Clinical and virological evolution of patients at high risk of severe COVID-19 treated with early administration of dual monoclonal antibodies

POSTER #299

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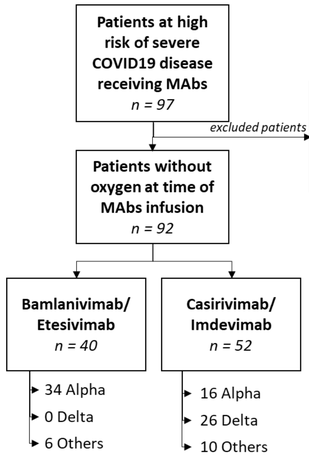
BACKGROUND

- An emergency use authorization was issued in March 2021 for two combinations of monoclonal antibodies (MAbs) for SARS-CoV-2 infected patients at high risk of severe COVID-19.
- We performed a cohort study of patients receiving early treatment with Bamlanivimab/Etesevimab (B/E) or Casirivimab/Imdevimab (C/I) in a Paris university hospital.

METHODS

- All patients receiving a MAbs therapy from March to October 2021 were included. Prescriptions were systematically advised by a multidisciplinary team.
- Both MAbs dual therapies were used up to May 12th, then only C/I, due to local emergence of Delta variant.
- Nasopharyngeal swabs (NPS) were performed at diagnosis and 7 days after infusion. Additional NPS were collected for hospitalized patients at day 3 and during follow-up until negative RT-PCR or patients discharge.
- NPS were tested by RT-PCR using either the Cobas® SARS-CoV-2 (Roche, Switzerland) on a Cobas® 6800 system or the NeuMoDX® SARS-CoV-2 Assay (QIAgen, Germany) on a NeuMoDx® 288 system. Cycle threshold (Ct) values of the ORF1ab or N targets were used as a proxy for viral load for the Cobas and the NeuMoDx assay, respectively.
- Full SARS-CoV-2 genome sequencing was conducted after acid nucleic extraction using the MagNA Pure LC Total Nucleic Acid Isolation Kit (Roche, Basel, Switzerland) and tiling PCR amplification according to the Artic protocol (ARTIC nCoV-2019 V3). Libraries were prepared with NEBNext Companion Module for Oxford Nanopore Technologies, Ligation Sequencing (SQK-LSK 109) and sequenced using MinION R9.4.1 flow cells. All sequences obtained have been deposited on GISAID.



Study flow chart

	All patients (n=92)	Bamlanivimab Etesivimab (n=40)	Casirivimab Imdevimab (n=52)	*p-value*
Age – *years, median [IQR]*	69 [57–79]	71 [59–83]	67 [55–76]	
Sex – *female, n(%)*	41 (46)	19 (47)	22 (42)	*p=0.62*
Coexisting conditions – *no (%)*				
BMI > 30	19/65 (29%)	11/29 (38%)	8/36 (22%)	*p=0.18*
Transplantation	25/92 (27%)	10/40 (25%)	15/52 (29%)	*p=0.81*
Chronic renal insufficiency	35/92 (38%)	15/40 (38%)	20/52 (38%)	*p=0.96*
Type II Diabetes	41/92 (45%)	16/40 (40%)	25/52 (48%)	*p=0.53*
Chronic heart insufficiency	18/92 (20%)	8/40 (20%)	10/52 (19%)	*p=1.0*
Chronic respiratory disease	12/91 (13%)	6/39 (15%)	6/52 (12%)	*p=0.8*
≥3 comorbidities	16/92 (17%)	7/40 (18%)	9/52 (17%)	*p=1.0*
Long term medication – *no (%)*				
Immunosuppressive therapy	46/92 (50%)	16/40 (40%)	30/52 (58%)	*p=0.07*
Chemotherapy	11/92 (12%)	3/40 (8%)	8/52 (15%)	*p=0.08*
Clinical outcomes				
Delay since symptoms onset – *days, median [IQR]*	3 [2–4]	3 [2–4]	3 [1–4]	*p=0.45*
Dexamethasone – *n(%)*	20/88 (23%)	8/38 (21%)	12/50 (24%)	*p=0.8*
Tocilizumab – *n(%)*	7/88 (8%)	2/38 (5%)	5/50 (10%)	*p=0.69*
O2 requirement – *n(%)*	35/88 (40%)	13/38 (34%)	22/50 (44%)	*p=0.39*
Hospitalization – *n(%)*	72/92 (78%)	26/40 (65%)	42/52 (81%)	*p=0.1*
Hospitalization duration – *median [days]*	13 [5–19]	15 [9–28]	7 [4–16]	***p=0.009***
ICU – *n(%)*	7/88 (8%)	2/38 (5%)	5/50 (10%)	*p=0.35*
Death related to COVID – *n(%)*	11/92 (12%)	5/40 (13%)	6/52 (12%)	*p=1.0*
WHO ordinal scale at J0 – *median [IQR]*	3 [3–5]	3 [1–5]	4 [3–5]	*p=0.09*
WHO ordinal scale at J7 – *median [IQR]*	3 [1–4]	3 [1–4]	3 [1–4]	*p=0.9*
Baseline Variant – *no (%)*				*p<0.001*
Historical	6 (7%)	3 (8%)	3 (6%)	
Alpha	50 (54%)	34 (85%)	16 (30%)	
Beta	6 (7%)	2 (5%)	4 (8%)	
Gamma	1 (1%)	1 (2%)	0	
Delta	26 (28%)	0	26 (50%)	
Unknown	3 (3%)	0	3 (6%)	
Virological follow-up				
NP Ct values at infusion[a] – *median [IQR]*	18.2 [14.9-23.7]	18.0 [14.8-23.1]	18.2 [15.7-24.3]	*p=0.6*
NP PCR <30 Ct at infusion[a] – *n(%)*	79/88 (90%)	36/39 (92%)	43/49 (88%)	*p=0.7*
NP <30 Ct at D7 after infusion[b] – *n(%)*	31/56 (55%)	19/30 (63%)	12/26 (46%)	p=0.28
NP <30 Ct D14 to D21 after infusion – *n(%)*	8/20	8/12	0/8	p=0.005
Patients with viral sequence(s) >D3 – *n*	18	10	8	
Patients with spike mutation(s) selection – *n(%)*	8/18	7/10	1/8	p=0.03

