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Brief communication

Challenging immunosuppression treatment in lung transplant recipients with kidney failure

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ABSTRACT

Kidney failure after lung transplantation is a risk factor for chronic kidney disease. Calcineurin inhibitors are immunosuppressants which play a major role in terms of postoperative kidney failure after lung transplantation. We report our preliminary experience with the anti-interleukin-2 monoclonal antibody Basiliximab utilized as a "calcineurin inhibitor-free window" in the setting of early postoperative kidney failure after lung transplantation. Between 2012 and 2015 nine lung transplant patients who developed kidney failure for more than 14 days were included. Basiliximab was administrated in three doses (Day 0, 4, and 20) whilst Tacrolimus was discontinued or reduced to maintain a serum level between 2 and 4 ng/mL. Baseline glomerular filtration rate pre transplant was normal for all patients. Seven patients completely recovered from kidney failure (67%, mean eGFR pre and post Basiliximab: 42.3 mL/min/1.73 m^2 and 69 mL/min/1.73 m^2) and were switched back on Tacrolimus. Only one of these patients still needs ongoing renal replacement therapy. Two patients showed no recovery from kidney failure and did not survive. Basiliximab might be a safe and feasible therapeutical option in patients which are affected by calcineurin inhibitor-related kidney failure in the early post lung transplant period. Further studies are necessary to confirm our preliminary results.

1. Introduction

Lung transplantation (LTX) is the treatment of choice of end stage lung diseases such as chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), interstitial lung disease (ILD), or idiopathic pulmonary arterial hypertension (IPAH) [1–3]. However, the outcome is limited by the recipients' rejection of the donor organ (50% of the patients at 5-year postprocedure) defined as pathological obliterative bronchiolitis (OB) [4]. The rejection rate has been significantly decreased by the introduction of the first calcineurin inhibitor (CNI) Cyclosporin in 1983. A further rejection reduction was made by the CNI Tacrolimus in 1994. Today CNIs are widely used as induction and maintenance immunosuppressant drugs [5,6]. Nevertheless, CNIs promote, for example, the genesis of inflammation and tumors as well as kidney failure (up to 83%) [7,8]. Due to their narrow therapeutic range and their administration mostly in combination with prophylactic antimicrobial drugs CNIs play a major role in terms of possible kidney failure after LTX especially in the early postoperative course [9]. However, CNIs remain the best treatment option for immunosuppression after LTX as Sirolimus is well known to affect the on-going surgical healing process. Additionally, it has impact on polyclonal anti-lymphocyte globulins (ALGs) or anti-thymocyte globulins (ATGs) which may lead to an increased risk for infection and sepsis [10–12].

Since 1998 the antibody-based drug Basiliximab is increasingly used for induction therapy in LTX patients with good overall survival and rejection outcomes in comparison to non antibody-based drugs like CNIs. Basiliximab is an interleukin 2 (IL2) receptor antagonist which inhibits T lymphocyte proliferation and differentiation and only minimal side effects were observed [11,13–15].

In the setting of applying CNIs as induction therapy after LTX and successive early postoperative kidney failure with the need of renal

Abbreviations: AF, Arterial fibrillation; ALG, Anti-lymphocyte globulin; ATG, Anti-thymocyte globulin; BAX, Basiliximab; BSSLTX, Bilateral sequential single lung transplantation; CMV, Cytomegalovirus; CVVH, Continuous veno-venous hemofiltration; DBD, Donation after brain death; DCD, Donation after circulatory death; OB, Obliterative bronchiolitis; CF, Cystic fibrosis; CNI, Calcineurin inhibitor; COPD, Chronic obstructive pulmonary disease; ECMO, Extracorporeal membrane oxygenation; eGFR, estimated Glomerular filtration rate; GI, Gastrointestinal; IL2, Interleukin 2; ILD, Interstitial lung disease; IPAH, Idiopathic pulmonary arterial hypertension; LTX, Lung transplantation; TLC, Total lung capacity.

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replacement therapy the treatment options are limited and only rare data is available in the literature. Due to the promising performance of Basiliximab we report our preliminary clinical experience with Basiliximab utilized in a "CNI-free window" to gain recovery from early postoperative kidney failure.

2. Materials and methods

We hereby present an observational single-center case series of nine patients. All patients were treated between August 2012 and January 2015 at Harefield Hospital, Royal Brompton & Harefield NHS Foundation Trust, UK. This study was approved by the Ethics Committee of the Royal Brompton & Harefield NHS Foundation Trust. A written informed consent is available for all patients. The group of patients included all recipients of bilateral sequential single lung transplantation (BSSLTX) presenting with acute peri-operative kidney failure. Kidney dysfunction was defined as the need for continuous veno-venous hemofiltration (CVVH). Usually, patients requiring CVVH had anuria and eGFR (estimated glomerular filtration rate) of 29 mL/min or less. As long as the kidney failure persisted a renal replacement therapy with continuous veno-venous hemofiltration (CVVH) was performed. The kidney failure had to last for more than 14 days post LTX and was defined as impossibility to wean the patients from CVVH because of anuria and/or metabolic acidosis with high urea/potassium levels. This decision was made considering that for the first 10 to 14 days after transplantation our recipients received antibiotics, antifungal and antiviral treatment as regular prophylactic regime. The combination of these drugs with CNI can cause acute kidney injury that is normally reversible once the regime is reduced to immunosuppression alone. Our protocol used 20 mg Basiliximab on day 1, 4, and 20. During this time Tacrolimus was discontinued or the dose was reduced to maintain at least a serum level between 2 and 4 ng/mL (Fig. 1). eGFRs were calculated at the time of LTX registration, on day before the Basiliximab treatment has begun, 30 days, and 60 days after the Basiliximab administration. Furthermore, Tacrolimus serum levels were recorded on the days 1, 4, and 20 of the Basiliximab treatment as well as 30 days and 60 days after the Basiliximab administration. Also nephrotoxic concomitant medications (e.g. antibiotics) were also recorded.

