Therapeutic monitoring of immunosuppressive drugs

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Organ transplantation and immunosuppressive therapies

Successful replacement of damaged or failing tissues with donations from living or deceased donors is now performed routinely for a wide range of organs (Figure 1). However, the risk of allograft rejection caused by an immune response from the recipient makes transplantation one of the most challenging and complex areas of medicine. Historical reports of transplantation have existed for thousands of years, but the first successful transplant of a whole organ in modern times was achieved by J. Hartwell Harrison and Joseph Murray in the USA in 1954, when a 23-year-old man dying from advanced glomerulonephritis received a healthy kidney from his identical twin brother. Today, it is estimated that approximately 107,000 solid organ transplantations are performed annually, which represents no more than 10 % of the global need.[2]

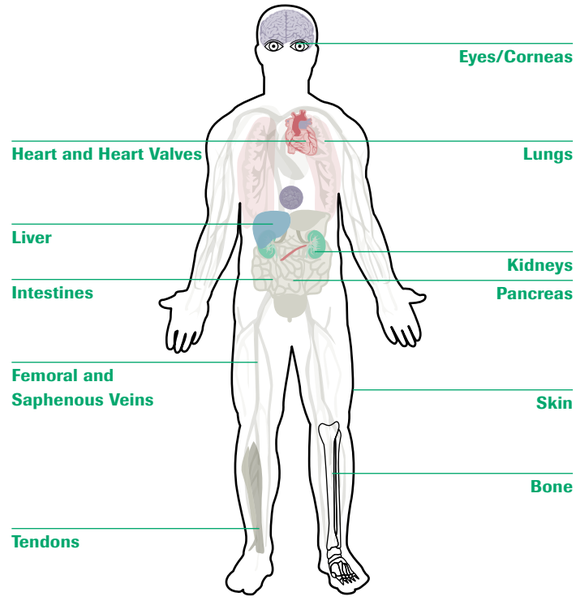

Figure 1: The most commonly transplanted tissues and organs

"Therapeutic monitoring of immunosuppressive drugs is currently an integral part of routine clinical practice for solid organ transplant patients."[1]

Immunosuppressive therapies

The development of potent immunosuppressive drugs (ISDs, summarized in Table 1) has greatly improved the short-term survival of transplant recipients during the last 20 years. Combinatorial drug regimens involving one or more ISDs are now often used to provide synergistic immunosuppressive effects while also minimizing toxicity through lower doses. In order to maintain a reasonable balance between efficacy and toxicity in each patient, clinicians and laboratory scientists endeavor to individually tailor therapy regimes (Table 2) within a framework of narrow and shifting therapeutic ranges, for which there is often a lack of robust clinical evidence.[3]

Drug class	Generic examples	Nature of compound
Calcineurin inhibitor	Cyclosporine Tacrolimus	Cyclic fungal peptide Macrolide antibiotic
Antiproliferative agent	Mycophenolate Azathioprine	Mycophenolic acid Purine analog
mTOR inhibitor	Sirolimus Everolimus	Macrolide antibiotic Macrolide antibiotic
Lymphocyte-depleting agent	Basiliximab Daclizumab Muromonab	Monoclonal antibody Monoclonal antibody Monoclonal antibody
Interleukin-2 receptor antagonist	Anti-thymocyte globulin	Polyclonal antibody
Corticosteroid	Prednisone	Steroid hormone

Table 1: The most commonly prescribed immunosuppressive drugs
Abbreviations: mTOR, mammalian target of rapamycin.

Therapy regimen	Phase of treatment	Common drug combination
Induction therapy	Given before, during, and immediately after transplantation	• Lymphocyte-depleting agent • Interleukin-2 receptor antagonist
Initial maintenance therapy	Given for up to several months after transplantation; drug doses are typically higher in order to minimize risk of acute rejection, which is greater during this period	• Corticosteroids • Calcineurin inhibitors • Antiproliferative agents • mTOR inhibitors
Core (long-term) maintenance therapy	Given lifelong after initial maintenance therapy; drug doses progressively minimized, substituted, or eliminated in order to minimize cumulative exposure and side effects	• Corticosteroids • Calcineurin inhibitors • Antiproliferative agents • mTOR inhibitors
Acute rejection therapy	Given for acute rejection events, which can occur any time after transplantation (greatest risk is within first few months following transplantation)	• Lymphocyte-depleting agent • Corticosteroids

Table 2: Immunosuppressive therapy regimens used in organ transplantation
Abbreviations: mTOR, mammalian target of rapamycin.

