Immunosuppressive therapy

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Immunosuppression

- **Purpose: to improve long-term outcome, to improve quality of life *(prevention and treatment of kidney allograft acute and chronic rejection)***
- **Expectations: effective and safe immunosuppressive therapy**
- **Reality:**
  - **Non-selective effects on immunological system**
    - ***Prevention of acute rejection episodes***
    - ***Infections and neoplasms***
    - ***Non-immunologic effects - drug toxicity***

Transplant tolerance –

kidney
< 1/3000

liver – 20%

Autor	n	Date of publication
Owens	6	1975
Uehling	1	1976
Zoller	9	1980
Strober	3	1989
Helg	1[a]	1994
Jacobsen i wsp.	1[a]	1994
Burlingham	1	1995
Sorof	1[a]	1995
Fisher i wsp	1	1996
Christensen	1	1998
Spitzer i wsp	1[b]	1999
Starzl i wsp	7	2004
Newell i wsp	16	2006
Roussey-Kesler i wsp	10	2006

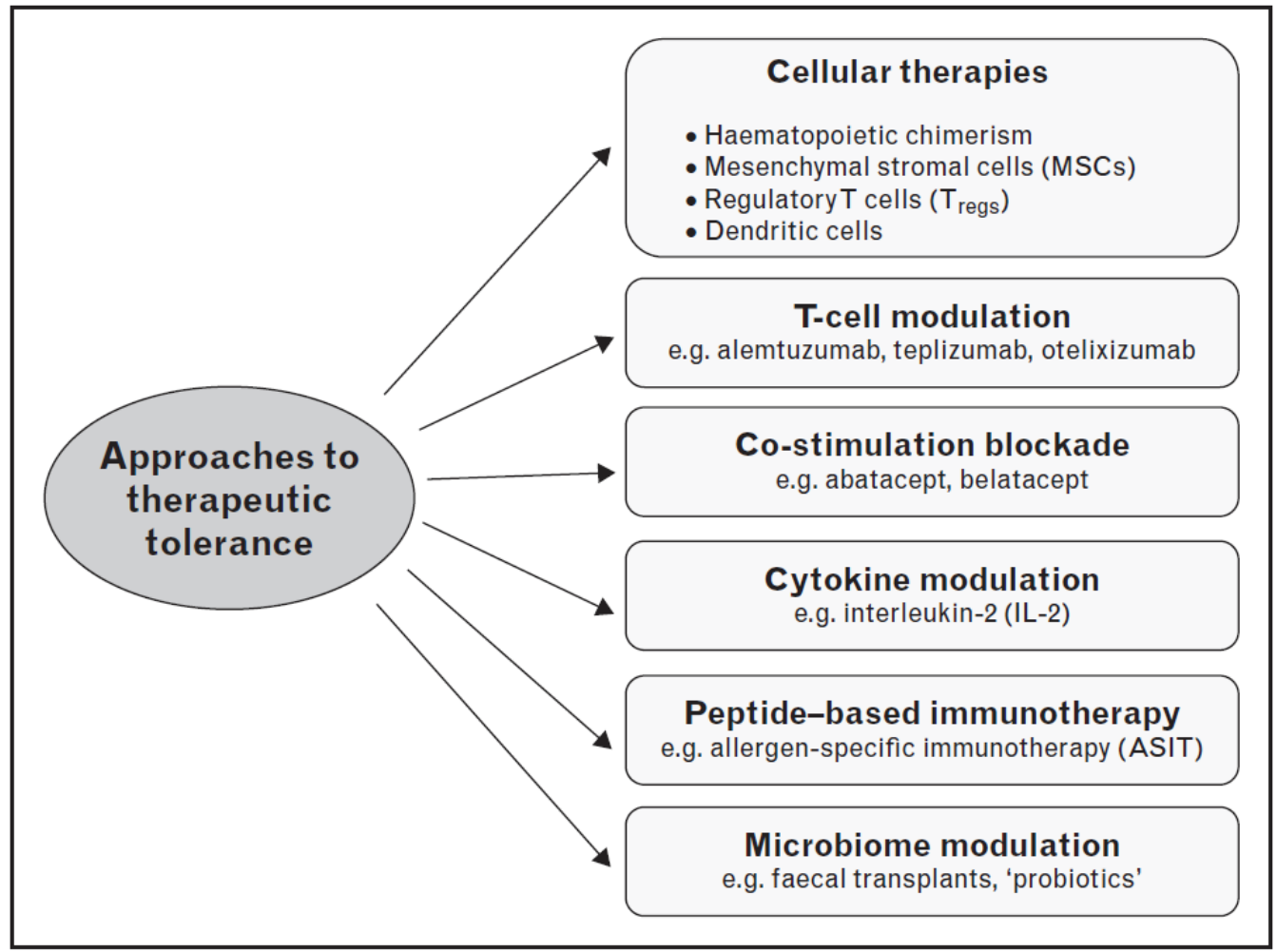


FIGURE 2. Approaches to therapeutic tolerance induction.

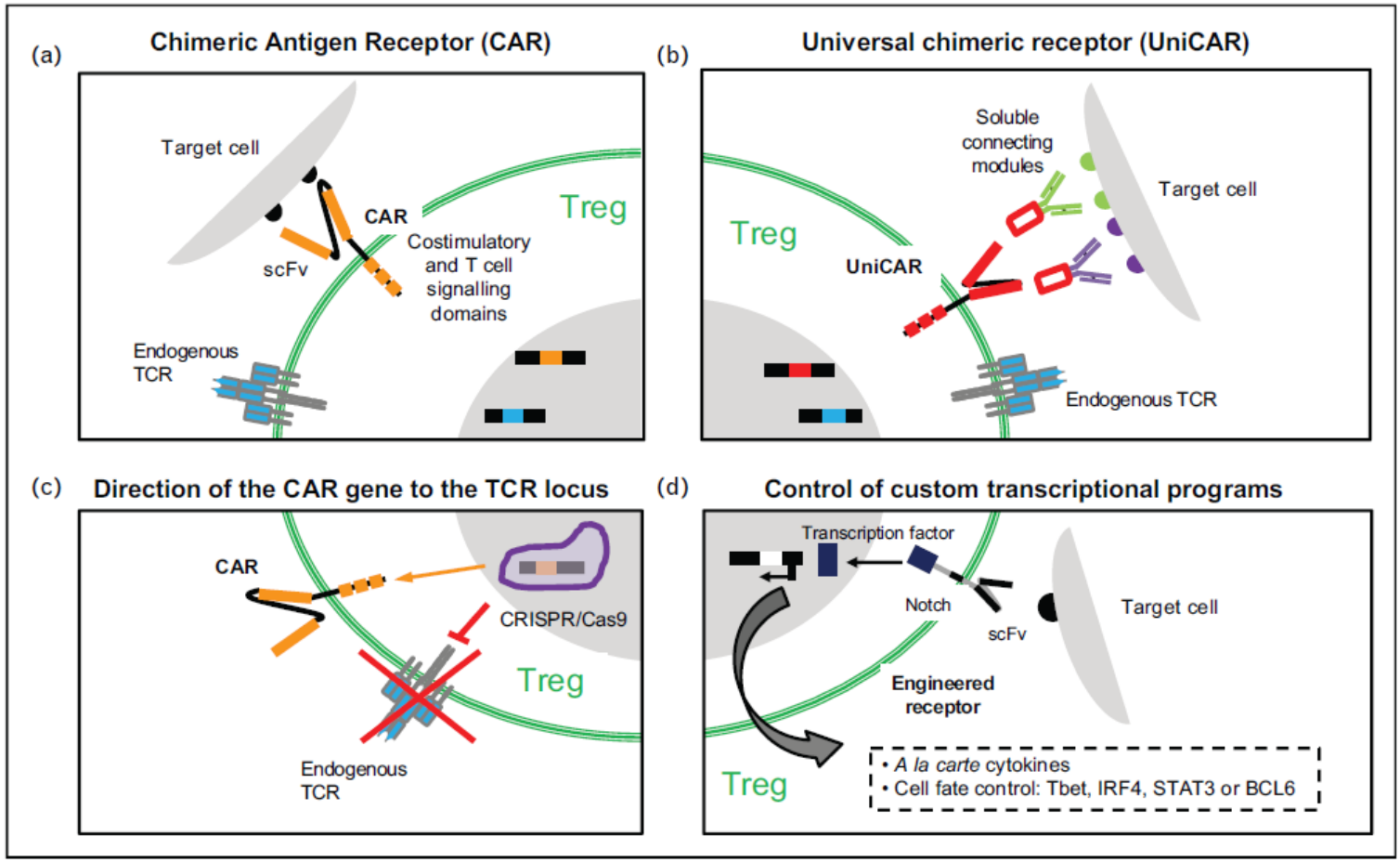
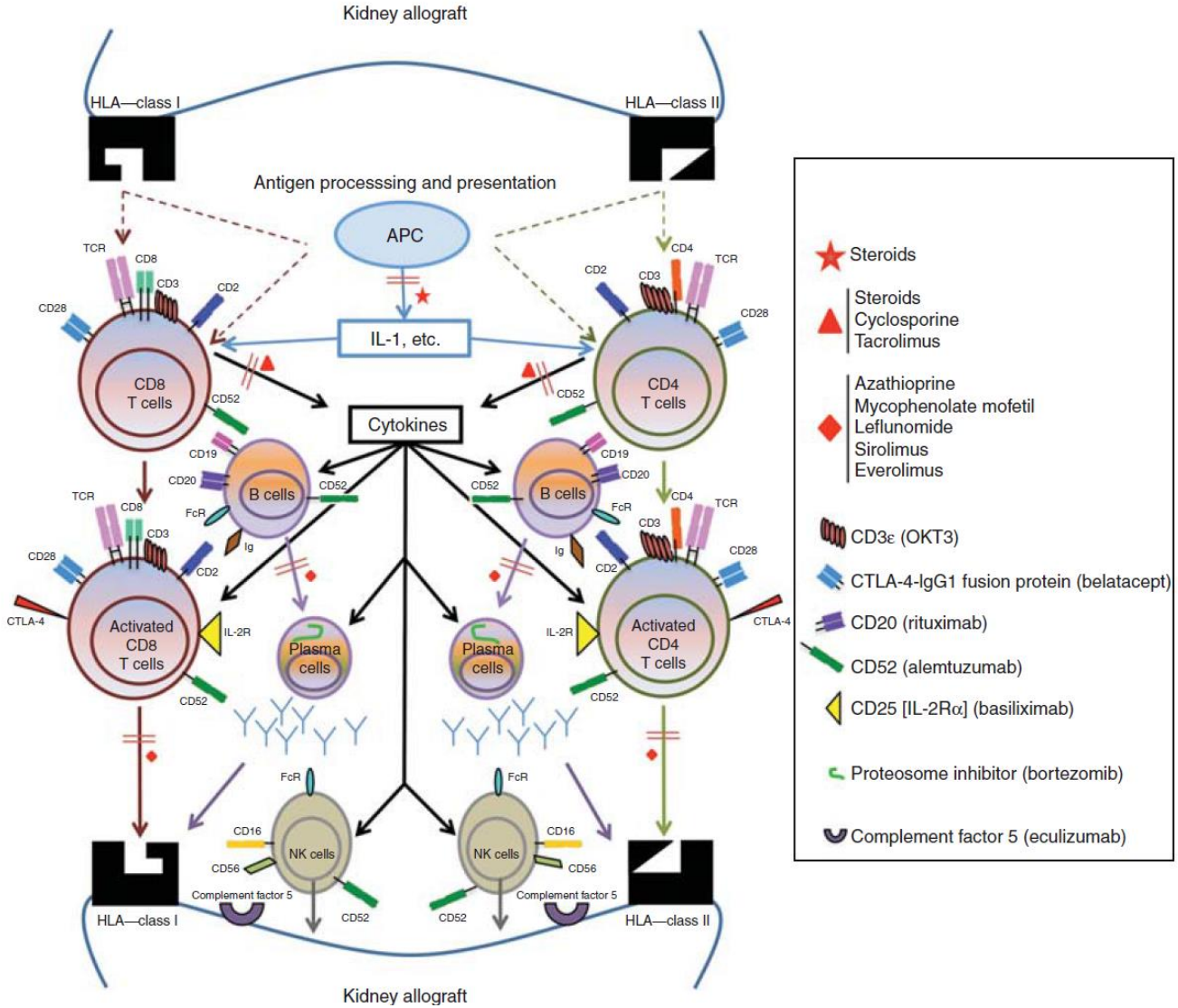


FIGURE 1. Novel approaches that may represent the future of antigen-specific Treg therapy. (a) Chimeric antigens receptor (CAR) technology: CARs are composed of an extracellular antigen–binding domain, often comprising a single-chain Ab (scFv), which is fused to intracellular signaling domains. CAR-expressing 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].


Kidney allograft
HLA—class I
HLA—class II
Antigen processsing and presentation
APC
IL-1, etc.
Cytokines
CD8 T cells
CD4 T cells
B cells
B cells
Activated CD8 T cells
Activated CD4 T cells
Plasma cells
Plasma cells
NK cells
NK cells
TCR
CD8
CD3
CD2
CD28
CD4
CD52
CD19
CD20
FcR
Ig
CTLA-4
IL-2R
CD16
CD56
Complement factor 5
HLA—class I
HLA—class II
Kidney allograft
Steroids
Steroids
Cyclosporine
Tacrolimus
Azathioprine
Mycophenolate mofetil
Leflunomide
Sirolimus
Everolimus
CD3ε (OKT3)
CTLA-4-IgG1 fusion protein (belatacept)
CD20 (rituximab)
CD52 (alemtuzumab)
CD25 [IL-2Rα] (basiliximab)
Proteosome inhibitor (bortezomib)
Complement factor 5 (eculizumab)

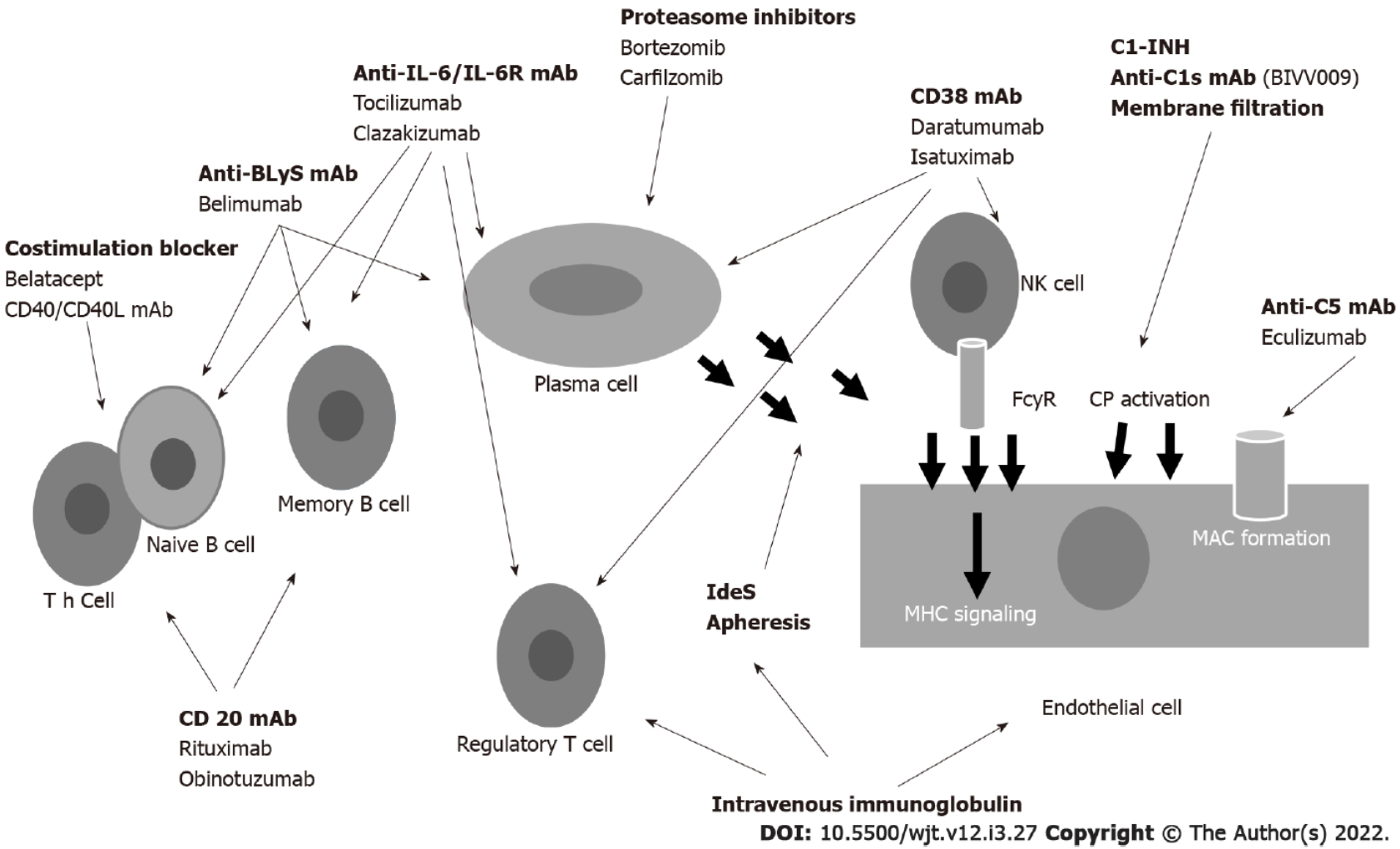


Figure 4 Drugs acting at different levels to control the antibody formation. BLyS: B Lymphocyte stimulating factor; mAb: Monoclonal antibody; C1-INH: C1 inhibitors; NK: Natural killer; Cp: Complement; FcyR: FcyReceptor; MAC: Membrane attacking complex; MHC: Major histocompatibility complex; IL: Interleukin.

