of the hospitals in the US, saw a 610% increase in requests for dexamethasone.[67] It is unlikely that the narrow clinical indication (i.e. use limited to ICU patients on respiratory support) was the cause for this surge in demand.

According to Ralph Baric at the University of North Carolina in Chapel Hill, US, 'in COVID-19 disease early administration of steroids can cause more harm than good because they may dampen the immune response before it has the virus at bay. The best time to start dexamethasone is when patients first need respiratory support.' (The Economist, *Technology Quarterly*, March 27, 2021). Shane Crotty cautions that if steroids are prescribed too early 'you could really shoot oneself in the foot because this might be somebody whose adaptive immune response is just getting going'.[43]

WHO guidance, 2020

In September 2020, the WHO issued the guidance entitled 'Corticosteroids for COVID-19'. This guidance was prompted by the RECOVERY trial and supported by a WHO sponsored prospective meta-analysis.[6,7] Their two recommendations were to use systemic corticosteroids in patients with severe and critical COVID-19, and to avoid corticosteroids in patients with non-severe COVID-19.

The prospective meta-analysis pooled data from seven randomised clinical trials that evaluated the efficacy of corticosteroids in 1703 critically ill patients with COVID-19. Patients were assigned to steroids (dexamethasone, hydrocortisone or methylprednisolone) (n = 678) or to usual care or placebo (n = 1025). The primary outcome was 28-day all-cause mortality. There were 222 deaths among the 678 patients randomised to corticosteroids and 425 deaths among the 1025 patients randomised to usual care or placebo. This corresponds to an absolute mortality risk of 33% for patients receiving corticosteroids compared with 41% for patients receiving usual care or placebo (OR: 0.7; 95% CI: 0.56 to 0.84; $P = 0.0003$). The WHO meta-analysis relative to the RECOVERY data is deconstructed in Table 2.

It can be seen that the RECOVERY data was a major contributor to the WHO meta-analysis (weight = 57%). Both hydrocortisone and methyl prednisolone were ineffectual. These trials were incomplete (underpowered) and although seeming to favour the use of steroids, did not demonstrate significant differences. Tomazini et al.[68] in Brazil recently reported on the completed CoDEX open-label randomised trial evaluating dexamethasone against standard care. In this well conducted trial, 151 patients were assigned to dexamethasone and 148 to standard care. Although there was an increase in the number of ventilator-free days over 28 days (i.e. days alive and free of mechanical ventilation), dexamethasone did not decrease 28-day mortality (56% in the dexamethasone group vs 61% the standard care group) (OR: 0.8; 95% CI: 0.50 to 1.28; $P = 0.43$).

We conclude that for patients receiving IMV, dexamethasone demonstrates efficacy and that corticosteroids other than dexamethasone are ineffective in COVID-19. We wait with anticipation for the follow-up report of the RECOVERY trial to assess the effect of age, obesity, cardiovascular disease, diabetes, and hypertension on the incidence of death.[69,70] In addition, a 180-day mortality assessment in RECOVERY would confirm sustained efficacy and help further the benefit-risk analysis. Carl Heneghan, director of the Centre for Evidence Based Medicine at the University of Oxford, UK, has suggested that a follow-up beyond 28 days and additional analyses would clarify whether dexamethasone could harm patients in the longer term.[65]

The future—from repurposed drugs to purposive science

A recent editorial in *The Lancet* calls for an increase in research towards a broader range of therapies.[71] In this complex situation, generated by several inter-related mechanisms, it is not possible to assign success to the inhibition of a putative and primary causal process. Misattribution of outcomes may have the effect of not recognising and funding epidemiology, public health and mechanistic research and development in COVID-19 ARDS. Furthermore, the COVID-19 model is mechanistically relevant to related, multicausal, common and fatal conditions, such as septic shock.[72]

Although morbidity and proximate cause of death is COVID-19, related to define pulmonary and coagulation complications, it is a

Table 2
WHO meta-analysis and the RECOVERY trial: association between corticosteroids and 28-day all-cause mortality (modified from[2,6]).

Drug/trial name	Steroids 28-day mortality (n/N]	No steroids 28-day mortality (n/N]	OR (95% CI); *P*-value	Weight, %
DEXAMETHASONE				
DEXA-COVID-19	2/7	2/12	2 (0.2–19)	1
CoDEX	69/128	76/128	0.80 (0.49–1.31); $P = 0.45$	19
RECOVERY – IMV	95/324	283/683	0.58 (0.44–0.78); $P = 0.0003$	**57**
HYDROCORTISONE				
CAPE COVID	11/75	20/73	0.46 (0.20–1.0)	7
COVID STEROID	6/15	2/14	4 (0.65–25)	1
REMAP-CAP	26/105	29/92	0.72 (0.38–1.3)	12
METHYL PREDNISOLONE				
STEROIDS-SARI	13/24	13/23	0.91 (0.29–2.9)	3
WHO OVERALL	222/678	425/1025	0.69 (0.56 to 0.84); $P = 0.0003$	
RECOVERY – ALL	482/2104	1110/4321	0.86 (0.76 to 0.97); $P = 0.017$	
WHO minus RECOVERY-IMV	127/354	142/342	0.79 (0.58–1.06); $P = 0.15$	
WHO plus RECOVERY-ALL	704/2782	1535/5346	0.84 (0.76–0.93); $P = 0.001$	
CoDEX – Final report[67]	85/151	91/148	0.8 (0.50–1.28); $P = 0.43$	
WHO plus CoDEX final report	238/701	440/1045	0.71 (0.58–0.86); $P = 0.0007$	