Individual patients require personalized immunosuppression

Cyclosporine, tacrolimus, mycophenolate, sirolimus, and everolimus are ISDs prescribed during maintenance therapy. They all display significant inter-patient (and occasionally intra-patient) pharmacokinetic variability, which can cause potentially severe side effects from doses that are either too high or too low. This makes them a logical choice for the application of therapeutic drug monitoring (TDM) and concentration-controlled dosing in order to maintain each patient's drug exposure within a 'therapeutic window'. Maintaining the concentration of a drug within a predefined therapeutic window for individual patients is complicated by many confounding variables:[3–11]

- Duration of use (cumulative exposure decreases risk of rejection but increases risk of toxicity)
- Liver and kidney function
- Delay in allograft function
- Pharmacogenomics of drug transport and metabolism
- Mismatches in donor and recipient ages, ethnicities, and human leukocyte antigen (HLA) types

Overview of monitored ISDs

Calcineurin inhibitors

Cyclosporine

The discovery of cyclosporine and its immunosuppressive activity represents one of the most significant breakthroughs in immunosuppressive therapy. It was first isolated from a soil-dwelling fungus, Tolypocladium inflatum, in 1972 and has since become a standard of care for maintenance immunosuppression in solid organ transplant recipients. The compound has very poor solubility in water and a modified microemulsion formulation has recently been developed in order to try and improve its bioavailability.

Side effects:

- Most significant and well recognized is nephrotoxicity, which can occur as both reversible acute manifestations and irreversible chronic manifestations[12,13]
  - All patients show histologic evidence of nephrotoxicity after 10 years and some will need renal replacement[12,13]
- Increased risk of hypertension, hyperlipidemia, hyperkalemia, metabolic acidosis, post-transplant diabetes mellitus, hirsutism, gingival hyperplasia, and symptoms of neurotoxicity ranging from tremors and headache to serious symptoms of agitation and confusion[14]

Tacrolimus

Tacrolimus is a macrolide antibiotic first identified as a product of the bacterium Streptomyces tsukubaensis in 1984 and subsequently found to possess potent immunosuppressive activity. Tacrolimus in vitro exhibits an immunosuppressive potency 50 – 100 times that of cyclosporine[15] and has been demonstrated to produce lower rates of acute rejection when used in the renal transplant setting.[16-27] Results from liver transplantation are less well reported, but most early studies report superiority of tacrolimus over cyclosporine.[28-31] A slow-release, once-daily formulation of tacrolimus has recently been developed and is approved in Europe, Canada, and Japan for use in both renal and hepatic transplantation.[3]

Side effects:

- Similar to cyclosporine but with lower incidence of hypertension and hyperlipidemia, but increased risk of diabetes mellitus[32]
- Gingival hyperplasia and hirsutism do not occur, but risk of alopecia instead
- Slight differences in side-effect profile may influence choice of calcineurin inhibitor depending on a patient's other clinical signs and symptoms

Antiproliferatives

Mycophenolate

Mycophenolate was isolated from Penicillium glaucum in 1896 and initial investigations revealed the compound possessed antineoplastic, antibacterial, antifungal, and antiviral activity. The immunosuppressive effect of mycophenolate was first described in 1969 and it has since become a component of the majority of maintenance regimens used following solid organ transplantation.[33] Mycophenolate has largely replaced azathioprine as the antiproliferative ISD of choice in solid organ transplantation. An alternative formulation, enteric-coated mycophenolate sodium, has been developed in an attempt to reduce gastrointestinal (GI) side effects of treatment.

Side effects:

- GI effects such as diarrhea, nausea, and abdominal pain
- Hematologic effects such as anemia, leukopenia, and thrombocytopenia
- Increased risk of first trimester miscarriage and congenital malformations; treatment of pregnant women avoided wherever possible[34]

Mammalian target of rapamycin (mTOR) inhibitors

Sirolimus

Sirolimus (originally, and occasionally still, referred to as 'rapamycin') is a macrolide antibiotic produced by the bacterium Streptomyces hygroscopicus and originally identified in soil samples taken from Easter Island in 1965. The drug was studied as a potential antifungal therapy from the mid-1970s to the early 1990s, but the discovery of the compound's immunosuppressive effect led to it being investigated in the transplantation setting. The drug has subsequently gained regulatory approval around the world for use in transplantation.

