NEW OPTIONS IN MAINTENANCE IMMUNOSUPPRESSION:

A Clinical Update on Managing Kidney Transplant Recipients

National Kidney Foundation®

INTRODUCTION

Kidney transplantation is the treatment of choice for most patients with kidney failure (end-stage renal disease, ESRD). Demand continues to increase as the number of adult candidates on the kidney waiting list in 2012 grew by nearly 4%.[1]

Significant progress has occurred over the past two decades in reducing the rate of rejection in kidney transplant recipients as a result of advances in screening and surgical techniques, the availability of more options for immunosuppression, and improved post-transplant care. Since 2004, acute rejection within the first year post-transplant has declined to about 10%. Longer-term outcomes are improving as well (Figure 1), although chronic rejection, frequently in the setting of non-adherence, remains an ongoing challenge and a major cause of kidney transplant failure.[2] About 17% of those on the kidney waiting list are for re-transplantation.[1]

In addition to continued low rates of acute rejection, the overall focus in kidney transplantation remains on preventing and treating other post-transplant complications, and improving long-term patient outcomes. Maintenance immunosuppression is a key component of post-transplant management, and it carries its own important benefits and known challenges.

Maintenance Immunosuppression in Kidney Transplantation

Maintenance immunosuppression is an integral part of minimizing the risk of rejection of the transplant kidney and improving patient quality of life. The discovery and development of a diverse array of these medications are major factors contributing to the notable achievements in kidney transplantation. Nevertheless, since immunosuppressive therapy is used lifelong following a kidney transplant, it can place patients at risk for multiple adverse effects (e.g., infections, cardiovascular disease, malignancy).

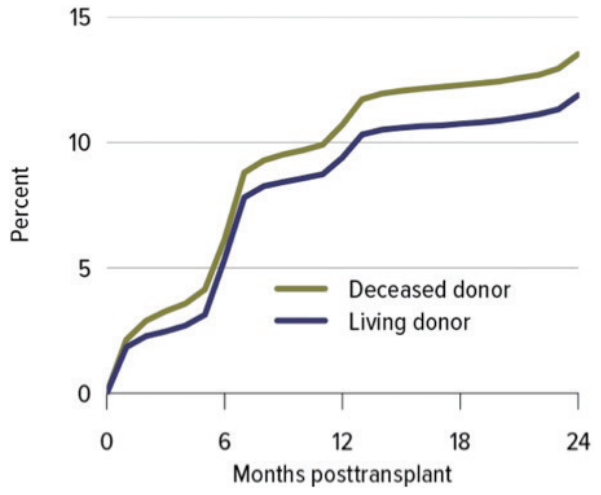

Figure 1: Incidence of first acute rejection among adult kidney transplant recipients, 2007-2011[2]

Multiple classes of immunosuppressive agents now exist, and the use of maintenance therapies evolved over the years. There are five overall classes of maintenance immunosuppressive agents: 1) calcineurin inhibitors (CNI) (e.g., tacrolimus and cyclosporine), 2) antiproliferative agents (e.g., mycophenolate mofetil (MMF), mycophenolate sodium, and azathioprine), 3) mTOR inhibitors (e.g., sirolimus and everolimus), 4) corticosteroids (e.g., prednisone and prednisolone), and 5) co-stimulation blockade (belatacept). Tacrolimus and mycophenolate have largely replaced cyclosporine and azathioprine in the US respectively, and together with prednisone comprise the most widely used treatment regimens.[1, 2]

The goals of immunosuppression are to maximize kidney function, minimize the risk of rejection, and mitigate the risk of adverse effects.[3, 4] To limit drug-specific toxicity, anti-rejection medications are typically given in combinations, so that each drug can be administered at lower doses while maintaining an adequate overall immunosuppression burden. Evidence-based clinical practice guidelines recommend using a combination of immunosuppressive medications as maintenance therapy that include a CNI and an antiproliferative agent, with or without corticosteroids.[3] Guidelines also suggest that tacrolimus be the first-line CNI used and that MMF be the first-line antiproliferative agent.

After carefully considering the likelihood of rejection, immunosuppressive regimens can be changed or tailored to the patient's immunological and adverse effect risk profile. Any decision to alter immunosuppression should be made only after fully informing the patient of the risks and benefits that are involved.

Kidney transplant recipients typically have a high pill burden, and non-adherence among patients with their immunosuppressive treatment regimen is considered a major risk factor for poor outcomes following kidney transplantation.[5, 6] Steps to prevent non-adherence can include identifying patients at risk, reducing the number and frequency of medications, treating depression or other psychological issues, and providing ongoing education, discussion, and counseling.[3, 4, 7]

New Options in Maintenance Immunosuppressive Therapy

Despite available therapies and interventions, challenges in long-term care remain, and new treatment options continue to be researched and developed, with the hope of minimizing the risk of rejection and adverse outcomes.[8, 9]

The potential of targeting costimulatory molecules (e.g., CD40, CD80, CD86) has been one area of ongoing investigation. These costimulatory inhibitors target molecules that play central roles in T cell activation. One such agent, belatacept (Nulojix®, Bristol-Myers Squibb), was

approved by the US Food and Drug Administration (FDA) in 2011 for use in kidney transplantation in combination with other maintenance agents. Belatacept is a monoclonal fusion antibody that binds to CD80 and CD86. Studies have shown that belatacept is associated with higher risk of early acute rejection than a cyclosporine-based treatment combination, although longer term, comparable outcomes in patient and graft survival, as well as possible improvements in longer-term kidney function, and a more positive cardiometabolic profile have been noted.[8, 10, 11, 12] An increased incidence of post-transplant lymphoproliferative disease (PTLD), which is associated with Epstein-Barr virus (EBV), has been observed with the use of belatacept.[11, 12] Therefore, the FDA approved belatacept only for use in EBV-seropositive kidney transplant recipients, and has issued a black box warning regarding PTLD.