Classification of immunosuppressive drugs used in organ transplantation

Inhibitors of T-cell dependent response

signal 1 inhibitors

Glucocorticosteroids (GS): methylprednisolone, prednisolone, prednisone

Calcineurin inhibitors: cyclosporine A, tacrolimus, tacrolimus MR, tacrolimus LCP, *voclosporine (registered in lupus nephropathy class III, IV)*

signal 2 inhibitors

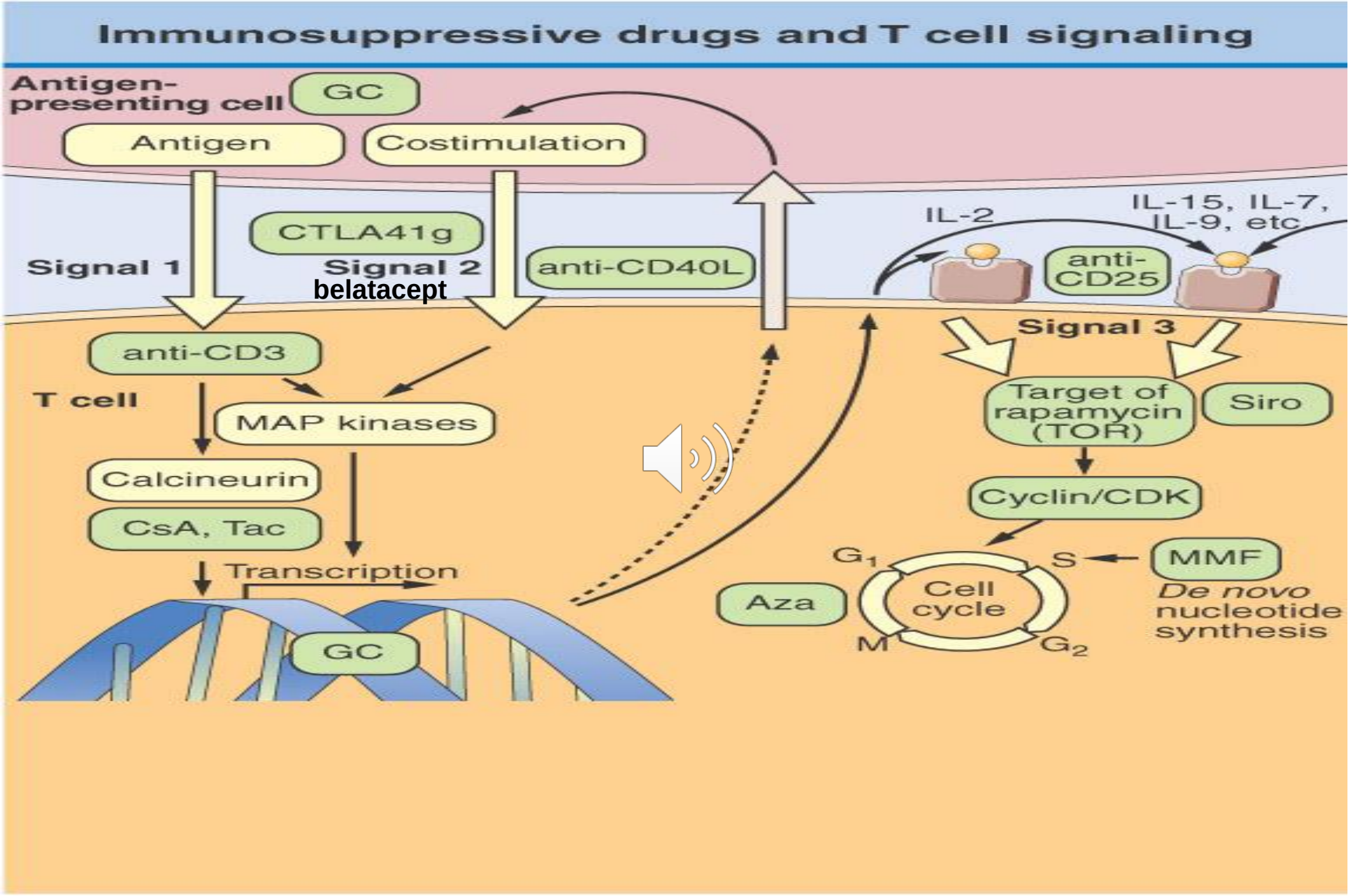
Co-stimulation inhibitors: anty- CD80/86 (belatacept), *anty-CD40 (iscalimab)*

Signal 3 inhibitors

***early signal 3 inhibitors* (mTOR i) – sirolimus, everolimus**
***late signal 3 inhibitors* – mycophenolate mofetil, mycophenolate sodium, azathioprine**

Biological agents

anty-thymocyte globulin, anty –CD52 (alemtuzumab), anty-IL2-R (basiliximab)



Classification of immunosuppressive drugs used in organ transplantation

Inhibitors of antibody mediated response (off label)

- **B-cell depleting drugs: anty-CD20 (rituximab, belimumab, obinutuzumab)**
- **Plasmocyte depleting drugs : bortezomib, carfilzomib, anty-CD38 (daratumumab)**
- **Complement inhibitors: anty-C1 esterase inhibitor, anty-C1 s (sutimlimab), anty-C5a (eculizumab, ravuizumab)**
- **IL- 6 inhibitors: clazakizumab, tocilizumab**
- **IVIG**
- **Plasmapheresis**
- **Imlifidase (IdeS)**

Table 1. Therapies for antibody-mediated rejection in kidney transplantation

Drug	Mechanism of action	Published Information in AMR treatment
IVIg	Inhibits B- and T-cell proliferation upregulates anti-inflammatory Th2 cytokines and antiidiotypic blockade of alloantibodies, and enhances clearance of pathogenic IgG through blockade of FcRn	High dose: 2 g/kg (max 140 g) [6] low dose with PLEX: 100 mg/kg [7]
Rituximab	mAb directed against CD20 antigen on the surface of B lymphocytes	375 mg/m^2 IV with PLEX/low-dose IVIg [8] 375 mg/m^2 IV with IVIg 0.5 g/kg every 3 weeks × 4 doses [9]
Imlifidase	Endopeptidase that cleaves all 4 IgG antibodies into F(ab)2 and Fc	0.25 mg/kg IV [10]
Bortezomib	First-generation reversible proteasome inhibitor	2 Cycles 3 months apart, each cycle 1.3 mg/m^2 IV twice weekly for 4 doses [11]
Carfilzomib	Second-generation irreversible proteasome inhibitor	None to date
Daratumumab	IgG1 κ humanized mAb directed against CD38	16 mg/kg IV weekly for 8 doses [12] 16 mg/kg IV weekly for 8 doses, every 2 weeks for 8 doses, monthly thereafter [13]
Tocilizumab	Recombinant humanized antihuman IL-6 receptor mAb binds both soluble and membrane-bound IL-6R	8 mg/kg IV monthly (max per dose: 800 mg) [14,15▪]
Clazakizumab	Genetically engineered, humanized IgG1 mAb; IL-6 ligand inhibition	12.5–25 mg SC monthly for 6–12 months [16▪▪,17▪]
Eculizumab	mAb–binding protein C5, inhibiting cleavage to C5a and C5b and formation of membrane attack complex C5b-9	1200 mg IV × 1 then 600 mg after PLEX or 900 mg weekly for 30 days [18] 600 mg IV weekly × 4, then 900 mg every 2 weeks for 22 weeks [19]
C1INH	Inhibits activation of complement and intrinsic coagulation pathway	5000 units IV (max 100 U/kg) on day 1, then 2500 units (max 50 U/kg) every other day for 6 doses [20]
Belatacept	Selective T-cell blockade by binding CD80 and CD86 receptors on APC to block CD28-mediated costimulation and blocks the alternative ligand CTLA-4	Conversion dose 5 mg/kg on days 1, 15, 29, 42, 57, and then monthly [21]

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SPECIAL ARTICLE

AJT

Plasma cell targeting to prevent antibody-mediated rejection

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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	β5
Ixazomib	Ninlaro	Takeda	Boronated	Oral	β5
Carfilzomib	Kyprolis	Amgen	Epoxyketone	IV	β5 + β5i
Oprozomib	n/a	Amgen	Epoxyketone	Oral	β5 + β5i
Marizomib	n/a	Nereus	Salinosporine	IV	β1

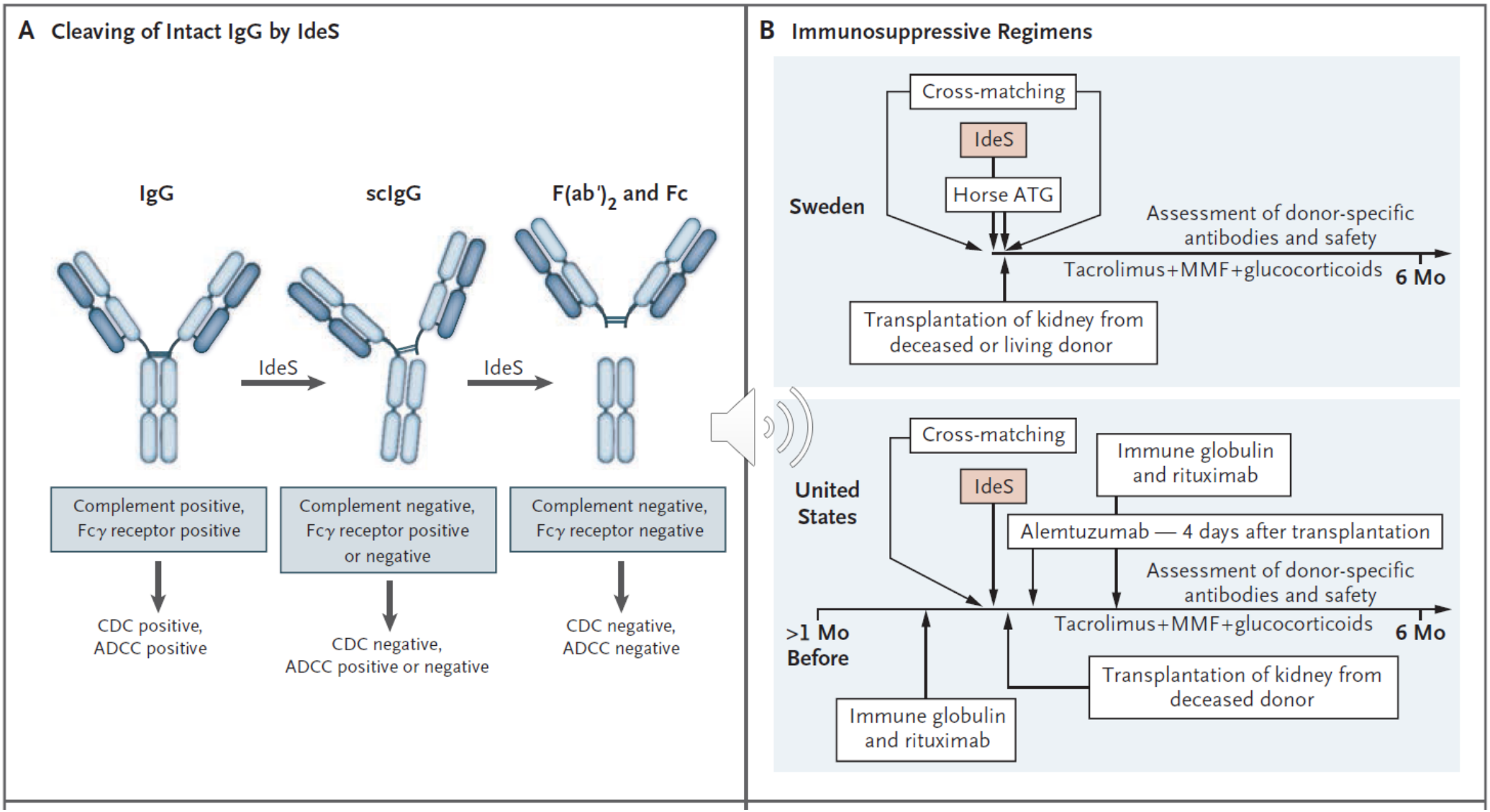
A Cleaving of Intact IgG by IdeS
IgG
scIgG
F(ab')2 and Fc
IdeS
IdeS
Complement positive, Fcγ receptor positive
Complement negative, Fcγ receptor positive or negative
Complement negative, Fcγ receptor negative
CDC positive, ADCC positive
CDC negative, ADCC positive or negative
CDC negative, ADCC negative
B Immunosuppressive Regimens
Sweden
Cross-matching
IdeS
Horse ATG
Assessment of donor-specific antibodies and safety
Tacrolimus+MMF+glucocorticoids
6 Mo
Transplantation of kidney from deceased or living donor
United States
Cross-matching
IdeS
Immune globulin and rituximab
Alemtuzumab — 4 days after transplantation
Assessment of donor-specific antibodies and safety
>1 Mo Before
Tacrolimus+MMF+glucocorticoids
6 Mo
Transplantation of kidney from deceased donor
Immune globulin and rituximab

TABLE 1 Demographics and baseline characteristics of the patients transplanted after imlifidase treatment

Characteristics	XM+, *n* = 39	AMR & XM+, *n* = 15	No AMR & XM+, *n* = 24	XM+, DD and cPRA ≥ 99.9%, *n* = 13	*p*-value[f,g]
Patient age (years); mean (SD)	43.2 (13.0)	44.5 (14.3)	42.3 (12.3)	45.3 (12.6)	0.904[f]
Female; *n* (%)	18 (46%)	6 (40%)	12 (50%)	5 (38%)	0.883[g]
Region, US; *n* (%)	28 (72%)	9 (60%)	19 (79%)	11 (85%)	0.468[g]
Race; *n* (%)					
White	30 (77%)	11 (73%)	19 (79%)	9 (69%)	0.998[g]
Black	4 (10%)	2 (13%)	2 (8%)	2 (15%)	
Asian	3 (8%)	1 (7%)	2 (8%)	1 (8%)	
Other	2 (5%)	1 (7%)	1 (4%)	1 (8%)	
Time on dialysis prior to imlifidase transplantation (years); mean (SD)	6.4 (5.6)	7.4 (6.1)	5.9 (5.4)	9.3 (7.2)	0.370[f]
Deceased Donor; *n* (%)	32 (82%)	13 (87%)	19 (79%)	13 (100%)	0.399[g]
Total CIT; mean (SD)	21.0 (10.0)	23.8 (11.5)	19 (8.5)	22.7 (9.6)	0.554[f]
Re-transplants; *n* (%)	27 (69%)	10 (67%)	17 (71%)	9 (69%)	1.000[g]
cPRA[a] (%); median (1st & 3rd quartile)	99.62 (94.92, 99.96)	99.80 (93.70, 99.99)	99.53 (96.55, 99.91)	99.99 (99.97, 100)	0.345[f]
Crossmatch positive; *n* (%)	39 (100%)	15 (100%)	24 (100%)	13 (100%)	NA
Pre-dose DSA[b] (MFI); median (1st & 3rd quartile)	7791 (4108, 16 320)	13009 (6515, 21 580)	5727 (2699, 9470)	16292 (7133, 21 824)	0.027[f]
Pre-transplant DSA[c] (MFI); median (1st & 3rd quartile)	774 (292, 1754)	1584 (904–3303)	576 (193–1387)	1292 (774, 2600)	0.032[f]
DGF[d]; *n* (%)	17 (44%)	7 (47%)	10 (42%)	6 (46%)	1.000[g]
DGF duration[e] (days); median (1st & 3rd quartile)	10 (6, 26)	24 (8, 28)	9 (4, 14)	12 (9, 23)	0.332[f]

Note: Patents with positive crossmatch (XM+) prior to imlifidase dosing, patents with or without an AMR and a subgroup with the highest unmet medical need in the US (XM+, DD and ≥99.9% cPRA).

Outcomes at 3 years posttransplant in imlifidase-desensitized kidney transplant patients

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Am J Transplant. 2021;21:3907–3918.

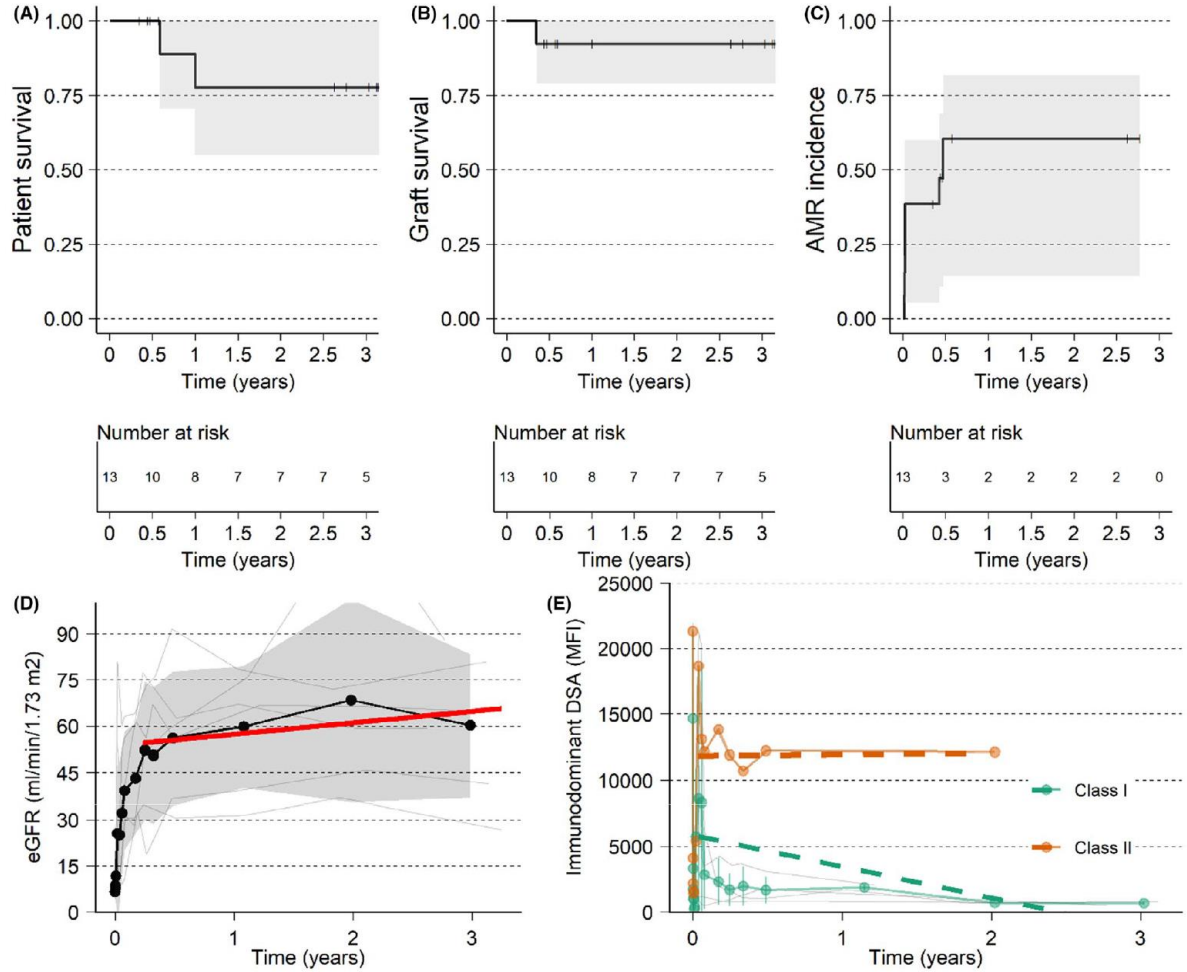


FIGURE 8 Outcome of the group with XM+, DD, and cPRA ≥ 99.9%. (A) Patient survival. (B) Graft survival, death censored. (C) Time to first AMR. (D) eGFR with individual patient data (thin gray lines), mean (black line with points), standard deviation (gray ribbon) and red line is a linear regression from 30 days up to 3 years. (E) Immunodominant DSA with individual patient data (thin gray lines), mean (colored lines with points and SD as error bars) and linear regression (dashed colored lines) from 14 days up to 2 years for HLA class I and II

Historical Development of Immunosuppressive Regimens

1954	First kidney transplantation across identical twins
1958/9	Irradiation
Appr. 1960	Oral Corticosteroids
1962	6-mercaptopurine, azathioprine (AZA), Imurane®
1963-78	Antithymocyte globulin (ATG, adjuvant to AZA+steroids (KTx)
1978	Cyclosporine (Sandimmun®)
1982	Cyclosporine + prednisone
1985	Cyclosporine + steroids + AZA (triple therapy)
1985-9	Triple therapy+ Antithymocyte globulin ALG for rejection)
1990 on	Optimal regimen varies: typically triple +/-ATG
1994	Tacrolimus (Prograf®) + steroids + other regimens (tacrolimus MR 2008)
1995/6	Mycophenolate mofetil (Cellcept®) replaces AZA
	» Cyclosporine (Neoral®) replacesCyA Sandimmune®
1998	Basiliximab (Simulect®)
1998/9	Daclizumab humanised antibody (Zenapax®) - withdrawn
1999/2000	Sirolimus, rapamycin (Rapamune®)
2002/3	Mycophenolate natrium (Myfortic)
2003	Everolimus (Certican®)
2010	Belatacept
2014	Tacrolimus LCP (Envarsus)
2021	Imlifidase (IdeaS)
Off label	anty-CD20 (rituximab), anty-CD52 (alemtuzumab), anty-C5 (eculizumab), bortezomib, anty-CD38 (daratumuma

Principles of immunosuppressive treatment

- **Combined**
- **More intensive in the early posttransplant period („induction”)**
- **Duration: till the end of the graft function**
- **Reduction in case of life threatenting:**
  - **opportunistic infections**
  - **lymphoproliferative disorders, malignancy**
- **Reduction in BK nephropathy**
- **Pregnancy – MPA (CellCept, Myfortic), PSI (Rapamune, Certican) contraindicated (teratogenicity)**
- **Trends:**
  - **individualisation**
  - **GS withdrawal**
  - **efforts to minimize CNI nephrotoxicity**