3. Results

The patient population of this study contains seven female and two male patients with end stage lung diseases (3× COPD, 2× bronchiectasis, 2× CF, 1× ILD, and 1× IPAH) between 20 and 67 years (mean: 44.4 years). The mean time on the waiting list was 531 days. One patient received an organ donated after circulatory death (DCD); eight patients received an organ donated after brain death (DBD). The lungs were matched to the recipients according to blood group, height, total lung capacity (TLC), time on the waiting list, and clinical status of the recipient at the time of transplantation (Table 1). The overall one-, three-, and six-year survival rates after LTX in our center are 90.5, 79.0, and 57.4%, respectively. All survivors were converted back to tacrolimus once they were weaned off CVVH and basiliximab (after day 20) whereas the therapeutic range was set between 5 and 10 ng/mL.

3.1. Case 1

A 55-year old female recipient underwent uneventful BSSLTX due to COPD. Postoperatively, she needed a cecostomy due to bowel obstruction. The recipient developed CVVH requiring kidney failure on day 1 after LTX. Basiliximab treatment was initiated on day 14 after LTX. CVVH has been no longer necessary since day 2 of the Basiliximab administration and the recipient was discharged in full renal recovery and is well after three years of follow-up.

3.2. Case 2

A 28-year old female recipient underwent uneventful BSSLTX due to CF. In the postoperative course the recipient needed antibiotic treatment because of aspiration pneumonia in consequence of gastroparesis and subsequent episodes of vomiting. The recipient developed kidney failure and required CVVH on day 11 after LTX. The Basiliximab treatment was started on day 60 after LTX. CVVH has been obsolete since day 9 of the Basiliximab administration and the recipient. However, the recipient died on day 124 after LTX due to sepsis.

3.3. Case 3

This 32-year old female recipient preoperatively needed extracorporeal membrane oxygenation (ECMO) and Novalung® implantation as bridge to transplantation due to IPAH. She underwent uneventful BSSLTX and developed an acute cellular rejection postoperatively which was treated with high-dose steroids. Pneumonia was treated with antibiotics. Additionally, the recipient developed CVVH requiring kidney failure on day 1 after LTX. Administration of Basiliximab was started on day 14 after LTX. CVVH has been no longer necessary since day 13 of the Basiliximab administration. The recipient could be discharged in full renal recovery and is well after three years of follow-up.

3.4. Case 4

This 30-year old female recipient underwent difficult lobular transplantation due to bronchiectasis. An episode of acute cellular rejection occurred within the first 20 days post LTX and was treated with high dose of steroids. She subsequently developed a bowel perforation which required surgery, followed by a peritonitis. The patient required prolonged treatment with systemic antibiotics (Meropenem,

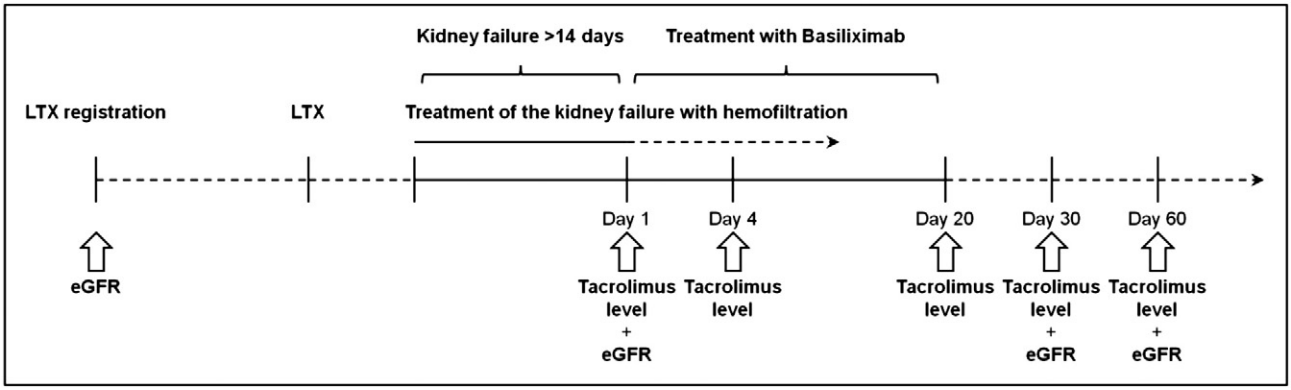

Fig. 1. Time line of the Basiliximab treatment.