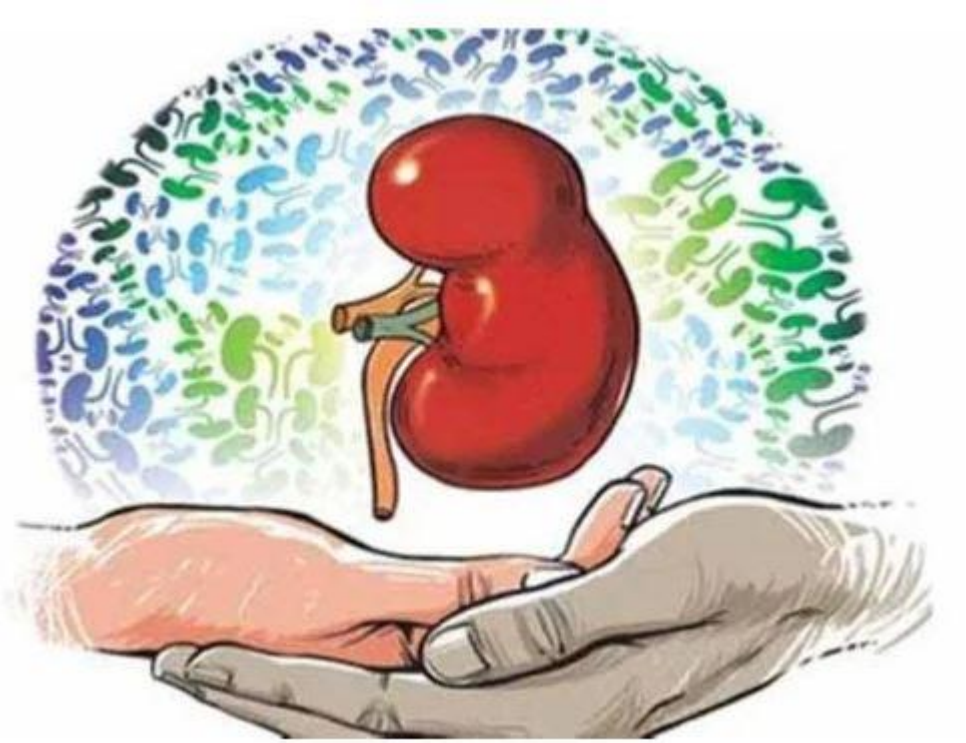

Different type of immunosuppression in renal transplantation

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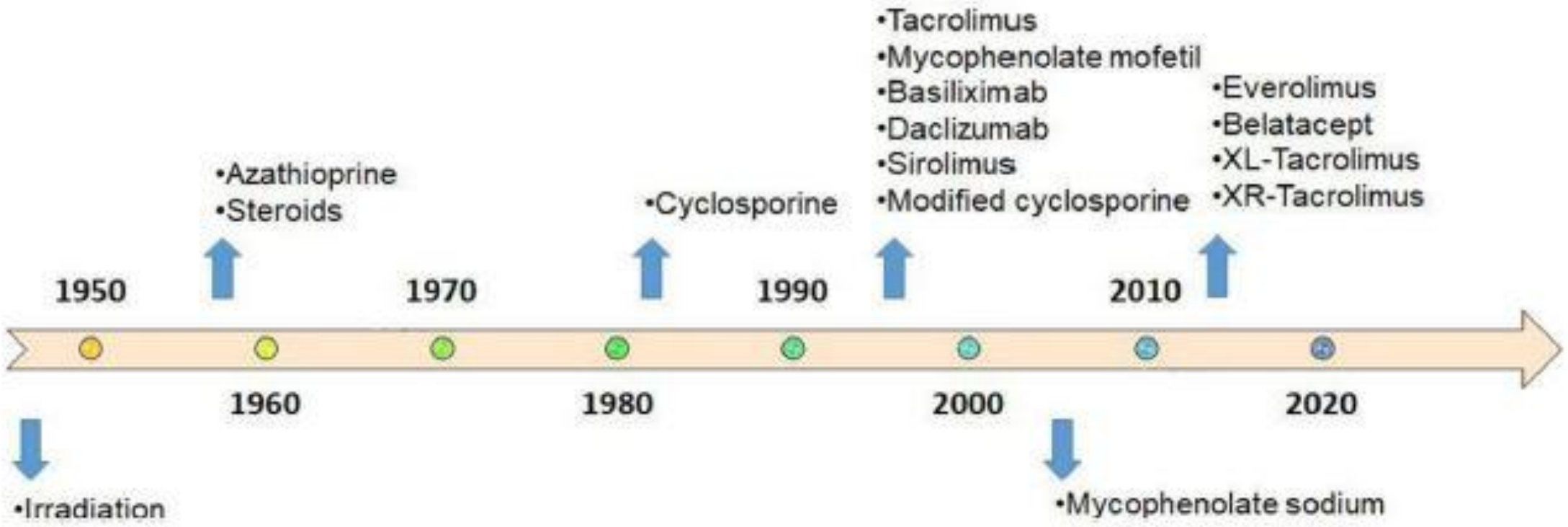
Introduction

- Organ transplantation is a life-saving procedure for many individuals with end-stage organ disease.
- Advances in maintenance immunosuppression over the past three decades have improved solid organ transplantation outcomes dramatically
- The need for lifelong maintenance immunosuppression (M-IMS) is nearly universal as risk of rejection is omnipresent.

