Solid Organ Transplantation

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LEARNING OBJECTIVES

1. Compare and contrast allocation models within solid organ transplantation (SOT).
2. Design an induction immunosuppressive pharmacotherapeutic plan that considers patient and allograft factors.
3. Evaluate the standard and novel maintenance immunosuppression regimens in a recipient of SOT.
4. Consider patient- and therapy-specific factors to develop treatment of antibody-mediated rejection in recipients of SOT.
5. Evaluate the utility of pharmacotherapy in prevention of chronic rejection in recipients of SOT.

ABBREVIATIONS IN THIS CHAPTER

AMR	Antibody-mediated rejection
BOS	Bronchiolitis obliterans syndrome
BPAR	Biopsy-proven acute rejection
CAV	Cardiac allograft vasculopathy
CD20	Cluster-of-differentiation 20
CLAD	Chronic lung allograft dysfunction
CNI	Calcineurin inhibitor
DSA	Donor-specific antibody
ECMO	Extracorporeal membrane oxygenation
eGFR	Estimated glomerular filtration rate
HCC	Hepatocellular carcinoma
IL2-RA	Interleukin 2 receptor antagonist
IVIG	Intravenous immune globulin
LAS	Lung allocation score
MELD	Model for end-stage liver disease

Table of other common abbreviations.

INTRODUCTION

The modern era of solid organ transplantation began with the introduction of cyclosporine in 1983, which provided adequate immunosuppression for the transplantation of all major solid organs. Optimal immunosuppression remains the core of successful solid organ transplantation. Induction immunosuppression involves high-intensity, short-course therapy; maintenance immunosuppression involves individualized long-term therapy; and rejection immunosuppression involves high-intensity, short-course therapy. The optimal use of all types of immunosuppression has been the focus of most of the clinical research in the area of transplantation.

Solid organ transplantation provides a survival benefit for patients with end-stage diseases of the kidney, liver, pancreas, small intestine, heart, and lung (Rana 2015). Although it is not a procedure that improves survival, certain quality-of-life improvements are realized with vascular composite allograft and uterus transplantation. The expected patient and graft survival following successful transplantation has been steadily increasing over the past decade, with one-year patient and graft survival a key metric for the accreditation of solid organ transplant programs and for national reporting (Table 1).

UPDATES IN ORGAN ALLOCATION AND DISTRIBUTION

The Organ Procurement and Transplantation Network (OPTN) is a public–private partnership created following passage of the National Organ Transplant Act in 1984. The goals of the OPTN are to increase transplantation rates and access to transplantation for patients in need, to promote a safe solid organ transplantation system, and to improve rates of survival following transplantation. The OPTN creates, maintains, evaluates, and updates policies related to solid organ transplantation, including organ allocation and distribution rules that apply throughout the United States.

01_1_Doligalski.indd 7 02/05/19 5:54 pm

Table 1. 1-Year and 5-Year Patient and Graft Survival

Organ	1-Year Patient Survival (%)	1-Year Graft Survival (%)	5-Year Patient Survival (%)	5-Year Graft Survival (%)
Kidney	96.8	94.5	85.4	77.7
Liver	91.3	89.2	74.6	71.4
Heart	90.5	90.7	78.4	77.8
Lung	86.4	85.4	52.7	50.3
Kidney/pancreas	97.3	96.1	88.9	82.2
Small bowel	82.2	76.9	57.2	51.2

Information from the Organ Procurement and Transplant Network, July 1, 2018

Organ allocation and distribution is guided by three ethical principles: medical utility maximizes the net benefit to the population affected; medical justice is fairness in distribution of resources; and respect for persons treats all with honesty and autonomy. Policies must also consider allowable ischemic times, which vary by organ. Ischemic time is the amount of time an organ goes without perfusion from either the donor or the recipient; the longer the ischemic time, the more damage is done to the tissue, resulting in potentially poor organ function and decreased longevity. Taken together, the guiding ethical principles and logistical considerations create a framework to guide policy decisions intended to minimize disparities and optimize outcomes following the transplant. As such, allocation and distribution models for the liver, kidney, heart, and lung have undergone changes in the past 10 years that have changed the clinical characteristics of patients receiving solid organ transplants in some cases.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with:

- General knowledge of the immune system, including activation against foreign antigen exposure
- Drug knowledge of the standard maintenance immunosuppressive therapies, including common adverse effects
- Common diseases leading to end organ failure and need for transplantation

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources are available for readers wishing additional background information on this topic.

- Halloran PF. Immunosuppressive drugs for kidney transplantation. N Engl J Med 2004;351:2715-29.
- Loupy A, Lefaucheur C. Antibody-mediated rejection of solid organ allografts. N Engl J Med 2018;379:1150-60.

Kidney

With up to 36 hours of ischemia time allowable, kidney transplant allows for the largest geographic donor pool. The kidney allocation system was changed in 2014 from a primarily wait-time-based system to one in which priority is given to patients who are highly sensitized because of significant previous antigen exposure, and higher-quality organs are prioritized for patients with the highest chances of survival after the transplant. In addition, wait time began upon dialysis initiation and was retroactively applicable (Israni 2014). The classification of organs as extended criteria (donor older than 60 years or older than 50 years with two of the following: hypertension, SCr over 1.5 mg/dL, or death secondary to stroke) was eliminated with implementation of the Kidney Donor Profile Index, which applies several donor factors to estimate the likelihood of graft failure following transplant (Israni 2014). In the months following initiation of that system, a bolus effect was seen wherein a high number of highly sensitized and previously disadvantaged patients were receiving transplants (Stewart 2016). Those highly sensitized patients require special immunosuppression consideration given their high risk of antibody-mediated rejection.

Liver

Liver transplant allocation is based on the model for end-stage liver disease (MELD) in adults and pediatric end-stage liver disease in pediatrics, with higher scores prioritized in conjunction with blood group. Further priority is granted to patients with conditions such as hepatocellular carcinoma (HCC), for which transplantation is curative. In 2013,

01_1_Doligalski.indd 8 02/05/19 5:54 pm

in an effort to decrease wait-list mortality and prioritize transplantation for the most ill candidates, the OPTN implemented Share 35, which mandates that liver donor offers be made—within an acceptable geographic region—to all transplant candidates with MELD scores higher than 35 (Kwong 2015). The impact of this change was significant in that it shifted the complexity and critical nature of liver recipients because more transplants are performed on patients with higher MELD scores and because patients with lower MELD scores are waiting longer (Nekrasov 2016). The applicability of older literature—especially pertaining to the immediate postoperative care of recipients of liver transplants—must be considered with caution because the patient population now receiving transplants is globally more critical than populations previously transplanted.

Heart

Limited by the shortest-allowable cold ischemia times, heart transplant allocation remained largely unchanged until recently, with the introduction of several new status levels. Unlike other allocation systems, heart allocation is based on therapies used for care in conjunction with blood group and sizing rather than on an objective scoring tool. With implementation in October 2018, the updated heart allocation system is anticipated to deprioritize those on stable mechanical circulatory support while prioritizing those with complications or significant decompensation such as requiring extracorporeal membrane oxygenation (ECMO) (OPTN website accessed 2018).

Lung

Lung transplant allocation underwent major revision in 2005, with the introduction of the lung allocation score (LAS). This complex algorithm consists of 18 objective items that estimate both wait-list mortality and posttransplant survival. Higher LASs are prioritized by blood group, height, and weight constraints for potential recipients. The LAS's greatest impact was a shift in the underlying disease states prioritized for transplantation, with rates of transplantation for a diagnosis of chronic obstructive pulmonary disease (COPD) falling sharply and rates of transplantation for interstitial pulmonary fibrosis rising (Gries 2007). The comorbidities and immunologic considerations encountered in those diseases make evaluation and application of clinical research prior to 2005 difficult in the LAS era.

INDUCTION IMMUNOSUPPRESSION

Induction immunosuppression is high-potency, short-course therapy provided upon transplantation or in the days following to reduce the risk of rejection. Induction immunosuppression may be used in recipients with high immunologic risk—in an effort to minimize maintenance immunosuppression long-term or to delay the initiation of maintenance immunosuppression. This is especially valuable in the setting of renal dysfunction, in which delayed initiation of calcineurin inhibitors is desired. As such, the decision to initiate more-potent induction immunosuppression may be made well prior to, immediately following, or in the days following transplantation.

Risk factors for acute rejection include organ transplanted, with organs exposed to the outside environment such as lung and small bowel, which are at higher risk than others; younger recipients; recipients with previous human antigen exposure from prior transplantation; pregnancy, blood product transfusions; recipients with prolonged ischemia times on the organ; and recipients of African American race (Terasaki 2004, Higgins 2006). Sensitization to human antigens through prior transplantation, blood transfusions, and pregnancy are significantly more important risk factors for acute rejection than are age and race, although age and race are factors to be considered in the assessment of a patient's overall immunologic risk.

Pharmacological agents most commonly used in induction immunosuppression are intravenous glucocorticoids, interleukin-2 receptor antagonists (IL2-RAs), antithymocyte immune globulins, and alemtuzumab (Table 2). Glucocorticoids and IL2-RAs do not cause T-cell depletion, and they provide less-intensive immunosuppression than do antithymocyte immune globulins and alemtuzumab, which lead to T-cell—and some B-cell—destruction. Depleting therapies are more commonly associated with infusion reactions such as cytokine release syndrome and hemodynamic instability, as well as increased risk of infectious and hematologic adverse events. Basiliximab (Simulect, Novartis; New Hanover, NJ), an IL2-RA, and rabbit antithymocyte globulin (Thymoglobulin, Genzyme; Cambridge, MA) are the only two agents with labeled indications for the prevention of rejection; those indications are limited to renal transplantation despite widespread use in other organ groups. Data comparing induction strategies are limited, with few randomized trials and multiple single-center pre- and postanalyses or registry data analyses.

