C1-esterase inhibitor treatment for antibody-mediated rejection after lung transplantation: two case reports

To the Editor:

Antibody-mediated rejection (AMR) after lung transplantation (LTx) is associated with poor prognosis [1]. Recent International Society for Heart and Lung Transplantation recommendations propose a standardised classification of lung AMR [2]. Based on the number of features present, this classification describes three different degree of certainty for AMR diagnosis. However, in the absence of a true gold standard, the management of potential AMR are subject to quite a high degree of uncertainty.

The currently used therapeutic regimen includes various combinations of intravenous immunoglobulin (*i.v.* Ig), plasmapheresis, rituximab and proteasome inhibitors, with unpredictable efficacy [3]. Recent studies of kidney transplantation suggest that anti-complement therapy may prevent or reverse AMR [4–11].

Here, we describe two cases of pulmonary AMR refractory to standard of care treatment with highly suspected complement activation. Diagnosis of AMR was based on International Society for Heart and Lung Transplantation recommendations and classified as probable and possible AMR in the two cases respectively [2].

The treatment for both patients was C1 esterase inhibitor (CI-INH, Berinert; one dose of 20 UI·kg^{-1} on days 1, 2 and 3, then twice a week for 6 months) because of the severity of AMR in both, the suspected complement-mediated process, and the failure of the current standard of care treatment for AMR (associating plasma exchange (PLEX), *i.v.* Ig (2 g·kg^{-1} for 2 days), rituximab (375 mg·m^{-2}), and pulsed steroids).

The first case we describe was a 22-year-old woman who underwent bilateral LTx under veno-venous extracorporeal membrane oxygenation for end-stage cystic fibrosis (figure 1a). After initial extubation on day 2, sudden-onset acute respiratory distress syndrome developed on day 10 (figure 1b, upper panel) requiring re-intubation with protective ventilation and prone positioning. Broad-spectrum antibiotic therapy was started, but results remained negative for bacterial, mycological and parasitic cultures, galactoman antigen, and viral multiplex-PCR. Bronchoalveolar lavage cytology revealed 1 200 000 cells·mL^{-1} including 95% unaltered neutrophil. The patient received a pulsed-steroids course on day 11 Protocol transbronchial biopsy (TBBx) on day 8 did not show A or B acute rejection but showed acute lung injury with negative C4d staining. Donor-specific antibody (DSA; single antigen bead assay, One Lambda) was detected (anti-human leukocyte antigen (HLA) DR17 with mean fluorescence intensity 887) and IgG lymphocytoxicity cross-match performed with day-1 serum was positive for B cells (cell death >20% above background) and negative for T cells. Probable acute AMR was ultimately diagnosed by the association of graft failure, DSA positivity, consistent histology, and exclusion of a concurrent diagnosis. The patient received intravenous pulsed steroids (days 12–14) and PLEX (days 13–18), associated with rituximab (day 19) and *i.v.* Ig (days 20 and 21).

On day 23, mechanical ventilation was still required because of unchanged ratio of arterial oxygen partial pressure to fractional inspired oxygen <100, and the AMR episode was considered refractory to standard of care treatment. Because an initial IgG cross-match was positive, suggesting complement activation, C1-INH treatment was initiated (days 23, 24 and 25, then twice a week) [9]. On day 36, after seven doses of C1-INH, the patient's respiratory status had significantly improved, with resolution of computed tomography (CT) scan opacities, which allowed for weaning from ventilation on day 46 and patient discharge on day 83.

C1-INH infusion was continued twice a week for 3 months, then once a week. On day 120, forced expiratory volume in 1 s (FEV_1) was 1750 mL (56% predicted); CT scan showed resolution of

