Clinical Microbiology and Infection 28 (2022) 1182–1183

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Commentary

Immunocompromised patients have been neglected in COVID-19 trials: a call for action

Marius Trøseid [1,*], Maxime Hentzien [2], Florence Ader [3], Sandra Wagner Cardoso [4], Jose R. Arribas [5], Jean-Michel Molina [6], Nicolas Mueller [7], Maya Hites [8], Fabrice Bonnet [9], Oriol Manuel [10], Dominique Costagliola [11], Beatriz Grinsztejn [4], Inge Christoffer Olsen [12], Yazdan Yazdapanah [13], Alexandra Calmy [2], On behalf of EU RESPONSE, COMBINE

[1] *Section of Clinical Immunology and Infectious Diseases, Oslo University Hospital, Oslo, Norway*
[2] *HIV/AIDS Research Unit, Geneva University Hospitals, Geneva, Switzerland*
[3] *Département des Maladies Infectieuses et Tropicales, Hôpital de la Croix-Rousse, Hospices Civils de Lyon Lyon, France*
[4] *Lab. De Pesquisa Clinica DST/AIDS, Instituto Nacional de Infectologia Evandro Chagas, Fiocruz, Rio de Janeiro, Brazil*
[5] *Infectious Diseases Unit, Hospital La Paz, Madrid, Spain*
[6] *Infectious Diseases Department, Saint-Louis APHP, Paris, France*
[7] *Division of Infectious Diseases, University Hospital, Zurich, Switzerland*
[8] *Cliniques Universitaires de Bruxelles—Hôpital Érasme, Université Libre de Bruxelles, Clinique des Maladies Infectieuses, Brussels, Belgium*
[9] *CHU de Bordeaux and Université de Bordeaux, INSERM U1219, F-33000 Bordeaux, France*
[10] *Infectious Diseases Service, Lausanne University Hospital (CHUV), Lausanne, Switzerland*
[11] *Institut Pierre Louis d'Epidémiologie et de Santé Publique, Sorbonne Université, INSERM, Paris, France*
[12] *Dept. of Research Support for Clinical Trials, Oslo University Hospital, Oslo, Norway*
[13] *Université de Paris, IAME, INSERM, Paris, France*

ARTICLE INFO

Article history:
Received 30 March 2022
Accepted 3 May 2022
Available online 25 May 2022

Editor: R. Chemaly

Keywords:
Antivirals
COVID-19
Guidelines
Immunocompromised
Trials

Although several innovative and repurposed drugs have been approved for the treatment of COVID-19 during the last year, we still do not have evidence-based knowledge on the best therapeutic strategy to treat immunocompromised patients. Most treatment guidelines are structured to whether the disease state is mild, moderate, or severe, and not sufficiently according to host factors including host immunity. Whereas the Omicron variant causes less severe diseases in the general population, this is not necessarily the case for individuals with an impaired immune system, such as organ transplant recipients, patients with hematological malignancies [1], active cancer or primary immunodeficiency, or individuals treated with immunosuppressive drugs for a variety of medical conditions. In addition, the disease is not self-limited in this population and includes an increased mortality risk because the course of the disease is unpredictable, non-linear, and often involves multiple episodes or protracted SARS coronavirus 2 (SARS-CoV-2) detection and treatment attempts. Persistence of SARS-CoV-2 replication in immunosuppressed patients despite the use of antiviral treatments can lead to virus evolution and accumulation of resistance mutations [2], as well as the possibility of generation of new variants of concern [3].

