

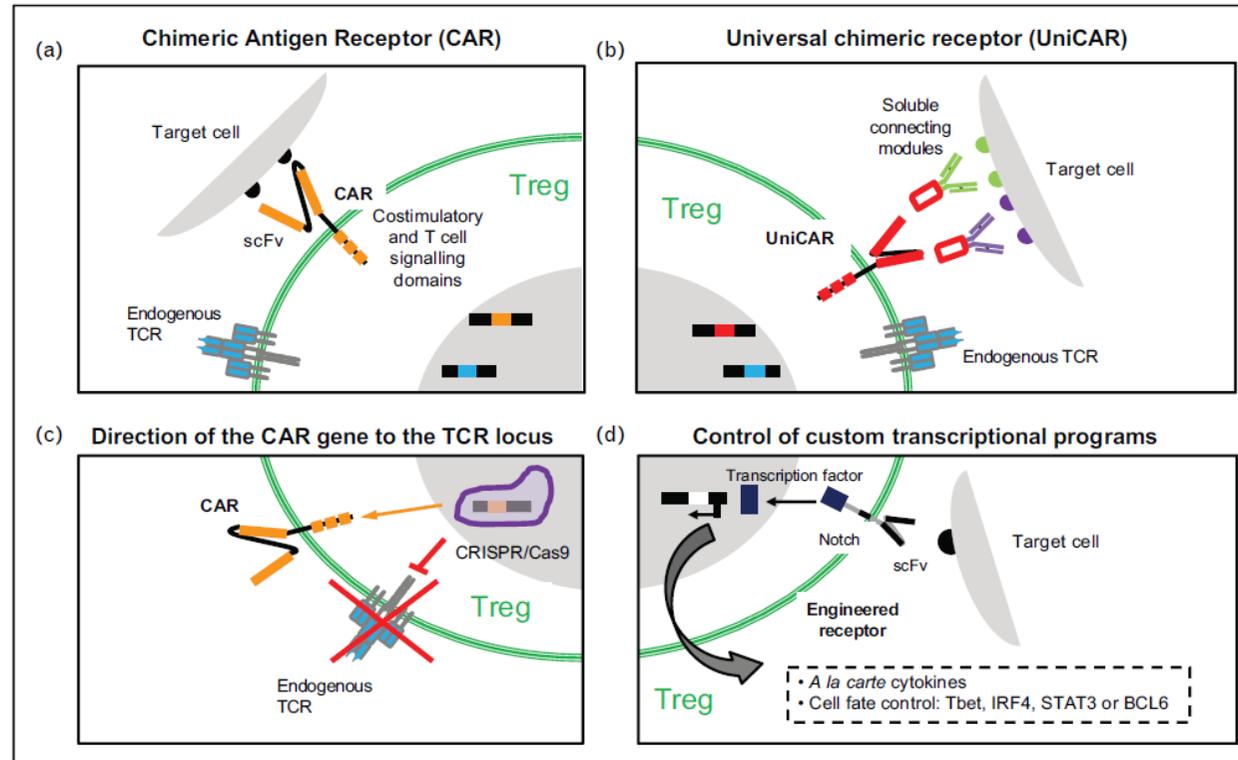
# **Leki i protokoły immunosupresyjne u chorych po przeszczepieniu narządów**

**Teresa Bączkowska**

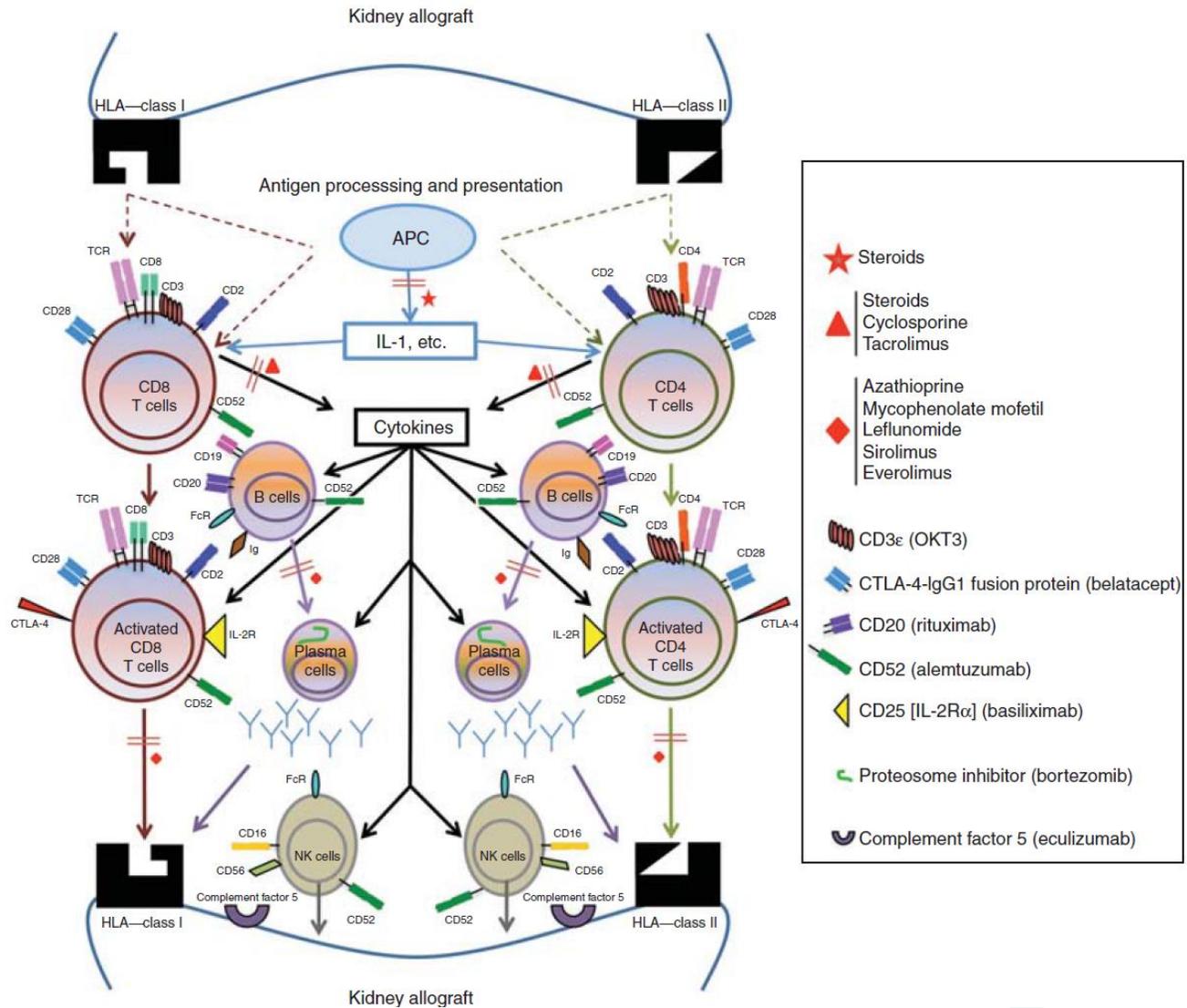
***Klinika Medycyny Transplantacyjnej i Nefrologii  
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Uniwersytetu Medycznego***

# Tolerancja alopreszczepu narządowego u ludzi ( nerka < 1/3000; wątroba do 20% )

<b>Autor</b>	<b>n</b>	<b>Data publikacji</b>
Owens	6	1975
Uehling	1	1976
Zoller	9	1980
Strober	3	1989
Helg	1 <sup>a</sup>	1994
Jacobsen i wsp.	1 <sup>a</sup>	1994
Burlingham	1	1995
Sorof	1 <sup>a</sup>	1995
Fisher i wsp	1	1996
Christensen	1	1998
Spitzer i wsp	1 <sup>b</sup>	1999
Starzl i wsp	7	2004
Newell i wsp	16	2006
Roussey-Kesler i wsp	10	2006



**FIGURE 1.** Novel approaches that may represent the future of antigen-specific Treg therapy. (a) Chimeric antigens receptor (CAR) technology: CARs are composed of an extracellular antigen-binding domain, often comprising a single-chain Ab (scFv), which is fused to intracellular signaling domains. CAR-expressing Tregs can bind and be activated by native antigens. (b) The universal CAR (UniCAR) approach: the CAR does not directly bind target cells, but instead utilizes a soluble 'connecting module' to engage the antigen(s) of interest. (c) Using genome editing to place the CAR gene within the TCR locus may allow more natural regulation of receptor expression and hence Treg function. (D) Control of custom transcriptional programs following target-antigen engagement: example of chimeric receptors engineered with the synthetic NOTCH approach [19].



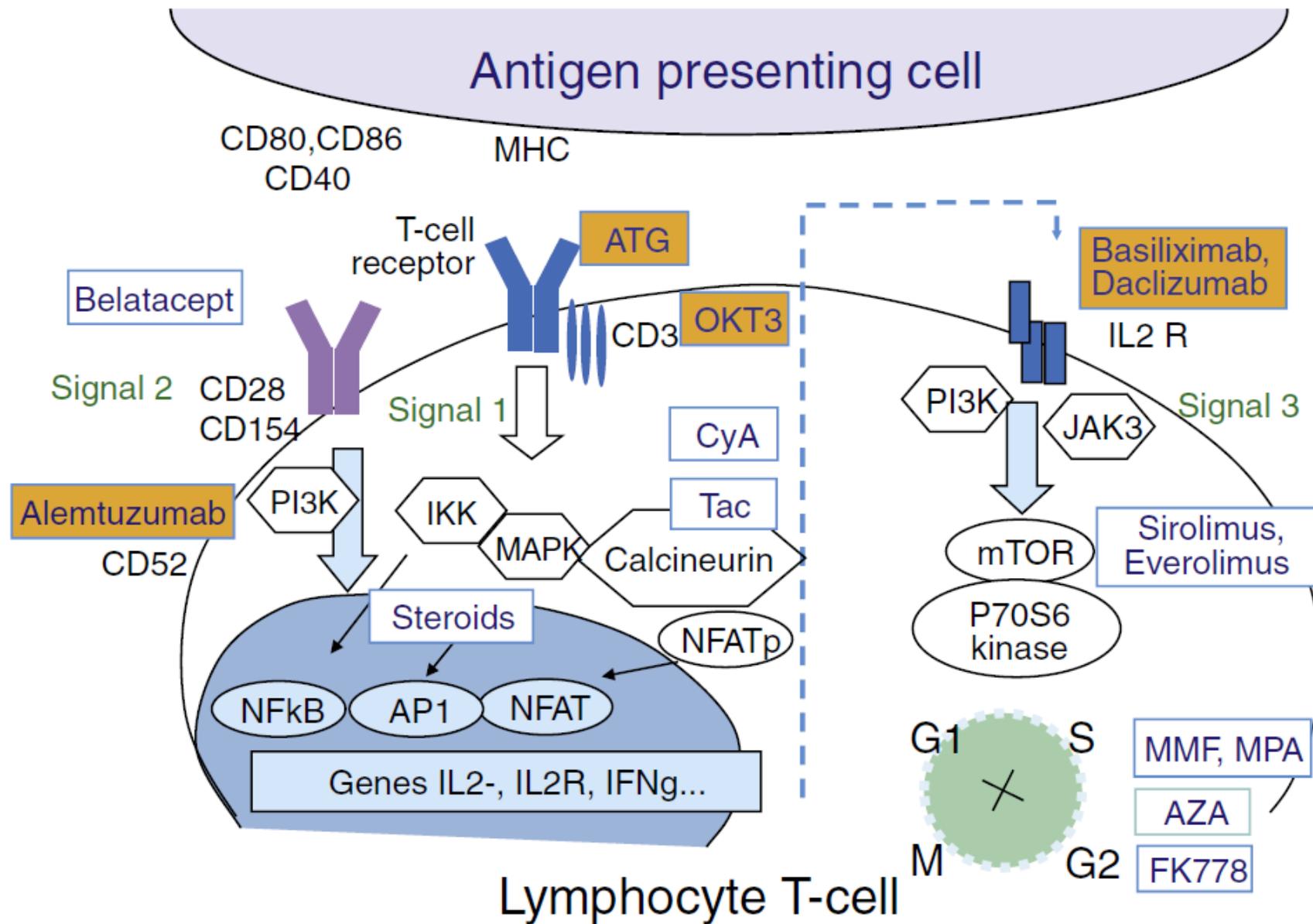
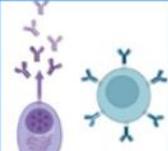
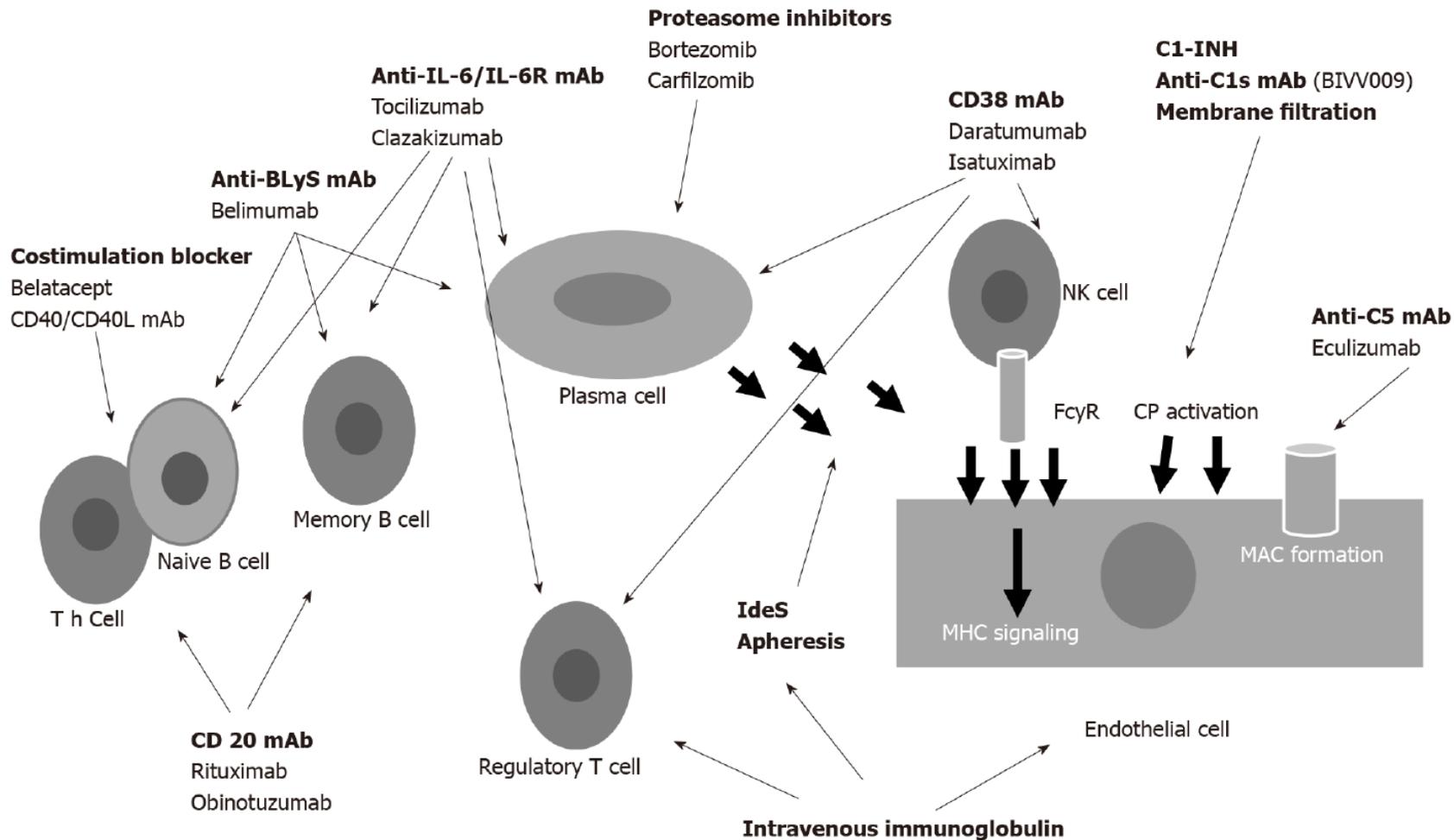


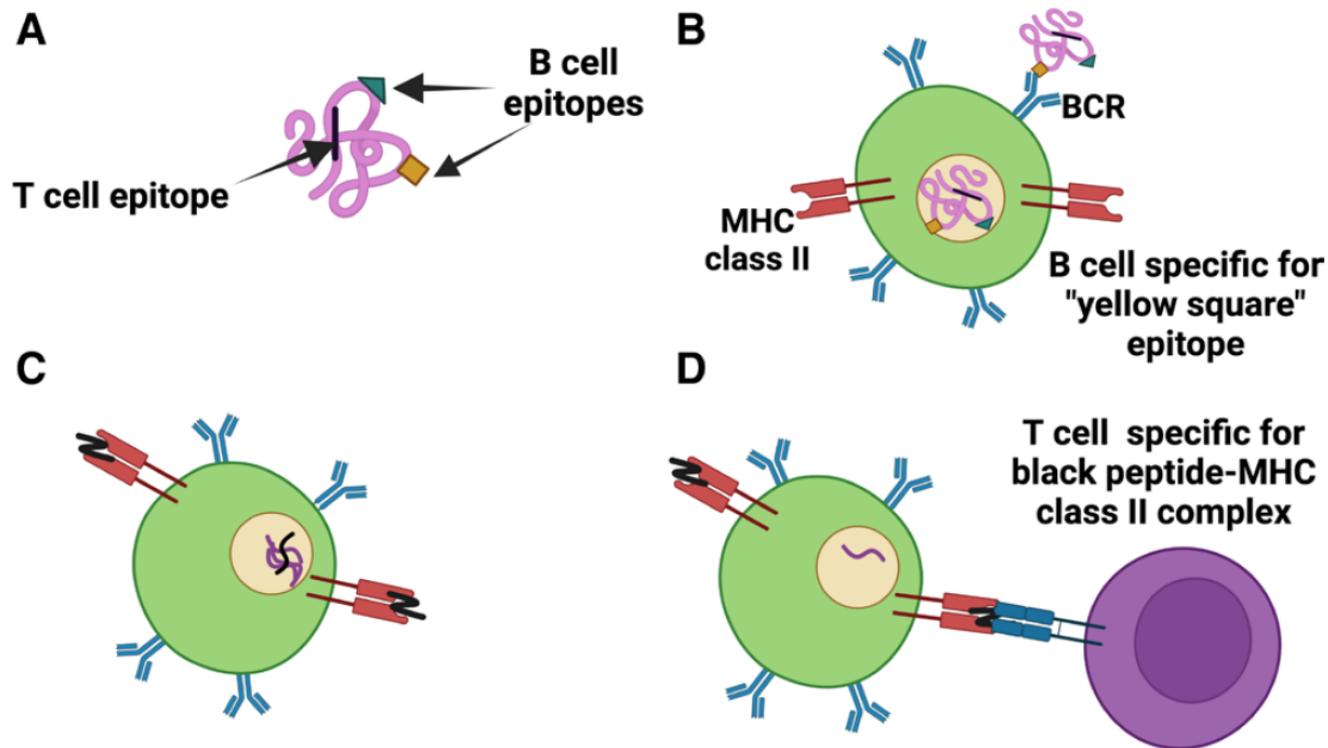
Figure 1. Cellular targets for induction agents used in liver transplantation.

	T cell 	B cell/ Plasma cell 	NK cell 	Monocyte Macrophage DC 
MPA	-inhibits T cell proliferation	-strong inhibition of plasma cell differentiation	-inhibits <i>ex vivo</i> NK cell functionality	-does not strongly affect monocyte function  -inhibits DC maturation
CNI	-inhibits IL-2 signaling and TCR signaling	-likely inhibits BCR signaling	-inhibits NK cell degranulation and IFN- $\gamma$ production	-limited effect on monocytes -CNI do not affect DC development
Belatacept	-competitive inhibition of the interaction between CD28 on T cells and CD80/86 on APC	-modulates B cell function directly and at the level of B cell- T follicular helper interaction  -reduces plasmablast differentiation	-might also inhibit NK cell activation since CD86 is described as an activating receptor on NK cells	-
GC	-interferes with T cell activation at various levels (TCR activation, differentiation, polarization)	- impair upstream BCR signaling  - moderate on antibody production	-reduce proliferation and ability to lyse cells	-inhibit the transcription of many pro-inflammatory cytokines
mTOR inhibitor	-inhibits T cell differentiation -favour Treg induction	-no inhibition of antibody formation <i>in vivo</i>	-little inhibitory efficacy regarding receptor modulation and cytokine production	-induction of autophagy facilitates the presentation of endogenous proteins on MHC classes I and II molecules in DC

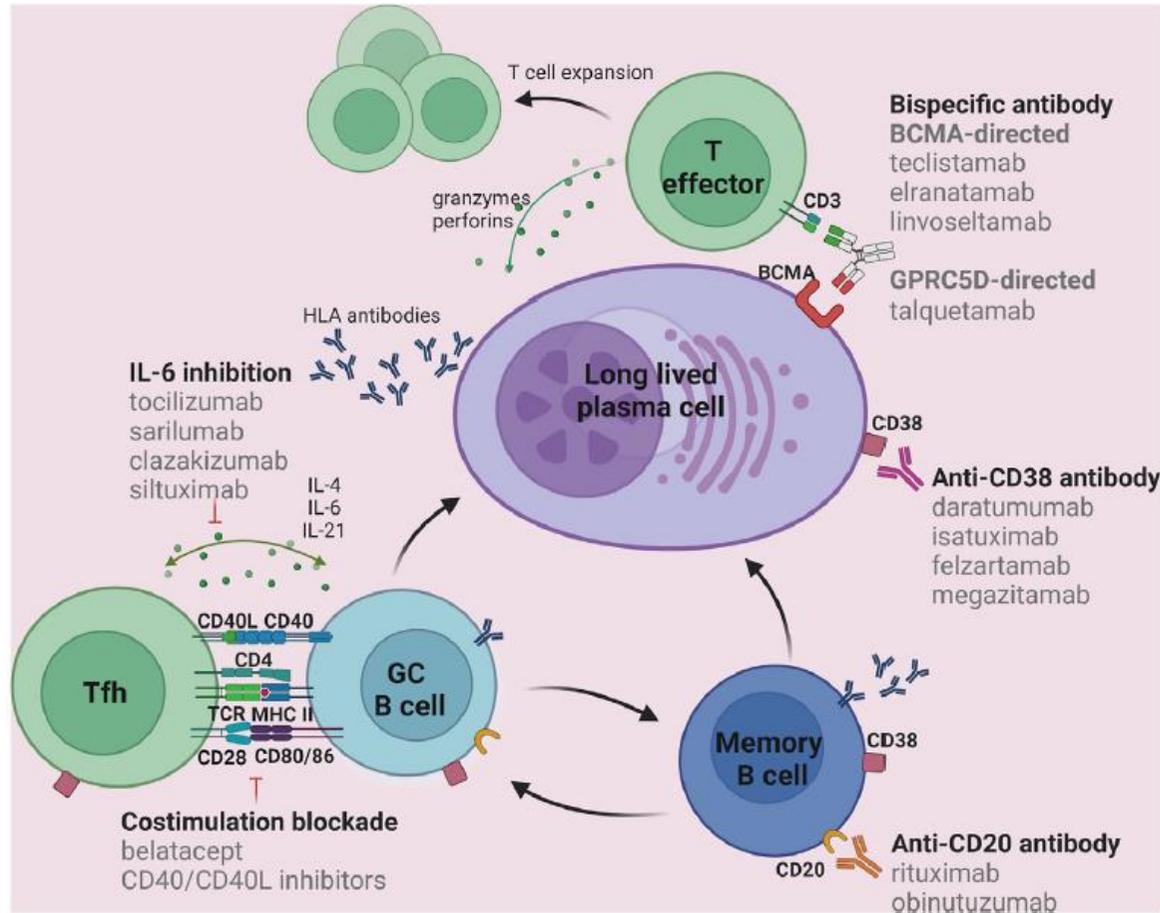
**FIGURE 1.** Overview of major effects of current maintenance immunosuppressants on different immune cells. APC, antigen-presenting cell; BCR, B cell receptor; CNI, calcineurin inhibitor; DC, dendritic cell; GC, glucocorticoid; IL, interleukin; MHC, major histocompatibility complex; MPA, mycophenolic acid; mTOR, mechanistic target of rapamycin; NK, natural killer; TCR, T cell receptor.



**Figure 4 Drugs acting at different levels to control the antibody formation.** BLyS: B Lymphocyte stimulating factor; mAb: Monoclonal antibody; C1-INH: C1 inhibitors; NK: Natural killer; Cp: Complement; FcyR: FcyReceptor; MAC: Membrane attacking complex; MHC: Major histocompatibility complex; IL: Interleukin.



