Real-world effectiveness of casirivimab plus indevimab in a dedicated ambulatory unit created for patients with early COVID-19 during a massive delta variant wave

Samuel Markowicz1 · Theo Trioux1 · Clémence Rulquin1 · Chloé Le Guillou1 · Rachida Ouissa1 · Cécile Loraux2 · Marion Saliege3 · Pierre-Marie Roger1

Received: 13 January 2022 / Accepted: 18 July 2022 / Published online: 27 July 2022
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2022

Abstract
Only limited real-life data are available on the effects of neutralizing monoclonal antibodies in high-risk patients who have early COVID-19 and do not require supplemental oxygen. We prospectively studied 217 patients infected by the delta variant who received casirivimab plus indevimab in a dedicated ambulatory unit created during our 4th COVID wave. Mean age was 64 years, 94% had at least one comorbidity, and mean duration of symptoms was 2.9 days. Oxygen requirement, hospitalization, and mortality rates were 10, 6, and 2.8%, respectively. These results suggest benefits of early administration of neutralizing antibodies in high-risk patients infected with the delta variant.

Keywords COVID-19 · Monoclonal antibodies · Real life · Delta variant · Ambulatory care

Introduction
Neutralizing monoclonal antibodies (NmAbs) represent an emerging class of treatment for COVID-19, targeting the viral spike protein and blocking the entry of SARS-CoV-2 into human cells [1]. Available placebo-controlled trials evaluating the effects of NmAbs in ambulatory patients who have mild to moderate disease and are at high risk for hospitalization showed a decreased viral load in treated patients [2, 3]. Patients were considered at high risk if they had an advanced age, chronic disease, and/or immune deficiency. Furthermore, randomized trials demonstrated that NmAbs significantly decreased the risk of hospitalization [4, 5]. In these studies, NmAbs were administered early in the course of disease (ideally within the first 5 days), in patients not requiring supplemental oxygen.

Based on these results, the French Drug Agency authorized since March 2021 the use of two combinations of NmAbs (bamlanivimab plus etesevimab and casirivimab plus indevimab) in selected ambulatory patients with confirmed SARS-CoV-2 infection.

With a predominantly unvaccinated population in Guadeloupe facing a major 4th COVID wave overwhelming the local healthcare capacity, large access to treatment with NmAbs in patients not requiring oxygen therapy was promoted. Because this wave was exclusively driven by the delta variant which has decreased sensitivity to bamlanivimab [6], casirivimab plus indevimab was selected to treat eligible patients in the reference Hospital of Guadeloupe.

Only few data are available on the real-life effectiveness of NmAbs. Recent data, mainly using bamlanivimab, showed a significantly reduced progression to severe disease [7, 8]. To our knowledge, no data have been published on the therapeutic effects of NmAbs in the setting of a delta variant wave.

The aim of our study was to describe the outcomes of high-risk patients who received early treatment by casirivimab and indevimab, in the real-life setting of a major COVID-19 wave due to the delta SARS-CoV-2 variant.
Methods

We performed a prospective observational study of patients who received casirivimab plus indevimab for mild to moderate forms of proven SARS-CoV-2 infection at the University Hospital of Guadeloupe (Pointe-à-Pitre, French West Indies), at the peak period of the 4th COVID-19 wave.

In order to facilitate outpatient care of eligible patients, the infectious disease team sets up a dedicated ambulatory unit allowing the administration of intravenous therapy to multiple patients, every day of the week. General practitioners were informed of the availability of this therapeutic option through webinars, and a dedicated phone line was created to directly refer eligible patients to our ID team.

Casirivimab plus indevimab combination was administered intravenously in the dedicated unit after patient consent was obtained, with a dosage of 1200 mg each, in a saline solution over one hour. Treated patients were observed during administration and for 1 h after infusion was complete, to monitor for immediate adverse events. For patients already hospitalized for another reason than COVID-19, infusion was directly done in the patient unit.

Eligible patients were high-risk adult patients (≥ 18 years old), who tested positive by PCR for SARS-CoV-2 on a nasopharyngeal swab, had symptoms for ≤ 5 days, and did not require oxygen supplementation. Patients with ≥ 1 of the following conditions were considered to be at high risk: immune deficiency, pre-defined chronic medical conditions (cardiovascular, pulmonary, renal or liver disease, and diabetes), severe obesity (BMI > 35 kg/m²), and age > 80 years. We excluded patients having symptoms for > 5 days and/or requiring oxygen therapy (at the exception of patients already receiving chronic oxygen therapy for cardiac or pulmonary disease). Children and pregnant women were also excluded.

