COVID-19 remedies

Repurposed drugs, inhibitors of inflammatory cytokines, neutralizing monoclonal antibodies and sera from convalescent patients will help ease the burden of COVID-19 on healthcare systems.

In regions most affected by the pandemic, a large fraction of patients hospitalized with COVID-19 (21% in the New York City area¹ and 33% in the United Kingdom²) do not survive the disease. Excess deaths will also increase because many non-urgent surgeries, treatments, consultations and follow-up appointments have been delayed or cancelled. Research laboratories, government agencies and biotechnology and pharmaceutical companies are thus working at unprecedented speed to find and test drugs and treatments that reduce the hospitalization rate and shorten the hospital stays of patients infected with COVID-19. Effective treatments would alleviate the burden on the healthcare system and allow for the implementation of public policies that would help economies to recover.

Four main treatment classes are being explored to fight COVID-19 by either inhibiting the virus or modulating the body's response to it: antiviral drugs, to inhibit viral replication; immunomodulatory drugs, to dampen an immune system in overdrive; neutralizing antibodies, to inhibit the virus and help the immune system clear the infection; and sera (the acellular fraction of circulating blood containing a wide range of antibodies, cytokines and other immunomodulators) from patients who have recovered from COVID-19.

Antivirals interfere with polymerases or other enzymes necessary for viral replication, and can thus reduce viral loads, ameliorate symptoms and limit infectivity. In AIDS, antiviral drug cocktails (which include HIV-specific nucleoside reverse-transcriptase inhibitors, protease inhibitors and integrase inhibitors) have made the disease chronic and manageable. Yet developing new antiviral drugs (for example, by using computational structure-based discovery³) is lengthy and costly⁴. High-throughput drug screening, in vitro or computational, can however speed up the testing of large libraries of approved drugs for antiviral activity against the coronavirus (severe acute respiratory syndrome coronavirus 2; SARS-CoV-2). Tens of such 'repurposed' candidate drugs⁵ (notably, antiretroviral protease inhibitors approved for the treatment of HIV) are being tested in patients with COVID-19 in hundreds of trials across the world. Broad-spectrum antivirals are also being

Credit: Kiyoshi Takahase Segundo / Alamy Stock Photo

clinically tested for effectiveness against SARS-CoV-2. So far, the intravenously delivered Remdesivir — an adenosine nucleoside triphosphate analogue, developed by Gilead, that interferes with the RNA polymerase enzyme from RNA viruses — is the only antiviral with effectiveness against COVID-19 (a shortening of time-to-recovery by four days), as per recent data from a double-blind, randomized, placebo-controlled trial of 1,063 patients with COVID-19 with evidence of lower respiratory tract involvement⁶.

Overactivation of the immune system, particularly in the lower respiratory tract, has been associated with COVID-19 severity and mortality⁷. This 'cytokine storm' involves an increase in immune factors (such as the cytokines interleukin-2 (IL-2), IL-6, tumour necrosis factor- α and interferon- γ) and can progress to acute respiratory distress syndrome. By dampening immune responses, cytokine inhibitors (small-molecule drugs, such as ruxolitinib, a Janus kinase inhibitor; or monoclonal antibodies such as

tocilizumab, an IL-6 inhibitor⁸) routinely used to treat patients with inflammatory or autoimmune diseases may also help ameliorate the course of patients with COVID-19. Blinded, randomized trials of cytokine inhibitors in patients with COVID-19 are ongoing⁹.

Antibody candidates can be isolated from the serum of patients who have mounted an effective immune response and have recovered from COVID-19, or from mice with a humanized immune system that have been infected with the virus or with viral antigens. The neutralizing activity of the antibodies is then assessed with assays using pseudotyped viral particles expressing viral antigens (particularly the spike protein in SARS-CoV-2). The top candidates are then produced via standard manufacturing processes for monoclonal antibodies, which typically involve the in vitro expansion of genetically modified immortal B-cell lines producing the desired antibodies. Biotechnology companies are rapidly developing antibody candidates; Eli Lilly, which partnered with AbCellera, is running

a phase I trial, and Regeneron plans to start human testing in weeks.

Experience during viral outbreaks of measles, mumps, H1N1 influenza, Ebola and the coronaviruses SARS-CoV-1 and Middle East respiratory syndrome in the past century suggests that sera from patients recovering from COVID-19 will improve outcomes (particularly for non-intubated patients¹⁰). Because such a 'passive immunization strategy' does not rely on the recipient's immune system (and therefore does not confer protection), it may be suitable to treat frail or immunocompromised individuals. However, blood-group matching, the risk of transmission of other viruses present in donor sera when directly transfused from donors, donor-dependent variability in antibody titres and specificity, and limitations in donor supply make convalescent sera difficult to scale up. Preparations of hyperimmune globulin from pooled and processed plasma (which are being developed by the [CoVig-19 plasma alliance](#), a consortium of six pharmaceutical companies) are costlier, yet in principle

are safer, more potent and reliable, do not require blood typing and can be scaled up.

It is reasonable to expect that there will soon be treatments in all four categories, and that their suitability to specific patients with COVID-19 will depend on disease stage, disease severity and clinical factors such as comorbidities and age. Some treatments will be most appropriate for patients with high viral titres, whereas others will perform better in patients with hyperinflammation. However, most first-generation treatments may have modest efficacy. Still, treatments can be layered and drugs re-dosed. With time, combinations of antivirals and of antivirals and cytokine inhibitors, cocktails of monoclonal antibodies and sera from recovered superdonors (those generating high levels of potent antibodies) may reach more patients. And some treatments may work prophylactically — a pressing need until a safe and efficacious vaccine is available.

Yet urgency should not get in the way of caution. Before any treatments are claimed to be effective or safe (as has unfortunately been the case with hydroxychloroquine),

sufficiently large randomized controlled trials and meta-analyses of trials are needed¹¹ to distinguish true signals from the unavoidable noise and biases inherent to clinical studies, especially those designed without a control group or with unmatched groups. For lousy data, however, we know the remedies.

Published online: 12 June 2020

<https://doi.org/10.1038/s41551-020-0579-9>

References

1. Richardson, S. et al. *JAMA* **323**, 2052–2059 (2020).
2. Docherty, A. B. et al. Preprint at <https://doi.org/10.1101/2020.04.23.20076042> (2020).
3. Parks, J. M. & Smith, J. C. *N. Engl. J. Med.* <https://doi.org/10.1056/NEJMcibr2007042> (2020).
4. Martin, L., Hutchens, M., Hawikins, C. & Radnov, A. *Nat. Rev. Drug. Discov.* **16**, 381–382 (2017).
5. Harrison, C. *Nat. Biotechnol.* **38**, 379–381 (2020).
6. Beigel, J. H. et al. *N. Engl. J. Med.* <https://doi.org/10.1056/NEJMoa2007764> (2020).
7. Huang, C. et al. *Lancet* **395**, 497–506 (2020).
8. Somers, E. C. et al. Preprint at <https://doi.org/10.1101/2020.05.29.20117358> (2020).
9. Ingraham, N. E. et al. *Lancet Respir. Med.* [https://doi.org/10.1016/S2213-2600\(20\)30226-5](https://doi.org/10.1016/S2213-2600(20)30226-5) (2020).
10. Liu, S. T. H. et al. Preprint at <https://doi.org/10.1101/2020.05.20.20102236> (2020).
11. Keshtkar-Jahromi, M. & Bavari, S. *Am. J. Trop. Med. Hyg.* **102**, 932–933 (2020).