**FIGURE 1.** Distinct epitopes on the same protein are recognized by B and T cells. A, Two conformational epitopes, a “green triangle,” and a “yellow square” represent B-cell epitopes in the protein and a linear “black peptide” represents the T-cell epitope in this protein. B, The BCR specific for a “yellow square” epitope on a B cell binds specifically to and endocytoses the protein antigen. C, In the late endosomal/lysosomal compartment, the endocytosed antigen is processed to peptides and the “black peptide” binds the MHC class II groove and is transported to the cell surface of the B cell. D, An activated  $CD4^+$  T cell specific for the black peptide (previously activated by DCs presenting the same black peptide on an identical MHC class II molecule) now recognizes the B cell that has processed and presented the black peptide on its MHC class II molecules. BCR, B-cell receptor; DC, dendritic cell; MHC, major histocompatibility complex.



**Figure 3.** Mechanisms of human leukocyte antigen (HLA) antibody rebound and pharmacologic targets for source control of HLA antibody production. A multipronged strategy that combines plasma cell depletion (eg, using anti-CD38 antibodies) with costimulation blockade (eg, using belatacept), Tfh inhibition (eg, using IL-6 inhibition) or B cell depletion (eg, using rituximab) may be most effective in achieving effective and durable control of HLA antibodies. Figure created in [Biorender.com](https://www.biorender.com). BCMA, B cell maturation antigen; IL-6, interleukin 6; Tfh, T follicular helper cell.

**TABLE 2.****Therapies targeting T-B collaboration**

Categories	Target	Reagent	Target	Clinical trial and indications	Target disease	NCT number
Costimulatory blockade	CD28	FR104/VEL-101	Pegylated anti-CD28 Fab' fragment	Phase I/II; phase I	Solid organ transplant	NCT05238493; NCT04837092
		Lulizumab	Pegylated anti-CD28 specific domain antibody	Phase IIa	Solid organ transplant, SLE	NCT04903054; NCT04066114; NCT-2265744
	CD80/86	Abatacept	CTLA4-Ig	FDA approved for rheumatoid arthritis and prophylaxis of acute GVHD	Rheumatoid arthritis, acute GVHD	
		Belatacept	CTLA4-Ig	FDA approved for kidney transplant patients	Solid organ transplant	
	CD40L	Ruplizumab (hu5C8) <sup>a</sup>	Anti-CD40L mAb	Discontinued because of thromboembolic events	Solid organ transplant	
		Toralizumab (IDEC-131) <sup>a</sup>	Anti-CD40L mAb	Discontinued because of thromboembolic events	Solid organ transplant	
		Toralizumab (IDEC-131) <sup>a</sup>	Anti-CD40L mAb	Discontinued because of thromboembolic events	Solid organ transplant	
	CD40	Dapirolizumab	Anti-CD40L mAb	Phase I	SLE	NCT01764594
		Iscalimab	Anti-CD40 mAb	Halted because of non superiority compared with CN1	Solid organ transplant	NCT03663335
		Bleselumab	Anti-CD40 mAb	Phase I	Solid organ transplant	NCT01780844; NCT01279538

Plasma cell–  
targeted  
therapy

Proteasome	Bortezomib	Proteasome inhibitor	FDA approved for multiple myeloma	Multiple myeloma	
	Carfilzomib	Proteasome inhibitor	FDA approved for multiple myeloma	Multiple myeloma	
CD38	Daratumumab	Anti-CD38 mAb	FDA approved for multiple myeloma	Multiple myeloma, solid organ transplant	
	Felzartamab	Anti-CD38 mAb	Phase III	Antibody-mediated rejection	NCT05021484
BCMA; CD3	REGN5458/9	Anti-BCMA <sup>+</sup> anti-CD3 bispecific mAb	Phase I/II	Multiple myeloma	NCT05137054
CD19	Inebilizumab	Humanized anti-CD19 mAb	Phase III	Neuromyelitis optic spectrum disorder	NCT02200770
CD20	Rituximab	Chimeric anti-CD20 mAb	FDA approved for non-Hodgkin's lymphoma, CLL, rheumatoid arthritis, granulomatous with polyangiitis, microscopic polyangiitis, pemphigus vulgaris		
	Ofatumumab	Humanized anti-CD20 mAb (IgG1k)	FDA approved for CLL, multiple sclerosis		
	Obinutuzumab	Humanized anti-CD20 mAb (defucosylated, IgG1)	FDA approved for CLL		

**TABLE 2. (Continued)**

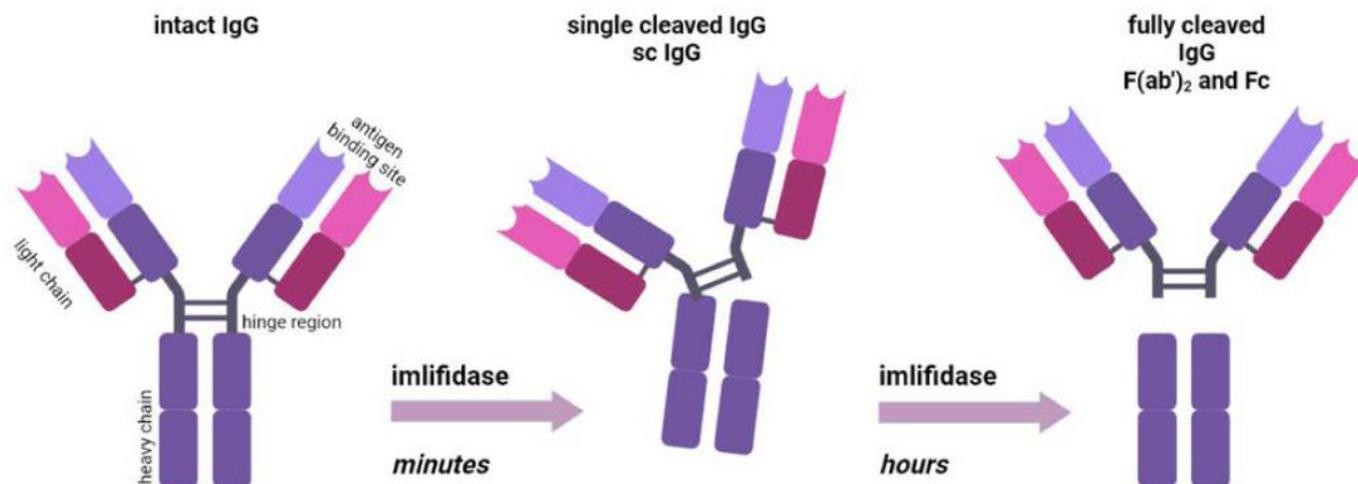
Categories	Target	Reagent	Target	Clinical trial and indications	Target disease	NCT number
Cytokine	IL-2	Aldesleukin	IL-2 (low dose)	Phase I/II	HCV vasculitis, GVHD, Type 1 diabetes, SLE, Solid organ transplant	NCT00574652; NCT00529035; NCT00525889; NCT04077684; NCT02417870
		Efavaleukin alfa	Mutant IL-2 Fc	Phase I/II	GVHD, SLE, Rheumatoid arthritis	NCT03422627; NCT03451422; NCT03410056
	IL-21	NNC0114-0006	Anti-IL-21 mAb	Phase II	Type 1 diabetes, Rheumatoid arthritis, Crohn's disease	NCT02443155; NCT01208506
		BOS161721	Anti-IL-21 mAb	Phase I/II	SLE	NCT03371251
		ATR-107	Anti-IL-21R mAb	Phase I	PK/PD study in healthy subjects	NCT01162889
	IL-6	Clazakizumab	Anti-IL-6 mAb (humanized IgG1)	Phase III	Solid organ transplant	NCT03744910
		Tocilizumab	Anti-IL-6Ra mAb	Phase III	Solid organ transplant	NCT04561986
	IL-7	RN168	Anti-IL-7Ra mAb	Phase I	Type 1 diabetes	NCT02038764
		OSE-127	Anti-IL-7Ra mAb	Phase II	Ulcerative colitis	NCT04882007

<sup>a</sup>Discontinued because of side-effect profile.

CLL, chronic lymphocytic leukemia; CNI, calcineurin inhibitor; CTLA4, cytotoxic T lymphocyte-associated protein 4; FDA, Food and Drug Administration; GVHD, graft-versus-host disease; HCV, hepatitis C virus; IL, interleukin; mAb, monoclonal antibody; PK/PD, pharmacokinetics/pharmacodynamics; SLE, systemic lupus erythematosus; TACI, transmembrane activator and CAML interactor.

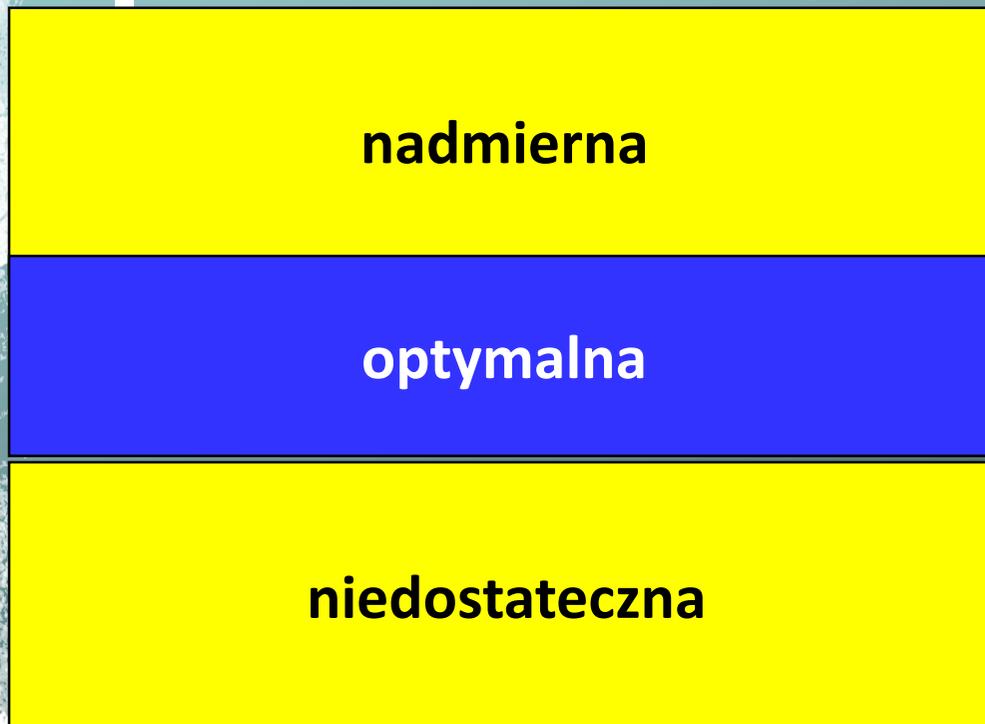
Daniel DiToro, MD, PhD,<sup>1,2</sup> Naoka Murakami, MD, PhD,<sup>3</sup> and Shiv Pillai, MBBS, PhD<sup>1</sup>

# Imlifidase Desensitization in HLA-incompatible Kidney Transplantation: Finding the Sweet Spot



**FIGURE 1.** Mechanism of action of imlifidase. Imlifidase cleaves intact IgG just below the hinge region in scIgG in a rapid first reaction in minutes. In a subsequent step, fully F(ab')<sub>2</sub> fragments and a fully separated Fc are generated within hours. Cleaved IgG is no longer able to exert its complement-dependent cytotoxicity and its antibody-dependent cellular toxicity functions. F(ab')<sub>2</sub>, antigen-binding fragment; Fc, fragment crystallizable; IgG, immunoglobulin G; scIgG, single-cleaved immunoglobulin G.

**Działania niepożądane, infekcje, nowotwory**



**odrzuć**

# Historyczny rys stosowania leków immunosupresyjnych

1954	Pierwsze udane przeszczepienie u bliźniąt jednojajowych
1958/9	Naświetlania promieniami X
Appr. 1960	doustne GS
1962	6-mercaptopurine, azathioprine (AZA), Imurane®
1963-78	Antithymocyte globulin (ATG, adjuvant to AZA+steroids (KTx)
1978	Cyclosporine (Sandimmun®) ( <i>Tolypocladium inflatum</i> : Jean Francois Borel - 1969; White, Calne - 1978)
1983	Cyclosporine + prednisone
1985	Cyclosporine + steroids + AZA (triple therapy)
1985-9	Trójlekowa IS + Antithymocyte globulin ALG or OKT3 (for rejection)
1990 on	Zmienne optymalne schematy IS : zazwyczaj trójlekowe +/-ATG
1994	Tacrolimus (Prograf®) + GS + inne schematy IS
1995/6	Mycophenolate mofetil (Cellcept®) zastępuje AZA Cyclosporine (Neoral®) zastępuje CyA Sandimmune®
1998	Basiliximab (Simulect®)
1998/9	Daclizumab humanised antibody (Zenapax®) - wycofany
1999/2000	Sirolimus, rapamycin (Rapamune®)
2002/3	Mycophenolate natrium (Myfortic) Everolimus (Certican®)
2007	Advagraf
2009	Belatacept
2014	Takrolimus -LCP (Envarsus)
2021	Imlifidaza

“Off label” alemtuzumab, rytuksymab, bortezomib, anty-IL-6, anty-CD40, anty-CD28, anty-C5a, ....

“Generyczne” leki immunosupresyjne (EMA od 2010r: 90% - 111%)

2005 (FDA) *Equoral (Cyklosporyna A)*

# Leki immunosupresyjne

## Inhibitory kalcineuryny:

cyklosporyna A, takrolimus, takrolimus MR-4, tacrolimus LCP,  
woklosporyna

## Inhibitory podziałów komórkowych;

wczesne: sirolimus, everolimus, *temsirolimus, ridaforolimus*

późne: azatiopryna, mykofenolan mofetilu, mykofenolan sodu,

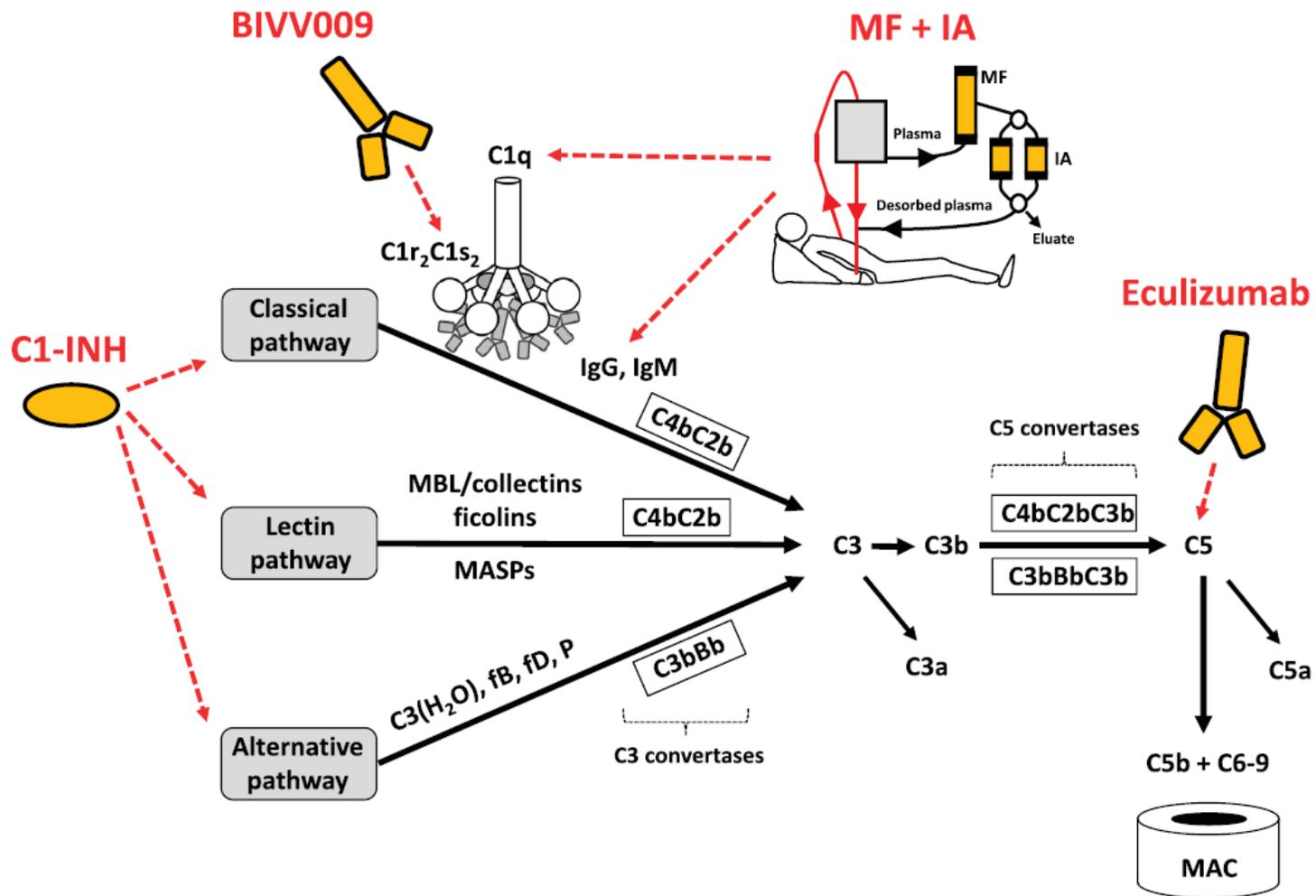
## Glikokortykosteroidy

## Czynniki biologiczne:

ATG, anty IL-2R (basiliximab), belatacept, *iscalimab*

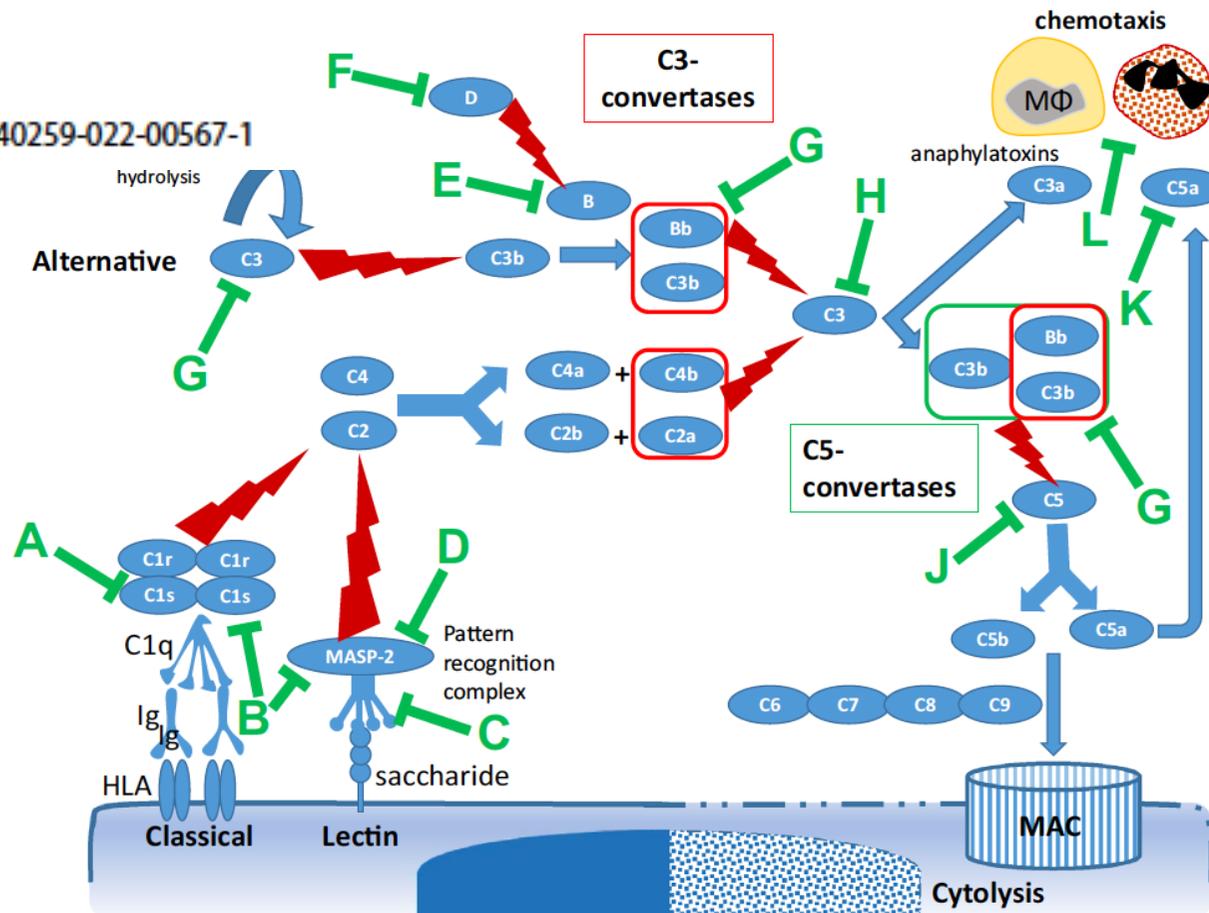
## Inne: Imlifidase

**Off label** anty-CD20, anty-CD52, bortezomib, carfilzomib, daratumumab,  
eculizumab, rawulizumab, tocilizumab, klazakizumab



**FIGURE 1.** Mode of action of 4 different strategies of complement interference evaluated in clinical transplantation. The C1 complex (C1q<sub>r</sub><sub>2</sub>s<sub>2</sub>), a key component of the CP, is activated upon antibody binding. Humanized monoclonal antibody BIVV009 targets its enzymatic subcomponent C1s and thereby blocks C4 and C2 cleavage and the formation of C4bC2b (C3 convertase). Treatment of patient plasma with membrane filtration (MF) plus IA allows for the depletion of antibodies (IgG, IgM) and C1q from the circulation. C1 inhibitor disassembles the C1 complex and blocks the activity of C1r and C1s. In the LP mannose-binding lectin (MBL)/collectins and ficolins recognize and bind carbohydrate patterns and subsequently activate MASPs which, in analogy to C1r/C1s, trigger the formation of C3 convertase. The AP is activated by amino groups of membrane proteins and carbohydrate patterns. Aged C3 molecules with hydrolyzed internal thioester—C3(H<sub>2</sub>O)—form together with fB—supported by fD and P—the fluid-phase C3 convertase. If this convertase cleaves native C3 in the vicinity of activating surfaces a membrane-associated C3 convertase is established (C3bBb). C1 INH may interfere also with lectin and the AP via interaction with MASPs and C3b, respectively. Humanized monoclonal antibody eculizumab binds with high affinity to C5 and prevents C5 convertase-mediated cleavage to C5a, a strong anaphylatoxin, and C5b, the initial trigger of MAC (C5b-9) assembly. IA, immunoadsorption; MAC, membrane attack complex; fB, factor B; fD, factor D; P, properdin; MASP, MBL-associated serine proteases.