CI, confidence interval; IMV, invasive mechanical ventilation; OR, odds ratio; RECOVERY, Randomised Evaluation of COVID-19 Therapy; WHO World Health Organisation.

systemic disease.[73] Based on pathophysiology, a comprehensive research and development approach would necessitate a broad portfolio. Unfortunately, the media blitz on steroids has resulted in a de-emphasis of related research in coprimary mechanisms, such as cytokine release,[74–77] the bradykinin-kallikrein system,[78–80] the complement cascade,[81–85] contact activation and coagulation[86,87] and neutrophil extracellular traps (NETosis).[88–91] The patterned response of the host reflects parallel and inter-related mechanisms. The initiating event is likely an interaction between the virus and endothelial elements in the blood vessels leading to immunothrombosis.[92,93]

Argument for mechanistic clinical trials

More than 95% of all trials in sepsis and ARDS fail to demonstrate a positive and reproducible mortality effect.[94] Armand Girbes and Harm-Jan de Grooth at the VU University Medical Center, Amsterdam, The Netherlands, point to the limitations of large trials with mortality end points in patients with sepsis and ARDS.[95] When patients with the same syndrome diagnosis do not share the same pathways that lead to death (the attributable risk), any therapy can only lead to small effects. Larger and more 'pragmatic' randomised trials are not the solution because they decrease diagnostic precision, the effect size and the probability of finding a beneficial effect. A logical approach is a focus on mechanistic research into the complexities of critical illness syndromes.

Conclusions

The success of dexamethasone in the treatment of serious COVID-19 patients receiving IMV has been an electrifying advance in therapeutics and we congratulate the RECOVERY investigators and await a follow-up report listing predisposing conditions, such as demographics (especially age and gender), relevant comorbidities, concomitant medicines, adverse effects and the 90-day mortality data.[96,97] This information would be of interest to an actionable audience, especially decision-makers in public health.[98]

In the management of a serious disease, on a pandemic scale, and in real time, therapeutic enthusiasm that is amplified by the media can be harmful. On 22 October 2020, the US Food and Drug Administration approved remdesivir, a putative antiviral drug, for the treatment of COVID-19. But does remdesivir reduce viral load?[99,100] Writing in *The Lancet Global Health*, Park et al.[101] note that misinterpretation of clinical research exists in the medical and scientific community as well as in the general public. COVID-19 clinical trials target five stages of the disease process: pre-exposure prophylaxis, post-exposure prophylaxis, outpatient treatment, hospital admission and late-stage admission to an ICU. The vast majority of these trials are performed in hospitalised patients (1134 of 1840 [60%]) and have received the widest medical, scientific and media attention. Enthusiastic dissemination by the media may confuse the public by encouraging self-medication, as well as decreasing opportunities and funding towards innovative outpatient treatments and public health initiatives. Clearly, the largest and most meaningful impact on COVID-19 can be achieved by effective early interventions to prevent hospital admission.

Ippolito et al.[102] at the Italian Ministry of Health (Istituto Nazionale per le Malattie Infettive Lazzaro Spallanzani, Rome), Italy, state that the path from generation of scientific and public health information to consumption and use of this information by the media contains several steps, each of which can lead to exaggeration, overstating the strength of causal inference or misinformation. In times of uncertainty, the balance between providing useful information and that which fuels inappropriate action, is especially delicate and risky. Kate and Emslie[103] at the MRC Social and Public Health Sciences Unit, Glasgow, UK, (now University of Stirling and Glasgow Caledonian University, respectively) revisit the 'prevention paradox in lay epidemiology'. Thirty-five years ago, Rose[104] explained that although individuals may not gain directly from population strategies, the beneficial effect of the 'population approach' for the present and for the future is enormous. In the absence of simple and universally applied public health measures, especially vaccination, COVID-19 will remain with us and spread — this virus knows no borders.

In closing, we believe that dexamethasone is of value in hospitalised COVID-19 patients receiving IMV. At this time, and pending the 180-day follow-up report on RECOVERY, the wide use of steroids for prevention and self-medication is discouraged. Regulators and policy makers in public health need access the detailed trial and follow-up data in order to update initial recommendations.[105] In an environment subject to media overdrive, simple, clear and evidence-backed messages trump (sic) 'U' turns in policies; restraint and caution are required.[106] All things considered, COVID-19 is the prototypic stress test for science and especially public health.[107]

Author statements

Acknowledgements

The authors thank the reviewers for their guidance.

Ethical approval

None sought.

Funding

This work has not received any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Competing interests

None declared.

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