Induction in Kidney Transplantation

The best data available to guide the choice of induction therapy are in the area of renal transplantation. The two largest groups of data for induction in kidney transplantation exist in the setting of triple maintenance immunosuppression with a calcineurin inhibitor—an antiproliferative agent—and corticosteroids, as well as in the setting of planned early corticosteroid withdrawal or avoidance. In addition, the patient's risk of rejection should be considered, and recipients should be stratified into lower and higher immunologic risk. The 2009 Kidney Disease: Improving Global Outcomes guidelines recommend the inclusion of a biologic agent for induction, with IL-2RA as first line (level of evidence 1B) and a lymphocyte-depleting therapy as first line for recipients at high immunologic risk (level of evidence 2B).

01_1_Doligalski.indd 9 02/05/19 5:54 pm

Table 2. Induction Immunosuppression Comparison

Agent	Mechanism of Action	Relative Duration of Immunosuppression	T-Cell Depleting	B-Cell Depleting	Standard Dosing	Adverse Effects
High-dose corticosteroids	Small molecule that inhibits IL-2 production	Days	None	None	500 mg – 1000 mg for 1 or 2 doses	Leukocytosis Hyperglycemia Hypertension Psychological disturbances
Basiliximab	Monoclonal antibody that blocks IL-2 activation of CD25	Days to weeks	None	None	20 mg on day of surgery and 4 days later	
Antithymocyte immune globulin	Polyclonal antibody that lyses T cells	Weeks	Significant depletion	Minimal depletion	1.5 mg/kg for 3 – 5 doses	Infusion reactions (cytokine release) Leukopenia Thrombocytopenia Infection
Alemtuzumab	Monoclonal antibody that lyses T cells and B cells	Weeks to months	Significant depletion	Moderate depletion	30 mg for 1 dose	Infusion reactions (cytokine release) Leukopenia Infection Cancers

Induction with antithymocyte globulin was compared with basiliximab in 278 patients following renal transplant, who had been prospectively randomized to receive either 1.5 mg/kg of antithymocyte globulin for 5 days or basiliximab 20 mg on postoperative days 0 and 4. Pretransplant sensitization, retransplantation, and prolonged cold ischemia times were low in both groups, and only 29% of the cohort was identified as African American—a relatively low percentage representing an overall low-immunologic-risk cohort. At one year, biopsy-proven acute rejection and corticosteroid-resistant rejection were lower in the antithymocyte globulin arm (15.6% vs. 25.5%, p=0.02, and 1.4% vs. 8%, p=0.005, respectively). Mortality or graft loss was similar. Infectious complications were more common in the antithymocyte globulin cohort (85.8% vs. 75.2%, p=0.03), as was leukopenia (33.3% vs. 14.6%, p<0.001) (Brennan 2006). In this immunologically-low-risk population, decreased rejection was seen with antithymocyte globulin at the expense of increased infectious complications.

The Induction with Tacrolimus (INTAC) Study Group evaluated choice of induction in the setting of early corticosteroid withdrawal, with stratification of groups by immunologic risk. High-risk recipients (n=139) were identified as having had repeat transplants, having current or peak panel-reactive antibodies of 20% or higher, or being of African American race. Those recipients were randomized to either one dose of alemtuzumab 30 mg or rabbit antithymocyte globulin for a cumulative dosage of 6 mg/kg. Low-risk recipients (n=335) were randomized to either alemtuzumab 30 mg at the time of transplantation or basiliximab 20 mg on postoperative days 0 and 4. All patients received tacrolimus, mycophenolate, and 5 days of glucocorticoid therapy. Alemtuzumab-treated patients had less biopsy-proven acute rejection (BPAR) at 6 months (3% vs. 15%, p<0.001) and 12 months (5% vs. 17%, p<0.001) compared with conventional therapy. That finding was driven by the benefit of alemtuzumab over basiliximab in the low-risk cohort. No difference in BPAR was seen for up to 3 years in the antithymocyte-globulin-versus-alemtuzumab high-risk cohort. No difference in patient or graft survival was seen between any group comparisons. Leukopenia was more common in the alemtuzumab cohort compared with conventional therapies (57% vs. 35%, p<0.001), as was any cancer (5% vs. 1%, p=0.03). In the low-risk cohort, serious infections were more common in alemtuzumab-treated patients (35% vs. 22%, p=0.02) (Hanaway 2011). Since the publication of this seminal paper, consistent data support the use of T-cell-depleting induction over IL2-RA therapy for successful early corticosteroid withdrawal (Martin 2011, Haynes 2014).

Induction in Liver Transplantation

The liver is the least-immunogenic organ and typically requires the least amount of immunosuppression, with underlying autoimmune disorders the exception. With the implementation of Share 35 policies, the percentage of liver transplant recipients with renal dysfunction or failure going in to

01_1_Doligalski.indd 10 02/05/19 5:54 pm

transplantation has increased, and the need for renal-sparing approaches has risen (Nekrasov 2016). Several single-center analyses were published in 2010 and 2011 demonstrating similar outcomes with respect to patient and graft survival, acute rejection episodes, and renal function in liver transplant recipients receiving IL2-RA induction compared with placebo. In those comparisons, the IL-2RA cohort had a higher MELD score and higher rates of pretransplant renal dysfunction. The analyses suggest that IL2-RA induction is beneficial for those with pre- or peritransplant renal dysfunction, allowing for renal sparing while not compromising graft and patient outcomes (Calmus 2010, Verna 2011). In 2014, a Cochrane review of 19 studies including 2067 liver transplant recipients was conducted. The authors found that all of the evidence was of low quality, and no benefit was seen from T-cell-specific antibody therapy or IL2-RA over placebo with respect to mortality or graft loss. Acute-rejection rates appeared to be reduced when T-cell-specific antibody induction was compared with no induction (RR 0.85, 95% CI, 0.75–0.96). Adverse events were less common with IL2-RA compared with T-cell-specific antibody therapy (Penninga 2014).

Induction in Heart Transplantation

No induction regimen for heart transplantation has shown improvement in patient or graft survival in a prospective evaluation. The 2010 International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients state that routine use of induction has not been shown to improve posttransplant outcomes. Induction with polyclonal antibodies may be beneficial in patients at high risk of rejection (Class IIb, LOE C) and when used to delay the initiation of calcineurin inhibitors in those at high risk of renal dysfunction (Class IIa, LOE B) (Costanzo 2010). More recently, analysis of ISHLT registry data from 9324 recipients identified an association between improved survival at 5 years (77% vs. 82%, p=0.005) and 10 years (65% vs. 67%, p=0.007) with antithymocyte immune globulin compared with basiliximab. In that same cohort, no difference was seen in 1-year survival rates (90% vs. 91%, p=NS). The rate of death from infection was higher in recipients of basiliximab compared with antithymocyte globulin at 10 years (7.8% vs. 6%, p=0.037), suggesting that the 2010 guideline recommendations may be revised to reflect a long-term benefit of antithymocyte globulin over IL-2RA therapy (Ansari 2015).

Induction in Lung Transplantation

A similar analysis comparing alemtuzumab, basiliximab, and no induction was conducted from the ISHLT registry in double-lung-transplant recipients (Furuya 2016). Both the alemtuzumab and basiliximab groups had improved survival over no-induction strategies up to 8 years posttransplant (median survival 2321 [alemtuzumab] vs. 2352 [basiliximab] vs. 1967 [no induction] days, p=0.001). At 5 years, the incidence of bronchiolitis obliterans syndrome (BOS) was decreased in the alemtuzumab cohort compared with either basiliximab or no induction (22.7% vs. 55.4% vs. 55.9%, p<0.001). Although data from 6117 lung transplant recipients were analyzed, the

Patient Care Scenario

You are the pharmacist on the kidney transplant team at your institution. A new surgeon has joined the team and wants to revise the immunosuppression protocols. Specifically, the new team member wants to minimize the use of corticosteroids as much as possible while avoiding excessively high rates of acute rejection in the first posttransplant year. Which of the following induction protocols is best to recommend?

A. Methylprednisolone 1000 mg IV × 2 for all kidney transplant recipients

B. Basiliximab 20 mg IV on postoperative days 0 and 4 for all kidney transplant recipients

C. Basiliximab 20 mg IV on postoperative days 0 and 4 for most kidney transplant recipients; antithymocyte immune globulin for 6 mg/kg in divided doses for very high immunologic risk recipients

D. Alemtuzumab 30 mg IV × 1 for all kidney transplant recipients

ANSWER

Answer D would be the most likely protocol for minimizing rejection while avoiding corticosteroids. The INTAC study demonstrated the benefit of alemtuzumab over basiliximab and antithymocyte immune globulin for the purposes of corticosteroid avoidance, although more incidences of leukopenia and infections occurred, and the benefit of alemtuzumab over alternatives was driven largely by the low-immunologic-risk cohort. There are no data for corticosteroid avoidance with corticosteroid-only induction (Answer A). The results of the INTAC and FREEDOM studies suggest basiliximab alone would be associated with high risk of rejection for corticosteroid avoidance. Answer C is less ideal given the benefit of alemtuzumab over basiliximab in low-immunologic-risk recipients.

1. Hanaway MJ, Woodle ES, Mulgaonkar S, et al. INTAC Study Group. Alemtuzumab induction in renal transplantation. N Engl J Med 2011; 364:1909-19.
2. Vincenti F, Schena FP, Paraskevas S, et al. A randomized, multicenter study of steroid avoidance, early steroid withdrawal or standard steroid therapy in kidney transplant recipients. Am J Transplant 2008; 8:307-16.

01_1_Doligalski.indd 11 02/05/19 5:54 pm

alemtuzumab cohort composed only 12% of the analysis, and 79.8% of those receiving alemtuzumab underwent transplant at a center performing more than 40 transplants per year. The variability in clinical practice between lung transplant centers, in expertise at high-volume centers, and in maintenance immunosuppression not assessed in this analysis limits the strength of conclusions that can be drawn from a retrospective analysis.