Side effects:

- About 30 – 50 % of patients discontinue therapy due to side effects[35]
- Common side effects include: hypertension, hyperlipidemia, anemia, thrombocytopenia, electrolyte disturbances (hypokalemia and hypophosphatemia), peripheral edema, abdominal pain, arthralgia, skin disorders, pyrexia, headache, nausea, diarrhea or constipation, and higher incidence of lymphoceles[36]
- High doses or drug levels can cause sirolimus-induced pneumonitis; fatalities have been reported in the cardiac transplantation setting[37]
- Capable of altering renal structure and function;[38] mTOR inhibitors worsen calcineurin inhibitor toxicity and delayed graft function is more frequent compared with other ISD classes[35]

Everolimus

Everolimus is a synthetic derivative of sirolimus designed for oral administration and generated by the introduction of a 2-hydroxyethyl group at position 40 of the sirolimus structure. Everolimus has been in clinical development since 1996 and displays superior pharmaceutical characteristics to sirolimus.[39] It is currently approved in Europe and the USA as an anti-rejection therapy for transplantation, as well as for treatment of malignant pancreatic neuroendocrine tumors and advanced renal cell carcinoma. Everolimus is also under investigation for its potential in other oncology settings, including cancers of the breast, stomach, and liver.

Side effects:

- Identical to sirolimus when used for immunosuppression

Mechanism of action

The various classes of ISD induce a state of immunosuppression by targeting different signaling pathways within lymphocytes (Table 3 and Figure 2).

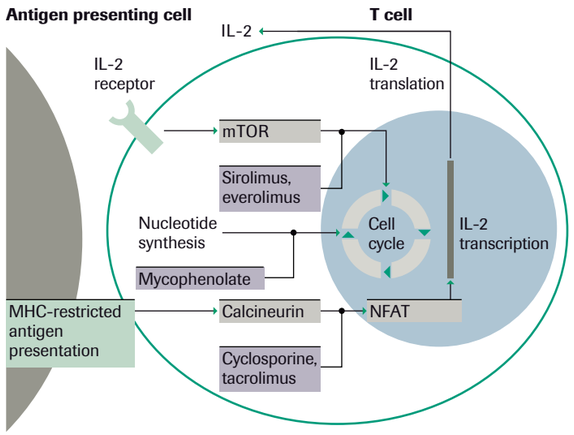

Figure 2: Intracellular pathways targeted by the three classes of monitored ISDs. The monitored ISDs used for maintenance of immunosuppression are grouped into three classes depending on which signaling pathway they affect: calcineurin inhibitors (cyclosporine, tacrolimus), antiproliferatives (mycophenolate), and mTOR inhibitors (sirolimus, everolimus). Abbreviations: IL-2, interleukin-2; MHC, major histocompatibility complex; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T cells.

Drug	Mechanism of action
Cyclosporine	• Inhibits the serine/threonine phosphatase calcineurin, which plays an important role in transcription of cytokines, e.g. IL-2, IL-4, TNF-α, and interferon-γ[40–42] • T cell activation and proliferation are inhibited; T cells especially sensitive due to low level of calcineurin expression[40–42]
Tacrolimus	• Essentially identical to cyclosporine but with some differences in intracellular binding partners
Mycophenolate	• Inhibits de novo synthesis of guanosine triphosphate (GTP) within cells[43] • Cell proliferation inhibited; lymphocytes especially sensitive due to inability to compensate for blockade of GTP synthesis via a salvage pathway[43]
Sirolimus	• Inhibits mTOR, a serine/threonine kinase downstream of the PI3K/Akt pathway that regulates several processes essential for cell metabolism, cell proliferation, and angiogenesis[39,44,45] • Cell cycle arrested during G1–S phase thus preventing clonal expansion of lymphocytes during immune reactions, including acute allograft rejections
Everolimus	• Identical to sirolimus

Table 3: Mechanism of action of the five monitored ISDs

Pharmacokinetics of ISDs

The measurement of drug concentrations in blood samples is sometimes described as 'pharmacokinetic drug monitoring' because it describes 'what the body does to the drug'. Pharmacokinetic TDM of ISDs relies on the assumption that an increase in dose will lead to a proportional increase in total drug exposure, as described by the full area under the curve (AUC) of a concentration-time graph. Data from ISD maintenance patients suggests this linearity does occur, although it may be less accurate in the early post-transplant period.[46–48] The need for multiple (8 –12), precisely-timed samples spread throughout the inter-dosing period makes direct measurement of AUC impractical both for patients and physicians. Therefore, single-point determinations or limited sampling strategies (LSSs) are routinely used for the estimation of AUC (Figure 3).