BioDrugs (2023) 37:5–19

<https://doi.org/10.1007/s40259-022-00567-1>

**Fig. 2** Overview of drugable complement targets. **A** Target: C1s, Drug(s): Sutimlimab, Mode of action: Inhibition of C1s protease. **B** Target: C1s/r, MASPs, Drug(s): C1-INH, CYNRIZE, berinert, ruconest, Mode of action: CP/LP inhibition, other serine proteases. **C** Target: Collectin-11, Drug(s): I-Fucose, Mode of action: Saturation of Collectin-11 binding. **D** Target: MASP-2, Drug(s): OMS721, Mode of action: Inhibition of MASP-2. **E** Target: FB, Drug(s): LNP023, Mode of action: Inhibition of AP C3 convertase. **F** Target: FD, Drug(s): ACH-4471, lampalizumab, Mode of action: Inhibition of AP C3 convertase. **G** Target: C3/C5 convertases, Drug(s): Mirococept, Mode of action: Inhibition of all C3/C5 convertases. **H** Target: C3, Drug(s): AMY-101, APL-2, Mode of action: Inhibition of C3

activation. **I** Target: Properdin, Drug(s): CLG561, Mode of action: Inhibition of AP amplification. **J** Target: C5, Drug(s): Eculizumab, ravulizumab, SKY59/RO7112689, tesidolumab; pozelimab, ABP959, SB12, Mode of action: Blockage of C5 activation; Drug(s): Coverzin, Mode of action: Inhibition of C5 activation, Drug(s): Zilucoplan, Mode of action: Allosteric inhib. of C5 activation. **K** Target: C5a, Drug(s): IFX-1, Mode of action: Blocks binding of C5a to C5aR1. **L** Target: C5aR1, Drug(s): Avacopan, Mode of action: Antagonist of C5aR1 receptor; Drug(s): IPH5, Blockade of C5aR1 signaling. *C1-INH* C1 esterase inhibitor, *MAC* membrane-attack-complex, *MASP* mannan-binding lectin-associated serine protease

**SPECIAL ARTICLE****Plasma cell targeting to prevent antibody-mediated rejection**

E. Steve Woodle<sup>1</sup>  | Simon Tremblay<sup>1</sup>  | Amy Rossi<sup>2</sup> | Cyd C. Rojas<sup>3</sup> |  
 Rita Alloway<sup>4</sup> | Krishna Roskin<sup>5</sup> | David Allman<sup>6</sup> | David Hildeman<sup>7</sup>

**TABLE 1** Proteasome inhibitors approved for use or in clinical development

Generic name	Trade name	Manufacturer	Chemical class	Administration route	Primary catalytic inhibition
Bortezomib	Velcade	Takeda	Boronated	IV,SQ	$\beta$ 5
Ixazomib	Ninlaro	Takeda	Boronated	Oral	$\beta$ 5
Carfilzomib	Kyprolis	Amgen	Epoxyketone	IV	$\beta$ 5 + $\beta$ 5i
Oprozomib	n/a	Amgen	Epoxyketone	Oral	$\beta$ 5 + $\beta$ 5i
Marizomib	n/a	Nereus	Salinosporine	IV	$\beta$ 1

# Zasady leczenia immunosupresyjnego

- **Połączenie leków IS o różnych punktach uchwytu**
- **Silniejsza immunosupresja we wczesnym okresie po transplantacji (“indukcja”)**
- **Czas trwania: do końca funkcjonowania przeszczepu/życia chorego**
- **Redukcja w przypadku wystąpienia zagrożenia życia w przebiegu**
  - **infekcji oportunistycznych**
  - **choroby limfoproliferacyjnej**
  - **nowotworu**
- **Redukcja w przypadku rozpoznania nefropatii BK**
- **W ciąży: MPA, PSI (sirolimus/everolimus) - przeciwwskazane**

# Monitorowanie leczenia immunosupresyjnego

- **Empiryczne**
- **Farmakokinetyczne, farmakodynamiczne**
  - TDM (HPLC)
  - immunologiczne
  - biopsje protokolarne
  - farmakogenetyka, - genomika
- **Badania randomizowane, rejestry**
  - przeżycia chorych i przeszczepów
  - częstość AR
  - powikłania

## Monitorowanie stężeń CNI

- Pole pod krzywą stężeń AUC (*area under the concentration-time curve*)
- Skrócone AUC (AUC<sub>0-4h</sub>, Bayesian model)
- C min (C<sub>0</sub>) - zła korelacja z AUC, skutecznością, toksycznością, najczęściej stosowany, praktyczny sposób
- C max (dla CsA max C<sub>2</sub>)
- EMIT, HPLC (UV, MS) - szybko-przepływowa on-line ekstrakcja leku z 1 próbki krwi (technika automatycznej przyspieszonej obróbki próbki)
- Ograniczenia: nie ocenia wpływu leków na układ immunologiczny

# TDM

## Leki o wąskim oknie terapeutycznym

- **Cyklosporyna –C0, C2**
- **Takrolimus –C0**
- **Syrolimus, ewerolimus-C0**
- **MMF, MPS - MPA nie jest oznaczane standardowo, C0  
lepiej AUC- skrócone 3 punkty**

**Table 2.** Models for tacrolimus CL/F for model informed precision dosing (MIPD) in adult kidney transplant recipients.

Author	Patients	Methods	Covariates tested	Final algorithm	Main findings
Campagne <i>et al.</i> (2018) [68]	<ul style="list-style-type: none"> <li>67 patients, Caucasian population</li> <li>&gt;6 months post-transplantation</li> <li>Clinical trial</li> <li>Oral twice-daily formulation</li> </ul>	<ul style="list-style-type: none"> <li>Sampling: 1 full PK profile per patient (pre-dose, 1, 2, 3, 4, 6, 8, 10 and 12 hours post-dose)</li> <li>PK analysis: NONMEM®, two-compartment model with first-order elimination and absorption with lag time</li> <li>Validation: internal (bootstrap, VPC, simulation), simulation trial</li> </ul>	Age, ABCB1, albumin, BMI, comedication, creat, CYP3A5, diabetes mellitus, eGFR, ethnicity, glucose, Hb, HCT, HDL, LDL, leukocytes, platelets, POD, sex, TBW, total cholesterol, triglycerides	${}^a\text{CL/F} = 19.7 \times 1.45^{\text{IM}} \times 2.25^{\text{EM}} \times e^{0.1283}$ $\text{V/F} = 234 \times [\text{TBW}/85.9] \times e^{0.4627}$	Extensive metabolizers (CYP3A5*1/*1) and intermediate metabolizers (CYP3A5*1/*3, *1/*6, *1/*7) require a two-fold and 1.5-fold higher dose, respectively, compared to poor metabolizers (CYP3A5*3/*3, *6/*6, *7/*7, *3/*6, *3/*7, *6/*7)
Rong <i>et al.</i> (2019) [69]	<ul style="list-style-type: none"> <li>49 <i>de novo</i> patients, 50% Caucasian and 50% Chinese population</li> <li>Retrospective cohort</li> <li>Oral twice-daily formulation</li> <li>Corticosteroid-free regimen</li> </ul>	<ul style="list-style-type: none"> <li>Sampling: 40 sparse samples from 21 patients (pre-dose and 2 hours post-dose), 280 intensive samples from 28 patients (pre-dose, 0.5, 1–4, 6, 8, 10 and 12 hours post-dose)</li> <li>PK analysis: Monolix®, two-compartment model with first-order absorption with a lag time, linear elimination</li> <li>Validation: internal (bootstrap, VPC)</li> </ul>	Age, BW, creat, eGFR, height, MMF dose, MMF dose-normalized AUC, POD, sex	$\text{CL/F} = 17.9 \times [\text{eGFR}/56]^{-0.885} \times e^{0.346}$ $\text{V/F} = 150 \times [\text{eGFR}/56]^{-2.13} \times e^{0.808}$	The estimated glomerular filtration rate is inversely correlated with tacrolimus clearance

# Wolumetryczne mikropóbkowanie absorpcyjne (Volumetric Absorptive Microsampling – VAMS®)

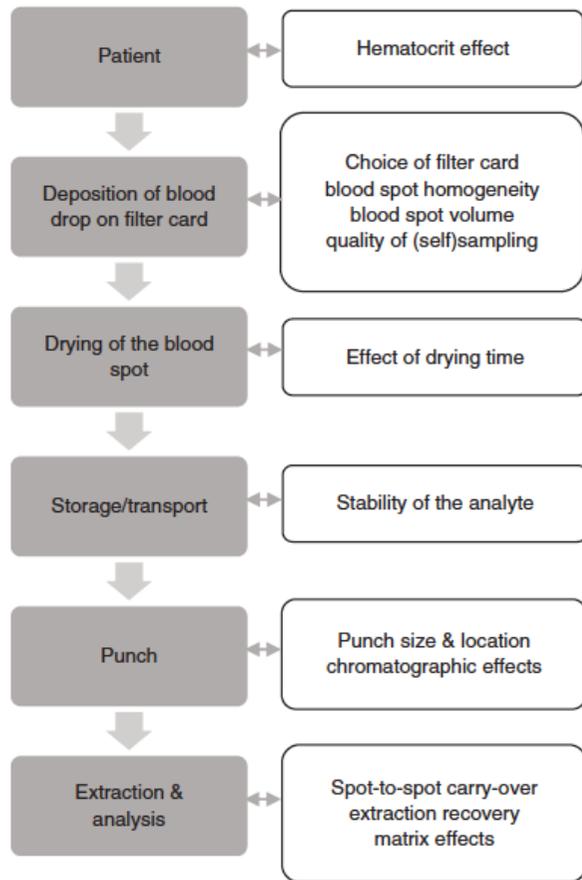
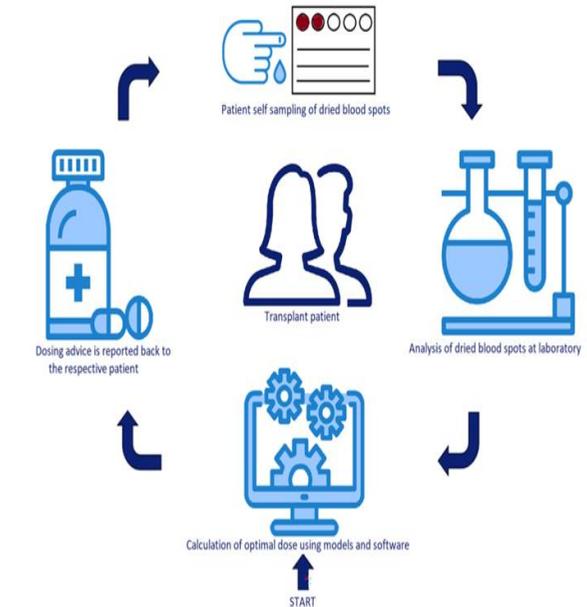


Figure 1: A summary of the important preanalytical factors for analysis of immunosuppressants with capillary DBS sampling.

## 'CLOSING THE LOOP'



Removing the physician from the equation: Patient-controlled, home-based therapeutic drug self-monitoring of tacrolimus

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 Dennis A. Hesselink<sup>1,2</sup>

Adrian Klak, Steven Pauwels and Pieter Vermeersch\*

## Preanalytical considerations in therapeutic drug monitoring of immunosuppressants with dried blood spots

**TABLE 3** Selected biomarkers and their clinical utility in kidney transplantation

Biomarkers	Potential clinical use
IFN- $\gamma$	Predicts rejection risk For risk stratification and selection of immunosuppression
IL-2	Predicts rejection risk For risk stratification and selection of immunosuppression
Serum soluble CD30	Predicts long-term allograft outcome
T cells CD26 and CD28 surface antigens	Associated with acute rejection and/or malignancy after transplantation
Regulatory T cells	Predicts acute rejection risk
Target enzyme activity: IMPDH	May predict acute rejection risk or MPA-associated side effects Better guide MPA therapy
Target enzyme activity: mTOR	Better guide mTOR inhibitor therapy
NFAT-regulated gene expression	May identify those at higher risk of acute rejection, opportunistic infections, cancers and cardiovascular risk Complements CNI pharmacokinetics to better guide CNI therapy
CXCs	Urinary CXCL-9 and CXCL-10 proteins as markers for kidney graft inflammation and alloimmune response Urinary CCL-2 as marker for inflammation and interstitial fibrosis in renal allografts
dd-cfDNA	Early detection of graft injury due to rejection, specific infections, or ischemia Serial dd-cfDNA determinations help to guide changes in immunosuppression, and to monitor minimization
CYP3A5	May help to determine the optimal starting tacrolimus dose

Abbreviations: CNI, calcineurin inhibitor; CXC, chemoattractant cytokines or chemokines; CYP, cytochrome P450; Donor-derived cell-free DNA, dd-cfDNA; IFN, interferon; IL, interleukin; IMPDH, inosine-monophosphate-dehydrogenase; MPA, mycophenolic acid; NFAT, Nuclear Factor of Activated T-Cell; mTOR, mammalian target of rapamycin.

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DOI: 10.1111/nep.14035

REVIEW ARTICLE

NEPHROLOGY  WILEY

Personalized immunosuppression after kidney transplantation

Chi Yuen Cheung<sup>1</sup> | Sydney Chi Wai Tang<sup>2</sup>

**Tabela 1. Wskazania do indukcji przeciwciałami poliklonalnymi i monoklonalnymi (anty CD25 IL2R) w zależności od poziomu ryzyka immunologicznego**

poziom ryzyka	MFI	Opis	przeciwciała poliklonalne	anty CD25 IL2R
I	Ab anty HLA niewykrywalne	Standardowe ryzyko odrzucania	nie wskazane	decyzja o podaniu zależy od innych czynników
II	DSA <2 000	Minimalne ryzyko nadostrego odrzucania (HR –Hyperacute Rejection) związane z niskim stężeniem DSA, ale wyższe niż w standardowym ryzyku odrzucania	do rozważenia w przypadku wcześniejszych transplantacji, transplantacji straconych w wyniku AMR i w przypadku XM CDC (+) w poprzednich typowaniach (widoczne w KLO zakładce "lista typowań")	wskazane podanie jeśli nie ma czynników wymienionych w kolumnie obok
III	DSA 2000-5000	Niskie ryzyko HR, ale zwiększone ryzyko wczesnego odrzucania typu humoralnego (AMR) z uszkodzeniem graftu	Wskazane	
IV	DSA >5000	Przeciwwskazanie do transplantacji pacjent czeka na innego dawcę (z innymi HLA)		

\*inne postępowanie dotyczy chorych bardzo dużego ryzyka immunologicznego opisanych w podrozdziale "Chorzy do retransplantacji i z PRA CDC >80%"

# Leczenie immunosupresyjne

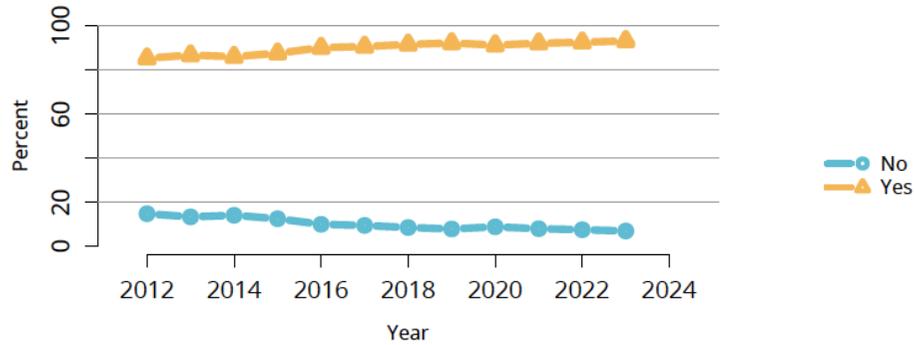
## Indukcja :

**Thymoglobulina, anty-IL2, rytuksymab, alemtuzumab**

## Immunosupresja podtrzymująca

**Tac/CsA + MMF/MPS and/or mTOR inhibitor or Aza or  
mTOR + GS**

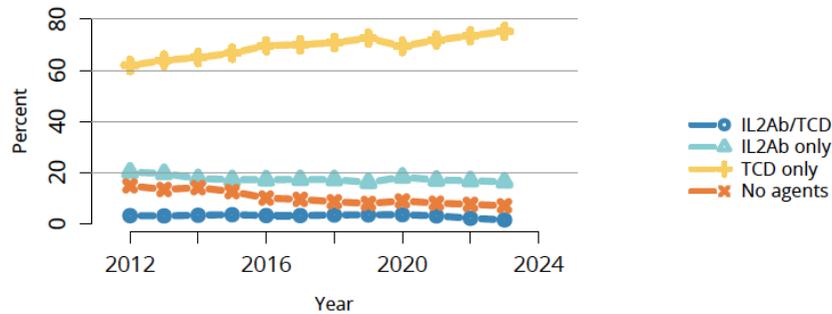
TAC/TAC MR/LCPT > CsA > SIR = EVERL = MMF/MPS > AZA



OPTN/SRTR 2023 Annual Data Report

**Figure KI 45: Induction agent use in adult kidney transplant recipients.** Immunosuppression at transplant reported to the OPTN.

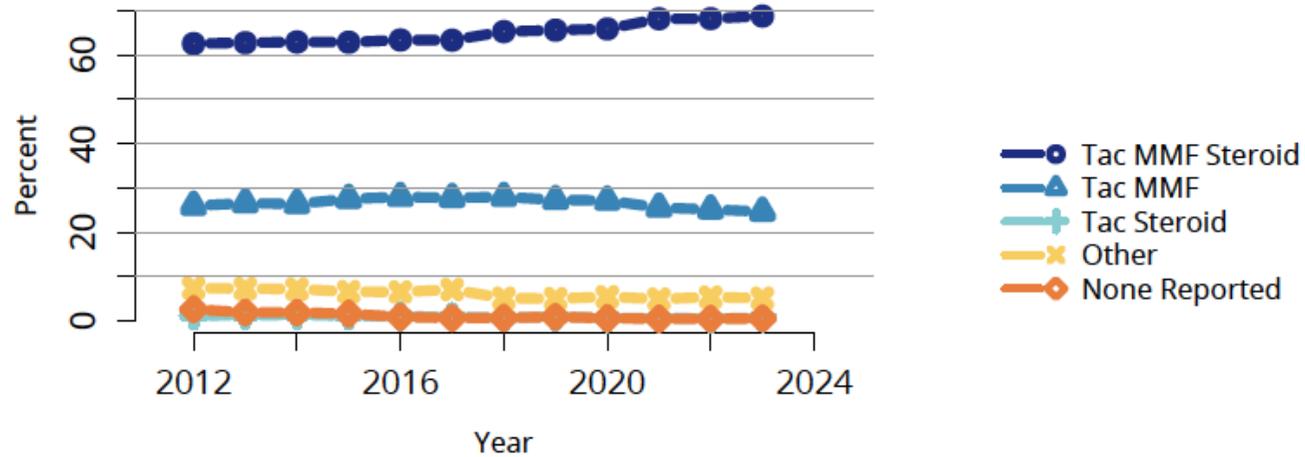
## OPTN Registry 2024



OPTN/SRTR 2023 Annual Data Report

**Figure KI 46: Type of induction agent use in adult kidney transplant recipients.** Immunosuppression at transplant reported to the OPTN. IL2Ab, interleukin-2 receptor antibody; TCD, T-cell depleting.

# OPTN Registry 2024



OPTN/SRTR 2023 Annual Data Report

**Figure KI 47: Immunosuppression regimen use in adult kidney transplant recipients.** Immunosuppression regimen at transplant reported to the OPTN. MMF, all mycophenolate agents; Tac, tacrolimus.

Standardowy schemat immunosupresji po transplantacji nerki to:

Inhibitor kalcyneuryny (TAC/TAC MR/LCPT/CsA) + MPA (MMF/MPS) + GS

- Takrolimus jest obecnie najczęściej stosowanym CNI a MMF najczęściej stosowanym MPA
- Skuteczność wszystkich postaci takrolimusu TAC, TAC MR i LCPT jest porównywalna
- Skuteczność MMF i MPS jest porównywalna

Schemat ten zapewnia roczne przeżycie przeszczepu w 90-95% i częstość epizodów

Inne schematy:

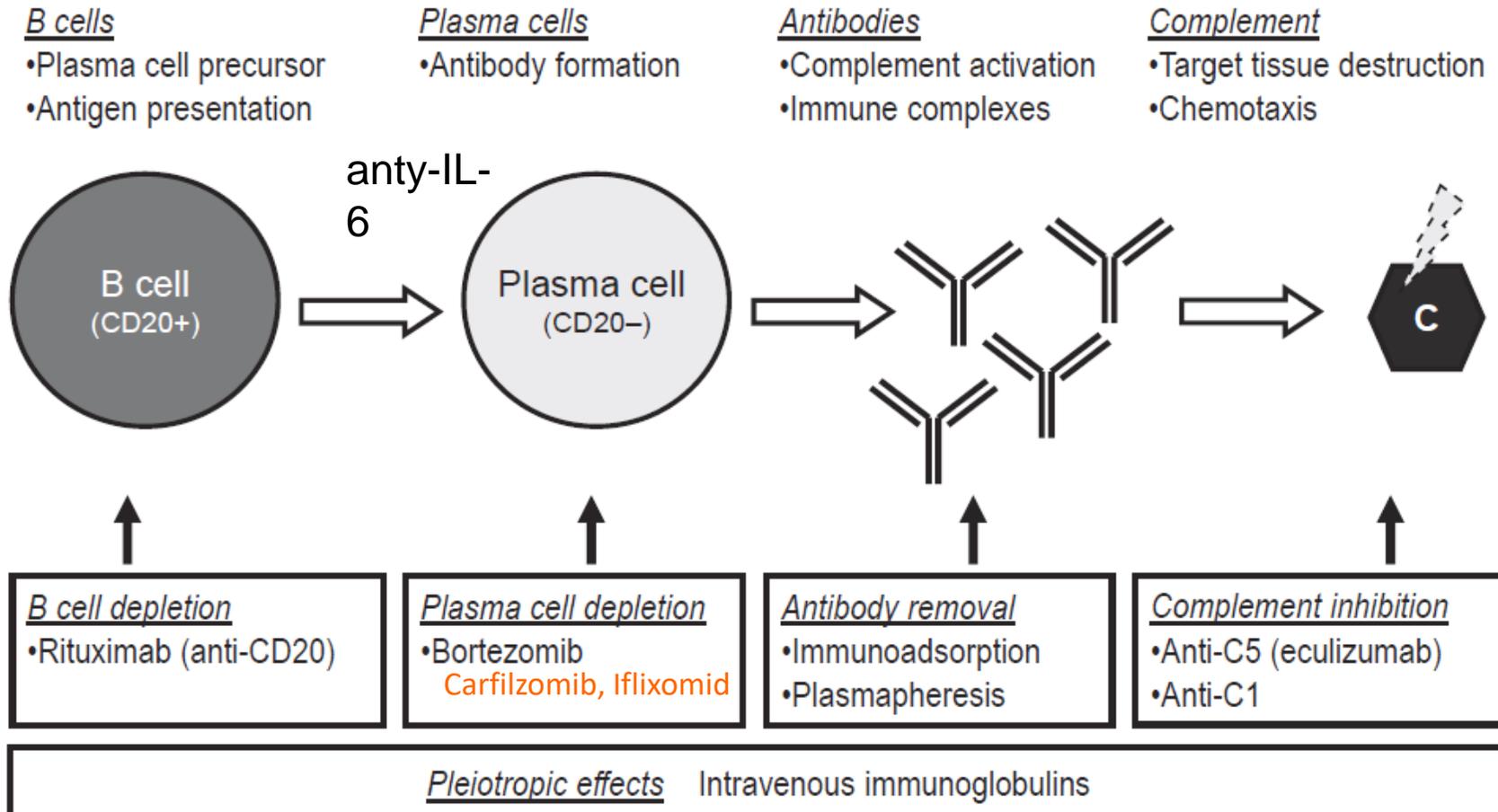
Inhibitory kalcyneuryny (TAC/TAC MR/LCPT/CsA) + mTORi (SIR/EVERL) +GS

mTORi(SIR/EVERL) +MPA (MMF/MPS)+GS

# **Leczenie odrzucania - T komórkowego**

- **Wlewy metylprednizolonu: 3-5 wlewów a` 250 – 500 mg przez 3 – do 5 dni**
- **Odrzucanie T -komórkowe, steroidooporne, naczyniowe**
  - **Tymoglobulina, Grafalon**

# Leczenie odrzucania humoralnego



**Bolusy metylprednizolonu, CNI, mTORi, MPA, ATG?, belatacept?,**

# Post-transplant surveillance and management of chronic active mediated rejection in renal transplant patients in Europe

## BACKGROUND

Antibody mediated rejection (ABMR) is the leading cause of immune-related allograft failure following kidney transplantation. Chronic active ABMR (CABMR) typically occurs after one-year post-transplant and is the most common cause of late allograft failure

## STUDY AIM

To assess common practices in Europe for post-transplant surveillance one year after kidney transplant, and diagnosis and management of CABMR.



Online survey  
15 minutes



58 questions  
multiple-choice/open

## METHODS AND COHORT



Transplant nephrologists  
Transplant surgeons  
Nephrologists  
N=56



**CRITERIA**  
Practicing 3-30 years  
5 patients/year with CABMR  
Perform DSA testing



February –  
November 2022

## RESULTS

### POST TRANSPLANT SURVEILLANCE

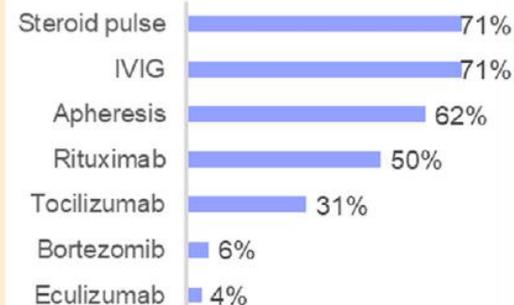


Observing clinical measures of graft function forms the cornerstone of post-transplant surveillance. This may be suboptimal, leading to late diagnoses and untreatable disease.

