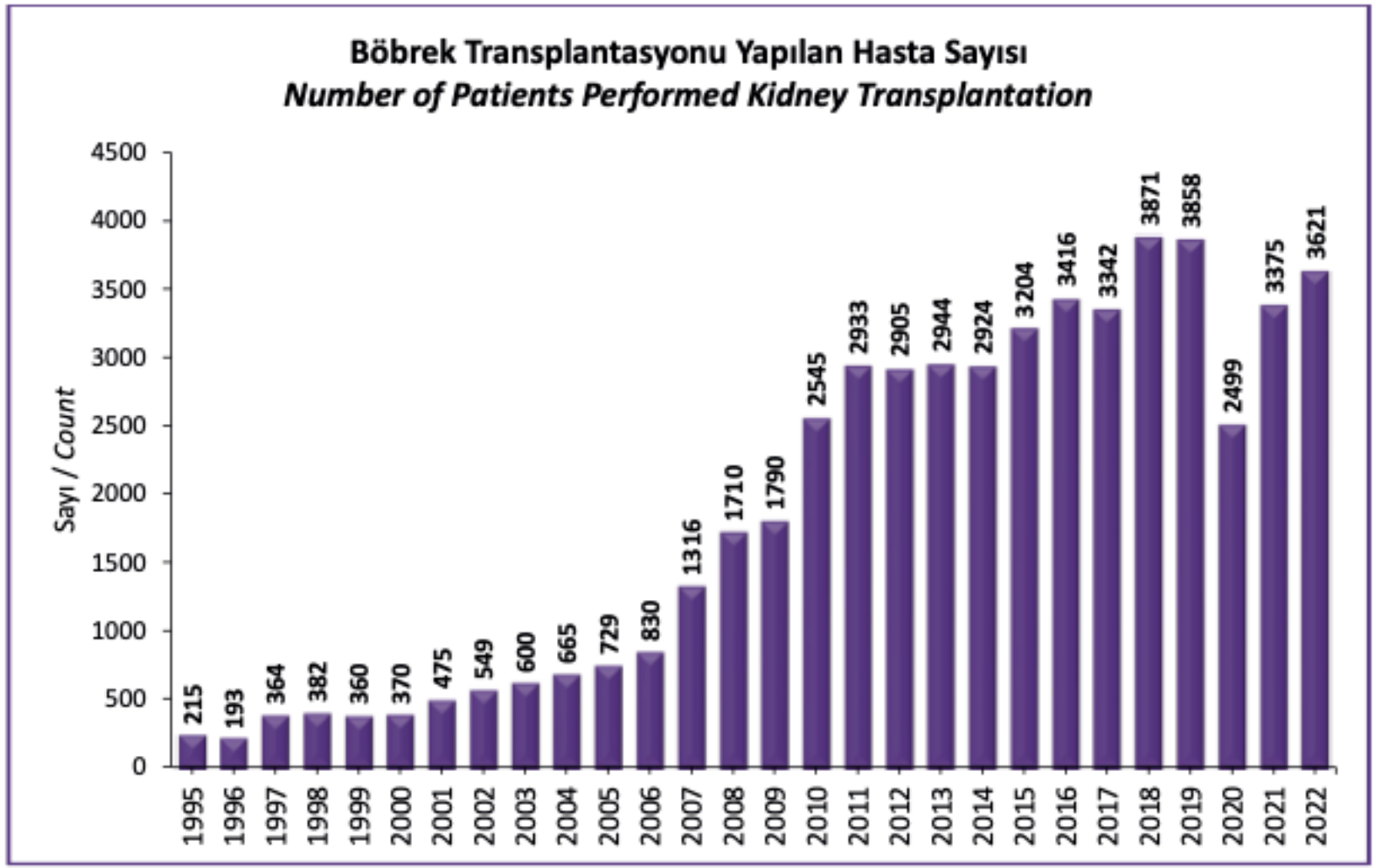
BÖBREK NAKLİNDE AKILCI İLAÇ KULLANIMI

Dr. Saliha YILDIRIM
21.04.2024

AKILCI İLAÇ KULLANIMI

Kişilerin hastalığına ve bireysel özelliklerine göre;

