

Immunosuppression after lung transplantation: the search for the holy grail continues

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Immunosuppressive (IS) therapy after lung transplantation (LTx) remains a matter of controversy. Treatment regimens and concepts vary significantly between centers worldwide. Although there is a broad consensus on a triple IS therapy, protocols differ by the preferred calcineurin inhibitor (CNI) [cyclosporine A (CsA) *vs.* tacrolimus], cell cycle inhibitor [mycophenolate mofetil (MMF) *vs.* azathioprine] and induction therapy (basiliximab, ATG, alemtuzumab, no induction).

In the November issue of the *American Journal of Transplantation*, Strueber *et al.* (1) presented a contribution to this ongoing discussion in the form of a single-center, prospective, randomized open label trial. In their study, the authors aimed to test whether everolimus is superior to MMF during the early maintenance IS phase. A total of 190 patients were screened and enrolled within the first two weeks after LTx. Until day 28 all patients received standard triple IS therapy with CsA, prednisolone and MMF without induction therapy. Randomization was performed on postoperative day 28. In the control arm, MMF treatment was continued, while patients in the intervention arm were switched to everolimus with a target blood level of 6–8 ng/mL. In addition, CsA dosage was reduced stepwise in the intervention arm. The trial was conducted over a total period of 6.5 years, with an individual follow-up of 24 months. Incidence of bronchiolitis obliterans syndrome (BOS) was defined as the primary endpoint, reviewed by two independent experts in a blinded manner.

Secondary endpoints included kidney function, incidence of acute rejection, infection, treatment failure and death. Treatment failure was defined by two or more episodes of acute rejection within 3 months, and these patients were switched to a tacrolimus-based rescue protocol. Based on previous studies indicating an increased risk of acute kidney failure (2) in transplant patients treated with everolimus, the study protocol also focused on drug safety and toxicity.

Only ninety-seven (51%) patients stayed in the study protocol for the full two-year follow-up. Fifty-two patients (55%) dropped out of the intervention group compared to 41 (44%) of the control group. The most common reason for discontinuation of the protocol was recurrent episodes of acute rejection. Survival at 24-months was equal in both arms, with 89% in the everolimus and 87% in the MMF group. When analyzing the overall study population, there was no difference in the incidence of BOS between the two groups. However, in the subgroup of patients who completed the study protocol, patients receiving everolimus had a significantly lower incidence of BOS than those receiving MMF (2% *vs.* 15%, $P=0.041$). The number of episodes of acute rejection was higher in the MMF group, while the number of administered steroid pulses was similar. Renal function did not differ between the two study arms at 12 and 24 months of follow-up. Adverse events (AE) were frequent in both groups, with over 80% of patients experiencing at least one event. Fifty-five patients (57%) in the everolimus group experienced at least one serious

adverse event (SAE); 50 cases were considered drug-related. In comparison, only 40 patients (42%) in the MMF group reported SAE, 18 of which were drug-related.

Everolimus is an IS medication derived from sirolimus. It binds to FK506 binding protein 12 (FKBP12), and the resulting complex inhibits the mammalian target of rapamycin (mTOR). This in turn blocks several downstream processes; ultimately leading to inhibition of interleukin-2 induced cellular proliferation, and cell cycle arrest. Anti-fibrotic activity has been observed *in vitro* with significant suppression of fibroblast proliferation in cells from lung transplant patients (3). This observation raised interest whether an everolimus-based IS protocol can prevent the development of BOS after LTx.

First approved in 2003 by the European Medicines Agency (EMA) for prevention of organ rejection in kidney transplantation, its spectrum of indications now includes heart and LTx. Typically, everolimus is used in combination with a CNI to facilitate CNI dose reduction. Several studies have recently been published evaluating everolimus in the setting of LTx. Most of these studies, however, have been retrospective in nature and address a delayed switch to everolimus in contrast to the *de novo* introduction after LTx investigated by Strueber *et al.* (1).

