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CORRESPONDENCE

# Tixagevimab/cilgavimab for Omicron SARS-CoV-2 infection in patients with haematologic diseases





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**TO THE EDITOR:**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is life-threatening for patients with haematologic malignancies [1]. The Omicron variant that emerged at the end of 2021 harbors multiple novel spike mutations, leading to immune escape from vaccination-induced antibodies [2]. The Omicron variant is associated with decreased hospital admission and mortality in immunocompetent patients [3]. In patients with hematologic malignancies, a mortality rate of 16.5% among hospitalized patients has been reported [4], which is lower than that observed during the COVID-19 waves of 2020 and 2021 [1]. However, it remains considerably higher compared to the mortality of immunocompetent patients [3]. Therefore, effective treatment remains indispensable to improve clinical outcomes in this population at high risk of severe evolution of Covid19.

While several monoclonal antibodies have been developed, some completely lost neutralizing activity against Omicron's original lineage (B.1.1.529) whereas others exhibit a highly reduced (tixagevimab-cilgavimab combination, ~12-fold decrease) or a partially reduced (sotrovimab) [2] activity. Low availability of sotrovimab coupled to its decreased neutralizing activity against Omicron BA.2, BA.3, BA.4, BA.5 and descendent lineages lead to the authorization of tixagevimab-cilgavimab 300–300 mg in France through a compassionate use program. It is indicated for the treatment of adults and adolescents with suspected or proven Omicron infection, who are at increased risk of progressing to severe COVID-19 and are unvaccinated or have a weak or absent response to vaccination (anti-S IgG < 260 BAU/ml). A large, randomized, double blind study recently reported that while tixagevimab-cilgavimab did not improve patient recovery, it was associated with a significantly lower mortality compared to placebo (hazard ratio, 0.70; 95% CI, 0.50–0.97, $p = 0.032$) [5]. However, only 57 of the 1417 included patients were immunocompromised (of whom 26 had a malignancy), and there is no available data regarding tixagevimab-cilgavimab's efficacy in the specific subset of patients with haematologic malignancies. Furthermore, the majority of patients in this study were infected with the Delta strain, which is not circulating anymore.

Given the scarcity of data, we performed a single center retrospective study aiming at analysing clinical outcomes in patients with haematologic malignancies, treated with tixagevimab-cilgavimab for an infection with the Omicron SARS-CoV-2 variant.

From January to July 2022, we included 13 patients hospitalized in the haematology department at Saint Antoine Hospital in France with an Omicron SARS-CoV-2 infection confirmed by a type-specific multiplex RT-PCR assay (Novaplex SARS-Cov-2 variant 1 and IV, Seegen) and with SARS-CoV-2 IgG anti-S < 260 BAU/ml (Alinity Abbott CLIA Assay), who were treated with intravenous tixagevimab-cilgavimab (300–300 mg) (Table 1). The Omicron sub-variant was BA.1 in five patients and BA.2 in eight patients. Median patient age was 67 years (range, 43–88). Nine patients had a lymphoid malignancy and four had a myeloid malignancy. All but one patient had a history of chemotherapy, including eight with ongoing chemotherapy. Eight patients had received B-cell targeting treatment within the last 12 months and three patients had a history of allogeneic hematopoietic cell transplantation (allo-HCT). Nine patients were vaccinated for COVID-19 (7 and 2 patients received 3 and 2 vaccine doses, respectively), four were unvaccinated and one received prophylactic casirivimab-imdevimab in addition to 3 doses of COVID-19 vaccine. Nevertheless, all patients had low anti-S IgG level at the time of diagnosis of SARS-CoV-2 infection [median, 24.8 BAU/mL (range, 0–103)]. Interestingly, two of the four unvaccinated patients were positive for anti-N IgG (Alinity Abbott CLIA Assay), indicating a history of COVID-19. In the 7 patients with serological assessment performed at a median of 52 days (range, 21–72) after tixagevimab-cilgavimab, median anti-S IgG increased to 2056.9 BAU/mL (range, 1045–3701.5), while anti-N IgG remain negative (except for the two patients with an history of COVID-19), indicating that anti-S IgG increase is related to the tixagevimab-cilgavimab administration and not to the immune response to SARS-CoV-2 infection.

