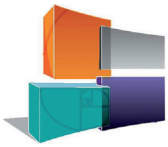
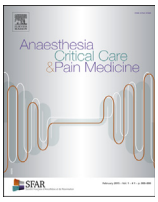
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Anaesth Crit Care Pain Med 39 (2020) 383–384



SFAR
Société Française d'Anesthésie et de Réanimation



Letter to the Editor

Just a little bit more patience...

ARTICLE INFO

Keywords:
COVID-19
Antiviral therapy
Clinical trials

Since the first cases of unexplained pneumonia occurred in China in November 2019, a new coronavirus, SARS-CoV-2, has officially been identified as the source of the global pandemic of coronavirus disease 2019 (COVID-19). Its explosive growth is not only putting healthcare systems under pressure but also physicians' understanding, with more than 7000 published references since January 2020 (https://www.ncbi.nlm.nih.gov/pubmed/). The number and pace of publications focusing on the treatment of COVID-19 is equally impressive, reaching more than 2000 articles, mostly represented by case reports, case series, observational cohorts, small clinical trials, expert opinions, review articles and recommendations of learning societies.

The review of Sanders et al. published on April 13, 2020 in the JAMA [1] is a well-documented work, with the screening of more than 1300 articles published over the last months [1]. At the beginning of April 2020, more than 100 trials analysing pharmacological therapies for COVID-19 in adult patients were recorded on ClinicalTrials.gov, but no published randomised clinical trials have yet been published. The authors drive the reader through repurposed drugs, including chloroquine and hydroxychloroquine, two agents used for malaria (prevention and treatment) and chronic inflammatory diseases (treatment); old antiviral agents such as lopinavir/ritonavir, used for HIV, and oseltamivir, used for influenza; interferon-alpha and -beta; and antihelminthic agents. Pending the evaluation of these agents, no convincing results are available that could lead to safe and curative clinical use. In the second part, Sanders et al. explore the newly developed antiviral agents. Remdesivir, the most advanced drug, already used for the treatment of Ebola, has recently received emergency authorisation by the United States Food and Drug Administration (FDA) for the treatment of some COVID-19 patients, but more than 100 other potential agents have demonstrated potential activity against coronaviruses. Finally, the authors give a wide but deceptive perspective on adjunctive therapies, including corticosteroids, for which published results remain at least negative or potentially harmful; anti-cytokine and immunomodulatory agents still under investigation despite their inclusion in the Chinese national treatment guidelines; and immunoglobulin therapy, with only anecdotal results that are impossible to interpret.

Each period of extreme medical tension generates its share of numerous publications, especially in cases of limited therapeutic options. Although at a lower level, similar observations were made when the SARS or MERS viruses emerged or when the first carbapenemase-producing *Enterobacterales* (CPE) were reported, even if the timeline was quite different. The review of Sanders et al. belongs to the avalanche of information delivered by all scientific journals to a concerned readership seeking updated data in an era of global uncertainty [1]. The usefulness of information found in these reviews is highly questionable, as these papers always cite the same publications and do not bring any new perspective. Their benefit for the readership does raise questions compared to the surrounding noise and confusion they generate. Desperate or anxious prescribers could be tempted by doubtful individual decisions based on mistaken beliefs or risky bets, ignoring adverse events or unpredictable reactions of non-validated therapies. Moreover, physicians should also understand that the inclusion of some drugs in national treatment guidelines or emergency authorisation by federal agencies is not a guarantee of quality or efficacy.

SARS-CoV-2 has been around for only a few months, during which the message has been that no therapies have been shown to be effective, and supportive care remains the best and only approved management [2,3]. The research of therapeutics against this new threat is at its very beginning. Prescribers cannot be satisfied with the mediocre results currently published from neither open-cohort nor high-quality randomised studies [4]. Today, the most common criteria for evaluating these new antiviral agents are improved clinical signs, shortened duration of the disease or decreased biomarker signals such as viral load in respiratory tract specimens by PCR measurement. Similar to any other new anti-infective agents, the evaluation of new antiviral therapies deserves ambitious therapeutic objectives based on relevant criteria and strong methodology. We need large-scale, multinational, randomised control trials, ideally in double-blind fashion, comparing a single agent with the reference management. Because of a pre-symptomatic contagious period of COVID-19 disease, the comparison of prophylactic regimens and curative approaches should also be investigated, possibly showing different capacities at various stages of the disease. Many conditions need to be specifically investigated, including the presence of underlying diseases, risks of clinical worsening, severity of the disease, age and sex. Pharmacokinetic issues must also be investigated, including the dosage, duration of therapy, and comparison between blood monitoring and pharmacodynamic targets.