A unique population to consider are those receiving transplantation for cystic fibrosis, wherein concerns about infectious complications are more pronounced than about other underlying lung diseases. An analysis of United Network for Organ Sharing found the median survival among patients receiving induction (n=791) was 93.8 months compared with 61.8 months without induction (n=930) ($p<0.001$). Most patients (65%) undergoing induction received basiliximab therapy compared with alemtuzumab (10%) or antithymocyte globulins (25%). Infectious complications, graft survival, acute rejection, and BOS were not assessed (Kirkby 2015).

MAINTENANCE IMMUNOSUPPRESSION

Traditional Maintenance Immunosuppression Regimens

Calcineurin Inhibitors

Contemporary maintenance immunosuppression typically consists of a calcineurin inhibitor, an antiproliferative agent, and corticosteroids. The clinical benefit of tacrolimus over cyclosporine is largely an academic question. Most U.S. transplant programs use tacrolimus de novo (from the beginning) despite limited data in all organ groups showing only marginal benefits with respect to BPAR and no clear patient or graft survival benefit. The mechanism of action of both cyclosporine and tacrolimus is to bind and block intracellular calcineurin, thereby preventing upregulation of nuclear transcription factors coding for cytokines—most importantly, interleukin-2 (IL2).

As narrow therapeutic index agents susceptible to metabolic variability secondary to genotypic variance, both tacrolimus and cyclosporine require therapeutic drug monitoring. Single-point, limited sampling, and full pharmacokinetic assessments are used in clinical practice. Genetic polymorphisms at the CYP3A5 allele have been associated with substantial variability in tacrolimus dosage requirements, with CYP3A5*1 and CYP3A5*7 associated with increased dosage requirements (Jacobson 2011). Renal toxicity, metabolic complications, electrolyte abnormalities, and neurotoxicities are common. Cyclosporine is more commonly associated with hypertension and hyperlipidemia, and tacrolimus is more likely to cause hyperglycemia and neurotoxicities (Halloran 2004). Renal toxicity and neurotoxicities are postulated to be related to Cmax concentrations, and metabolic complications are concentration-independent toxicities. Nephrotoxicity with resultant renal failure is the most significant limitation of calcineurin inhibitor therapy, with 16.5% of non-renal-transplant recipients experiencing chronic renal failure and 4.8% requiring renal replacement therapy following transplantation (Ojo 2003).

Antimetabolites

Mycophenolate is usually the antimetabolite of choice for de novo use in combination with calcineurin inhibitor therapy, given limited data suggesting an improvement in clinical outcomes. A comparison of available antimetabolites is outlined in Table 3.

Corticosteroids

Corticosteroids are pivotal components of all of the traditional maintenance immunosuppressive regimens. An in-depth review of complications from chronic corticosteroid use is covered elsewhere in this book.

Table 3. Comparison of Available Antimetabolite Agents

Generic Name	Brand Name	Typical Dosing	ADME	Key Drug Interactions	Toxicities
Mycophenolate mofetil	CellCept	500 mg – 1500 mg BID	Enterohepatic recirculation with active renal tubular secretion	Acyclovir, valganciclovir, valacyclovir	Pancytopenias, gastrointestinal toxicities
Mycophenolic acid	Myfortic	360 mg – 1080 mg BID			
Azathioprine	Imuran	1 – 3 mg/kg daily (typical dose 50 – 150 mg daily)	Rapidly bioavailable and activated to 6-mercaptopurine; eliminated partially by xanthine oxidase	Allopurinol, warfarin	Pancytopenias, hepatotoxicity

Information from manufacturers' package inserts.

01_1_Doligalski.indd 12 02/05/19 5:54 pm

Table 4. Pharmacokinetics of Available Tacrolimus Formulations

	Tacrolimus Immediate-Release Capsules (Prograf)	Tacrolimus Extended-Release Capsules (Astagraf XL)	Tacrolimus Extended-Release Tablets (Envarsus XR)
Bioavailability	17 – 20%	12 – 20%	30%
T_{max}	1.5 hr	2 hr	6 hr
Protein binding	99%		
Metabolism	Liver (3A4) > Gut (3A4/PgP) > Kidney		
Metabolites	8 (major metabolite = 31-demethyl tacrolimus)		
$T_{1/2}$	31 hr	38 hr	31 hr

Novel Maintenance Immunosuppressive Regimens

Extended-Release Tacrolimus Products

Two extended-release tacrolimus products are commercially available: tacrolimus extended-release capsules (ER-tacrolimus) (Astagraf XL; Astellas, Northbrook, IL) and tacrolimus extended-release tablets, also known as LCP-tacrolimus (LCP-tacrolimus) (Envarsus XR; Veloxis, Cary, NC). The pharmacokinetic properties differ substantially between the two products (Table 4).

The steady-state pharmacokinetic comparison of all FK-506 formulations (ASTCOFF) study was a three-way, head-to-head pharmacokinetic comparison between the available tacrolimus formulations. In that open-label, prospective, randomized, three-period crossover study, 32 stable renal transplant recipients received 1 week of the three available tacrolimus products, with a 16-point, 24-hour pharmacokinetic analysis performed on day 7 of each therapy. Transplant recipients with estimated glomerular filtration rates (eGFRs) of less than 25 mL/min/1.73m^2 and with body mass indexes (BMIs) of less than 19 kg/m^2, those with severe gastroparesis or gastrointestinal conditions, or those taking concomitant CYP3A4/5 inhibitors or inducers were excluded.

The median age of participants was 48.3 years, with 74.2% of participants identifying as white and 90.3% having undergone living-related renal transplants 6.1 years previously. Median BMI at enrollment was 30.4 kg/m^2. The Cmax achieved by LCP-tacrolimus was 17% lower than that achieved by either ER-tacrolimus or IR-tacrolimus (p=0.002 and p=0.006, respectively), with no difference in Cmax between ER-tacrolimus and IR-tacrolimus (p=NS). Investigators found excellent correlation between C_0 and $AUC_{0\text{-}24h}$ for all three products assessed (0.92 [LCP-T], 0.92 [ER-tac], 0.81 [IR-tac]). Regarding exposure normalization and dosage conversion, the authors found that 30% less LCP-tacrolimus was needed to achieve an $AUC_{0\text{-}24h}$ similar to IR-tacrolimus, whereas 8% more ER-tacrolimus was needed in comparison to IR-tacrolimus (Tremblay 2017).

Data comparing clinical outcomes of IR-tacrolimus with extended-release formulations are limited to noninferiority studies, with no significant differences found in patient and graft outcomes (Bunnapradist 2013, Silva 2014). The differences in clinical outcomes were evaluated between specific predefined subgroups by means of analysis of data pooled from two phase 3 trials in 862 de novo renal transplant recipients receiving basiliximab induction, tacrolimus, mycophenolate, and corticosteroids at the discretion of the transplant center.

The primary end point of both phase 3 studies was 12-month treatment failure, a composite of death, graft loss, loss to follow-up, or a BPAR grade of 1A or higher. A reduction in the composite end point was seen in African American transplant recipients (13.8% ARR, p=0.054) and recipients older than 65 years of age (13.5% ARR, p=0.04). No statistically significant difference was observed based on sex, although female recipients had a numerically lower event rate in the LCP-tacrolimus arms (5.6% ARR, p=NS) (Bunnapradist 2016).

Extended-Release Tacrolimus and Genetic Variability

Given that the known CYP3A5 genotypic variance affecting tacrolimus disposition is more common among African American transplant recipients (Oetting 2015), the Study of Extended Release Tacrolimus in African-Americans (ASERTAA) sought to characterize—in a prospective, multicenter, crossover fashion—the pharmacokinetic profile of LCP-tacrolimus compared with IR-tacrolimus in 50 clinically stable African American renal transplant recipients. The LCP-tacrolimus was administered at 85% of the total daily dosage of stable IR-tacrolimus. Eight patients were taking concurrent CYP3A4/5 inhibitors (azithromycin, n=6; diltiazem, n=1; amiodarone, n=1), which were continued throughout the study. Full pharmacokinetic analyses were performed after 7 days of stable therapy. Fifty-one percent of participants expressed CYP3A5*1. After the use of IR-tacrolimus, a 33% higher Cmax was observed in the expressor group, with similar $AUC_{0\text{-}24h}$ and Cmin values. Following 7 days of LCP-tacrolimus therapy, the $AUC_{0\text{-}24h}$, Cmax, and C_0 between expressors and nonexpressors was similar. With

01_1_Doligalski.indd 13 02/05/19 5:54 pm

respect to dosage conversion between formulations, despite a 15% dosage reduction upon conversion from IR-tacrolimus to LCP-tacrolimus, Cmin levels were increased for both expressors (RGM 121.8, p=0.05) and nonexpressors (RGM 111.1, p=0.1), suggesting further dose reduction to about 80% of total IR-tacrolimus daily dose (Trofe-Clark 2018).

Extended-Release Tacrolimus and Tremor

The Switching STudy of Kidney TRansplant PAtients with Tremor to LCP-TacrO (STRATO) evaluated the effect of conversion from IR-tacrolimus to LCP-tacrolimus on tremor by way of an accelerometry device, patient-reported quality of life, and independent, blinded, movement disorder using the Fahn–Tolosa–Marin (FTM) tremor-rating scale. Thirty-eight kidney transplant recipients completed the study and received 7 days of IR-tacrolimus, with tremor evaluations on day 7, and then 7 days of LCP-tacrolimus, with tremor evaluations on day 14. The patient population was 76% male, 82% white race, and 37% living-donor recipients. Mean time from transplant to enrollment was 16 months. The mean absolute decrease in FTM score was 5.35, p<0.0001, with improvements in all test domains: functional disabilities, specific motor tasks and functions, and tremor severity as well as improvements in accelerometry measurements. Improvements were also seen in patient-reported quality-of-life measures (all of them p<0.05), and 87% of patients rated their tremor as "much better" (32%) or "a little better" (55%) on the Clinical Global Impressions scale. Only 3% of patients rated their tremors as "worse" with LCP-tacrolimus (Langone 2015).