OPTN Registry 2020

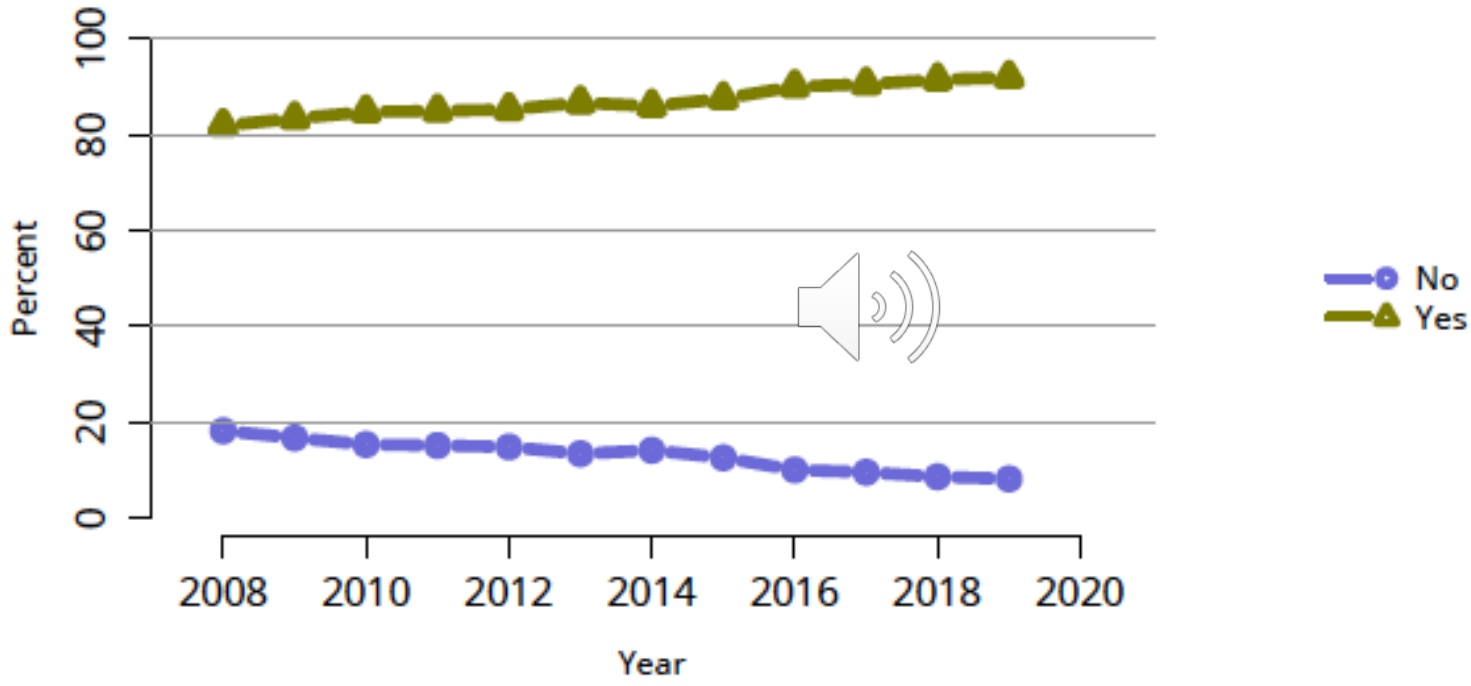


Figure KI 81. Induction agent use in adult kidney transplant recipients.
Immunosuppression at transplant reported to the OPTN.

OPTN Registry 2020

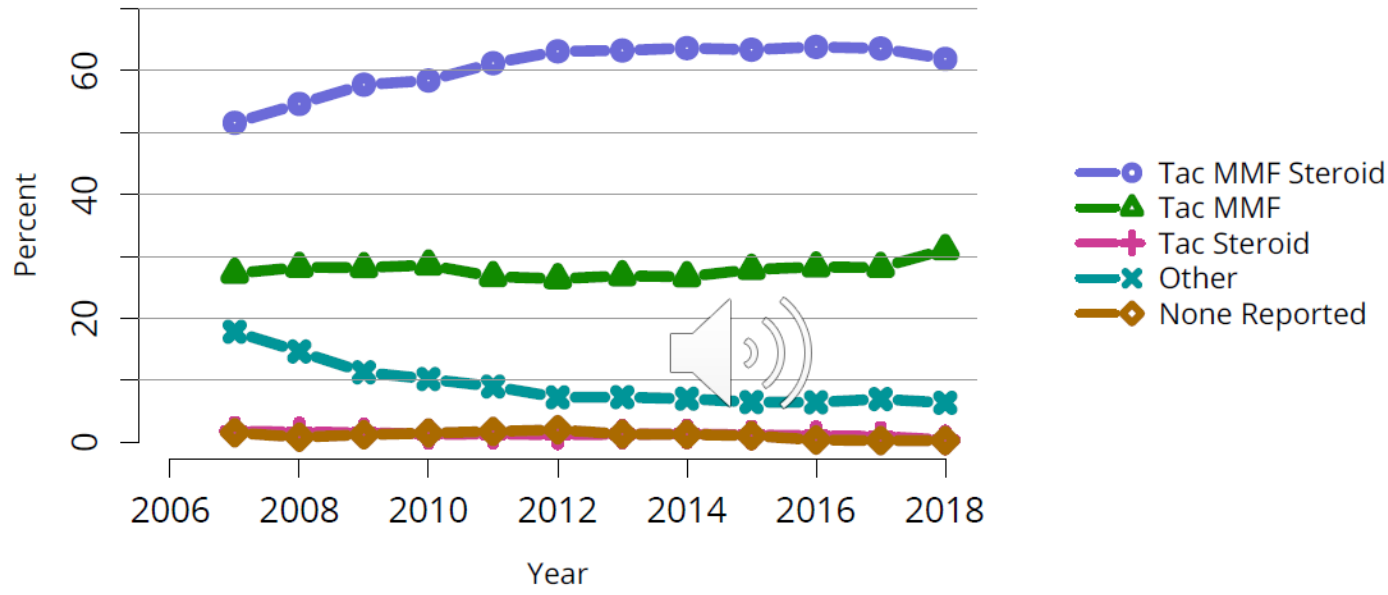


Figure KI 71. Immunosuppression regimen use in adult kidney transplant recipients. Immunosuppression regimen at transplant reported to the OPTN. Tac, tacrolimus. MMF, mycophenolate mofetil.

Induction therapy

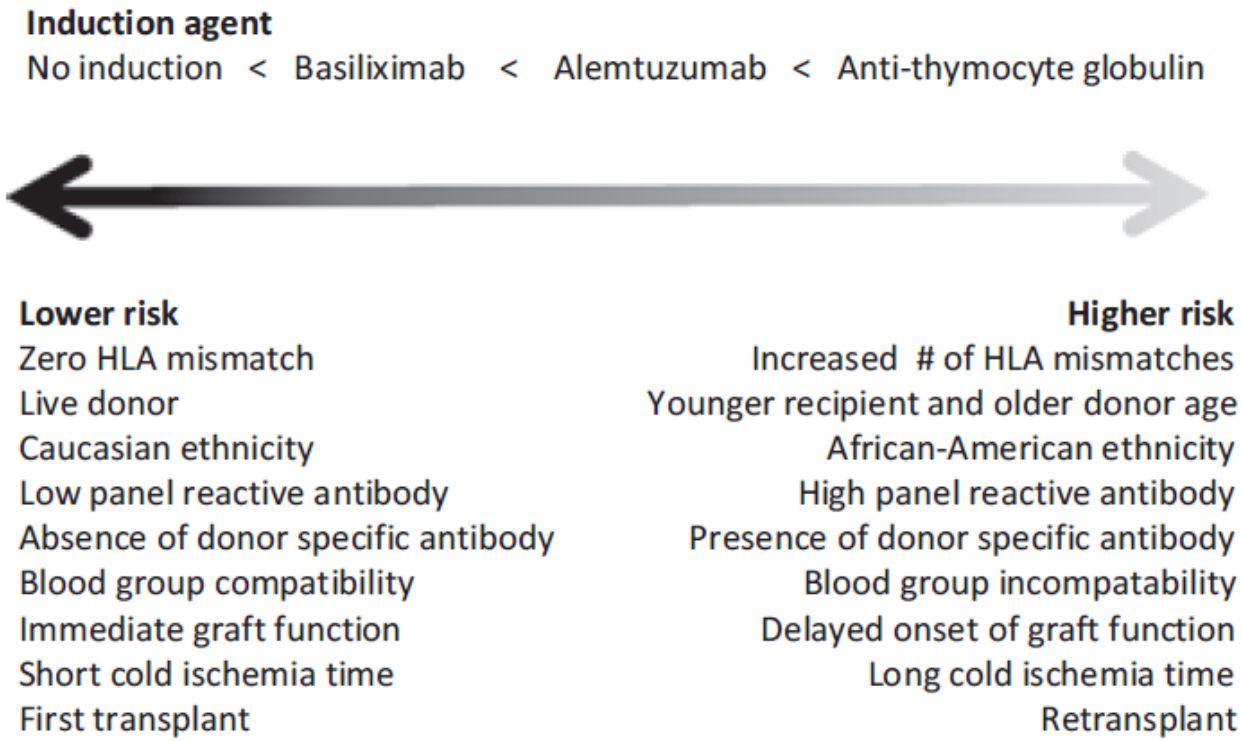


Figure 2 Induction therapy choice based on risk assessment.

Indication for induction therapy with antibodies - cont

Risk level	MFI	Description	Polyclonal Antibodies (ATG)	Monoclonal anty-CD25 IL-2R
I	Anty-HLA not detectable	Standard risk of rejection	not recommended	decision to give induction depends on other factors
II	DSA <2000	Low risk of hiperacute rejection (HR), but higher than in standard risk	to consider for retransplants and loss of previous graft in the course of AMR	indicated if there are no risk factors in the previous column
III	DSA 2000-5000	Low risk of HR, but high risk of early AMR or in previous tissue typing XM CDC positive	indicated	
IV	DSA >5000	Contraindication for transplantation, patient waits for another donor (with different HLA)		

MFI – mean fluorescence intensity, DSA – donor specific antibodie,
AMR – antibodies dependent rejection , XM CDC – complement dependent cytotoxicity

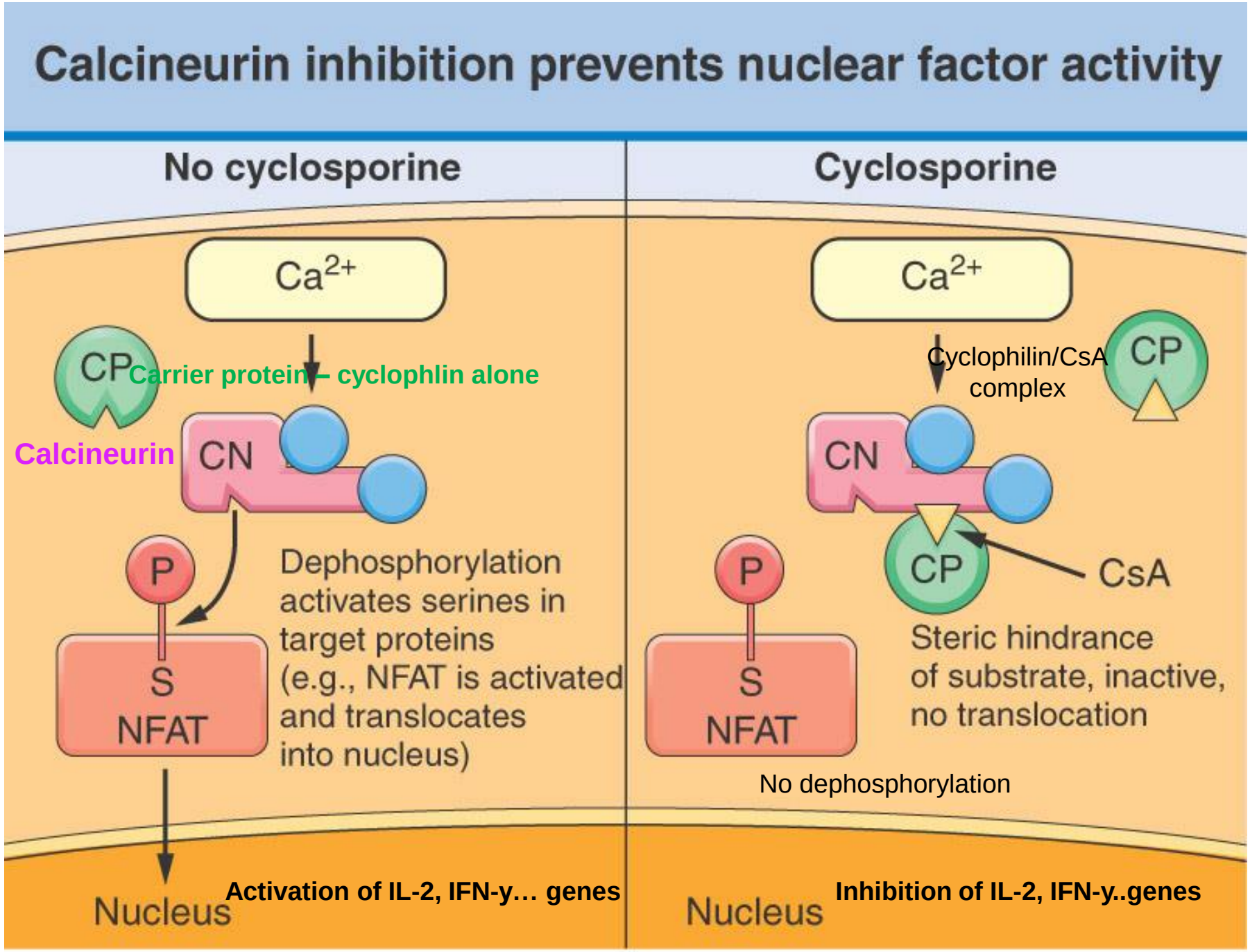
Immunosuppressive schema

- **Maintenance immunosuppression:**

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

Potency of immunosuppressive action:

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



Cyclosporine A (CsA)

- Structure - cyclic polypeptide
- Absorption: variable, depends on diet and bile production
- Metabolism: cytochrom P450- CYP3A4; 15 metabolites
- Excretion: in bile, T1/2 6,3 - 20,4h
- **Narrow therapeutic window, high intra-, interpatient variability - repeated laboratory monitoring of through (C0) or C2 CsA blood level is required**
- Dosage: oral - 8-10mg/kg/d in 2 doses (first doses greater),
  i.v.- 1/3 oral dose

Cyclosporine A - adverse reactions

1. NEPHROTOXICITY:
- dose - related, reversible renal vasoconstriction → GFR decrease
- interstitial fibrosis, artheriolopathy
- hemolytic-uremic syndrome (HUS)
- electrolyte abnormalities (hyperkalemia, hypomagnesemia), hyperuricemia (gout)

2. HEPATOTOXICITY
3. NEUROTOXICITY - **tremor**, seizures
4. *gingival hyperplasia*
5. ***hirsutism***
6. hypertension, hyperlipidemia, diabetes
7. thrombembolic events

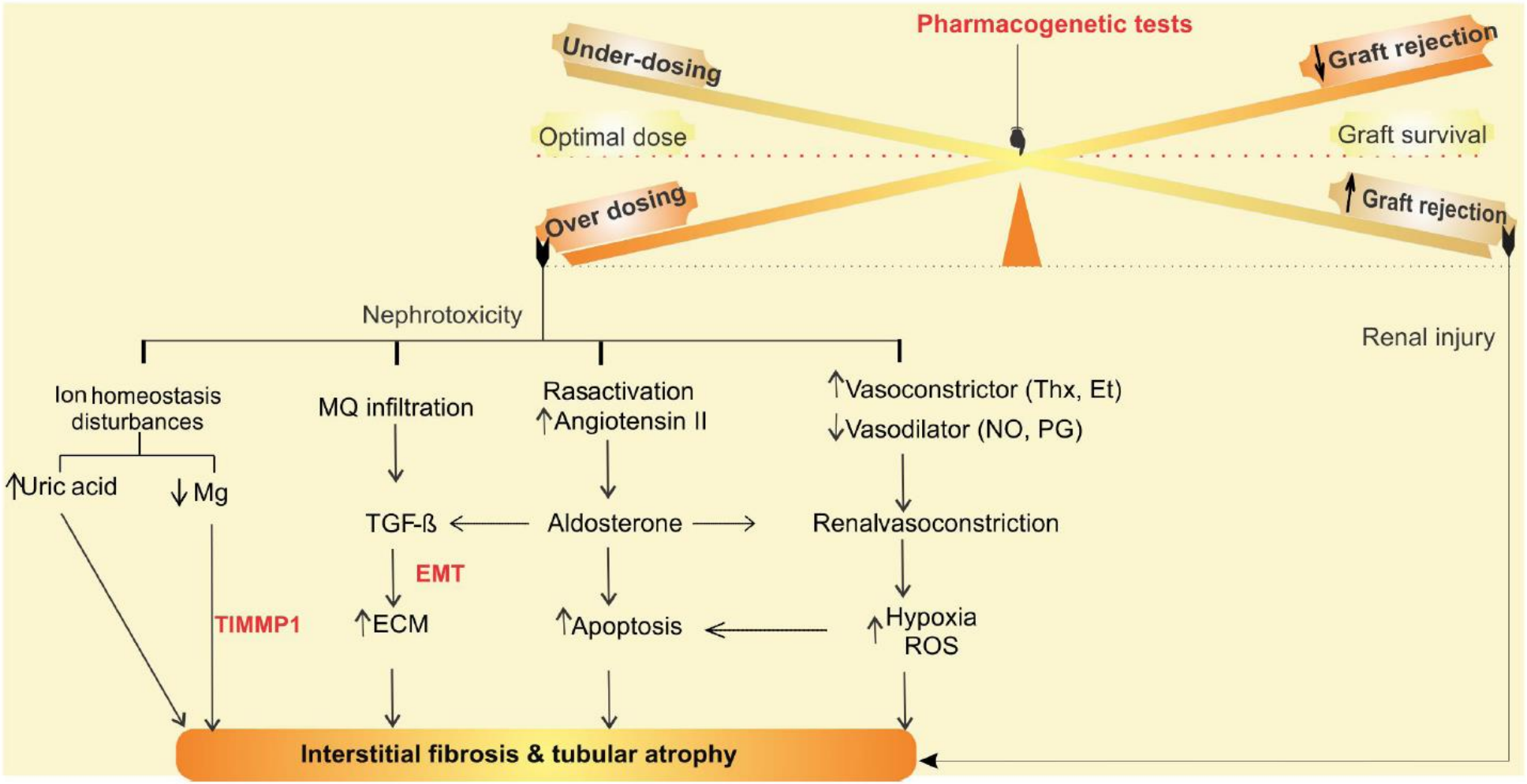


Fig. 1. Impact of CsA on nephrotoxicity and renal IF/TA. CsA is contributed in development of renal IFTA through different pathways. It promotes renal fibrosis through renal vasoconstriction and hypoxia. Moreover, it activates Ras and macrophage infiltration. Angiotensin II-induced aldosterone secretion participates in the development of IF/TA through increased renal vasoconstriction, TGF-β expression and apoptosis. CsA also disturbs Ion homeostasis and leads IFTA. CsA: cyclosporine, PG: prostaglandins, NO: nitric oxide, Thx: thromboxane, Et: endothelin, ROS: reactive oxygen species, RAS: renin–angiotensin system, EMT: epithelial-mesenchymal transition, MQ: macrophage,