The following endpoints were systematically assessed: oxygen requirement, hospitalization (except for patients already hospitalized for another reason than COVID-19), intensive care unit admission, and death. NmAbs therapeutic failure was defined as the occurrence of any of these events.

Sociodemographic, clinical, laboratory and outcome data were prospectively collected. Clinical follow-up was performed by phone at days 7 and 30. For virological follow-up, control PCR test (to be done between days 7 and 14) was ordered at time of discharge.

Statistical analysis

Data were analyzed using StatView software version 5.0, and statistical significance was established at α = 0.05. Continuous variables were compared using the Mann–Whitney test, and proportions were compared using the Fisher’s exact test.

Results

The study included 217 patients with confirmed COVID-19 who received intravenous NmAbs between July 29 and September 18, 2021. All SARS-CoV-2 infections were confirmed by PCR and due to the delta variant.

The demographic, clinical, and biological characteristics of patients are summarized in Table 1. The mean age was 64 years, and the vast majority of the patients (94%) had at least one comorbidity, the most frequent (54%) being diabetes; 13% of patients were immunocompromised, the main reason being kidney transplantation. Partially vaccinated patients with one injection represented 21% of cases; none was fully vaccinated or had previous COVID-19 infection. Hospital-acquired infections represented 9% of all infections and were confirmed by serial PCR. In terms of clinical presentation, 197 patients (91%) were symptomatic (all with symptoms < 5 days); the remaining 20 patients (9%) were asymptomatic but had evidence of early acquisition by serial PCR. The mean duration of symptoms before treatment was 2.9 days; cough (52%) and fever (44%) were the most common symptoms.

The only serious adverse event identified during the study period was a hypersensitivity reaction which rapidly improved with medical management.

According to our definition, 26 (12%) patients had an unfavorable outcome: 22 (10%) required supplemental oxygen in hospital or at home, 13 (6%) required hospital admission, 1 (0.5%) required intensive care unit admission, and 6 (2.8%) died. Only one death occurred among the 13 transplant recipients (8%).

PCR was controlled between days 7 and 14 post-infusion in 119 patients and was positive in only 44 of these cases (37%).

When comparing patients with favorable and unfavorable outcome, we found older age and presence of dyspnea at baseline to be significantly associated with an unfavorable outcome (p = 0.002 and p < 0.001, respectively; see Table 1).

Death cases are detailed in Table 2: All patients had major comorbidities, 3/6 were immunocompromised, and 4/6 deaths occurred within hospital due to respiratory failure.

Discussion

In this prospective single center observational study done in the challenging setting of a predominantly unvaccinated Afro-Caribbean population facing a COVID-19 wave driven...
### Table 1  Main characteristics of the patients according to the outcome

| Characteristics | Total n = 217 (100%) | Favorable outcome n = 191 (88%) | Unfavorable outcome n = 26 (12%) | p |
|-----------------|----------------------|---------------------------------|----------------------------------|---|
| Age (years, mean±std dev) | 64±18 | 63±17 | 73±18 | 0.002 |
| Sex-ratio (M/F) | 0.88 | 0.91 | 0.73 | 0.609 |
| Underlying conditions | | | | |
| At least one comorbid condition | 204 (94) | 180 (94) | 24 (92) | >0.999 |
| Diabetes | 118 (54) | 103 (54) | 15 (58) | 0.717 |
| Hypertension | 78 (36) | 70 (37) | 8 (31) | 0.557 |
| Obesity | 46 (21) | 41 (21) | 5 (19) | 0.793 |
| Chronic renal disease/dialysis | 31 (14) | 30 (16) | 1 (4) | 0.185 |
| Immunosuppression | 29 (13) | 24 (13) | 5 (19) | 0.348 |
| Charlson’s score | 2.49 ± 1.58 | 2.48 ± 1.59 | 2.57 ± 1.57 | 0.587 |
| Partially vaccinated (1 injection) | 35 (21) | 31 (21) | 4 (20) | >0.999 |
| Health-care associated infections | 19 (9) | 16 (8) | 3 (12) | 0.867 |
| Duration of symptoms (days) | 2.9 ± 1.3 | 2.9 ± 1.3 | 2.9 ± 1.2 | >0.999 |
| Clinical symptoms | | | | |
| Dyspnea | 34 (16) | 23 (12) | 11 (44) | <0.001 |
| Fever | 94 (44) | 82 (43) | 12 (46) | 0.772 |
| Cough | 113 (52) | 99 (52) | 14 (54) | 0.847 |
| Flu-like syndrome | 76 (35) | 70 (37) | 6 (23) | 0.173 |
| Ageusia/anosmia | 16 (7) | 14 (7) | 2 (8) | >0.999 |
| Biological data on admission | | | | |
| Lymphocytes/mL (median [range]) | 1110 [90–9510] | 1201 [90–4620] | 990 [116–9510] | 0.497 |
| C-reactive protein (mg/L, median[range]) | 18 [1–365] | 18 [1–365] | 12 [1–266] | 0.561 |
| Positive SARS-CoV2 PCR on days 7–14 | 44/119 (37) | 39/106 (37) | 5/13 (38) | 0.906 |