Belatacept-Based Immunosuppression Regimens

Belatacept is the newest drug with a labeled indication for solid organ transplantation. An immune checkpoint inhibitor, belatacept is a second-generation CTLA-4-Ig fusion inhibitor with 10 times the T-cell-activation blocking that abatacept—a first-generation agent with clinical utility in rheumatoid arthritis—has. Belatacept binds to CD80/86 on antigen-presenting cells, thereby blocking the interaction between CD80/86 and CD28 on T cells and preventing costimulation in the T-cell-activation pathway. CTLA-4 is upregulated on activated T-effector cells and is required for optimal functionality of regulatory T cells (Webber 2016).

Administered as an intermittent IV infusion, belatacept uses weight-based dosing, with adjustments needed when the patient's weight changes by more than 10%. According to the Nulojix package insert, if infusion dates are missed, a 3-day window around the planned dose is allowed. Belatacept has a boxed warning for the increased risk of a lymphoproliferative disorder associated with Epstein–Barr virus mismatch (e.g., donor EBV+, recipient EBV–) following transplantation, and thus therapy is contraindicated in that patient population.

Belatacept Clinical Utility

The clinical utility of belatacept has been documented in two phase III studies, the Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT) and BENEFIT-EXT along with publication of up to 7 years of follow-up data. The studies evaluated the role of belatacept compared with cyclosporine in combination with mycophenolate and maintenance corticosteroids following basiliximab induction in de novo renal transplant recipients of either standard (BENEFIT) or extended-criteria (BENEFIT-EXT) donor organs.

The choice of cyclosporine as compared with tacrolimus as the primary comparator for belatacept was mandated by the FDA. Each study had three arms: two dosing schemes for belatacept (a less-intense [LI] arm and a more-intense [MI] arm) and a cyclosporine arm (Box 1). The primary end point of the initial approval studies was a coprimary end point of patient/graft survival, incidence of acute rejection, and a renal impairment end point (percent with a measured glomerular filtration rate of less than 60 mL/min/1.73 m^2 at month 12 or a decrease in glomerular filtration rate of greater than or equal to 10 mL/min/1.73 m^2 between months 3 and 12). The 12-month analyses of the BENEFIT and BENEFIT-EXT demonstrated improvement in renal function with comparable patient and graft outcomes. The BENEFIT study found an increased risk of acute rejections among patients receiving belatacept (MI belatacept, 22%; LI belatacept, 17%; and cyclosporine, 7%), whereas rejection rates were similar in the BENEFIT-EXT population (18% vs. 14%, p=NS). The severity of rejection episodes in the BENEFIT study was higher, with only one moderate-to-severe rejection in cyclosporine-treated patients (2%), whereas 10% of the MI-belatacept-treated and 5% of the LI-belatacept-treated patients had moderate or severe rejections (Durrbach 2010, Vincenti 2010).

In the BENEFIT analysis at 7 years, 447 of the 660 treated patients had data available for evaluation. Both patient and graft survival were significantly higher in the belatacept-treated patients (HR MI belatacept, 0.57; 95% confidence interval [CI], 0.35 to 0.95; p=0.02; HR LI belatacept,

Box 1. Belatacept Dosing Regimens in BENEFIT Studies

Moderate-intensity dosing regimen

- 10 mg/kg on days 1 and 5
- 10 mg/kg at weeks 2, 4 ,6, 8, 10, 12, 16, 20, and 24
- 5 mg/kg every 4 weeks following last 10-mg/kg dosage

Low-intensity dosing regimen[a]

- 10 mg/kg on days 1 and 5
- 10 mg/kg at weeks 2, 4, 8, and 12
- 5 mg/kg every 4 weeks following last 10-mg/kg dosage

[a]Also an FDA-approved dosing regimen.

01_1_Doligalski.indd 14 02/05/19 5:54 pm

0.57; 95% CI, 0.35 – 0.94; p=0.02). The estimated GFR was also significantly higher in belatacept-treated patients compared with the GFR of cyclosporine at 7 years (70.4 vs. 72.1 vs. 44.9 mL/min/1.73m^2, p<0.001). Acute rejection rates at 7 years remained higher in the belatacept-treated patients (24.4% vs. 18.3% vs. 11.4%, p≤0.001), although the majority of rejection episodes occurred in the first year (Vincenti 2016). In the 7-year follow-up of the BENEFIT-EXT population, 374 of the 543 enrolled patients were analyzed. No differences in 7-year patient survival, graft survival, or acute rejection rates were noted. Mean estimated GFR was significantly higher in both belatacept arms compared with cyclosporine (53.9 vs. 54.2 vs. 35.3 mL/min/1.73 m^2 for MI belatacept, LI belatacept, and cyclosporine, respectively [p<0.001]) (Durrbach 2016).

Belatacept Conversion

Limited data exist regarding conversion from traditional immunosuppression to a belatacept-based regimen. A phase II study prospectively randomized patients from 6 to 36 months post kidney transplant to either continue calcineurin inhibitor (n=89) or convert to belatacept (n=84). Belatacept 5 mg/kg was given on days 1, 15, 29, 43, and 57 and then every 28 days thereafter; calcineurin inhibitor doses were decreased to 40% to 60% on days 15 and 20, to 30% on day 23, and none on day 29 and beyond. The primary end point change in estimated GFR at 12 months was significantly higher in the belatacept cohort (60.5 vs. 56.5 mL/min/1.73m2, p=0.006). No episodes of acute rejection occurred in the calcineurin inhibitor cohort; six patients (7%) treated with belatacept were treated for mild-to-moderate acute rejection (Rostaing 2011).

Belatacept- and Corticosteroid-Sparing Regimens

There is significant interest in adding the renal-protective benefits of a belatacept-based regimen to the benefits of a corticosteroid-free regimen, which would minimize the micro- and macrovascular complications associated with these therapies. The premise was investigated in a National Institutes of Health–sponsored study with three arms: arms 1 and 2 consisted of alemtuzumab induction with corticosteroid avoidance and either tacrolimus/mycophenolate (group 1) or belatacept/mycophenolate/short-term tacrolimus (group 2); group 3 used belatacept based on FDA-approved therapy of basiliximab induction with mycophenolate/belatacept/corticosteroids. Nineteen renal transplant recipients were enrolled before enrollment paused because of thrombotic complications and before enrollment was ultimately permanently halted because of the number of rejection episodes in groups 2 and 3. The unexpectedly high rate of thrombotic events was postulated to be secondary to either technical challenges or the infusion of two protein therapies shortly before or following graft reperfusion leading to a prothrombotic state. Ultimately, the small number of cases made it impossible to draw definitive conclusions (Newell 2017). The high rates of early acute rejection seen in groups 2 and 3 mirror, to some extent, the before-1-year rejection data in the BENEFIT and BENEFIT-EXT studies.

The results of the Belatacept-Based Early Steroid Withdrawal Trial, which completed enrollment in 2016 and has been presented only in abstract format thus far, will be critical for understanding the clinical applicability of lymphocyte-depleting induction therapy in combination with belatacept and corticosteroid weaning in renal transplant recipients (Woodle 2016).

Belatacept in Nonrenal Transplantation

Outside of de novo renal transplantation, the use of belatacept has been limited to case reports and series in cardiothoracic-transplant recipients who have severe calcineurin inhibitor toxicities. A phase II study in 260 liver transplant recipients was halted because of an increased rate of death and graft loss in the belatacept-treated patients at 12 months. Two cases of posttransplant lymphoproliferative disorder and one case of progressive multifocal leukoencephalopathy were described in the belatacept-treated patients, again raising questions regarding the safety of this novel therapy (Klintmalm 2014).

mTOR Inhibitor-Based Regimens

Two mTOR inhibitors used for maintenance immunosuppression in solid organ transplantation—sirolimus and everolimus—are available. Neither agent has been used extensively for de novo use in any solid organ transplant population. The mTOR inhibitors are narrow therapeutic index agents requiring therapeutic drug monitoring with trough levels. They also have large volumes of distribution, which necessitates that loading doses achieve therapeutic concentrations within the first week of therapy. With a prolonged half-life, infrequent dose adjustments should be made given a prolonged time to achieve steady state. Everolimus contains a hydroxyl group added to the sirolimus molecule in an attempt to improve the bioavailability of the compound. The resultant pharmacokinetic differences include a lower volume of distribution and a shorter half-life (Table 5). The toxicity profiles of mTOR inhibitors have been well described and make their routine clinical use challenging (Ensor 2013). Those toxicities include wound-healing complications, hyperlipidemia/hypertriglyceridemia, cytopenias, and, rarely, severe pulmonary toxicity.

Despite the limitations, several proposed advantages pertain to the use of mTOR inhibitors, including their antiviral, antitumor, and antiproliferative properties. Early investigation of mTOR inhibitors—specifically, sirolimus—found high rates of drug discontinuation because of adverse events and increased rates of BPAR, with some benefits with respect to renal function and antiviral benefits.