CNI - carcinogenesis

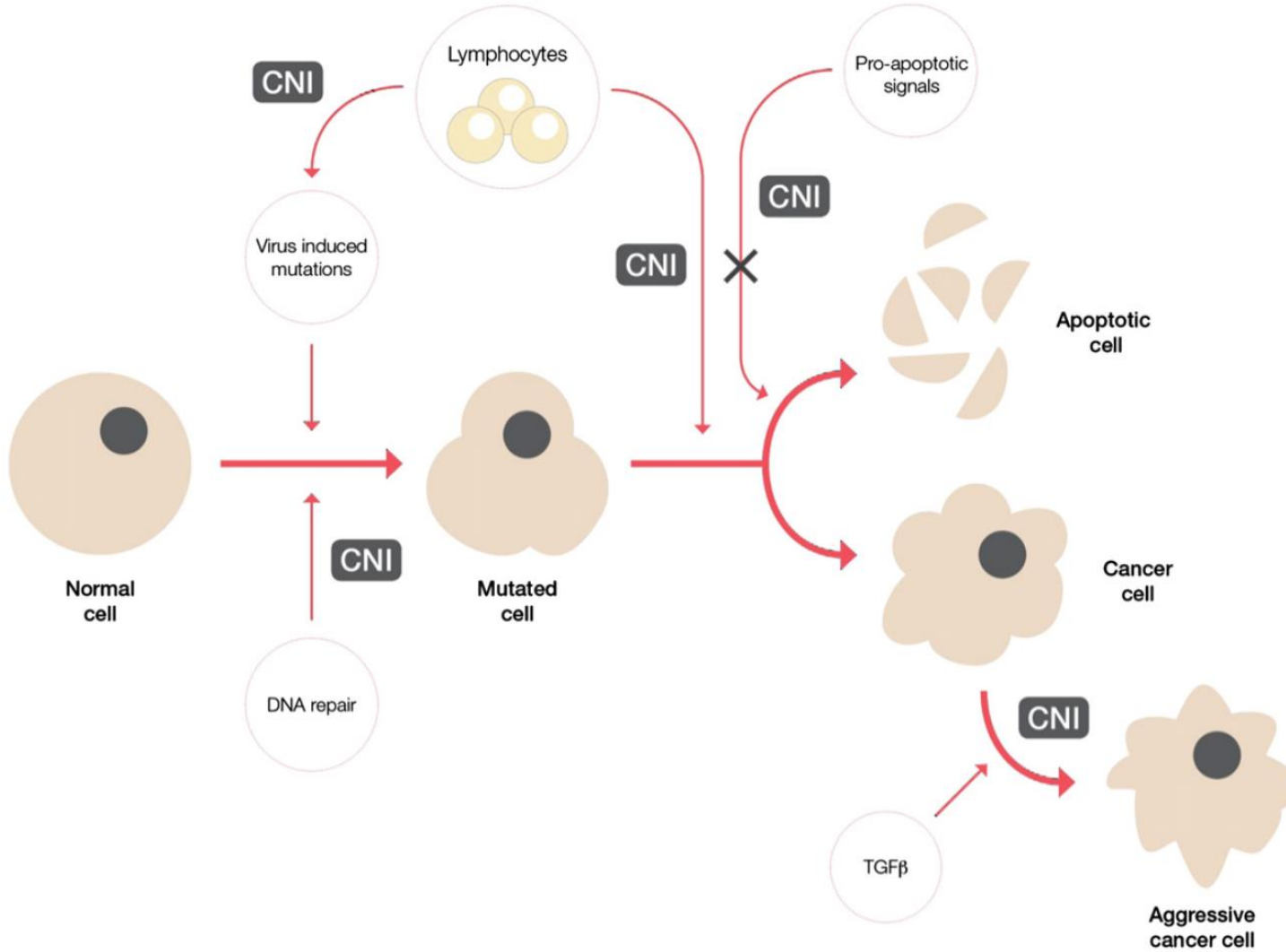
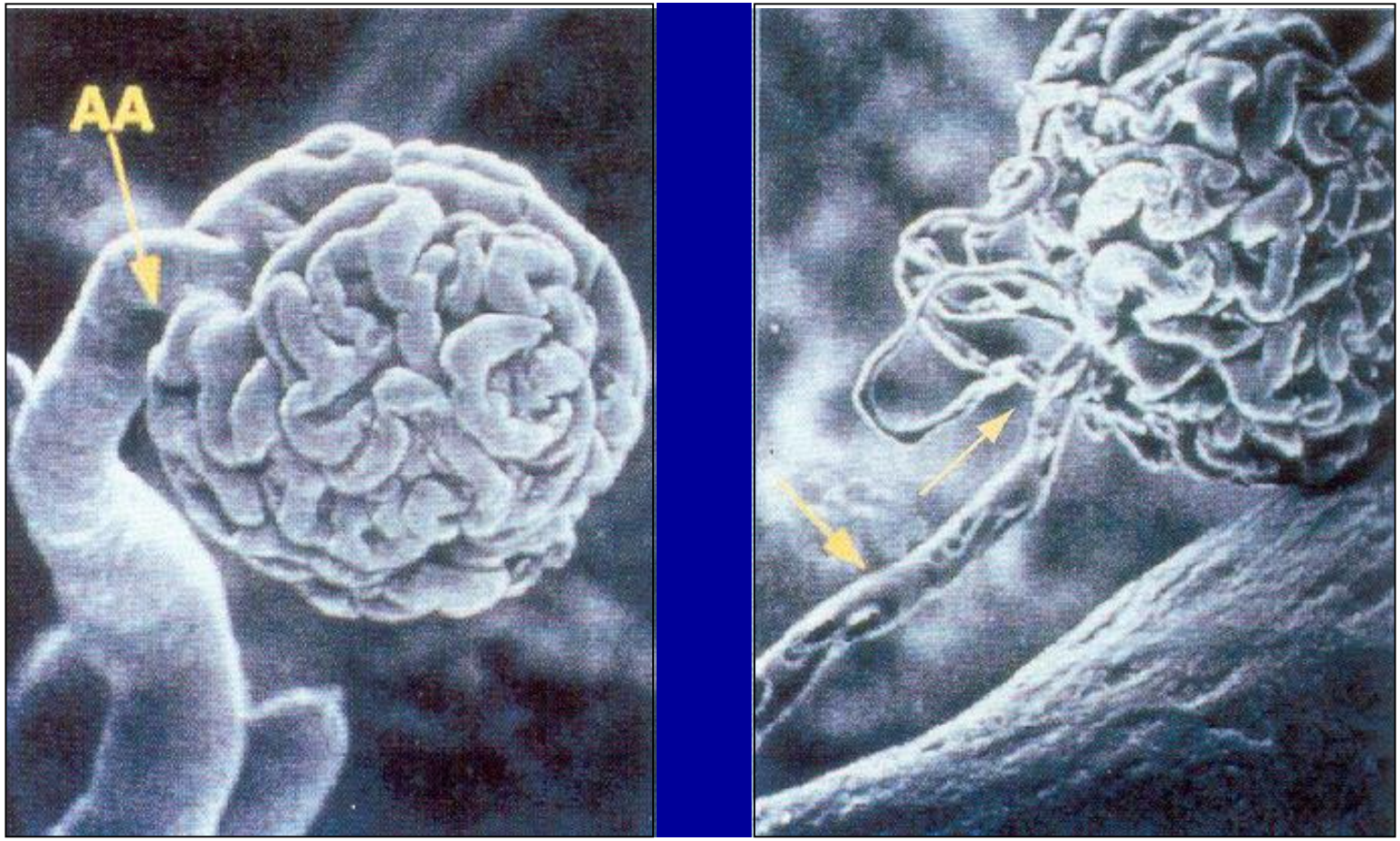


Fig. 1. Immunosuppression-driven oncogenesis. Adapted from Gutierrez-Dalmau and Campistol 2007 [42]. CNI=calcineurin inhibitors; TGFβ=transforming-growth factor β.

Acute nephrotoxicity of CsA

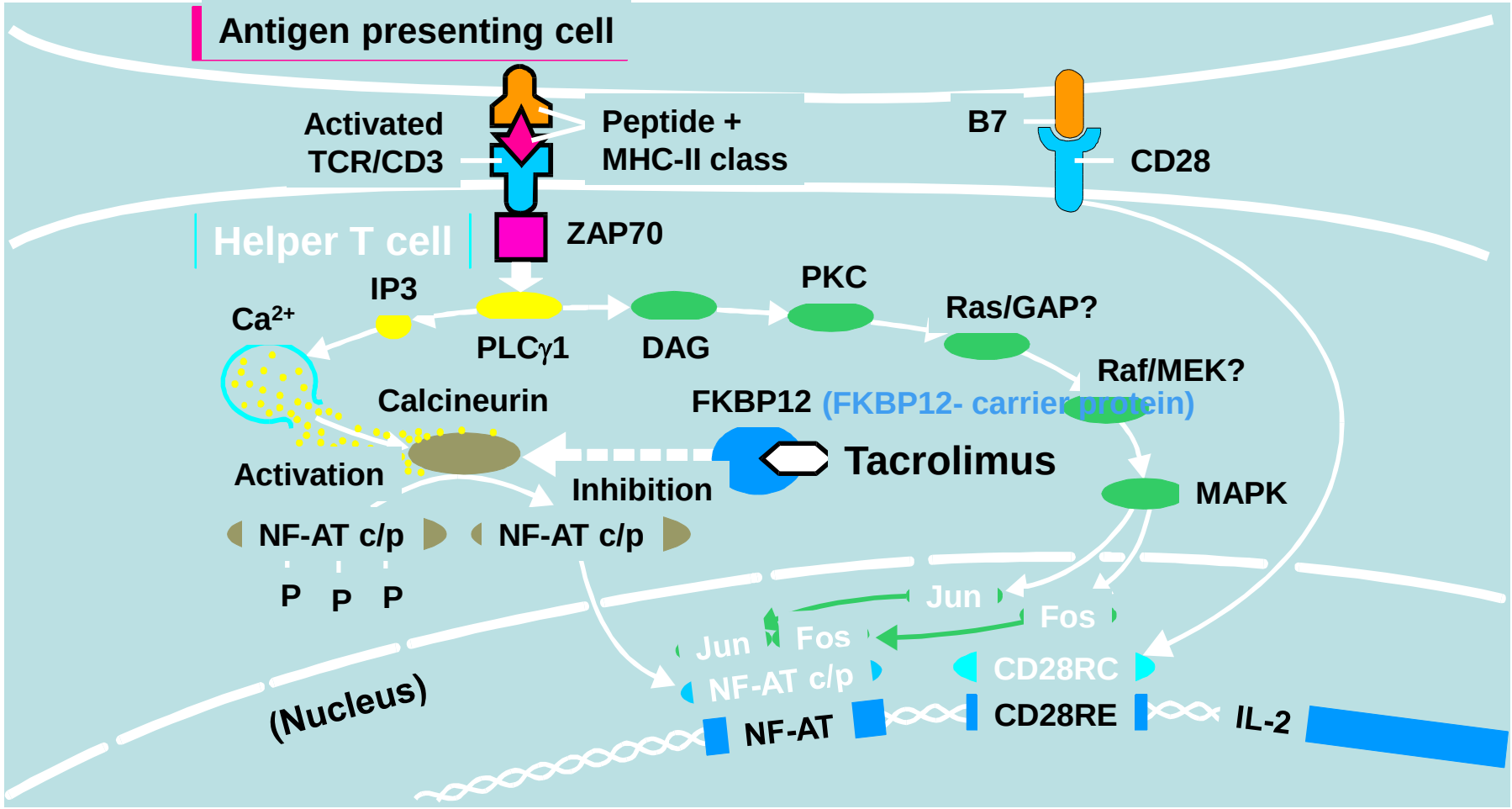


Principles and Practice of Renal Transplantation, 2000

Tacrolimus

- Macrolide antibiotic isolated from *Streptomyces tsukubaensis*
- Used in maintenance immunosuppressive therapy, acute rejection, 10-100x more potent than CsA (greater affinity of the FK-FKBP12 complex for calcineurin)
- Absorption independent of bile, variable: 4-63% (mean 20%), meal reduces bioavailability by 25%, drug should be administered 1 hour before or 2 hours after a meal
- Erythrocytes/plasma 20: 1; in plasma 98% with albumin, alfa 1 AGP
- tmax 0.5-8 h, average 2 h, Cmin - good drug exposure index, saturation 4-8 weeks after transplantation
- Narrow therapeutic window, high inter-, intra-individual variability - drug concentration monitoring
- Dose orally form 0,17- 0.20 mg /kg/day; if i.v. - 20-30% of the oral dose
- metabolism - cytochrome P450 CYP3A4, CYP 3A5 mainly hydroxylation, demethylation in liver (much less dependent on CYP3A4 in the intestine, gp 150)
- Elimination: Bile> 90% (mainly as metabolites, <2% in urine)

Molecular mechanism of action of tacrolimus



Calcineurin inhibitors and mTOR inhibitors interactions (2)

Drugs *increasing* CI and mTORi concentrations (inhibition of cytochrome P 450):

- large doses of corticosteroids
- ketoconazole, fluconazole, itrakonazol, posiconazol, voriconazol
- verapamil (Isoptin), diltiazem (Dilzem)
- erythromycin, clarithromycin
- Metoclopramide
- Grapefruit juice

Calcineurin inhibitors and mTOR inhibitors interactions (3)

Drugs *decreasing* CI and mTORi concentration (induction of cytochrom P 450):

- rifampin
- phenytoin
- phenobarbitol
- carbamazepine
- octreotide
- ticlopidine
- St. John's wort

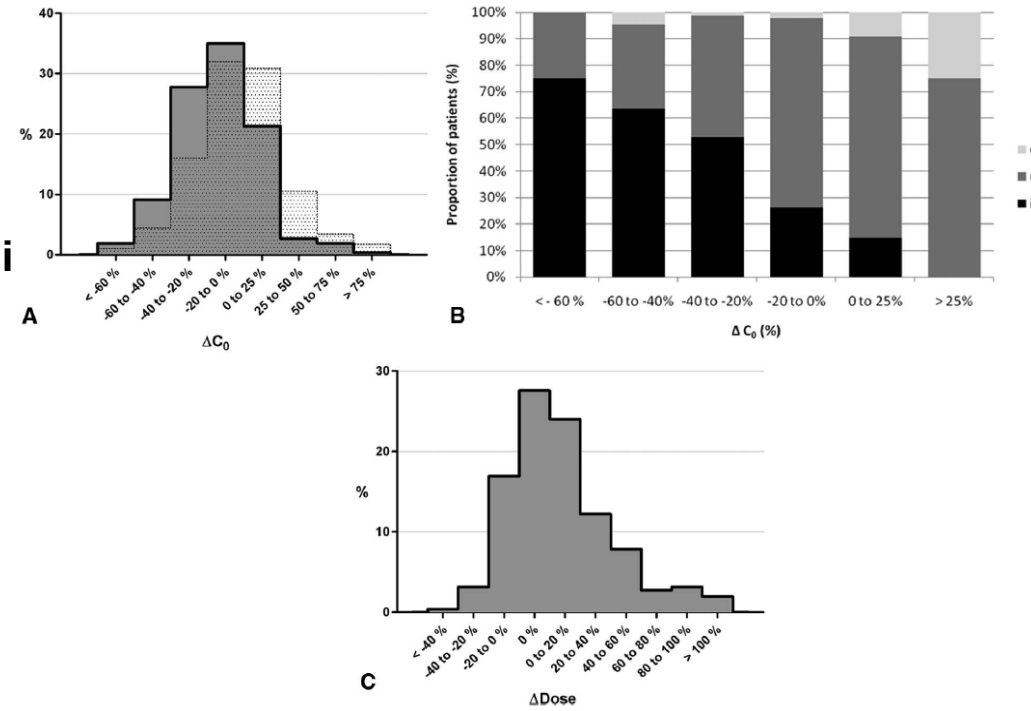
Side effects	CsA	tacrolimus
Nephrotoxicity	++	++
Neurotoxicity	+	++
Hypertension	++	+
Postrtransplant diabetes	+	++
Hyperlipidemia	++	+
Hiperurycemia	++	+
Alopecia	+ / -	++
Hirsutism	++	+ / -
Gingival hyperplasia	++	+ / -
HUS	++	+
Hyperkaliemia	++	++
Hypomagnezemia	++	++
Hepatotoxicity	++	+
Gastric complications	+ / -	++

New calcineurin inhibitors

- **MR-4 (Advagraf) - once a day, 1:1 conversion AUC 20% lower than “standard” tacrolimus**
- **Tacrolimus-LCP (Envarsus) - once a day, 1:1 conversion AUC 15 - 20% higher than “standard” tacrolimus**
- ***Voclosporine - CsA derivative - off label)***
- **Generics formulae of CsA, tacrolimus (Equoral)**

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

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



De Jonge i wsp, Transplantation, 2010, 90, 523

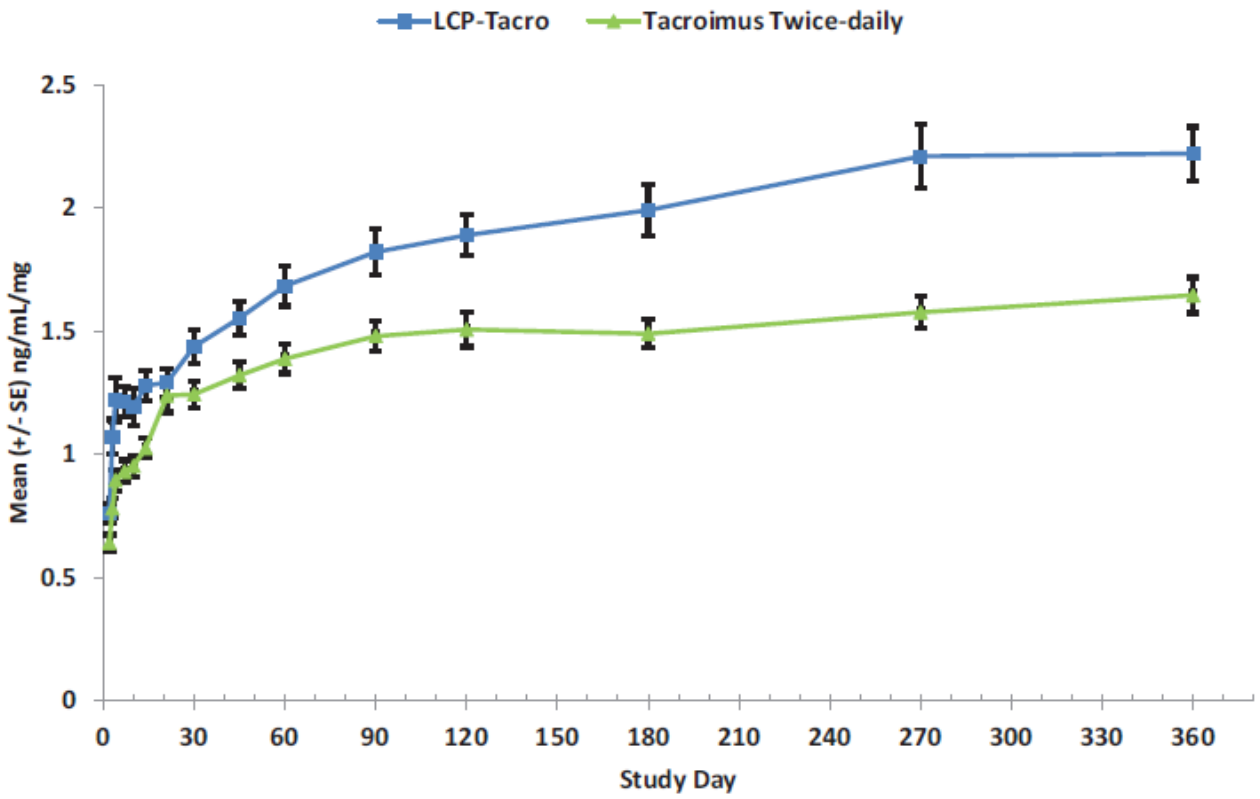
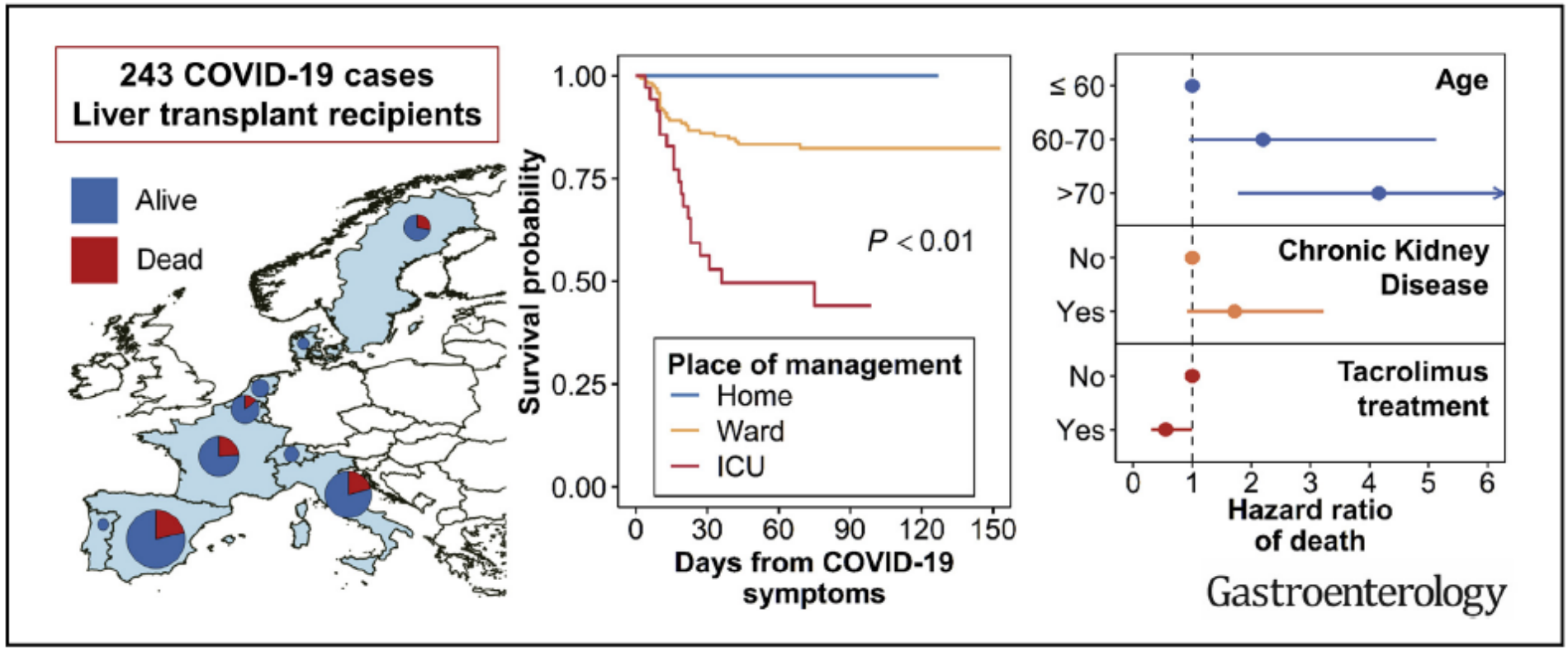


Figure 3: Tacrolimus trough level (ng/mL) achieved per total daily dose (mg) (modified intent-to-treat set).