Less than half of patients who develop CABMR receive treatment beyond optimization of immune suppression

### CABMR TREATMENT

Intravenous Immunoglobulin (IVIg), steroid pulse and apheresis are most prescribed to treat CABMR. While biologics can feature as part of treatment, there is no single preferred agent



[Rostaing, et al. Transpl. Int. 2023](#)

[doi: 10.3389/ti.2023.11381](https://doi.org/10.3389/ti.2023.11381)



GRAPHICAL ABSTRACT |

**Lionel P. E. Rostaing<sup>1\*</sup>, Georg A. Böhmig<sup>2</sup>, Ben Gibbons<sup>3</sup> and Muhammed Mahdi Taqi<sup>3\*</sup>**

*Transpl Int 36:11381.*

*doi: 10.3389/ti.2023.11381*

# CNI - leki o wąskim indeksie terapeutycznym

(TDM - zależność pomiędzy ekspozycją na lek a efektami klinicznymi)

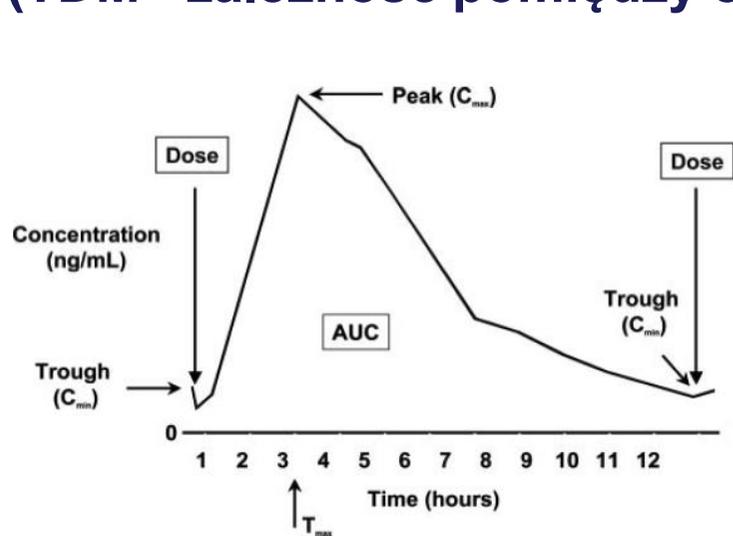
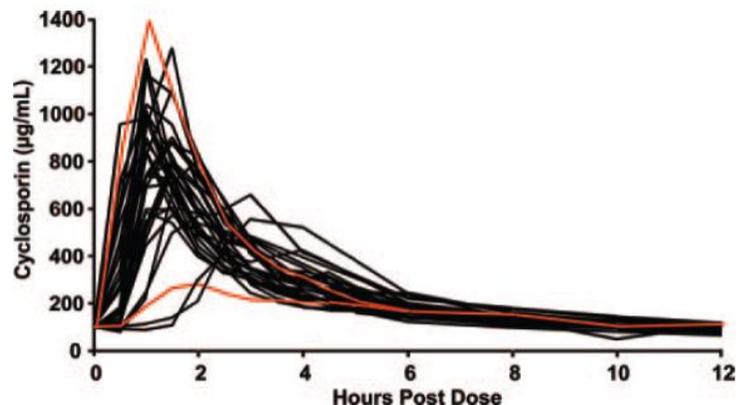


Figure 1. Drug levels during the course of a dosing interval. The drug concentration is lowest ( $C_{min}$ ) just before the dose is taken, then rises to a peak level ( $C_{max}$ ) at a certain time after the dose ( $T_{max}$ ). The concentration then falls back to  $C_{min}$  before the next dose. The area under the concentration-time curve (AUC) describes total drug exposure during the entire dosing interval.



## Cyklosporyna A (Sandimmun, Neoral)

Całkowity klirens: 29 L/h (20 - 50 L/h)

Biodostępność 16 - 55% (lipofilna Sandimmun 1-89%)

T<sub>max</sub> 2-3h, T<sub>1/2</sub> 8h - po zmianie dawki kontrola po 4-5x T<sub>1/2</sub>

Farmakokinetyka zmienia się w czasie, 30 metabolity

## Takrolimus

Całkowity Klirens: 15 - 70L/h

Lipofilny, biodostępność 25% (5 - 93%)

T<sub>max</sub> do 3h, T<sub>1/2</sub> 12-18h, po zmianie kontrola po 2.5 dobie

Wchłanianie niezależne od żółci

Farmakokinetyka zmienia się w czasie, 8 metabolity

## Advagraf

AUC 15 - 20% niższy przy konwersji 1:1

Envarsus AUC wyższy o 20-30%

## Voclosporyna

Generyczne: Cyklosporyna A, takrolimus

Motoryka przewodu pokarmowego

(biegunka ↑ ekspozycję na takrolimus)

Choroby współistniejące (układu krążenia, wątroby, nerek, jelit, cukrzyca)

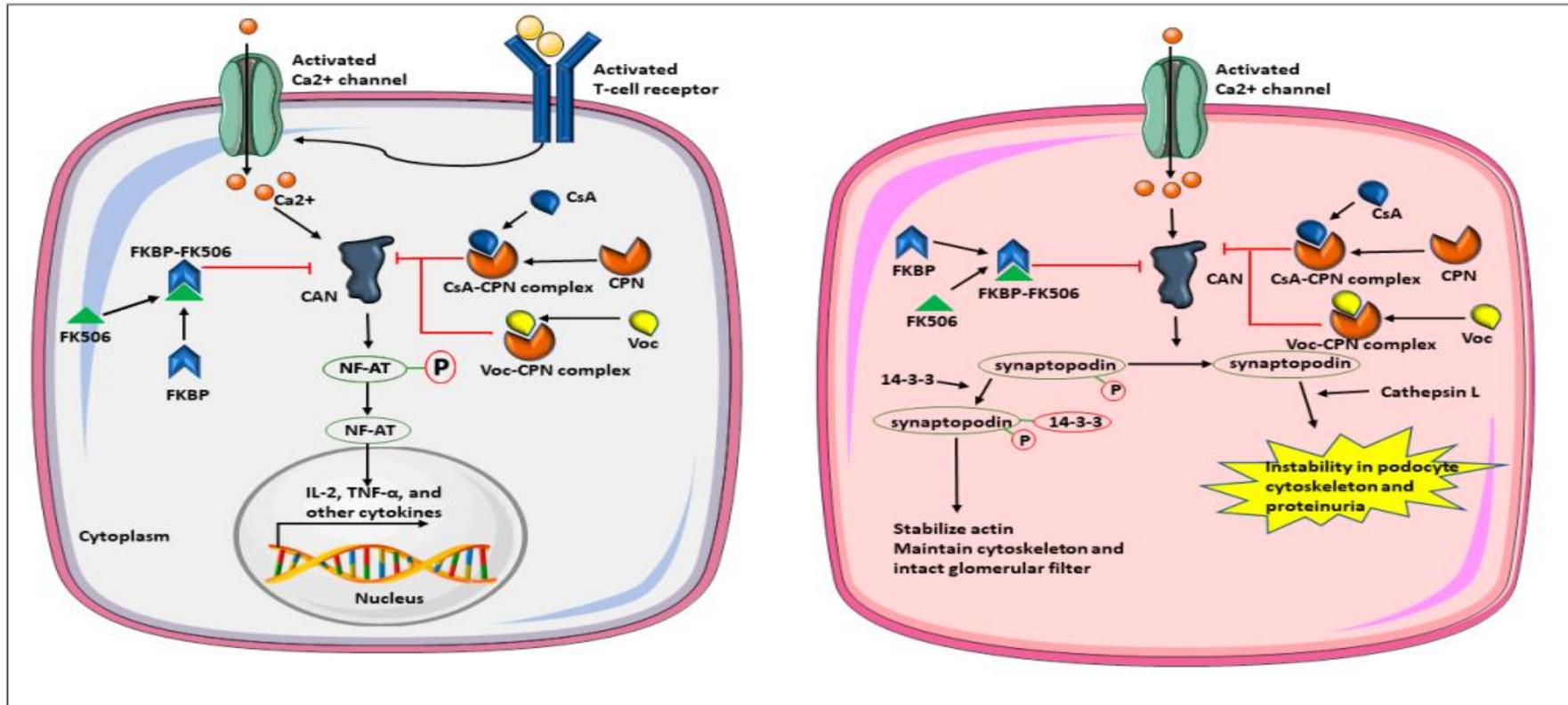
Hct, albuminy, hepatitis B, C - takrolimus

Wiek, płeć, rasa, masa ciała,

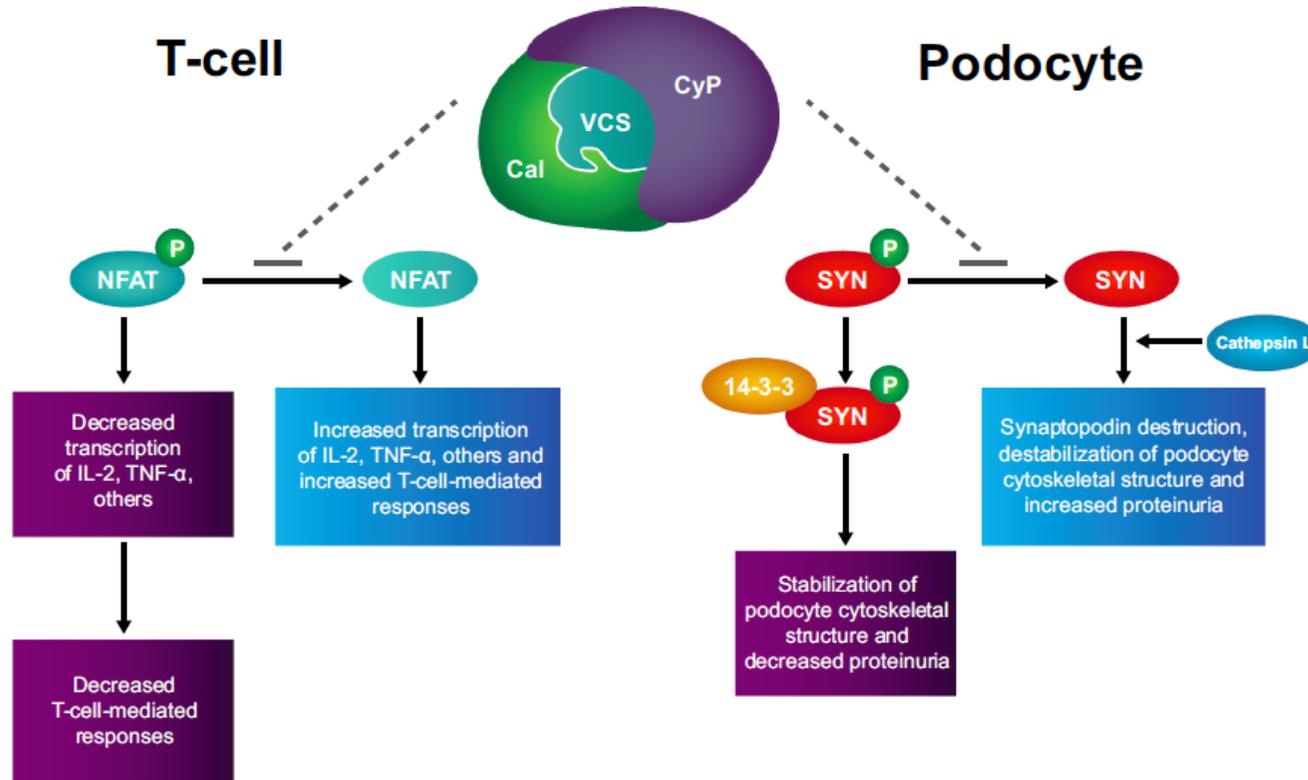
Pokarm ↓ wchłanianie leku

Interakcje lekowe

# Inhibitory kalcyneuryny – mechanizm działania



# Cyklosporyna, woklosporyna



**Figure 1.** In T-cells, voclosporin (VCS) binds cyclophilin A (CyP), and the resulting complex (VCS–CyP) binds and competitively inhibits calcineurin (Cal) from dephosphorylating phosphorylated nuclear factor of activated T-cells (NFAT-P) to nuclear factor of activated T-cells (NFAT) [46]. When dephosphorylated, NFAT activates translation and transcription of various cytokines (IL-2, TNF- $\alpha$ , others), which promotes T-cell proliferation [40]. In podocytes, calcineurin activity is involved in destabilization of the podocyte actin cytoskeleton. Phosphorylated synaptopodin (SYN-P) binds with 14-3-3 protein, which stabilizes the actin cytoskeleton of the podocyte. When activated, calcineurin dephosphorylates synaptopodin, which marks it for destruction by cathepsin L, subsequently leading to podocyte cytoskeleton destabilization and increased proteinuria. By inhibiting this dephosphorylation pathway, VCS maintains SYN-P, which protects synaptopodin from destruction and thus promotes actin cytoskeleton stabilization [50,53].

# Cyklosporyna A (CsA)

- cykliczny 11-aminokwasowy polipeptyd
- *Sandimmun* : dobrze rozpuszczalna w tłuszczach, źle wchłania się z przewodu pokarmowego, wchłanianie zmienne, zależne od diety, wytwarzania żółci, biodostępność śr. 30%)
- *Neoral* : mikroemulsyjna postać CsA (połączona z surfaktantem) - biodostępność (70%)
- *postacie generyczne : SangCsA, Cyclosporine USP, Gengraf, Eqoral*
- $t_{1/2}$  : 7-11 godzin,  $C_{max}$  1-4 godz.
- 60 - 70% CsA związana wewnątrzkomórkowo z erytrocytami, 9% leukocyty, 4% osocze, 21% lipoproteiny, 8% z białkami osocza)
- postać doustna 8 - 10 mg/kg m.c./dobę (roztwór, kapsułki), dożylna (amp) - 1/3 dawki *i.v.*, wlew 2 h do żyły obwodowej (nadwrażliwość na rozpuszczalnik)

# Takrolimus IR, MR-4, LCP

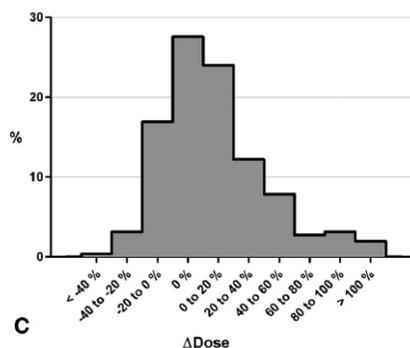
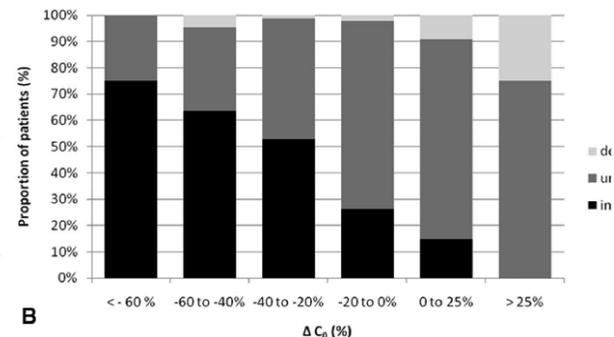
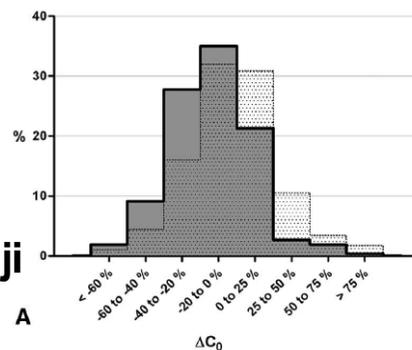
- **Antybiotyk makrolidowy izolowany z *Streptomyces tsukubaensis***
- **Stosowany w leczeniu immunosupresyjnym podtrzymującym, ostrym odrzucaniu, 10-100x silniejszy od CsA - większe powinowactwo kompleksu FK-FKBP12 do kalcineuryny**
- **Wchłanianie niezależne od żółci, zmienne, posiłek zmniejsza biodostępność o 25%,**
- **erytrocyty/osocze 20:1; w osoczu 98%z albuminami i  $\alpha$ 1 AGP**
- **Cmin - dobry wskaźnik ekspozycji na lek, wysycenie 4-8 tyg (Hct, albuminy, duże dawki glikokortykosteroidów)**
- **metabolizm- cytochrom P450 CYP3A4, CYP 3A5 głównie w wątrobie hydroksylacja, demetylacja (w znacznie mniejszym stopniu zależny od CYP3A4 w jelicie, gp 150) metabolit M II- 31-0-demetylowany - 100% aktywności immunosupresyjnej)**
- **wydalenie: żółć >90% (głównie w postaci metabolitow, < 2% z moczem)**

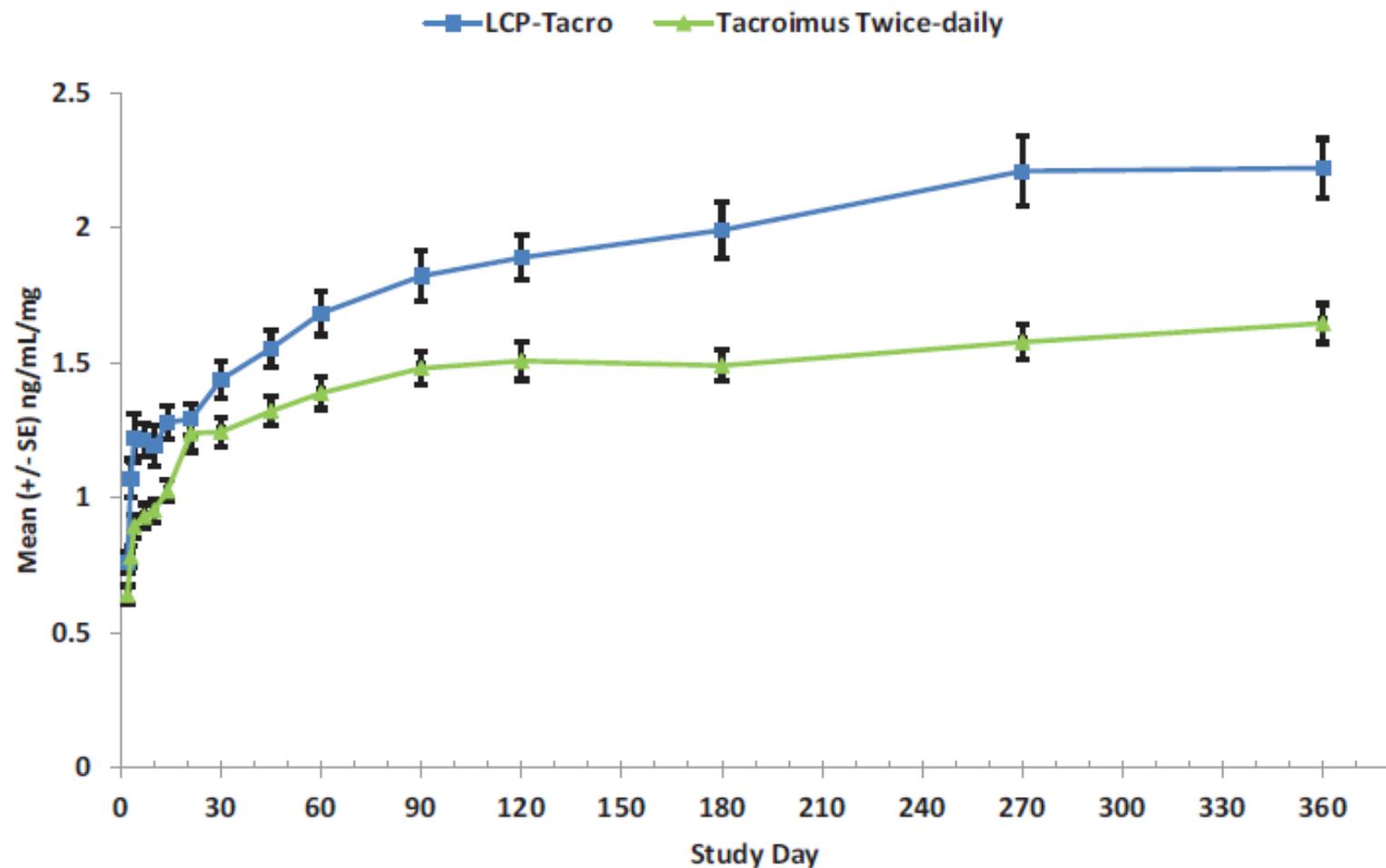
# Takrolimus bid versus takrolimus MR-4 o.d. (Advagraf) (chorzy po kTx konwersja 1:1, n=384)

- $\downarrow C_0$ : -12.7 - 24.4%;  $p < 0.0001$
- u 38% chorych  $\downarrow C_0 > 20\%$
- $\uparrow$  dawki u 52.2% chorych po konwersji
- $\uparrow$  dawki o 14.7 - 28.8% ( $p < 0.0001$ )
- u 28 % chorych  $\uparrow$  dawki  $> 20\%$

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de Jonge et al.





**Figure 3: Tacrolimus trough level (ng/mL) achieved per total daily dose (mg) (modified intent-to-treat set).**

# CNI - nefrotoksyczność

Ostra /czynnościowa/

Kłębuszek

mikroangiopatia zakrzepowa  
(HUS)

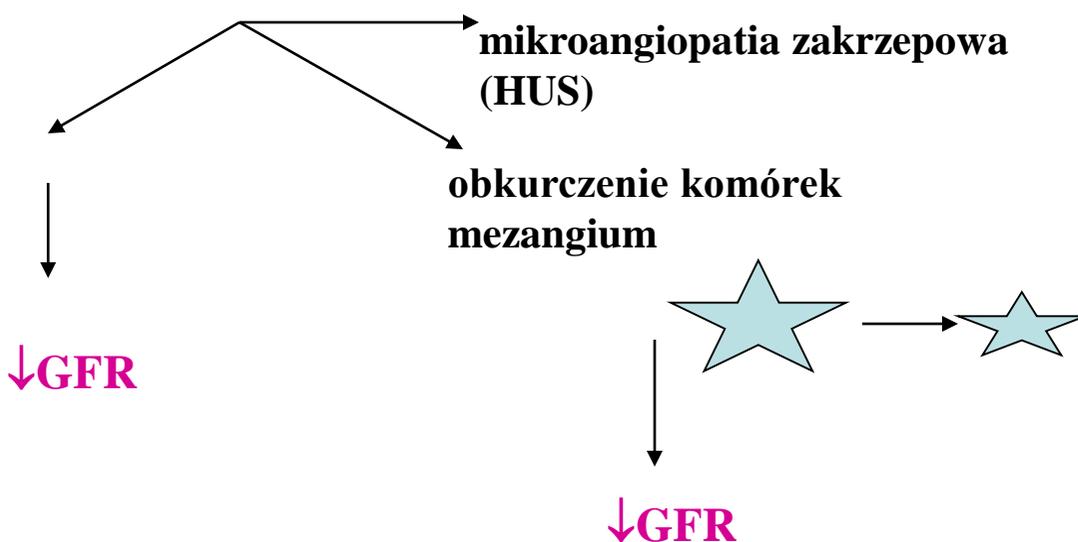
obkurczenie komórek  
mezangium

↓GFR

↓GFR

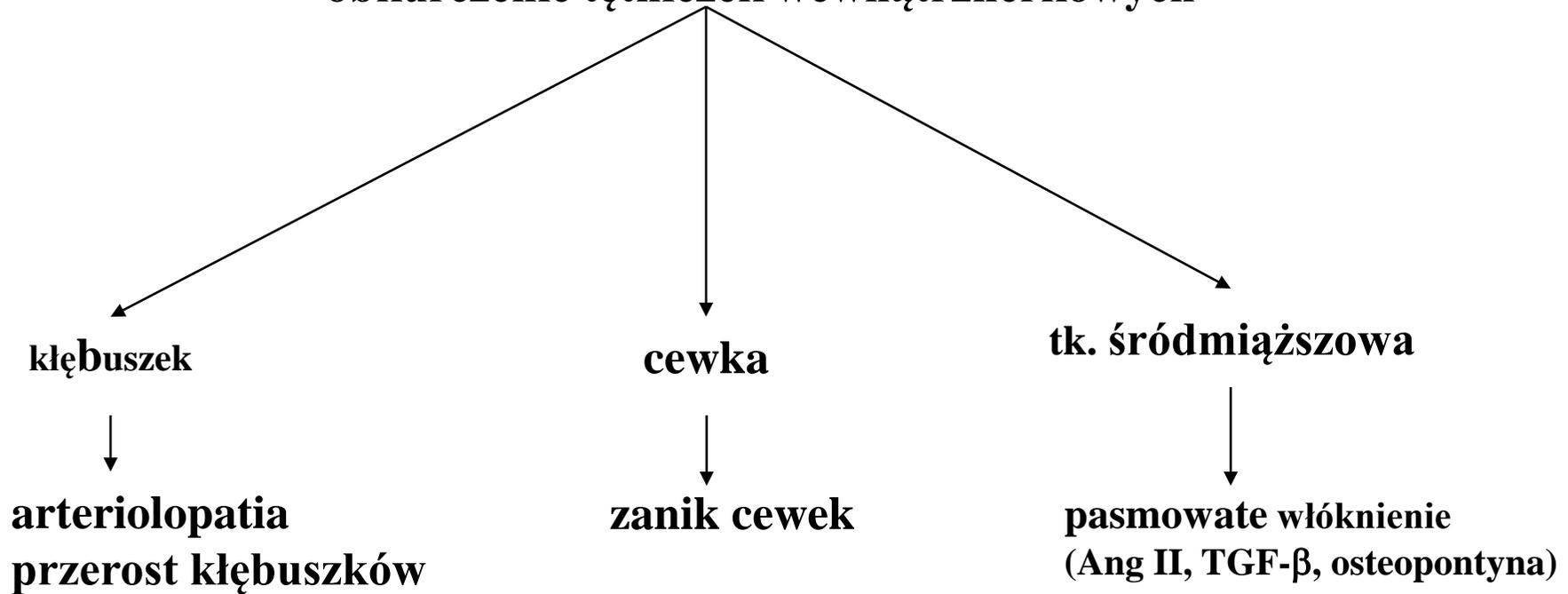
cewka proksymalna  
olbrzymie mitochondria,  
zwyrodnienie wodniczkowe

