EDITORIAL

Knowledge is coming so fast that a meta-analysis of COVID-19 treatment is always too late

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by Pei et al,
see p. 726

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide from the beginning of 2020. The infection is mostly asymptomatic, but about 20% of patients with COVID-19 (coronavirus disease 2019) may develop a severe or even critical course leading to pneumonia, acute respiratory distress syndrome, and multiorgan failure.[1] Apart from the virus-related damage of the lungs, the disease mechanism remains unclear, but it seems to be linked to overproduction of proinflammatory cytokines, termed a cytokine storm, responsible for organ damage and death.[2] Since the development of a new therapeutic molecule is time-consuming, physicians and scientists started to search among old medications used for various indications to identify drugs that may be repurposed to treat SARS-CoV-2 infection. Lack of clear indicators of recovery, which could serve as an endpoint to compare the effectiveness of different regimens, and no valuable standard of care as a comparator in randomized trials were major problems faced by researchers. They were partly solved by the World Health Organization with an ordinal scale for clinical improvement, which was adapted for data analysis in a number of clinical studies.[3]

In this issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Pei et al[4] evaluated the impact of antiviral agents, glucocorticoids, antibiotics, and intravenous immunoglobulin on the clinical outcomes of patients with COVID-19. The authors carried out a systematic review and meta-analysis of PubMed, Embase, Web of Science, Cochrane Library databases. Finally, the analysis included 3421 references and 6 studies. Since numerous reports of clinical trials and real-world experience studies were published in mid-2020, the major limitation of the study is that article retrieval was finished by April 7, 2020.

Five retrospective studies that reported on the effectiveness of antiviral agents and were covered by Pei et al[4] included data on the use of oseltamivir, ganciclovir, lopinavir / ritonavir, and interferon α. Pooled results revealed that antiviral agents may contribute to survival benefit. Unfortunately, the authors did not investigate remdesivir, which is the first drug approved for the treatment of COVID-19 at the European Union level and has emergency use authorization issued by the United States Food and Drug Administration. It is currently the only antiviral agent with effectiveness confirmed in large, randomized clinical trials in hospitalized patients with COVID-19 requiring supplemental oxygen therapy. Unfortunately, it does not demonstrate effectiveness in those receiving high-flow oxygen, mechanical ventilation, or extracorporeal membrane oxygenation.[5,6] Although HIV-1 protease inhibitors such as lopinavir / ritonavir have a structural basis for the inhibition of the SARS-CoV-2 protease and there are in vitro data on their possible efficacy, currently available clinical data do not support their role in the treatment of COVID-19.[7,8] Due to some in vitro activity, favipiravir and umifenovir, both approved in some countries for the treatment of influenza, are currently studied, but there have been no supportive data until now.[9]

Pei et al[4] analyzed 5 retrospective studies reporting on glucocorticoid (methylprednisolone) use, and pooled results demonstrated an association with an increased risk of death. The major limitation of these studies was lack of data on dosing and treatment duration. Unfortunately, Pei et al[4] could not include recent reports from the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial, which is currently the only large, randomized study on glucocorticoids and showed clinical benefits of using dexamethasone in patients requiring ventilation, but no evidence of benefits in those who did not require oxygen therapy.

Five retrospective studies on antibiotics were included in the meta-analysis by Pei et al.[4] None of them reported on the types of antibiotics, dosing,

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or time of therapy initiation and its duration, so it is difficult to derive firm conclusions based on the available information. However, the authors found no association between antibiotic use and mortality. Azithromycin, a macrolide antibiotic, is the drug most frequently considered for COVID-19 treatment. A small study showed that it reduced time to viral clearance when used with hydroxychloroquine, and, despite the significant limitation of that study, ie, lack of preclinical or in vitro data, the drug was widely used early during the pandemic.[10] Due to the increasing evidence of no efficacy and numerous cases of serious cardiac arrhythmia caused by antimalarials—chloroquine and hydroxychloroquine, also widely used for COVID-19—FDA revoked its previously issued emergency authorization. Updated guidelines do not recommend these drugs as a primary regimen.[11,12] The story of antimalarials was accompanied by confusion caused by conflicting guidelines issued by the World Health Organization. Owing to poor efficacy data and safety concerns related to the risk of QT interval prolongation and cardiac arrhythmia, currently, there is no role for azithromycin, chloroquine, and hydroxychloroquine in the treatment of COVID-19. Further data are needed to evaluate the potential role of antiparasitic ivermectin and antiprotozoal nitazoxanide, which were demonstrated to be effective in single studies only.

When transfused, neutralizing antibodies can provide passive immunity against targeted pathogens. Initial findings from Wuhan suggested the efficacy of convalescent plasma administered early in the course of the disease.[13] However, recently, FDA suspended its approval for convalescent plasma use owing to lack of effectiveness. The results of the study by Pei et al[4] revealed no effects of intravenous immunoglobulin use on mortality. Ongoing clinical trials will elucidate the role of the monoclonal neutralizing antibody against SARS-CoV-2, but the bioavailability of passively infused antibodies in tissues and the possibility of the emergence of a resistant viral mutation under its selective pressure remain unclear.[14]

The inhibitors of cytokine receptors were not included in the meta-analysis by Pei et al,[4] but they are currently recognized as a potential treatment to calm the cytokine storm, which seems to be life-saving if initiated at the appropriate time. Tocilizumab, an inhibitor of the interleukin-6 receptor is the most frequently considered drug, but it has not been studied in randomized trials yet. As recently shown, it may improve the clinical status in patients with COVID-19 by reducing the inflammatory response, which is reflected by the regression of lung lesions and a reduced need for oxygen therapy or mechanical ventilation, but randomized trials are necessary to provide more evidence on its efficacy and safety.[15]

After several months of fighting between different, sometimes strange, ideas of therapy for COVID-19, we are coming to the conclusion, which is obvious for infectiologists, that the only efficient drug to cure the viral disease is an antiviral drug. The same conclusion can be derived from the study by Pei et al,[4] but the authors did not include remdesivir in the analysis, which is currently the main player on the scene. Antiviral therapy should be implemented in the phase of active infection as fast as possible, otherwise its use has no sense. However, it looks like antiviral therapy alone may not be sufficient in severe COVID-19, and a combination with an immunomodulating agent may help attenuate cytokine release syndrome. A majority of patients clear the virus and survive easily, so, unfortunately, we do not know which patient has a poor prognosis and needs medication. We still do not know the optimal regimen to cure COVID-19. New data are emerging so fast that a meta-analysis of COVID-19 treatment comes always too late.

ARTICLE INFORMATION

DISCLAIMER The opinions expressed by the author are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

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