Timeline of maintenance immunosuppression in renal transplant



Pharmacotherapy. 2022;42:599–633.

BACKGROUND

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

GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) criteria

Level of evidence	Quality certainty	Meaning
A	High	The true effect is close to estimated effect
B	Moderate	The true effect is probably close to estimated effect
C	Low	The true effect may be markedly different from estimated effect
D	Very low	The true effect is probably markedly different from estimated effect
Recommendation level	**Strength of recommendation**	**Meaning**
1	Strong	Panel confident recommendation benefit outweighs risk
2	Weak	Panel uncertain, consider individual patient factors

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

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

Clinical Trial > Lancet. 2002 Mar 2;359(9308):741-6. doi: 10.1016/S0140-6736(02)07875-3.

Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: a randomised multicentre study

Raimund Margreiter [1];
European Tacrolimus vs Ciclosporin Microemulsion Renal Transplantation Study Group

- The 6-month open study involved 560 patients in 50 European centres. 287 patients were randomly assigned tacrolimus and 273 ciclosporin microemulsion plus azathioprine and corticosteroids.
- The **rate of BPAR** was significantly **lower with tacrolimus** than with ciclosporin (56 patients [19.6%] vs 101 [37.3%]; 17.7% difference [95% CI 10.3-25.1]; p<0.0001).

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

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

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

- *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.**

Am J Transplant 2010 Dec;10(12):2632-43

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

- *Recommendation (2B kidney)*. There may be benefit to the use of **MPA over azathioprine** for the prevention of acute rejection.
- In 2007, the FDA changed the pregnancy rating of MMF from

"C" to "D" meaning there is positive evidence of human fetal risk.

- Current guidelines recommend discontinuing MPA and considering the risks and benefits of transitioning patients who are, or are **planning on becoming pregnant**, to azathioprine

Role of Mycophenolate Sodium

- In **kidney transplant**, two RCTs and one retrospective case control assessed MPS versus MMF.
- The first study, a double blind RCT of 322 stable kidney transplant patients found similar rates of neutropenia and GI side effects at 3 months and 12 months in those on MPS versus MMF.
- Rates of BPAR and efficacy failure were similar. Overall incidence of infections was similar, but the number of serious infections was significantly lower with MPS (8.8% vs.16.0%; $p < 0.05$)

Comparative Study > Transplantation. 2010 Feb 27;89(4):446-51.
doi: 10.1097/TP.0b013e3181ca860d.

Mycophenolate mofetil versus enteric-coated mycophenolate sodium: a large, single-center comparison of dose adjustments and outcomes in kidney transplant recipients

Hans W Sollinger [1], Aimee K Sundberg, Glen Leverson, Barbara J Voss, John D Pirsch

- larger retrospective case control of 1704 patients found **significantly higher BPAR with MMF vs. MPS** (30% vs. 22%, $p = 0.0004$) with a significantly higher risk of drug discontinuation and dose reduction (hazard ratio = 1.507, $p = 0.0002$ and 1.703, $p < 0.0001$, respectively)

•. Transplantation 2010 Feb 27;89(4):446-51.

Randomized Controlled Trial > Transplantation. 2011 Feb 27;91(4):470-8.
doi: 10.1097/TP.0b013e318205568c.

Enteric-coated mycophenolate sodium versus mycophenolate mofetil in renal transplant recipients experiencing gastrointestinal intolerance: a multicenter, double-blind, randomized study

Anthony J Langone [1], Laurence Chan, Paul Bolin, Matthew Cooper

- A multicenter, double-blind,RCT of 396 kidney transplant patients with self-reported GI symptoms found that **EC-MPS patients had a significantly greater decrease in the Gastrointestinal Symptom** Rating Scale indigestion syndrome dimension versus MMF patients ≥ 0.3 (62% vs. 55%, $p = 0.15$)

Conclusion

- Conversion from MMF to EC-MPS may be associated with **improvements in presence and severity of GI symptoms**, particularly in patients with indigestion, diabetes, on steroids, and in patients converted between 6 and 12 months posttransplantation.

What is the Role of azathioprine in modern M-IMS?

- *Recommendation (1C kidney, pancreas, liver, heart, lung)* Azathioprine is the antimetabolite of choice for all transplant recipients that are, or desiring to become, **pregnant**.
- *Recommendation (1B kidney, heart, lung; 2C pancreas; 1D intestine)* . A zathioprine may be used in place of MPA in those **intolerants to MPA products**, such as gastrointestinal toxicity, that require an antimetabolite.

