Benefit of monoclonal antibodies in early treatment of COVID-19 after lung transplantation: a retrospective analysis in two centres

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To the Editor:

Transplant recipients are at risk for poor outcomes from coronavirus disease 2019 (COVID-19) due to frequent medical comorbidities and presence of immunosuppression. Observational cohort studies suggest that patients after lung transplantation (LTx) with COVID-19 may have higher mortality in comparison to other solid organ transplant recipients. In a US retrospective analysis in the beginning of 2020, 78% of infected transplant patients were hospitalised and 19% died within 28 days [1]. Recently, both mortality and hospitalisation rate have declined in transplanted patients [2] and reduced mortality has been associated with vaccination [3].

A variety of prophylactic and therapeutic treatments are being developed or repurposed to combat COVID-19. Anti-spike monoclonal antibodies (mABs) bind and neutralise SARS-CoV-2 in infected patients and thereby are a novel class of antivirals shown to be effective in preventing hospitalisation and death [4]. Low hospitalisation rates and mortality after mAB treatment were reported in retrospective case series in transplant patients [5]. In 2021, the European Medical Agency granted use of two mABs as early treatment in COVID-19 high-risk patients [6], of which just casirivimab–imdevimab was available in Germany.

The aim of the present study was to describe the association of mAB treatment with disease outcome in LTx patients with COVID-19. A retrospective analysis in the two largest German lung transplant centres (Hannover and Munich) was performed of all patients with positive PCR of SARS-CoV-2 during follow-up care between 1 January 2020 and 31 December 2021. Follow up after COVID-19 was recorded for at least 14 days or until death, whichever occurred first. The use of mAB as early treatment of COVID-19 was recorded. Patients with pre- or post-exposure use of mAB were not included.

Patients signed informed consent (ICF) for anonymised data analysis in retrospective studies within the German Center for Lung Research (DZL). The use of the DZL-ICF to conduct retrospective analysis was covered by ethics committee's vote (number 2923-2015).

COVID-19 severity was scored according to the WHO scale [7] with recording of the highest stage during follow-up after infection. In brief, mild disease was defined as constitutional symptoms without signs of pneumonia or respiratory failure. Moderate disease had signs of pneumonia without respiratory failure (blood oxygen saturation (S_{pO_2}) ⩾94%, no use of oxygen). Severe disease was defined as respiratory rate ⩾30 breaths·min^{-1}, S_{pO_2} <94%, use of oxygen or opacities >50% on pulmonary imaging. Critical disease was defined as respiratory failure with need of mechanical respiratory support, presence of septic shock or multiple organ failure. COVID-19-related death was defined as death during hospitalisation for COVID-19 without discharge.

Chronic lung allograft dysfunction (CLAD) was defined according to recently established criteria [8].

Shareable abstract (@ERSpublications)
Treatment with monoclonal antibodies was associated with improved survival in COVID-19 after lung transplantation (LTx). Age was a negative independent predictor of survival in this cohort of 133 COVID-19 cases after LTx. https://bit.ly/3kx5CBw

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Casirivimab–imdevimab were used each as 600 mg single dose infusions (or 4000 mg each in hospitalised patients) according to national criteria [9]. In vaccinated individuals, testing for antibodies against spike protein was recommended but not mandatory before use.

Monoclonal Allocation Screening Score (MASS) was previously published to stratify patients based on emergency use authorisation (EUA) in the US [10]. This score was used to assign criteria to predict severe COVID-19 according to the EUA criteria: age ⩾65 years (2 points), body mass index ⩾35 kg m^{-2} (2), diabetes mellitus (2), chronic kidney disease (3), cardiovascular disease in a patient ⩾55 years (2), chronic respiratory disease in a patient ⩾55 years (3), hypertension in a patient ⩾55 years (1), and immunocompromised status (4). For this study, a glomerular filtration rate of 30 mL min^{-1} per 1.73 m^2 and presence of CLAD were used to define chronic kidney and respiratory disease, respectively. Presence of cardiovascular disease, hypertension and respiratory disease were scored irrespective of patient age. Diagnosis of hypertension was based on daily use of antihypertensive drugs, except monotherapy with diltiazem, β-blocker or diuretics.

Metric variables were expressed as medians and interquartile ranges. Univariate analyses were performed using the Mann–Whitney test for continuous variables and chi-square test for categorical variables. Binary logistic regression analyses were conducted with COVID-19-related death as the dependent variable. The level of significance was set at ⩽0.10 for including variables identified by univariate analysis between groups.

During the study period, 1631 LTx recipients were followed in both centres. Of these, 133 (8.2%) were infected by SARS-CoV-2 with a median follow-up of 71 days (37–345 days). Six patients (5%) remained asymptomatic, 45 developed mild (34%) and 26 (19%) moderate disease. 25 patients developed severe disease (19%) and 32 (24%) critical disease. 33 patients (25%) died median 27 days (15–51 days) after COVID-19. 30 deaths (22%) were judged to be COVID-19-related. Three patients died unrelated to COVID-19 after discharge 107, 123 and 227 days after COVID-19 from CLAD. Two of these cases had pre-existing CLAD and the third case developed CLAD *de novo* after COVID-19. In these three cases, triggering of CLAD onset or progression by the infection cannot not be excluded but clinical course and imaging findings were not compatible with a post-COVID-19 condition.

