Extracorporeal life support allows lung transplant in anti-MDA5+ rapidly progressive interstitial lung disease

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To the Editor:

Anti-melanoma differentiation-associated gene 5 antibody (anti-MDA5) dermatomyositis (DM) is a rare subtype of idiopathic inflammatory myopathy, associated with severe interstitial lung disease (ILD) [1]. A subset of anti-MDA5 DM patients with rapidly progressive ILD (RP-ILD) have a very poor prognosis, with reported mortality rates reaching 80–84% [1, 2]. In this clinical setting, the use of extracorporeal life support (ECLS) is questionable, as reported in several studies that emphasise the futility of a bridge-to-recovery strategy [2, 3]. In this respect, emergency lung transplantation of previously unlisted patients on ECLS is under debate [4–6]. Yet, new therapeutic regimens, especially the early association of calcineurin inhibitors and cyclophosphamide [7], Janus-kinase inhibitors (JAKi) [8] or plasma exchange [9], have been recently associated with better outcomes of anti-MDA5 DM, fuelling hopes for a successful treatment of RP-ILD patients. Data on the outcome of anti-MDA5 RP-ILD requiring ECLS in the modern era are therefore urgently awaited.

This French, multicentre, retrospective study, conducted from 2013 to 2021 included all patients with anti-MDA5 DM RP-ILD requiring ECLS (ECMO: extracorporeal membrane oxygenation; or $ECCO_2R$: extracorporeal carbon dioxide removal). The diagnosis of anti-MDA5 DM relied on clinical and radiological signs evocative of DM and ILD and the presence of anti-MDA5 antibodies, as previously reported [1]. Anti-MDA5 antibody detection was performed using line-immunoassays (Euroimmun, Germany; or D-Tek, Belgium). RP-ILD was defined as a rapid worsening of respiratory symptoms over the preceding 3 months [1]. Continuous variables are expressed as mean or median (range) and compared using t-test or Wilcoxon's rank test; categorical variables are expressed as n (%) and compared using Chi-squared tests.

The database is registered with the "*Commission Nationale de l'Informatique et des Libertés*" (number 2223905) and was approved by the institutional review board of the French Society for Respiratory Medicine (reference: CEPRO 2020–067). In accordance with the ethical standards of our hospital's institutional review board, the Committee for the Protection of Human Subjects, and French law, written informed consent was not needed because this observational study did not modify existing diagnostic or therapeutic strategies; however, patients were informed of their inclusion in the study.

15 patients requiring ECLS were included in the study: venovenous (VV)-ECMO n=13, $ECCO_2R$ n=1 and venoarterial (VA)-ECMO n=1 (refractory right ventricle cardiogenic shock secondary to ILD). Table 1 reports the characteristics of patients at intensive care unit (ICU) admission and their evolution under ECLS. The female-to-male ratio was 4 and the age at ICU admission was a mean of 50 (32–67) years. All but three patients had primary RP-ILD (secondary RP-ILD respectively 9, 24 and 134 months after the diagnosis of ILD). The diagnosis of anti-MDA5 DM was known at ECLS initiation for eight patients. Two patients received ECLS support (1 ECMO VA, 1 ECMO VV) as a bridge-to-transplantation strategy and both underwent ECLS before mechanical ventilation. 12 patients received corticosteroids and six immunosuppressants before ICU admission, while these drugs were administered to 13 and 11 ICU patients, respectively. Five patients underwent lung transplantation after a median of 8 (4–20) days on ECMO, none were previously listed for a lung transplantation. After a median follow-up of 25 (3–93) months, all transplanted patients were alive at the conclusion of the study (four discharged home, one still hospitalised) and no relapse of DM or ILD was noted. All other patients, not listed for lung transplantation, died after a median of 30 (4–52) days on ECMO. Two patients were disqualified for lung

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Anti-MDA5 RP-ILD has a poor prognosis and a high mortality rate. This study found that emergency lung transplantation in anti-MDA5 RP-ILD patients requiring ECLS has a favourable disease outcome, irrespective of prior treatment regimen. https://bit.ly/3gHKPt6

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TABLE 1 Characteristics of 15 patients with anti-melanoma differentiation-associated gene 5 antibody (MDA5)-associated rapidly progressive interstitial lung disease (RP-ILD) requiring extracorporeal life support (ECLS)