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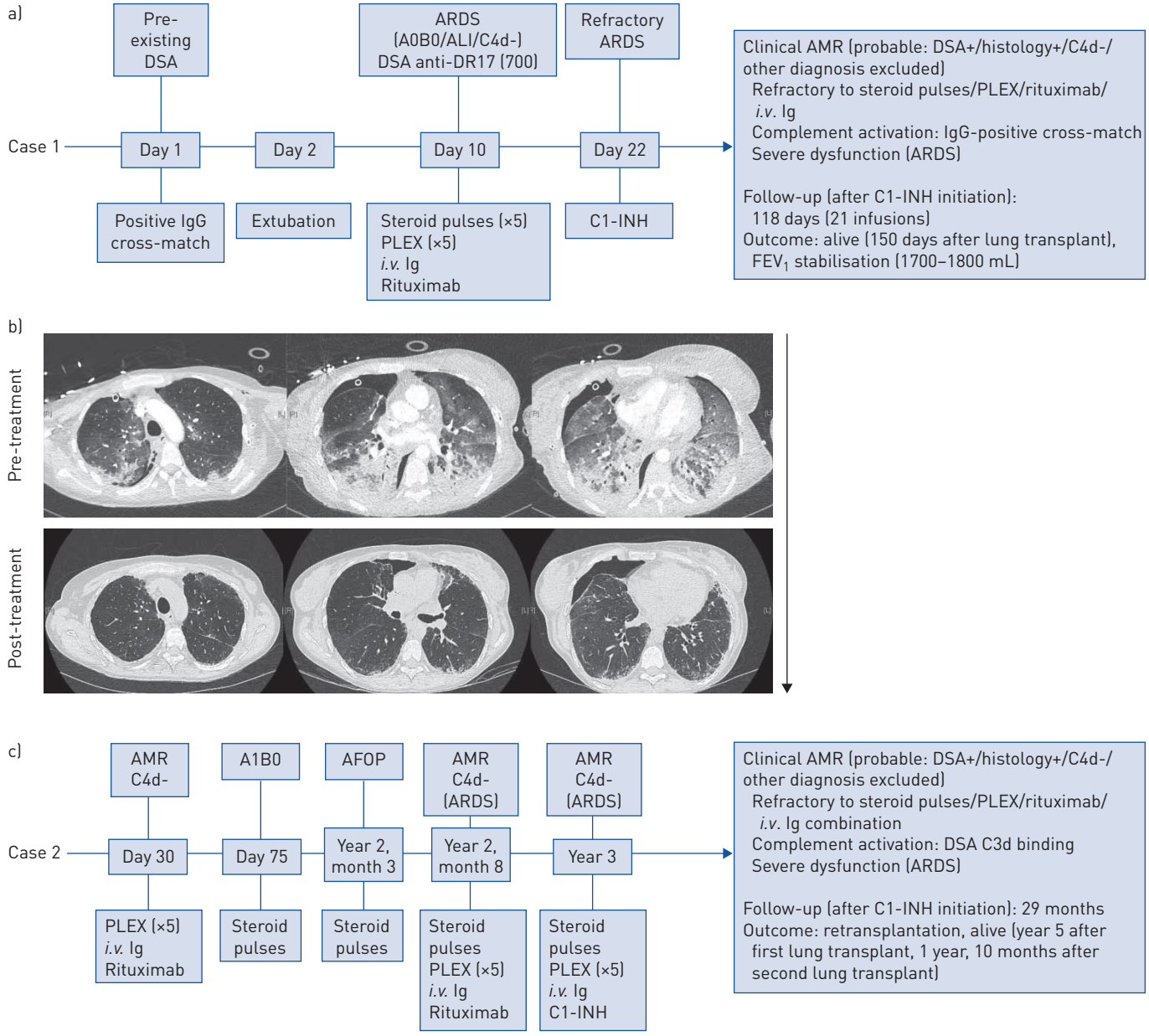

FIGURE 1 a) Timeline for case 1, 22-year-old woman who underwent bilateral lung transplantation for end-stage cystic fibrosis. b) Case 1: lung computed tomography (CT) scan before C1 esterase inhibitor (C1-INH) initiation on day 10 and CT scan at month 4 after first lung transplantation. c) Timeline for case 2, 38-year-old woman who underwent bilateral lung transplantation for cystic fibrosis. DSA: donor-specific antibody; ARDS: acute respiratory distress syndrome; ALI: acute lung injury; PLEX: plasma exchange; AMR: antibody-mediated rejection; FEV_1: forced expiratory volume in 1 s; AFOP: acute fibrinous and organising pneumonia.

consolidation opacities (figure 1b, lower panel). C1-INH and *i.v.* Ig were stopped on day 180 post-transplantation and the day-270 FEV_1 was 2.170 L (66% predicted).

The second case we report is that of a 38-year-old woman who underwent bilateral LTx for cystic fibrosis (figure 1c). The post-transplantation course was complicated by several episodes of lung function deterioration. On day 30 post-transplantation, probable clinical AMR was diagnosed, as characterised by graft failure, several circulating HLA DSAs, neutrophilic capillaritis and alveolar damage seen on TBBx. PLEX, *i.v.* Ig and rituximab treatment was started. On day 75, acute cellular rejection (A1B0) occurred, which resolved with intravenous pulsed steroids.

On day 820, acute fibrinous and organising pneumonia developed and was successfully treated with pulsed steroids. On day 970, the patient showed probable AMR (presence of DSAs (anti-A26 (1129) and anti-DQ2 (3119) antibodies), TBBx showing diffuse alveolar damage and acute fibrinous and organising pneumonia but without C4d staining), which was inconsistently improved with pulsed steroids, PLEX,

rituximab and *i.v.* Ig. Subsequent restrictive allograft syndrome led to enrolment in a pulmonary rehabilitation programme to prepare for possible re-transplantation.