Unfavorable outcome was defined by oxygen requirement, hospital admission, and/or death.

### Table 2  Death cases of COVID-19 infections treated with neutralizing antibodies

| Case | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 |
|------|--------|--------|--------|--------|--------|
| Sex  | Male   | Female | Male   | Male   | Female |
| Age (years) | 65 | 79 | 79 | 81 | 88 |
| Comorbid conditions | Renal transplant; peripheral arteriopathy | Stroke; obesity; obstructive sleep apnea | Pulmonary fibrosis | COPD, pneumothorax | Cardiopathy; chronic renal disease |
| Imunosuppression (type) | Yes (combination) | No | Yes (steroids) | No | No |
| Duration of symptoms before treatment (days) | 4 | 4 | 4 | 2 | 1 |
| Clinical features | Flu syndrome | Fever; flu syndrome; anosmia | Increasing dyspnea, cough | Increasing dyspnea | Dyspnea and cough |
| Lymphocytes/µL | 940 | 770 | 330 | 290 | 670 |
| C-reactive protein (mg/L) | 65 | 229 | 230 | 119 | 4 |
| Respiratory degradation | No | Yes | Yes | Yes | No |
| Cause of death | Unknown | ARDS | ARDS | ARDS | Stroke |
| Occurrence | Home | Hospital | Hospital | Hospital | Home |
by the delta variant, we observed relatively low hospitalization and mortality rates in patients receiving early treatment with casirivimab-indevimab for mild to moderate COVID-19.

The main limitation of our observational study is the absence of a control group, making difficult to measure the effectiveness of casirivimab and indevimab. However, to our knowledge, there is no published data available on the effectiveness of NmAbs in patients infected with the delta variant. We were unable to compare the outcomes of our patient to those of patients not receiving NmAbs, due to the lack of precise data on the risk of hospitalization and mortality due to delta variant in these specific vulnerable populations. Comparison with previous studies on NmAbs is difficult due to important heterogeneity between studies. Weinreich et al. found in their randomized trial a hospitalization rate as low as 1%, but the patient mean age was 48 years, and the main reason for treatment was obesity [5]. Another real-life study found a hospitalization rate similar to our finding (6%), but lower mortality (0.6%): Here again, mean age was lower (59 years), and only 30% of patients had an underlying comorbidity (as compared with 94% of the patients in our study) [7]. Thus, our results need to be interpreted considering that our study population was relatively vulnerable, with older and more comorbid patients. Another explanation for our results could be the higher virulence of the delta variant, more frequently leading to hospitalizations than previous SARS-CoV-2 variants [9].

On the other hand, relatively poor outcomes were observed in the “casirivimab plus indevimab French cohort,” which found hospitalization rates over 20% and mortality rates over 5%. In this cohort, 65% of patients were immunocompromised [10]. Similarly, mortality rates ranging from 13 to over 30% in solid organ transplants were observed elsewhere [11], while only one death occurred in our study among 13 transplant recipients (8%). Our data suggest that the early use of NmAbs in high-risk patients who are infected with the delta variant but do not require supplemental oxygen may be effective at reducing the risk of hospitalization and death. This potential benefit is particularly interesting in the case of a major COVID-19 wave overwhelming healthcare capacities, as this was the case during the study period.

When assessing the factors predicting treatment failure, we found older age to be associated with a poor outcome [7], but also found an association with the presence of dyspnea (without desaturation <94%). To our knowledge, this finding has not been reported previously and may reflect a greater respiratory involvement. Unlike others, we did not find an association between the duration of symptoms before infusion and the clinical outcomes [7, 8].

This study illustrates the feasibility of rapidly creating a dedicated ambulatory unit with a specialized medical team, to administer intravenous treatment to several patients per day at an early stage of COVID-19. The relatively high number of treated patients also supports the possibility to quickly and effectively spread the information of a new therapeutic strategy to the medical community. Remarkably, only 277 COVID-19 patients received NmAbs during the same study period in France [10], as compared with 217 treated patients in our much smaller territory. This suggests a high catchup of COVID-19 patients eligible to receive NmAbs, knowing that 1576 patients were admitted to our local emergency department during that period.