01_1_Doligalski.indd 15 02/05/19 5:54 pm

Table 5. Pharmacokinetic Properties of mTOR Inhibitors

	Sirolimus	Everolimus
V_d	12 L/kg	1.5 – 5 L/kg
A	F = 15 – 27%	F = 19 – 25%
D	92% plasma protein bound	74% plasma protein bound
M	CYP 3A3/4 and PgP substrate 7 metabolites (<10% of activity)	CYP 3A3/4 and PgP substrate 6 metabolites (<1% of activity)
E	91% feces $t_{1/2}$ 62 hr	80% feces $t_{1/2}$ 30 hr

mTOR Inhibitors in Kidney Transplant

The Efficacy Limiting Toxicity Elimination Study evaluated the role of sirolimus in minimizing calcineurin-inhibitor-associated renal dysfunction in kidney transplant recipients. In total, 1645 patients who had had renal transplants were randomized to one of four study arms: standard-dosage cyclosporine (goal trough 100 – 300 ng/mL), reduced-dose cyclosporine (goal trough 50 – 100 ng/mL), reduced-dose tacrolimus (goal trough 3 – 7 ng/mL), or sirolimus (goal trough 4 – 8 ng/mL). All patients received IL-2 RA induction as well as maintenance mycophenolate and corticosteroids. The primary end point was eGFR at 12 months, with rejection and patient or graft survival as secondary end points. Most of the participants were white, with 30% living-related transplants and an average cold ischemia time of 16 hours. Despite a goal of 3 – 7 ng/mL, the mean tacrolimus level throughout the study period was higher than 6 ng/mL. All end points favored the low-dosage tacrolimus arm, with that cohort having the highest eGFR at 12 months (65.4 vs. 56.7 – 59.4, p<0.001) and the lowest rate of BPAR (15.4 vs. 27.2 [low-CSA] vs. 30.1 [std-CSA] vs. 40.2 [sirolimus], p<0.001). Conversely, the sirolimus arm had the worst outcomes of all arms, with the lowest eGFR, the highest rates of rejection, and the lowest allograft survival. Incidences of serious adverse events were higher in the sirolimus arm compared with the other arms (53.2 vs. 43.4 – 44.3, p<0.05) and more often led to study drug discontinuation (7.8 vs. 1.8 – 3.1%, p<0.001) (Ekberg 2007).

mTOR Inhibitors in Heart Transplant

More recently, Scandinavian Heart Transplant Everolimus de Novo Study with Early Calcineurin Inhibitor (CNI) Avoidance (SCHEDULE) investigators sought to determine the effects of everolimus initiation with early CNI withdrawal in 110 de novo heart transplant recipients in a randomized, open-label study with 36 months of follow-up. It is notable that study enrollment occurred at five heart transplant centers in Scandinavia.

Table 6. SCHEDULE Treatment Arms

	Arm 1	Arm 2
Induction	Antithymocyte globulin	
Calcineurin inhibitor	Cyclosporine goal 75 – 175 ng/mL for 7 weeks, then discontinued	Cyclosporine goal 75 – 175 ng/ml
mTOR inhibitor	Everolimus goal 3 – 6 ng/mL for 7 weeks and then Everolimus goal 6 – 10 ng/mL thereafter	None
Antimetabolite	Mycophenolate at 1500 – 2000 mg/day	
Corticosteroid	Prednisone per center protocol	

Information from Andreassen AK, Andersson B, Gustafsson F, et al. Everolimus initiation with early calcineurin inhibitor withdrawal in de novo heart transplant recipients: three-year results from the randomized SCHEDULE study. Am J Transplant 2016;16:1238-47.

The study protocol is summarized in Table 6. SCHEDULE's primary end points were renal function and progression to cardiac allograft vasculopathy (CAV) as measured by intravascular ultrasound.

Median BMI was 25, and 98% were white, with only 22% of heart transplant recipients with prior left ventricular assist device implant. Rates of pretransplant diabetes and hypertension were low (19% and 4%, respectively). In the intention-to-treat population, eGFR at 36 months was significantly higher in the everolimus arm compared with cyclosporine (77.4 mL/min vs. 59.2 mL/min, p<0.0001). That difference persisted in the per-protocol comparison as well. With respect to CAV, everolimus-treated patients had smaller increases in mean intimal thickness (0.10 mm vs. 0.15 mm, p=0.019). Both arms had progression in maximal intimal thickness, and no difference in percentage of patients with CAV diagnosis defined as a maximal intimal thickness greater than 0.5 mm was seen between the arms (43.2% [everolimus] vs. 53.8% [cyclosporine], p=0.104).

More biopsy-proven acute rejection grade 2R or higher was seen in the everolimus arm (39% vs. 14%, p=0.006), and all were treated successfully with corticosteroids. No significant differences in serious adverse events were noted in this small population (Andreassen 2016). Given the concerns about wound-healing complications, a post hoc analysis was conducted to assess wound healing and surgical events. No differences were noted in this relatively healthy population at low risk of wound-healing complications (low BMI, low diabetes rate, low prior eft ventricular assist device rate) (Rashidi 2016).

01_1_Doligalski.indd 16 02/05/19 5:54 pm

mTOR Inhibitors in Liver Transplant

The H2304 Study Group assessed the efficacy of everolimus initiation in the early posttransplant period to spare long-term renal dysfunction in 719 liver transplant recipients. Despite a focus on renal outcomes, the primary end point of the study was a composite of treated BPAR, graft loss, or death. The eGFR assessment between groups was an a priori secondary end point. Patients were randomized at postoperative day 30 to one of three arms: everolimus and reduced-exposure tacrolimus, everolimus with tacrolimus elimination, or standard tacrolimus. Induction immunosuppression and mycophenolate use prior to day 30 were administered per center-specific protocol. Corticosteroids were continued after day 30 (enrollment/randomization) per center-specific protocol but were required to be continued until at least 6 months posttransplant.

Liver transplant recipients with poor graft function, those with rejection in the first month, those with eGFR of less than 30 mL/min/1.73m^2, and those with a proteinuria greater than 1 g/24h were excluded from study. Of the 1147 patients who entered the run-in period, 428 were either excluded (n=99), or they discontinued from the study (n=329) before day 30 and randomization. The tacrolimus elimination arm was discontinued following a safety review that found an increased incidence of BPAR. No difference in the primary end point was seen out to 3 years of follow-up between the everolimus/reduced-tacrolimus arms and the tacrolimus arms (11.5% vs. 14.6%, p=0.334). Mean eGFR by modification-of-diet-in-renal-disease assessment was significantly higher at 36 months in the everolimus/reduced-tacrolimus arm compared with standard tacrolimus (78.7 vs. 63.5 mL/min/1.73 m^2, p<0.001). That difference was present in the intention-to-treat and per-protocol comparison (Fischer 2015).

Of particular interest is the antitumor effects of mTOR inhibitors for hepatocellular carcinoma (HCC) liver transplant recipients because everolimus has a labeled indication for the treatment of renal cell carcinoma. A prospective, open-label, randomized trial was conducted in 525 liver transplant recipients with prior HCC who were randomized between postoperative weeks 4 – 6 to either addition of sirolimus to tacrolimus-based therapy or continuation of standard tacrolimus immunosuppression. The primary end point was HCC recurrence-free survival at 8 years. No difference in recurrence-free survival was seen between the two groups (64.5% vs. 70.2%, p=0.28) at 8 years, although a statistically significant benefit in the sirolimus arm was seen at years 3 and 4 (74.7% vs. 87.7%, p=0.01, and 73.3% vs. 84.9%, p=0.02, respectively) (Geissler 2016).

mTOR Inhibitors as Antivirals

The antiviral properties of have been well summarized (Bowman 2017). The most-compelling antiviral effects of the clinical use of mTOR inhibitors in solid organ transplant are related to anticytomegalovirus (anti-CMV) properties. In 2015, Tedesco-Silva and colleagues assessed the utility of mTOR-containing regimens in the development of CMV in 288 de novo renal transplant recipients not treated with any anti-CMV prophylaxis (preemptive anti-CMV strategy). Rates of CMV development at 1 year following transplant were significantly lower in everolimus-treated recipients receiving either basiliximab or antithymocyte globulin induction in combination with low-dosage tacrolimus and prednisone compared with a standard regimen of basiliximab induction followed by a triple-maintenance regimen of tacrolimus, mycophenolate, and prednisone (4.7% [rATG/EVR] vs. 10.8% [BAS/EVR] vs. 37.6% [control]). No differences in incidences of acute rejection, wound-healing complications, or proteinuria were seen between the three groups, although the basiliximab-induced everolimus population had lower eGFRs at 12 months compared with the control arm (60.6 vs. 69.5 mL/min/1.73m^2, p=0.021). The clinical value of the findings is significantly limited by the widespread availability of adequate anti-CMV prophylaxis (Tedesco-Silva 2015).

REJECTION

Acute rejection can be mediated by T cells, B cells, or both. Acute cellular rejection is rejection mediated by T cells and is the classical rejection understood since the inception of solid organ transplantation. The understanding of treatment of acute cellular rejection has not changed significantly in the past 20 years with the availability of increased maintenance immunosuppression, oral or intravenous corticosteroids, and lymphocyte-depleting therapies such as antithymocyte globulin or alemtuzumab, which are treatment modalities. More immunosuppressive agents such as lymphocyte-depleting therapies are reserved for either steroid-resistant or high-grade rejection in all solid organ transplants.

With the 1997 publication of the Banff classification of kidney transplant rejection, acute antibody-mediated rejection, also known as humoral rejection, was first defined as a unique pathophysiological event separate from T-cell-mediated rejection. Since then, all solid organ groups have published similar consensus statements on the diagnostic criteria for antibody-mediated rejection (Berry 2013, Demetris 2016, Levine 2016, Haas 2018).

Antibody-Mediated Rejection Pathophysiology and Diagnosis

Globally, antibody-mediated rejection occurs when B cells are activated to plasma cells, producing antibodies directed against antigens expressed by the donor organ and that are capable of fixing complement and causing cell lysis. Two criteria are necessary for the diagnosis of acute antibody-mediated rejection: histologic evidence of acute injury in the transplanted organ and either evidence of circulating donor-specific antibodies (DSAs) or biopsy-proven evidence of antibody-vascular-endothelium interactions—most

01_1_Doligalski.indd 17 02/05/19 5:54 pm

commonly seen as complement-split product (C4d) deposition. Antibody-mediated rejection affects primarily the graft macro- and microvasculature. Unlike T-cell-mediated rejection, microvascular damage typically occurs gradually—without acute dysfunction within the transplanted organ—although the spectrum of disease severity is variable. Although noninvasive diagnostic modalities are under investigation and the widespread availability of single-antigen bead assays enable detection and semiquantification of donor-specific antibodies, allograft biopsy is required for definitive diagnosis of antibody-mediated rejection (Loupy 2018).

Antibody-Mediated-Rejection Therapies

The available evidence to guide pharmacotherapy for antibody-mediated rejection (AMR) is lacking. All of the currently available therapy targets either (1) the removal of circulating antibodies, (2) the reduction of active B cells and plasma cells, or (3) complement activation. Plasmapheresis and intravenous immune globulins (IVIGs) were the mainstays of therapy until recently. With the introduction of anti-CD20 antibodies, proteasome inhibitors, and complement inhibitors, the therapeutic options have expanded, although their clinical use has been limited to single-center retrospective case series and reports.