Gastroenterology 2021;160:1151–1163

Protective Role of Tacrolimus, Deleterious Role of Age and Comorbidities in Liver Transplant Recipients With Covid-19: Results From the ELITA/ELTR Multi-center European Study

Luca S. Belli,[1] Constantino Fondevila,[2] Paolo A. Cortesi,[3] Sara Conti,[3] Vincent Karam,[4] Rene Adam,[4] Audrey Coilly,[5] Bo Goran Ericzon,[6] Carmelo Loinaz,[7] Valentin Cuervas-Mons,[8] Marco Zambelli,[9] Laura Llado,[10] Fernando Diaz-Fontenla,[11] Federica Invernizzi,[12] Damiano Patrono,[13] Francois Faitot,[14] Sherrie Bhooori,[15] Jacques Pirenne,[16] Giovanni Perricone,[1] Giulia Magini,[17] Lluis Castells,[18] Oliver Detry,[19] Pablo Mart Cruchaga,[20] Jordi Colmenero,[2] Frederick Berrevoet,[21] Gonzalo Rodriguez,[22] Dirk Ysebaert,[23] Sylvie Radenne,[24] Herold Metselaar,[25] Cristina Morelli,[26] Luciano G. De Carlis,[27] Wojciech G. Polak,[28] and Christophe Duvoux,[29] for all of the centers contributing to the ELITA-ELTR COVID-19 Registry


243 COVID-19 cases
Liver transplant recipients
Alive
Dead
1.00
0.75
0.50
0.25
0.00
Survival probability
P < 0.01
Place of management
Home
Ward
ICU
0
30
60
90
120
150
Days from COVID-19 symptoms
≤ 60
60-70
>70
Age
No
Yes
Chronic Kidney Disease
No
Yes
Tacrolimus treatment
0
1
2
3
4
5
6
Hazard ratio of death
Gastroenterology

Key clinical trials of voclosporin sponsored by Aurinia Pharmaceuticals

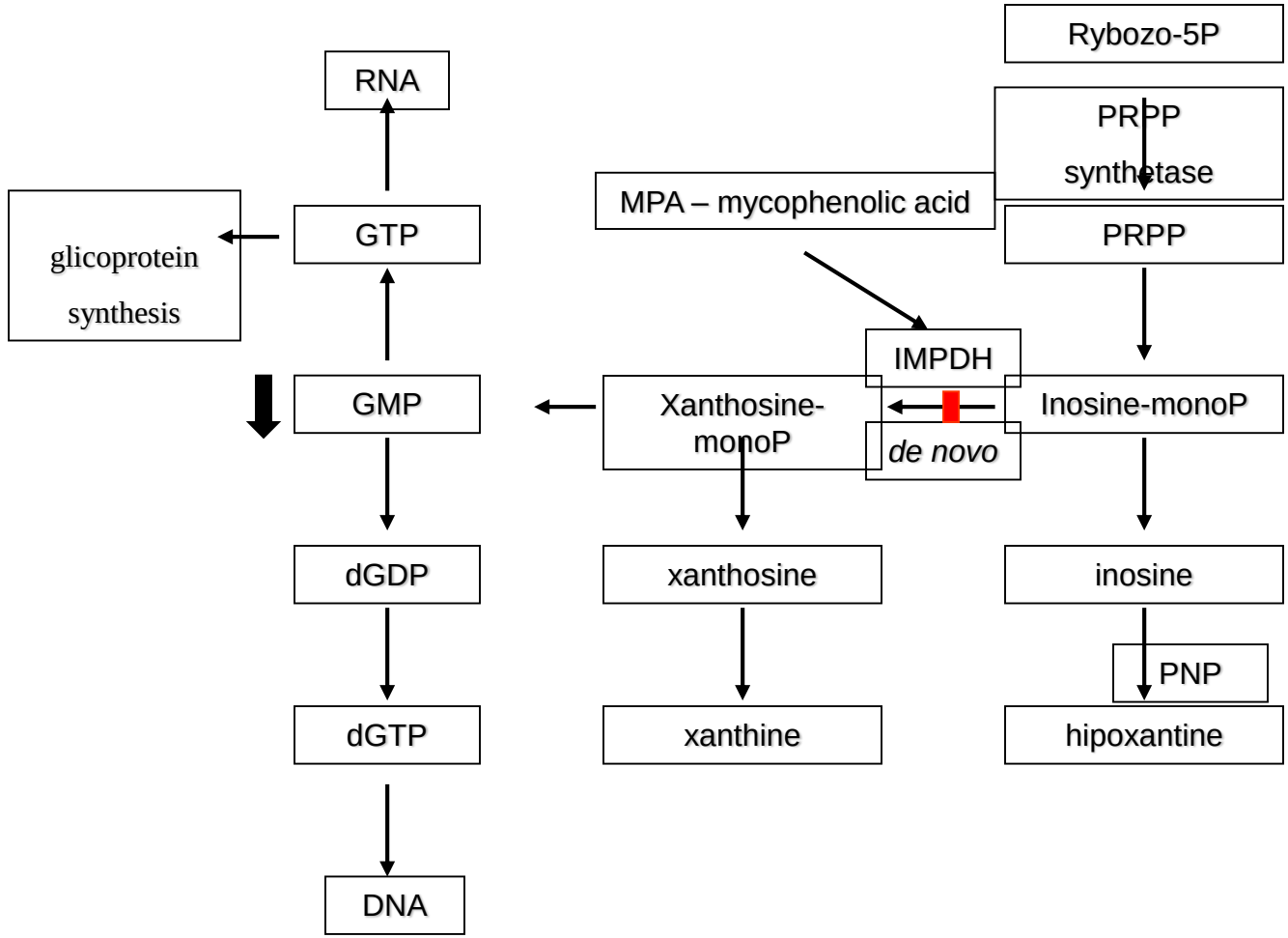
Drug(s)	Indication	Phase	Status	Location(s)	Identifier
Voclosporin, SOC	Lupus nephritis	II	Completed	Malaysia	NCT02949973, AUR-VCS2014-01, AURION
Voclosporin, placebo, SOC	Lupus nephritis	II	Completed	Multinational	NCT02141672, EudraCT2012-003364-51, SLCTR2015-001, AUR-VCS2012-01, AURA-LV
Voclosporin, tacrolimus	Kidney transplant recipients with COVID-19	II	Ongoing	Netherlands	NCT04701528, EudraCT2020-001467-82, P020-051, NL73762-058-20, VOCOVID
Voclosporin	Focal segmental glomerulosclerosis	II	Terminated	Dominican Republic, USA	NCT03598036, AUR-VCS2017-03
Voclosporin, placebo, SOC	Lupus nephritis	III	Completed	Multinational	NCT03021499, EudraCT2016-004045-81, JapicCTI183821, AUR-VCS2016-01, AURORA 1
Voclosporin, placebo, SOC	Lupus nephritis	III	Ongoing	Multinational	NCT03597464, EudraCT2016-004046-28, JapicCTI184112, AUR-VCS2016-02, AURORA 2

SOC standard-of-care

Mycophenolate mofetil (MMF)- CellCept
Mycophenolate sodium (MPS) - Myfortic

- derivative of mycophenolic acid (MPA)
- mechanism of action:
- 1. MPA selectively inhibits **inosine monophosphate dehydrogenase** (IMPDH) in *de novo* pathway of purine synthesis, producing potent cytostatic effects on T and B lymphocytes
- 2. inhibits antibodies and smooth muscle cells synthesis
- CellCept: 50% reduction of first acute rejection episodes
- dosage: 2 x 1,0 g
- contraindication: pregnancy
- adverse reactions: diarrhea, leukopenia, vomiting
- Increased risk of infections (oportunistic)
- monitoring: WBC, (therapeutic drug monitoring non obligatory)

MMF/MPS (MPA) - mechanism of action



Azathioprine (Imuran)

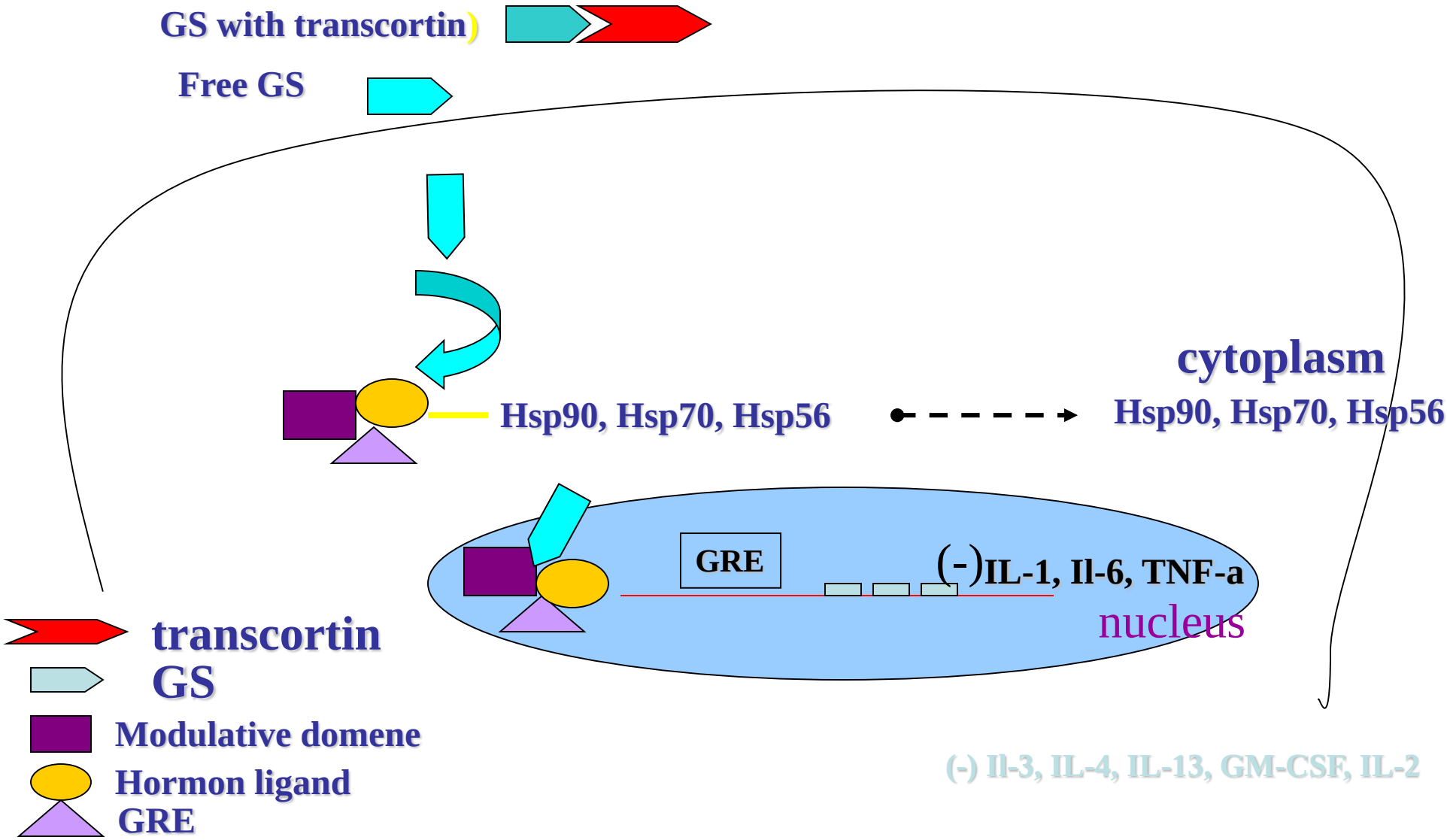
- mechanism of action:6-MP is antimetabolite, which interferes with DNA and RNA synthesis → inhibition of lymphocytes T and B proliferation

  - **contraidication:** hypersensitivity

  - **adverse reactions:** leukopenia, thrombocytopenia, anemia
  - hepatotoxicity
  - nausea and vomitig
  - alopecia

  - **interactions:** **<u>ALLOPURINOL</u>** - (xantine oxidase!), ACE-I - agents affecting myelopoesis (myelotoxicity!!!)
  - **dosage**: 1-3mg/kg/d, WBC monitoring

GS- mechanism of action



Glucorticosteroids - adverse reactions

- osteoporosis
- aseptic necrosis of bone

- emotional liability, insomnia
- peptic ulcer disease
- cataracts

- hypertension ----------
- diabetes----------
- hyperlipidemia----------

} atherosclerosis

- obesity
- impaired wound healing
- acne

- cushingoid facies
- growth suppression in children

Glucocorticosteroids (GS)

- prednisolon (*Fenicort* i.v. *Solupred* p.o.)
- prednison = 11-keto metabolite of prednisolon (*Encorton* p.o.)
- metylprednisolon (*Solu-Medrol* i.v., Medrol, Metypred p.o)

Day 0:	250 mg methylprednizolon
Day 1:	250 mg methylprednizolon
Day 2	125 mg methylprednizolon
> day 2	0,5 mg/kg prednisone

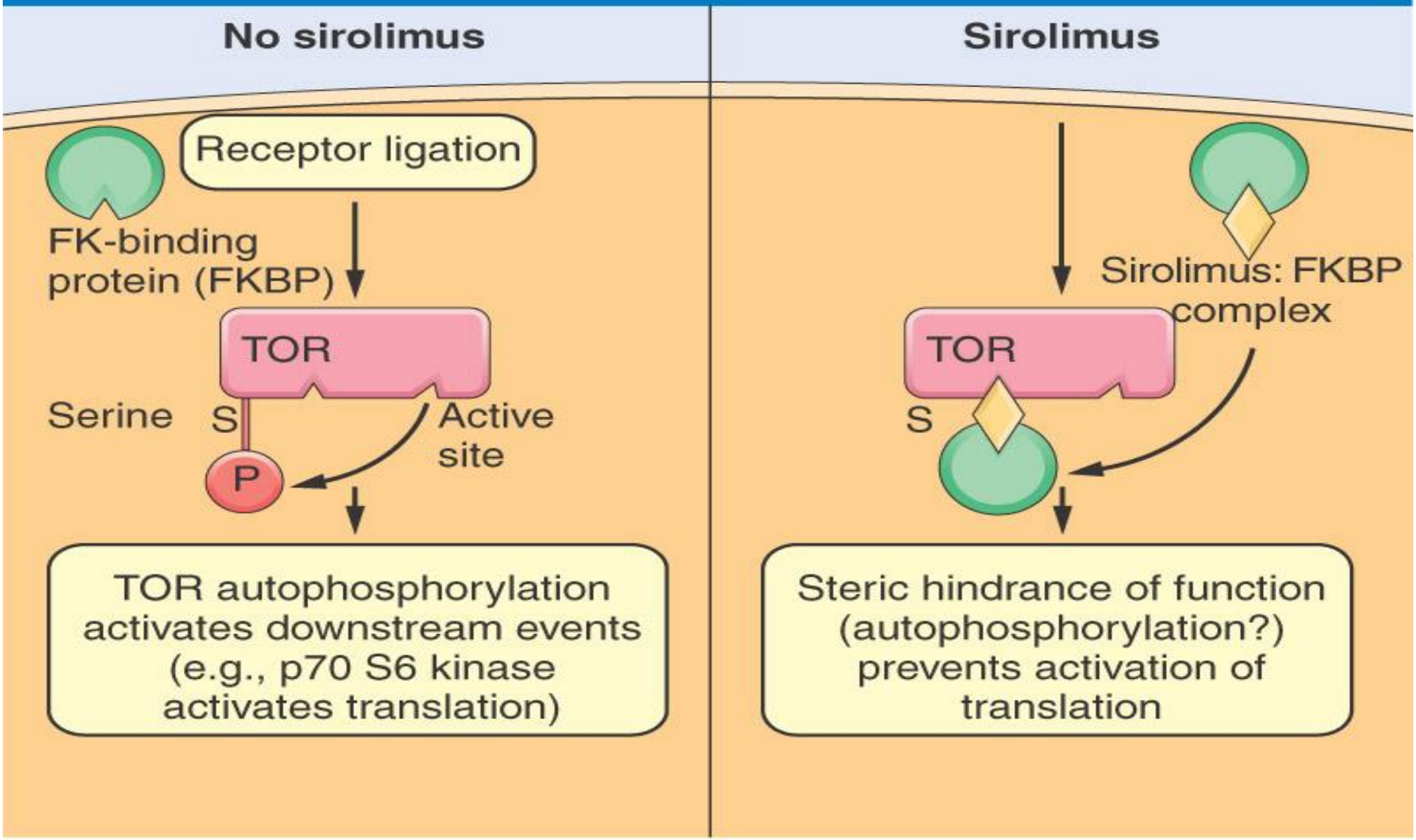
slow reduction of dose to 7,5 – 5 mg after 3 months

► ► ►PREVENTION OF ADRENOCORTICAL FAILURE: STRESS, ANAESTHESIA, VOMITING….etc,
►►►► PLEASE administer GS intravenously!!!