- **Uygun ilacı,**
- **Uygun sürede,**
- **Uygun dozda,**
- **En düşük maliyetle** kolayca sağlayabilmeleri



Türkiye 2022 Yılı Ulusal Nefroloji, Diyaliz ve Transplantasyon Kayıt Sistemi Raporu

2022 yılı sonu itibarıyla böbrek replasman tedavisi (BRT) uygulanan prevalan hastaların (çocuk hastalar dahil) BRT tipine göre dağılımı

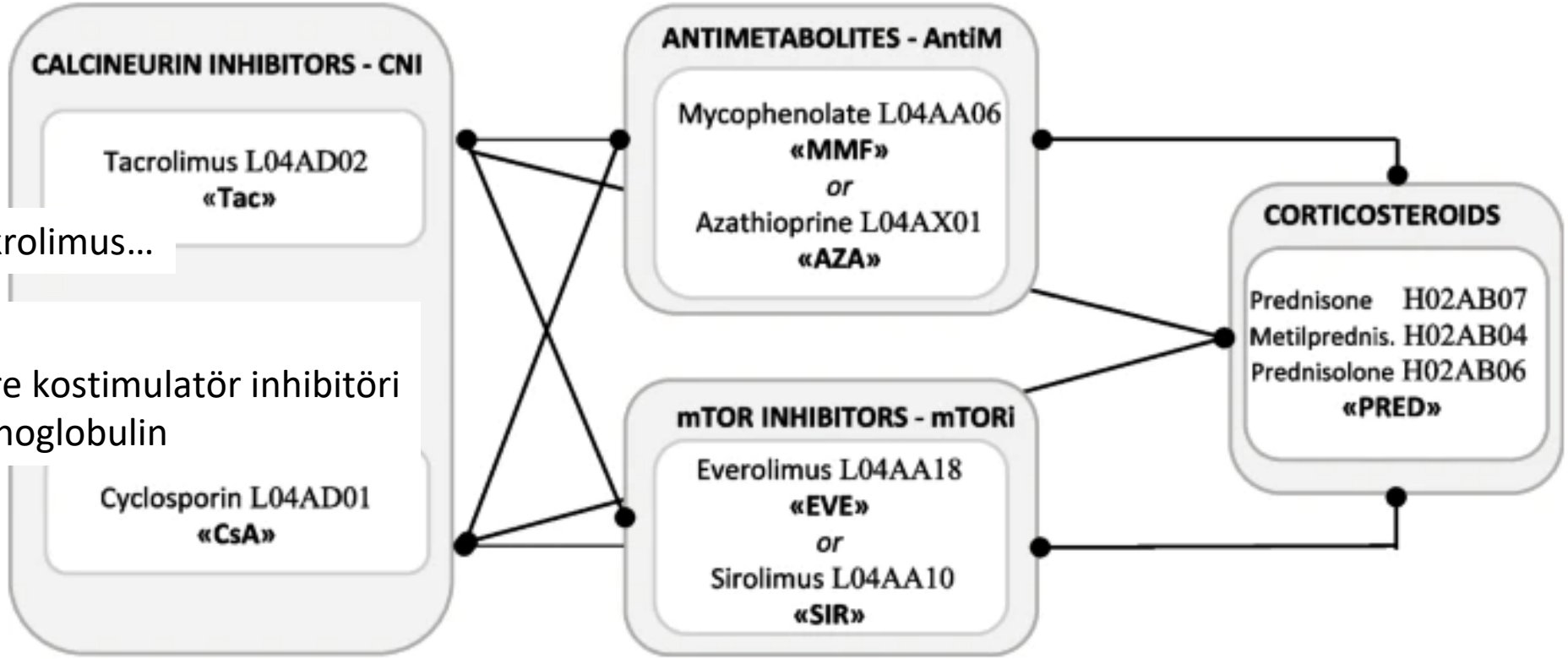
	n	%
Merkez hemodiyalizi / *In-center hemodialysis*	60.466	69,77
Ev hemodiyalizi / *Home hemodialysis*	1.257	1,45
Periton diyalizi / *Peritoneal dialysis*	3.552	4,10
Böbrek transplantasyonu / *Kidney transplantation* *	21.390	24,68
Toplam / *Total*	86.665	100,00