Variables	Subjects n[#]	Survivors (n=5)	Non-survivors (n=10)	p-value
Female		4 (80)	8 (80)	1
Body mass index, kg·m^{-2}	4/9	25.0 (20.3–31.2)	29.4 (18.8–38.5)	0.2
Age at ICU admission, years		50.4 (46–53)	50.0 (32–67)	0.9
Smoking		0 (0)	1 (10)	0.1
Myositis/ILD characteristics				
Fever		9 (75)	3 (60)	0.2
Skin lesions		6 (60)	3 (60)	1
Articular involvement		3 (30)	1 (20)	0.7
Muscular involvement		2 (20)	1 (20)	1
Radiological diagnosis	3/8			
NSIP		1/3 (33)	1/8 (12)	
OP		0/3 (0)	2/8 (25)	
NSIP/OP overlap		1/3 (33)	5/8 (62)	
Indeterminate		1/3 (33)	0/8 (0)	
Pneumomediastinum		0 (0)	3 (30)	0.2
Laboratory parameters				
Ferritin, µg·L^{-1}	2/6	1004 (460–1004)	1555 (681–2282)	0.3
C-reactive protein, mg·L^{-1}	3/8	55 (20–73)	56 (14–94)	1
Creatine kinase, IU·L^{-1}	4/10	106 (11–263)	121 (52–381)	0.4
Lactate dehydrogenase, IU·L^{-1}	5/8	417 (360–663)	689 (379–1338)	0.06
Clinical course before ICU admission				
No treatment		0 (0)	3 (30)	0.2
Corticosteroids		5 (100)	7 (70)	1
Immunosuppressants[¶]		2 (40)	4 (40)	0.3
Plasma exchange		2 (40)	1 (10)	0.3
Secondary RP-ILD		0 (0)	2 (20)	0.3
Time from MDA5 diagnosis to ICU admission, days		−2 (−14–633)	3 (−35–270)	0.3
Time from hospital admission to ICU, days		4 (2–77)	9 (1–61)	0.6
MDA5 DM diagnosis at ECLS initiation		4 (80)	4 (40)	0.4
In-ICU characteristics				
Years at ECLS initiation		2019 (2015–2021)	2016 (2013–2021)	0.2
Day-0 SAPS II	4/10	33 (16–52)	50 (17–78)	0.2
Day-0 SOFA score	4/10	7 (2–10)	8 (2–15)	0.4
Vasopressors		5 (100)	9 (90)	0.5
Mechanical ventilation		5 (100)	9 (90)	0.5
Time from mechanical ventilation to ECMO, days		0 (−7–33)	4 (0–13)	0.5
Renal replacement therapy		1 (20)	5 (50)	0.3
ECLS characteristics				
VV-ECMO		4 (80)	9 (90)	0.6
VA-ECMO		1 (20)	0 (0)	0.5
$ECCO_2R$		0 (0)	1 (10)	0.1
Time on ECLS, days		10 (4–29)	30 (8–52)	0.06
RESP score[+]	3/9	0 (−3–1)	1 (−2–1)	0.4
ECLS specific complications		1 (20)	6 (60)	0.1
Limb ischaemia		0 (0)	1 (10)	0.5
Insertion-site haemorrhage		0 (0)	3 (30)	0.2
Cannula-related infection		1 (20)	4 (40)	0.4
Specific treatments in ICU		3 (60)	10 (100)	0.03
Corticosteroids		3 (60)	10 (100)	1
Immunosuppressants		3 (60)	8 (80)	0.4
Cyclophosphamide		3 (60)	4 (40)	0.1
Calcineurin inhibitors		1 (20)	4 (40)	0.6
Tofacitinib		1 (20)	1 (10)	0.4
Plasma exchange		3 (60)	7 (70)	0.3

Continued

TABLE 1 Continued

Variables	Subjects n[#]	Survivors (n=5)	Non-survivors (n=10)	p-value
Outcome				
Time in ICU, days		61 (47–163)	31 (13–59)	0.02
Time in hospital, days	4/10	148 (79–218)	46 (29–77)	0.007
ECLS weaning		5 (100)	0 (0)	0.001
In-hospital mortality		0 (0)	10 (100)	0.001
Lung transplant		5 (100)	0 (0)	0.001
Time from MV to transplant, days		20 (0–41)	NA	NA
Time from ECLS to transplant, days		8 (4–20)	NA	NA
Time from transplant to extubation, days		22 (11–117)	NA	NA
In-ICU-acquired infection		4 (80)	9 (90)	0.6
Pneumonia		3/4 (75)	9/9 (100)	0.1
Viral infection[§]		0/4 (0)	5/9 (56)	0.06
Fungal infection[f]		2/4 (50)	4/9 (44)	0.8
Bloodstream infection		2/4 (50)	6/9 (67)	0.6

Continuous variables are expressed as mean or median (range) and compared with t-test or Wilcoxon's rank test; categorical variables are expressed as n (%) and compared with Chi-squared tests. [#]: numbers of survivor/non-survivor data available. [¶]: cyclophosphamide, n=4 (2 survivors, 2 non-survivors); methotrexate, n=1 (non-survivor); mycophenolate mofetil, n=2 (1 survivor, 1 non-survivor); rituximab, n=2 (non-survivors); calcineurin inhibitors, n=3 (2 survivors, 1 non-survivor). [+]: the Respiratory ECMO survival prediction (RESP) score is designed to assist prediction of survival for adult patients undergoing extracorporeal membrane oxygenation (ECMO) for respiratory failure. [§]: cytomegalovirus, n=3; respiratory syncytial virus, n=1; herpes simplex virus, n=1. [f]: *Candida* mediastinitis, n=1 (survivor); bloodstream *Candida*, n=3 (non-survivors); *Aspergillus fumigatus*, n=1 (survivor). ICU: intensive care unit; NSIP: non-specific interstitial pneumonia; OP: organising pneumonia; DM: dermatomyositis; SAPS-II: Simplified Acute Physiology Score II; SOFA: Sequential Organ Failure Assessment; VV: venovenous; VA: venoarterial; $ECCO_2R$: extracorporeal carbon dioxide removal; MV: mechanical ventilation; NA: not available.

transplantation, one because of grade I obesity and acute kidney injury, requiring renal replacement therapy, and one due to the occurrence of coronary heart disease at the pre-transplantation assessment, respectively. For the remaining patients, emergency lung transplantation in the context of active inaugural disease was not consensual and lung recovery was the expected outcome. Once the absence of lung recovery was confirmed, emergency transplantation was no longer an option because of the duration of intensive care hospitalisation and the resulting complications. The latter patients all died of refractory acute respiratory distress syndrome secondary to not recovering RP-ILD, despite aggressive treatment. Notably, eight patients died following a decision of care withdrawal.

The prognosis of anti-MDA5 RP-ILD seems inevitably poor, despite aggressive immunosuppression and the use of ECLS. Recent reports on the efficacy of JAKi in anti-MDA5 DM are encouraging, however only one successful treatment of patients requiring ECLS has been reported to date [3]. The use of ECLS as a bridge-to-emergency lung transplantation has been advocated for patients with ILD, even those not listed prior to ECMO implantation [6]. However, this strategy is highly debated, especially in anti-MDA5 RP-ILD where data on short and long-term outcomes are scarce.

The results presented here provide crucial information for the management of anti-MDA5 RP-ILD. First, we highlight the refractory nature of the anti-MDA5 RP-ILD disorder requiring ECLS. No anti-MDA5 RP-ILD patient, irrespective of the treatment regimen they receive, including the few patients receiving the most recent biologics such as JAKi, should be weaned from the ECLS. This finding strongly argues against a bridge-to-recovery strategy in this patient population. Second, every patient that could undergo bridge-to-transplantation was discharged alive from ICU and solely transplanted patients eventually survived. None was previously listed for lung transplantation. The intention to proceed to transplantation had been envisaged for two patients before hospital admission and ICU admission, respectively, and for the remainder of the patients while they were in the ICU. Two patients undergoing ECMO were awake and able to provide consent for transplant. The remaining patients were sedated and consent was obtained from relatives. It is of note that none were extubated while awaiting lung transplantation. The lack of discussion with the patients prior to transplantation raises an important ethical issue. However, taking into account the unfavourable prognosis of these patients, emergency transplantation without optimal reflection delay was considered acceptable. It is therefore crucial to evaluate the feasibility of lung transplantation in patients

with MDA5 RP-ILD as early as possible. Third, emergency lung transplantation was possible in patients treated with vasopressors, mechanical ventilation and ECLS. Moreover, the early outcome was favourable in all of them. Notably, the median time from ECLS to transplantation was short (8 days), suggesting that a favourable outcome may rely on the prompt implementation of a bridge-to-transplantation strategy. It is worth noting that two patients were awake while on ECMO and able to perform physiotherapy, which may be associated with favourable outcomes [10]. Lastly, the frequency and severity of in-ICU acquired infection together with the futility of a bridge-to-recovery strategy seriously questions the usefulness of immunosuppressive treatment in ICU patients. Moreover, in these critically ill patients, the occurrence of severe infections compromises even more the perspective of a lung transplantation.

The present study has several strengths and limitations. First, it is a small series with retrospective design, but it is the largest cohort reported to date. Second, despite a favourable, early evolution of lung transplantation, the long-term outcome, in particular the risk of relapse, needs to be investigated further. Third, the success of transplantation in the cohort included in this study probably benefited from a selection bias as the criteria for lung transplant listing was not protocolised and the results described here might therefore not be relevant for the treatment protocol of every anti-MDA5 RP-ILD patient. Finally, apart from the administration of the JAKi tofacitinib in two patients, all others received a conventional treatment regimen. A bridge-to-recovery strategy is therefore likely to benefit from a more generalised use of JAKi and calcineurin inhibitors [7, 8].

The bridge-to-recovery strategy in anti-MDA5 RP-ILD patients requiring ECLS despite specific prior treatment leads to undesirable results, pointing to the drawbacks of this approach. In contrast, a bridge-to-emergency lung transplantation is not only feasible, but also associated with a favourable outcome and appears therefore as the sole hope of survival for patients requiring ECLS. Further studies are needed to evaluate the efficacy of a bridge-to-recovery strategy considering new therapeutical biologics, in particular the use of JAKi.

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