Table 1. Epidemiological, clinical and virological data for included patients.

[a] From 3 days pre-infusion to D1 post-infusion
[b] D7 +/- 48h

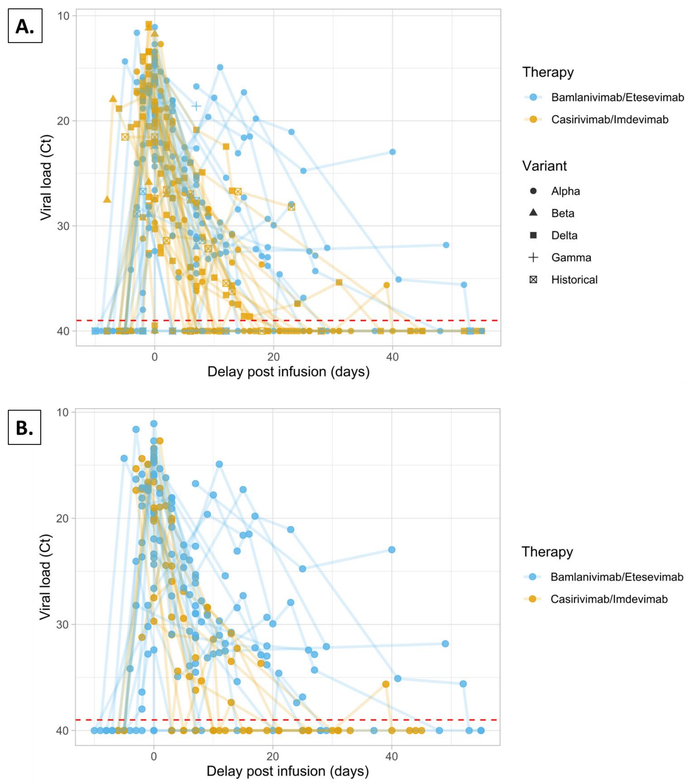


Figure 1. Viral load kinetics follow-up of included patients.

Viral load kinetics, estimated by Ct values, (A) according to viral variants and monoclonal antibodies biotherapy; (B) for Alpha variants only according to monoclonal antibodies biotherapy and (C) according to the presence of new spike mutations, indicated by the red color, and the nature of the respiratory samples, depicted by the shapes.

BAL: Broncho-Alveolar Lavage; Bronch. Asp.: Bronchial Aspirate; NPS: Naso-Pharyngeal Swab.