44 patients (33%) were treated with casirivimab–imdevimab with a median latency of 3 days (interquartile range 1–5, range 0–16 days) after symptom onset. 18 patients (41%) received mAB as outpatients; none of these developed severe or critical disease. Four patients were later hospitalised after mAB treatment because of non-pulmonary reasons (diarrhoea, deteriorating kidney function, arrhythmia, pseudothrombopenia). Of the 26 hospitalised patients with mAB treatment, 17 had mild to moderate and nine (35%) severe and critical disease. In 31 patients with mAB infusion within less than 5 days after symptom onset, just a single patient (3%) developed severe disease after mAB. In 89 patients without mAB, treatment maximum disease severity was severe or critical in 47 (53%). Of vaccinated patients with known serology before mAB infusion (n=30), 24 (80%) had very low levels of SARS-CoV-2 spike-IgG antibodies (<30 binding antibody IU·mL^{-1}).

Table 1 demonstrates patient characteristics and comparison of survivors and non-survivors. Use of mAB was independently associated with survival after COVID-19 while higher age was associated with COVID-19-related death.

Our results confirm reports and randomised controlled trials of benefits of mABs in high risk populations for severe COVID-19. Out of 5607 patients included in the assessment report of the European Medical Agency, just 0.7% were immunosuppressed and patients after organ transplantation were not reported [6]. To our knowledge, our series is the largest series involving LTx patients with COVID-19 treated with mABs.

Pre-emptive therapy is a main principle of management in transplant medicine and early treatment is well established in medicine [11]. In this retrospective series, early treatment with mABs was associated with improved outcome, similar to studies in other community acquired respiratory viruses after LTx [12].

In our series, age was the most important risk factor for severe/critical COVID-19 and death in the LTx population, while other EUA criteria and the MASS were not independently associated with negative outcome, in contrast to other studies.

Vaccination is still the best prevention against COVID-19 in LTx patients. In comparison to our unvaccinated LTx patients, COVID-related death was reduced from 29% in unvaccinated to 18 and 12% in fully vaccinated and boosted patients, respectively. This effect was confirmed by a British retrospective cohort analysis of 143 fully vaccinated transplant recipients [3].

TABLE 1 Patient characteristics of coronavirus disease 2019 (COVID-19) survivors and non-survivors after lung transplant (LTx)

Covariate	Group comparison		Univariate	Multivariate analysis	
	LTx recipients with COVID-19-related death (n=30)	LTx recipients surviving COVID-19 (n=103)	p-value	OR (95% CI)	p-value
Gender female	12 (40)	51 (49)	0.382		
Age at COVID-19, years	60 (53–66)	55 (43–63)	**0.012**	**1.054 (1.009–1.101)**	**0.018**
Age at COVID-19 ⩾65 years	11 (37)	18 (17)	**0.023**		
Time after transplant, years	6.9 (3.3–11.4)	5.5 (2.1–9.4)	0.183		
Transplant procedure			0.714		
Bilateral	24 (87)	94 (90)			
Unilateral	3 (10)	6 (6)			
Combined	1 (3)	4 (4)			
Underlying disease			0.189		
Emphysema	4 (13)	24 (23)			
Pulmonary vascular disease	2 (7)	12 (12)			
Cystic fibrosis/bronchiectasis	3 (10)	17 (17)			
Pulmonary fibrosis/interstitial lung disease	19 (63)	39 (38)			
Other	2 (7)	11 (11)			
Comorbidities					
Body mass index ⩾35 kg m^{-2}	0 (0)	0 (0)			
Glomerular filtration rate ⩽30 mL min^{-1} per 1.73 m^2	8 (27)	15 (15)	0.123		
Diabetes	11 (37)	35 (34)	0.785		
Pre-existing chronic lung allograft dysfunction	12 (40)	26 (25)	0.115		
Hypertension	11 (37)	49 (48)	0.291		
Cardiovascular disease	8 (27)	21 (20)	0.464		
Monoclonal allocation screening score	9 (6–10)	7 (5–9)	**0.044**	1.083 (0.912–1.287)	0.364
Immunosuppression					
Tacrolimus	24 (80)	91 (88)	0.239[#]		
Ciclosporine	6 (20)	12 (12)			
Purine antagonist	28 (93)	100 (97)	0.403		
Proliferation signal inhibitor	2 (7)	10 (10)	1.000		
Prednisolone	30 (100)	103 (100)	1.000		
Variant era			0.232		
Wildtype (until 22 Feb 2021)	14 (47)	40 (39)			
Alpha variant (23 Feb 2021 to 28 June 2021)	5 (17)	9 (9)			
Delta variant (29June 2021to 31 Dec 2021)	11 (37)	54 (52)			
Vaccination status			0.128		
None	20 (67)	48 (46)			
Full immunisation	7 (23)	32 (31)			
Booster immunisation	3 (10)	23 (22)			
Treatment with casirivimab–imdevimab			**0.002**		
None	27 (90)	62 (60)		Reference	
Late (⩾5 days after symptoms)	3 (10)	10 (10)		**0.131 (0.035–0.484)**[¶]	**0.002**
Early (<5 days after symptoms)	0 (0)	31 (30)			

Data are presented as n (%) or median (interquartile range), unless otherwise indicated. [#]: use of tacrolimus or ciclosporine is exclusive and no patient used neither; p-value refers to both. [¶]: odds ratio refers to the comparison of any monoclonal antibody treatment versus none.

Limitations of our study are still a low number of patients and its retrospective design. Most patients were treated during the era of predominance of the delta variant of SARS-CoV-2 and efficacy of mABs cannot be transferred other variants. In addition, the majority of patients receiving mABs were vaccinated and the effect of mAB in this population is less well documented. Also, the role of improved management of severe/critical COVID-19 after mAB treatment in our cohort is difficult to assess given the low numbers.

Early antiviral treatment will change with the development of new variants of SARS-CoV-2, because some mABs are unable to neutralise virus variants such as omicron, and drug resistance may occur. New generations of mAB [13], novel compounds [14] and repurposed drugs [15] are necessary to prevent death and hospitalisation in populations at very high risk.

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