Coming from the renowned LTx center in Hannover, this prospective study is an important work addressing the role of mTOR inhibitors in LTx. Despite being limited to one center, the authors were able to recruit 190 patients. This is a number comparable to recent multi-center studies of mTOR inhibitors in LTx (4). The single-center approach by Strueber *et al.* has the clear advantage of a well-established and uniform IS regimen in the control group, which is often a limitation of multi-center approaches.

In order to obtain a homogenous patient population the study authors applied strict inclusion and exclusion criteria, and only included patients with a favorable perioperative course. Although this strategy facilitates the comparison between groups, it has to be noted that the study population does not necessarily represent a standard lung transplant group.

The authors addressed the known problem of interobserver variability by defining BOS in a stringent manner, and by adding an international, independent expert review for diagnosis. While the reviewers did agree on BOS status (yes/no) in 92% of cases, the time of BOS onset was agreed upon in only 64%. This fact highlights the difficulty in recognizing BOS despite international guidelines and individual expertise (5).

A major limitation of this prospective work is the high rate of patients who did not finish the two-year study protocol; 43% of patients in the MMF group and 55% in the everolimus group. Due to the high dropout rate the study was underpowered to find a statistically significant reduction in the incidence of BOS and acute rejection. However, it provides a variety of other important findings relevant the use of everolimus in LTx.

Although the authors demonstrated general safety of everolimus as a first-line IS medication, several patients had to discontinue the protocol due to intolerance of the drug. The number of drug-related AE and especially SAE was significantly higher in the everolimus study arm.

One issue giving cause for particular concern was the development of thrombotic microangiopathy (TMA) in five patients in the everolimus group. This diagnosis resulted in a dismal outcome with one death and two patients remaining dialysis-dependent. Recognized as a rare complication after LTx, TMA has been mainly associated with the use of CNI in combination with sirolimus as well as ischemia reperfusion injury (6-8). The reported high rates of TMA in the everolimus group should be addressed critically in future studies. There were no cases of TMA in the control arm.

There are only few sizable trials studying the use of everolimus after LTx. In a multi-center study with 33 participating centers, Snell *et al.* (2) compared everolimus versus azathioprine in combination with CsA in a maintenance IS setting, starting the mTOR inhibitor anywhere between three and 36 months post-transplant. The most striking finding of this double-blind randomized controlled trial (RCT) was better preservation of lung function in the everolimus group, and the number of episodes of acute rejection was significantly lower. However, treatment discontinuation, acute renal injury, and SAE were more common in the everolimus group.

The other major multi-institutional trial comparing everolimus to a mycophenolic acid-based formulation was published in 2015 by Glanville *et al.* (4). This randomized open-label study included 165 patients and compared delayed-onset everolimus to mycophenolate sodium (MPS) as opposed to MMF. Similar to the study from Hannover, the trial by Glanville and colleagues reported high dropout rates of 42% in the MPS group and 55% in the everolimus group. Consequently, it was underpowered to find differences in freedom from BOS. Both studies came to similar results regarding general drug safety and found a lower incidence of acute rejection and CMV infections in

the everolimus groups. Glanville *et al.* additionally reported a higher risk of gastrointestinal AEs in patients receiving mycophenolic acid.

The present study by Streuber *et al.* adds important evidence on everolimus induced nephrotoxicity. Currently, there is conflicting data regarding this subject in the literature. An everolimus based IS protocol facilitates CNI dose reduction, which in theory should reduce the detrimental effects of CNI on kidney function. Some studies have found improved kidney function after changing from CNI monotherapy to CNI/everolimus in combination (9,10). Others have shown an increase in creatinine levels and a significantly higher risk of TMA in everolimus-based protocols (2,8).

Finally, many LTx centers follow other strategies in order to reduce CNI related side effects. Induction therapy with T-cell depleting agents or IL-2 receptor antagonists allow for lower dosages of CNI and cell cycle inhibitors in the early post-transplant course, potentially reducing nephrotoxicity. We, and others, have shown that induction therapy with ATG and alemtuzumab allows a significant reduction of maintenance IS with low rejection rates and excellent long-term results (11-13).

In conclusion, we believe that this work is an important contribution and helps to define the future role of everolimus in LTx. However, its superiority over existing IS protocols has yet to be demonstrated. The search for the holy grail continues.....

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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