hiperkalemia, hipomagnezemia,  
kwasica hiperchloremiczna,  
Hiperurycemia, ↑ATN



# CNI - nefrotoksyczność cd.

**przewlekła /strukturalna/- długotrwałe  
obkurczenie tętniczek wewnątrznerkowych**



# CNI - nowotworzenie

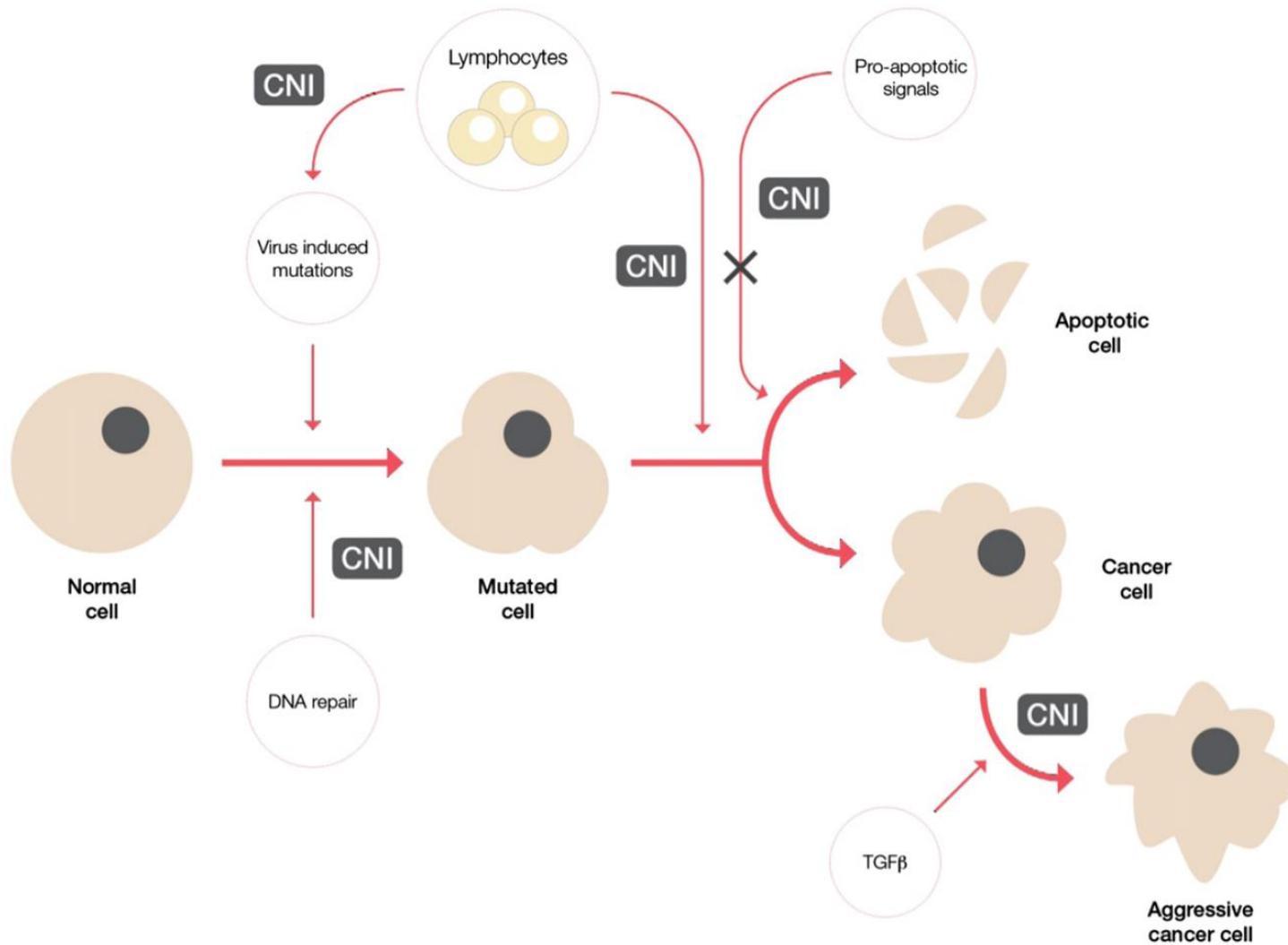


Fig. 1. Immunosuppression-driven oncogenesis. Adapted from Gutierrez-Dalmau and Campistol 2007 [42]. CNI=calcineurin inhibitors; TGFβ=transforming-growth factor β.

# CNI - PTDM

- **CNI toksyczne dla komórek  $\beta$  wysepek trzustkowych**

**Langerhansa -  $\downarrow$ wytwarzanie insuliny**

- **toksyczność odwracalna, zależna od dawki**

# CNI - neurotoksyczność

**Drżenia, drgawki**

**Bóle głowy**

**Bezsenna**

**zaburzenia widzenia**

**ślepoty korowej**

**śpiączka**

**niedowład**

**ataksja mózdkowa**

**rzadko polineuropatia**

**obwodowa, miopatia**

*skurcz naczyń*

*niedobór magnezu*

# Nefrotoksyczność CNI

- 
- Próby leczenia
    - Antagoniści kanału wapniowego (nie przy przeroście dziąseł po CsA), wazodylatacyjne PG, NO
    - iACE, antagoniści receptora AT-1, *spironolakton*
    - Monitorowanie C0, C2, AUC<sub>0-4</sub>
    - Modyfikacja leczenia immunosupresyjnego: MMF, MPS, mTORi,
      - anty-CD25, belatacept ( zmniejszenie dawki lub odstawienie CNI)
    - inhibitory HMGC0A
    - Suplementacja magnezu

# CNI - interakcje

- **Nasilenie nefrotoksyczności przy równoczesnym stosowaniu:**
  - ☐ aminoglikozydów
  - ☐ amfoterycyny B
  - ☐ wankomycyny
  - ☐ NLPZ
- **Nasilenie ryzyka hiperkaliemii (diuretyki oszczędzające potas)**
- **Nasilenie uszkodzenia mięśni gładkich przy stosowaniu inhibitorów HMGCoA reduktazy**

Objawy uboczne	Cyklosporyna	Takrolimus	Voclosporyna
Nadciśnienie tętnicze	++	+	+
Nefrotoksyczność	++	++	+
Zmniejszenie eGFR	+	+	+
Arytmia/ryzyko sercowe	+	+	-
Anemia	+	+	+
Neurotoksyczność/drgawki	+	++	+
Zaburzenia z p. pokarmowego	+	++	+
Przerost dziąseł	++	-	+
Dyslipidemia	++	+	-
Gynekomastia	+	-	-
Alopecia	-	++	+
Cukrzyca potransplantacyjna	+	++	-
ZUM		+	+
Hyperkalemia	++	+	+
Powikłania kosmetyczne	++	+	-
Hyperurykemia	++	+	-
Hirsutism / hypertrichosis	++	-	-

:

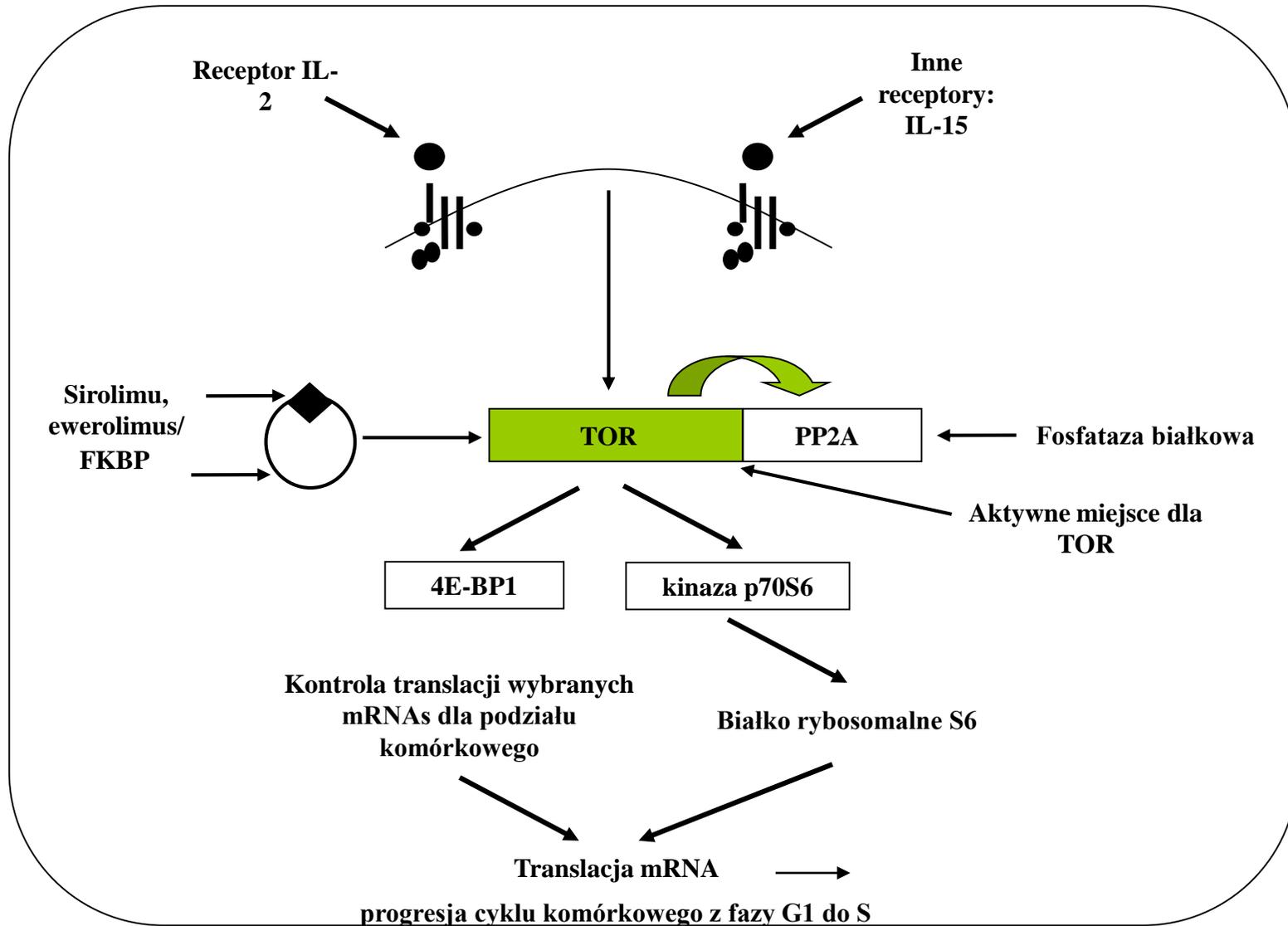
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*Cells, 2023, 12, 2440*

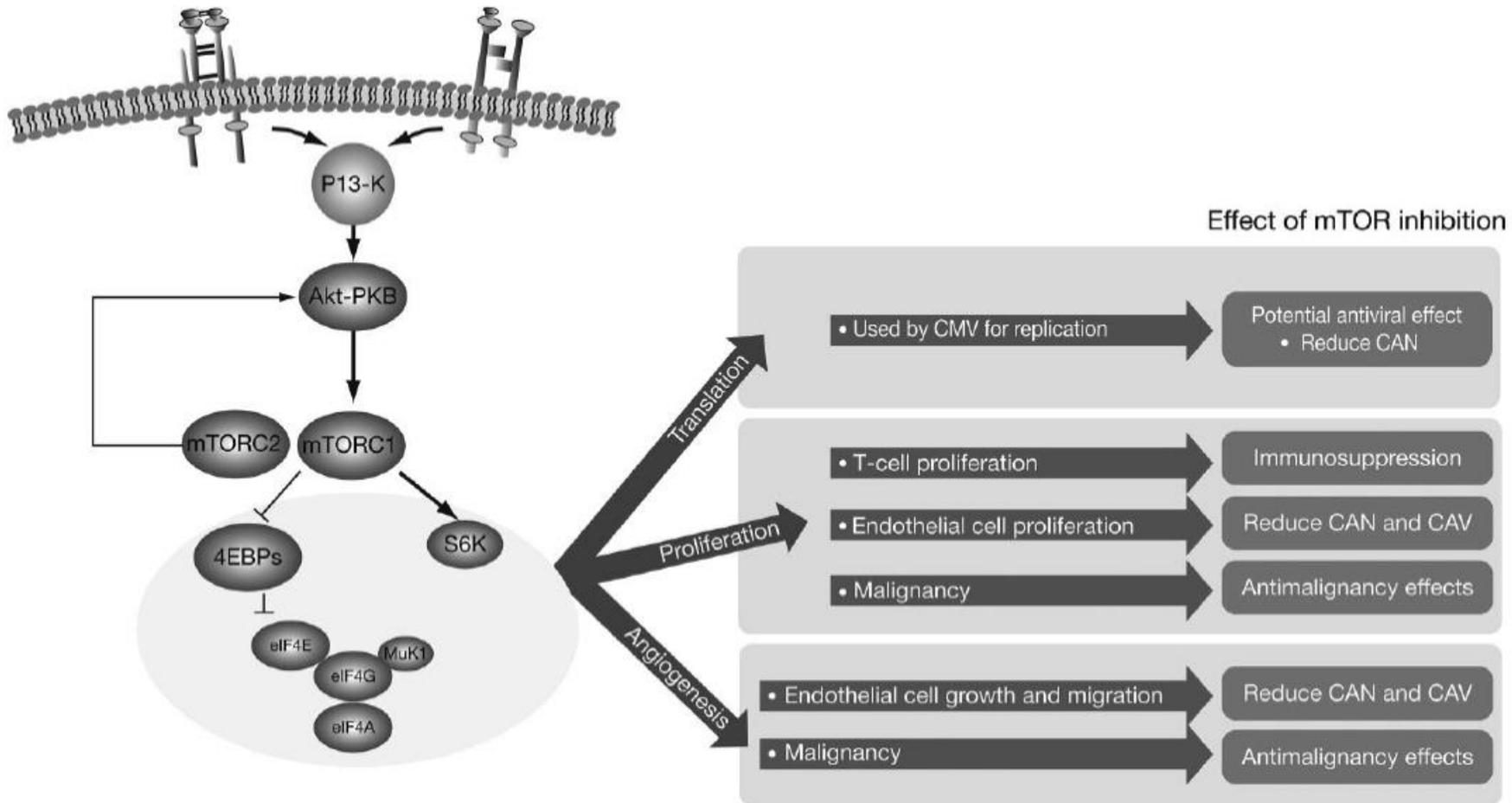
# Sirolimus

- **Makrolid wyizolowany z grzyba *Streptomyces hygroscopicus*, z Wyspy Wielkanocnej (Rapa Nui)**
- **Stosowany w profilaktyce i w leczeniu ostrego odrzucania, siła działania immunosupresyjnego zbliżona do MPA?**
- **Strukturalne podobieństwo z takrolimusem (wewnątrzkomórkowo wiąże się z tą sama immunofiliną - FK-BP12), mechanizm działania immunosupresyjnego odmienny**
- **Rozpuszczalny w tłuszczach, zła doustna biodostępność ok. 15%,  $t_{1/2}$  62h,  $t_{max}$  1-2h**
- **Ulega w wysokim odsetku sekwestracji w erytrocytach (pomiar stężenie leku we krwi pełnej)**
- **Metabolizowana w wątrobie, jelicie (cytochrom P450 CYP3A4, substrat dla Gp)**
- **Wydalanie z kałem, klirens nerkowy minimalny (modyfikowanie dawki leku przy uszkodzeniu wątroby)**
- **Jednoczesne przyjmowanie CsA i rapamycyny zwiększa AUC dla sirolimusu o 240% (odstęp 4 godz)**

# mTOR inhibitory -mechanizm działania



# Plejotropowe efekty hamowania mTOR



# EVEROLIMUS

---

**Nowa pochodna rapamycyny - everolimus  
(Certican, SDZ RAD) - inhibitor mTOR**

**Lepsza biodostępność, krótszy czas półtrwania 16-19 h**

**Działa synergistycznie z CsA, nasila nefrotoksyczność CNI, pozwala na redukcję dawki CsA przy zachowanej skuteczności, redukcja przy uszkodzeniu wątroby**

**Dawkowanie 2 x 0.75 – 2x1.5 mg**

**Działanie antyproliferacyjne- hamowanie, zapobieganie przewlekłemu odrzucaniu, angiogenezie w nowotworach?**

*Temsirolimus, ridaforolimus - leki przeciwnowotworowe*

# Inhibitory mTOR - objawy uboczne

- Hiperlipidemia (hipertgrójglicerydemia, hipercholesterolemia)
  - Hepatotoksyczność (zwiększona aktywność aminotransferaz)
  - Trombocytopenia, niedokrwistość, rzadziej leukopenia
  - Zapalenie płuc, w tym niezwiązane z czynnikiem infekcyjnym
  - Chłonnokotki
  - Bóle brzucha, biegunka
  - Nefrotoksyczność znacznie rzadziej, niż po CNI
  - Upośledza gojenie ran
  - Zakażenia grzybicze, wirusowe, bakteryjne
  - Mikroangiopatia zakrzepowa/zespół hemolityczno-mocznicowy
  - Diabetogenne
  - Obrzęki obwodowe
  - Białkomocz
  - Zaburzenia spermatogenezy
  - Owrzodzenia jamy ustnej
- Odstawienie z powodu AE: 0 - 60% (śr 20%)**

*Exceptional Case*

## Severe everolimus-associated pneumonitis in a renal transplant recipient

Simona Alexandru<sup>1</sup>, Alberto Ortiz<sup>1</sup>, Sonia Baldovi<sup>1</sup>, Jose Maria Milicua<sup>2</sup>, Elena Ruíz-Escribano<sup>2</sup>, Jesús Egido<sup>1</sup> and Juan José Plaza<sup>1</sup>

<sup>1</sup>Nephrology Unit and <sup>2</sup>Intensive Care Unit, Fundación Jiménez Díaz-Capio, Universidad Autónoma, Madrid, Spain

- **Z/lub bez czynnika infekcyjnego**
- **Patomechanizm: nieznan**
- **Bezpośredni toksyczny efekt?**
- **Reakcja nadwrażliwości typu późnego?**
- **Efekt zależny od dawki?**
- **Możliwość związania z PCHN (GFR <40 mL/min)**

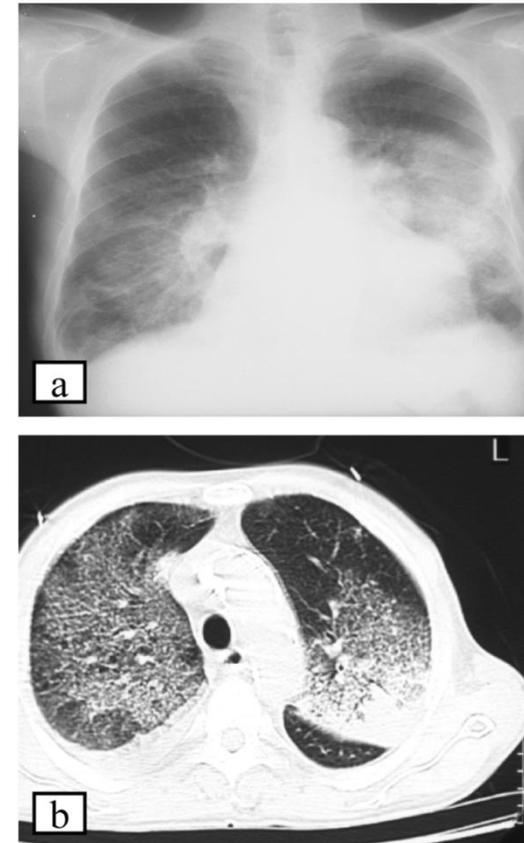


Fig. 1. The chest radiography (a) and pulmonary CT scan (b) at admission, showing bilateral pulmonary lobes.

# Interakcje CNI, mTORi

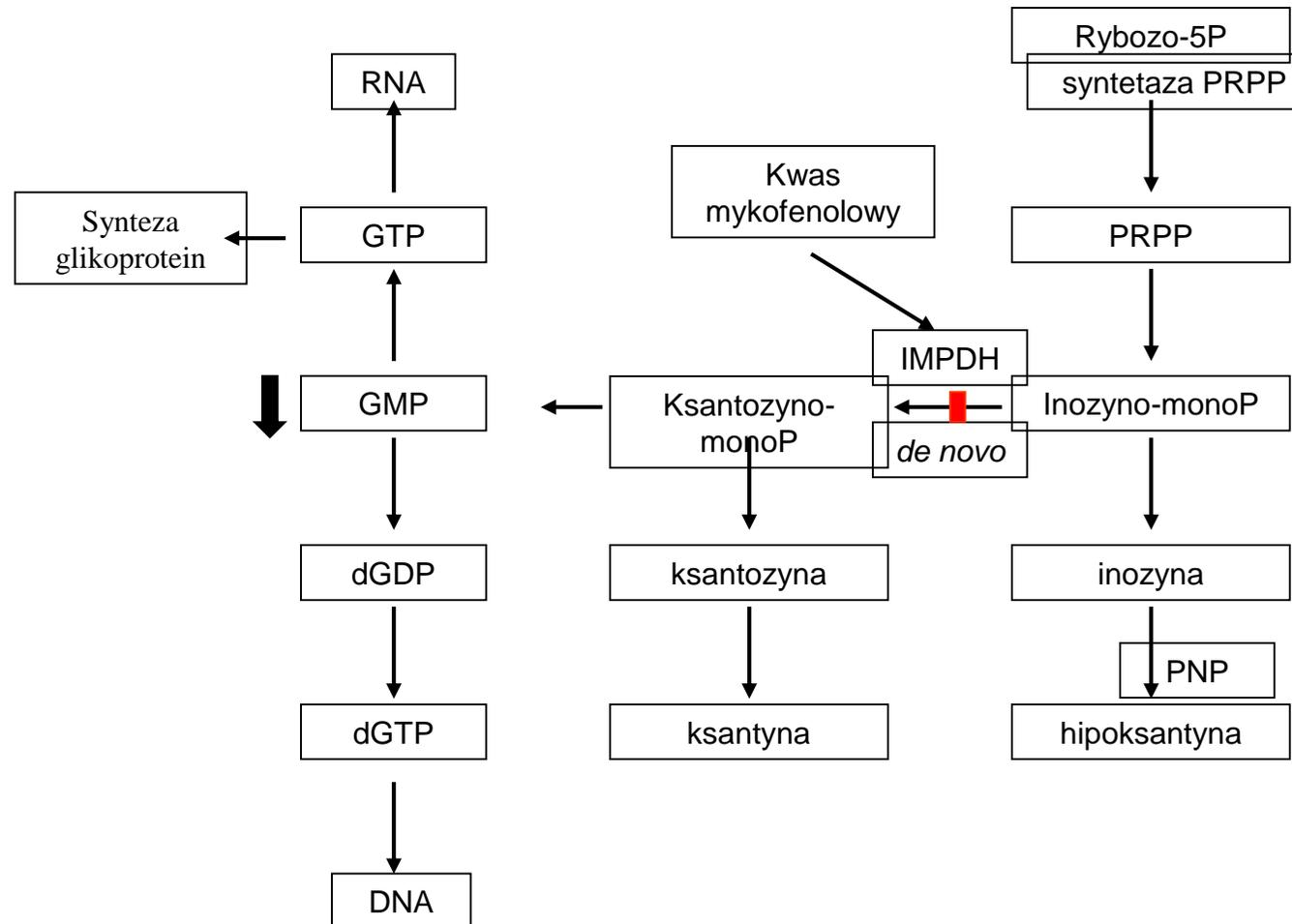
- **Inhibitory CYP3A4**

- ☐ klarytromycyna
- ☐ klotrimazol
- ☐ danazol
- ☐ GS(duże dawki)
- ☐ diltiazem
- ☐ erytromycyna
- ☐ flukonazol
- ☐ itrakonazol
- ☐ ketokonazol
- ☐ mikonazol
- ☐ ranitydyna
- ☐ sok grejfrutowy
- ☐ verapamil
- ☐ metoklopramid

- **Induktory CYP3A4**

- ☐ karbamazepina
- ☐ fenobarbital
- ☐ fenytoina
- ☐ rifampicyna
- ☐ troglitazone
- ☐ tiklopidyna
- ☐ barbiturany

# Mechanizm działania mykofenolanu mofetylu/sodu (kwasu mykofenolowego - MPA)



# MPA

- Nie wykazuje niekorzystnych interakcji z innymi lekami immunosupresyjnymi- może być z nimi kojarzony.
- Standardowe dawkowanie 2x1.0 g MMF, 2x720 mg MPS zapewnia właściwą immunosupresję u większości pacjentów.
- Monitorowanie leku (MPA całkowity): C<sub>0</sub> 1.0 - 3.5 mg\*h/L, AUC 30-60 mg\*h/L (*przy zredukowanej dawce CNI 75 mg\*h/L?, CAESAR*)
  - w pierwszym tygodniu po kTx; follow-up: po 1 tygodniu, 1 i 2 miesiącach (*wyższe dawki 3.0 g?, 2,160 g?*)
  - przy planowaniu zmian w leczeniu immunosupresyjnym
  - w odrzucaniu przeszczepu,
  - hipoalbuminemii (*wolny*),
  - niewydolności nerek, niewydolności wątroby (*wolny*),
  - wystąpieniu poważnych objawów niepożądanych (*wolny?*)
  - podejrzeniu non-compliance
  - Monitorowanie acyl-MPAG: objawy uboczne?

