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What progress has been made in treatment of immunocompromised COVID-19 patients?

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Summary

While immunocompromised patients are at very high risk of developing severe COVID-19, few of them have been enrolled in studies aimed at evaluating treatments. In the early stages of research on this disease, glucocorticoid therapy became the standard of care for patients requiring oxygen supplementation. It has been demonstrated that the neutralizing monoclonal antibody combination of Casirivimab and Imdevimab reduced (by 28 days) mortality in COVID-19 patients admitted to hospital who were seronegative at baseline, but not in those who were seropositive. There is still a need to determine the place of available various antivirals (Molnupiravir or Nirmatrelvir plus Ritonavir) and passive immunotherapies (Sotrovimab...) as well as convalescent plasma therapy in immunocompromised settings.

We now have a clear idea of the different sequences in COVID-19 pathophysiology, and they can be broken down into two main phases: virus replication and host immune response. The latter is responsible for most potentially severe clinical signs of COVID-19. Given what has been developed for immunocompromised patients at risk of (or infected with) an opportunistic infection, we now have a therapeutic arsenal including prophylactic, preemptive or curative treatments (Fig. 1).

Consecutive COVID-19 waves have shown that it does not affect all population groups equally and that immunocompromised patients are at very high risk of developing severe disease (Table 1).

Given the urgent need to identify treatments reducing hospital admission and mortality, potential candidates have been evaluated in massive platform trials. Since very few immunocompromised patients were enrolled in these studies, it was not possible to obtain adequate result stratification. In July 2020, the RECOVERY trial nonetheless provided evidence that dexamethasone treatment resulted in lower 28-day mortality among the 6425 enrolled patients receiving either invasive mechanical ventilation or oxygen alone [1]. Few details were provided on coexisting pathologies other than chronic organ disease, HIV and diabetes.

In June 2020, glucocorticoid therapy became the standard of care for COVID-19 patients requiring oxygen supplementation. The experience-based approach of COVID-19 management in immunocompromised patients has demonstrated that corticosteroids may not be sufficient to reverse the course of the disease, one reason being that the addition of an antiviral palliates the lack of viral clearance.

Convalescent plasma therapy was brought into use during 2020 as the first passive antiviral immunotherapy. Several neutralizing monoclonal antibodies were subsequently evaluated in generic platform clinical trials. One year after generalization of dexamethasone use, the RECOVERY trial demonstrated that the neutralizing monoclonal antibody combination of Casirivimab and Imdevimab reduced 28-day mortality in patients admitted to hospital with COVID-19 who were seronegative (without having mounted an autonomous humoral immune response) at baseline but not in those who were seropositive [2]. In the seronegative subset, few data were available on the baseline immune status of enrolled patients, which meant that it was not possible to draw conclusions concerning the immunocompromised patients most likely to benefit from the above approach.

At present, due to the epidemiological dominance of the Omicron variant and to generalized vaccination, hospitalized patients are mainly elderly, immunosenescent or immunocompromised patients. Clinical forms of COVID-19 range from persistent, mild forms in elderly patients to severe forms in profoundly immunocompromised patients in onco-hematology and transplantation units.

Currently, there is a knowledge gap on the optimal timing and the appropriate place of (a) available antivirals such as Molnupiravir or Nirmatrelvir plus Ritonavir, which pose the problem of drug interactions with possible immunosuppressive treatments, or (b) passive immunotherapies such as Sotrovimab and convalescent plasma therapy in immunocompromised settings [3–6] (Table 2). Management of the various subsets of...
immunocompromised patients often relies on experience-based approaches progressively constructed by physician teams rather than robust evidence-based results from randomized controlled trials. That said, management algorithms have been improved and refined over time to optimally fit the "real-life" patient conditions.

In 2021, the new variants, including Omicron, necessitated adaptation of monoclonal antibody strategies according to their neutralizing capacities. The two formulations effectively neutralizing the Omicron variant are Sotrovimab and Tixagevimab–Cilgavimab [7]. Sotrovimab presents the advantage of not targeting the receptor-binding domain of the spike glycoprotein, which is the least impacted by mutation sites. The Tixagevimab–Cilgavimab combination presents the advantage of having a long half-life (of at least 90 days) via an antibody recycling process, resulting in an estimated 83% of residual protection (on the delta strain) at 6 months [8]. In this combination, only Cilgavimab maintains satisfactory activity on the Omicron strain [7]. The combination is...
contraindicated in the event of coronary pathology (recent myocardial infarction, symptomatic coronary insufficiency, acute coronary syndrome...).

Among the antiviral molecules, Molnupiravir seems to be the most impacted by the Omicron variant, post-hoc analyses are not favorable, and it has not been approved in France [9]. Data from clinical trials conducted on strains identified prior to Omicron are now obsolete (Table 3).

Convalescent plasma has not demonstrated efficacy in generic randomized platform trials, which involved heterogenous populations in which few immunocompromised patients were included [10,11]. Promising results arose from a series of 17 consecutive serene patients with profound B-cell lymphopenia and prolonged COVID-19 patients who received 4 units of COVID-19 convalescent plasma and had a favorable outcome [13]. As regards the subset of patients immunocompromised at baseline (126 patients) randomized in the REMAP-CAP trial, potential benefit (posterior probability of superiority of 89.8%) was found for those receiving convalescent plasma. Finally, in a retrospective case-control study using a propensity score analysis, Hueso et al. observed decreased mortality of 63% among anti-CD20–exposed patients with B-cell lymphoid disease in the convalescent plasma-treated group compared to the untreated subgroup [14]. These different results suggest that convalescent plasma therapy is beneficial in COVID-19 patients with B-cell depletion who are unable to mount a humoral immune response.

To conclude, management of immunocompromised patients is often based on results that are often outdated and extrapolated from small-scale studies. Patients who should be offered treatment as a matter of priority are those who are profoundly immunocompromised and have unsatisfactory or negligible response to the current complete vaccination regimen (anti-spike-antibody concentration < 260 BAU/mL). To date, based on the PROVENT trial (conducted on non-Omicron strains), it seems justified to offer these patients pre-exposure prophylaxis with Tixagevimab–Cilgavimab every 6 months [8]. In post-exposure treatment, the Tixagevimab–Cilgavimab combination may likewise be proposed, in the absence of an alternative, notwithstanding data from the STORMCHASER trial (also conducted on non-Omicron strains), which proved inconclusive with regard to length of hospitalization and mortality [15].

Given the current dominance of the Omicron variant, non-responders to vaccination (a) with at least one risk factor for developing a severe disease, (b) mild COVID-19 without any oxygen requirement and (c) time since symptom onset not exceeding 5 days should be offered Sotrovimab. The 5-day time lapse warrants discussion insofar as these patients may undergo prolonged viral shedding and an initial phase of viral replication after prolonged incubation.

Finally, in profound immunocompromised patients with severe disease associated with oxygen requirement, passive immunotherapy (Tixagevimab–Cilgavimab or Sotrovimab) should be immediately considered in the framework of a compassionate use program. Convalescent plasma should be a priority in cases of B-cell depletion or profound hypogammaglobulinemia and, possibly, in solid organ transplant patients. Inclusion in randomized controlled clinical trials is advisable, even though they are not fully adapted to management of these patients.

Administration of a 4th vaccine dose appears to have short-term interest in low responders to vaccination [16]. The patients who seem to benefit the most have received kidney transplants. It should also be noted that booster campaigns in immunocompromised patients take time.

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**Authors’ contributions**

All authors contributed equally to this work.

**Declaration of interest**

The authors declare no conflict of interest.

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