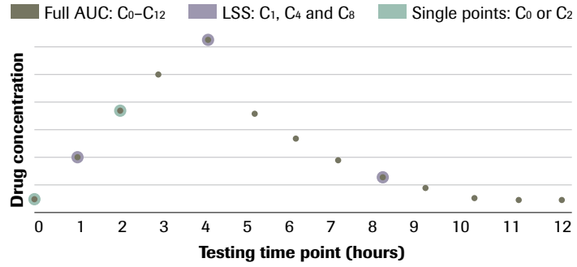

Figure 3: Comparison of sampling requirements for different drug-monitoring strategies. Measurement of a patient's total drug exposure after dosing requires regular samples taken throughout the inter-dosing period. In contrast, limited sampling and single-point strategies estimate AUC from measurements taken at either several or a single time point. Abbreviations: AUC, area under the curve; ISD, immunosuppressive drug; LSS, limited sampling strategy.

Full AUC

- Multiple samples taken regularly throughout the post-dose period
- Regarded as the gold standard for pharmacokinetic monitoring of drug levels

Limited sampling strategies

- Multiple regression analysis involves several measurements (usually two to four) taken within the first few hours after dosing and subsequent extrapolation based on an equation derived from a sample population
- Bayesian modeling collates a set of pharmacokinetic profiles in order to model population pharmacokinetic parameters; demographic information and clinical characteristics are included in order to enhance the model's predictive capability

Single-point determinations

- Often taken immediately prior to next dose and therefore reflect the trough concentration (C_0), but can also be taken at other pre-specified time points, e.g. 2 hours after dosing (C_2) for cyclosporine and 6 or 8 hours after dosing (C_6, C_8) for mycophenolate
- Rely on correlation between a drug's concentration at a specific time point and full AUC
- Commonly used in the majority of transplant centers

Each of the pharmacokinetic monitoring strategies provides distinct advantages and disadvantages to physicians and clinical scientists (Table 4). The five main ISDs display different pharmacokinetic profiles, which affects how each of them can be most effectively monitored (Table 5). An appropriate monitoring strategy needs to consider inter-patient variability in order to ensure therapy remains well tolerated and effective (Figure 4).

Pharmacokinetic monitoring strategy	Advantages	Disadvantages
Full AUC	• Most reliable measure of drug exposure • Best relationship to clinical outcomes	• Patient and healthcare staff must be available for taking of multiple samples throughout post-dose period
LSS – multiple regression analysis	• Greater precision than single-point determinations • Relatively easy to calculate using basic statistics programs	• Precise timekeeping needed for samples (errors in timing lead to errors in estimations) • Patients need to be available in the early post-dose period, usually for at least 2 hours • Extrapolations should only be made using data obtained from the same type of population (i.e. same allograft type, same ISD regimen, etc.)
LSS – Bayesian modeling	• Estimations can reflect age, race, sex, and clinical characteristics such as co-medications and renal function • Not dependent on precisely controlled sampling times	• Complex calculations require specialized statistics programs, knowledgeable operators, and lengthy data entry • Precision for each drug depends on availability and quality of population pharmacokinetic profiles
Single-point determination	• Simple and common procedure • Patients only need to be available at single time point, which can be immediately prior to next dose	• Correlation between measurements and AUC varies between ISDs • Measurements provide little information on pharmacokinetic characteristics of patients • Accurate timing relies on patient availability and recall of time of last dose

Table 4: Key features of different pharmacokinetic drug monitoring strategies[49-52]
Abbreviations: AUC, area under the curve; ISD, immunosuppressive drug; LSS, limited sampling strategy.