The lack of evidence and guidelines is a consequence of almost absent inclusion of immunocompromised patients in registration clinical trials. As shown in Table 1, only 5% immunocompromised patients were included in the PINE-TREE trial (GS-US-540-9012) on remdesivir [4], less than 1% in the EPIC-HR trial (Evaluation of Protease Inhibition for Covid-19 in High-Risk Patients) on nirmatrelvir and ritonavir [5], and completely excluded from the COMET-ICE trial (Covid-19 Monoclonal Antibody Efficacy Trial—Intent to Care Early) on sotrovimab [6]. Moreover, for immunomodulators, such as tocilizumab and baricitinib, immunocompromised patients have been largely excluded from trials due to safety concerns. As a consequence, and as a paradox, current treatment algorithms for immunocompromised patients with the Omicron variant are

* Corresponding author. Marius Trøseid, Section of Clinical Immunology and Infectious Diseases, Oslo University Hospital, Oslo 0372, Norway.
E-mail address: marius.troseid@medisin.uio.no (M. Trøseid).

https://doi.org/10.1016/j.cmi.2022.05.005

Table 1
Proportion of immunocompromised participants in registration trials of antiviral drugs

Drug	Remdesivir	Nirmatrelvir/ritonavir	Sotrovimab
Primary end point	Hospitalization or death within 28 days	Hospitalization or death within 28 days	Hospitalization or death within 29 days
Population	Symptoms ≤7 days, at least one risk factor	Symptoms <5 days, high risk patients	Symptoms <5 days, at least one risk factor
Immuno-compromized, %	5	<1	Excluded
Efficacy data, *n* (%)	2/279 (0.7) (remdesivir); 15/283 (5.3) (placebo); p = 0.008; RRR = 87%	3/389 (0.8) (nirmatrelvir); 27/385 (7.0) (placebo); p < 0.0001; RRR = 89%	3/291 (1) (sotrovimab); 21/292 (7) (placebo); p = 0.002; RRR = 85%
Publication	Gottlieb et al. [4]	Hammond et al. [5]	Gupta et al. [6]

RRR, relative risk reduction.

largely based on superimposed results from trials performed on immunocompetent patients from the pre-Omicron era.

The following several questions require urgent response: (a) Is the antiviral or clinical effect of antiviral monoclonal antibodies (mAbs) and direct acting antivirals (DAA) reduced in immunocompromised patients? (b) Could this lead to suboptimal treatment efficacy and increased risk of antiviral resistance and persistent shedding? (c) If so, could this partially or fully be overcome by increasing the treatment duration of DAAs, increasing the dosage of mAbs, or combining two or more of these treatments? (d) Is enhanced immunosuppression a wise strategy in already immunocompromised patients, or is the risk of invasive bacterial and fungal superinfections too high? (e) Finally, how should we individualize treatment decisions in a heterogeneous population with very different risk profiles?

Immunocompromised individuals have been under-represented in trials, but are likely to be over-represented among patients with severe or persisting symptoms due to SARS-CoV-2, as they have impaired response to vaccination [7]. Unfortunately, long-acting mAbs for passive immunization are not available in many countries, whereas in some countries where those options are available, hospitals have been using a lottery system to allocate scarce COVID-19 drugs to these patients [8]. With the widespread increase of the Omicron variants being increasingly resistant to most existing antiviral mAbs [9], immunocompromised individuals have even less options for treatment or prevention. In addition, administration of oral nirmatrelvir and ritonavir to certain subgroups, such as organ transplant recipients, is difficult because of drug-drug interactions [5].

Consequently, there is an urgent need for more robust knowledge on how to treat this large and neglected group of patients. First, ongoing clinical trials, including platform trials, should prioritize the inclusion of these patients, with well-defined subgroups and relevant primary or core secondary endpoints. For immunomodulators this could be safety, whereas viral clearance and resistance mutations could be relevant endpoints when testing antivirals. Innovative design should be implemented for testing various drug combinations, and given the heterogeneity of conditions in immunocompromised individuals, basket trials as in oncology to assess targeted therapies could also be an option. Finally, collaboration between trials running similar arms should be encouraged to generate evidence more rapidly. As this kind of research will be the responsibility of academic researchers, access to both funding and drugs [10] are critical to allow such studies to be implemented with great urgency. We hereby urge relevant trials, funders, and drug companies to respond to this call for action so that together we can fill the knowledge gaps and improve the care for a large and neglected patient group.

