Real-world Effectiveness of Casirivimab Plus Indevimab in a Dedicated Ambulatory Unit Created for Patients With Early COVID During a Massive Delta Variant Wave

Samuel Markowicz (✉ sam.markowicz@gmail.com)

Centre Hospitalier Universitaire Pointe-a-Pitre Abymes <https://orcid.org/0000-0002-1227-9702>

Theo Trioux

Centre Hospitalier Universitaire Pointe-a-Pitre Abymes

Clemence Rulquin

Centre Hospitalier Universitaire Pointe-a-Pitre Abymes

Chloé Le Guillou

Centre Hospitalier Universitaire Pointe-a-Pitre Abymes

Rachida Ouissa

Centre Hospitalier Universitaire Pointe-a-Pitre Abymes

Cécile Loraux

Centre Hospitalier Universitaire Pointe-a-Pitre Abymes

Marion Saliège

Centre Hospitalier Universitaire Pointe-a-Pitre Abymes

Pierre-Marie Roger

Centre Hospitalier Universitaire Pointe-a-Pitre Abymes

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Abstract

Only few data are available on real-life effectiveness of neutralizing monoclonal antibodies to avoid hospitalization in high-risk patients with early COVID-19 not requiring supplemental oxygen. Our study analyzed the efficacy of casirivimab plus indevimab to prevent unfavorable outcomes in these patients. A dedicated Hospital Day Unit was created to treat during our 4th COVID wave 217 patients infected by the Delta variant. Mean age was 64 years, 94% had at least one comorbidity, and mean duration of symptoms was 2.9 days. Oxygen request, hospitalization, and mortality rates were respectively of 10, 6, and 2.8%. These results suggest efficacy of neutralizing antibodies infused in a dedicated ambulatory unit created for high-risk patients infected with a Delta variant at an early stage.

Introduction

Neutralizing monoclonal antibodies (NmAbs), an emerging passive neutralizing therapy for COVID-19, have been recently introduced against SARS-CoV-2, targeting the viral spike protein and blocking the entry of the virus in human cells [1]. The results of the trials comparing these NmAbs to a placebo in ambulatory patients with mild to moderate disease and at high risk for hospitalization showed a viral load decrease in treated patients [2, 3]. Patients were considered at risk for hospitalization if they had an advanced age, chronic disease and/or immune deficiency. Randomized trials have also proven efficacy of this therapy to avoid hospitalization in these patients [4, 5]. These benefits were observed if NmAbs were administered early in the history of the disease (ideally within the first 5 days), in patients not on supplemental oxygen.

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

With a predominantly unvaccinated population in Guadeloupe facing a dramatic 4th COVID wave and overwhelming the local healthcare capacity, large access to treatment with NmAbs in patients not requiring oxygen therapy was created. Because this wave was exclusively driven by the Delta variant whose sensitivity to bamlanivimab has been proven to be diminished [6], casirivimab plus indevimab was chosen to treat all selected patients in the reference Hospital of Guadeloupe.

Only few data are available on real-life effectiveness of NmAbs in clinical practice, but recent data showed a significant reduction of progression to severe disease, using mainly bamlanivimab [7]. To our knowledge, no data have been published on the therapeutic impact of NmAbs in the setting of a Delta variant wave.

Our study analyzed the efficacy of the combination of casirivimab and indevimab to prevent unfavorable outcomes in patients with confirmed Delta SARS-CoV-2 infection in an early stage and at risk for severe COVID.

Methods

It is a prospective analysis of patients treated by casirivimab plus indevimab for mild to moderate forms of Covid-19 in the University Hospital of Guadeloupe (Pointe-à-Pitre, French West Indies), during the peak period of our 4th Covid wave.

In order to deliver extended outpatient care to these patients, the Infectious Disease team created a "Hospital Day" unit allowing daily access to intravenous treatments for several patients per day. Family doctors were informed through webinars of the availability of these treatments for outpatients, and a dedicated phone line was created to contact our ID ward.

All patients had SARS-CoV-2 infection confirmed by RT-PCR on nasopharyngeal swab: 197 (91%) were symptomatic with symptoms lasting less than 5 days, and 20 (9%) were asymptomatic but with sufficient proof of an early acquisition by serial PCR. All positive samples were screened for Delta variant in a reference lab (Institut Pasteur, Paris, France).

All sociodemographic, clinical, laboratory and outcomes data were collected prospectively. The following indications for NmAbs were retained: immune deficiency, defined chronic medical conditions (chronic cardiovascular, pulmonary, renal or liver disease, and diabetes), severe obesity (BMI > 35 kg/m²) and age > 80 years.

Patients requiring oxygen therapy were excluded, except patients already receiving chronic oxygen therapy for cardiac or pulmonary chronic disease.

Casirivimab plus indevimab combination was administered intravenously in the dedicated unit after patient's agreement, with a dosage of 1200 mg each, in a saline solution during one hour. Clinical monitoring during infusion and one hour after the end of it was realized, to ensure the absence of immediate adverse event.

Clinical follow-up was provided by phone consultation at Day 7 and 30. Oxygen requirement, hospitalization, intensive care admission and deaths were systematically screened. The occurrence of one of these events defined a therapeutic failure of NmAbs. Virological follow-up with a PCR test to be realized between day 7 and day 14 was prescribed at discharge.