In five patients, SARS-CoV-2 infection was diagnosed with a routine PCR test performed at patient admission before chemotherapy administration, three of them were asymptomatic and two had mild symptoms (rhinitis). These five patients received tixagevimab-cilgavimab according to the compassionate use program at a median of 3 days (range 2–4) after SARS-CoV-2 infection diagnosis and all recovered without additional COVID-19 treatment. The remaining eight patients were symptomatic, and all required supplemental oxygen. Of note in some of this patients, COVID19 pneumonia was preceded by a long asymptomatic or mild COVID19, since median time between COVID-19 diagnosis and initiation of oxygen was 17 days (range, 2–45). Tixagevimab-cilgavimab was administered in the 8 patients at time of hospitalisation and oxygen initiation. Six patients had an inflammatory syndrome and received steroids alone ($n = 4$ dexamethasone) or tocilizumab and steroids ($n = 1$ dexamethasone and $n = 1$ prednisolone). Treatment with tixagevimab-cilgavimab ± steroids was effective in three patients who completely recovered from SARS-CoV-2 infection with no additional treatment. Three patients persistent COVID-19 symptoms with positive nasopharyngeal PCR remained positive for SARS-CoV-2 and after initial improvement (oxygen withdrawal), suddenly worsened with acute respiratory distress at day 41, 18, and 21 post tixagevimab-cilgavimab administration, leading to death. Only one of these patients was admitted to the intensive care unit, the remaining two patients were ineligible because of their comorbidities. One patient, who did not initially improve, received convalescent plasma and clinically recovered thereafter, but had prolonged viral shedding

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**Table 1.** Clinical characteristics and outcomes of patients with hematological malignancies and SARS-CoV-2 infection treated with tixagevimab-cilgavimab.

| Patient | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age (years) | 62 | 78 | 67 | 62 | 72 | 58 | 71 | 88 | 49 | 71 | 63 | 72 | 43 |
| BMI (kg/m$^2$) | 21 | 30 | 28 | 19 | 17 | 29 | 22 | 23 | 27 | 17 | 30 | 26 | 26 |
| Sex | F | M | M | M | F | F | M | M | F | F | M | M | M |
| Malignancy | CLL | CLL | L-HES | NHL | MDS | NHL | NHL | MM | MDS | AITL | AML | NHL | AML |
| Current status | Untreated | Progressing disease | Stable disease | CR | CR | PR | CR | CR | CR | CR | Progressing disease | PR | CR |
| History of chemotherapy | – | Ongoing | Ongoing | Ongoing | Previous | Ongoing | Previous | Previous | Previous | Ongoing | Ongoing | Ongoing | Ongoing |
| Cell therapy | – | – | – | – | Allo-HCT | – | – | – | Allo-HCT | – | Allo-HCT | – | – |
| History of anti-CD 19 therapy within the last 12 months | – | Anti-CD20 monoclonal antibody and Ibrutinib | – | Anti-CD20 monoclonal antibody | Anti-CD20 monoclonal antibody[a] | Anti-CD20 monoclonal antibody | Anti-CD20 monoclonal antibody | – | Anti-CD20 monoclonal antibody[a] | – | Anti-CD20 monoclonal antibody[a] and Venetoclax | Anti-CD20 monoclonal antibody | – |
| SARS CoV-2 variant | Omicron BA.1 | Omicron BA.1 | Omicron BA.2 | Omicron BA.2 | Omicron BA.1 | Omicron BA.1 | Omicron BA.1 | Omicron BA.2 | Omicron BA.2 | Omicron BA.2 | Omicron BA.2 | Omicron BA.2 | Omicron BA.2 |
| Anti-S IgG prior to hospitalization(BAU/ml) | 3.92 | 0 | 224 | 51.35 | 44.19 | 2 | 0 | 0 | 18.36 | 37.18 | 58.21 | 103 | 24.84 |
| Anti-N IgG prior to hospitalization(index) | 0,01 | 0,04 | 0,04 | 0,02 | 0,04 | 0,05 | 0,01 | 0,00 | 0,06 | 8,08 | 0.04 | 0.01 | 4.89 |
| Anti-S IgG 6 weeks post T/C[b] (BAU/ml) | – | – | – | 2543.5 | 1045 | 1045.2 | – | – | 3701.5 | 1750.1 | 2056.9 | – | 3603.8 |
| Anti-N IgG 6 weeks post T/C[b] (index) | – | – | – | 0.01 | 0.03 | 0.35 | – | – | 0.03 | 2.19 | 0.05 |  | 6.0 |
| Vaccine status, days between last dose and infection | 3 doses, 46 days | 3 doses, 148 days[c] | 3 doses, 170 days | 3 doses, 152 days | 2 doses, 309 days | 2 doses, 208 days | 3 doses, 50 days | 3 doses, 181 days | Unvaccinated | Unvaccinated | Unvaccinated | 3 doses, 212 days | Unvaccinated |
| SARS-CoV-2 symptoms | COVID-19 pneumonia | COVID-19 pneumonia | Asymptomatic | Asymptomatic | COVID-19 pneumonia | COVID-19 pneumonia | COVID-19 pneumonia | COVID-19 pneumonia | COVID-19 pneumonia | Rhinitis | COVID-19 pneumonia | Rhinitis | Asymptomatic |
| Additional COVID-19 treatment | Dexamethasone, oxygen | Dexamethasone, oxygen | No | No | Dexamethasone, oxygen | Oxygen | Dexamethasone, oxygen | Dexamethasone, oxygen Remdesivir[d] tocilizumab, convalescent plasma | Prednisolone, oxygen, tocilizumab | No | Oxygen | No | No |
| COVID-19 outcome post T/C | Recovery | Worsening, deaths at D4 of T/C. No ICU | Recovery | Recovery | Initial recovery, worsening at D41 of T/C death at D42, no ICU | Recovery | Recovery | Stability, convalescent plasma at D12 of T/C, clinical recovery, PCR negativity at 4 months | Initial recovery, worsening and ICU admission at D18 of T/C, death at D23 | Recovery | Initial recovery worsening at D21 of T/C, death at D31, no ICU | Recovery | Recovery |