# MPA - objawy uboczne

- Zaburzenia żołądkowo-jelitowe (zależność od dawki MMF) : biegunka ( 30%), nudności (19%), wymioty (12%) - MPA obecny w dużych stężeniach w enterocytach j.cienkiego, enterocyty w 50% zależą od syntezy puryn *de novo*, MPA - atrofia kosmków jelitowych?
- Mielotoksyczność: niedokrwistość ( 25%), leukopenia ( 23%), trombocytopenia (10%), neutropenia <500/dL u 2% biorców nerki i 2.8% biorców serca (3g)
- Zwiększone ryzyko rozwoju infekcji oportunistycznych - CMV (działanie p/ko *Pneumocystis carini*)
- Działanie teratogenne

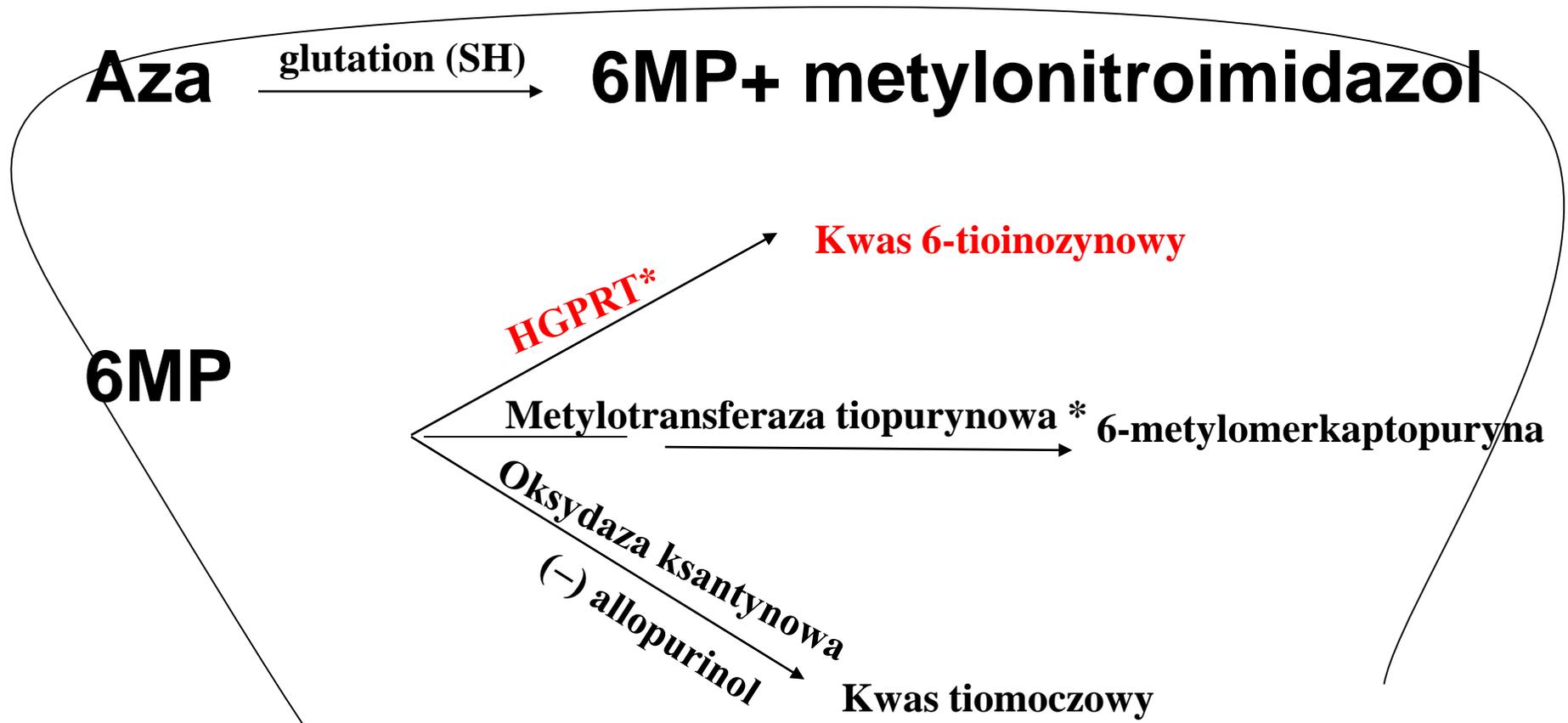
# MYKOFENOLAN SOD

## ERL080

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- **Myfortic - dojelitowa postać mykofenolanu sodu -aktywna substancją jest MPA - zmniejszenie powikłań gastro-enterologicznych**
- **Dawkowanie 2x720 mg**
- **Porównywalny do MMF w skuteczności u biorców nerki, rzadziej konieczność zmian dawkowania**
-

# Azatiopryna -metabolizm



**\* działanie immunosupresyjne, objawy uboczne**

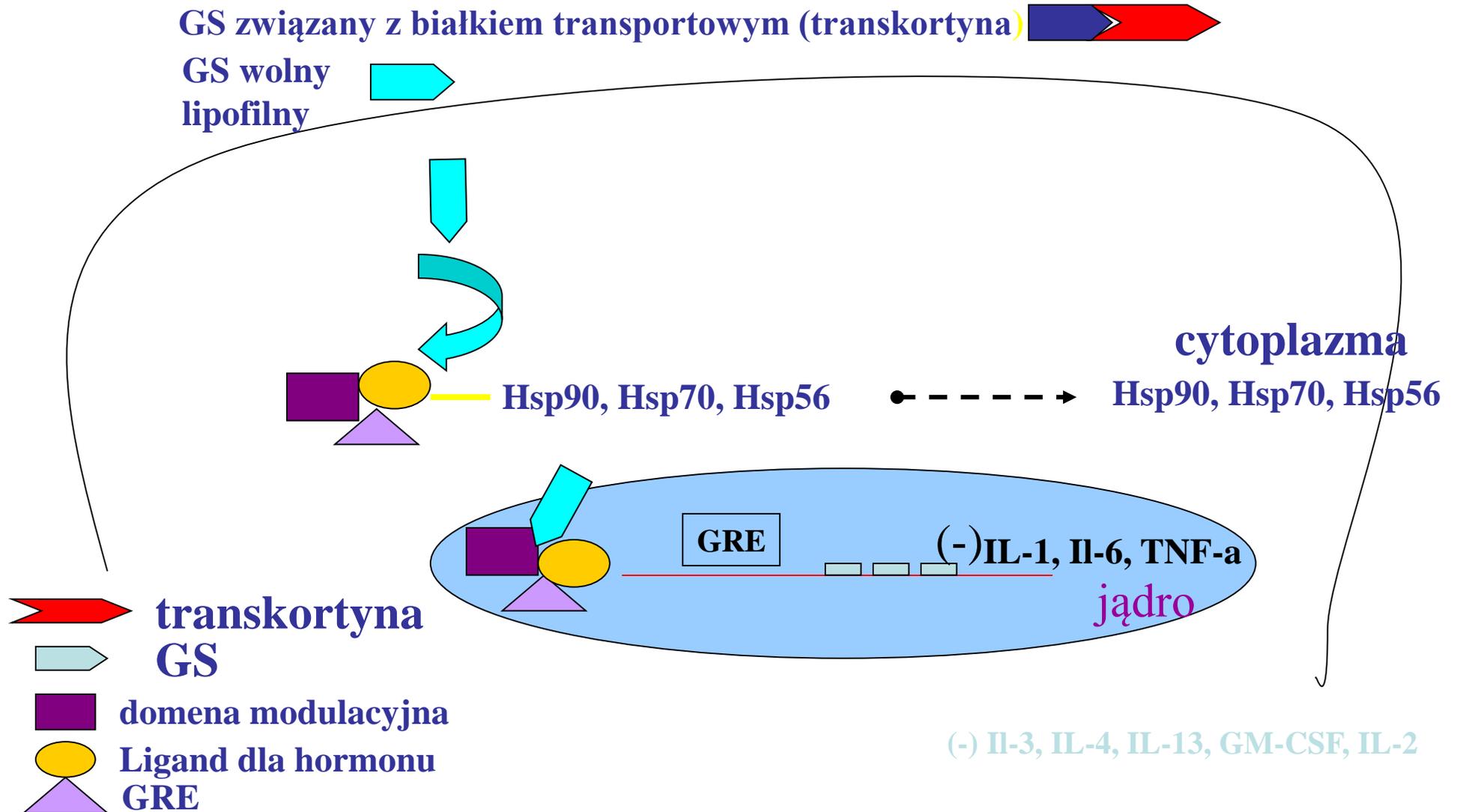
brak HGPRT- z. Lesh-Nyhana

przy allopurinolu redukcja dawki Aza o 66-75%

polimorfizm genu dla metylotransferazy tiopurynowe (Azjaci) - czynniki ryzyka cytopenii

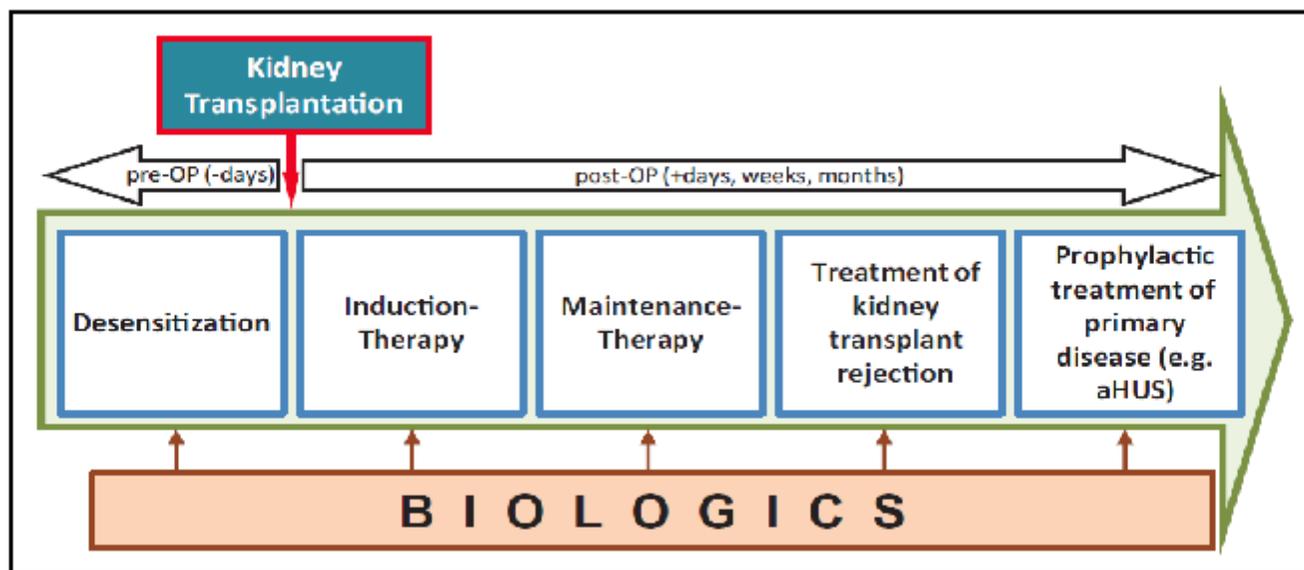
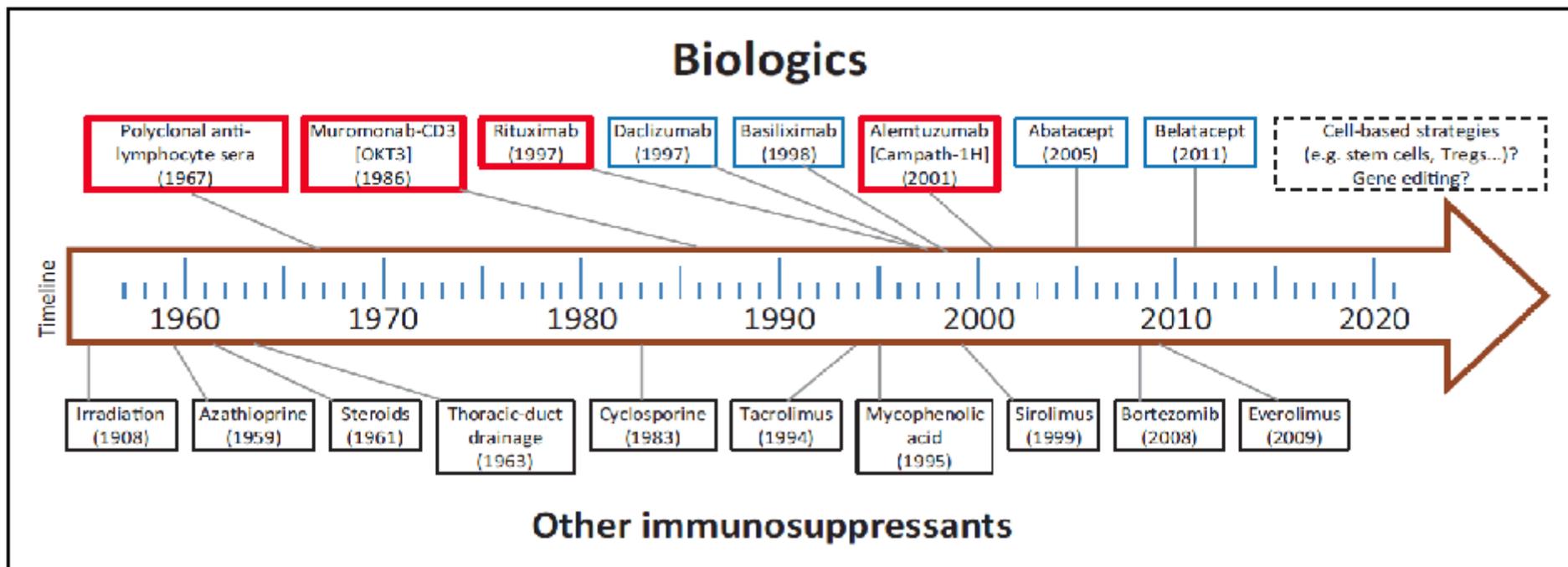
# GS- mechanizm działania

(związany bezpośrednio z wiązaniem się kompleksu GS-R z sekwencją DNA odpowiedzialną za wytwarzanie cytokin)



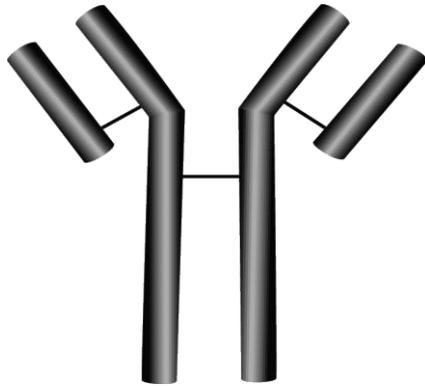
# GS- mechanizm działania cd.

- **Limfocyty B**
  - ↑ katabolizm immunoglobulin
  - ↓ wytwarzania immunoglobulin
- Na poziomie translacji ↓  $\text{IL-1}\beta$ , TNF
- **Nieswoiście przeciwzapalnie Fosfolipidy**
  - (-) fosfolipaza A2 → ↓ AA
  - ↑ lipokortyny
  - ↑ GS

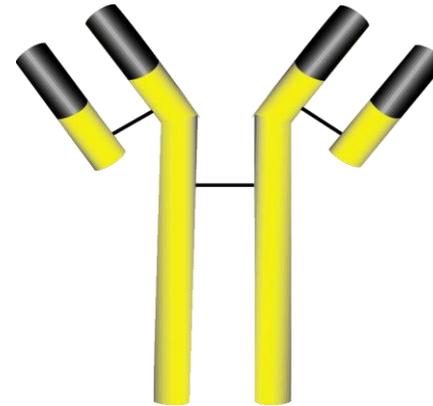


**FIGURE 2.** Various indications for use of biologic agents in the management of renal transplant patients in relation to timing

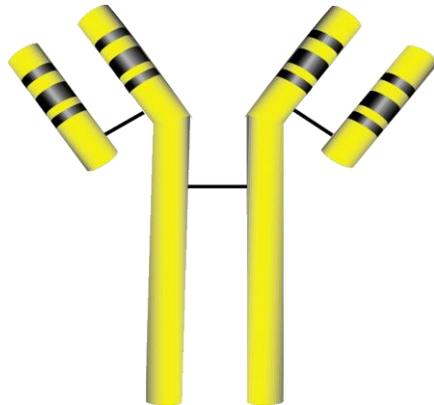
# Rodzaje przeciwciał



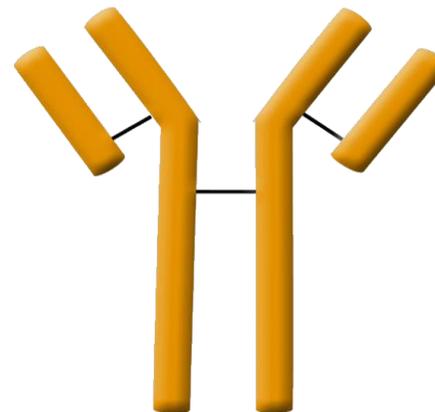
**Muromonab-CD3  
(monoclonal)**



**Basiliximab  
(chimeric monoclonal)**



**Daclizumab  
(humanized monoclonal)**

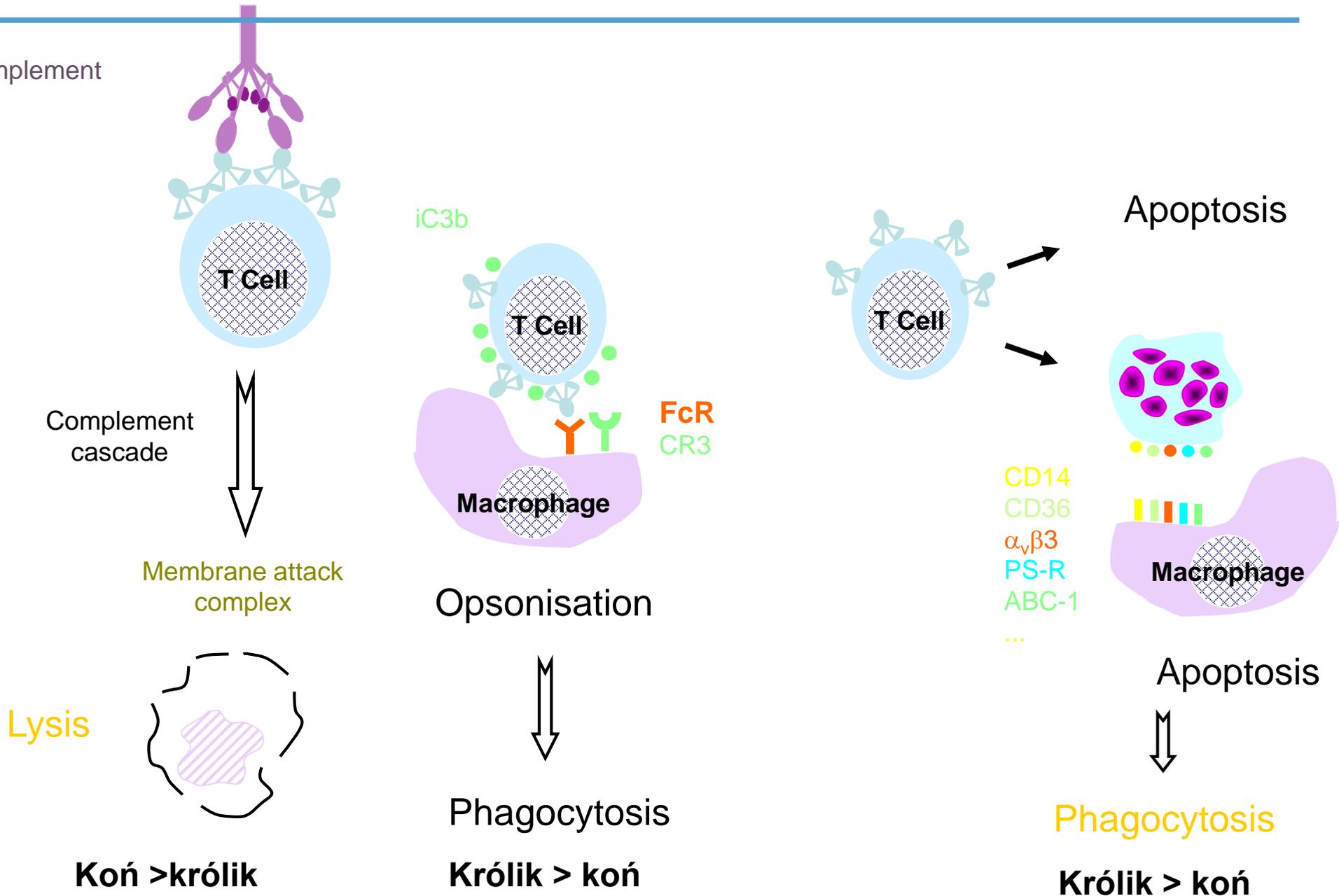


**Antithymocyte globulin  
(polyclonal)**

-  Mysie
-  Ludzkie
-  Królicze, końskie

# ATG :mechanizmy deplecji limfocytów T

Human Complement  
(C1q...)