ASKP1240 (Astellas Pharma), another costimulatory inhibitor, is a fully human anti-CD40 monoclonal antibody. It has shown comparable safety and tolerability in Phase I trials.[13] Phase II trials for use in combination with other maintenance immunosuppressants are ongoing.

Another active area of development includes reformulations of tacrolimus, which is used by about 90% of kidney transplant recipients.[1] Decreasing systemic exposure to CNIs like tacrolimus, or their metabolites, has been a focus for preventing and treating CNI toxicity and adverse events.[14] Prolonged release formulations, which can require less frequent doses and/or lower doses, can help address pill burden and nonadherence.

In 2013, the FDA approved once-daily tacrolimus extended-release capsules (Astagraf®, Astellas Pharma). Studies showed comparable efficacy and safety with twice-daily tacrolimus.[15, 16] Lower pharmacokinetic (PK) trough levels were observed, compared to twice-daily tacrolimus. Studies indicate that systemic amounts of this extended-release tacrolimus can be lower than expected, suggesting that an increase from the initial dose might be needed in order to obtain trough levels similar to twice-daily tacrolimus.[8, 17, 18]

LCP-Tacro (Envarsus® XR, Veloxis Pharmaceuticals), a newer once-daily formulation of tacrolimus, was approved by the FDA in 2015 for conversion from twice-daily tacrolimus in kidney transplant recipients. LCP-Tacro is produced through a formulation process that decreases a drug's particle size to a molecular level, which is aimed at increasing its bioavailability. Different tacrolimus products are not interchangeable.

A Phase III noninferiority trial and a Phase II study indicated that LCP-Tacro has comparable efficacy and safety to twice-daily tacrolimus, and a 30% lower dose requirement.[19, 20] PK data showed a comparatively lower peak concentration and longer time until reaching the peak concentration for LCP-Tacro than that of twice-daily tacrolimus. Despite this "flatter PK profile," the overall drug exposure, reflected by total area-under-the-curve, was at least equivalent, if not higher, for LCP-Tacro than twice daily tacrolimus. PK differences allows LCP-Tacro to be released more evenly throughout a 24 hour period. PK comparisons from the Phase II study are shown in Figure 2. These studies also demonstrated that kidney transplant recipients could be safely converted from twice-daily tacrolimus to LCP-Tacro.

These findings were more recently confirmed by the ASTCOFF study, which compared LCP-Tacro with other once-daily and twice-daily tacrolimus formulations.[21] A 30% dose reduction requirement for LCP-Tacro was also observed, in addition to a comparatively flatter PK profile (e.g., lower peak-to-trough fluctuation).

The ASERTAA trial compared LCP-Tacro to a twice-daily tacrolimus formulation among African American patients. The study showed a comparatively flatter PK profile, in addition to a 20% dose reduction requirement for LCP-Tacro within this patient population.[22]

A common side effect of tacrolimus is tremor, which can substantially impact quality of life. Data from the STRATO study suggests improved quality of life with moderate to severe tremor experienced by kidney transplant recipients who switch from a twice-daily tacrolimus to LCP-Tacro.[23]

Phase III clinical data in *de novo* kidney transplants showed that LCP-Tacro demonstrated non-inferiority to twice-daily tacrolimus, with one-year treatment failure rates of 18.3% and 19.6%, respectively, which is within a pre-specified 10% non-inferiority margin.[24]

SUMMARY

A wider array of options in immunosuppressive therapies contributed greatly to the reduction in acute rejections within the first year of a kidney transplant. Research in both novel therapies and modifications to existing therapies represent new opportunities to broaden the spectrum of available options in the continuing effort to improve long-term outcomes.

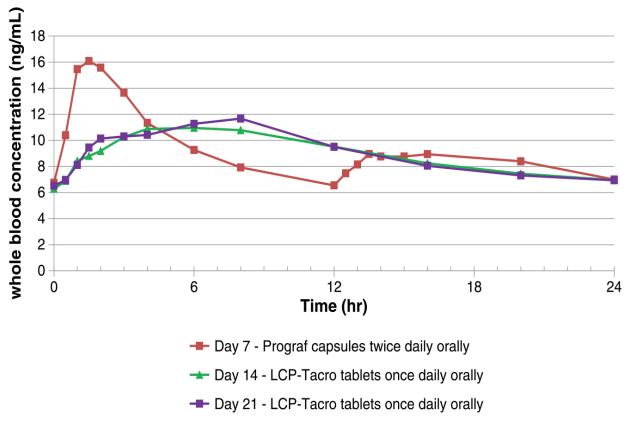

Figure 2: Mean whole–blood Tacrolimus concentration in patients on days 7, 14, and 21 versus time[20]

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