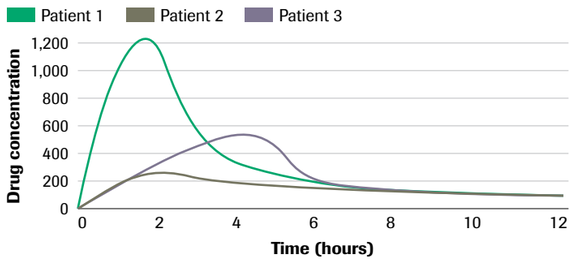

Figure 4: Pharmacokinetics of immunosuppressive drugs. Concentration-time profiles of immunosuppressive drugs display considerable inter-patient variability. Variation is likely due to pharmacogenomic differences in drug transport and metabolism, as well as variation in liver and kidney function. The three profiles represent patients with similar trough levels (C_0) but very different peak concentrations (C_{max}). Patient 1 would be at risk of toxic effects from the high doses necessary to prevent allograft rejection in Patient 2, whereas Patient 2 is at risk of allograft rejection from the low doses required by Patient 1. Measurements taken 2 hours after dosing could be used to accurately estimate C_{max} in Patients 1 and 2, but C_{max} in Patient 3 would be underestimated at this time point.

Drug	Pharmacokinetics
Cyclosporine	• Highly lipophilic with variable and incomplete absorption from GI tract[14] • Distributed largely outside the blood volume; distribution within blood is concentration-dependent: 41–58 % in erythrocytes, 33–47 % in plasma (90 % protein-bound), 5–12 % in granulocytes, and 4–9 % in lymphocytes[14] • No major metabolic pathway but predominantly influenced by cytochrome P450 isozymes CYP3A4 and CYP3A5, as well as the efflux pump p-glycoprotein[53] • Peak concentrations in plasma (C_{max}) occur approximately 3.5 hours after dosing; terminal half-life ($t_{1/2}$) is approximately 19 hours[14]
Tacrolimus	• Similar to cyclosporine, same metabolic and excretory pathways • C_{max} occurs approximately 1.5 hours after oral dosing; $t_{1/2}$ in renal transplant patients is approximately 9 hours[54]
Mycophenolate	• Absorption after oral administration is rapid and essentially complete[34] • Does not extensively distribute into the cellular fraction of blood; 97 % within plasma is bound to albumin[34] • Metabolized predominantly by uridine diphosphate-glucuronosyltransferase (UGT) isozymes within the liver, intestine, and kidneys[55] • Metabolites excreted via the kidney, but pharmacologically inactive major metabolite excreted into bile, subsequently deconjugated by colonic bacteria and reabsorbed as active mycophenolate[34] • C_{max} occurs 1–2 hours after dosing;[56] $t_{1/2}$ is approximately 18 hours[34] • Enterohepatic recirculation estimated to account for 10–60 % of total exposure, reflected by second peak in concentration-time curve 6–12 hours after dosing[57] • Absorption of enteric-coated form delayed until neutral pH of small intestine is reached and therefore C_{max} occurs 4 hours after administration; C_0 measurements (12-hour dosing) are 25 % higher compared with original formulation[58]
Sirolimus	• Systemic availability following administration is low[59] • Extensively distributed within the cellular component of blood; 92 % within plasma is bound to proteins (mainly albumin)[59] • Substrate for both CYP3A4 and p-glycoprotein; extensively metabolized in the liver and intestinal wall, as well as transported back into the gut lumen by enterocytes[35,60-62] • C_{max} occurs approximately 2 hours after administration; $t_{1/2}$ after multiple dosing in stable renal transplant patients estimated at 60 hours[59]
Everolimus	• Similar to sirolimus, same metabolic and excretory pathways • C_{max} reached 1–2 hours after oral administration; $t_{1/2}$ is 18–35 hours in renal transplant patients and 35–40 hours in liver transplant patients[63-67]

Table 5: Pharmacokinetic profiles of the five main ISDs

Therapeutic drug monitoring of ISDs

TDM is one method that has been used to address the issue of ISD toxicity (Table 6), although the evidence for any specific therapeutic window in each setting is often sparse. Indeed, there is a general need for the evaluation and comparison of differing TDM regimens in large, multicenter, randomized, prospective trials. A lack of evidence demonstrating a positive effect of TDM in terms of patient outcomes makes its use controversial for some ISDs, e.g. mycophenolate.