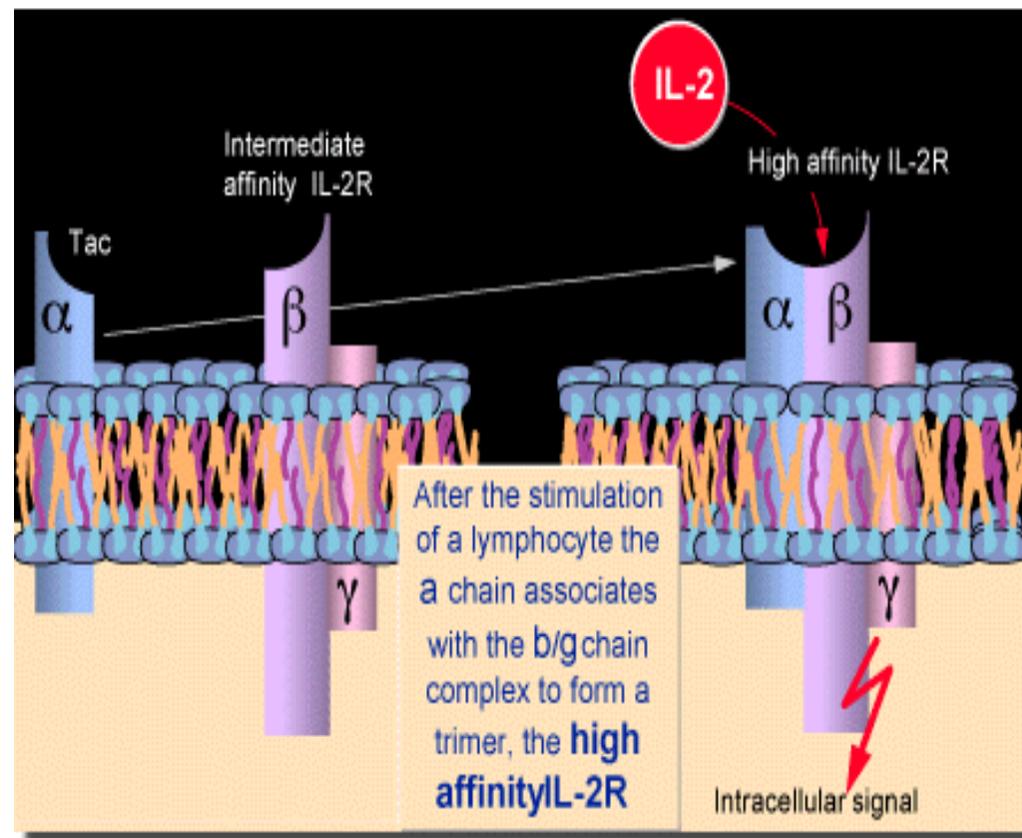


# Zastosowanie rATG

- **Indukcja- zmniejszenie częstości procesu ostrego odrzucania u chorych wysokiego ryzyka immunologicznego**
- **Indukcja**
  - **Ograniczanie GS**
  - **Ograniczanie CNI**
- **Leczenie nasilonego procesu ostrego komórkowego odrzucania naczyniowego**
- **Leczenie steroidoopornego odrzucania**
- **Indukcja tolerancji**

# INTERAKCJA IL-2 Z RECEPTOREM

- W stanie spoczynku receptor dla IL-2 na limfocycie T wykazuje ekspresję łańcuchów  $\beta$  i  $\gamma$
- Po aktywacji - następuje natychmiastowa ekspresja łańcucha  $\alpha$  oraz połączenie łańcuchów  $\alpha$ ,  $\beta$  i  $\gamma$  w kompleks bardzo aktywnie wiążący IL-2
- Potencjalne związanie IL-2 z receptorem przekształciłoby limfocyt T w komórkę efek-torową
- Przeciwciało blokuje połączenie łańcuchów  $\alpha$ ,  $\beta$  i  $\gamma$  receptora , przez co uniemożliwia związanie IL-2 z całym receptorem



**Bez indukcji**

**Bzyliksymab**

**Surowica antytymocytarna**

**Niskie ryzyko**

0 niezgodności HLA

Żywy dawca

Rasa kaukaska

Niskie PRA

Nieobecność DSA

Zgodność grup krwi

Natychmiastowe podjęcie funkcji

Krótki CIT

Pierwsze przeszczepienie

**Wysokie ryzyko**

Rośnie wraz z niezgodnością HLA

Młody biorca i starszy dawca

Afro-Amerykanie

Wysokie PRA

Obecność DSA

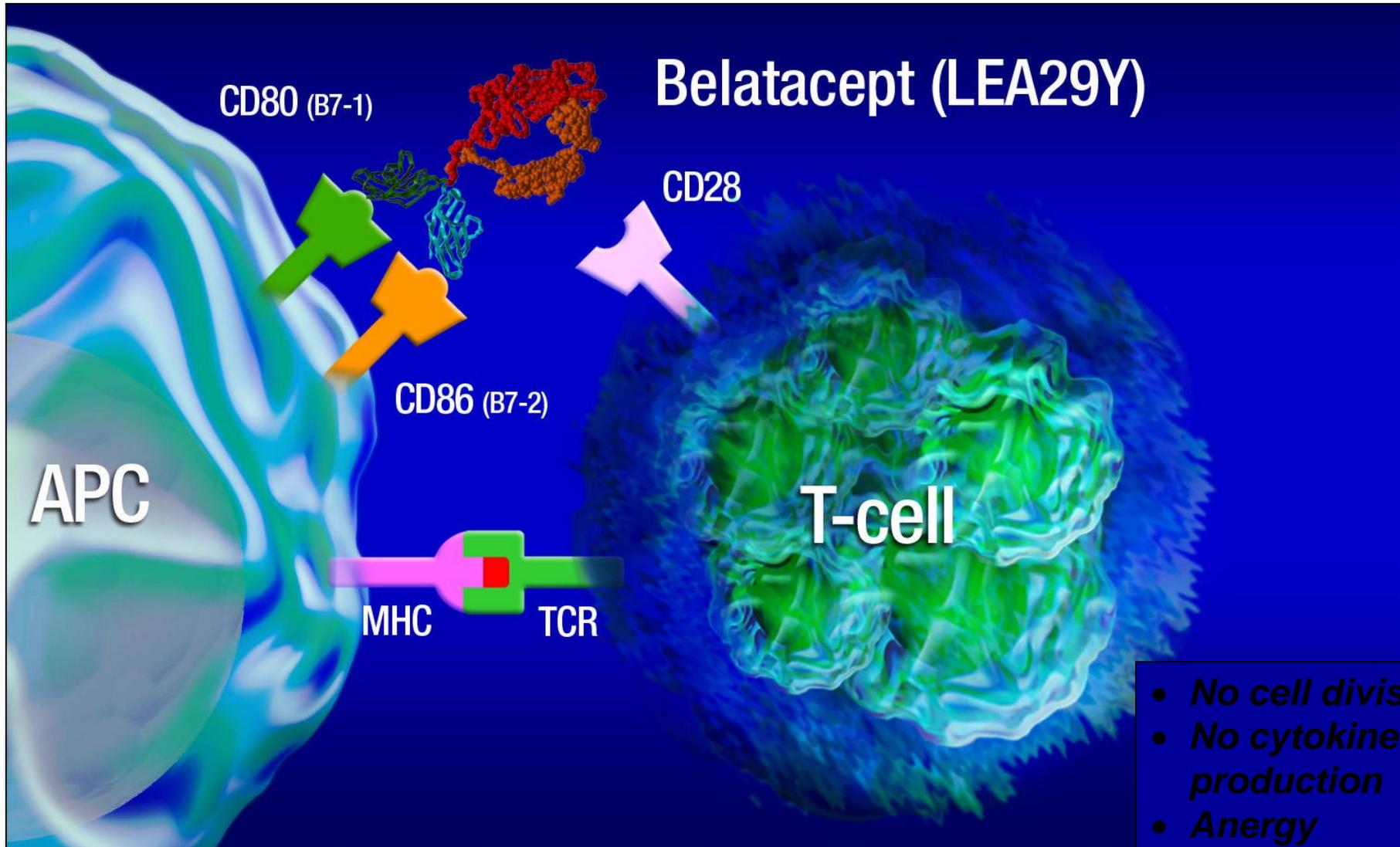
Niezgodność grup ABO krwi

DGF

Długi CIT

Retransplantacja

**Belatacept (LEA29Y) potently and selectively  
blocks T-cell activation**



- *No cell division*
- *No cytokine production*
- *Anergy*
- *Apoptosis*

**Table 1.** Summary of belatacept studies in kidney transplantation

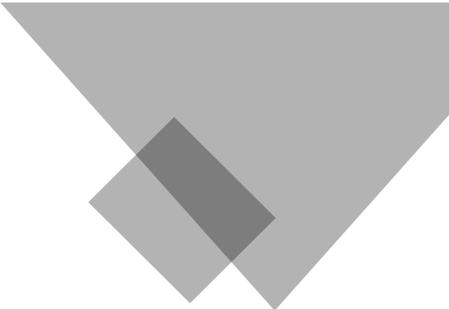
Study ID (author, year)	Study design	Study objective	Patient population	Results
<i>De Novo Belatacept in Kidney Transplantation</i>				
Mannon, 2020 [17]	Prospective, randomized, multicenter trial	Evaluate the safety and efficacy of calcineurin avoidance and rapid steroid elimination with <i>de novo</i> belatacept	Adult kidney transplant recipients on belatacept based immunosuppression with CNI avoidance and steroid withdrawal	The incidence of rejection limits the avoidance of CNI and corticosteroids withdrawal in patients on belatacept maintenance therapy
Woodle, 2020 [18]	Prospective, randomized, open label, multicenter trial	Study the efficacy and safety of simultaneous calcineurin inhibitor avoidance and rapid steroid withdrawal under T-cell depleting induction immunosuppression regimen	Adult first-time kidney transplant recipients	Higher rate of rejection in patients with belatacept based immunosuppression as compared to calcineurin inhibitor based immunosuppression irrespective of the induction immunosuppression agent, up to 2 years posttransplant. No significant difference in death or death censored graft loss between groups
Kaufman, 2021 [19 <sup>***</sup> ]				
Kirk, 2014 [20]	Randomized trial	Assess the role of donor bone marrow and sirolimus in improving the efficacy of belatacept.  Reported on the 5-year outcomes of this cohort	Non-HLA identical living donor adult kidney transplant recipients	Combination of belatacept and sirolimus reduced the risk of kidney allograft rejection in the absence of CNI and steroids, following alemtuzumab induction.  10% of patients developed clinical rejection after the first year, which resolved after treatment. Five-year patient and graft survival rates were 100% and 95%, respectively.
Schmitz, 2020 [21]				

### Conversion to Belatacept from Calcineurin Inhibitors in Kidney Transplantation

Budde, 2021 [22 <sup>■</sup> ]	Prospective, randomized, open label study	Evaluate the efficacy and safety of conversion from calcineurin inhibitor based to belatacept-based maintenance immunosuppression	Stable adult kidney transplant recipients 6–60 months posttransplant	Similar rates of graft survival (98% vs. 97%) in both groups.  Higher rate of rejection (8% vs. 4%) in the belatacept group at 24 months post conversion.
Gupta, 2020 [23 <sup>■</sup> ]	Retrospective study	Assess patient and graft survival in patients converted to belatacept	Adult transplant patients who were converted from tacrolimus to belatacept for acute/subacute allograft dysfunction and a biopsy-proven diagnosis of interstitial fibrosis/tubular atrophy (IFTA) without evidence of any rejection	Patient survival was 94% with a death-censored graft survival of 85%.  7/53 patients had acute rejection at median 6 months post conversion.  Improved GFR from baseline to 6 months postconversion
Kumar, 2020 [24 <sup>■</sup> ]	Prospective study. Patients with biopsy-proven chronic active AbMR were converted from tacrolimus to belatacept	Assess the efficacy of belatacept in the treatment of chronic active AbMR	Adult kidney transplant recipients with biopsy proven chronic active AbMR and high degree of chronicity	Improvement in GFR at 6 months and at 12 months post conversion  Pre- and postconversion biopsies did not show any worsening in microvascular inflammation or chronicity. The paired tissue gene expression analysis showed improved mean total rejection score and a trend toward improved antibody-mediated rejection score
Jain, 2020 [25]	Case Series	Study the effect of combination therapy with bortezomib and belatacept in kidney transplant recipients with early, severe acute antibody mediated rejection	Kidney transplant recipients with early severe antibody mediated rejection which did not respond to treatment with plasmapheresis, IVIG and steroids	There was improvement in renal function, antibody mediated rejection scores and eradication of donor specific antibodies with combined bortezomib and belatacept therapy
Badell, 2021 [26 <sup>■</sup> ]	Open labeled randomized trial	Compare belatacept to immunosuppression discontinuation upon re-initiation of dialysis in failed allograft patients to evaluate HLA antibody formation	Kidney transplant recipients with a failing or failed renal allograft with no donor-specific antibodies (DSAs)	Patients on belatacept had delayed onset of DSA formation, fewer DSAs with high intensity and less increases in class I and II panel reactive antibody and calculated panel reactive antibody

**Table 1** (Continued)

<b>Study ID (author, year)</b>	<b>Study design</b>	<b>Study objective</b>	<b>Patient population</b>	<b>Results</b>
Belatacept in Multi-Organ Transplant Recipients				
Cristea, 2021 [27 <sup>a</sup> ]	Case Series	Study the safety and efficacy of belatacept in liver transplant recipients	Kidney transplant recipients who had previously received a liver transplant	All patients had preserved kidney and liver allograft function, and no graft losses, patient deaths, rejection of liver or kidney allografts, or infectious complications reported
Stock, 2020 [28]	Phase 2, multicenter, open-label, randomized trial	Compare belatacept based maintenance immunosuppression to a CNI-based regimen in simultaneous kidney and pancreas transplant recipients	Recipients of simultaneous kidney and pancreas transplant	Renal function and frequency and severity of kidney rejection was similar between both groups  Higher incidence of pancreas rejection in the belatacept group, all of which happened after CNI withdrawal  No antibody mediated rejection of kidney or pancreas in both groups



## Belatacept and Metabolic Considerations

Muller,  
2021 [29<sup>■</sup>]

Single-center cohort  
study

Compare abnormalities of  
glucose metabolism in  
tacrolimus- vs. belatacept-  
treated kidney transplant  
recipients

Adult kidney transplant  
recipients on belatacept or  
calcineurin inhibitor based  
immunosuppression

belatacept treated patients had 93%  
lower odds of developing diabetes  
and prediabetes than those on  
tacrolimus (OR, 0.08; 95% CI,  
0.02–0.35;  $P < 0.001$ ). Patients on  
tacrolimus also had higher  
hemoglobin A1c levels, lower  
insulin release, and higher insulin  
sensitivity compared to those on  
belatacept

## Vaccine and Infectious Complications in Belatacept Treated Patients

Karadkhel, 2020 [30 <sup>■</sup> ]	Retrospective cohort study	Assess the impact of belatacept on patient and graft survivals in CMV seronegative kidney transplant recipients	Adult CMV seronegative first kidney transplant recipients	Increased risk of CMV primary-infection, higher rate of first line treatment failure and prolonged course of viral replication in patients
Chavarot, 2021 [33 <sup>■</sup> ]	Prospective, cohort study	Study the immune response after 2 and 3 doses of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination	Adult kidney transplant recipients on belatacept	Lower patient and graft survival The immune response to SARS-CoV-2 vaccination was much weaker and the incidence of antibody positivity was much lower in patients receiving belatacept
Mitchell, 2022 [34 <sup>■</sup> ]	Case-control study	Study the impact of third severe SARS-CoV-2 vaccination	Kidney transplant recipients on belatacept compared with those not on belatacept.	The belatacept group had significantly lower antispike seroconversion than the controls after the third dose of SARS-CoV-2 vaccination
Osmandoja, 2022 [35 <sup>■</sup> ]	Retrospective study	Assess the serological response of up to five doses of the SARS-CoV-2 vaccine	Adult kidney transplant recipients	Belatacept treated patients had a lower serologic response even after five doses of SARS-CoV-2 vaccination as compared to the patients not receiving belatacept
Noble, 2022 [36 <sup>■</sup> ]	Retrospective cohort study	Assess immune response after SARS-CoV-2 vaccination in kidney transplant recipients	Kidney transplant recipients receiving belatacept compared to the tacrolimus group	There was a low immune response after SARS-CoV-2 vaccination in kidney transplant recipients, with significantly lower antibody response in patients treated with belatacept as compared to the ones treated with tacrolimus.
Ou, 2021 [37 <sup>■</sup> ]	Prospective cohort study	Assess immune response after SARS-CoV-2 vaccination in kidney transplant recipients belatacept based immunosuppression vs. nonbelatacept based immunosuppression	Adult kidney transplant recipients	There was a significantly reduced incidence of detectable antibodies in patients on belatacept based immunosuppression compared to nonbelatacept based immunosuppression (0% vs. 14% and 5% vs. 50%) after the first and second vaccine dose respectively

## Belatacept and Malignancies

Wang,  
2020 [39]

Retrospective cohort  
study

Investigate the risk of skin  
cancer in patients on  
belatacept

Adult kidney transplant patients  
converted to belatacept from  
calcineurin inhibitor

Belatacept was associated with  
decreased incidence of keratinocyte  
carcinomas and squamous cell  
carcinomas (SCC), and an  
increased survival free of an  
additional SCC, compared to  
patients maintained on a CNI

## What's new in organ transplantation

**Table 1.** Summary of clinical states of costimulation blockers in the pipeline

Agent	Mechanism of action	Clinical stage	Method of administration
Belatacept	CTLA-4 Ig: Selectively Blocks CD28-CD80/286 Interaction	FDA approved	Intravenous
Abatacept	First Generation CTLA-4 Ig: Selectively Blocks CD28-CD80/286 Interaction	Phase 2	Subcutaneous
VEL-101	Pegylated anti-CD28 Fab' antibody fragment selectively against CD 28; Spares CTLA-4 Signaling	Phase 1/2	Intravenous/ subcutaneous
Lulizumab	Pegylated anti-CD28 antibody	Phase 2	Subcutaneous
Iscalimab	CD40 antibody and inhibits CD40-CD40L interaction	Phase 2	Intravenous
Bleselumab	Human IgG4 anti-CD40 antibody	Phase 2	Intravenous
TNX-1500	Fc-modified Anti-CD154 (CD40L) antibody	Preclinical/ Phase 1	Intravenous
Tegoprubart	Synthetic IgG1 targeting CD154 and CD40/CD40L	Phase 1	Intravenous
Dazodalibep	Anti-CD154 monoclonal antibody	Phase 2	Intravenous

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; Ig, immunoglobulin.

# Anty-CD20 (RITUXIMAB)

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**Anty-CD20** – chimera mysio-ludzka przeciwko cząsteczce CD20, obecnej na powierzchni limfocytów B, nieobecna na plazmocytach

Liza, apoptoza limfocytów B, wtórnie ↓IgM, IgG

Off label u chorych po Tx, PTLD

Wysokie ryzyko infekcji (11.8%) i zgonu związanego z infekcją (9.1%) u chorych leczonych rituksimabem (n=77) vs 1.55% w grupie kontrolnej (n=902); p= 0.0007 (*Kamar N, Am J Transplant, 2010, 10, 89-98*)

*LEUKOENCEPHALOPATHIA, RALI(rituximab associated lung injury), late onset of neutropenia, trombocytopenia, zespół uwalniania cytokin, powikłania sercowo-naczyniowe?*

# Bortezomib

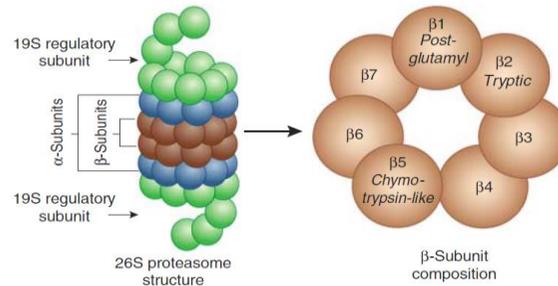


Figure 1 | 26S Proteasome structure.

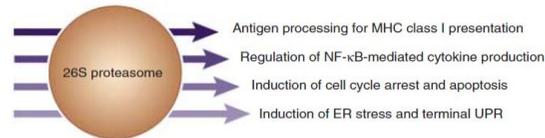


Figure 2 | Primary mechanisms of proteasome inhibitor-mediated immunomodulation. ER, endoplasmic reticulum; MHC, major histocompatibility complex; NF- $\kappa$ B, nuclear factor-kappa B; UPR, unfolded protein response.

- Bortezomib selektywny, odwracalny inhibitor 26S proteasomu (Velcade)
- Deplecja plazmocyto $\nu$  (nowotworowych i nienowotworowych)

# IdeS: A Bacterial Proteolytic Enzyme with Therapeutic Potential

Björn P. Johansson, Oonagh Shannon, Lars Björck\*

Division of Infection Medicine, Department of Clinical Sciences, Biomedical Center (BMC), Lund University, Lund, Sweden

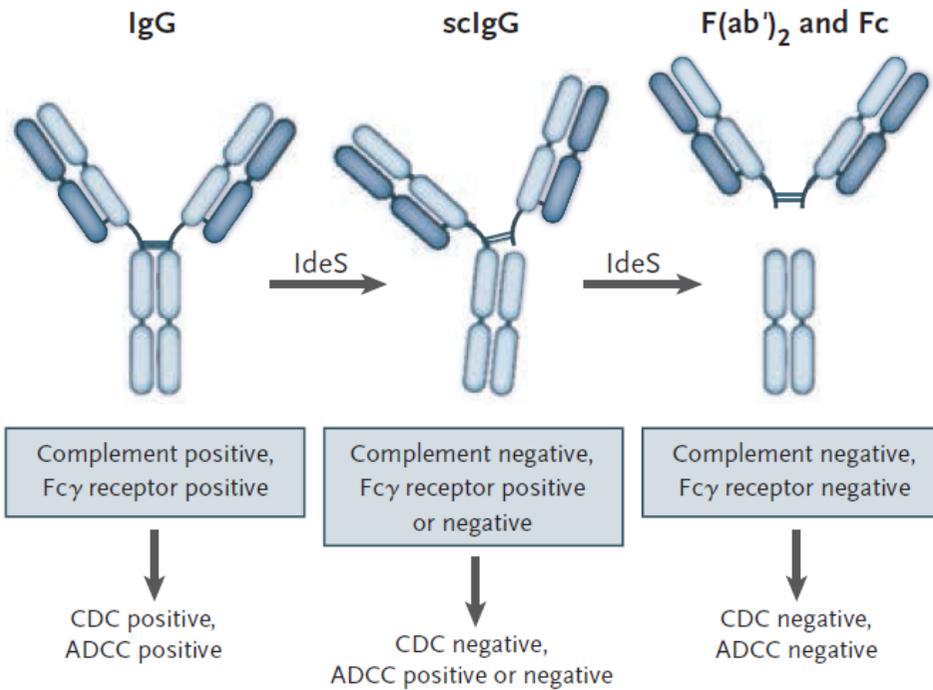
## Abstract

**Background:** IdeS, a proteinase from *Streptococcus pyogenes*, cleaves immunoglobulin (Ig)G antibodies with a unique degree of specificity. Pathogenic IgG antibodies constitute an important clinical problem contributing to the pathogenesis of a number of autoimmune conditions and acute transplant rejection. To be able to effectively remove such antibodies is therefore an important clinical challenge.

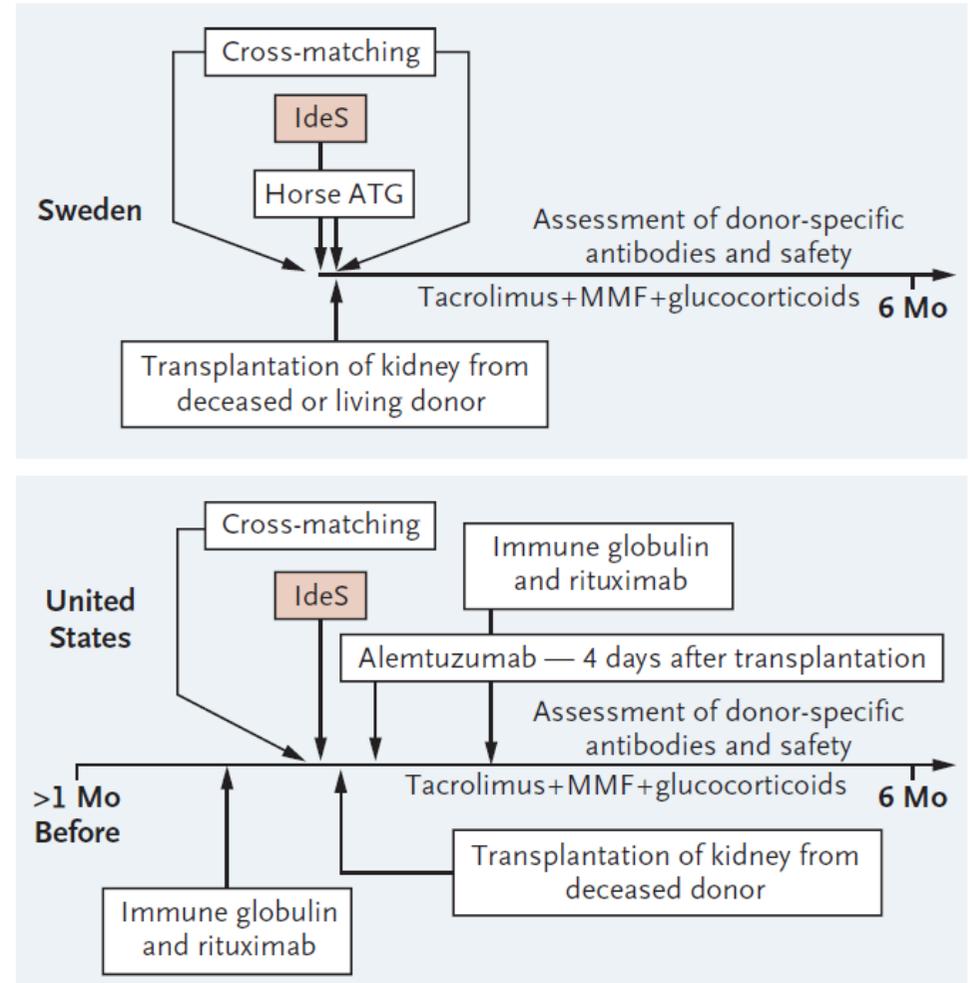
**Methodology/Principal Findings:** IdeS was found to specifically and efficiently cleave IgG in human blood *in vitro* (20 µg of IdeS caused a complete degradation of IgG in one ml of human whole blood in 15 minutes) and to clear IgG from the blood stream of rabbits *in vivo* (no IgG was detected six hours following an intravenous injection of 5 mg of IdeS) without any side effects. In a mouse model of immune thrombocytopenic purpura (ITP), polyclonal IgG antibodies against platelet surface antigens were used to induce a lethal disease. These profoundly thrombocytopenic animals were treated and cured by a single injection of IdeS.

**Conclusions/Significance:** Novel information is provided concerning the IgG-cleaving activity of IdeS *in vitro* and *in vivo*. The highly specific and rapid elimination of IgG *in vivo*, the dramatic effect in a mouse model of ITP, and the lack of side effects in the treated animals, indicate that IdeS could also be used to treat IgG-driven diseases in humans.