In summary, our data suggest a beneficial effect of casirivimab-indevimab combination in high-risk patients with mild to moderate COVID-19 due to delta variant, to prevent oxygen requirement, hospitalization, and death. Our experience also illustrates that it is possible to rapidly and effectively disseminate information on a new therapeutic tool and to urgently create dedicated ambulatory units for treatment administration.

Acknowledgements From the University Hospital of Guadeloupe, our thanks go to Elodie Curlier, Isabelle Fabre, Isabelle Lamaury, Marion Broudic, Pierre Alphonse, and Lisa Sildillia, for their participation in patient care during the COVID-19 crisis. Our thanks also go to Julien Coussement for reviewing the manuscript.

Author contribution All authors contributed to the study conception and design.

Samuel Markowicz: methodology, formal analysis, investigation, writing-review and editing. Pierre-Marie Roger: methodology, investigation, formal analysis, writing-review and editing. Theo Trioux: methodology, data collection. Clémence Rulquin: data collection. Rachida Ouissa: data collection. Chloé Le Guillou: data collection. Marion Saliège: methodology, formal analysis, data collection. Cécile Loraux: formal analysis, investigation, data collection.

Data availability Original data will be made available upon request.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. The protocol was approved by the local ethical committee.

Consent for publication The authors have seen the final version of the manuscript and approved submission for publication.

Conflict of interest The authors declare no competing interests.

References

1. Marovich M, Mascola JR, Cohen MS (2020) Monoclonal antibodies for prevention and treatment of COVID-19. JAMA 324(2):131–132. https://doi.org/10.1001/jama.2020.10245
2. Weinreich DM, Sivapalasingam S, Norton T et al (2020) REGN-COV2, a Neutralizing antibody cocktail, in outpatients with
3. Chen P, Nirula A, Heller B et al (2020) SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. N Engl J Med. https://doi.org/10.1056/NEJMoa2029849

4. Dougan M, Nirula A, Azizad M et al (2021) Bamlanivimab plus etesevimab in mild or moderate Covid-19. N Engl J Med 385(15):1382–1392. https://doi.org/10.1056/NEJMo2102685

5. Weinreich DM, Sivapalasingam S, Norton T et al (2021) REGEN-COV antibody combination and outcomes in outpatients with Covid-19. N Engl J Med 385(23):e81. https://doi.org/10.1056/NEJMo2108163

6. Planas D, Veyer D, Baidaliuk A et al (2021) Reduced sensitivity of SARS-CoV-2 variant delta to antibody neutralization. Nature 596(7871):276–280. https://doi.org/10.1038/s41586-021-03777-9

7. Verderese JP, Stepanova M, Lam B, et al (2021) Neutralizing monoclonal antibody treatment reduces hospitalization for mild and moderate COVID-19: a real-world experience [published online ahead of print, 2021 Jun 24]. Clin Infect Dis. ciab579. https://doi.org/10.1093/cid/ciab579

8. Ganesh R, Philpot LM, Bierle DM et al (2021) Real-world clinical outcomes of bamlanivimab and casirivimab-imdevimab among high-risk patients with mild to moderate coronavirus disease 2019. J Infect Dis 224(8):1278–1286. https://doi.org/10.1093/infdis/jiab377

9. Taylor CA, Patel K, Pham H, et al. (2021) Severity of disease among adults hospitalized with laboratory-confirmed COVID-19 before and during the period of SARS-CoV-2 B.1.617.2 (delta) predominance - COVID-NET, 14 States, January-August 2021. MMWR Morb Mortal Wkly Rep. 2021;70(43):1513-1519. https://doi.org/10.15585/mmwr.mm7043e1. Published 2021 Oct 29

10. Autorisation temporaire d’utilisation de cohorte : Casirivimab et Imdevimab. Résumé du rapport de synthèse périodique. Période du 16 juin 2021 au 15 août 2021. https://ecrf.eurapharma.fr/CSOnline/api/downloadfile/get?path=STREAM&id=EURA0322-820-3348405-1641253511,97004

11. Azzi Y, Bartash R, Scalea J, Loarte-Campos P, Akalin E (2021) COVID-19 and solid organ transplantation: a review article. Transplantation 105(1):37–55. https://doi.org/10.1097/TP.0000000000003523

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.