Drug	Therapeutic drug monitoring
Cyclosporine	• Standard clinical practice for many years[10] • Target C_0 usually 150 – 300 ng/mL during the first 3 months following transplantation, followed by 100 – 200 ng/mL thereafter[3,14] • Sub-optimal correlation between C_0 and AUC, correlation between AUC and C_2 much higher[68–71] • Many transplant centers rely on C_0 measurements – no published evidence that C_2-guided dosing improves clinical outcome[3,72]
Tacrolimus	• Strongly recommended but no consensus regarding target AUC[73] • Target C_0 usually 5 –10 ng/mL during first year of immunosuppression with a regimen of mycophenolate, corticosteroids, and induction therapy[73] • Most transplantation centers rely on C_0 measurements but correlation with AUC is controversial and generally higher during the first weeks or month following transplantation[73] • In contrast to cyclosporine, C_2 measurements correlate less well with AUC compared with C_0[73]
Mycophenolate	• Utility controversial, recent guidelines state insufficient evidence to recommend use in maintenance patients[49,50,74] • Guidelines recommend AUC between 30 – 60 µg.hr/mL when administered with cyclosporine following kidney or heart transplantation[6,75,76] • Target C_0 of 1.0 – 3.5 mg/L recommended when administered with cyclosporine, modified to 1.9 – 4.0 mg/L if used with tacrolimus[6,75–77] • Poor correlation between C_0 and AUC, especially in early post-transplantation period;[78] measurements taken 6 or 8 hours after dosing (C_6, C_8) consider enterohepatic recirculation and may be more precise[79–81] • Inverse correlation between exposure to cyclosporine and exposure to mycophenolate, possibly due to inhibition of biliary excretion[3]
Sirolimus	• C_0 monitoring recommended for all patients[35,60–62] • Target C_0 is 16 – 24 ng/mL for the first year following transplantation and 12 – 20 ng/mL thereafter when used in patients at low to moderate immunologic risk and as part of a regimen including cyclosporine withdrawal[35,60–62] • Cyclosporine inhibits metabolism and transport, and so its withdrawal may cause concentrations to decrease unless dosage is modified[35,60–62] • Patients with mild, moderate, or severe hepatic impairment have 43 %, 94 %, or 189 % higher mean values for AUC, respectively, compared with values from individuals with normal hepatic function; effect of renal impairment on pharmacokinetics not known[35,60–62]
Everolimus	• Recommended for all solid organ transplant recipients[82,83] • Target C_0 is 3 – 8 ng/mL;[82,83] 6 –10 ng/mL shown to be effective in calcineurin inhibitor withdrawal regimens[84,85] • Similar to sirolimus, blood concentrations may decrease if cyclosporine exposure is reduced[85] • Cyclosporine dose and target C_0 should be reduced when used in a regimen with everolimus in order to minimize risk of nephrotoxicity[85]

Table 6: Therapeutic drug monitoring of immunosuppressive drugs
Abbreviations: AUC, area under the curve; C_0/C_2/C_6/C_8, drug concentration before dosing (trough level), 2 hours, 6 hours, and 8 hours after dosing; C_{max}, peak serum concentration.

ISDs in organ-specific settings

Kidney transplantation

Current ISD regimens, which are usually based on the combined use of a calcineurin inhibitor and antiproliferative agent either with or without corticosteroids, provide 1-year graft survival rates above 90 % and 1-year patient survival rates above 95 %.[86-88] In the last 10 years there has been a change in preference favoring the use of tacrolimus over cyclosporine.[89] Indeed, 87 % of kidney recipients in the USA receive tacrolimus as their initial calcineurin inhibitor.[89] Clinical guidelines from an independent, international body (Kidney Disease: Improving Global Outcomes; KDIGO)[90] recommend tacrolimus as the first-line calcineurin inhibitor, and this was endorsed in a recent position statement published by the European Renal Best Practice (ERBP) Work Group on Kidney Transplantation.[91] This preference for tacrolimus was not supported in a recent commentary on the guidelines authored by Canadian authorities.[92] The KDIGO guidelines also recommend mycophenolate as first-line antiproliferative, recommend that TDM be performed for calcineurin inhibitors (C_0 levels for tacrolimus and either abbreviated AUC, C_0, or C_2 levels for cyclosporine), and suggest that mycophenolate monitoring should also be performed.[90] The Canadian authorities do not recommend the monitoring of mycophenolate.

Heart transplantation

It is estimated that more than 5,000 heart transplants are performed worldwide every year, with tacrolimus, mycophenolate, and prednisone being the predominant ISD choices.[93] A full set of clinical guidelines and corresponding levels of supporting evidence has been published by a task force established by the Registry of the International Society for Heart and Lung Transplantation (ISHLT).[83,94] Demographic data show that, compared with the average recipient of 10 years ago, the average heart transplant recipient of today is likely to exhibit a higher number of characteristics associated with a risk of morbidity and mortality following transplant. Despite this trend toward treating 'riskier' patients, median survival has steadily improved from 8.5 years during 1982 –1992 to 10.9 years during 1993 – 2002, and this has improved further since 2003.[93] The risk of mortality is highest in the first 6 months and the improvements in survival are largely due to improvements during this period. The long-term survival of those patients who survive to 1 year has not improved in the last 20 years and it is likely that approaches which improve survival during this longer term period will be needed in order to further improve overall median survival.[93]

Lung transplantation

Data evaluating immunosuppressive regimens in the pulmonary transplant setting are scarce and mostly from small, randomized studies or derived from single-center experience and empirical expert opinion.[95] No consensus exists on optimal or standardized ISD therapy and the drugs and methods used are those that have been adopted from other transplantation settings.[95] Maintenance immunosuppression is usually based on a combination of calcineurin inhibitor, antiproliferative, and corticosteroid.[95] The most recent data available (2002 – 2011) report that tacrolimus and mycophenolate were the most commonly used calcineurin inhibitor and antiproliferative, respectively.[96] Either of the mTOR inhibitors may also be introduced, usually as a substitute for one of the other drug classes.

Lung transplantation is an exceptional setting compared with other solid organs due to the pronounced immunogenicity of the pulmonary parenchyma, which leads to considerable side effects from the high load of ISDs required. The alveolar surface of the lungs comprises an air-blood diffusion barrier approximately 100 m^2 in area and represents the largest site of contact between an individual and the environment.[97] This continual exposure to risk is likely to explain why the rates of infection and rejection seen in lung transplant patients are double those observed in heart transplantation. For example, during the period 3 – 5 years after transplantation, infectious complications account for approximately 20 % of deaths in lung transplant patients compared with only 11 % of deaths in heart transplant patients, and chronic rejections account for 29 % of deaths in lung transplant patients compared with 10 % of heart transplant patients.[93,96] Following transplantation, the survival half-life of heart transplant patients is more than 10 years, whereas for lung transplant patients this figure is only 5.5 years.[93,96]

Liver transplantation

Liver transplantation has become an extremely successful treatment option for patients with end-stage liver disease and 1-year survival rates now exceed 80 %.[98] A further indication of the success of liver transplantation is the survival of some patients for more than 30 years following transplant.[99] Calcineurin inhibitors are currently the cornerstone of ISD therapy for liver transplantation and 95 % of patients receive them at time of discharge.[100] Cyclosporine-based triple therapy involving mycophenolate and corticosteroids was used until the late 1990s but tacrolimus has now largely replaced cyclosporine due to some evidence of superiority in preventing rejections.[28-31,101]

Nephrotoxicity is a known side effect of calcineurin inhibitor therapy and 20 % of liver transplant recipients experience chronic renal failure within 5 years.[3] Renal failure after liver transplant is associated with poor prognosis and a high mortality rate ranging between 44 – 50 %.[102,103] Limiting the risk of nephrotoxicity in liver transplant patients is therefore a high priority and major motivation for shifting patients to renal-sparing regimens involving dose reduction, delayed introduction, and even total avoidance of calcineurin inhibitors. Antiproliferatives (and potentially also the mTOR inhibitors) are frequently introduced, with 60 % of patients receiving mycophenolate (or less commonly azothioprine) at time of discharge.[103]

Future outlook

TDM must continually prove and improve its accuracy, efficacy, and clinical value when used as part of increasingly complex immunosuppressive regimens. Innovation within the TDM of ISDs is currently being driven by the two forces predominant within healthcare today: one motivated by the need for greater standardization of therapy across different centers and regions; and another driven by the need to provide therapy that is increasingly 'personalized'. To resolve any contradiction between these two forces, clinical guidelines are likely to become ever more detailed and provide recommendations for smaller, more defined patient populations. Hopefully, healthcare systems that allow such detailed guidelines to be delivered uniformly will be established in parallel thus ensuring that ISD therapy remains as effective and well tolerated as possible.

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