### A Cleaving of Intact IgG by IdeS



### B Immunosuppressive Regimens

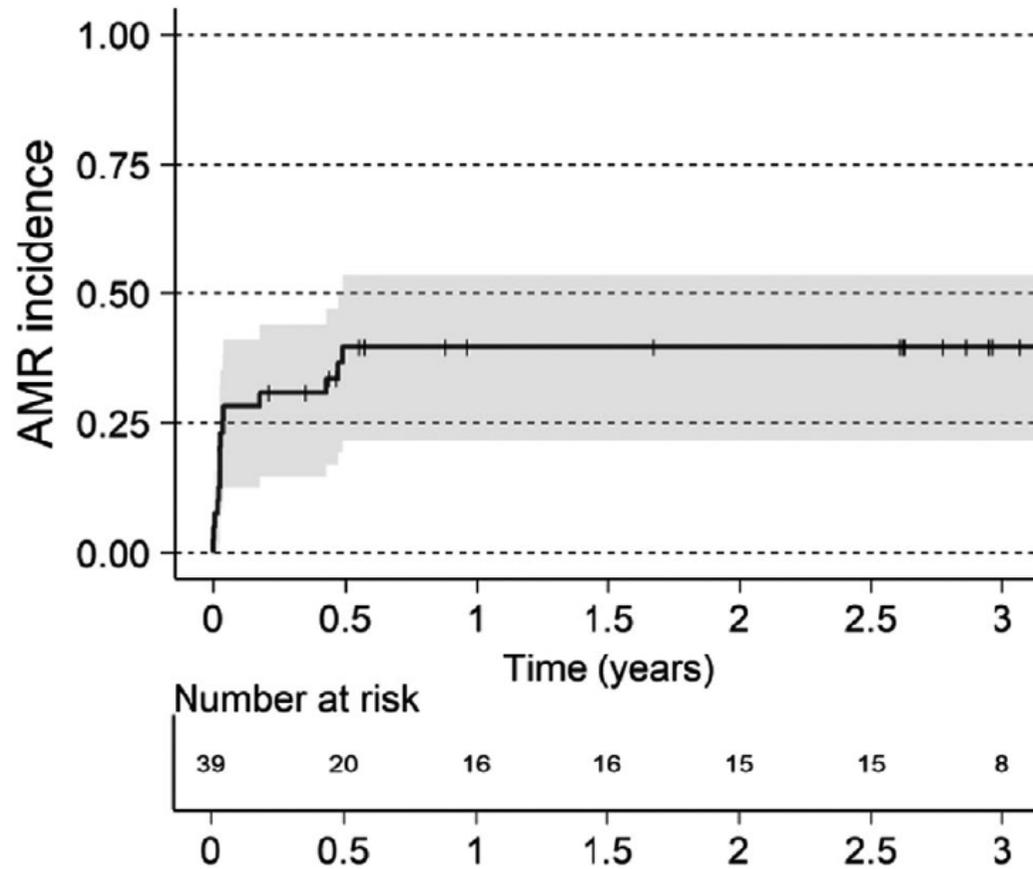


**TABLE 1.****Clinical studies with imlifidase in kidney transplantation**

	Year of publication	No. of patients	Immunodominant DSA	Treatment next to imlifidase	Follow-up	AMR	Patient survival	Death-censored graft survival
Jordan et al <sup>14</sup>	2017	25	DSA negative (n = 3) Luminex positive (n = 2) FACS positive (n = 20)	Horse ATG (n = 11) alemtuzumab, rituximab, IVIG (n = 14)	6 mo	n = 10	100%	96%
Jordan et al <sup>15</sup>	2021	19 (1 not transplanted because of infusion reaction)	>20 000 (n = 7) 10 000-20 000 (n = 3) <10 000 (n = 9)	Horse ATG or alemtuzumab, rituximab, IVIG	6 mo	n = 7	100%	89%
Lonze et al <sup>16</sup>	2018	7 (subgroup analysis in 1 center out of the 19 patients described by Jordan & Legendre et al <sup>15</sup> )	MFI >20 000 (n = 4) 15 000-20 000 (n = 2) 10 000-14 999 (n = 1)	alemtuzumab, rituximab, IVIG	6 mo	n = 3	100%	100%
-----								
Three-year follow-up of the patients described in the initial reports:								
Kjellmann et al <sup>43</sup>	2021	39 (FACS-positive patients from a total of 46 patients: n = 43 from 3 reports and 3 additional patients)	FACS positive (n = 39) Median MFI level 7791 (interquartile range, 4108–16 320)	as described	3 y	38%	90%	84%

AMR, antibody-mediated rejection; ATG, antithymocyte globulin; DSA, donor-specific antibody; FACS, flow cytometric crossmatch; MFI, mean fluorescence intensity.

Annelies E. de Weerd, MD, PhD,<sup>1</sup> Dave L. Roelen, PhD,<sup>2</sup> Jacqueline van de Wetering, MD, PhD,<sup>1</sup> Michiel G.H. Betjes, MD, PhD,<sup>1</sup> Sebastiaan Heidt, PhD,<sup>2</sup> and Marlies E.J. Reinders, MD, PhD<sup>1</sup>



**FIGURE 6** Time to first AMR. Visualized using reverse Kaplan-Meier estimate for cumulative incidence of AMR for XM+ patients. Patients without AMR are censored last known visit or death, indicated in graphics as a thin vertical line

**TABLE 3.****Planned studies with imlifidase in kidney transplantation**

Registration	Setting	Design	Target number of patients	intervention	Primary outcome
NCT03897205	Phase II, antibody-mediated rejection	Randomized controlled	n = 20 for imlifidase n = 10 for plasma exchange	Pulse steroids, IVIG, and rituximab with -0.25 mg/kg imlifidase or -5–10 plasma exchange	Maximum DSA reduction during 5 d after treatment completion
NCT04935177 ConfideS United States	Phase III, desensitization	Randomized controlled	n = 64 in a 1:1 ratio of imlifidase versus “best available treatment”	-0.25 mg/kg imlifidase or -any combination of plasma exchange, IVIG, anti-CD20, or eculizumab	eGFR at 12 mo (MDRD equation)
NCT05369975 PAES Europe	Phase III, desensitization	Postauthorization study with 2 noncomparative reference cohorts to assess the impact of differences in posttransplantation management and outcome in less sensitized patients	n = 50 for imlifidase n = 50–100 for concurrent reference cohort n = 100 for historical reference from the Collaborative Transplant Study registry	Imlifidase 0.25 mg/kg	Graft failure-free survival 1 y after transplantation after imlifidase treatment
NCT05049850	Phase II, DSA rebound after desensitization	Single arm	n = 12 with either cPRA $\geq 99.9\%$ or $\geq 98\%$ with at least 1 y kidney exchange participation	Belatacept and bortezomib 3 wk before imlifidase; rituximab 8 d and IVIG 10 d after imlifidase	Proportion of patients with DSA rebound

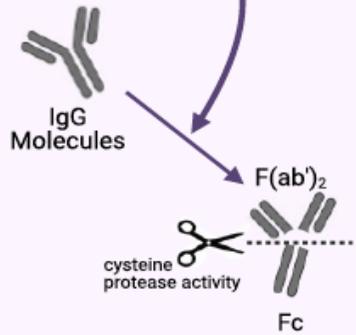
cPRA, calculated panel-reactive antibody; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; NCT, national clinical trial (identifier).

# A Novel Approach for Highly Sensitized Patients on the Kidney Transplant Waiting List: IMLIFIDASE

Imlifidase is the pharmacological name for Immunoglobulin G Degrading Enzyme of *Streptococcus pyogenes* (*IdeS*).



- ### ADVANTAGES
- High specificity for IgG
  - Near-total elimination of IgG within 2-6 hours
  - Simple administration procedure 4-6 hours prior to transplantation procedure
  - Improvement in allograft survival and kidney functions after transplantation
  - Low risk for adverse effects



- ### DRAWBACKS
- IgG rebound within two weeks after transplantation need for strong post-transplant immunosuppression.
  - Infusion-related allergic and infectious complications
  - Possibilities for re-administration limited

## Recommended Immunosuppression Scheme with Imlifidase

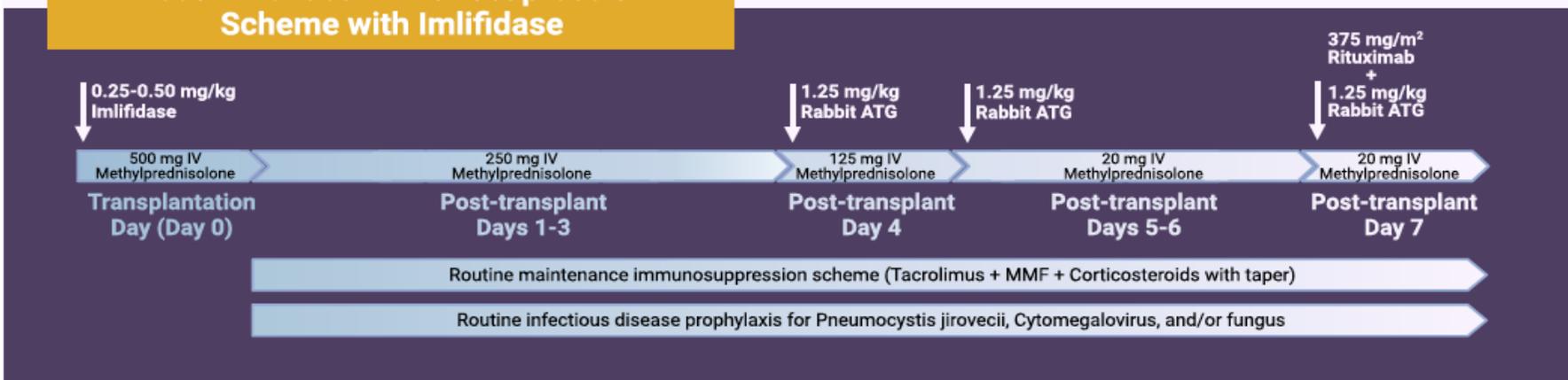
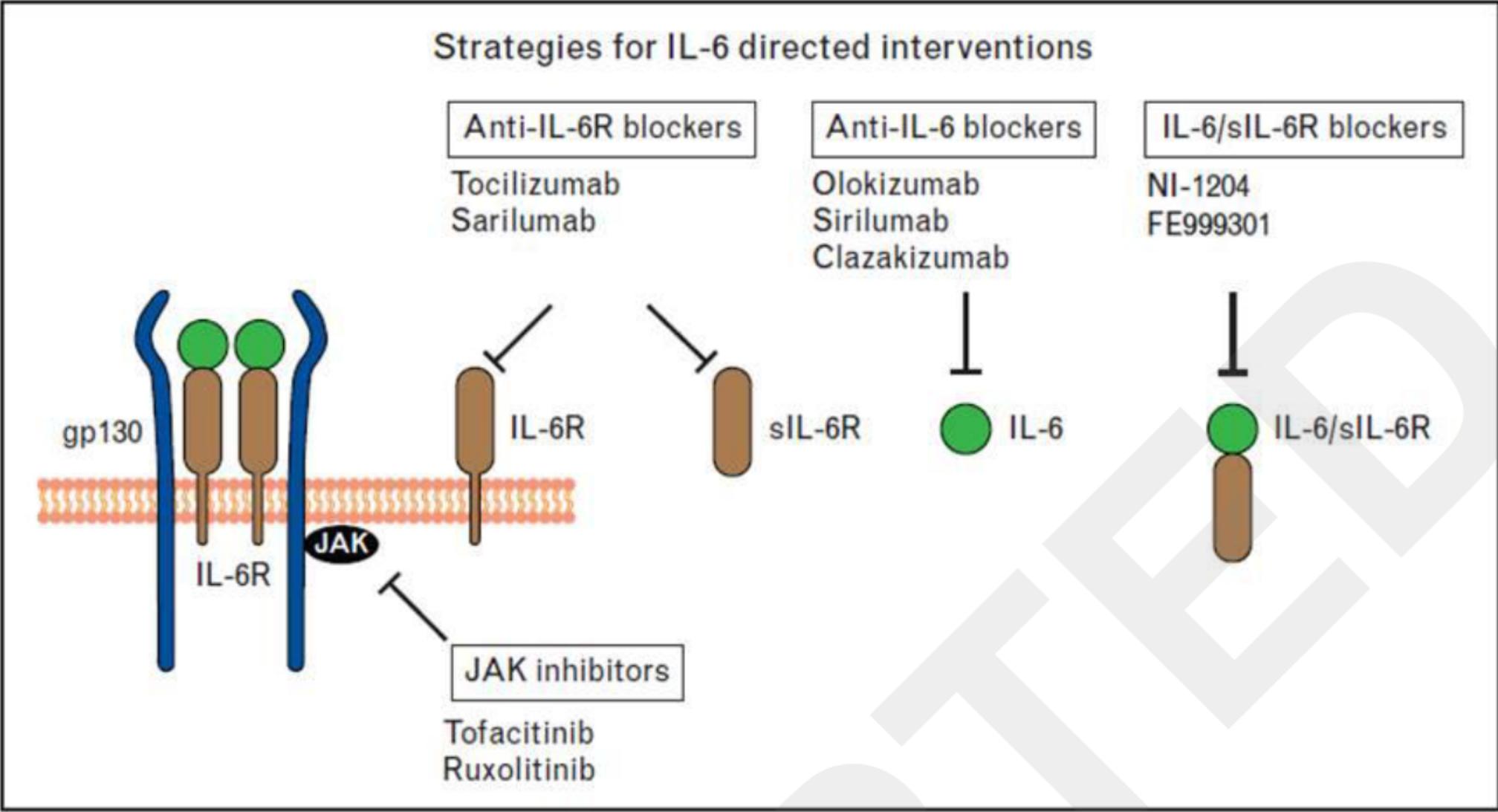


Figure 2: Recommended dosage scheme of imlifidase with standard immunosuppressive regimens. b.i.d.: two times a day; IV: intravenous.

Figure 5



# Mechanizmy działania IgG iv

- Neutralizacja krążących Ab
- Hamowanie wydzielania cytokin
- Hamowanie wiązania fragmentów dopełniacza z komórkami docelowymi
- Hamowanie proliferacji T i B limfocytów poprzez hamowanie produkcji przeciwciał
- Hamowanie aktywności komórek śródbłonna
- Hamowanie cytotoksyczności limfocytów CD8
- Zwiększona apoptoza limfocytów B



**TABLE 1.****Application of nanotechnology in transplantation**

<b>Applications in transplantation</b>	<b>Platforms</b>	<b>Description</b>
Delivery of immunosuppressants and other drugs	Nanoparticles	Nanoparticles allow for a targeted, sustained and more controlled drug delivery dosage, reducing the side effects of indiscriminate prolonged used.
	Liposomes and peptide amphiphiles	The use of lipid-based delivery platforms and peptide amphiphiles help in the delivery of water-insoluble therapeutics, increasing drug efficacy.
Donor specific tolerance and rejection	Nanochannel membranes	Nanochannel membranes offer a constant, sustained release and can be tuned in channel size (2-200 nm) and density to achieve a clinically relevant, constant delivery of drugs. It has shown constant in vivo delivery for periods ranging from 1 to 6 months.
	Nanobodies	Nanobodies (therapeutic fragments of antibodies) present advantages in size, stability, and low immunogenic potential and can be used to stimulate inhibitory pathways and shut off immune cells to prevent allograft rejection.
	Biocapsules and nanoglands	The use of biocapsules and nanogland platforms, allows the exchange of nutrients and metabolites while inhibiting the permeation of antibodies and the infiltration of immune cells. They are designed to maintain cell proximity while ensuring sufficient separation to simulate the in vivo environment.
Imaging, diagnostics, and other uses	Nanoparticles (eg, gold, iron oxide, quantum dots)	Often used to deliver contrast agents to assist in delineating anatomy and physiology for medical imaging, the use of nanoparticles in diagnostic imaging has exhibited a 6-fold contrast enhancement compared with the use of free contrast agents.

# TDM

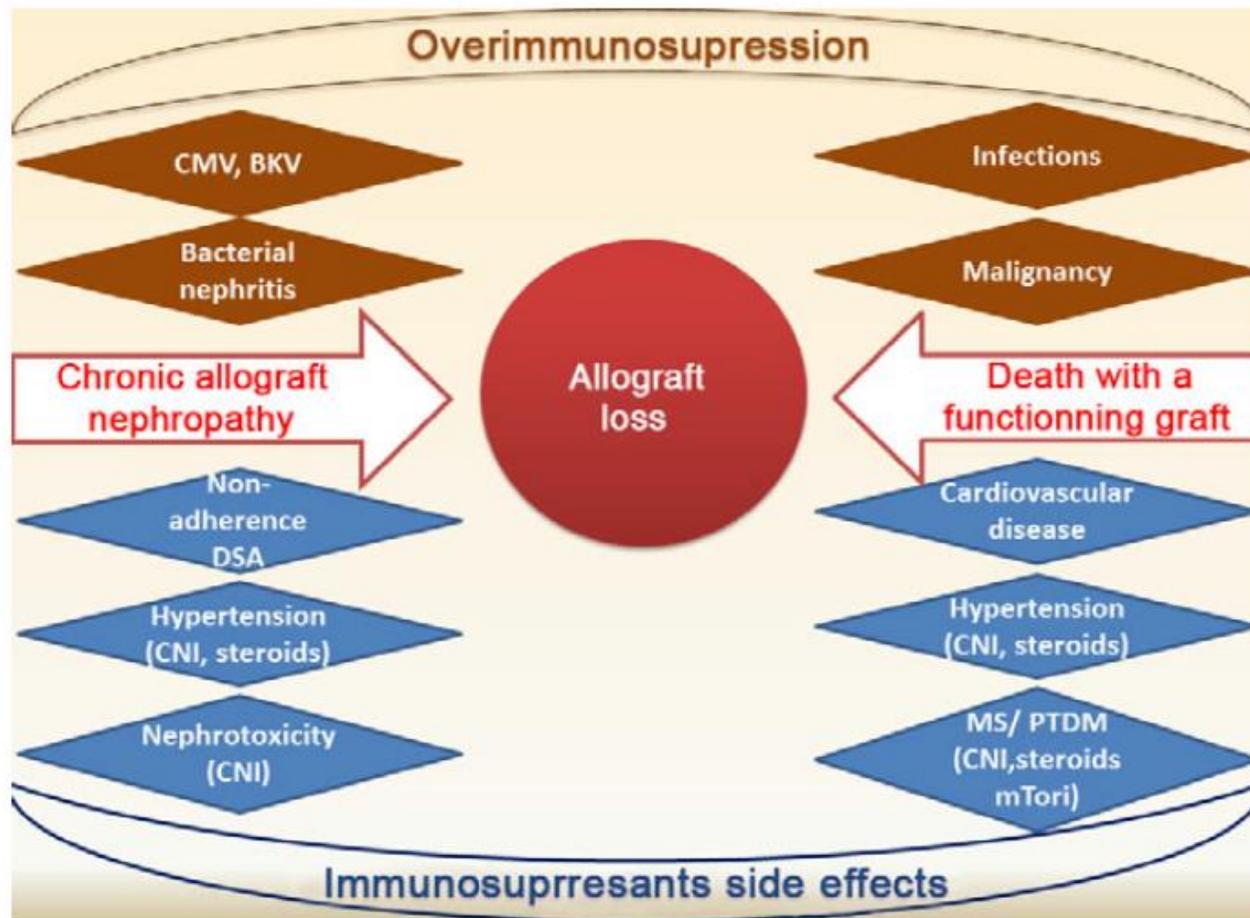
## Leki o wąskim oknie terapeutycznym

- **Cyklosporyna –C0, C2**
- **Takrolimus –C0**
- **Syrolimus, ewerolimus-C0**

**MMF, MPS - MPA nie jest oznaczane standardowo, C0 lepiej AUC-  
skrótowe profile 3 punktowe**



# Powikłania po transplantacji



## Podsumowanie

Optymalna immunosupresja:

- Powinna zapobiegać odrzucaniu przeszczepu T komórkowemu oraz powstawaniu DSA i związanemu z nimi odrzucaniu zależnemu od przeciwciał.
- Powinna zapewniać jak najdłuższe przeżycie przeszczepu i pacjenta
- Powinna być bezpieczna (minimalizacja działań niepożądanych)
- Powinna zapewniać dobrą jakość życia
- Powinna być oparta na czynnikach ryzyka dawca/biorca – spersonalizowana

# Schematy leczenia immunosupresyjnego

## Standardowy schemat immunosupresji

- **Inhibitor kalcyneuryny (cyklosporyna albo takrolimus) + lek antyproliferacyjny (mykofenolan mofetylu/mykofenolan sodu lub syrolimus/ewerolimus)+ GS**

## Najczęściej stosowany w Polsce i na świecie schemat immunosupresji

- **Takrolimus+mykofenolan mofetylu+glikokortykosteroidy (ponad 90% biorców narządów)**

Do każdego schematu można zastosować leczenie indukcyjne (przeciwciała poliklonalne lub anty-CD25). Jego stosowanie zapewnia roczne przeżycie przeszczepu w 90-95% i częstość epizodów ostrego odrzucania nie przekraczającą 10-20%.

# Dobór schematu IS

*Grupa optymalna (biorca, dawca w przedziale wiekowym 20-50 lat, krótki czas niedokrwienia, pierwsza transplantacja, dobór HLA: <3 niezgodności HLA, PRA<20%)*

**CsA/TAC + MMF/MPS + GS**

**lub**

**Przeciwciało anty-CD25 + obniżona ekspozycja na CsA/TAC + ewerolimus +GS**

*Umiarkowane ryzyko (starszy biorca: wiek po 60 roku życia lub PRA 20% -50% lub TIT > 24 h lub dawca o rozszerzonych kryteriach)*

**Przeciwciało anty-CD25 + TAC/CsA + MMF/MPS + GS**

*Biorcy o wysokim ryzyku niepowodzenia: (PRA > 50%, drugi i kolejne przeszczepy od zmarłego dawcy stracone z przyczyn immunologicznych)*

**Thymoglobulina lub ATG + TAC + MMF/MPS + GS**

**Wskazane monitorowanie DSA**

# Dobór schematu IS

## *Starszy dawca i starszy biorca*

Przeciwciało anti-CD25 + TAC/CsA + MMF/MPS + niskie dawki GS.

lub

Przeciwciało anti-CD25 + mTORi z redukcją dawek TAC/CsA+ GS

## *Podwyższone ryzyko sercowo-naczyniowe*

*(przebyty zawał, operacje na naczyniach wieńcowych, epizod mózgowy)*

Przeciwciało anti-CD25 + TAC/CsA + MMF/MPS + GS

lub

Przeciwciało anti-CD25 + CsA/TAC + mTORi +GS

# Dobór IS

## *Biorca otyły*

CsA/TAC + MMF/MPS + niskie dawki GS

## *Biorca z cukrzycą*

CsA/TAC + MMF/MPS + GS

## *Biorca z hiperlipidemią*

Wskazanie do stosowania TAC i przeciwwskazanie  
do inhibitorów mTOR

## *Biorca z nadciśnieniem tętniczym źle kontrolowanym*

TAC + MMF/MPS + GS

# Dobór IS

***Biorca z nowotworem w wywiadach lub rozwój nowotworu de novo***

***Nowotwór w wywiadzie***

Przeciwciało anty- CD25 u pacjentów z planowanym odstawianiem CNI

CsA/TAC + mTORi + GS

lub

CsA/TAC + MMF/MPS + GS

po trzech miesiącach odstawić CNI (tylko chorzy niskiego ryzyka immunologicznego) i starać się zostawić chorego na mTORi lub MMF/MPS + GS ewentualnie mTORi + MMF/PPS + GS

***Rozwój nowotworu de novo:***

zwykle pacjent w chwili rozpoznania nowotworu otrzymuje MMF/MPS + CNI + GS

późna konwersja MMF/MPS lub CNI na mTORi - próba pozostawienia chorego na

mTORi+GS, lub mTORi + MMF/MPS + GS (u chorych niskiego ryzyka immunologicznego)

***Biorca z tuberous sclerosis complex/lymphangiomyomatosis/angiomyolipoma***

Przeciwciało anty-CD25 + CsA/TAC + mTORi +GS

lub

Przeciwciało anty-CD25 +TAC/CsA+ MMF/MPS+ GS następnie wczesna konwersja MMF/MPS na mTORi -dotyczy chorych z niskim ryzykiem immunologicznym

# Dobór IS

## **Zakażenie CMV**

CsA/TAC+MMF/MPS+GS – wskazana profilaktyka anty-CMV.

lub

Przeciwciało anty-CD 25+ CsA/TAC + mTORi +GS, schemat wskazany u biorców CMV-seronegatywnych otrzymujących narząd od CMV-seropozytywnego dawcy, u biorców CMV-seropozytywnych otrzymujących mTORi można rozważyć niestosowanie profilaktyki anty-CMV.

Thymoglobulina/ATG - wskazana profilaktyka anty-CMV

## **Biorca HCV (+)**

CsA/TAC+MMF/MPS+GS (niska dawka)

Thymoglobulina/ATG- nie zalecane

## **Biorca HBV (+)**

CsA/TAC+MMF+GS

lub

Thymoglobulina/ATG - nie zalecane

Jak najszybciej odstawić GS, lamiwudyna/entekawir/ tenofowir od dnia transplantacji przewlekłe

# Dobór IS

## ***Biorca HIV (+)***

**Przeciwciało anty- CD25+CsA/TAK+MMF+GS**

**Thymoglobulina/ATG- nie zalecane**

**Należy stosować jednocześnie z immunosupresją terapię antyretrowirusową, dawki leków immunosupresyjnych powinny być modyfikowane w zależności od rodzaju terapii antyretrowirusowej.**

## ***Zakażenie BKV***

**Thymoglobulina/ATG - zwiększa ryzyko zakażenia BKV**

**Przeciwciało anty-CD25- nie zwiększa ryzyka zakażenia BKV**

**CsA+mTORi+GS- optymalny schemat, najmniejsze ryzyko zakażenia BKV i nefropatii BK.**

**Tak+MMF+GS –zwiększone ryzyko zakażenia BKV i nefropatii BK.**