PSI (mTOR inhibitors): sirolimus, everolimus

- Chemical structure: macrocyclic antibiotics
- Mechanism of action: form a complex with immunophilin FKBP (but **does not inhibit calcineurin**) and block growth factor-driven cell proliferation → inhibition of lymphocyte proliferation (G1 → S inhibition)
- Synergism with CsA and Tacro, ½ dose of CNI!
- Side effects: thrombocytopenia, leucopenia, anemia, hyperlipidemia, lymphocele, impaired wound healing, HUS, diabetes, proteinuria, edema, pulmuno-toxicity, mouth ulcer, infertility, teratogenicity

Action of sirolimus



PSI (mTOR inhibitors): sirolimus (Rapamune), everolimus (Certican)

- **Monitoring:**
  - **whole blood level**
  - **WBC**
  - **serum lipids**

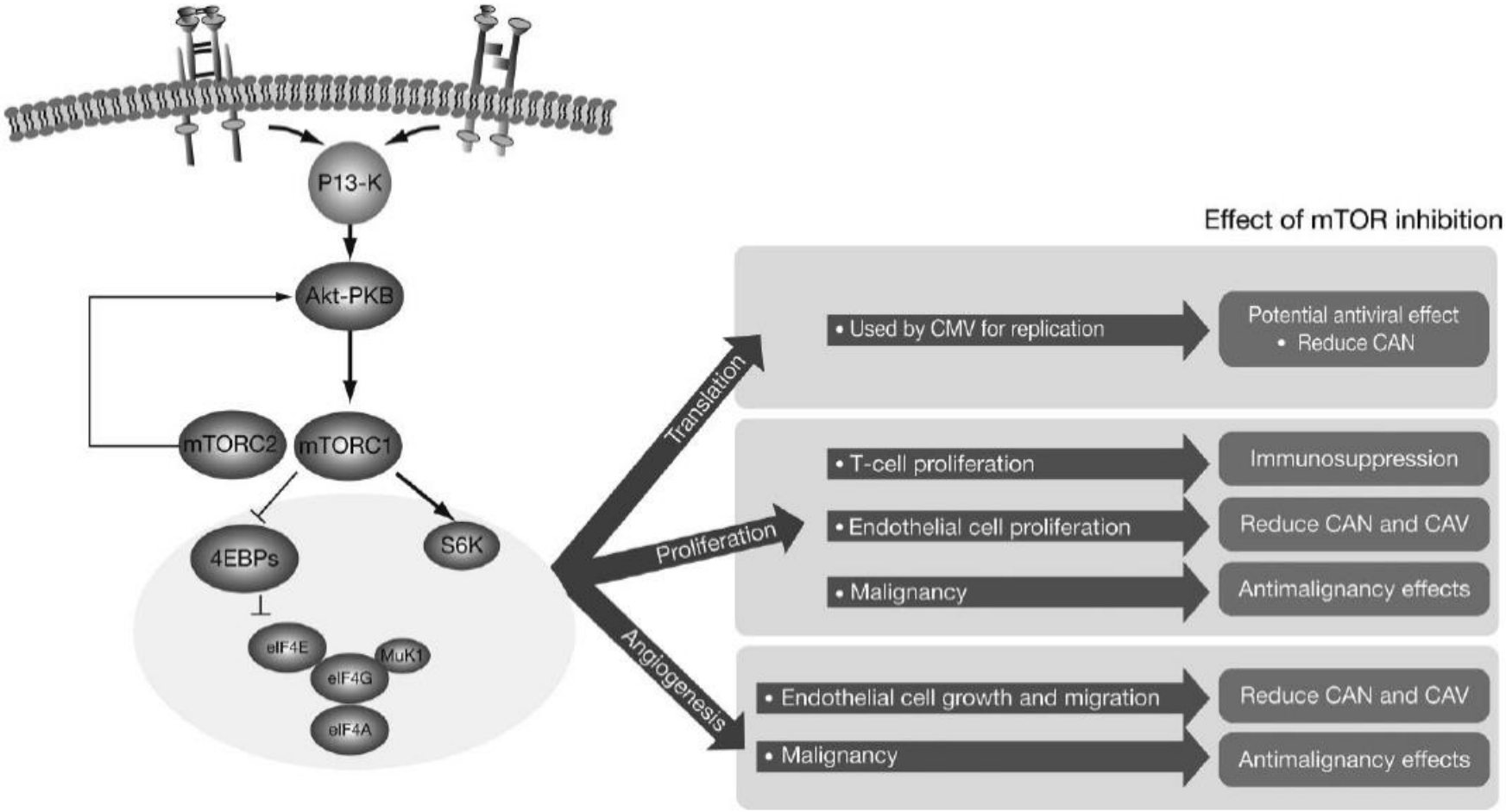
- **Sirolimus - T1/2 = 62h → 1x/24h, check blood level min. 7 days after dose changing**

- **Everolimus T1/2 = 26h → BID, check blood level min. 5 days after dose changing**

- **Metabolism: liver, jejunum (cytochrom P450 CYP3A4, gp130) → interactions**

- **Decreased incidence of malignancy, antitumor activity**

mTOR - pleiotropic mechanism of action



CAN
(chronic allograft nephropathy)

CAV
(chronic allograft vasculopathy)

ORIGINAL ARTICLE

AJT

Two-year outcomes in de novo renal transplant recipients receiving everolimus-facilitated calcineurin inhibitor reduction regimen from the TRANSFORM study

Stefan P. Berger[1] | Claudia Sommerer[2] | Oliver Witzke[3,4] | Helio Tedesco[5] | Steve Chadban[6] | Shamkant Mulgaonkar[7] | Yasir Qazi[8] | Johan W. de Fijter[9] | Federico Oppenheimer[10] | Josep M. Cruzado[11] | Yoshihiko Watarai[12] | Pablo Massari[13] | Christophe Legendre[14] | Franco Citterio[15] | Mitchell Henry[16] | Titte R. Srinivas[17] | Flavio Vincenti[18] | Maria Pilar Hernandez Gutierrez[19] | Ana Maria Marti[19] | Peter Bernhardt[19] | Julio Pascual[20] | on behalf of the TRANSFORM investigators

TABLE 3 Efficacy endpoints at month 24 by CNI subgroups (full analysis set)

	TAC-receiving patients				CsA-receiving patients			
n (%)	EVR + rCNI N = 915	MPA + sCNI N = 917	Difference (95% CI)	*P* value	EVR + rCNI N = 100	MPA + sCNI N = 95	Difference (95% CI)	*P* value
Primary endpoint[a]	429 (46.9)	391 (42.6)	4.3 (−0.4, 9.1)	.071	54 (54.0)	50 (52.6)	1.5 (−12.8, 15.7)	.842
tBPAR, graft loss, or death	148 (17.8)	126 (16.8)	1.0 (−4.8, 6.8)	.733	19 (19.2)	18 (19.1)	0.0 (−11.1, 11.2)	.994
tBPAR	102 (12.4)	83 (11.7)	0.7 (−4.7, 6.2)	.790	15 (15.5)	15 (16.0)	−0.5 (−10.9, 9.9)	.929
Graft loss	31 (3.5)	25 (2.8)	0.7 (−1.0, 2.3)	.429	5 (5.0)	5 (5.3)	−0.3 (−6.5, 5.9)	.922
Death	29 (3.8)	33 (4.3)	−0.5 (−2.8, 1.7)	.642	3 (3.2)	2 (2.2)	1.0 (−3.7, 5.7)	.684
eGFR < 50 mL/min per 1.73 m^{2}[a]	415 (45.4)	374 (40.8)	4.6 (−0.1, 9.4)	.055	53 (53.0)	47 (49.5)	4.2 (−10.1, 18.5)	.566

P value for no difference ([EVR + rCNI] − [MPA + sCNI] = 0).

CI, confidence interval; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; EVR, everolimus; MPA, mycophenolic acid; rCNI, reduced-exposure CNI; sCNI, standard-exposure CNI; TAC, tacrolimus; tBPAR, treated biopsy-proven acute rejection

[a]Represents raw incidence rates; all remaining values are Kaplan-Meier incidence rates.

- **CMV, BKV**

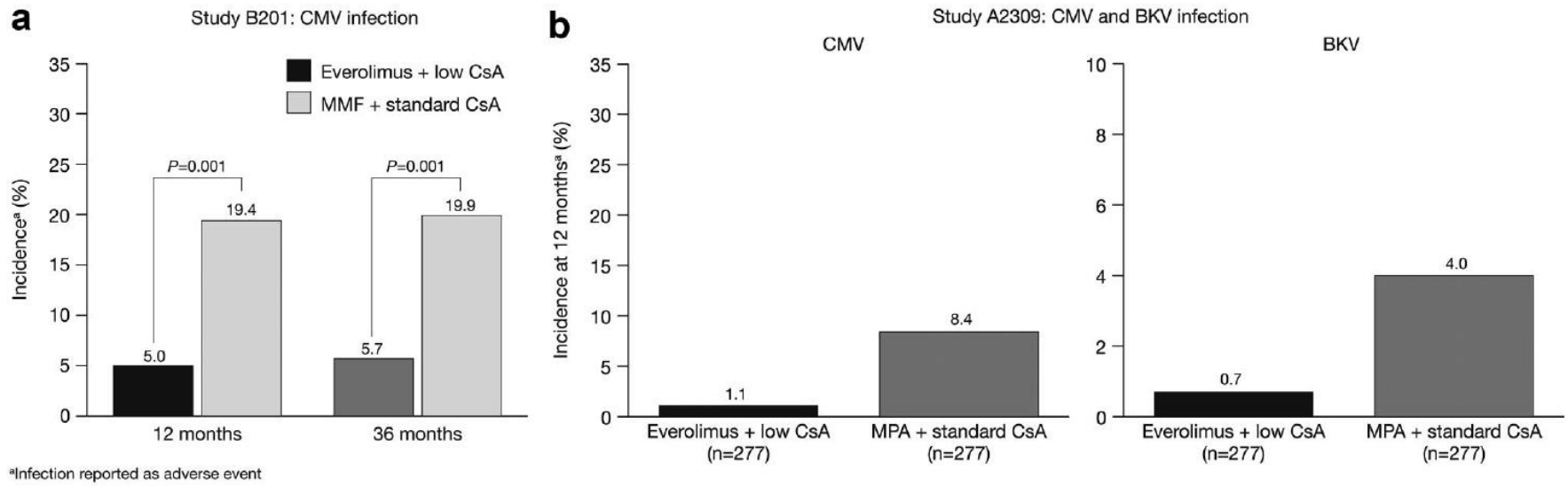
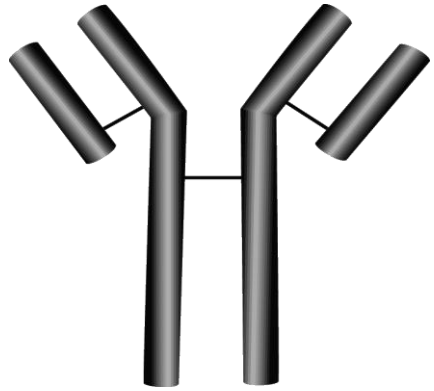
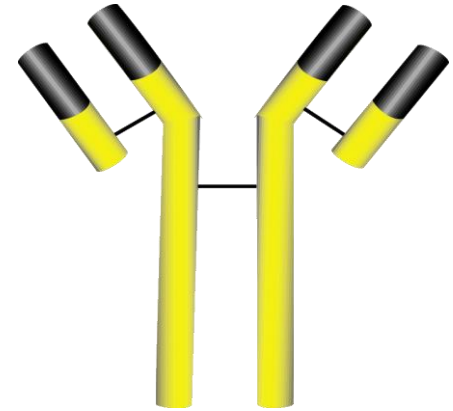


FIGURE 4. (a) Everolimus significantly reduced the incidence of cytomegalovirus (CMV) infection in Study B201; (b) everolimus significantly reduced the incidence of CMV and BK virus (BKV) infection in Study A2309. CsA, cyclosporine A; MMF, mycophenolate mofetil; MPA, mycophenolic acid.

Types of antibodies



anti-CD3
(monoclonal)

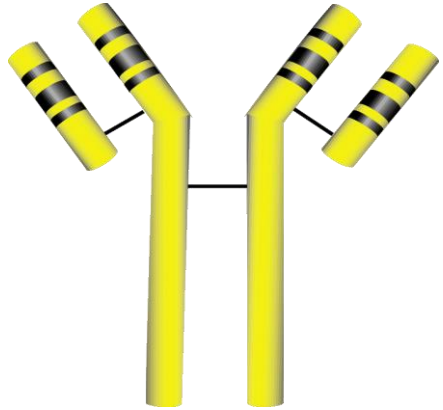


anti-CD25 (anti-IL2R) - basiliximab
(chimeric monoclonal)

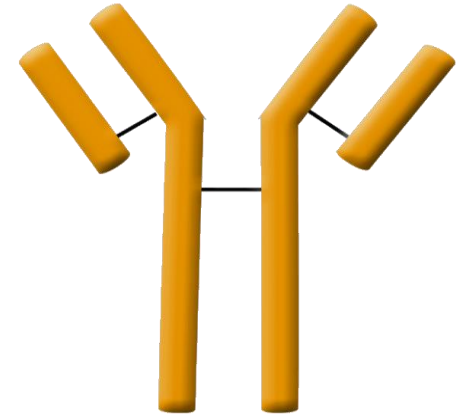
Murine

Human

Rabbit



antiCD25 (anti-IL2R) - daclizumab
(humanised monoclonal)



ATG
(polyclonal)

Polyclonal antibodies
antithymocyte globulin (Thymoglobuline/Grafalon)

- **Production: immunisation of rabbits with human lymphocytes**

- **Mode of action:**
  - **1. lymphocytes are lysed or cleared into the reticuloendothelial system**
  - **2. their surface antigens may be masked by the antibody**

- **Administration: 1. premedication with GS, metamizole, antihistaminic**
- **2. slow infusion i.v. - central line (min. 4 hours infusion)**

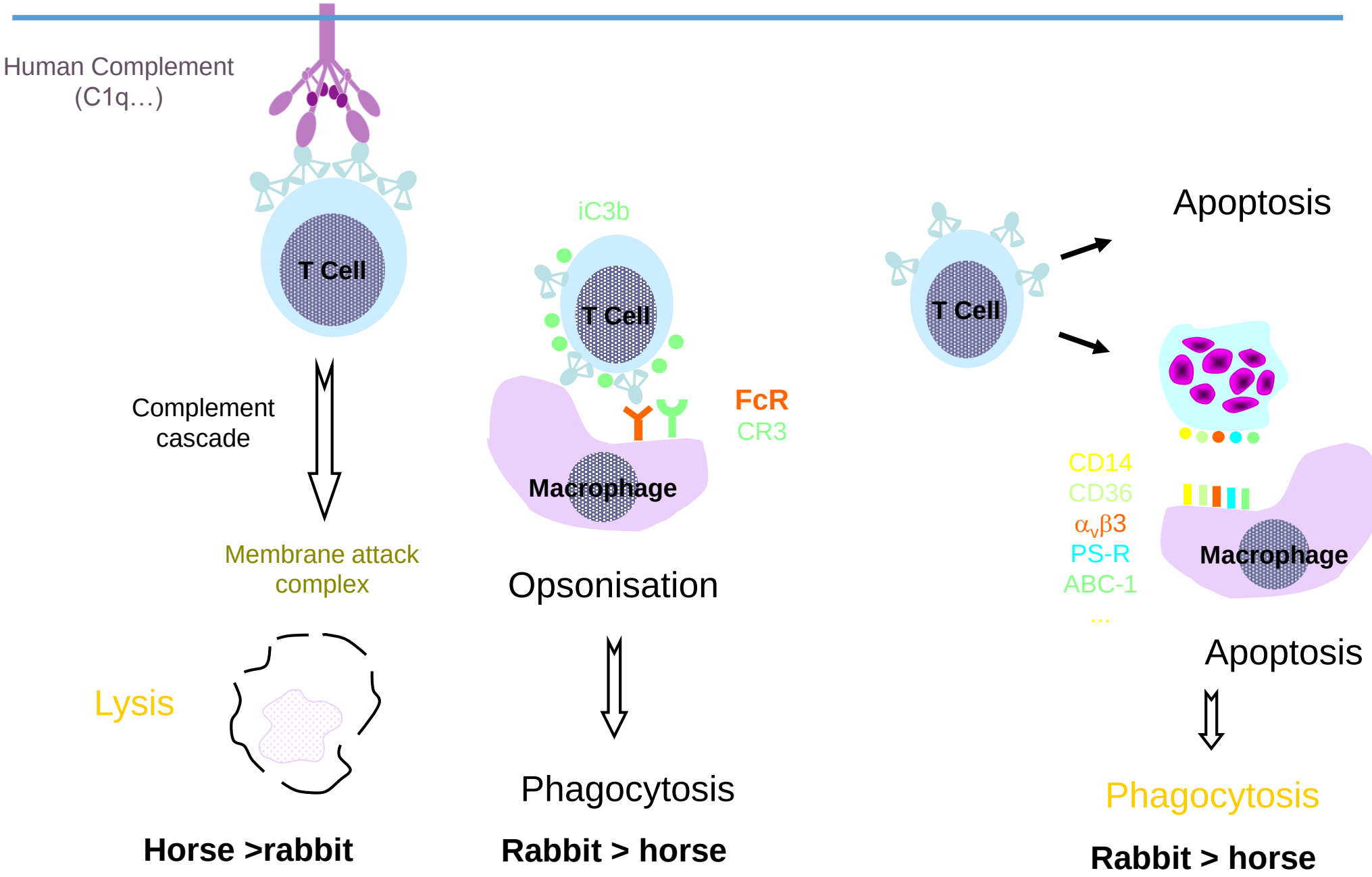
- **Duration of treatment: 3-14 days**

- **Indication: 1. prophylaxis of rejection (high immunogical risk, GS/CNI avoidance/reduction)**
- **2. treatment of acute severe or steroid-resistant rejection**
- **3. Tolerogenic properties?**
- **Monitoring: WBC, CD3 (20/mm3)**

Polyclonal antibodies - adverse reactions

- **fever, chills**
- **leukopenia, thrombocytopenia**
- **Hemolysis**
- **phlebitis, clotted A/V fistula**
- **Anaphylaxis**
- **other risk:**
- **1. opportunistic infection (CMV, EBV)**
- **2. neoplasm, lymphoproliferative disease**

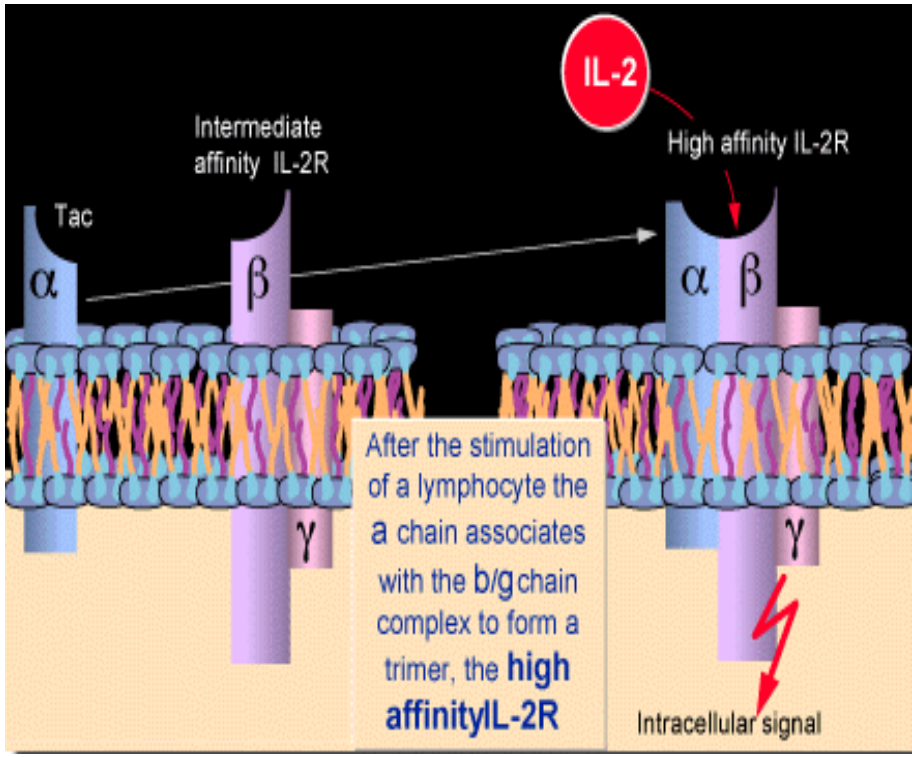
ATG - depletion of limphocytes T



Anti - CD25 (anti- IL-2Rα) antibody

- **Mechanism of action:**

IL-2Rα = CD25 - is expressed on activated lymphocytes
(IL-2 + IL-2Rα) => lymphocyte proliferation
anti- CD25 (anti-IL2Rα) is interleukin 2 antagonist