Transparency declaration

M.T. has participated in Eli Lilly's European advisory board on COVID-19 therapeutics pro bono. B.G. has received consulting fees from Janssen and payment or honoraria from Janssen, Merck and M.S.D.. J.M.M. has received grants from Gilead and consulting fees from Gilead, ViiV and Merck. N.J.M. has received consulting fees from Takeda and M.S.D., and support for attending meetings from Biotest. M.He. has received payment or honoraria from ViiV and Gilead, and support for attending meetings from ViiV, Gilead, Menarini and Pfizer. M.Hi. has received honoraria and travel support from Pfizer and Gilead. D.C. has received Grant from Janssen (payed to Inserm), and payment for lectures from Gilead and Pfizer. J.R.A. has received consulting fees from MSD, Serono, Astra Zeneca, Pfizer, GSK, Lilly and Sobi, and payment or honoraria from MSD and GSK. A.C. has received research grant from MSD and meeting support from MSD, AbbVie, Gilead, ViiV.

The EU-RESPONSE project has received funding from the EU Horizon 2020 Research and Innovation programme, under the grant number 101015736.

Author contributions

M.T. and A.C. drafted the first version of the manuscript. All co-authors critically reviewed and approved the final version of the manuscript.

References

[1] Nieman CU, Cuncha-Bang C, Helleberg M, Ostrowski SR, Brieghel C. Patients with CLL have similar high risk of death upon the omicron variant of COVID-19 as previously during the pandemic. medRxiv 2022. https://doi.org/10.1101/2022.03.01.22271685.
[2] Gandhi S, Klein J, Robertson A, Pena-Hernandez MA, Lin MJ, Roychoudhury P, et al. De novo emergence of a remdesivir resistance mutation during treatment of persistent SARS-CoV-2 infection in an immunocompromised patient: a case report. Nat Commun 2022;13. https://doi.org/10.1038/s41467-022-29104-y.
[3] Kemp SA, Collier DA, Datir RP, Ferreira IATM, Gayed S, Jahun A, et al. SARS-CoV-2 evolution during treatment of chronic infection. Nature 2021;592:277–82. https://doi.org/10.1038/s41586-021-03291-y.
[4] Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, Perez G, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. N Engl J Med 2022;386:305–15. https://doi.org/10.1056/NEJMoa2116846.
[5] Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. N Eng J Med 2022;386:1397–408. https://doi.org/10.1056/NEJMoa2118542.
[6] Gupta A, Gonzales-Rojas Y, Juarez E, Casal MC, Moya J, Falci DR, et al. Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. N Engl J Med 2021;385:1941–50. https://doi.org/10.1056/NEJMoa2107934.
[7] Lee A, Wong S, Chai L, Lee S, Lee M, Muthiah M, et al. Efficacy of COVID-19 vaccines in immunocompromised patients: systematic review and meta-analysis. BMJ 2022;376:e068632. https://doi.org/10.1136/bmj-2021-068632.
[8] National Public Radio. Shots: health News. Evusheld, COVID drug for the immunocompromised, is in short supply. National Public Radio; 2022. Available at: https://npr.org. [Accessed 25 March 2022].
[9] Takashita E, Kinoshita N, Yamayoshi S, Sakai-Tagawa Y, Fujisaki S, Ito M, et al. Efficacy of antiviral agents against the SARS-CoV-2 Omicron subvariant BA.2. N Engl J Med 2022;386:1475–7. https://doi.org/10.1056/NEJMc2201933.
[10] Drugs for Neglected Diseases Initiative. Pfizer blocking research to generate evdience on optimal use of novel antiviral for COVID-119 patients in low- and middle-income countries. Available at: https://dndi.org/press-releases/2022/pfizer-blocking-research-to-generate-evidence-optimal-use-novel-antiviral-covid19-low-and-middle-income-countries/. [Accessed 25 March 2022].