*** Yaklaşık sayı** / *Approximate number*

Türkiye 2022 Yılı Ulusal Nefroloji, Diyaliz ve Transplantasyon Kayıt Sistemi Raporu

Transplantasyon ve Tedavi

1. İmmünsupresif tedavi



Uzun etkili takrolimus…

Belatacept…
Selektif T hücre kostimulatör inhibitöri
Fc IgG1 immunoglobulin

Rosa A.C. BMC Nephrol **24**, 320 (2023)

Transplantasyon ve Tedavi

2. Non-immünsupresif tedavi

- Profilaksi
  - *CMV*
  - *PCP*
  - *BK viremi*
  - *Hepatit C , B*
- Hipertansiyon
- Diyabet
- Dislipidemi
- Diğer Tedaviler
  - *Kemik mineral*

3. Diğer Tedaviler

- Malignite tedavisi
- Enfeksiyon tedavisi
- …

Böbrek nakil hastasına yeni bir ilaç vermek…

- Nefrotoksisite
- Kemik iliği supresyonu
- İlaç etkileşimleri

Böbrek naklinde ilaç etkileşimleri

CNI metabolizmasını inhibe eden ilaçlar

Class	Inhibiting Drugs
Antibacterials (macrolide)	Clarithromycin, erythromycin
Antidepressant	Fluvoxamine, nefazodone
Azole antifungals	Fluconazole, itraconazole Posaconazole, voriconazole
Calcium channel blockers	Diltiazem, verapamil
Foods	Grapefruit/grapefruit juice Pomegranate/pomegranate juice
Protease Inhibitors (HCV)	Boceprevir, telaprevir
Protease Inhibitors (HIV)	Atazanavir, darunavir Fosamprenavir, indinavir Nelfinavir, ritonavir, saquinavir
Others	Amiodarone, Dalfopristin/quinupristin

Class	Inducing Drug
Antiseizure medications	Carbamazepine Fosphenytoin Oxcarbazepine Phenobarbital Phenytoin
Antituberculosis	Rifabutin Rifampin
Antiviral	Efavirenz
Others	Bosentan Modafinil St. John's wort (*Hypericum perforatum*)

CNI metabolizmasını uyaran ilaçlar

Antifungal/CNI etkileşimi

- Saad, et al. *Pharmacotherapy.* 2006:26(12) 1730-44.
- Nivoix Y, et al. *Clin Pharmacokin*. 2008:47(12)

Drug	Tacrolimus	Cyclosporine	Sirolimus
Fluconazole (Doses >200mg/day)	**40%**	**40%**	**50-70%**
Posaconazole	**75-80%**	**~0-30%**	
Itraconazole	**50-60%**	**50-60%**	
Voriconazole	**66%**	**50%**	**90%****

**** Kombinasyon önerilmez****

Diğer etkileşimler

Artmış nefrotoksisite riski: NSAID, aminoglikozidler, amfoterisin B…

Artmış kemik iliği supresyonu: Valgansiklovir, kemoterapetikler…

Statin ve CNI kombinasyonuyla artmış rabdomiyoliz riski (pravastatinle en az, simvastatinle en fazla)