RESULTS

- Overall, 92 patients (20 ambulatory) received a MAbs dual therapy for a documented SARS-CoV-2 infection.
- Patients had a median age of 69 years [IQR=57-79], 46% were female.
- Among included patients 25 (27%) were solid organ recipients, 12 (13%) had a chronic respiratory disease, 19 (29%) had a BMI>30, 35 (38%) had a chronic renal insuficiency, 41 (45%) had type II diabetes and 18 (20%) had chronic cardiac insufficiency. Overall, 16/92 presented 3 or more comorbidities.
- Regarding treatments, 46 (50%) were receiving immunosuppressive treatment and 11 (12%) were receiving chemotherapy.
- No statistically significant differences were observed across B/E and C/I treatment groups (**Table 1**).

- The median delay between symptoms onset and monoclonal antibodies infusion was at 3 [IQR: 2-4] days. The median WHO ordinal severity scale for all patients at D0 of infusion was at 3 [3-5].
- This scale was at 3 [1-5] and 4 [3-5] at D0 for patients treated by B/E and C/I, respectively, and at 3 [1-4] at D7 post-infusion for both arms.
- Main outcomes criteria were similar with both treatments with 11 patients (12%) that died (6 with B/E and 7 with C/I), including 10 deaths directly related to COVID-19 worsening, and, among the surviving patients, 53 (60%) that did not required any oxygen therapy.
- The hospitalization duration, among hospitalized patients, was significantly different with a median at 15 [9-28] and 7 [4-16] days for B/E and C/I arms, respectively (*p=0.009*, **Table 1**).
- No severe adverse event related to MAbs occurred during patients follow-up.

- Regarding viral variants identified among included patients, 50 (54%) were Alpha, 26 (28%) Delta and 13 (14%) other variants. In accordance to recommendations, all Delta variants were treated with C/I therapy.
- Patients presented similar initial viral loads at infusion in both arms with an overall median Ct value at 18.2 [14.9-23.7].
- A similar viral decay at day 7 post-infusion was observed among patients under B/E and C/I with 19/26 (73%) and 16/24 (66%) having a NPS Ct value <30 (p=0.75), respectively.
- However, a lower viral decay was observed between D14 and D21 post-infusion for B/E vs C/I, with 8/12 vs 3/14 patients presenting a NPS Ct value <30 (p=0.045) (**Table 1** and **Figure 1**).
- Different spike mutations emergence were observed among several patients. The observed mutations included Q493R, S254F, E484K/G, F490V, S494P, A626S and E654A in 5, 2, 2, 1, 1, 1 and 1 patients, respectively. All were detected from 5 to 18 days after MAbs infusion and occurred with an Alpha variant under B/E therapy, except for one patients with a Delta variant under C/I therapy (**Table 2**).

Table 2. New mutation appearance in the spike gene.

The type of respiratory samples is indicated and highlighted by the bold police for upper respiratory tract samples and italic police for lower respiratory tract samples.

BAL: Broncho-Alveolar Lavage; Bronch. Asp.: Bronchial Aspirate; NPS: Naso-Pharyngeal Swab.

Patient	Variant	Monoclonal antibodies bitherapy	Delay between infusion and mutation detection (days)	Type of respiratory sample	New mutations in spike gene
			10	**NPS**	**Q493R**
			14	**NPS**	**Q493R**
			17	**NPS**	**S494P**
# 1	Alpha	B/E	18	*BAL*	*Q493R E484K(minor)*
			23	**NPS**	**S494P**
			27	*Bronch. Asp.*	*E484K*
			31	*Bronch.Asp.*	*E484K*
# 2	Alpha	B/E	7	**NPS**	**Q493R**
			31	*BAL*	*Q493R*
# 3	Alpha	B/E	11	**NPS**	**Q493R A626S**
# 4	Alpha	B/E	9	**NPS**	**E484G**
			15	**NPS**	**F490V Q493R**
# 5	Alpha	B/E	5	**NPS**	**Q493R**
# 6	Alpha	B/E	4	**NPS**	**E654A**
# 7	Alpha	B/E	4	**NPS**	**S254F**
# 8	Delta	C/I	6	**NPS**	**S254F**

CONCLUSION

- In this work, we described the safety and efficacy of early MAbs therapies administration in a cohort of 92 patients at risk of severe COVID-19.
- The B/E therapy presented slightly slower viral decay than C/I and several emergence of new spike mutations were observed, especially with Alpha variant under B/E therapy presenting a slow viral decay.
- Thus, emergence of resistance, if less frequent than with monoclonal monotherapy, is possible and highly depending of the monoclonal antibodies used. The development of such therapies will require a close virological follow-up of patients' cohorts, especially in the light of the rapid variants replacement still ongoing today for SARS-CoV-2.