Plasmapheresis/Plasma Exchange and Intravenous Immune Globulins

Plasmapheresis and intravenous immune globulins are the traditional therapies used for the treatment of AMR. A recent survey found that most transplant centers use plasmapheresis (25/28, 89.2%) and IVIG (24/28, 85.7%) as first-line therapy for AMR (Burton 2015). Plasmapheresis is a procedure that requires a large-bore intravenous catheter from which blood volume is removed and separated into red blood cells and plasma—with the return of only red blood cells to the recipient. The plasma is then replaced with colloid: either fresh-frozen plasma or albumin. Typically, three to eight sessions are performed either daily or every other day. The physical removal of circulating antibodies also removes specific drugs, increases the risk of infection, and is a resource-intensive therapy. With the physical removal of circulating antibodies, concern about antibody rebound arises, usually necessitating the use of plasmapheresis in combination with immune globulins.

The IVIGs have a labeled indication for immune deficiencies but offer a variety of other immune-mediated benefits in solid organ transplantation. At high dosages (1–2 g/kg), IVIG is proposed to have benefits in the treatment of AMR, including regulation of B-cell populations, induction of B-cell apoptosis, inhibition of dendritic cell and macrophage function, inhibition of complement-mediated inflammation, increased anti-inflammatory cytokine production, and neutralization of anti-HLA antibodies (Jordan 2009).

Many AMR treatment protocols hold several sessions of plasmapheresis followed by low-dosage IVIG to prevent antibody rebound each day, with high dosages of IVIG administered at the completion of plasmapheresis therapy. Complications of IVIG therapy include renal dysfunction and fluid overload—especially with higher dosages, high-sucrose-content products, and high-osmolar products. Products with low osmolarity and low sucrose content have higher titers of anti-isohemagglutinins; such products have been associated with increased risk of hemolysis in patients with A, B, or AB blood types receiving high dosages or prolonged courses of therapy (Jordan 2011). Limited data demonstrate improvements in short-term outcomes, including stabilization of renal function in renal transplant recipients or clearance of circulating antibodies. Long-term data do not exist (Montgomery 2000, Rocha 2003). No head-to-head comparisons of the clinical benefits of various plasmapheresis/IVIG schedules exist, and therefore practice varies between transplant centers.

Anti-CD20 Antibodies

Many B cells—including pre-B, immature B, mature B, active B, and memory B cells—express the cluster-of-differentiation 20 (CD20) on their cell surfaces. That CD20 expression is lost when activated B cells become plasma cells. The use of the anti-CD20 monoclonal antibody, rituximab, in AMR therapy has been described in a recent survey, with 8 of 28 (28.6%) transplant centers reporting use of rituximab in the routine treatment of AMR (Burton 2015).

Rituximab use is associated with infusion reactions, including hypotension. The reporting of adverse effects specifically in transplant evaluations appears to show limited toxicities. In 2009, Lefaucheur and colleagues reported on a retrospective cohort of 24 renal transplant recipients, 12 of whom had received high-dose IVIG (2 g/kg every 3 weeks $\times$ 2) and 12 of whom had received four sessions of plasmapheresis, IVIG (100 mg/kg after each plasmapheresis followed by 2 g/kg every 3 weeks $\times$ 2), and rituximab at 375 mg/m^2 $\times$ 2 doses, 2 weeks apart. All patients also received for three intravenous doses of methylprednisolone 500 mg. Graft survival at three years following AMR treatment was significantly higher in the plasmapheresis/IVIG/rituximab cohort compared with IVIG alone (91.7% vs. 50%, p=0.02). Patients receiving plasmapheresis/IVIG/rituximab also had more-significant decreases in the intensity of donor-specific antibody levels at 3 months posttreatment. Among those not on dialysis, there was no difference in eGFR at 3 years (44.7 vs. 43.3 mL/min/1.73m^2, p=NS) (Lefaucheur 2009).

Given that the 2009 study compared one therapy (IVIG) with three therapies (plasmapheresis/IVIG/rituximab), the Effects of Rituximab on Acute Antibody-Mediated Rejection in Renal Transplantation (RITUX ERAH) study sought to determine the effect of the addition of rituximab to plasmapheresis and IVIG in a prospective, randomized fashion among renal transplant recipients with biopsy-proven AMR at 21 transplant centers in France. Only recipients with AMR diagnosed within the first transplant year were included.

01_1_Doligalski.indd 18 02/05/19 5:54 pm

All patients received three doses of methylprednisolone 500 mg IV followed by an oral taper starting at 1 mg/kg; plasmapheresis was performed a total of six times, with 100 mg/kg IVIG administered daily after each session followed by 1 g/kg daily for 2 days upon completion of plasmapheresis. Those randomized to rituximab received 375 mg/m^2 $\times$ 1 dose halfway through plasmapheresis therapy. The primary end point was graft loss or failure of renal recovery at day 12. The secondary end points were 1-year posttreatment graft and patient survival, eGFR, safety, and intensity of donor-specific antibodies. Forty patients were randomized, and 38 were included in the modified intention-to-treat analysis. The a priori power calculations determined a sample size of 64 was needed to detect a difference in the primary end point. No graft losses occurred at day 12. Lack of improvement in renal function occurred in 52.6% of the rituximab arm and 57.9% of the placebo arm (p=NS). No difference in patient and graft survival at 12 months was detected, Both groups demonstrated a reduction in DSA intensity, and both showed histologic improvement in damage at 1 month and 6 months following treatment biopsies. Lack of adequate power and a short follow-up for the primary end point likely limit the applicability of those results to general practice (Sautenet 2016).

Proteasome Inhibition

Bortezomib and carfilzomib are potent inhibitors of active plasma cells by inhibition of the intracellular proteasome critical for protein degradation. The inhibition of proteasome functionality leads to rapid cell death. Carfilzomib irreversibly binds to the proteolytic core of the 26s proteasome; bortezomib is a reversible inhibitor. The irreversible inhibition of carfilzomib means that the timing of doses around concurrent plasmapheresis and IVIG is less critical than with bortezomib therapy, because bortezomib is readily removed by plasmapheresis even 48 hours following administration.

Given that the progression of active B cells to plasma cells is not affected by previously discussed therapies, the use of proteasome inhibitors to abrogate the humoral response has been proposed. Administered as either subcutaneous or intravenous doses, bortezomib and carfilzomib are associated with dose-limiting pancytopenias, hepatotoxicity, and peripheral neuropathy. Renal dysfunction, too, has been reported with carfilzomib, as have case reports of carfilzomib-induced cardiac toxicity, thereby limiting the potential use of carfilzomib in patients with renal or cardiac transplants.

Several small, observational studies have suggested a benefit to bortezomib therapy in renal transplant recipients. Bortezomib in Late Antibody-Mediated Kidney Transplant Rejection Trial investigators investigated the effect of bortezomib to slow the progression of chronic AMR in 44 renal transplant recipients in a randomized, prospective study. Bortezomib was given intravenously at 1.3 mg/m^2 as two cycles consisting of four doses each on days 1, 4, 8, and 11. Among those randomized to bortezomib (n=21), no difference was seen in eGFR or graft survival at 2 years (33 vs. 42 ml/min per 1.73 m^2; p=0.31; 81% vs. 96%; p=0.12). Bortezomib was associated with thrombocytopenia and gastrointestinal upset (Eskandary 2018).

The outcomes of 14 lung transplant recipients with AMR treated with a combination of plasmapheresis, IVIG, and carfilzomib were recently described; no comparator group was studied; and the presence of circulating DSAs capable of complement fixation at days 16 and 42 was the primary end point. Secondary end points included DSA intensity, pulmonary function testing, chronic lung allograft dysfunction (CLAD) progression, and death following AMR therapy. Patients received eight sessions of plasmapheresis, nine doses of IVIG at doses of either 100 mg/kg or 500 mg/kg, and six doses of carfilzomib 20 mg/m^2 on days 1, 2, 8, 9, 15, and 16. At days 16 and 42, only 4 of 14 treated patients (28.5%) continued to have complement-fixing circulating antibodies. Intensity of circulating antibodies decreased, and pulmonary function returned to pre-AMR levels following therapy in those who responded. Those with responses to therapy had less CLAD compared with those who did not respond (25% vs. 83%, p=0.04). Two of the 14 carfilzomib-treated patients (14.3%) required dose reductions or delays in therapy because of adverse events, with six (44%) developing transient thrombocytopenia and two (14%) becoming cases of severe acute kidney injury, with one (7%) progressing to ESRD requiring dialysis (Ensor 2017).

Complement Inhibition

The final step in antibody-mediated cell damage occurs via antibody-mediated complement activation. Therefore, the use of complement inhibitors to reverse antibody-mediated rejection is an attractive option. Two of the main pathways of the complement activation system have therapeutic targets: the C1 esterase inhibitor and the C5 inhibitor eculizumab. The C1 esterase is critical for initiation of the classical antibody activation pathway, and C5 is the rate-limiting step of all complement activation from the classical, alternative, and mannose-binding-lectin pathways.

A phase 2b prospective, double-blind, placebo-controlled, randomized study evaluated the use of C1 esterase inhibitor in addition to center-specific standard of care, including plasmapheresis, IVIG, and/or anti-CD20 mAb for the treatment of acute AMR in a group of 18 high-immunologic-risk (44% with both ABO- and human-leukocyte-antigen(HLA)-incompatible) renal transplant recipients. Within 72 hours of diagnosis of AMR, patients were randomized to 5000 units of C1 esterase inhibitor followed by 2500 units of C1 esterase inhibitor every other day for six doses or placebo. At posttreatment day 20 biopsy, there was no difference in resolution of AMR between C1-esterase-inhibitor- and placebo-treated patients. Similarly, no difference in graft function at posttreatment day 20 or 90 was observed. Given that 14 of the 18 patients were from a single center, a post hoc analysis of those patients and

01_1_Doligalski.indd 19 02/05/19 5:54 pm

their protocol 6-month biopsies was performed. None of the C1-esterase-inhibitor-treated patients had evidence of transplant glomerulopathy. Three of the seven placebo-treated patients had evidence of glomerulopathy. Only one adverse event of blurred vision was attributed to C1 esterase inhibitor therapy (Montgomery 2016).