- **Types of antibodies and preparations:**

1.**chimeric - basiliximab (Simulect)**

2.humanised - daclizumab (Zenapax) - withdrawn

Anti-IL-2Ra = anti-CD25

- **Indication: PROPHYLAXIS OF REJECTION**
- **Tolerance: very good**
- **Efficacy: high, but less powerful than ATG**
- **Administration:**
- **Basiliximab (Simulect): day 0 and 4th after Tx - 20mg iv**
-

Acute rejection frequency

Aza+Pred	60%-80%
CsA+Pred+Aza	40-50%
CsA+Pred+MMF, $C_{0\ CsA}$	25-30%
CsA+Pred+Rapa	25-30%
CsA+Pred+MMF, $C_{2\ CsA}$	11%
Tac+Pred	30%
Tac+Pred+Aza	25%
Tac+Pred+MMF	20-8%
Tac+Pred+Rapa	20%
Rapa+Pred+MMF	35-40%

Treatment of acute T cell mediated rejection (cellular) - ACR

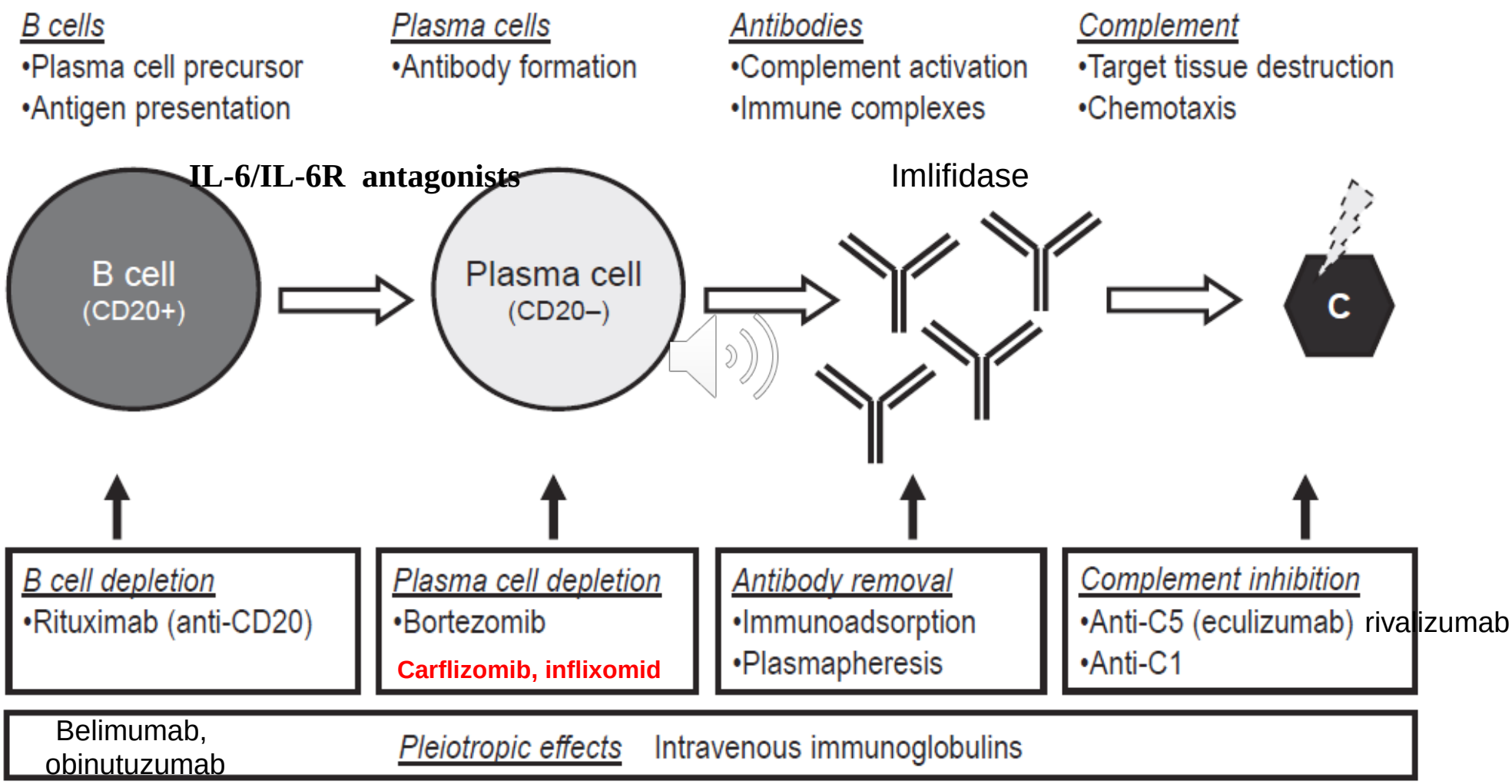
- **pulse steroids 250-500mg i.v. for 3-5 days**

- **Thymoglobuline, ATG-Grafalon**
- *Indications:*
- 1. acute vascular rejection moderate or severe
- 2. steroid resistant rejection

- *if UNSTABLE GRAFT FUNCTION*:

- **Conversion** from CsA -----> to Tacro
- from Aza -----> to MMF (if not performed yet)
  increase the dose of oral steroids

Antibody medated rejection (ABMR) - treatment



Treatment of acute and chronic antibody mediated rejection

Table 1. Efficacy and side effects of interventions for the prevention or treatment of antibody-mediated graft injury

	Desensitization protocols	Acute ABMR treatment	Chronic ABMR treatment	Potential adverse events	Cost
1. PLEX	+	+	±	Hypotension, bleeding, hypovolemia	+
2. IVIG	+	+	±	Allergy, headache, myalgia, fever	+
3. Rituximab (Rx)	++	++	+?	Infections, neutropenia, infusion reactions	++
4. Bortezomib (Bx)	ND	+++	+?	Myelosuppression, neuropathy GI toxicity	++
5. Eculizumab (Ex)	NA	++	+?	Meningococcal infection, hypertension	+++
6. Splenectomy (Sx)	++	++	+?	Infections, thrombocytosis	+
7. PLEX + IVIG	++	++	±	Additive	Additive
8. IVIG + Rx	++	++	+		
9. PLEX + IVIG + Rx	+++	+++	NA		
10. PLEX + IVIG + Sx	+++	+++	+?		
11. PLEX + IVIG + Rx + Bx	ND	+++	+		
12. PLEX + IVIG + Rx + Ex	NA	++++	ND		

ND, no data; NA, not applicable; ±, occasional; ?, few data, not exactly known.

New immunosuppressive drugs

- **Antibodies:**
- **- B-cell-depending monoclonal anti-CD20 antibody (*rituximab)***
- **- humanized monoclonal anti- C5 antibody *(eculizumab, Solaris)***
- **- anty-CD80/86 (belatacept)**
- **- anty IL-6 (tocilizumab)**

- **Small molecule drugs**
  - **Bortezomib (Velcade)**
  - **Imlifidase (IdeS), clazakizumab**

Anti-CD20 (RITUXIMAB)

- ***Anty-CD20 –*** **chimeric monoclonal anti-CD 20 antibody, selectively depletes B-cells**

- **Prophylaxis, treatment of antibody-mediated rejection in patients at high immunological risk**
- **ABOi transplantation or positive cross-match in living donor recipients**
- **Side effects: high risk of infections (11.8%) and death related to infection disease (9.1%) in patients treated with rituximab (n=77) vs 1.55% in the control group (n=902); p= 0.0007**

LEUKOENCEPHALOPATHIA, RALI (rituximab associated lung injury), cytokine release syndrome, leucopenia

HUS reccurence after kidney transplantation

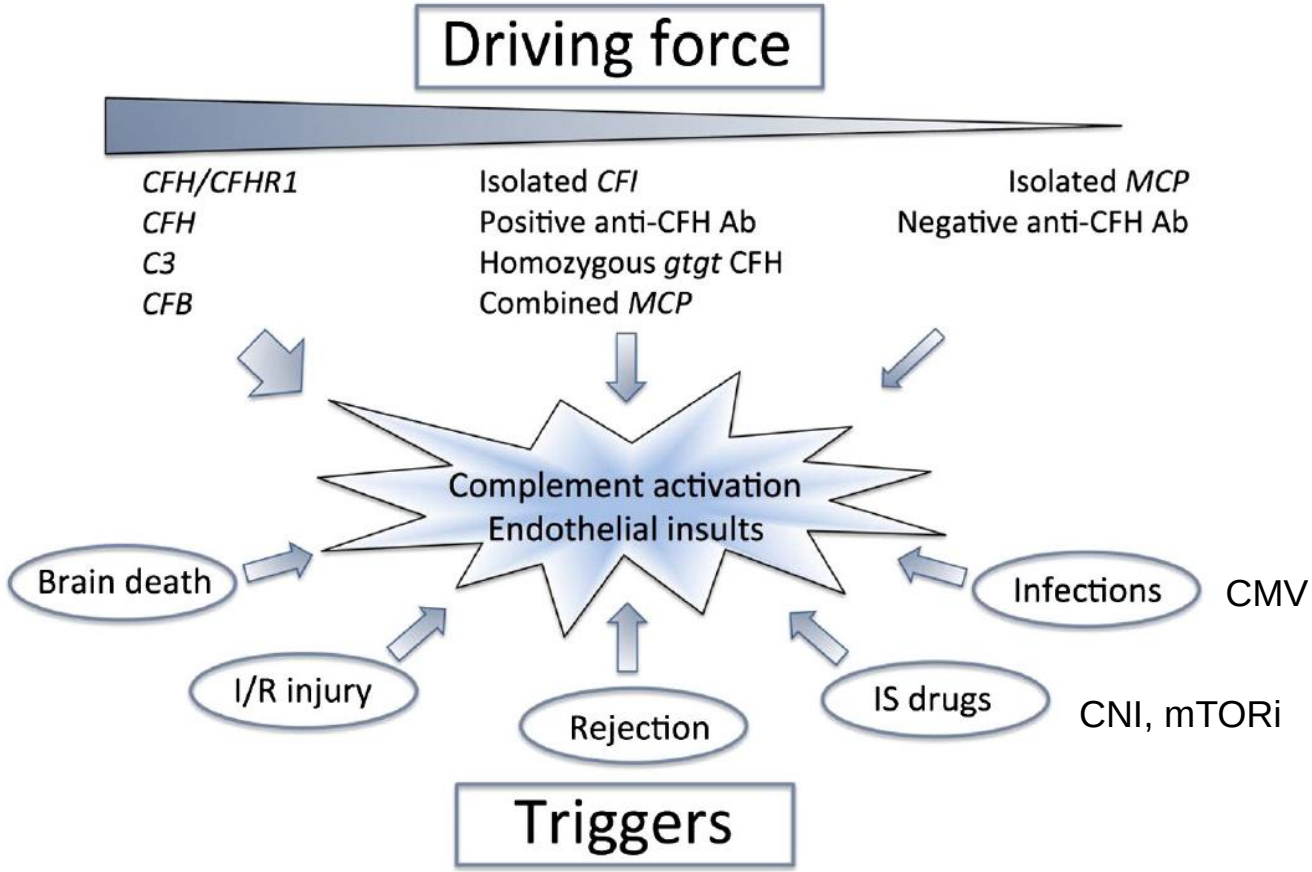


Fig. 1. Paradigm for aHUS recurrence. aHUS results from an interplay between a genetic susceptibility, leading to complement overactivation on the endothelium surface, and environmental factors, which induce endothelium damages. Abbreviations: Anti-CFH Ab, anti-complement factor H antibody; *CFH*, complement factor H; homozygous *gtgt* CFH, homozygous at-risk *gtgt* CFH haplotype; complement factor H; *CFH/CFHR1*, hybrid complement gene resulting of gene conversion between CFH and CFHR1; *CFI*, complement factor I; *C3*, complement component 3; I/R, ischemia reperfusion; IS, immunosuppressive drugs; *MCP*, membrane cofactor protein.

Eculizumab

Table 1. Eculizumab use in renal transplantation, published in reports, and/or being evaluated in clinical trials.

Indication to use eculizumab	Reference	Reference and clinical trial identifier
Prevention and/or treatment of aHUS recurrence after renal transplantation	[5,7,9,10,12,14,15]	
Treatment of *de novo* TMA after renal transplantation	[20,21]	
Treatment or prevention of AMR in patients with high immunological risk receiving kidney from deceased donors or living-related donors	[25–28]	[29] NCT00670774 [32] NCT01106027 [33] NCT01567085 [34] NCT01095887 [35] NCT 01895127 [36] 02113897
Prevention of delayed graft function after IRI		[38] NCT01919346 [39] NCT02145182
Enabling renal transplantation in patients with history of catastrophic antiphospholipid antibody syndrome		[40] NCT01029587

aHUS – atypical hemolytic-uremic syndrome; TMA – thrombotic microangiopathy; AMR – antibody-mediated rejection; IRI – ischemia-reperfusion injury.

New complement suppressive strategies

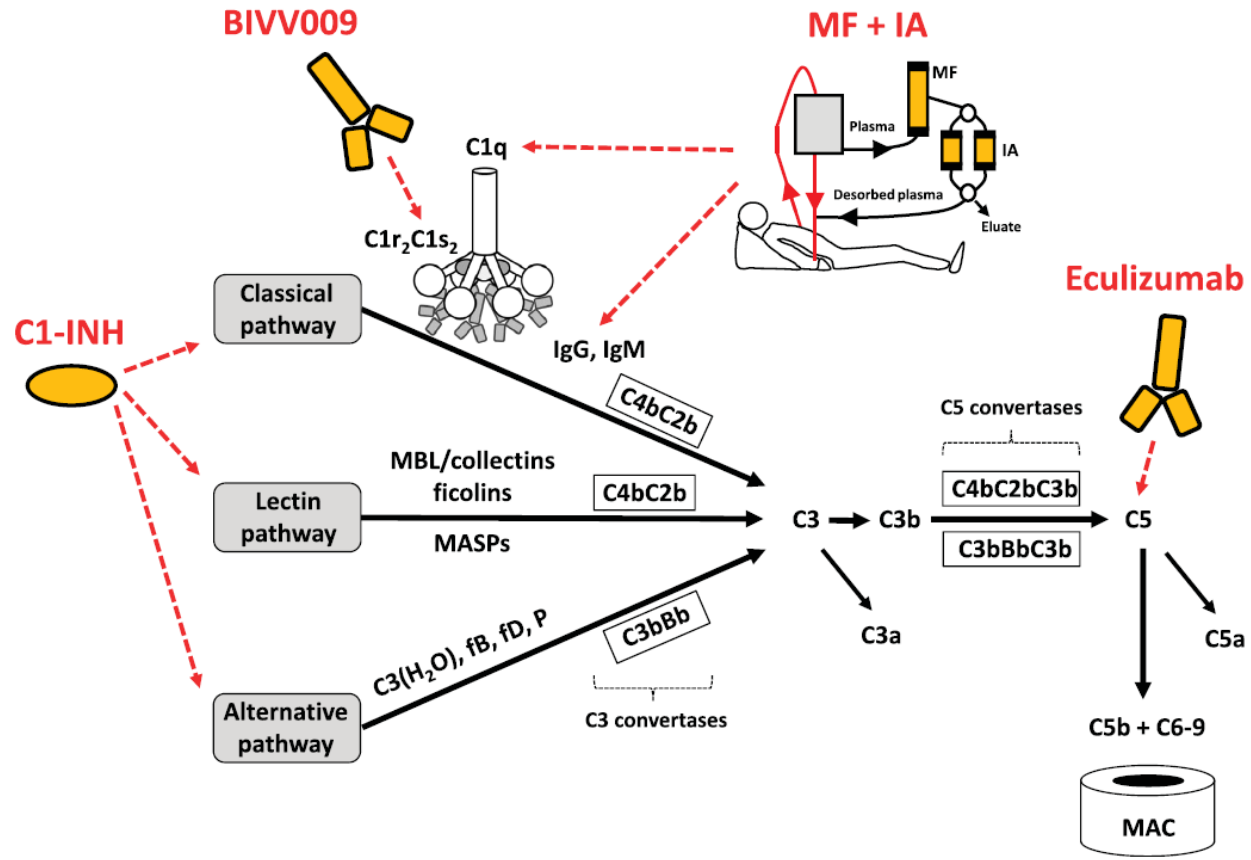
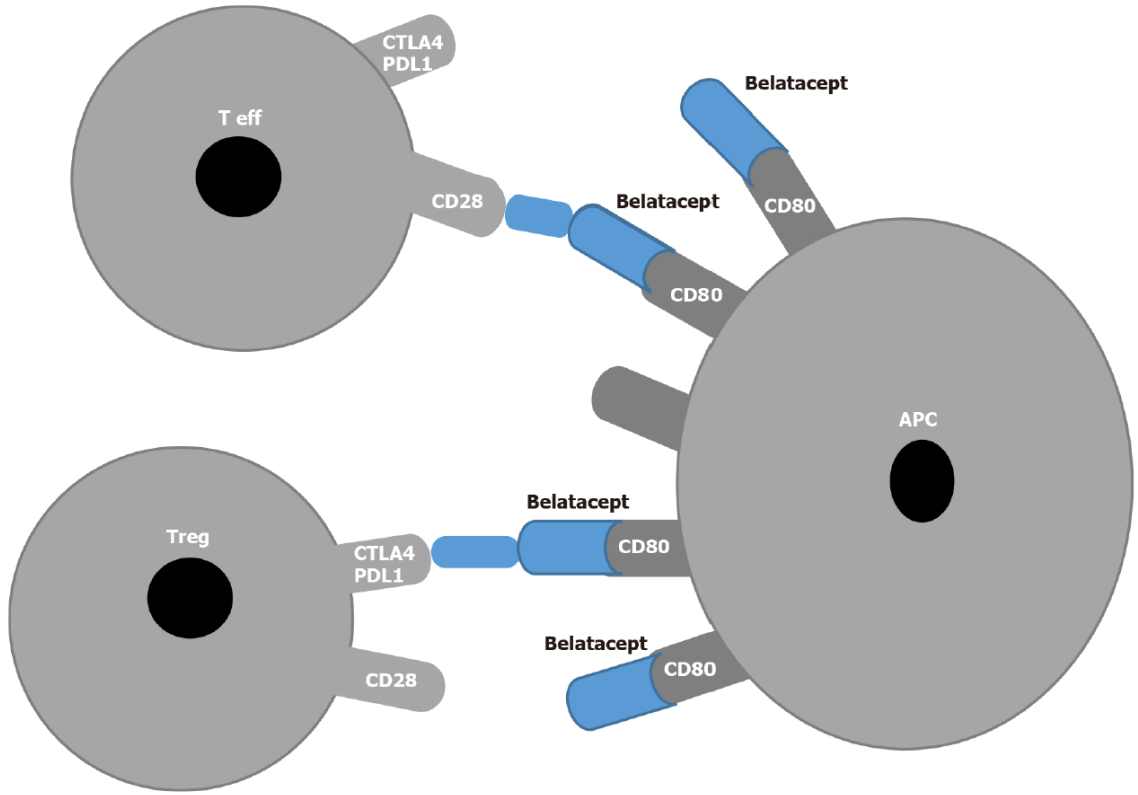


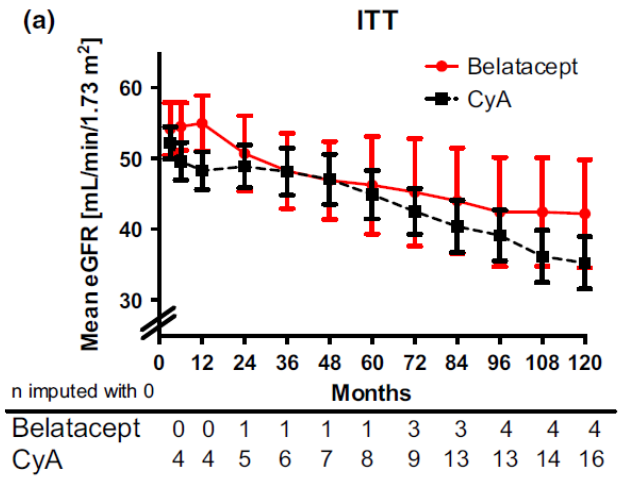
FIGURE 1. Mode of action of 4 different strategies of complement interference evaluated in clinical transplantation. The C1 complex ($C1qr_2s_2$), a key component of the CP, is activated upon antibody binding. Humanized monoclonal antibody BIVV009 targets its enzymatic subcomponent C1s and thereby blocks 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—$C3(H_2O)$—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.