Kolşisin ve CNI kombinasyonuyla artmış rabdomiyoliz riski

Diğer etkileşimler

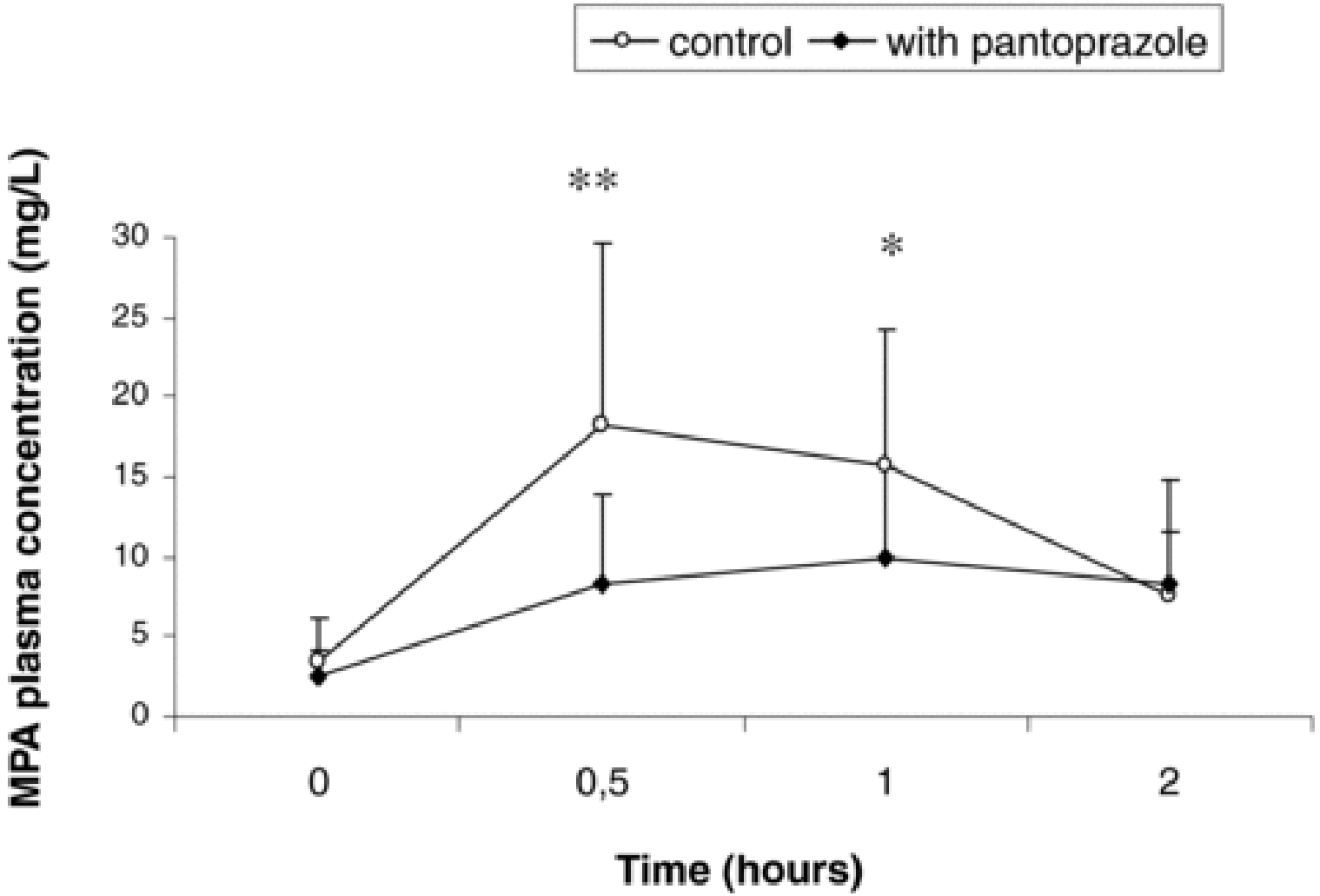
PPI ve Mikofenolat mofetilin beraber kullanılması MMF emilimini azaltır, enterik kaplı mikofenolat sodyum tercih edilebilir

Fosfor bağlayıcılar mikofenolat mofetil ve enterik kaplı mikofenolat sodyumun emilimini azaltır