Life-threatening forms of COVID-19 should also be investigated in detail, but there is very little time to carry out these investigations with thoroughness and regularity. These desperate conditions are no reason to give anyone the licence to do anything. Compassionate use is obviously an interesting and generous approach, but the question arises of how to evaluate new anti-infective agents in times of emergency. The evaluation of multiple

https://doi.org/10.1016/j.accpm.2020.05.004

drugs in a single multi-arm trial such as the European Discovery trial saves time. However, even if favourable results are obtained, it would not be enough to consider these therapeutics as routine options. Multi-arm adaptative designs are more efficient, informative and ethical than fixed-design trials [5]. They can be used through all phases of clinical research. Their principle aims at favouring a drug at the expense of another one if interim analysis brings promising signals. Today, more than 42 multi-arm studies are recruiting COVID-19 patients worldwide, as reported by ClinicalTrials.gov.

A new and worrisome situation is the deleterious availability of pre-reviewed manuscripts, leading to an implausible background noise in the scientific field, not taking into account the additional and detrimental effects of social media. Unfortunately, international media stay tuned to the latest breaking news, thereby reinforcing confusion. Nevertheless, live mapping of ongoing research and evidence synthesis, such as independent collaborative websites (metaevidence.org) or institutional websites (covid-nma.com), may help clinicians stay up to date on recently updated projects.

In summary, the strength of this review of Sander et al. lies in its honesty and accuracy in the analysis of the potential, but unproven, therapeutic tools for COVID-19.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for Coronavirus disease 2019 (COVID-19) A review. JAMA 2020 [Epub Apr13 2020 doi: 10.100/jama.2020.6019].

[2] Recommandations d'experts portant sur la prise en charge en réanimation des patients en période d'épidémie à SARS-CoV2. SRLF-SFAR-SFMU-GFRUP-SPILF-SPLF mise en oeuvre avec la mission COREB nationale. https://sfar.org/download/recommandations-dexperts-portant-sur-la-prise-en-charge-en-reanimation-des-patients-en-periode-depidemie-a-sars-cov2/?wpdmdl=25387&refresh=5eae7f66ca9951588494182.

[3] Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. Clin Infect Dis 2020. http://dx.doi.org/10.1093/cid/ciaa478 [Epub Apr 27. Pii:ciaa478].

[4] Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020. http://dx.doi.org/10.1016/S0140-6736(20)31022-9 [Epub April 29].

[5] Pallmann P, Bedding AW, Choodari-Oskooei B, Dimairo M, Flight L, Hampson LV, et al. Adaptive designs in clinical trials: why use them, and how to run and report them. BMC Med 2018;16:29. http://dx.doi.org/10.1186/s12916-018-1017-7.

Philippe Montravers[a,b,c,*], Christian de Tymowski[a,b,d], Maksud Assadi[a,b], Sonia Yung[a,b], Elie Kantor[a]

[a]*Département d'Anesthésie-Réanimation, CHU Bichat-Claude Bernard, DMU PARABOL, HUPNVS, AP–HP, Paris, France*

[b]*Université de Paris, Paris, France*

[c]*Inserm UMR 1152, Université de Paris, Paris, France*

[d]*Inserm UMR 1149, Université de Paris, Paris, France*

[*]Corresponding author at: Département d'Anesthésie-Réanimation, CHU Bichat-Claude Bernard, 46, rue Henri-Huchard, 75018 Paris, France

E-mail address: philippe.montravers@aphp.fr (P. Montravers).

Available online 13 May 2020