Results

The study included 217 patients with confirmed COVID-19 and treated with infusions of 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. Mean age was 64 years, and the vast majority (94%) had at least one comorbid condition, the most frequent (54%) being diabetes; 13% of patients had immune suppression, the main reason being immunosuppressive drugs for renal transplant. Partially vaccinated patients with one injection represent 21% of cases, none were fully vaccinated nor had Covid-19 infection in the past. Health-care infections represent 9% of all infections and were confirmed by serial PCR. Mean duration of symptoms before treatment was 2.9 days; cough (52%) and fever (44%) were the most common clinical presentations.

Table 1

Main characteristics of the patients according to the outcome. Unfavorable outcome was defined by oxygen requirement, hospital admission, and/or death.

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 Day 7-14	44/119 (37)	39/106 (37)	5/13 (38)	0.906

The only serious adverse event due to the infusion observed during the study period was a hypersensitivity reaction that rapidly improved with medical management.

According to our definition, outcome was unfavorable in 26 (12%) patients: 22 (10%) required supplemental oxygen in hospital or at home, 13 (6%) required hospitalization, 1 (0.5%) went to intensive care unit, and 6 (2.8%) died.

PCR was controlled between Day 7 and Day 14 after treatment in 119 patients and was positive in only 44 (37%) cases.

When comparing patients with favorable and unfavorable outcome, only older age and presence of dyspnea at baseline were significantly more frequent in patients of the latter group: $p=0.002$ and $p<0.001$, respectively (see Table 1).

The 6 death cases are detailed in Table 2: all patients had heavy comorbidities, 3/6 were immunosuppressed, and 4/6 died of respiratory degradation in hospital.

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

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex	Male	Female	Male	Male	Female	Female
Age (years)	65	79	79	81	88	94
Comorbid conditions	Renal transplant; peripheral arteriopathy	Stroke; obesity; obstructive sleep apnea	Pulmonary fibrosis	COPD, pneumothorax	Cardiopathy; chronic renal disease	Rheumatoid arthritis; asthma; peripheral arteriopathy
Immunosuppression (type)	Yes (combination)	No	Yes (steroids)	No	No	Yes (steroids)
Duration of symptoms before treatment (days)	4	4	4	2	1	3
Clinical features	Flu syndrome	Fever; flu syndrome; anosmia	Increasing dyspnea, cough	Increasing dyspnea	Dyspnea and cough	Dyspnea and cough
Lymphocytes / μL	940	770	330	290	670	1640
C-Reactive Protein (mg/L)	65	229	230	119	4	41
Respiratory degradation	No	Yes	Yes	Yes	No	Yes
Cause of death	Unknown	ARDS	ARDS	ARDS	Stroke	ARDS
Occurrence	Home	Hospital	Hospital	Hospital	Hospital	Home

Discussion

In this prospective monocentric study, we report low hospitalization and mortality rates with the use of casirivimab plus indevimab combination for mild to moderate COVID-19 infection in real-life clinical practice, during a massive COVID wave due to the Delta variant in a predominantly unvaccinated Afro-Caribbean population.

The main limitation of our study is that there is no control group, and it is therefore difficult to ensure the benefit of the treatment. Nevertheless, comparison with the other available data suggest it strongly.

Weinreich et al found in their clinical trial a hospitalization rate as low as 1%, but mean age was 48 years and main reason for treatment was obesity [5]. Others found in real-life setting similar hospitalization rate to our data (6%), but lower mortality (0.6%): here again, mean age was lower (59 years) and only 30% of patients had comorbidities [7]. Thus, our results can be explained by a more vulnerable population with older and more comorbid patients. Another explanation for our results could be the higher virulence of the Delta variant, leading more frequently to hospitalizations

than previous variants of concern [9]. To our knowledge, no efficiency data of NmAbs on Delta variant have been published until now.

On the other hand, the outcomes of the “casirivimab plus indevimab French cohort” show hospitalization rates over 20% and mortality rates over 5%, which is much higher than our data, but in a population with 65% of patients being immunosuppressed [10]. Similarly, mortality rates in solid organ transplants reported in the literature range from 13 to over 30% [11], while we only had one death among our 13 transplanted patients (8%). Thus, even if we don't have a control group, all these data suggest a benefit of treating with NmAbs high-risk patients infected with the Delta variant of Covid-19 not requiring supplemental oxygen, to avoid hospitalization and deaths, which is particularly important in Covid waves overwhelming hospital capacities.

When analyzing the predictive factors for treatment failure, older age was logically associated with poor outcome [7], but we also found an association with the presence of dyspnea experienced by the patient (without lowering the saturation < 94%). To our knowledge, this has never been reported in the literature, and probably reflects a greater respiratory involvement. Unlike others, we haven't found any correlation with duration of symptoms before infusion [7, 8].

This study illustrates the feasibility of creating rapidly a Hospital Day Unit with a dedicated and specialized medical team, allowing to treat with intravenous treatments several patients per day at an early stage of the disease. It also shows the possibility to spread quickly and effectively the information of a new therapeutic strategy to the medical community. We can consider our strategy highly effective as only 277 patients were treated during the same study period with NmAbs in France [10], while 217 cases were treated on our much smaller territory. This suggests a high catchup of COVID patients targeted by NmAbs when we know that 1576 patients were admitted to our emergency department during that period.

In summary, our data highly suggest benefit of casirivimab plus indevimab combination in mild to moderate Covid-19 due to Delta variant in high-risk patients to avoid oxygen request, hospitalization, and deaths. This should incite to the rapid dissemination of medical information on new therapeutic tools and to the creation of dedicated ambulatory units.

Declarations

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Conflicts of interest

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

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.

Consent for publication

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

Data availability

Original data will be made available upon request.

Ethical approval

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

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