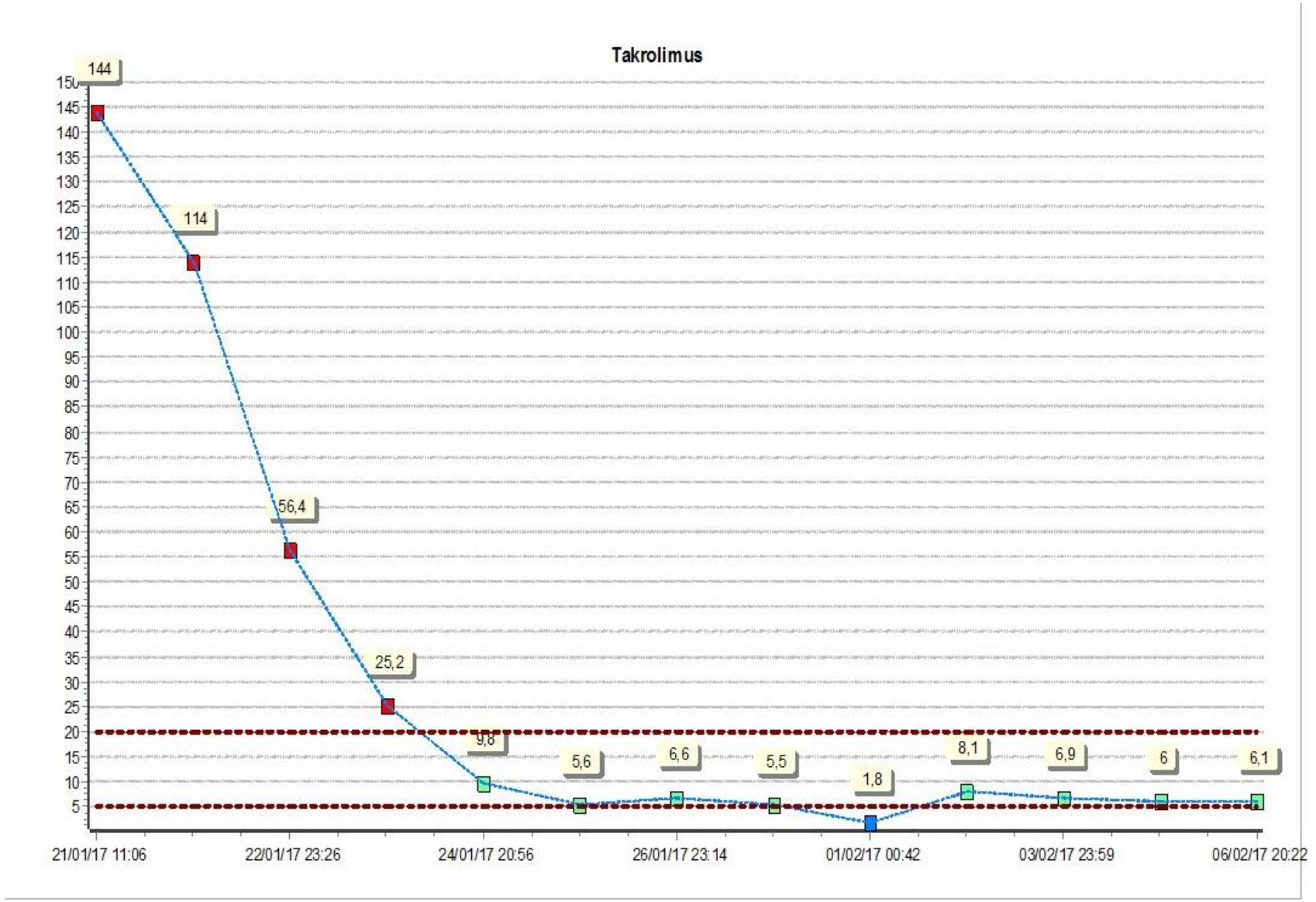
Allopurinol ve azatiopurin kombinasyonunda ciddi lökopeni, ciddi kemik iliği supresyonu

PPI/MMF ETKİLEŞİMİ

Kofler, et al. *Am J Transplant* 2009;9:1650-56



- **36 y erkek**
- **Tx tarihi 2017**
- **HCV için tedavi alıyor**



GASTROENTEROLOGY & HEPATOLOGY
The Independent Peer-Reviewed Journal

Gastroenterol Hepatol (N Y). 2018 Dec; 14(12): 687–705.

PMCID: PMC6383160
PMID: 30804716

Update on the Management of Hepatitis C Virus Infection in the Setting of Chronic Kidney Disease and Kidney Transplantation

Nyan L. Latt, MD

Based on the HCV-TARGET real-world study as well as the MAGELLAN-2 trial, patients with HCV genotype 2, 3, 5, or 6 infection who are receiving a kidney transplant can be treated with either glecaprevir/pibrentasvir or sofosbuvir/daclatasvir.[40,41] Sofosbuvir-based pangenotypic regimens, such as sofosbuvir/velpatasvir and sofosbuvir/ velpatasvir/voxilaprevir, can also be considered; however, there is a paucity of evidence demonstrating the efficacy of these regimens in kidney transplant recipients. Figure 2 displays the proposed management algorithm and guideline for kidney transplant recipients who receive HCV antibody–positive, NAT-negative or -positive kidneys.