*BMI* body mass index, *F* female, *M* male, *CCL* chronic lymphocytic leukemia, *L-HES* Lymphocytic variant hypereosinophilic syndromes, *MM* multiple myeloma, *AITL* angioimmunoblastic T-cell lymphoma, *AML* acute myeloid leukemia, *MDS* myelodysplastic syndrome, *CR* complete response, *PR* partial response, *alloHCT* allogeneic hematopoietic cell transplantation, *T/C* tixagevimab-cilgavimab, *D* day.

[a]For EBV viraemia.

[b]Median time period between tixagevimab-cilgavimab treatment and the serology is 44 days.

[c]This patient also received casirivimab-imdevimab 1 month prior to the SARS-CoV-2 infection.

[d]Remdesivir was administered 3 weeks before tixagevimab-cilgavimab when the patient had mild COVID19. (rhinitis).

(4 months). One patient had a rapidly worsening COVID-19 pneumonia and died 4 days post tixagevimab-cilgavimab administration (not eligible for intensive care treatment).

Despite a small and heterogeneous patient population, this study is the first to report detailed outcomes after curative treatment with tixagevimab-cilgavimab for Omicron SARS-CoV-2 infection, in patients with hematologic malignancies. We found that asymptomatic patients that receive tixagevimab-cilgavimab at a dose of 300–300 mg did not developed severe COVID-19, despite being at high risk, and could immediately resume their chemotherapy without adversely affecting their hematologic disease. This finding suggests that while prophylactic tixagevimab-cilgavimab 300–300 mg is effective in preventing Omicron SARS-CoV-2 infection [6, 7], it may remains effective in preventing the progression to severe COVID-19 in patients with a haematologic malignancy and asymptomatic or pauci-symptomatic Omicron SARS-CoV-2 infection. Of note we could not exclude that in those patients COVID19 could have recover spontaneously in the absence of tixagevimab-cilgavimab administration.

In the eight patients with Omicron COVID-19 pneumonia requiring oxygen, three completely recovered after administration of tixagevimab-cilgavimab alone ($n = 1$) or combined with dexamethasone ($n = 2$). Of note, these 3 patients had omicron BA1 despite tixagevimab-cilgavimab being less active against omicron BA1 compared to BA2 [2]. In addition, one patient recovered after additional administration of convalescent plasma [8, 9]. While the remaining four patients died, we must highlight that tixagevimab-cilgavimab alone ($n = 1$) or combined with anti-inflammatory treatment ($n = 2$) lead to a clinical recovery with oxygen weaning in three of them. Nevertheless, those patients had a prolonged viral shedding with persistently positive nasopharyngeal PCRs and presented an acute respiratory distress syndrome secondary to the SARS-CoV-2 pneumonia 3–6 weeks later. This highlights the importance of close monitoring of such patients and the necessity of developing new strategies to prevent worsening in patients with prolonged viral shedding. Repeated administration of tixagevimab-cilgavimab may be worthy of investigation since there is a dose-effect in neutralizing the Omicron variant [6]. Furthermore, convalescent plasma remains effective for Omicron neutralisation [10] and its early administration in patients who remain SARS-CoV-2 positive should be considered.

Overall, in the current Omicron and vaccine era, while COVID-19 clinical outcomes have significantly improved, it remains life-threatening in patients with haematologic malignancies. In patients who are infected with the Omicron SARS-CoV-2 variant, unvaccinated or who did not respond to vaccination and did not receive prophylactic tixagevimab-cilgavimab, preemptive tixagevimab-cilgavimab at a dose of 300–300 mg seems effective. In patients with SARS-CoV-2 pneumonia who require oxygen, additional therapeutic strategies must be developed.

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## DATA AVAILABILITY

All data supporting this letter are provided in the manuscript (Table 1).

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## AUTHOR CONTRIBUTIONS

AO recruited patients, collected, assembled and analyzed data, and wrote the first draft of the manuscript. ZV, EB, RD, AD, YA, LR, NS, AB, AB, TA, ZM, PC, OL, KL, MM recruited patients, collected data and helped write the manuscript. J.G. and A.S. performed virological test and helped write the manuscript. MM and FM designed the study, assembled and analyzed data, supervised research, analyzed data, helped with writing the manuscript and revised the manuscript.

## COMPETING INTERESTS

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## ADDITIONAL INFORMATION

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