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

- *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.
- 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

Steroid Withdrawal

- However, the long-term benefits (and risks) of steroid-free regimens are unclear. A well-performed randomized control trial with 5-year follow-up demonstrated **no differences in graft or patient survival**, cardiovascular risk factors, weight gain, or incidence of post-transplant diabetes, **with more acute rejection** in the early corticosteroid withdrawal arm and fewer bone complications in the steroid-containing arm

Clin J Am Soc Nephrol v.16(8); 2021 Aug

Steroid Withdrawal

- The increase in acute rejection rates in early corticosteroid withdrawal can be mitigated, but not entirely eliminated, by the use of depleting antibody induction
- Overall, the overwhelming evidence suggests that steroid withdrawal after kidney transplantation significantly **increases the risk of acute rejection** yet provides comparable short- and medium-term graft survival, but withdrawal **has limited effect** on traditionally considered steroid-related side effects.

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

- *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
- *Recommendation* (*1A kidney; 2B pancreas; 1B liver; 2B heart)* mTORi may also be considered as a **replacement to CNI** to minimize CNI-associated kidney dysfunction
- *Recommendation (2C kidney)*. **Antimetabolites** can be replaced by a mTORi when used in combination with low-dose CNI as a kidney-sparing strategy.

BK Polyoma Virus

- We suggest **screening** all KTRs for BKV with quantitative plasma NAT (2C) at least:
- Monthly for the first 3–6 months after transplantation (2D);
- Then every 3 months until the end of the first post-transplant year (2D);
- Whenever there is an **unexplained rise** in serum creatinine (2D);
- After treatment for **acute rejection**. (2D)
- We suggest reducing immunosuppressive medications when BKV plasma NAT is persistently greater than 10,000 copies/ml .(2D)

Review

BK Virus Infection and BK-Virus-Associated Nephropathy in Renal Transplant Recipients

Margherita Borriello [1], Diego Ingrosso [1], Alessandra Fortunata Perna [2], Angela Lombardi [1], Paolo Maggi [3], Lucia Altucci [1] and Michele Caraglia [1,4,*]

- BKVN **affects up to 10% of renal transplanted** recipients, and results in graft loss in up to 50% of those affected
- Unfortunately, treatments for BK virus infection are restricted, and there is no efficient prophylaxis.

Genes 2022, 13, 1290.
https://doi.org/10.3390/genes13071290

BK Nephropathy

- Recent guidelines suggest **stepwise immunosuppression reduction** for kidney transplanted patients with BK viremia of more than 1000 copies/mL lasting for 3 weeks, or a one-shot detection of more than 10,000 copies/mL in sera, showing a probable BKVN.
- In cases of refractory BK nephropathy and hemorrhagic cystitis, **cidofovi**r has been used for treatment (IV and intra-vesicular), although efficacy has not been clearly demonstrated

Genes 2022, 13, 1290.
https://doi.org/10.3390/genes13071290

BK Nephropathy

- **Fluoroquinolones** also show potential as anti-viral agents against BKV-associated disease. Indeed, it was recently demonstrated that this class of antibiotics restrain BKV replication **in vitro**
- However, data on this class of antibiotics are still inconsistent.
- A phase III clinical trial involving 154 Canadian kidney transplanted patients demonstrated that levofloxacin, and likely other fluoroquinolones, are **ineffective in preventing or treating** this infection . Recent guidelines state that the latter antibiotics are **not recommended** for prophylaxis or therapy

In conclusion

- Despite the virological basis, the published randomized clinical trials are **not** adequate **to replace the immunosuppressant therapy** (tacrolimus with cyclosporine A and mycophenolate with leflunomide or mTOR inhibitors).
- Moreover, they do not legitimize the additive use of cidofovir, intravenous immunoglobulins or leflunomide.
- **Re-transplantation** after allograft rejection due to BKVN may be successful if BKV
- DNAemia is completely cleared, independent of failed allograft nephrectomy

EPSTEIN-BARR VIRUS AND POST-TRANSPLANT LYMPHOPROLIFERATIVE DISEASE

- We suggest monitoring **high-risk** (donor EBV seropositive/recipient seronegative) KTRs for EBV by NAT (2C):
- Once in the **first week** after transplantation(2D);
- Then at least **monthly** for the first 3–6 months after transplantatio(2D);
- Then **every 3 months** until the end of the first post-transplant year (2D);
- Additionally after treatment for **acute rejection**. (2D)

Epstein-Barr Virus and Post-transplant Lymphoproliferative Disease

- We suggest that EBV-seronegative patients with an increasing EBV load have **immunosuppressive medication reduced**. (2D)
- We recommend that patients with EBV disease,including PTLD, have a reduction or cessation of immunosuppressive medication. (1C)

Treatment of PTLD

› Am J Transplant. 2011 Feb;11(2):336-47. doi: 10.1111/j.1600-6143.2010.03387.x. Epub 2011 Jan 10.

Reduction of immunosuppression as initial therapy for posttransplantation lymphoproliferative disorder(★)

R Reshef [1], S Vardhanabhuti, M R Luskin, D F Heitjan, D Hadjiliadis, S Goral, K L Krok, L R Goldberg, D L Porter, E A Stadtmauer, D E Tsai

- The first line treatment is reduction of immunosuppression(RIS) to enhance alloreactive T cell immunity.
- Response rate to RIS alone range widely,from **43 to 63%**
- For patients who are **not response** to RIS or **at high risk of developing rejection** and are not candidate for RIS, **Rituximab** monotherapy is often the next line of treatment for CD20+ PTLD

Treatment of PTLD

- Prospective trial of rituximab monotherapy evaluating three or four weekly doses reported overall response rates of 44-79% with a complete response 25-53%
- Long term survival for patients who achieve CR with rituximab alone is excellent with disease specific survival of 88% at 10 years

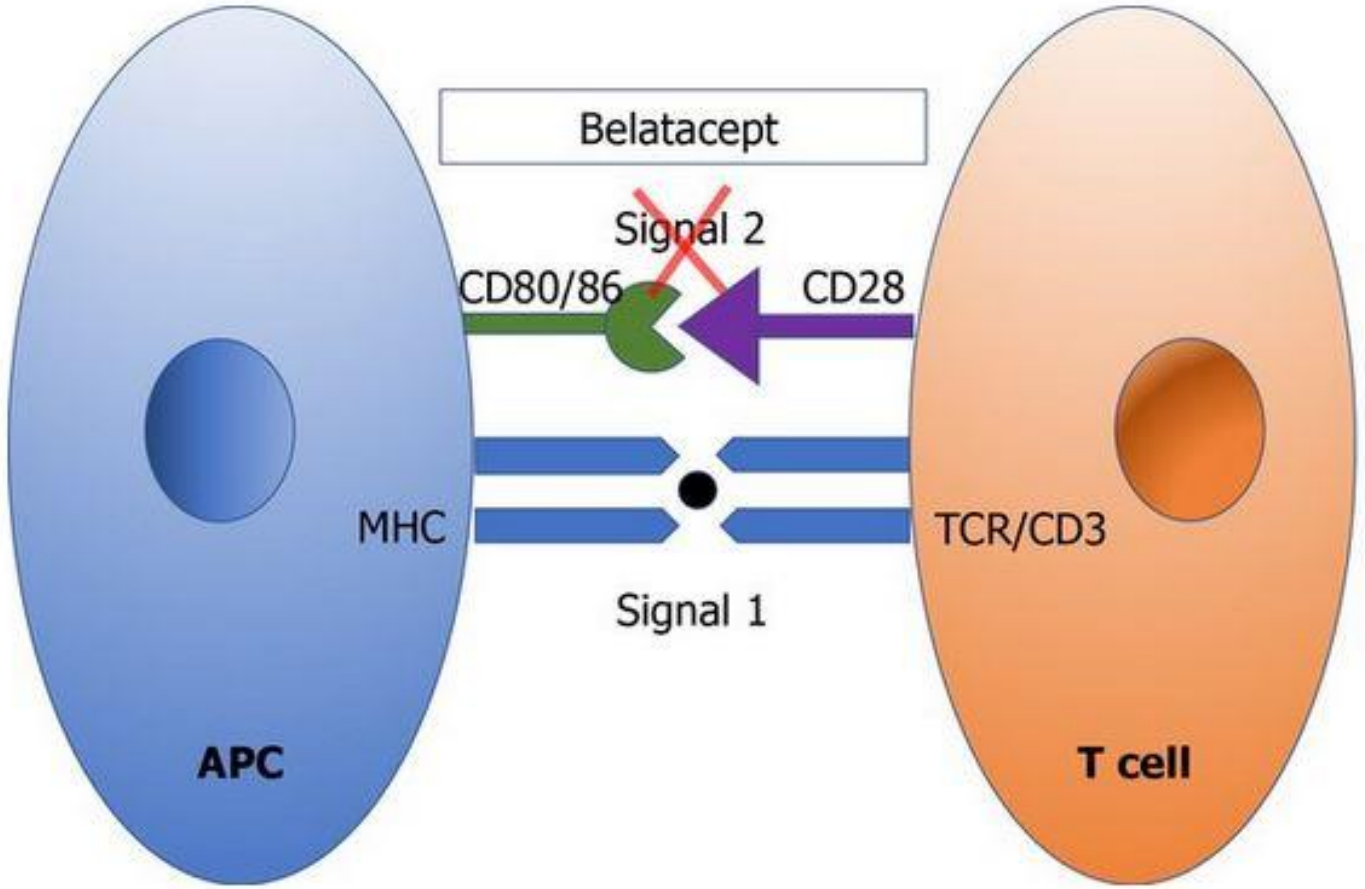
Am J Transolant 2005 Dec;5(12):2901-6

Non-Calcineurin Inhibitor–Based Regimens

- Calcineurin inhibitors are associated with a higher risk of post-transplant diabetes, elevated BP, worsening hyperlipidemia, neurotoxicity, and acute and chronic nephrotoxicity
- Currently, only one calcineurin inhibitor–free regimen, **Belatacept**, a selective T cell costimulation blocker 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.

Clin J Am Soc Nephrol v.16(8); 2021 Aug

Belatacept:T-cell costimulation blocking agent



J Am Soc Nephrol. 2021 Dec; 32(12): 3252–3264.
Published online 2021 Dec. doi: 10.1681/ASN.2021050628

PMCID: PMC8638403
PMID: 34706967

Conversion from Calcineurin Inhibitor– to Belatacept-Based Maintenance Immunosuppression in Renal Transplant Recipients: A Randomized Phase 3b Trial

Klemens Budde,[1] Rohini Prashar,[2] Hermann Haller,[3] Maria C. Rial,[4] Nassim Kamar,[5] Avinash Agarwal,[6] Johan W. de Fijter,[7] Lionel Rostaing,[8] Stefan P. Berger,[9] Arjang Djamali,[10] Nicolae Leca,[11] Lisa Allamassey,[12] Sheng Gao,[12] Martin Polinsky,[12] and Flavio Vincenti[13]

Conclusion: Switching stable kidney transplant recipients from CNI-based to belatacept-based immunosuppression was associated with a similar rate of death or graft loss, improved kidney function, and a numerically higher BPAR rate, but a lower incidence of dnDSA.

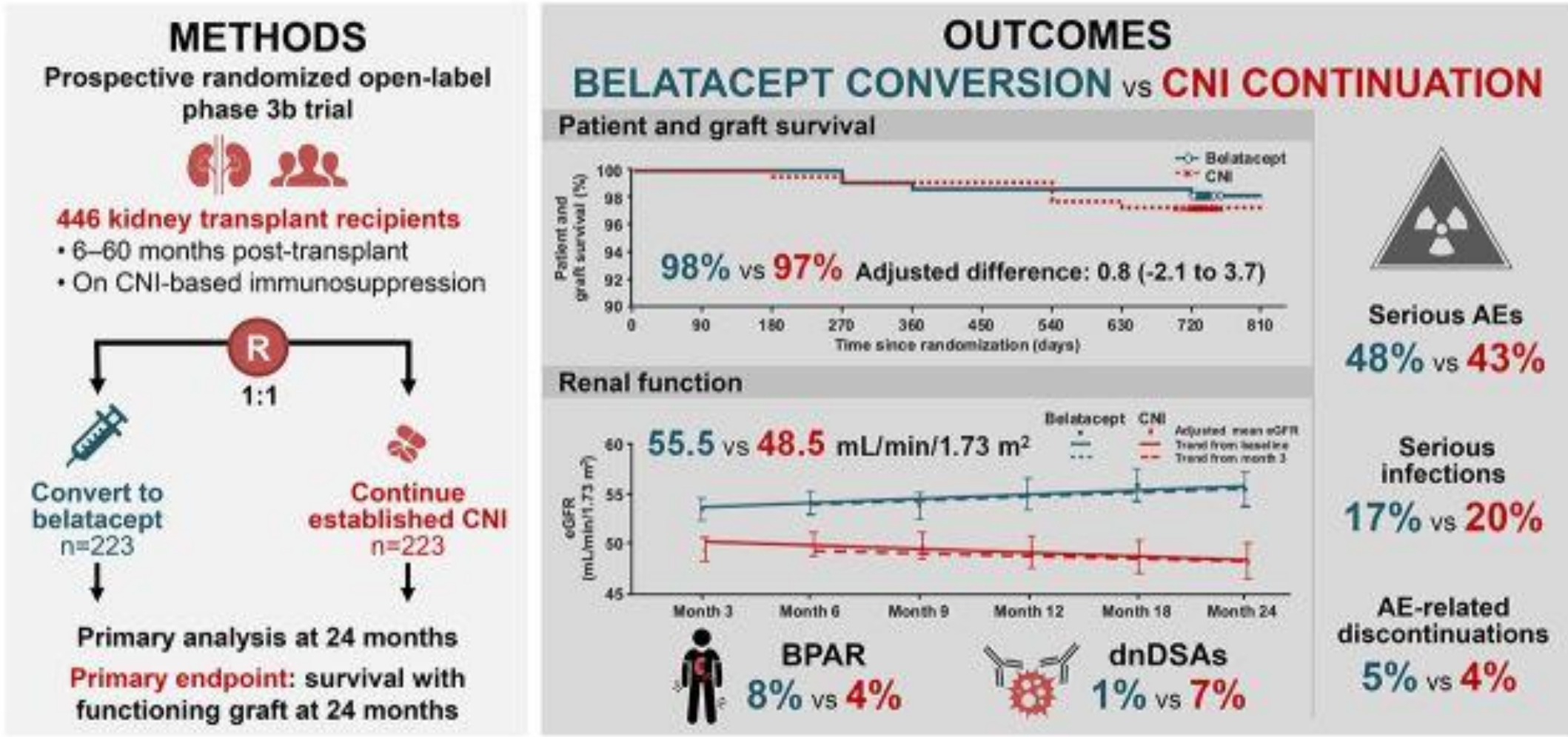
Conversion from Calcineurin Inhibitor– to Belatacept-Based Maintenance Immunosuppression in Renal Transplant Recipients

- **Methods**
- Stable adult kidney transplant recipients 6–60 months post-transplantation under CNI-based immunosuppression were randomized (1:1) to switch to belatacept or continue treatment with their established CNI.
- The primary end point was the percentage of patients surviving with a functioning graft at 24 months.

Conversion from Calcineurin Inhibitor– to Belatacept-Based Maintenance Immunosuppression in Renal Transplant Recipients

- Overall, 446 renal transplant recipients were randomized to belatacept conversion (*n*=223) or CNI continuation (*n*=223). **The 24-month rates of survival with graft function were 98% and 97%** in the belatacept and CNI groups, respectively (adjusted difference, 0.8; 95.1% CI, −2.1 to 3.7).
- **BPAR** 8% versus 4% of patients respectively, and *de novo* donor-specific antibodies (**dnDSAs**) 1% versus 7% , respectively.
- The 24-month **eGFR was higher with belatacept** (55.5 versus 48.5 ml/min per 1.73 m^2 with CNI).
- Both groups had similar rates of serious adverse events, infections, and discontinuations, with no unexpected adverse events. One patient in the belatacept group had **PTLD**.

Conversion from Calcineurin Inhibitor– to Belatacept-Based Maintenance Immunosuppression in Renal Transplant Recipients



doi: 10.1681/ASN.2021050628

Conversion from Calcineurin Inhibitor– to Belatacept-Based Maintenance Immunosuppression in Renal Transplant Recipients

- In a study evaluating long-term dnDSA incidence in kidney transplant recipients, **nearly all on CNI-based immunosuppression**, approximately 25% of patients developed dnDSAs 10 years after transplant.
- Immunosuppression strategies are needed for minimizing CNI exposure to reduce late transplant failure rates.
- **Conversion to mammalian target of rapamycin inhibitors** has shown variable degrees of improvement in renal function in several studies; however, risks of rejection, development of dnDSAs, and in some cases, graft failure were shown to be **higher than those with CNIs**

Conversion from Calcineurin Inhibitor– to Belatacept-Based Maintenance Immunosuppression in Renal Transplant Recipients

- Compared with kidney transplant recipients receiving cyclosporin, those receiving **belatacept** showed **an improved cardiovascular** and **metabolic profile**, reduced incidence of chronic allograft nephropathy, **reduced incidence of dnDSAs**, and improved renal function and in living or standard criteria deceased donor kidney recipients, better long-term (7-year) patient and graft survival.

Conversion from Calcineurin Inhibitor– to Belatacept-Based Maintenance Immunosuppression in Renal Transplant Recipients

- However, a **higher incidence of biopsy-proven acute rejection (BPAR)** was noted with belatacept than with cyclosporin. The majority of BPAR episodes occurred during the first 6 months

- Although the overall safety profile was similar between belatacept and cyclosporin, belatacept was associated with an **increased risk of post-transplant lymphoproliferative disorder (PTLD),** particularly in Epstein–Barr virus (EBV)–seronegative individuals

Non-Calcineurin Inhibitor–Based Regimens

- Two randomized phase 3 trials: BENEFIT and BENEFIT-EXT
- In these studies, 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; outcomes with this dosing regimen are summarized below.

Non-Calcineurin Inhibitor–Based Regimens

- 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 (mean measured GFR at month 12 in belatacept-treated patients with acute rejection was 61 versus 51 ml/min/ per 1.73 m^2 in cyclosporin-treated patients without acute rejection).

Non-Calcineurin Inhibitor–Based Regimens

- Patients enrolled to **BENEFIT-EXT** were recipients of extended criteria donor kidneys, kidneys with an anticipated cold ischemia time ≥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**.

Analyses of BENEFIT and BENEFIT-EXT performed at 7 years post-transplantation

- In analyses of **BENEFIT** performed at 7 years post-transplantation, belatacept-based immunosuppression was associated with a **reduction** in the risk of **death** or **graft loss** compared with cyclosporin-based immunosuppression (HR, 0.57; 95% CI, 0.35 to 0.94; *P*=0.02) ,
- In **BENEFIT-EXT**, the risk of **death** or **graft loss** at 7 years post-transplantation was similar between the groups (HR, 0.93; 95% CI, 0.63 to 1.36; *P*=0.70)

Analyses of BENEFIT and BENEFIT-EXT performed at 7 years post-transplantation

- Despite the difference in acute rejection between belatacept and cyclosporin at 7 years, **belatacept-based immunosuppression was associated with superior kidney function in both studies** as eGFR maintained a positive slope and increased by +1.39 ml/min per 1.73 m^2 per year in BENEFIT and +1.51 ml/min per 1.73 m^2 per year in BENEFIT-EXT
- Additionally, patients treated with belatacept were noted to have **lower *de novo* DSA formation** lower BPs with fewer antihypertensive medications, better LDL control, and a lower incidence of post-transplant diabetes

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

- 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

Personalized immunosuppression in elderly renal transplant recipients

- The number of elderly people (more than 65 y/o) has increased considerably over the last decades, due to a rising life expectancy and ageing populations(from 8% of the total world population in 2015 to 16% in the year 2050)
- Elderly patients often receive kidneys from elderly donors while younger donor kidneys are preferentially reserved for younger recipients.
- Although the **rate of acute rejection after transplantation is lower in the elderly**, these rejections may lead to graft loss more frequently, as kidneys from elderly donors have marginal reserve capacity.
- On the other hand, elderly patients have a higher risk to die from **infectious** complications, and thus less immunosuppression would be preferable.

Pharmacological Research 130 (2018) 303–307

Benefits of transplantation in the elderly

- Although RT is beneficial in elderly patients with a reduction in mortality rate and an improved quality of life compared to dialysis mortality and quality of life only improve with a functioning graft.
- The 10-year renal allograft survival rate of deceased donor kidneys is

close to 50%

- Elderly patients with ESRD benefit from RT, even when kidneys from older donors are used. Their immune system is less reactive and therefore they are **less prone to acute allograft rejection** and graft loss

Pharmacokinetics

- Staatz et al. a **lower dose of tacrolimus** in elderly patients could still be effective and was possibly safer than the standard dose.
- Despite receiving lower doses of ciclosporin and tacrolimus, elderly recipients often had higher predose concentrations of CNIs compared to younger recipients
- Tang et al. demonstrated that the PK of **MPA** is not affected by the physiological changes in the elderly.
- Also elderly patients do not need dose adjustments for **basiliximab** as the PK does not change with age

Overview of published data on pharmacokinetic parameters of tacrolimus in elderly people (≥65 years)

Author	Year	Age of patients	Main findings
David-Neto et al. [23]	2016	Elderly: ≥65 years Control: 35 ± 6 years	• Mean TAC dose was lower in elderly (8.6 mg ± 4.8 vs 12.1 ± 5.1 mg). • Mean trough levels (C_{min}) were the same in both groups • Elderly vs control: Adj C_{max} [465 ± 271 vs 341 ± 235] (Adj for dose/body weight) • Elderly vs control: Adj TAC-AUC [2652 ± 1730 vs 2793 ± 1253] (Adj for dose/body weight) • Body clearance was lower in elderly [0.35 ± 0.31 vs 0.76 ± 0.42]
Melilli et al. [75]	2015	Elderly: ≥65 years (35%) non-elderly: < 65 years	• TAC level at 5–7 days was lower in elderly vs patients < 65 years (8.05 ng/ml vs 7.1 ng/ml) • At 1, 3 and 6 months the levels between the groups were equal.
Robertsen et al. [76]	2015	Elderly: 60–78 years	Differences between original and generic TAC formulations: • $AUC_{0\text{-}12}$ of the generic formulation was 1.17 [90%-CI 1.10–1.23] • C_{max} ratio 1.49 [90%-CI 1.35–1.65]
Jacobson et al. [24]	2012	Elderly: 65–84 years Middle age: 35–64 years Young: 18–34 years	• Elderly had a higher normalized TAC trough with a lower median dose (1–2 mg/day lower) compared to middle and young age

Pharmacodynamics

- PD describe the **efficacy** and **toxicity** of drugs.
- Tang et al. measured 5'monophosphate dehydrogenase (IMPDH) activity in MPA treated elderly (±65.8 years) and younger (±43.7 years) recipients after RT. As no changes between the two groups were found in IMPDH activity, the authors concluded that **age does not affect the PD of MPA**
- PD of CNIs can be measured by means of the calcineurin activity, which is associated with acute rejection
- However, no studies were carried out to link calcineurin activity to ageing.

Pharmacodynamics

- The classic immunosuppressive drugs have been selected based on inhibition of T-cell activation.
- During ageing, a **shift** takes place towards the **differentiation of memory cells.**
- As a result the antigen-recognition repertoire is decreased and the immune system is therefore unable to protect the host properly against new pathogens

Optimization of therapy

- Based on the fact that the elderly patient has a reduced immune response to the transplanted organ, it may be possible to **reduce the overall immunosuppressive load.**
- One could propose to leave out **basiliximab** induction therapy in elderly patients, as the benefits of induction therapy may be less because they have a reduced IL-2 response.
- in elderly patients, one may encounter **severe infectious** complications for which a rapid reduction of the immunosuppressive load might be needed.
- Another option would be to **taper glucocorticoids** more rapidly in elderly patients.

Optimization of therapy

- **Everolimus-based therapy** has the potential to improve outcome after transplantation as it allows for CNI free or minimized CNI-based treatment.
- Elderly patients often receive ECD kidneys from elderly donors, and as a result,renal function after transplantation is often disappointing. In order to reduce the proportion of patients with an eGFR below 30 mL/min per 1.73m2, an everolimus-based immunosuppressive regimen may be beneficial.
- Also, because IL-2 production is decreased in the elderly, tacrolimus could be less effective. In patients with lower IL-2 concentrations, it may therefore be attractive to **replace tacrolimus by everolimus**.

Immunosuppression in HIV-positive kidney transplant recipients

- End-stage kidney disease (ESKD) is a common complication in patients infected with HIV.
- While, initially,kidney transplantation was considered an **absolute contraindication** in HIV-positive candidates, it has now become the optimal ESKD therapy due to improvement in long-term survival with HIV disease and successful suppression with antiretroviral therapies (ART), leading to a better survival than remaining on dialysis

Curr Opin Organ Transplant 2023, 28:279–289

Immunosuppression in HIV-positive kidney transplant recipients

- Immunosuppression management in HIV-positive KTR is complex and **challenging**, mainly because of the difficulty of maintaining a proper balance between rejection and infection
- **Factors limiting the access include**: uncontrolled HIV, comorbidities, substance abuse, and socio-economic factors impacting access to transplantation

PRETRANSPLANT SELECTION PROCESS

- According to criteria outlined in the HIV-TR study, it is recommended that kidney transplantation candidates should be on :
- Stable ART for at least 6months,
- undetectableHIV viral load,
- CD4 count greater than 200 cells/mlduring the last 3 months before kidney transplantation,
- No active opportunistic infections
- No active malignancies
- No history of progressive multifocal leukoencephalopathy, chronic cryptosporidiosis,central nervous system lymphoma, or Kaposi sarcoma

Induction agent choice

- Induction immunosuppression is recommended in all HIV-positive KTR
- The induction agent should be chosen according to the immunological risk.
- **ATG** can be used successfully in HIV-positive KTR, lowering the risk of rejection without a clear increase in the risk of infection, graft loss, or mortality in the short- term.
- Locke et al. showed that ATG usage was lower than anti-IL2R-Ab (25.8 vs. 33.5%) in HIV-positive KTR and significantly lower than its use in HIV negative KTR (25.8 vs. 43.5%, $P<0.001$).

ATG and anti-IL2R-Ab

- HIV-TR study : Stock et al 2010 on 150 patients 76 on Anti-IL2R Ab and 48 on ATG was associated with graft loss (HR:2.5;95% CI: 1.1-5.6; P=0.03)
- **ATG significantly decreased mean CD4+ at 1 year** but not at 3 years after kidney Tx (-238 vs -135 cells/microliter, P < 0.001 I year and -57 vs 52 cells/microliter, P=0.05 3 years)
- ATG was significantly associated with CD4 + % change from baseline at year 0.2 after KT (P=0.004) ,but not significantly over time (P=0.66)
- ATG was associated with twice as many **serious infections** per follow up year as patients who did not receive such agents (0.9 vs 0.4 , p=0.002)
- No difference regarding VL, DGF , AR , Neoplasm , Morbidity

ATG and anti-IL2R-Ab

- Despite the potentially less accurate data on rejection and infection, the **AST-IDCOP** offered recommendations regarding induction immunosuppression using either ATG or anti-IL2R-Ab, but for **high immunologic risk candidates**, a lymphocyte depleting agent is recommended as **first line**.
- On the contrary, the **BTS** recommends that in the majority of cases, induction should be based on an anti-IL2R-Ab agent.
- lack of a randomized comparison between ATG and anti-IL2R-Ab on important outcomes, we sustain **the use of anti-IL2R-Ab in most cases and ATG only in selected situations.**

Maintenance immunosuppression in HIV kidney transplant

- According to the AST-IDCOP and BTS guidelines, maintenance immunosuppressive regimens for HIV-positive KTR should include **tacrolimus, mycophenolate**, and **long-term steroids**
- **Belatacept** can be used, particularly as conversion from CNI in HIV-positive KTR with cardiometabolic complications or to prevent nephrotoxicity from CNI

- **Thank you for your attention**