On day 1095, the patient was admitted for probable pneumonia associated with septic shock, requiring 4 days of invasive ventilation. Chest radiography showed significant improvement on the day of ventilator weaning; however, she was reintubated 2 days later because of new-onset radiographic opacities. Bronchoalveolar lavage fluid analysis did not show bacterial, mycologic, viral or pneumocystis pneumonia infection. Pulsed steroids were administered (days 2003–2007) for a suspected acute cellular rejection episode, without TBBx because of the patient's clinical condition. With lack of improvement, possible clinical AMR was ultimately diagnosed (persistent DSA positivity (anti-A26 (1570), anti-DR7 (510), and anti-DQ2 (1024) antibodies), graft dysfunction, and exclusion of concurrent diagnosis), although in the absence of TBBx and PLEX started on day 2007. Nevertheless, the respiratory status progressively worsened, and refractory AMR was then considered. Because the initial anti-DQ2 DSA strongly activated complement (positivity on C3d binding test) [12], complement-mediated AMR was considered, and C1-INH was initiated on day 2015 (days 1, 2 and 3), then twice a week [9].

On the day of C1-INH initiation, the patient required maximum ventilator support, including paralytics and deep sedation. However, 8 days after starting the therapy (four doses), the respiratory status had rapidly improved, in parallel with a marked decrease in superimposed ground-glass opacities, which allowed for weaning from ventilation. The patient returned to rehabilitation 1 month later. C1-INH was continued (twice a week for 7 months), associated with monthly *i.v.* Ig, which allowed for a stable clinical state, although severely altered, and re-transplantation 7 months later was successful. Histology of the explanted lung showed lesions of bronchiolitis obliterans and fibrous endarteritis of the pulmonary artery wall without neutrophil infiltrates and no diffuse alveolar damage.

We describe the first two cases of the use of C1-INH for acute pulmonary AMR. The initiation of C1-INH was decided by a multidisciplinary team, with severe graft dysfunction classified as probable and possible AMR in case 1 and 2, respectively, according to the current definition [2]. The cases were considered refractory to standard of care treatment and complement activation was considered. The condition of both patients had worsened to the point of discussing palliative care, and C1-INH was initiated only as a last resort. The complement involvement was suggested by C3d binding ability or positive IgG cross-match. C4d staining was negative in both cases, which does not preclude an AMR diagnosis [13]. CI-INH therapy has previously been evaluated for ischaemia reperfusion prevention [14], but given the absence of prior experience in LTx for acute AMR treatment, the decision relied on a *post hoc* analysis of several studies using a complement inhibitor for kidney transplantation, showing high response rate in patients with complement activating DSAs [15].

The evaluation of the efficacy of CI-INH in this preliminary report is clearly limited by 1) the type of AMR, classified as probable or possible, 2) the complicated history of the patients, especially patient 2 (with repeated events of deteriorating function, chronic dysfunction and enhanced immunosuppression before the use of C1-INH), and 3) the possible delayed response to previous AMR therapies before CI-INH initiation. Nevertheless, the extent and rapidity of clinical and radiological improvement was unexpected as compared with previous similar cases [16].

A potential concern with use of these agents is the risk of infection in these patients. Despite this limitation, these preliminary clinical experiences may suggest further appropriate evaluation of complement inhibition as part of a multi-faceted approach to pulmonary AMR after LTx.

François Parquin[1], Elise Cuquemelle[1], Eve Camps[2], Jérôme Devaquet[3], Mathilde Phillips Houllbracq[3], Edouard Sage[4,5], Olivier Brugière[6], Morgan Le Guen[5,7], Elisabeth Longchampt[8], Stéphanie Malard[9], Clément Picard[7], Jean Luc Taupin[9] and Antoine Roux[5,6], the FOCH Lung Transplant group
[1]Thoracic Intensive Care Unit, Foch Hospital, Suresnes, France. [2]Pharmacy Dept, Foch Hospital, Suresnes, France. [3]Intensive Care Unit, Foch Hospital, Suresnes, France. [4]Thoracic Surgery Dept, Foch Hospital, Suresnes, France. [5]Université Versailles-Saint-Quentin-en-Yvelines, Versailles, France. [6]Pneumology, Adult Cystic Fibrosis Center and Lung Transplantation Dept, Foch Hospital, Suresnes, France. [7]Anesthesiology Dept, Foch Hospital, Suresnes, France. [8]Pathology Dept, Foch Hospital, Suresnes, France. [9]Laboratoire Régional d'Histocompatibilité, Saint-Louis Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France.

Correspondence: Antoine Roux, Hopital Foch, Pneumologie, 40 rue Worth, Suresnes, France. E-mail: a.roux@hopital-foch.org

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