Opportunities in CNI management

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A GUIDANCE REPORT AND CLINICAL CHECKLIST BY THE CONSENSUS ON MANAGING MODIFIABLE RISK IN TRANSPLANTATION (COMMIT) GROUP

Short-term patient and graft outcomes continue to improve after kidney and liver transplantation, with 1-year survival rates over 80%

however, improving longer-term outcomes remains a challenge.

Improving the function of grafts and health of recipients would not only enhance quality and length of life, but would also reduce the need for retransplantation, and thus increase the number of organs available for transplant.

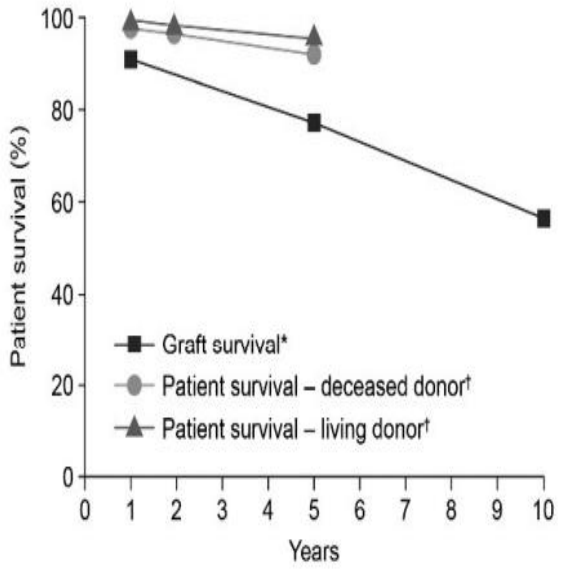
The clinical transplant community needs to identify and manage those patient modifiable factors, to decrease the risk of graft failure, and improve longer-term outcomes

- Most kidney transplant recipients (KTRs) currently receive CNI therapy, which has remarkably reduced acute rejection (AR) episodes and improved early graft survival

  However, long-term CNI exposure may induce irreversible nephrotoxicity, resulting in progressive graft dysfunction

  The CNI can also promote cardiovascular events and malignancies, which are the leading causes of premature death with a functioning graft

  This discrepancy has prompted investigations into CNI retention strategies, which maintain adequate immunosuppressive effects without compromising safety



Population	Period	% Adjusted survival rates (standard error (SE) or 95% confidence interval)			
		One year	Two years	Five years	Ten years
Grafts	2005–2008	90.6 (SE 0.4)	–	77.0 (SE 0.6)	56.5 (SE 0.8)
Patient – deceased donor	2004–2008	97.4 (97.2–97.6)	96.1 (95.9–96.4)	91.8 (91.4–92.2)	–
	2007–2011‡	97.6 (97.4–97.8)	96.4 (96.1–96.6)	–	–
Patient living donor	2004–2008	98.7 (98.4–99.0)	98.1 (97.7–98.4)	95.6 (95.0–96.1)	–
	2007–2011‡	99.1 (98.9–99.3)	98.4 (98.2–98.7)	–	–

FIGURE 1. 1- to 10-year graft and patient survival rates after kidney transplantation.*1-year and cumulative 5- and 10-year age-adjusted kidney graft survival rates calculated for 2005 to 2008 by period analysis; †Survival probabilities were adjusted for age, sex and cause of end-stage renal disease (data shown in figure for period 2004-2008); ‡Data from 2007 to 2011 period not shown in figure. Figure based on data from Gondos 2013 and Kramer 2016.[3,5]

TABLE 1.

Major modifiable risk factors for graft loss

Nonadherence

Intrapatient variability in immunosuppressive exposure

Underimmunosuppression/overminimization of immunosuppression

Adverse effects related to immunosuppression

DSAs

Early ischemic injury and DGF (kidney)/EAD and nonanastomotic biliary strictures (liver)

Cardiovascular and metabolic complications

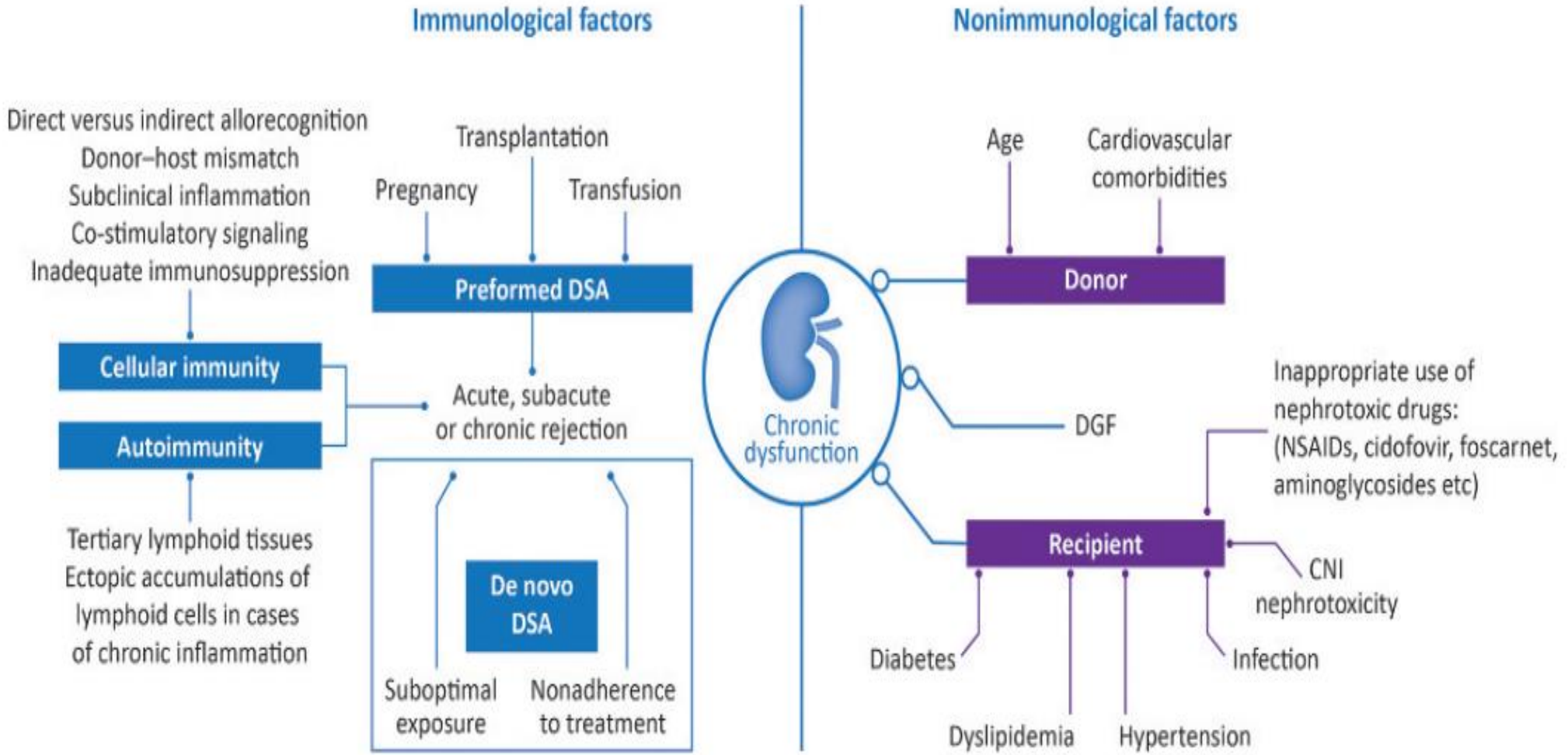


FIGURE 3. Causes of late graft loss in kidney transplant recipients. Figure based on data from Jevnikar 2008, Pazhayattil 2014, Sellarés 2012, Lefaucheur 2010, Koenig 2016, Valenzuela 2013, Siedlecki 2011 and Puttarajappa 2012.[18-25]

KIDNEY TRANSPLANT: NEW OPPORTUNITIES AND CHALLENGES

Cyclosporine and tacrolimus both bind intracellular immunophilins and thereby prevent transcription of IL-2 and production of T cells.

The drugs work similarly but have different binding sites. Cyclosporine has largely been replaced by tacrolimus because its reliability of dosing and higher potency are associated with lower rejection rates.

Tacrolimus is typically given twice daily (1–6 mg/dose). Twelve-hour trough levels are followed (target: 8–12 ng/mL early on, then 5–8 ng/mL after 3 months posttransplant).

Side effects : hypertension and hypercholesterolemia, but less so than with cyclosporine. hyperglycemia tends to be worse with tacrolimus than with cyclosporine, combining tacrolimus with steroids frequently leads to diabetes. Tacrolimus can also cause acute and chronic renal failure, especially at high drug levels, as well as neurotoxicity, tremors, and hair loss.

CNI and sirolimus are metabolized through the same cytochrome P450 pathway (CYP3A4), so they have common drug interactions

Oral bioavailability of tacrolimus is poor (25% mean), and is highly variable among individuals (range, 5-90%)

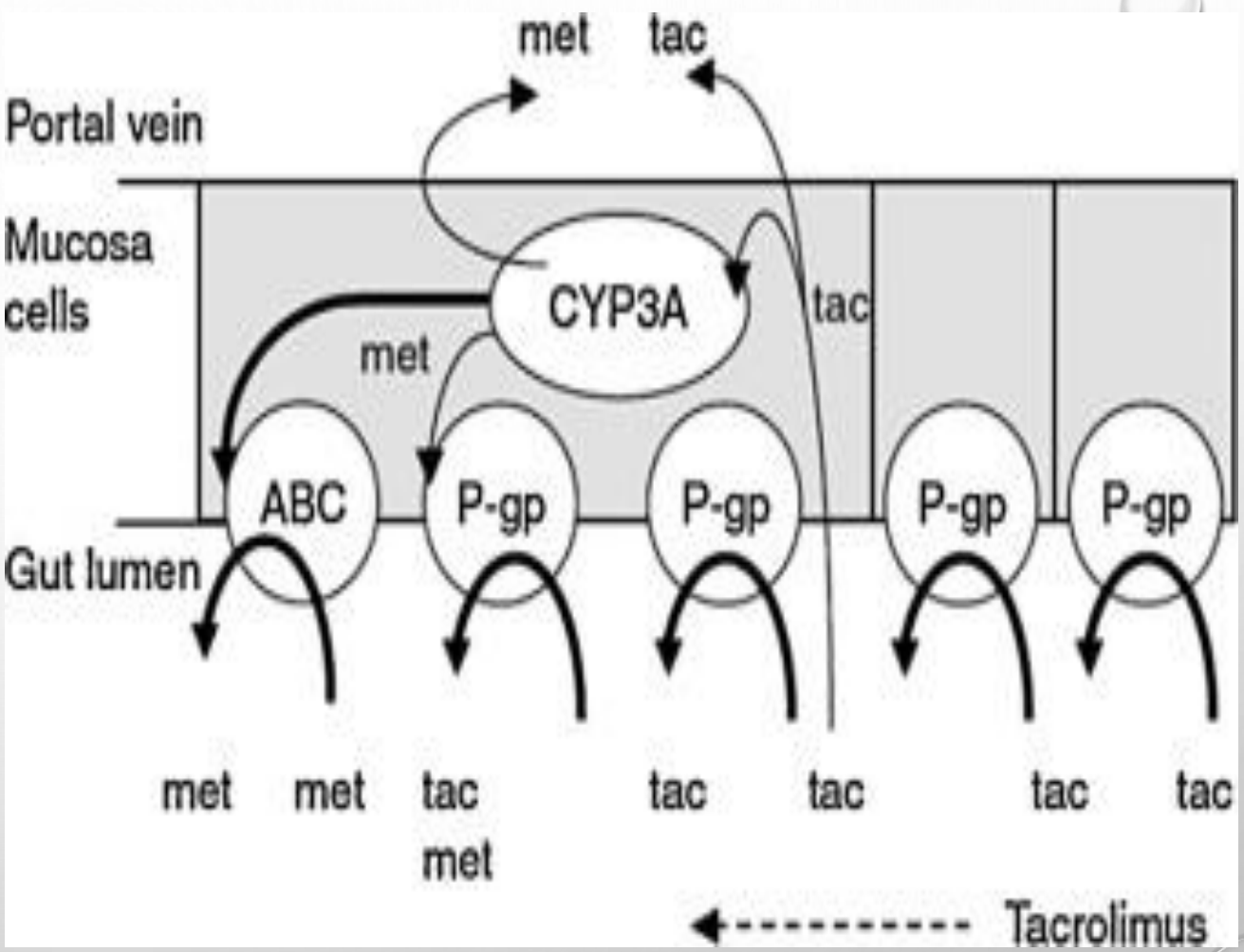
Tacrolimus : absorbed throughout the gastrointestinal tract.
The immediate-release formulation is mainly absorbed in the small bowel. There is extensive presystemic metabolism by the CYP3A enzymes in the gut wall and first-pass metabolism in liver, which limits its oral bioavailability.

Expressers of the CYP3A5 enzyme (as is more often the case in black and Asian patients) do require higher dosages to reach therapeutic tacrolimus exposure.The recently developed prolonged-release formulation in tablet form (also known as LCP-tacrolimus) is released and absorbed more distally in the gut.
This newer formulation of prolonged-release tacrolimus in tablets has shown some differences in terms of pharmacokinetics but longterm clinical outcome data is yet to be established.

After absorption, tacrolimus diffuses extensively in blood cells and tissues.
In the plasma, 90% of tacrolimus is bound to proteins
After being metabolized by the liver, the inactive metabolites are bile-excreted

The metabolisation of tacrolimus in the gut may be affected by CYP3A5 expression affecting bioavailability, which may be around 50% lower in CYP3A5 expressers in comparison to CYP3A5 nonexpressers

it may be beneficial to identify CYP3A expression before transplantation to better predict tacrolimus blood concentrations and reduce (nephro-) toxicity directly after transplantation



Factor	Effect on tacrolimus whole blood concentrations	Effect on unbound tacrolimus plasma concentrations	Reference
Bio-variables			
Anemia	↓⇔	↑↑↑	(38,39,74,77,149)
Blood transfusion	↑⇔	↓↓↓	(74)
Hypo-albuminemia	⇔	↑↑↑	(74,77)
High AGP	⇔	↓	(74,167)
Low HDL	⇔	↑	(74,168)
Low LDL	⇔	↑	(74,168)
Low VLDL	⇔	↑	(74,168)
Organ dysfunction			
Ileus	↓↓↓	⇔	(14,54)
Restored gut motility	↑↑↑	⇔	(14)
Diarrhea	↑↑	⇔	(17,19,63,169)
Low Pgp (shock, inflammation)	↑↑	⇔	(40,62,63)
ECMO	↓↓	↓	(52–54)
Liver dysfunction	↑	⇔	(75)
Cholestasis	↑	⇔	(75)
Kidney dysfunction	⇔	↑	(170)

Azole antifungals are potent inhibitors of CYP3A4 and P-glycoproteins, and lead to increased serum concentrations of tacrolimus.

A significant reduction in the tacrolimus dosage should be anticipated, with recommendations for dose reduction in the ranges of 40% (fluconazole), itraconazole (50-60% reduction), 66% (voriconazole), and 75% (posaconazole).

we recommend reducing the dose at the time of triazole treatment initiation, and not wait for the first tacrolimus concentration after starting a triazole regimen.

Other significant interactions may be experienced when using other medications sharing CYP3A metabolism

In hemodynamically unstable patients, the motility of the intestinal tract is significantly altered. This has a major impact on tacrolimus bioavailability, since intraluminal transport to the duodenum is limited

in situations of inflammation, ischemia-reperfusion injury, diarrhea and shock, Pgp expression in the gut wall may be reduced leading to decreased Pgp levels and an increase in whole blood tacrolimus trough concentrations up to 100%

the intrinsic pharmacokinetic and pharmacodynamic properties of tacrolimus, including erratic absorption, a variable first-pass effect, and unpredictable metabolism, may be responsible for its large intrapatient and inter-subject exposure variability.

variability within individual :defined as an alternation between episodes of overexposure and underexposure to immunosuppression within a timeframe in which the dosage itself remains constant.
IPV of tacrolimus is usually assessed by the coefficient of variance or by standard deviations of trough concentrations.
Persistent significant variability may be responsible for alloimmune activation during low exposure and toxicity or low immunity during overexposure.

FIGURE 7. Concept figure depicting tacrolimus exposure variability. On the left, patient A keeps all tacrolimus trough concentrations within a narrow range and no significant variability is observed. On the right, patient B shows a wide fluctuation of trough concentrations, alternating periods of overimmunosuppression and underimmunosuppression, thus indicating significant exposure variability.

SLIGHTLY MODIFIABLE CONTRIBUTORS TO TACROLIMUS VARIABILITY

TABLE 4.

Determinants of IPV of tacrolimus[103,120,121,123,124]

	Factors	Interventions
Nonmodifiable	• Pharmacogenetics: polymorphisms in CYP3A genes • Circadian rhythm of tacrolimus exposure	Not applicable
Slightly modifiable	• Nonadherence • Gastrointestinal events (diarrhea, vomiting) • Any clinical situation motivating liver graft dysfunction • Low serum proteins (hypoalbuminemia) • Anemia	(a) More frequent assessment of tacrolimus trough concentrations and refined dose adjustments (b) Correction of the underlying factors whenever possible (c) Additional precaution needed when the patient experiences liver allograft rejection, infections, liver impairment, vascular/biliary complications or recurrence of primary liver disease (d) Specific measures to improve adherence (see dedicated section)
Highly modifiable	• Food (dietary fat content, grapefruit juice, pomelo) • Drug–drug interactions: antifungals, antivirals, other immunosuppressants, and other drugs • Herbal products • Uncontrolled generic substitution	(a) Patient education (b) Healthy diet. Avoid food contents and herbal products interfering with hepatic CYP3A and/or intestinal CYP3A4 enzymes (c) Anticipate and avoid drug interactions (d) If significant variability occurs, consider switching to prolonged-release tacrolimus capsules

Factors are classified according to their detectability and the ease with which they can be modified in routine clinical practice.
CYP3A, cytochrome P450 family 3 subfamily A.

The calcium channel blocker diltiazem has been used as a tacrolimus sparing agent due to its effect as an inhibitor of tacrolimus metabolism. Evidence in kidney transplant patients suggests that CYP3A5 expressers are more susceptible to diltiazem induced tacrolimus metabolism than nonexpressers.

A dedicated comment about hepatitis C antivirals is warranted. With the introduction of new, more potent antivirals, many transplant patients with HCV may receive therapy after transplantation.

Sofosbuvir, the cornerstone of most antiviral protocols, and its combinations with ledipasvir or daclatasvir, is usually well tolerated with tacrolimus.

the first-generation PI, telaprevir and boceprevir, and the combination ombitasvir/paritaprevir/ritonavir+/−dasabuvir, have a major impact on tacrolimus metabolism, increasing tacrolimus trough concentrations exponentially; therefore, these drugs should be avoided whenever possible.

- Another potential source of tacrolimus variability is conversion to generic formulations; however, the evidence is scarce and of low quality Bioequivalence between generic tacrolimus and its innovator has been demonstrated in healthy volunteers and kidney transplant recipients

Indeed, there are no data to firmly suggest that generics are not equivalent and therefore unsafe. However, for narrow therapeutic index drugs, concerns exist regarding the safety of generic substitution given the clinical consequences linked to both overexposure and underexposure.

CLINICAL AND SAFETY OUTCOMES OF CONVERSION ORIGINAL TACROLIMUS TO GENERIC TACROLIMUS IN TURKISH KIDNEY TRANSPLANT RECIPIENTS

Based on the results of our study, renal outcomes are safe and the drugs could be changed safely.

In patients with documented variability receiving tacrolimus twice daily, conversion to once-daily prolonged-release tacrolimus capsules may be helpful.

Substitution to generic tacrolimus formulations, if considered, should be attempted only in stable patients and under close monitoring of trough concentrations.

Generic substitution should only be carried out if subsequent substitutions from one generic to another generic will not be attempted.

EXTENDED RELEASE VERSUS IMMEDIATE RELEASE TACROLIMUS IN KIDNEY TRANSPLANT RECIPIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Comparing between the two tacrolimus formulations, there were no significant differences of eGFR, CrCl, Scr, BPAR, graft survival, and patient survival at different times over 4 years after transplantation.

. 2018 Oct;74(10):1249-1260. doi: 10.1007/s00228-018-2512-7. Epub 2018 Jun 30.

Prolonged-release once-daily formulation of tacrolimus (LCPT) versus standard-of-care tacrolimus in *de novo* kidney transplant patients across Europe

Randomized controlled trial in 10 EU countries

- LCPT [n=200]
- Immediate release tacrolimus (IR-Tac)
- Prolonged release tacrolimus (PR-Tac) [n=201]

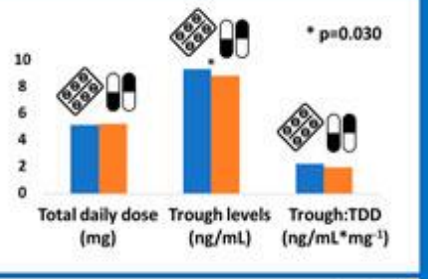
401 Kidney transplant recipients randomized de novo after transplant

Dosing between wk.3 and mo.6

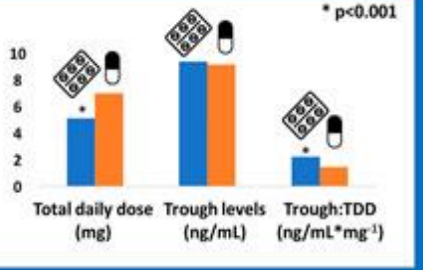
Lower total daily dose [TDD (SD)]
- LCPT 5.17 (2.97) mg
- IR/PR-Tac 6.28 (3.56) mg

Subgroup analysis

LCPT vs. IR-Tac



LCPT vs. PR-Tac



Efficacy and Safety

No significant difference in in treatment failure rates

- LCPT 9.0%
- IR-Tac 8.1%
- PR-Tac 9.6%

No significant difference in renal function over 6 months post-tx

No significant difference in serious adverse events (SAEs)

ESOT Leading the way in transplantation

Klemens Budde, et al. *Transpl. Int.* 2022
doi: 10.3389/ti.2021.10225

Transplant International

between overimmunosuppression, and underimmunosuppression, which is linked to reduced graft survival and poor patient outcomes for both kidney and liver transplant recipients

. Although the term "immunosuppressive burden" is a useful concept, it cannot readily be measured.

These, and other observations, led to the principles that whereas CNIs reduced acute rejection episodes in the immediate posttransplant period, in the long term, CNIs were nephrotoxic, causing fibrotic kidney lesions and leading to poor long-term graft survival

TABLE 5.

Results of studies investigating CNI-free/minimization regimens[161,176-178]

Study type	No. of participants	Intervention	Results
ELITE-Symphony study (large, 1-year, multicenter, randomized, controlled study). The study was then extended to 3 years	1645 renal transplant recipients	Patients were treated with either: – MMF and corticosteroids (prednisone or equivalent), standard-dose cyclosporine Or – MMF, corticosteroids (prednisone or equivalent), and daclizumab induction, with low-dose cyclosporine, low-dose tacrolimus, or low-dose sirolimus	– The most favorable outcome for controlling acute rejection and providing good renal function was obtained in the low-dose tacrolimus arm, with the worst outcomes in the CNI-free arm[a] – At the 3-year follow-up, these differences had reduced over time and were often not significant, but many patients were switched from sirolimus and cyclosporine to tacrolimus
Large meta-analysis of 56 randomized clinical trials	11 337 renal transplant recipients	– Patients were treated with three different early CNI-sparing strategies: CNI avoidance, CNI minimization and the delayed introduction of CNIs	– The use of mTORi, in combination with MMF and no CNIs, increased the odds of graft failure (OR, 1.43; 95% CI, 1.08-1.90; $P = 0.01$) – CNI-sparing strategies were associated with fewer cases of DGF (OR, 0.89; 95% CI, 0.80-0.98; $P = 0.02$), improved graft function, and fewer cases of new-onset diabetes
DIAMOND study (multicenter, 24-week, randomized study)	857 liver transplant recipients	Patients were treated with: – Prolonged-release tacrolimus (initial dose 0.2 mg/kg/day) + MMF Or – Prolonged-release tacrolimus (0.15-0.175 mg/kg/day) + basiliximab + MMF Or Prolonged-release tacrolimus (0.2 mg/kg/day delayed until Day 5) + basiliximab + MMF	Lower-dose prolonged-release tacrolimus capsules (initially 5-15 ng/mL, then 4-12 ng/mL after 3 months)[b], administered with MMF and basiliximab immediately posttransplant, was associated with a significant renal function benefit and a significantly lower incidence of BCAR, compared with a higher-dose (5-15 ng/mL until day 42 then 5-12 ng/mL) prolonged-release tacrolimus-based regimen

Strategies for Prevention of Underimmunosuppression
In kidney transplantation, it is important to stratify patients according to their immunological risk

Pretransplant risk factors, including patients with a "higher risk" immunological risk status[188]

- Sensitized from previous blood transfusion(s), previous transplant, or pregnancies
- HLA mismatch (particularly HLA-DR mismatch)
- PRA >0% (HLA antibodies)
- Preformed HLA-DSA
- Younger age at time of transplant
- Adolescents are at higher risk of nonadherence
- Black recipient ethnicity
- Previous graft loss as a result of immunological reasons

Aim for tacrolimus target trough levels of 5 to 10 ng/mL in the first year after transplantation

Identify patients potentially at higher risk of underimmunosuppression, incuding:

young patients, adolescents and patients who have previously lost a graft due to immunological causes.

The standard CNI protocol is generally advisable in higher risk patients with trough target levels of tacrolimus between 5 and 10 ng/mL

Any minimization strategies involving CNI reduction, avoidance or late conversion should be carefully evaluated in each patient and the risks and benefits weighed.

ADVERSE EFFECTS RELATED TO IMMUNOSUPPRESSION IN KIDNEY AND LIVER TRANSPLANTATION

immunosuppressive agents inhibit the immune system beyond the alloimmune response, particularly when immunosuppression levels are high. This results in adverse effects, including generic effects (eg, increased risk of infections and certain cancers), class effects (eg, renal impairment with CNIs), and drug-specific side effects.

The clinical impact of toxicities associated with immunosuppression has led to the concept of minimization of immunosuppression and combination of drugs in low concentration

Therapeutic drug monitoring of trough levels is performed; however, trough levels only provide an indirect measure of immunosuppression. Overimmunosuppression is often late to be identified, generally after the diagnosis of related adverse effects.

Although the reduction of immunosuppression is common practice in patients with infection or neoplasm, there are no clear guidelines on how modification of the immunosuppressive regimen should be managed for the different types of adverse events.

Risk stratification, preventative measures and early detection of adverse events in liver and kidney transplant recipients are therefore paramount for graft and patient survival


Time of transplantation
<4 weeks
1-12 months
>12 months
Infections in solid organ transplant recipients
Infections of complex surgical patients
• Line infection
• Wound infection
• Aspiration
• Anastamotic leaks
• Graft ischemia
• Clostridium difficile colitis
Antimicrobial-resistant species
• Methicillin-resistant Staphylococcus aureus (MRSA)
• Extended-spectrum ß-lactamase (ESßL) Gram-negative bacilli
• Vancomycin-resistant Enterococcus (VRE)
• Candida species (non-albicans)
Donor-derived
• Cytomegalovirus
• Epstein–Barr virus
• BK polyomavirus
• Primary biliary cholangitis
• Hepatitis B/hepatitis C
Recipient-derived (latent or colonized)
• Aspergillus
• Pseudomonas
• Strongyloides
• Trypanosoma cruzi
Opportunistic infections
• Pneumocystis jirovecii*
• Cytomegalovirus*
• Epstein–Barr virus*
• Other herpes viruses*
• Nocardia species*
• Listeria monocytogenes*
• Hepatitis B virus*
• Hepatitis C virus
• Toxoplasma gondii*
• Strongyloides stercoralis*
• Leishmania species
• Trypanosoma cruzi*
• Mycobacterium tuberculosis
• Community-acquired respiratory viruses
• BK polyomavirus
• Clostridium difficile
• Cryptococcus neoformans
Anastamotic complications
*Many infections prevented by appropriate prophylaxis
Community-acquired pneumonia
Urinary tract infections
Late opportunistic infections
• Molds and Cryptococcus
• Nocardia species
• Rhodococcus species
Late viral infections
• CMV (colitis/retinitis)
• Hepatitis (HBV, HCV)
• HSV encephalitis
• JC polyomavirus leading to progressive multifocal leukoencephalopathy (PML)
• Skin cancer
• Posttransplant lymphoproliferative disorder (PTLD)
Sources of infection
Donor- or recipient-derived
Nosocomial, technical, donor/recipient
Activation of latent infections, relapsed, residual, opportunistic infections
Community-acquired

TABLE 13.

Effect of maintenance immunosuppression on cardiovascular risk factors in kidney and liver transplant patients

	Corticosteroids	Cyclosporine	Tacrolimus	mTORi	Belatacept	Azathioprine	Mycophenolate
Lipids	↑↑	↑↑	↑	↑↑↑	↑↑	↔	↔
Hypertension	↑↑	↑↑	↑		↑	↔	↔
Diabetes	↑↑	↑	↑↑			↔	↔
eGFR	↔	↓	↓	↔	↔	↔	↔
Acute rejection	↓	↓↓	↓↓	↓	↓	↓	↓

Direction of arrows shows effect, with number of arrows demonstrating semi-quantitative effect. Data not available for effect of belatacept on cardiovascular risk factors in liver transplant recipients. Table based on data from Gillis 2014 and Jardine 2011.[289,362]

Certain biomarkers associated with risk of infection, such as low levels of IgG, complement C3 fraction, MBL levels,or low CD4- and CD8-positive T-cell counts, may eventually provide a role in helping to predict infection in liver and kidney transplant recipients.

Two assays have been developed in this field. The Cylex ImmuKnow Cell Function Assay (CICFA) measures T-cell function by the release of ATP from CD4-positive lymphocytes in culture after a mitogenic stimulus.

The T-cell IFN-γ enzyme-linked immunospot (ELISPOT) assay quantifies memory T-cells in peripheral blood that respond to donor HLAs or CMV antigens.

The clinical utility of both these biomarker assays in clinical practice is yet to be determined.

The risk of cancer is increased after kidney transplantation; the relationship between cancer incidence and immunosuppression depends on the type of cancer, the immunosuppressive burden, and time posttransplant.

The Standardized Incidence Ratios (SIR) for the most common malignancies in kidney transplant recipients include:
Kaposi's carcinoma , nonmelanoma skin cancer , and cancer of the lip

Certain immune characteristics in the recipient, such as an increased number and proportion of regulatory T-cells, may prove to be useful in stratifying cancer development after transplantation

Challenges of calcineurin inhibitor withdrawal following combined pancreas and kidney transplantation: results of a prospective, randomized clinical trial

In the setting of kidney transplantation, long-term data from large randomized clinical trials comparing a CNI-free, belatacept-based immunosuppressive regimen to a CNI-based regimen demonstrate that a CNI-free, belatacept-based regimen leads to improved renal function, allograft survival, and lower rates of NODAT, hypertension, and dyslipidemias.[1]

American Journal of Transplantation

SYSTEMATIC REVIEW article

Front. Immunol., 03 September 2021
Sec. Alloimmunity and Transplantation
Volume 12 - 2021 | https://doi.org/10.3389/fimmu.2021.663602

Conversion From Calcineurin Inhibitors to Mammalian Target of Rapamycin Inhibitors in Kidney Transplant Recipients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Systematic review and meta-analysis of calcineurin inhibitors on long-term prognosis of renal transplant patients

a landmark study published in 2003 that analyzed 10-year surveillance biopsy results of 120 KTR, revealed that the prevalence of CNI nephrotoxicity was 100% at 10 years post kidney transplantation

CNI nephrotoxicity was a significant contributor to CAN,(historically defined as chronic IFTA, vascular occlusive changes, and glomerulosclerosis), and suggested that CNIs were unsuitable for long-term immunosuppression due to these adverse effects

the transplant community has invested significant efforts in reducing the use of CNIs or minimizing their usage as much as possible , marking the beginning of the “CNI-sparing regimen” era in the early decades of the 21st century

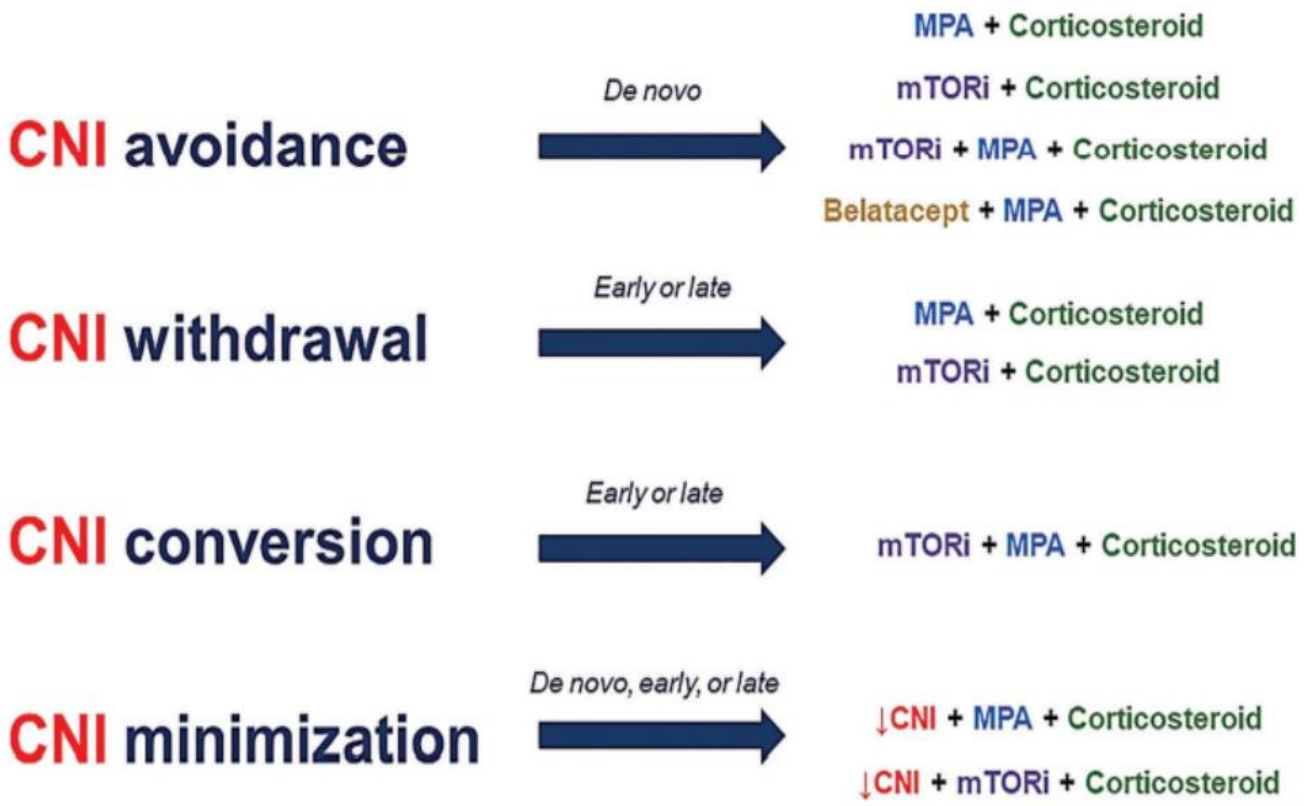


Figure 1. Concept of CNI-sparing strategy. The "early period" denotes interventions applied within 4–6 months after transplantation, while the "late period" refers to interventional timing after that. CNI, calcineurin inhibitor; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitor.

Table 1. Example of key randomized controlled trials in maintenance immunosuppression in kidney transplantation and an overview of their outcomes.

CNI avoidance	CNI withdrawal	CNI conversion	CNI minimization
• ELITE-Symphony [85] • ORION [72] • BENEFIT [103] • SPEISSER [65]	• CAESAR [66] • ORION [72] • Creeping Creatinine Study [64] • Rapamune Maintenance Regimen Study [63]	• CONVERT [88] • CONCEPT [68] • SMART [70] • Spare the Nephron Study [74] • ZEUS [75] • HERAKLES [77] • ASCERTAIN [73] • ELEVATE [78]	• CAESAR [66] • ELITE-Symphony [85] • OPTICEPT [67] • A2309 Study [71] • EVEREST [69] • ASSEST [76] • TRANSFORM [95]
○ **Increased risk of rejection [72, 85, 103]** ○ Some showed better GFR [103] ○ Some showed increased risk of graft loss [85] (non-belatacept study)	○ **Increased risk of rejection [66, 72]** ○ Some showed better GFR and lower viral infection rate [63, 64]	○ **Better GFR [68, 70, 73–75, 77, 78, 88]** ○ **Lower viral infection rate [70, 74, 77, 78, 88]** ○ Some showed higher rejection rate and lower cancer rate [68, 75, 78, 88]	○ **Better GFR [67, 85]** ○ Some showed lower viral infection rate [66, 71, 95]

Among the “no CNI regimen” strategies, including avoidance, withdrawal, and conversion, it is important to emphasize that the CNI conversion and withdrawal strategy can be influenced by large variations in the timing of intervention.
This timing can range from early (within 4–6 months after transplantation) to late (after 4–6 months after transplantation).

studies with early intervention might encounter higher rates of acute rejection due to allo-sensitization after CNI removal, whereas studies with late intervention might be more likely to achieve successful conversion or withdrawal due to T cell exhaustion after a longer period post-transplantation

As a result

the standard regimen of TAC/MPA/corticosteroids remains the cornerstone of immunosuppression for kidney transplantation, as it has consistently demonstrated superior outcomes in terms of reducing allograft rejection and improving allograft survival

Nonetheless, CNI-sparing strategies still hold value, particularly for ---
1-low-to-moderate immunological risk but a heightened risk for viral infections or malignancies
2-who cannot tolerate CNIs, such as those with a history of CNI-induced TMA
Most modern CNI-sparing strategies, like CNI minimization in the TRANSFORM study, have exhibited excellent and comparable short-term outcomes when compared with the standard regimen

THANKS FOR YOUR ATTENTION