- Glecaprevir + Pibrentasvir 12 hafta (GFR <30 ml/dakika olanlarda) Takrolimus serum seviyeleri takip edilir, gerekirse doz ayarı yapılır, siklosporin >100 mg/günlük dozlarda kullanılmaz)

What GP's need to know about the renal transplant patient

By Dr. Yvonne Ryan trainee North East training scheme and Professor Peter Conlon Consultant Nephrologist, Department of Nephrology, Beaumont Hospital Dublin.

Medications to avoid
Non Steroidal Anti Inflammatories
Anti fungals: Fluconazole, ketoconazole, itraconazole
Macrolides; Clarithromycin, Erythromycin etc
Other Antibiotics; Rifampicin
Diltiazem, verapamil
Allopurinol if the patient is taking Azathioprine/Imuran


https://reference.medscape.com/drug-interactionchecker
https://www.drugs.com/drug_interactions.html

Transplant International / Volume 30, Issue 5 / p. 502-509

Original Article | Free to Read

Higher calcineurin inhibitor levels predict better kidney graft survival ir with *de novo* donor-specific anti-HLA antibodies: a cohort study

ORIGINAL ARTICLE

Therapeutic Drug Monitoring of Tacrolimus-Personalized Therapy: Second Consensus Report

Brunet, Mercè PharmD, PhD[1]; van Gelder, Teun MD, PhD[2]; Åsberg, Anders PhD[3]; Haufroid, Vincent PharmD, PhD[4,5]; Hesselink, Dennis A. MD, PhD[6]; Langman, Loralie PhD[7]; Lemaitre, Florian PharmD, PhD[8]; Marquet, Pierre MD, PhD[9]; Seger, Christoph PhD[10]; Shipkova, Maria MD[11]; Vinks, Alexander PharmD, PhD[12,13]; Wallemacq, Pierre PharmD, PhD[14]; Wieland, Eberhard MD[11]; Woillard, Jean Baptiste PharmD, PhD[15]; Barten, Markus J. MD[16]; Budde, Klemens MD, PhD[17]; Colom, Helena PharmD, PhD[18]; Dieterlen, Maja-Theresa MD[19]; Elens, Laure PhD[20]; Johnson-Davis, Kamisha L. PhD[21]; Kunicki, Paweł K. PhD[22,23]; MacPhee, Iain MD[24]; Masuda, Satohiro PhD[25]; Mathew, Binu S. MD[26]; Millán, Olga PhD[1]; Mizuno, Tomoyuki MD[12,13]; Moes, Dirk-Jan A. R. PharmD, PhD[27]; Monchaud, Caroline PharmD, PhD[15]; Noceti, Ofelia PharmD, PhD[28]; Pawinski, Tomasz PhD[23]; Picard, Nicolas PharmD, PhD[15]; van Schaik, Ron MD[29]; Sommerer, Claudia MD[30]; Vethe, Nils Tore PhD[31]; de Winter, Brenda PharmD, PhD[32]; Christians, Uwe MD, PhD[33]; Bergan, Stein PhD[31]

Author Information

Therapeutic Drug Monitoring 41(3):p 261-307, June 2019. | ***DOI:*** 10.1097/FTD.0000000000000640

