Proliferation Signal Inhibitors
After Lung Transplantation

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The proliferation signal inhibitors (PSIs) or mammalian target of rapamycin (mTOR) inhibitors, sirolimus and everolimus, are two of the most recent immunosuppressants introduced for use in lung transplantation.¹

The mechanism of action of PSIs is distinct from calcineurin inhibitors (CNIs), and complementary when utilized together.²³ PSIs bind to the cytoplasmic protein FKBP-12², inhibiting a protein kinase, the mammalian target of rapamycin (mTOR). The mTOR is a key regulatory pathway for several biologic processes.⁴ Inhibition of mTOR results in blockade of T and B cell proliferation in response to cytokine signals.²

Sirolimus was the first PSI available for use, while everolimus was later introduced with improved bioavailability and a distinct pharmacokinetic profile. The half-life of everolimus is 28 hours, considerably shorter than sirolimus (62 hours), which allows for steady state to be achieved more rapidly (4 vs. 6 days).⁵ PSIs are oxidized by the hepatic CYP3A isoenzyme⁶,⁷ and are substrates of P-glycoprotein (p-gp), an intestinal efflux pump.⁸ Thus, significant drug interactions result with inhibitors or inducers of CYP3A and p-gp, such as azole antifungals.

Similar to CNIs, PSIs display a narrow therapeutic index.⁸,⁹ Target concentrations are dependent on many factors including time since transplant, number and severity of rejection and infection episodes, and concomitant immunosuppressants.⁷ When combined with CNIs, a trough should be targeted in the lower range of the therapeutic window.¹ In the absence of a CNI, trough levels up to 12 ng/mL have been evaluated; however, higher troughs are associated with increased adverse effects with little incremental gain in efficacy.¹⁰

Major adverse effects that have limited the use of PSIs after lung transplantation include impaired wound healing, particularly of the bronchial anastomosis, and pneumonitis. PSIs are known to cause delayed wound healing as a result of their antiproliferative effects, and sirolimus has been associated with cases of bronchial anastomotic dehiscence.¹¹,¹²,¹³ Historically, PSIs have not routinely been introduced before the third post-operative month unless the endobronchial anastomoses have healed. Sirolimus, and, less commonly, everolimus¹⁴, have been associated with a non-infective pneumonitis in lung transplant recipients. This is characterized by bilateral alveolo-interstitial lung infiltrates.¹⁵ Treatment consists of drug discontinuation, and symptom resolution typically occurs within three months.¹⁶

Although PSIs do not directly affect glomerular filtration, they may cause histologic changes consistent with tubular toxicity.¹⁷ In acute renal failure, PSIs can inhibit full recovery of renal function by slowing glomerular healing. PSIs can also cause or worsen proteinuria; this effect may be explained by loss of the antiproteinuric effect of CNIs, interference with albumin reabsorption, or inhibitory effects on vascular endothelial growth
Other commonly reported side effects include dose-dependent reversible dyslipidemia (38-57%) and myelosuppression.  

Increasing data have supported the use of PSIs in kidney and heart transplantation, but there remains a lack of strong clinical data in lung transplantation. Early reports suggested that the antiproliferative effects of PSIs might be protective against the development of BOS; however, this has not been borne out by definitive studies comparing rates of BOS in patients receiving everolimus compared to azathioprine (AZA) or mycophenolate mofetil (MMF). Today, PSIs are utilized in lung transplantation in patients with renal impairment attributed to CNIs or when other immunosuppressants are ineffective or contraindicated. 

PSI use in patients with renal impairment has evolved over time. Initially, PSIs were combined with CNIs to allow lower CNI exposure and to stabilize CNI-induced renal damage. Many trials, however, have shown no improvement in renal function after reduction of CNI exposure and have revealed additive nephrotoxicity with the combination. Today, many patients with CNI nephropathy are switched to a PSI alone or in combination with an antiproliferative agent.

Neurotoxicity attributed to CNIs is problematic, the manifestations of which range from simple tremors or headaches to encephalopathy and seizures. The PSIs are an alternative option when adverse effects persist despite CNI substitution or dose modification. Both PSIs cross the blood brain barrier; however, neurotoxicity has not yet been reported with their use.

The incidence of cytomegalovirus (CMV) infection is significantly less in patients treated with PSIs as compared to MMF or AZA. Given the detrimental effects of CMV infection on morbidity and long term outcomes in lung transplantation, this is a distinct advantage for PSIs.

The role of PSIs in lung transplantation has yet to be specifically defined. Compared to CNIs, the PSIs offer therapeutic advantages that can be useful in some recipients – relatively less nephrotoxicity, neurotoxicity, and a lower predilection to CMV infection. Their use, however, has not demonstrated improved survival and further evaluation is required to define their role in therapy.  

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The authors have no conflicts of interest to disclose.

References: