THE BEST COMBINATION THERAPY IN KIDNEY TRANSPLANTATION

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Introduction

- Organ transplantation is a life-saving procedure for many individuals with end-stage organ disease.
- The need for lifelong maintenance immunosuppression (M-IMS) is nearly universal as risk of rejection is omnipresent.
- Nonadherence to M-IMS is a contributing cause of poor post-transplant outcomes, with barriers to medication access a leading risk factor for nonadherence.
- Current M- IMS practices involve a multi-drug regimen tailored to the individual based on rejection risk, organ characteristics, comorbidities, and side effects with modifications made as these factors change.

The modern era of M-IMS began in the 1990s with the emergence of modified cyclosporine, tacrolimus, and mycophenolic acid (MPA) which has led to significant improvements in one-year allograft survival among all organ recipients by decreasing the rate of rejection.

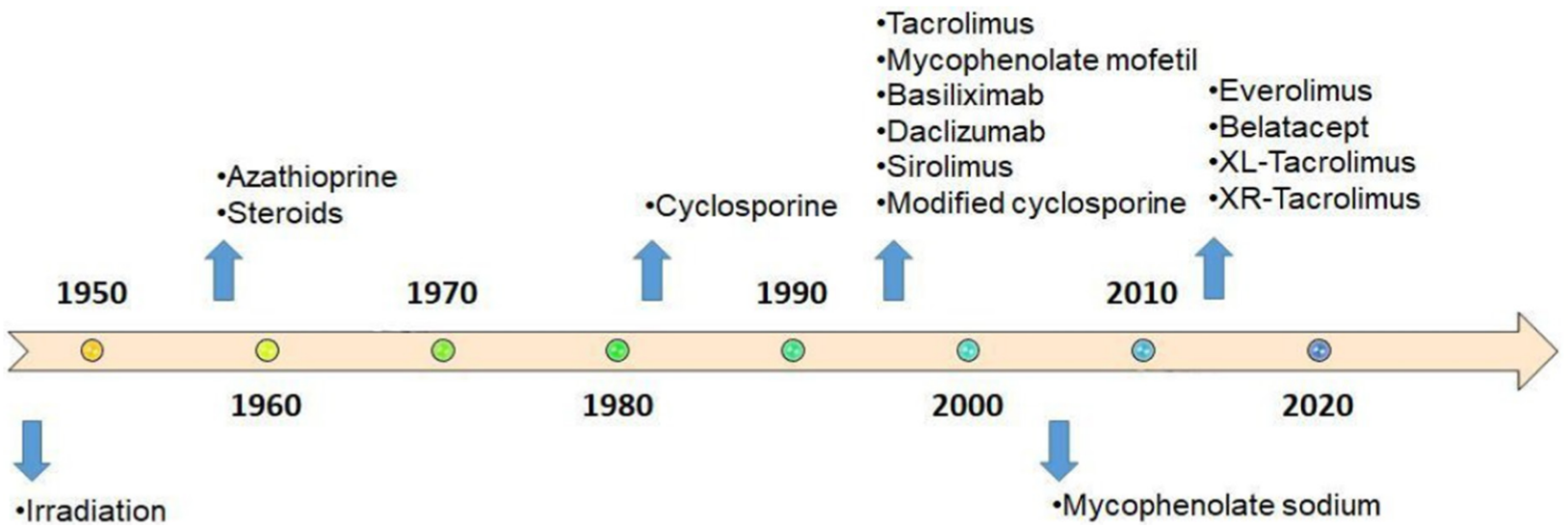


FIGURE 1 Timeline of maintenance immunosuppression

Pharmacotherapy. 2022;42:599–633

Introduction

- The 2019 Organ Procurement and Transplantation Network Annual Data Report shows the most common M-IMS regimen prescribed at discharge was tacrolimus, mycophenolate mofetil (MMF), and corticosteroids for kidney (65%), pancreas (67%), liver (65%), heart (86%), and lung (80%) transplant recipients.

KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary

Bertram L. Kasiske[1], Martin G. Zeier[2], Jeremy R. Chapman[3], Jonathan C. Craig[4], Henrik Ekberg[5], Catherine A. Garvey[6], Michael D. Green[7], Vivekanand Jha[8], Michelle A. Josephson[9], Bryce A. Kiberd[10], Henri A. Kreis[11], Ruth A. McDonald[12], John M. Newmann[13], Gregorio T. Obrador[14], Flavio G. Vincenti[15], Michael Cheung[16], Amy Earley[17], Gowri Raman[17], Samuel Abariga[17], Martin Wagner[17] and Ethan M. Balk[17]

Table 1 | KDIGO nomenclature and description for grading recommendations

	Implications		
Grade[a]	**Patients**	**Clinicians**	**Policy**
Level 1 'We recommend'	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be adopted as a policy in most situations.
Level 2 'We suggest'	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require debate and involvement of stakeholders before policy can be determined.

INDUCTION THERAPY

1.1: We recommend starting a combination of immunosuppressive medications before, or at the time of, kidney transplantation. (1A)

1.2: We recommend including induction therapy with a biologic agent as part of the initial immunosuppressive regimen in KTRs. (1A)

1.2.1: We recommend that an IL2-RA be the first-line induction therapy. (1B)

1.2.2: We suggest using a lymphocyte-depleting agent, rather than an IL2-RA, for KTRs at high immunologic risk. (2B)

INITIAL MAINTENANCE IMMUNOSUPPRESSIVE MEDICATIONS

2.1: We recommend using a combination of immunosuppressive medications as maintenance therapy including a CNI and an antiproliferative agent, with or without corticosteroids. (1B)

2.2: We suggest that tacrolimus be the first-line CNI used. (2A)

2.2.1:We suggest that tacrolimus or CsA be started before or at the time of transplantation, rather than delayed until the onset of graft function. (2D tacrolimus; 2B CsA)

2.3: We suggest that mycophenolate be the first-line anti-proliferative agent. (2B)

2.4: We suggest that, in patients who are at low immunological risk and who receive induction therapy, corticosteroids could be discontinued during the first week after transplantation. (2B)

2.5: We recommend that if mTORi are used, they should not be started until graft function is established and surgical wounds are healed. (1B)

LONG-TERM MAINTENANCE IMMUNOSUPPRESSIVE MEDICATIONS

3.1: We suggest using the lowest planned doses of maintenance immunosuppressive medications by 2–4 months after transplantation, if there has been no acute rejection. (2C)

3.2: We suggest that CNIs be continued rather than withdrawn. (2B)

3.3: If prednisone is being used beyond the first week after transplantation, we suggest prednisone be continued rather than withdrawn. (2C)

SCREENING and GRAFT MONITORING

- Detecting kidney allograft dysfunction as soon as possible will allow timely diagnosis and treatment that may improve outcomes.
- Suggest including a kidney allograft ultrasound examination as part of the assessment of kidney allograft dysfunction. [R 8.4 (2C)]

ROUTINE SCREENING AFTER KIDNEY TRANSPLANTATION

Screening Test	Screening Intervals by Time After Transplantation					
	1 week	1 month	2-3 months	4-6 months	7-12 months	>12 months
Creatinine[a]	Daily	2-3 per week	Weekly	Every 2 weeks	Monthly	Every 2-3 months
Urine protein[b]	Once		Every 3 months			Annually
Complete blood count[c]	Daily	2-3 per week	Weekly	Monthly		Annually
Diabetes[d]	Weekly		Every 3 months			Annually
Lipid profile[e]	–	–	Once	–	–	Annually
Tobacco use[f]	Prior to discharge		–	–	–	Annually
BKV NAT[g]	Monthly			Every 3 months		–
EBV NAT (seronegative)[h]	Once	Monthly		Every 3 months		–
Blood pressure, pulse, height, body weight	Each clinical visit					

National Kidney Foundation®

KDOQI

Managing KIDNEY TRANSPLANT RECIPIENTS

Based on select guidelines from KDOQI US Commentary on the *2009 KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients*. To view full publication, visit **www.kdoqi.org**

INITIAL IMMUNOSUPPRESSION

Recommend starting combination immunosuppressive (IS) therapy before, or at the time of, transplant [R 1.1 (1A*)] except perhaps for transplantation between identical twins.

INDUCTION THERAPY

- Recommend a biologic agent as part of initial IS medication. [R 1.2 (1A)]
- Intended to improve the efficacy of immunosuppression by:
  - Reducing acute rejection, or
  - Allowing a reduction of other components of the regimen, such as calcineurin inhibitors (CNIs) or corticosteroids.

First-line induction therapy: recommend using an interleukin 2 receptor antagonist (IL2-RA). [R 1.2.1 (1B)]

Induction therapy for high immunologic risk: recommend using lymphocyte-depleting agent. [R 1.2.2 (2B)]

KDOQI Commentary:

Individual US transplant centers determine immunosuppression protocols based on their particular patient population, organ source, experience, ease of use, and cost of therapy. Ethnic diversity of the population and the number of high-risk patients vary in different regions of the US, which explains in part variations in protocols used in different centers.

2006 OPTN/SRTR ANNUAL REPORT

Induction Immunosuppression

- 78% used induction therapy, composed of:
  - Thymoglobulin in 39%
  - Interleukin 2 receptor antagonist in 28%
  - Alemtuzumab in 9%
  - Other in 2%
- 22% did not receive induction therapy

Initial Immunosuppression (at discharge)

- 94% on CNI, composed of:
  - 15% CsA
  - 79% Tac
- 87% on MPA
- 9% on mTOR inhibitor
- 26% steroid free

Maintenance Immunosuppression (1 year and beyond)

- 99% on CNI
- 87% on MPA
- 18% on mTOR inhibitor
- 20% steroid free

CNI, calcineurin inhibitors; CsA, cyclosporine; MPA, mycophenolic acid compounds; mTOR, mammalian target of rapamycin; OPTN/SRTR, Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients; Tac, tacrolimus.

KDOQI Commentary:

In the US, decisions on immunosuppression are made by the transplant center and any alterations should always be made in concert with them. Dosing of immunosuppression should at all times take into account the individual patient's risk profile, balancing rejection with the adverse effects of medications.

Received: 16 February 2022 | Revised: 29 March 2022 | Accepted: 8 April 2022

DOI: 10.1002/phar.2716

PHARMACOTHERAPY accp

SPECIAL ARTICLE

Consensus recommendations for use of maintenance immunosuppression in solid organ transplantation: Endorsed by the American College of Clinical Pharmacy, American Society of Transplantation, and the International Society for Heart and Lung Transplantation

Joelle Nelson[1,2,3] | Nicole Alvey[4,5] | Lyndsey Bowman[6] | Jamie Schulte[7] | Maria Cristina Segovia[8] | Jennifer McDermott[9,10] | Helen S. Te[11] | Nikhil Kapila[8] | Deborah Jo Levine[12] | Robert L. Gottlieb[13] | Jose Oberholzer[14] | Maya Campara[15,16]

Is tacrolimus the most efficacious CNI for prevention of allograft rejection and loss at 12 months or longer?

1.1. Recommendation (1A kidney, pancreas, liver; 1D intestine; 2B heart, lung). Tacrolimus is superior to CyA-ME for the prevention of allograft rejection. Additionally, it is superior for reducing the severity of rejection in kidney and pancreas transplants.

1.2. Recommendation (1A kidney, pancreas; 1B liver) . Tacrolimus is associated with improved allograft survival compared to CyA-ME.

Are extended-release formulations of tacrolimus as effective as immediate release formulation?

2.1. Recommendation (1A kidney; 1B liver; 1C heart). Once daily, extended-release formulations of tacrolimus are equally efficacious as IR-TAC for the prevention of acute rejection and patient and allograft survival.

2.2. Recommendation (1B kidney, pancreas, liver; 1C heart; 2D lung). Kidney, liver, heart, and lung transplant recipients on LCP-Tacrolimus have comparable tacrolimus exposure as those receiving IR-TAC with a reduced mean total daily dose (TDD).

What is the role of extended-release formulations of tacrolimus in modern M-IMS?

3.1. Recommendation (1B kidney; 1C liver, heart) . Complex medication regimens involving multiple daily doses have shown to decrease patient medication adherence. Decreased medication adherence is associated with worse outcomes. Once daily tacrolimus products may improve the rate of adherence compared to twice daily tacrolimus.

3.2. Recommendation (1B kidney; 1D pancreas). Due to pharmacokinetic differences, LCPT abrogates peak-related side effects of tacrolimus, such as tremors, in transplant recipients.

3.3. Recommendation (1C kidney). LCPT may be advantageous in recipients who are African American, elderly (≥65) and presumed or proven rapid metabolizers.

Can tacrolimus monotherapy be safely used as M-IMS to prevent allograft rejection and loss at 12 months?

5.1. Recommendation (2A kidney). Tacrolimus monotherapy in the setting of alemtuzumab induction immunosuppression is as effective at preventing BPAR and achieves similar 1-year patient and allograft survival as IL2-receptor antagonist induction followed by tacrolimus and MPA in low immunologic risk transplant recipients.

No recommendation can be made for tacrolimus monotherapy in recipients of high immunologic risk.

Ideal Calcineurin Inhibitor Targets

- In the **Symphony trial**, although tacrolimus trough (tacrolimus C0) level goals were protocol specified at 3–7 ng/ml, the actual achieved tacrolimus C0 exposure averaged 6.4 ng/ml at 12 months and 6.5 ng/ml at 36 months. Thus, a more appropriate interpretation of the Symphony trial is that a tacrolimus C0 dose range of 5–8 ng/ml should be considered the standard of care.

- Appropriate tacrolimus trough goals must be adjusted downward when using tacrolimus in combination with mTOR inhibitors, such as everolimus or sirolimus, due to a synergistic nephrotoxic effect noted with this combination.

TRANSFORM trial (2018)

- 2037 subjects were randomized to reduced-dose tacrolimus (tacro-limus C0 2–4 ng/ml) in combination with everolimus or standard tacrolimus/mycophenolate–based immunosuppression (tacrolimus C0 6–10 ng/ml).
- At 12 months post- transplant, no differences were noted between treatment arms for the combined end point of treated biopsy-proven acute rejection or eGFR,50 ml/min per 1.73 m^2 , graft loss, or death. There were fewer reported CMV and BKV events in the EVR arm, with higher discontinuation rates in the everolimus arm.
- **Different side effect profiles may make one strategy better suited for an individual patient.**

ANTIMETABOLITES

Is MPA the superior antimetabolite in preventing allograft rejection and/or loss at 12 months?

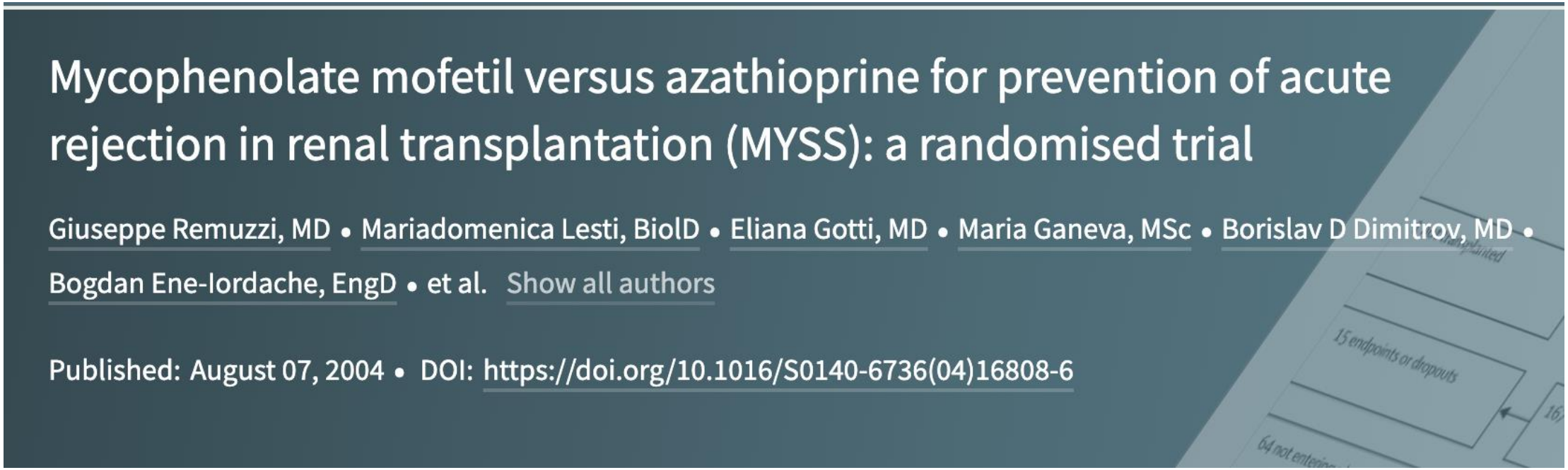
6.1. Recommendation (2B kidney). There may be benefit to the use of MPA over azathioprine for the prevention of acute rejection.

Where can MPS be advantageous over MMF?

7.1. Recommendation (1A kidney; 1B pancreas, heart; 2C liver) .

MMF dose reductions are associated with increased rejection rates. Transplant recipients with gastrointestinal side effects may benefit from conversion to enteric-coated MPS. It is a safe and effective alternative to MMF.

In kidney transplant, two RCTs compare MMF to azathioprine in combination with CyA-ME and corticosteroids:



Mycophenolate mofetil versus azathioprine for prevention of acute rejection in renal transplantation (MYSS): a randomised trial

Giuseppe Remuzzi, MD • Mariadomenica Lesti, BiolD • Eliana Gotti, MD • Maria Ganeva, MSc • Borislav D Dimitrov, MD • Bogdan Ene-Iordache, EngD • et al. Show all authors

Published: August 07, 2004 • DOI: https://doi.org/10.1016/S0140-6736(04)16808-6

336 (168 patients per group) kidney transplants randomly assigned to either MMF or azathioprine found similar rate of clinical rejection at 6 and 21 months. Of note, steroids were tapered at 6 months in stable patients.

CLINICAL TRANSPLANTATION

Short-term combination of mycophenolate mofetil with cyclosporine as a therapeutic option for renal transplant recipients

A prospective, multicenter, randomized study[1]

Sadek, Sami[2 8]; Medina, José[3]; Arias, Manuel[4]; Sennesael, Jacques[5]; Squifflet, Jean-Paul[6]; Vogt, Bruno[7] on behalf of the Neo Int-05 study group

Author Information

Transplantation 74(4):p 511-517, August 27, 2002.

A prospective, open-label, multicenter, randomized study of 477 kidney recipients compared three groups: those on 3 months of MMF followed by 9 months of azathioprine, 12 months of MMF, and 12 months of azathioprine. Investigators found significantly lower acute rejection and treatment failure rates with MMF-containing groups (43.7% and 43.2% vs. 58.6%, $p < 0.01$; 23.4% and 21% vs. 32%, $p < 0.04$, respectively).

Two RCTs also compared both antimetabolites in the setting of tacrolimus.

CLINICAL TRANSPLANTATION

Randomized trial of tacrolimus + mycophenolate mofetil or azathioprine versus cyclosporine + mycophenolate mofetil after cadaveric kidney transplantation: results at three years

Gonwa, Thomas[1,2]; Johnson, Christopher; Ahsan, Nasimul; Alfrey, Edward J.; Halloran, Philip; Stegall, Mark; Hardy, Mark; Metzger, Robert; Shield, Charles III; Rocher, Leslie; Scandling, John; Sorensen, John; Mulloy, Laura; Light, Jimmy; Corwin, Claudia; Danovitch, Gabriel; Wachs, Michael; VanVeldhuisen, Paul; Leonhardt, Maryanne; Fitzsimmons, William E.

Author Information

Transplantation 75(12):p 2048-2053, June 27, 2003. | **DOI:** 10.1097/01.TP.0000069831.76067.22

Method: Two hundred twenty-three recipients of first cadaveric kidney allografts were randomized to receive tacrolimus (TAC) + mycophenolate mofetil (MMF), TAC + azathioprine (AZA), or cyclosporine (Neoral; CsA) + MMF.

Conclusion: All three immunosuppressive regimens provided excellent safety and efficacy. However, the best results overall were achieved with TAC+MMF. The combination may provide particular benefit to kidney allograft recipients with DGF. In patients who experienced DGF, graft survival was better at 3 years in those patients receiving TAC in combination with either MMF or AZA as compared with the patients receiving CsA with MMF.

CLINICAL TRANSPLANTATION

RANDOMIZED TRIAL OF TACROLIMUS (PROGRAF) IN COMBINATION WITH AZATHIOPRINE OR MYCHOPHENOLATE MOFETIL VERSUS CYCLOSPORINE (NEORAL) WITH MYCOPHENOLATE MOFETIL AFTER CADAVERIC KIDNEY TRANSPLANTATION[1, 2]

Johnson, Christopher[3]; Ahsan, Nasimul; Gonwa, Thomas; Halloran, Philip; Stegall, Mark[4]; Hardy, Mark; Metzger, Robert; Shield, Charles III; Rocher, Leslie; Scandling, John; Sorensen, John; Mulloy, Laura; Light, Jimmy; Corwin, Claudia; Danovitch, Gabriel; Wachs, Michael; VanVeldhuisen, Paul; Salm, Kim; Tolzman, Diane; Fitzsimmons, William E.

Author Information

Transplantation 69(5):p 834-841, March 15, 2000.

A prospective open-label randomized study of 223 first-time kidney transplants compared three groups: tacrolimus/MMF, CyA-ME/ MMF, and tacrolimus/azathioprine. There was no difference in 12-month BPAR or patient and allograft survival, but corticosteroid-resistant rejection (4.2% in tacrolimus/MMF vs. 10.7% in CyA-ME/ MMF and 11.8% in the tacrolimus/azathioprine) and moderate to severe (Banff II–III) rejection was lowest in the tacrolimus/MMF group.

Is corticosteroid withdrawal a safe and effective immunosuppression strategy in the era of modern M-IMS?

9.1. Recommendation (1B kidney, liver, heart; 1C pancreas). While corticosteroids remain the cornerstone of M-IMS for most patients, sustained effort to eliminate corticosteroids due to their metabolic complications has been successfully attempted.

Corticosteroid withdrawal has been successfully done in low and moderate risk kidney transplant recipients, but may result in higher incidence of BPAR with similar patient and allograft survival.

Corticosteroid withdrawal has been associated with improvement in metabolic endpoints such as hyperlipidemia, serum triglycerides, need for insulin to treat diabetes, and changes in HgA1c. Two-thirds of kidney transplants are maintained on corticosteroids long term

CORTICOSTEROID WITHDRAWAL

- Early corticosteroid withdrawal (within the first week post-transplant) is a common immunosuppression strategy, as approximately 30% of all kidney transplant recipients are maintained on tacrolimus/mycophenolate steroid-free immunosuppression at 1 year following transplant in the United States.
- The increase in acute rejection rates in early corticosteroid withdrawal can be mitigated, but not entirely eliminated, by the use of depleting antibody induction.

Randomized Controlled Trial > Ann Surg. 2008 Oct;248(4):564-77.
doi: 10.1097/SLA.0b013e318187d1da.

A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term, low-dose corticosteroid therapy

E Steve Woodle [1], M Roy First, John Pirsch, Fuad Shihab, A Osama Gaber, Paul Van Veldhuisen;
Astellas Corticosteroid Withdrawal Study Group

Methods: Adult recipients of deceased and living donor kidney transplants without delayed graft function were randomized to receive prednisone (5 mg/d after 6 months posttransplant) or CSWD. Blinding was maintained for 5 years. [386 patients CSWD (n = 191), CCS (n = 195)]

Conclusions: Early CSWD, compared with CCS, is associated with an increase in BCAR primarily because of mild, Banff 1A, steroid-sensitive rejection, yet provides similar long-term renal allograft survival and function.
CSWD provides improvements in cardiovascular risk factors (triglycerides, NODAT requiring insulin, weight gain). Tacrolimus/MMF/antibody induction therapy allows early CSWD with results comparable to long-term low dose (5 mg/d) prednisone therapy

Original Investigation

FREE

February 3, 2021

Early Corticosteroid Cessation vs Long-term Corticosteroid Therapy in Kidney Transplant Recipients

Long-term Outcomes of a Randomized Clinical Trial

E. Steve Woodle, MD[1]; John S. Gill, MD, MS[2,3,4]; Stephanie Clark, PhD[5]; et al

Key Points

Question Do long-term kidney transplant outcomes differ in patients treated with and without maintenance corticosteroids?

Findings In a randomized clinical trial that allocated 385 patients to maintenance immunosuppressive treatment with tacrolimus and mycophenolate mofetil with or without corticosteroids, there was no difference in kidney allograft survival between treatment groups during the median follow-up of 15.8 years after transplant.

Meaning Corticosteroids may not be necessary as part of a calcineurin-based multiple drug immunosuppressive regimen in kidney transplant recipients.

Multicenter Study > J Am Soc Nephrol. 2020 Jan;31(1):175-185.
doi: 10.1681/ASN.2019040416. Epub 2019 Dec 18.

Early Steroid Withdrawal in Deceased-Donor Kidney Transplant Recipients with Delayed Graft Function

Sunjae Bae [1 2 3], Jacqueline M Garonzik Wang [2], Allan B Massie [1 2], Kyle R Jackson [2], Mara A McAdams-DeMarco [1 2], Daniel C Brennan [4], Krista L Lentine [5], Josef Coresh [1 3 4], Dorry L Segev [6 2]

Methods: Using the Scientific Registry of Transplant Recipients, we studied 110,019 adult deceased-donor KT recipients between 2005 and 2017.

Conclusions: Higher graft loss and mortality in deceased donor recipients with delayed graft function who underwent early corticosteroid withdrawal.

What is the role of mTORi in the context of kidney function?

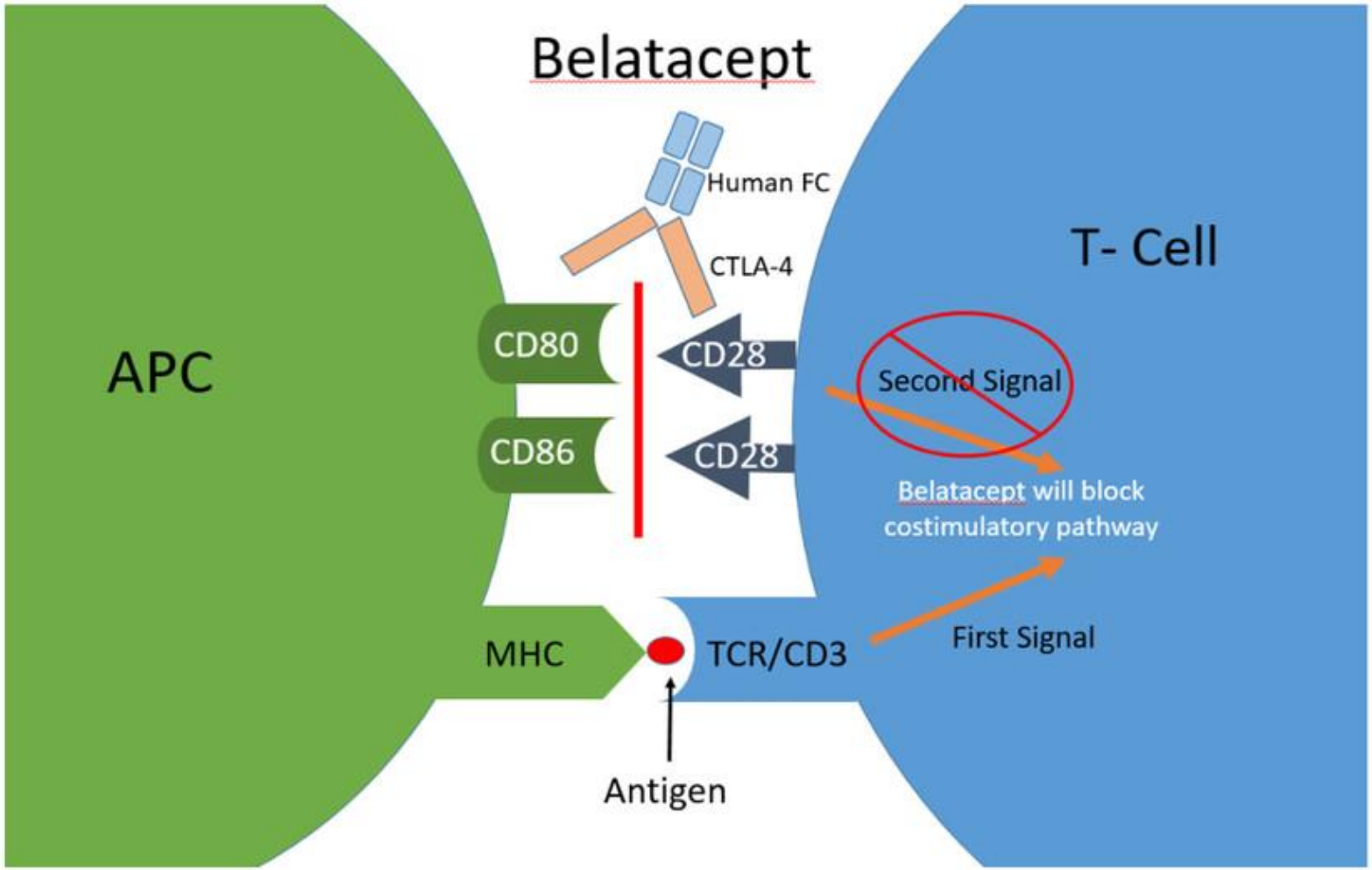
10.1. Recommendation (1A kidney; 1B liver, lung; 2B heart) . mTORi may be considered in combination with low-dose CNI, MPA, with or without corticosteroids to minimize CNI-associated kidney dysfunction.

10.2. Recommendation (1A kidney) mTORi may also be considered as a replacement to CNI to minimize CNI-associated kidney dysfunction.

10.3. Recommendation (2C kidney). Antimetabolites can be replaced by a mTORi when used in combination with low-dose CNI as a kidney-sparing strategy.

NONCALCINEURIN INHIBITOR–BASED REGIMENS

- Currently, only one calcineurin inhibitor–free regimen, belatacept in combination with mycophenolate and corticosteroids, is US Food and Drug Administration (FDA) approved for use in adult kidney transplant recipients seropositive for Epstein–Barr virus.
- Belatacept is a soluble fusion protein that binds to CD80 and CD86 on the surfaces of antigen-presenting cells, thereby inhibiting CD28- mediated T cell co-stimulation.
- The regulatory approval of belatacept was, in part, on the basis of the results from two randomized phase 3 trials: BENEFIT and BENEFIT- EXT (differed primarily in the donor population that was utilized for transplantation)



APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FC, fragment crystallizable (region); MHC, major histocompatibility complex; TCR, T-cell receptor.

Belatacept mechanism of action

BELATACEPT

- Two dosing regimens of belatacept (“more intense” and “less intense”) were compared with a cyclosporin-based immunosuppression regimen.
- Under the FDA-approved “less intense” regimen, belatacept 10 mg/kg is administered intravenously on days 1 and 5 and weeks 2, 4, 8, and 12 post-transplantation, and 5 mg/kg belatacept is given every 4 weeks thereafter.
- **In BENEFIT, patients were transplanted with a living or standard criteria deceased donor kidney**. At 12 months post-transplantation, the acute rejection rates for belatacept and cyclosporin were 17% and 7%, respectively; however, GFR was higher in the belatacept arm, even in those with rejection.

BELATACEPT

- **Patients enrolled to BENEFIT-EXT were recipients of extended criteria donor kidneys**, kidneys with an anticipated cold ischemia time of almost 24 hours, or kidneys donated after cardiac death. At 12 months post- transplantation, 18% of patients randomized to belatacept and 14% of those randomized to cyclosporin experienced acute rejection.

Acute rejection episodes under belatacept-based treatment tend to occur **early** in the post-transplantation period, with a **low incidence of late rejections**.

Can patients be safely converted to belatacept to eliminate or minimize CNI exposure?

16.1. Recommendation (2B kidney). It is safe to convert stable, living, or deceased donor, low immunologic risk transplant recipients from CNI to belatacept.

While such a conversion has been shown to improve kidney allograft function, along with a **modest decrease in the development of NODAT and hypertension**, these benefits must be weighed with an increased risk of acute rejection and infection, particularly CMV.

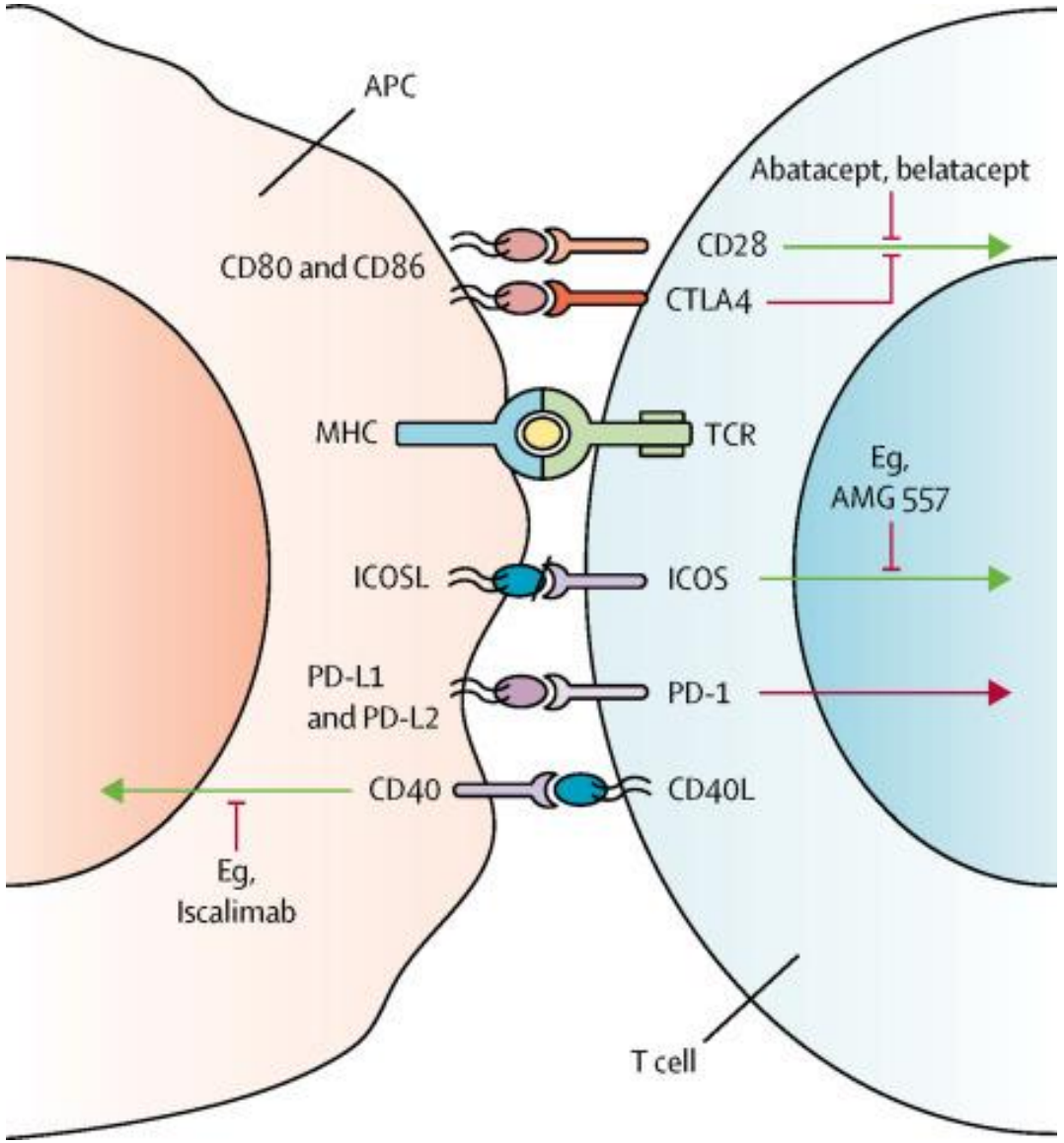
Table 1. Examples of knowledge gaps in key clinical trials and potential next steps

Trial Name	Key Findings	Gaps/Opportunities	Future Strategies (Applicable to All Studies)
Symphony	Tacrolimus superior to cyclosporin or sirolimus for the end points of 1-yr acute rejection, GFR	Optimal MMF dose unknown Using nondepleting induction, no DSA assessment	Risk stratify patients for enrollment into minimization/withdrawal studies not only on the basis of traditional clinical and immunologic risk factors but also on novel immunologic assessments (*e.g.*, baseline T cell reactivity, epitope matching)
TRANSFORM	Everolimus/low calcineurin inhibitor/ prednisone is noninferior to standard calcineurin inhibitor/ mycophenolate/prednisone	No long-term outcomes of DSA, proteinuria, GFR	
BENEFIT	Belatacept with superior GFR despite higher AR rates than cyclosporin	Control arm not standard of care	Investigate end points beyond 1 year graft survival, patient survival, rejection (*e.g.*, iBox, GFR, histological end points)
Astellas corticosteroid withdrawal	Tacrolimus/mycophenolate with comparable graft survival and GFR despite higher AR than tacrolimus/ mycophenolate/prednisone	Details regarding rejection and effect on outcomes not described No DSA data or formal histologic assessments	Utilize emerging biomarker assessments to risk stratify patients for enrollment and randomization to determine timing of protocol-specified immunosuppression change/increase/decrease, and as surrogate end points (*e.g.*, blood genomic profiling, molecular assessment of kidney transplant biopsy tissue, urinary chemokines and mRNA, blood donor–derived cellfree DNA)
CONVERT	Calcineurin inhibitor to sirolimus conversion at 6–120 mo was associated with inferior outcomes in those with GFR<40 and proteinuria in those above GFR 40	Randomized by GFR and not by histologic features (*e.g.*, IFTA with lack of glomerulosclerosis)	
ZEUS	Cyclosporin to everolimus conversion at 4.5 mo was associated with higher GFR but more rejection and higher discontinuation rate	No DSA data or formal histologic assessments	
BEST	Belatacept/early steroid withdrawal with depleting antibody induction was not superior to TAC/early steroid withdrawal	No long-term GFR follow-up or formal histologic assessments	

MMF, mycophenolate; DSA, donor-specific antibody; AR, acute rejection; IFTA, interstitial fibrosis and tubular atrophy; TAC, tacrolimus.

Are There New Immunosuppression Agents on the Horizon?

At present, there is a paucity of novel maintenance immunosuppressive agents in the pipeline. Iscalimab, an anti- CD40 mAb, has been studied in a phase 2 trial, and other agents targeting co-stimulation blockade are in preclinical development.



FINALLY

- Long-term immunosuppression management remains a balancing act, with efforts being made to maximize outcome (patient and graft survival) and minimize toxicity.
- Thus far, no immunosuppression regimen has proven to be without a potential pitfall.
- Efforts, however, are underway in the transplant community to take a more balanced approach to immunosuppression by utilizing tools, such as donor-derived cell free DNA, gene expression profiling, and HLA matching/DSA monitoring, to achieve a personalized approach to long-term immunosuppression management.

TOXICITY PROFILES OF IMMUNOSUPPRESSIVE MEDICATIONS

Adverse Effect	Steroids	CsA	Tac	mTORi	MMF	AZA
New-onset diabetes mellitus	↑	↑	↑↑	↑		
Dyslipidemias	↑	↑		↑↑		
Hypertension	↑↑	↑↑	↑			
Osteopenia	↑↑	↑	(↑)			
Anemia and leucopenia				↑	↑	↑
Delayed wound healing				↑		
Diarrhea, nausea/vomiting			↑		↑↑	
Proteinuria				↑↑		
Decreased GFR		↑	↑			

AZA, azathioprine; CsA, cyclosporine A; GFR, glomerular filtration rate; MMF, mycophenolate mofetil; mTORi, mammalian target of rapamycin inhibitor(s); Tac, tacrolimus.
↑ indicates a mild-moderate adverse effect on the complication.
↑↑ indicates a moderate-severe adverse effect on the complication.
(↑) indicates a possible, but less certain adverse effect on the complication.

*See table on page 11: Rating Guideline Recommendations.

ACUTE REJECTION and CHRONIC ALLOGRAFT INJURY

POSSIBLE RISK FACTORS FOR ACUTE REJECTION

- The number of human leukocyte antigen (HLA) mismatches
- Younger recipient age
- Older donor age
- African-American ethnicity (in the United States)
- Panel-reactive antibody (PRA) >30%
- Presence of a donor-specific antibody
- Blood group incompatibility
- Delayed onset of graft function
- Cold ischemia time >24 hours

TREATMENT OF ACUTE REJECTION

- Recommend biopsy before treating acute rejection, unless the biopsy will substantially delay treatment. [R 6.1 (1C)]
- Treat subclinical and borderline acute rejection. [R 6.2 (2D)]
- Suggest adding MMF, if appropriate. [R 6.5 (2D)]

Acute Cellular Rejection

- Recommend using corticosteroids for the initial treatment. [R 6.3 (1D)]
- Suggest adding or restoring prednisone in patients not on steroids who have a rejection episode. [R 6.3.1 (2D)]
- Suggest using lymphocyte-depleting antibodies or OKT3 if [R 6.3.2 (2C)]:
  - Nonresponsive to corticosteroids
  - Acute cellular rejection is recurrent.

Antibody-Mediated Acute Rejection

- Suggest treating with one or more of the following alternatives, with or without corticosteroids [R 6.4 (2C)]:
  - Plasma exchange
  - Intravenous immunoglobulin
  - Anti-CD20 antibody
  - Lymphocyte-depleting antibody.

SCREENING FOR RECURRENT DISEASES				
Disease	**Screening (in addition to serum creatinine)**	**Minimum Screening Frequency**	**Diagnostic Tests (in addition to kidney biopsy)**	**Potential Treatment**
FSGS[a]	Proteinuria	Daily for 1 week, weekly for 4 weeks, every 3 months for 1 year, then annually		Plasmapheresis
IgA nephropathy[b]	Proteinuria, microhematuria	Once in the first month, every 3 months in the first year, then annually		
MPGN[b]	Proteinuria, microhematuria		Serum complement levels	
Anti-GBM disease[b]	Proteinuria, microhematuria		Anti-GBM antibodies	Plasmapheresis
Pauci-immune vasculitis[b]	Proteinuria, microhematuria		ANCA	Cyclophosphamide and corticosteroids
HUS[c]	Proteinuria, platelet count	During episodes of graft dysfunction	Platelet count, peripheral blood smear, LDH	Plasmapheresis

[a]See R 10.1 (2C)
[b]See R 10.2 (2C) [c]
See R 10.3 (2D)

OVERVIEW OF RISK FACTORS AND TREATMENT GOALS FOR CVD	
Reduce Risk for:	**Goals**
New-onset diabetes after transplantation (NODAT)	• HbA_{1c}: 7.0-7.5% [R 15.2.2 (not graded)] • Avoid targeting HbA_{1c} ≤6.0%, especially if hypoglycemic reactions are common. [R 15.2.2 (not graded)]
Hypertension	• <130/80 mm Hg if ≥18 years of age [R 16.1.2 (2C)] • <90th percentile for sex, age, and height if <18 years old [R 16.1.2 (2C)]

Dyslipidemias	• Adults:
	  ◦ LDL: <100 mg/dL [R 16.2.2.2]
	  ◦ Non-HDL: <130 mg/dL [R 16.2.2.3]
	• Adolescents:
	  ◦ LDL: <130 mg/dL [R 16.2.2.2]
	  ◦ Non-HDL: <160 mg/dL [R 16.2.2.3]