Binita M. Kamath, Vicky Ng, Rulan S. Parekh, Cedric Manlhiot, Seema Mital

First published: 03 September 2018
https://doi.org/10.1111/petr.13285

The association between *CYP3A5* genotype and tacrolimus dose requirement is consistent (Grading A I). So far, pharmacodynamic and immunologic biomarkers have not entered routine monitoring, but determination of residual nuclear factor of activated T cells–regulated gene expression supports the identification of renal transplant recipients at risk of rejection, infections, and malignancy (B II). In addition, monitoring intracellular T-cell IFN-g production can help to identify kidney and liver transplant recipients at high risk of acute rejection (B II) and select good candidates for immunosuppression minimization (B II). Although cell-free DNA seems a promising biomarker of acute donor injury and to assess the minimally effective C_0 of tacrolimus, multicenter prospective interventional studies are required to better evaluate its clinical utility in solid organ transplantation. Population PK models including *CYP3A5* and *CYP3A4* genotypes will be considered to guide initial tacrolimus dosing. Future studies should investigate the clinical benefit of time-to-event models to better evaluate biomarkers as predictive of personal response, the risk of rejection, and graft outcome.

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *CYP3A5* Genotype and Tacrolimus Dosing

Table 2 Dosing recommendations for tacrolimus based on *CYP3A5* phenotype

CYP3A5 phenotype[a]	Implications for tacrolimus pharmacologic measures	Therapeutic recommendations[b]	Classification of recommendations[c]
Extensive metabolizer (CYP3A5 expresser)	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5–2 times recommended starting dose.[d] Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Intermediate metabolizer (CYP3A5 expresser)	Lower dose-adjusted trough concentrations of tacrolimus and decreased chance of achieving target tacrolimus concentrations.	Increase starting dose 1.5–2 times recommended starting dose.[a] Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	Strong
Poor metabolizer (CYP3A5 nonexpresser)	Higher ("normal") dose-adjusted trough concentrations of tacrolimus and increased chance of achieving target tacrolimus concentrations.	Initiate therapy with standard recommended dose. Use therapeutic drug monitoring to guide dose adjustments.	Strong

[a]Typically, with other CYP enzymes, an extensive metabolizer would be classified as a "normal" metabolizer, and, therefore, the drug dose would not change based on the patient's genotype. However, in the case of CYP3A5 and tacrolimus, a CYP3A5 expresser (i.e., CYP3A5 extensive metabolizer or intermediate metabolizer) would require a higher recommended starting dose and the CYP3A5 nonexpresser (i.e., poor metabolizer) would require the standard recommended starting dose. [b]This recommendation includes the use of tacrolimus in kidney, heart, lung, and hematopoietic stem cell transplant patients, and liver transplant patients in which the donor and recipient genotypes are identical. [c]Rating scheme is described in **Supplementary Data** online. [d]Further dose adjustments or selection of alternative therapy may be necessary because of other clinical factors (e.g., medication interactions, or hepatic function).

Five-year follow-up of a phase I trial of donor-derived modified immune cell infusion in kidney transplantation

Results: The 10 MIC patients had an excellent clinical course with stable kidney graft function, no donor-specific human leukocyte antigen antibodies (DSA) or acute rejections, and no opportunistic infections. In comparison, a retrospectively matched control group receiving standard immunosuppressive therapy had a higher frequency of DSA (log rank $P = 0.046$) and more opportunistic infections (log rank $P = 0.033$). Importantly, MIC patients, and in particular the four patients who had received the highest cell number 7 days before surgery and received low immunosuppression during follow-up, continued to show a lack of anti-donor T lymphocyte reactivity *in vitro* and high $CD19^{+}CD24^{hi}CD38^{hi}$ transitional and $CD19^{+}CD24^{hi}CD27^{+}$ memory B lymphocytes until year five after surgery.

Conclusions: MIC infusions together with reduced conventional immunosuppression were associated with good graft function during five years of follow-up, no *de novo* DSA development and no opportunistic infections. In the future, MIC infusions might contribute to graft protection while reducing the side effects of immunosuppressive therapy. However, this approach needs further validation in direct comparison with prospective controls.

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Volume 14 - 2023 |

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Matthias

ior authors.

1172/JCI133595.

Sonuç olarak…

- Böbrek nakli kronik böbrek hastalığının en iyi tedavisi
- Çoklu ilaç kullanımı…
- İlaç etkileşimleri…
- İlaç yan etkileri…
- Genetik ve immunoloji…
  - Her hasta birbirini aynı mı?
  - Kişiselleştirilmiş immunsupresyon?
  - Daha düşük doz immunsupresyon ama daha düşük rejeksiyon mümkün mü?

Teşekkürler