The clinical utility of eculizumab for treatment of AMR has been examined largely in a high-immunologic-risk renal transplant population as prophylaxis for the development of AMR (Cornell 2015, Jordan 2016, West-Thielke 2018) or in case reports on refractory treatment-resistant AMR. In those reports, eculizumab at doses of 600 mg – 1200 mg was administered every week to every 2 weeks. Prospective data on the efficacy of eculizumab for treatment of AMR are not available.

The cost of eculizumab therapy combined with the risks of infectious complications specifically from encapsulated organisms limits widespread use of eculizumab in the treatment of AMR. When used for its labeled indications for atypical hemolytic uremic syndrome, myasthenia gravis, or paroxysmal nocturnal hemoglobinuria, meningococcal immunization 2 weeks prior to initiation of eculizumab therapy is required. Because a 2-week delay in the treatment of an acute AMR is not possible, the package insert suggests vaccinations followed by prophylactic antibiotics to avoid life-threatening meningococcal infections.

CHRONIC ALLOGRAFT INJURY

Chronic Allograft Injury Pathophysiology and Risk Factors

Chronic allograft injury is a multifactorial process that has both immunologic and nonimmunologic mediators. Immunologic mediators include incidence and severity of acute cellular rejection and the development of DSAs and antibody-mediated rejection. Tacrolimus-based immunosuppression has been associated with decreased chronic rejection in renal transplant recipients. A history of acute rejection and even subclinical acute rejection are associated with increased development of chronic rejection (Haas 2018), thereby highlighting the importance of appropriate maintenance immunosuppression in the prevention of chronic rejection. Nonimmunologic mediators include CMV disease, ischemia-reperfusion injury, and metabolic abnormalities such as hypertension, hyperlipidemia, and hyperglycemia.

The presentation of chronic allograft injury differs from organ to organ but is an irreversible process leading to graft dysfunction. In renal transplant recipients, chronic allograft injury appears histologically as interstitial fibrosis and tubular atrophy. In cardiac transplant recipients, an overproliferation of the cardiac allograft vasculature leads to narrowing of cardiac vessels, or CAV. In liver transplantation, chronic injury presents as cholestatic dysfunction with ductopenia and loss of arterioles. The understanding of chronic injury in lung transplantation has evolved during the past decade, with an expansion from merely bronchiolitis obliterans syndrome to a global definition of CLAD that consists of both BOS and restrictive allograft syndrome (Verleden 2014). In addition to the immunologic risk factors, community-acquired respiratory viral infections have also been associated with CLAD development (Magnusson 2018), as has exposure of lung tissue to stomach acid through gastroesophageal reflux disease (Tangaroonsanti 2017).

Nonimmunosuppression Therapy for Chronic Allograft Injury

Given the limited availability for treatment of chronic rejection and the irreversible nature of chronic allograft injury, much of the pharmacotherapeutic approach is focused on prevention strategies. In addition to modification of immunologic and viral risk factors, several non-immunosuppressive pharmacological therapies have shown promise for prevention of chronic rejection and prolonged graft survival.

Statins

The pleiotropic effects of statins have been thoroughly described (Liao 2005). In chronic rejection of heart allografts, an overproliferation and inflammation of coronary arteries leads to decreased cardiac myocyte perfusion and exertional symptoms in severe cases. In addition to their lipid lowering effects, statins may improve endothelial function via enhanced endothelial nitric oxide activity, decreased smooth muscle cell proliferation and decrease inflammation through inhibition of adhesion molecules responsible for recruitment of inflammatory cells (Niwa 1996).

In 1995, 12-month outcomes of 97 heart transplant recipients randomized to receive either placebo or pravastatin 40 mg daily were reported. In this short follow-up period, those patients treated with a statin had a significantly higher survival (94% vs. 78%, p=0.025), lower CAV (6.8% vs. 20%, p=0.049), and smaller maximal intimal thickness (0.11 mm vs. 0.23 mm, p=0.002) (Kobashigawa 1995). Ultimately 81% of the control group started on a statin within the 10-year follow up. Despite this, intention to treat analysis demonstrated a continued survival benefit for the pravastatin arm (68% vs. 48%, p=0.026) despite similar cholesterol levels. Ten-year freedom from CAV and death was also higher in the pravastatin intention-to-treat cohort (43% vs. 20%, p=0.009) (Kobashigawa 2005). Based on these data, the ISHLT 2009 guidelines recommend statin therapy for all adult heart transplant recipient's regardless of cholesterol level as a Class 1, Level of Evidence A recommendation.

To determine if choice of statin affected outcomes simvastatin 10 mg daily was compared with pravastatin 20 mg daily in 50 heart transplant recipients. At one year, no difference in mortality or CAV was found, although simvastatin was associated with lower LDL cholesterol levels (–23% vs. –11%, p=0.02). No adverse events were noted in either group, and

01_1_Doligalski.indd 20 02/05/19 5:54 pm

survival compared with a control group not receiving a statin was significantly higher with both therapies (92% vs. 91% vs. 80%, p=0.04) (Mehra 2002).

Azithromycin

Similarly to statins, erythromycin and azithromycin have anti-inflammatory effects specific to the bronchial epithelial cells, in which macrolides decrease the cytokine-induced endothelin-1 expression (Wales 1999). Azithromycin has found routine clinical use in those with cystic fibrosis and bronchiectasis.

The first report of azithromycin use in lung transplantation was in 2005, when the slowing of progression in 11 lung transplant recipients with established BOS with an FEV1 of 40% of predicted at baseline, and no change at 10 months following initiation of azithromycin (Shitrit 2005). In 2010, a retrospective analysis was conducted of 178 lung transplant recipients who developed BOS. Azithromycin was started at 250 mg daily for 5 days, followed by either 250 mg three times a week for those with total body weight less than 70 kg or 500 mg three times a week for over 70 kg. Azithromycin use was significant in both the univariate and multivariate analysis with improved survival when started during BOS stage 1 before progression to stage 2 (Jain 2010).

To evaluate the effectiveness of azithromycin for the prevention of CLAD, not just for the slowing of progression once BOS/CLAD developed, 83 lung transplant recipients were randomized to either azithromycin 250 mg daily or placebo with 7 years of follow-up. At 7 years, CLAD-free survival was significantly higher in the azithromycin treated patients compared with placebo (72% vs. 49%, p=0.043). There was no difference seen in the proportion of patients with restrictive allograft syndrome or BOS-type CLAD. Even though no difference in graft loss was observed (53% vs. 40%, p=0.27), those taking azithromycin had significantly better lung function as determined by FEV1 (Ruttens 2016).

Unless contraindications dictate or significant adverse events arise, routine azithromycin use should be considered in all lung transplant recipients as both prophylaxis for and treatment of CLAD in lung transplant recipients. Only limited data exist to guide recommendations with regard to the risks of azithromycin therapy (e.g., QTc prolongation).

Practice Points

Solid organ transplantation is an increasingly complex, chronic disease state requiring a careful balance of pharmacotherapy to prevent both rejection and immunosuppression-associated toxicities.

- **Changes to organ allocation meant to reduce wait-list mortality and improve posttransplant survival have changed the patient population receiving solid organ transplantation and the posttransplant care needed.**
- **Induction immunosuppression with lymphocyte-depleting therapy can be used to delay introduction of nephrotoxic or metabolically toxic maintenance drugs.**
- **Novel maintenance immunosuppression regimens with belatacept- or mTOR-inhibitor-based therapies are associated with improved renal function at the cost of increased rates of acute rejection—especially in the first year following the transplant.**
- **Extended-release tacrolimus formulations have alternative pharmacokinetic properties that may be beneficial in adverse-effect management.**
- **Antibody-induced graft injury is an evolving clinical concern that leaves limited pharmacotherapeutic options.**
- **Chronic allograft injury is a multifactorial process with both immunologic and nonimmunologic mediators; nonimmunosuppressive therapies such as statins and azithromycin have value in the prevention of chronic injury in heart and lung transplant recipients.**

CONCLUSION

Solid organ transplantation is a lifesaving procedure for many patients with irreversible end-stage disease. Adequate immunosuppression is critical to patient and graft outcomes, with induction, maintenance, and rejection therapy key to positive outcomes. Advances in pharmacotherapy have led to longer graft survival, but more research is needed to clearly define the roles of emerging therapies and to minimize the toxicities associated with both standard and novel immunosuppression.

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01_1_Doligalski.indd 22 02/05/19 5:54 pm

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01_1_Doligalski.indd 23 02/05/19 5:54 pm

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01_1_Doligalski.indd 24 02/05/19 5:54 pm

Self-Assessment Questions

1. The following patients present for an initial transplant evaluation. For which one will the wait time for transplantation be most dependent upon the therapies provided for their disease?
   A. A 68-year-old woman with end stage renal disease due to diabetes with an estimated GFR less than 20 mL/min
   B. A 66-year-old man with interstitial pulmonary fibrosis on 2L of oxygen
   C. A 52-year-old man with alcoholic cirrhosis
   D. A 58-year-old woman with NYHA class IV heart failure secondary to ischemic cardiomyopathy
2. Given the changes in organ allocation policies, which one of the following studies is still most applicable to current day practice?
   A. A 2005 study the effect of antibody desensitization on time to transplant in highly sensitized kidney transplant recipients
   B. A 2011 evaluation of a process improvement project meant to reduce length of stay in liver transplant recipients
   C. A 2015 study comparing corticosteroid dosing in heart transplant recipients
   D. A 2003 evaluation of COPD therapies on wait list mortality in lung transplant candidates

Questions 3–4 pertain to the following case.

A.B. is a 29-year-old African American woman with a diagnosis of end stage renal disease secondary to lupus nephritis. Her medical history is significant for a previous transplant at age 17 from her brother, which failed 2 years ago secondary to nonadherence. A.B. is actively listed for a repeat transplant. Her surgical history is also significant for section four cesarian sections.

3. Given A.B.'s lupus nephritis, the nephrologist plans to continue maintenance corticosteroids in addition to tacrolimus and mycophenolate for maintenance immunosuppression. Which one of the following induction agents is best to recommend for A.B.?
   A. Methylprednisolone 1000 mg at time of anesthesia induction
   B. Basiliximab 20 mg IV on postoperative day 0 and 4
   C. Anti-thymocyte immune globulin 1.5 mg/kg daily for a total of 6 mg/kg
   D. Alemtuzumab 30 mg IV on postoperative day 0 and 2
4. Which one of the following maintenance immunosuppression regimens, in combination with prednisone, is best to recommend for A.B.?
   A. Cyclosporine and sirolimus
   B. Tacrolimus and azathioprine
   C. Sirolimus and mycophenolate
   D. Belatacept and sirolimus
5. A 68-year-old white man is awaiting kidney transplant secondary to hypertension and diabetes mellitus type 2. His medical history is significant for COPD requiring frequent antibiotic therapy for exacerbations and maintenance prednisone of 5 mg daily. He has no pre-existing antibodies. Which one of the following induction immunosuppression regimens is best to recommend for this patient?
   A. Alemtuzumab 15 mg IV at the time of anesthesia induction
   B. Basiliximab 20 mg IV on postoperative day 0 and 4
   C. Antithymocyte immune globulin 1.5 mg/kg daily for a total of 6 mg/kg
   D. Alemtuzumab 30 mg IV at the time of anesthesia induction

Questions 6 and 7 pertain to the following case.

B.A. is a 24-year-old white man with cystic fibrosis (CF)-associated lung disease. His medical history is significant for infections including *Pseudomonas aeruginosa*, *mycobacterium abscessus*, and *Aspergillus fumigatus.*

6. Which one of the following immunosuppression induction strategies is best to recommend for B.A.?
   A. Methylprednisolone 1000 mg at time of anesthesia induction
   B. Basiliximab 20 mg IV on POD 0 and 4
   C. Anti-thymocyte immune globulin 1.5 mg/kg daily for a total of 6 mg/kg
   D. Alemtuzumab 30 mg IV at the time of anesthesia induction
7. B.A. is transplanted and begins having significant tremor, limiting his ability to write and draw in his job as a political cartoonist. His current medications include tacrolimus 2 mg PO BID (last trough 10.5, goal 10-12 ng/mL), mycophenolate mofetil 1000 mg PO BID, and prednisone 20 mg daily. Which one of the following is best to recommend for B.A.?
   A. Decrease tacrolimus to 1 mg BID for a goal of 6-8ng/mL
   B. Decrease tacrolimus to 2 mg in AM and 1 mg in PM for a goal of 8-10ng/mL
   C. Change tacrolimus to ER-tacrolimus at a dose of 4.5 mg daily, goal 10-12ng/mL
   D. Change tacrolimus to LCP-tacrolimus at a dose of 3 mg daily, goal 10-12ng/mL

01_1_Doligalski.indd 25 02/05/19 5:54 pm

Questions 8-10 pertain to the following case.

L.H. is a 68-year-old African American woman (weight 90 kg) s/p left ventricular assist device removal and heart transplant 2 weeks ago due to ischemic cardiomyopathy. Her medical history is significant for left ventricular assist device pump thrombosis requiring replacement with three sternotomies to date, hypertension and diabetes. Her SCr is 2.1 mg/dl. All other laboratory data are normal. L.H. received corticosteroid only induction and is currently on tacrolimus 10 mg BID with a steady state trough level of 9.8, goal 10-12ng/mL and increasingly more frequent headaches.

8. Genetic typing confirms that L.H. has a CYP3A5*1 allele. Which of the following is best to recommend for L.H.?

   A. Change to tacrolimus 7 mg PO TID
   B. Change to LCP-tacrolimus 14 mg daily
   C. Change to LCP-tacrolimus 16 mg daily
   D. Change to LCP-tacrolimus 18 mg daily

9. L.H.'s primary cardiologist asks about the potential role for everolimus in preventing CAV. Which of the following is the most concerning issue for initiation of everolimus in L.H.?

   A. Wound healing complications
   B. Increased risk of rejection
   C. Increased risk of triglyceride-induced pancreatitis
   D. Development of proteinuria

10. L.H. would like to do everything she can to protect her new heart. Which one of the following is best to initiate to reduce her risk of developing CAV?

   A. Diltiazem 240mg daily
   B. Atorvastatin 20 mg daily
   C. Azithromycin 250 mg daily
   D. Aspirin 81 mg daily

11. A 36-year-old white woman (weight 70 kg) is awaiting kidney transplantation for polycystic kidney disease. She has no other significant medical history. The patient is Epstein–Barr virus IgG+, CMV IgG+, and has a PRA of 0%. She has a living donor in her sister, and surgery is scheduled for 2 weeks from today. She is interested in a maintenance immunosuppression regimen that will "make the most" of her sister's kidney. Which one of the following is best to recommend for this patient?

   A. Basiliximab induction, belatacept 700 mg on days 1, 5, week 2, 4, 8, and 12 then 350 mg every month thereafter, mycophenolate 1000 mg PO BID, and prednisone 5 mg daily
   B. Basiliximab induction, belatacept 700 mg on days 1, 5, week 2, 4, 6, 8, 10, 12, 16, 20, and 24; 350 mg every month thereafter, mycophenolate 1000 mg PO BID, and prednisone 5 mg daily
   C. Alemtuzumab induction, belatacept 700 mg on days 1, 5, week 2, 4, 8, and 12 then 350 mg every month thereafter, mycophenolate 1000 mg PO BID, one month of prednisone 5 mg daily then stop
   D. Anti-thymocyte immune globulin induction, tacrolimus (goal 8-10ng/mL), mycophenolate 1000 mg PO BID and prednisone 5 mg daily for 1 year; discontinuation of tacrolimus and initiation of belatacept 70 mg on days 1, 5, week 2, 4, 6, 8, 10, 12, 16, 20, and 24 weeks then 35 mg every month thereafter

12. In which one of the following patients would be most likely to benefit from an mTOR inhibitor?

   A. A 45-year-old man s/p kidney transplant who would like to start sirolimus in order to reduce the risk of renal toxicities from tacrolimus
   B. A 52-year-old woman s/p liver transplant for Hepatitis C/hepatocellular carcinoma (HCC) who is interested in starting everolimus to prevent the long-term recurrence of her HCC
   C. A 29-year-old man s/p lung transplant who is interested in starting sirolimus to prevent chronic rejection
   D. A 38-year-old woman s/p kidney transplant who can't tolerate valganciclovir and would like to start everolimus to reduce risk for CMV development

13. A 44-year-old Asian woman who is post–liver transplant (2 years ago) has persistent tremors on tacrolimus 4 mg BID (trough 6.2, goal 5–7 ng/mL) and mycophenolate 500 mg BID. The decision is made to convert her from tacrolimus to LCP-tacrolimus to attempt to help her tremors. The patient is prescribed LCP-tacrolimus 6 mg daily. Her first post-conversion level is 3.2ng/mL. She reports she's been taking one 5 mg and one 1 mg capsule each morning since starting. Which one of the following is the most likely cause of this patient's subtherapeutic level?

   A. She is likely a CYP3A5*1 expressor and needed a higher dose of LCP-tacrolimus.
   B. She was inadvertently dispended ER-tacrolimus instead of LCP-tacrolimus.
   C. She is a CYP3A5*1 non-expressor and needed a higher dose of LCP-tacrolimus.
   D. She was prescribed an inappropriate dose based on best available dosage conversion information and should have received 7 mg daily.

14. A 34-year-old woman has a medical history that includes kidney transplant (6 years ago). Her medical history is also significant for diabetes and diabetic neuropathy. The patient is blood group O. She presents with acute elevation in her SCr to 4.2 mg/dL (baseline 1.4 mg/dL)

01_1_Doligalski.indd 26 02/05/19 5:54 pm

and new donor-specific antibodies (DSAs) are now present. A biopsy is positive for antibody mediated rejection (AMR). Which of the following treatment strategies is best to recommend for this patient's AMR?

A. Plasmapheresis × 8 sessions plus bortezomib 1.2 mg/m^2 × 4
B. Plasmapheresis × 6 sessions, each followed by 100 mg/kg of intravenous immune globulin (IVIG) and 1g/kg at the completion of plasmapheresis
C. Plasmapheresis × 6 sessions, each followed by 100 mg/kg of IVIG and 1g/kg at the completion of plasmapheresis, rituximab 375 mg/m^2 × 1
D. Plasmapheresis x 8 sessions, each followed by 100 mg/kg of IVIG, carfilzomib 20 mg/m^2 × 6 doses

15. Which of the following patients would be most likely to benefit from azithromycin therapy?

A. A 58-year-old man on 15L of home oxygen with COPD awaiting lung transplantation
B. A 72-year-old woman s/p lung transplant 10 years ago with bronchiolitis obliterans syndrome (BOS) stage 3 on 6L of home oxygen
C. A 62-year-old man s/p lung transplant 5 weeks ago for hypersensitivity pneumonitis, at home completing pulmonary rehabilitation
D. A 23-year-old woman s/p lung transplant 2 days ago, currently on ECMO for primary graft dysfunction with shock liver

01_1_Doligalski.indd 27 02/05/19 5:54 pm

Learner Chapter Evaluation: Solid Organ Transplantation

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.
12. The activity met the stated learning objectives.
13. If any objectives were not met, please list them here.

OTHER COMMENTS

14. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
15. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

01_1_Doligalski.indd 28 02/05/19 5:54 pm