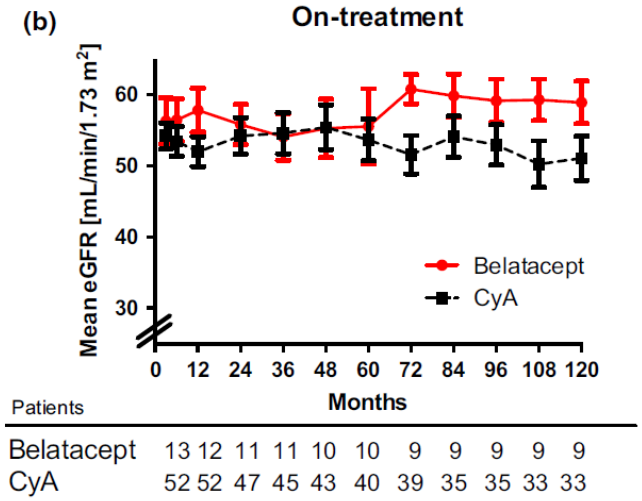
Inhibition of the costimulatory signal (signal 2)

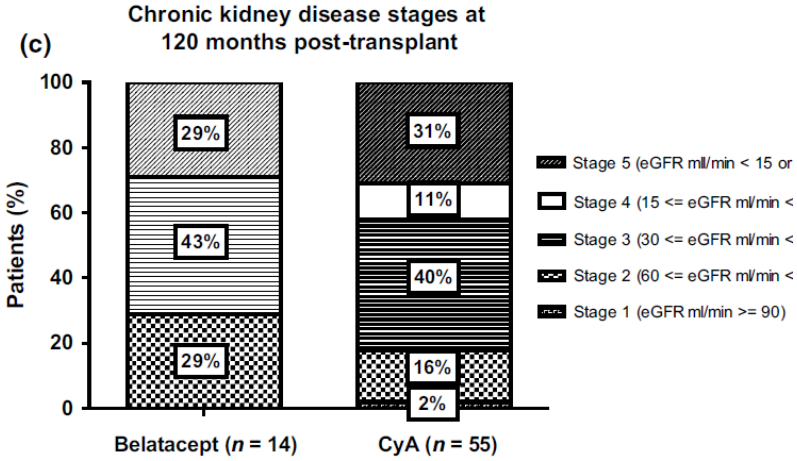


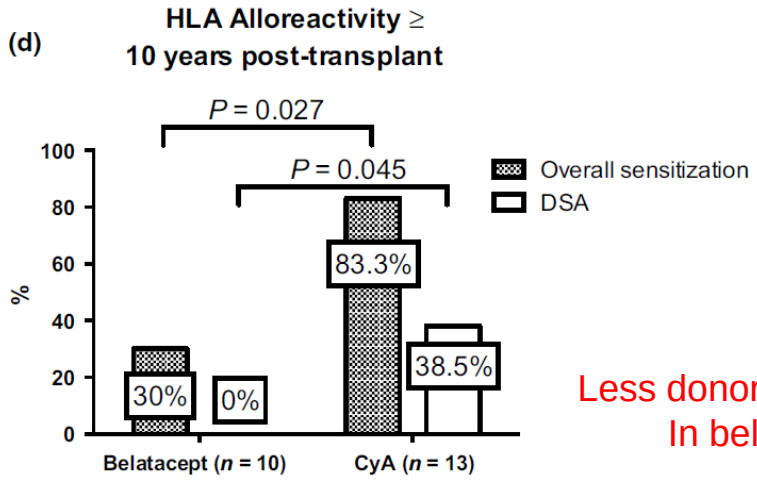
DOI: 10.5500/wjt.v12.i3.27

Figure 1 Block of co-stimulation with Belatacept. APC: Antigen presenting cell; T eff: T effector; T reg: Regulatory T cells; PDL1: Programmed cell death receptor ligand 1; CTLA4: Cytotoxic T-lymphocyte-associated antigen 4.









Less donor specific antibodies
In belatacept group

CLINICAL RESEARCH www.jasn.org

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

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

ϑΑΣΝ, 32, 3252–3264, 2021

Table 2. Treatment effect on patient and graft survival (primary end point), BPAR, and renal function at 24 months

End Points	Belatacept Conversion, *n*=223		CNI Continuation, *n*=223
Patient and graft survival			
Patients surviving with a functioning graft	219 (98%)		217 (97%)
Adjusted difference from CNI (95.1% CI)		0.8 (−2.1 to 3.7)	
Graft loss or death	4 (2%)		6 (3%)
Graft loss	0		2 (1%)
Death	4 (2%)		4 (2%)
Death with a functioning graft	4 (2%)		4 (2%)
BPAR			
Patients with cellular (Banff IA or higher) or antibody-mediated BPAR	18 (8%)		9 (4%)
Adjusted difference from CNI (95.1% CI)		4.1 (−0.4 to 8.5)	
All Banff grade (1A or higher) acute cellular rejection events	20 (9%)		6 (3%)
Mild acute (IA)	2 (1%)		4 (2%)
Mild acute (IB)	1 (<1%)		0
Moderate acute (IIA)	7 (3%)		1 (<1%)
Moderate acute (IIB)	6 (3%)		0
Severe acute (III)	4 (2%)		1 (<1%)
All humoral rejection events	5 (2%)		5 (2%)
Humoral only	0		3 (1%)
Humoral and cellular	5 (2%)		2 (1%)
Renal function			
Mean adjusted eGFR, ml/min per 1.73 m^2 (95% CI)			
Month 12	55.0 (53.5 to 56.6)		49.3 (47.7 to 50.8)
Month 18	55.9 (54.3 to 57.6)		48.9 (47.2 to 50.5)
Month 24	55.5 (53.8 to 57.3)		48.5 (46.7 to 50.3)
Mean adjusted change from baseline at month 24 in eGFR, ml/min per 1.73 m^2	+5.2		−1.9
Adjusted difference from CNI (95.1% CI)		7.0 (4.5 to 9.6)	
P value		<0.001	

Data are *n* (%) unless otherwise stated.

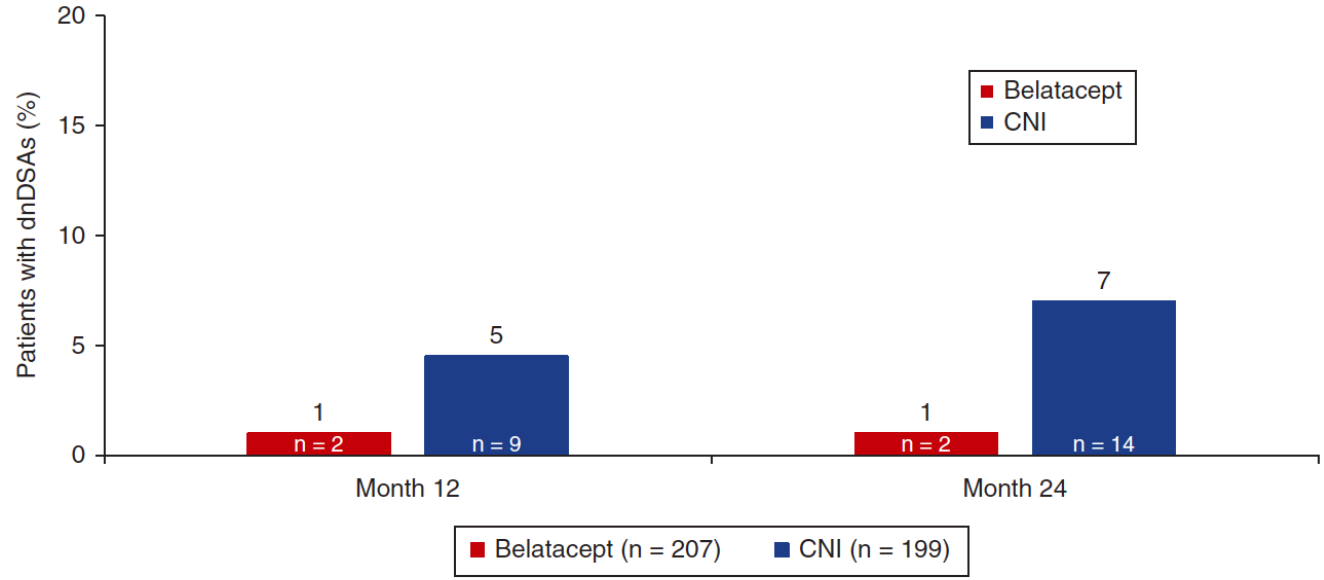


Figure 5. Analysis of the prevalence of dnDSAs indicated that 1% of patients in the belatacept group and 7% of patients in the CNI group developed dnDSAs at 24 months postrandomization.

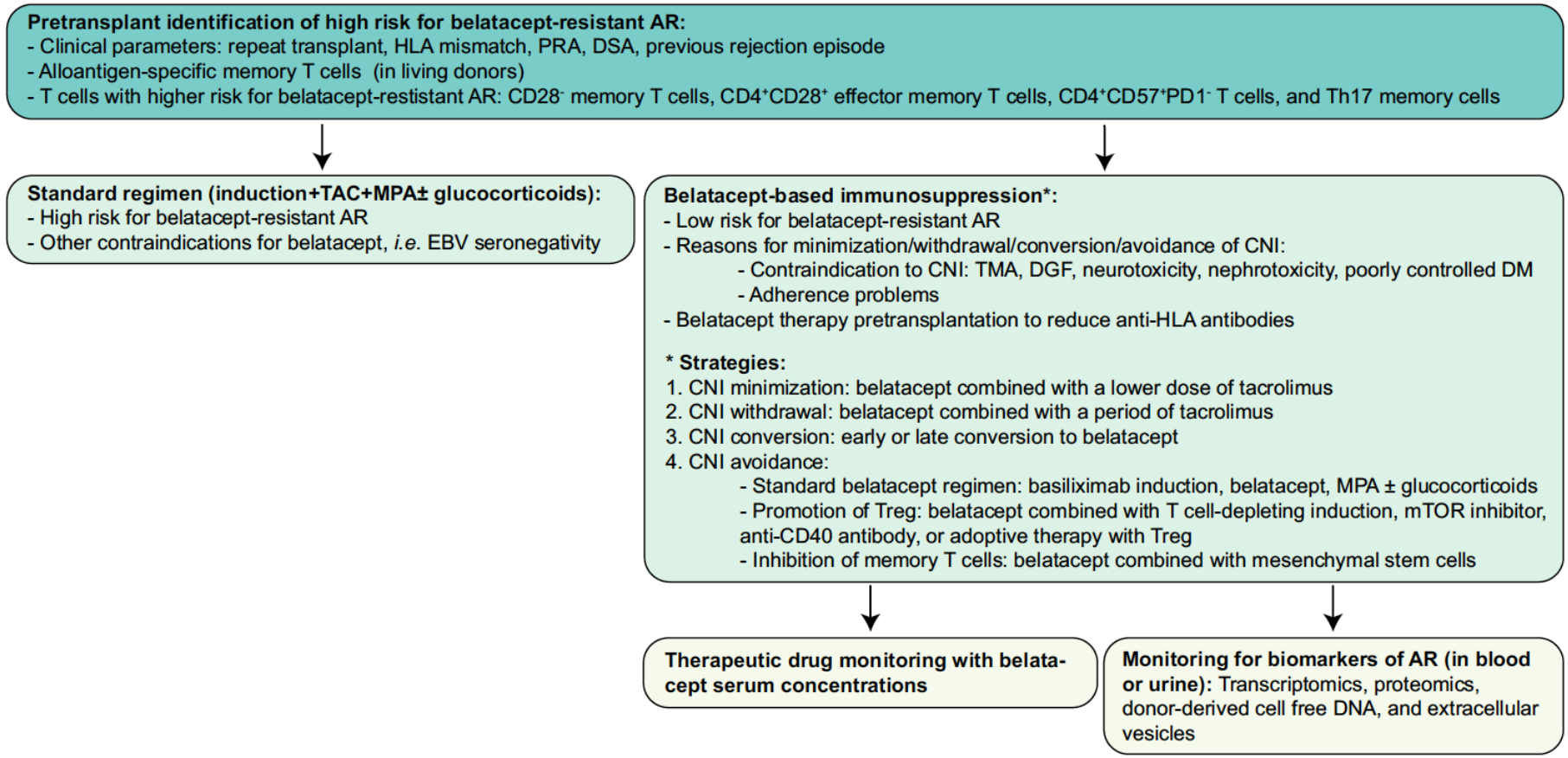

Pretransplant identification of high risk for belatacept-resistant AR:
- Clinical parameters: repeat transplant, HLA mismatch, PRA, DSA, previous rejection episode
- Alloantigen-specific memory T cells (in living donors)
- T cells with higher risk for belatacept-restistant AR: CD28⁻ memory T cells, CD4⁺CD28⁺ effector memory T cells, CD4⁺CD57⁺PD1⁻ T cells, and Th17 memory cells
Standard regimen (induction+TAC+MPA± glucocorticoids):
- High risk for belatacept-resistant AR
- Other contraindications for belatacept, *i.e.* EBV seronegativity
Belatacept-based immunosuppression*:
- Low risk for belatacept-resistant AR
- Reasons for minimization/withdrawal/conversion/avoidance of CNI:
- Contraindication to CNI: TMA, DGF, neurotoxicity, nephrotoxicity, poorly controlled DM
- Adherence problems
- Belatacept therapy pretransplantation to reduce anti-HLA antibodies
* **Strategies:**
1. CNI minimization: belatacept combined with a lower dose of tacrolimus
2. CNI withdrawal: belatacept combined with a period of tacrolimus
3. CNI conversion: early or late conversion to belatacept
4. CNI avoidance:
- Standard belatacept regimen: basiliximab induction, belatacept, MPA ± glucocorticoids
- Promotion of Treg: belatacept combined with T cell-depleting induction, mTOR inhibitor, anti-CD40 antibody, or adoptive therapy with Treg
- Inhibition of memory T cells: belatacept combined with mesenchymal stem cells
Therapeutic drug monitoring with belatacept serum concentrations
Monitoring for biomarkers of AR (in blood or urine): Transcriptomics, proteomics, donor-derived cell free DNA, and extracellular vesicles

Table 1. Summary of belatacept studies in kidney transplantation

Study ID (author, year)	Study design	Study objective	Patient population	Results
De Novo Belatacept in Kidney Transplantation				
Mannon, 2020 [17]	Prospective, randomized, multicenter trial	Evaluate the safety and efficacy of calcineurin avoidance and rapid steroid elimination with *de novo* 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] Kaufman, 2021 [19▪▪]	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
Kirk, 2014 [20] Schmitz, 2020 [21]	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. Majority of the patients were able to be weaned to belatacept monotherapy

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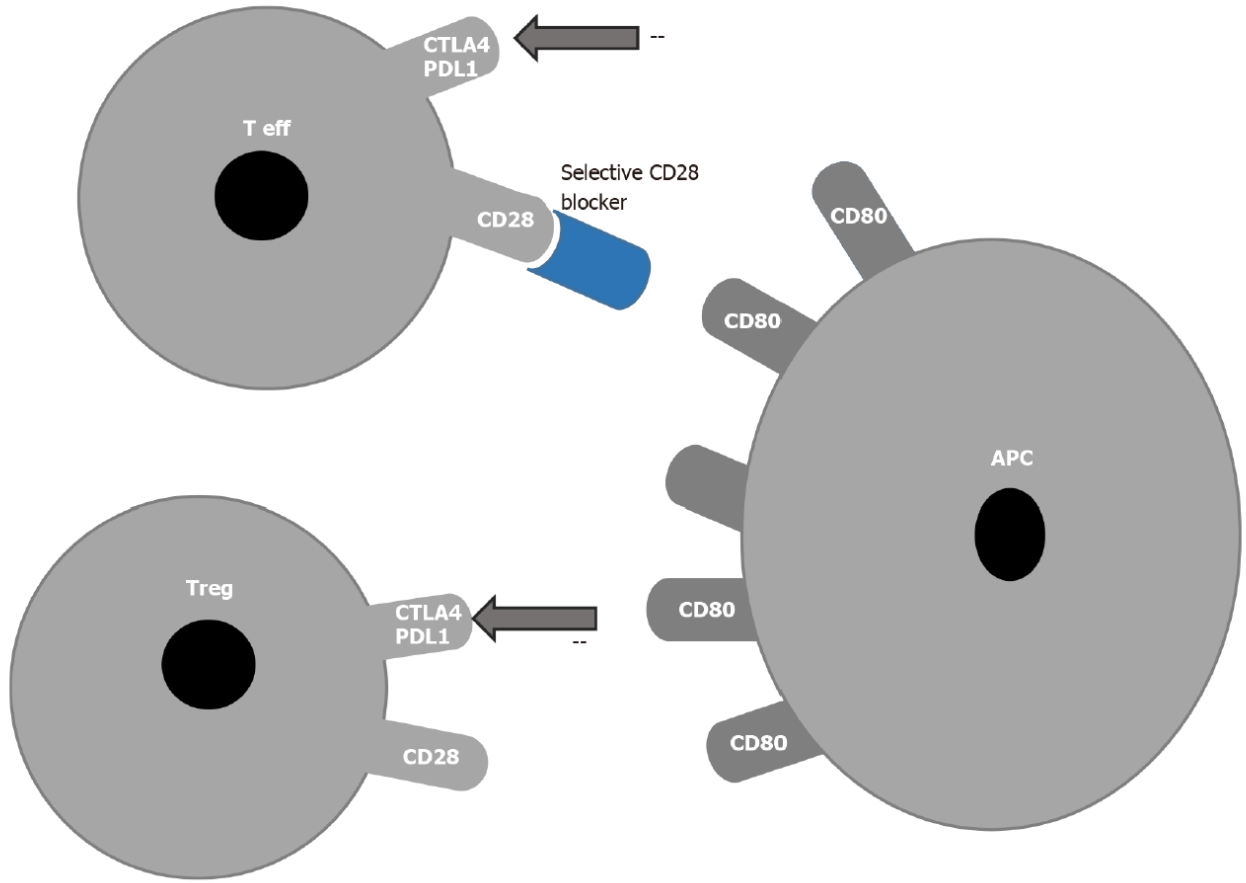
DOI:10.1097/MOT.0000000000001033

Conversion to Belatacept from Calcineurin Inhibitors in Kidney Transplantation				
Budde, 2021 [22▪▪]	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▪]	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▪]	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▪]	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

DOI:10.1097/MOT.0000000000001033



DOI: 10.5500/wjt.v12.i3.27

Figure 2 Block of co-stimulation with anti CD28. APC: Antigen presenting cell; T eff: T effector; T reg: Regulatory T cells; PDL1: Programmed cell death receptor ligand 1; CTLA4: Cytotoxic T-lymphocyte-associated antigen 4.

Bortezomib (Velcade)

- **Bortezomib selective, reversible inhibitor of the 26S proteasome (Velcade)**
- **Depletes malignant and nonmalignant plasma cells**
- **May decrease anti-HLA antibodies in patients with high DSA levels during desensitization or during treatment of antibody mediated rejection (AMR in renal transplant recipients**

Mechanisms of action of IVIg

- **neutralisation of circulating Ab through idiotype-anti-idiotype interactions**
- **inhibition of secretion of cytokines**
- **inhibition of the binding of complement fractions to their target cells**
- **inhibition of T and B cell proliferation with downregulation of antibody synthesis**
- **inhibition of endothelial cell activation**
- **inhibition of CD8 T cell cytotoxicity**
- **increased apoptosis of B cells**

IdeS: A Bacterial Proteolytic Enzyme with Therapeutic Potential

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Abstract

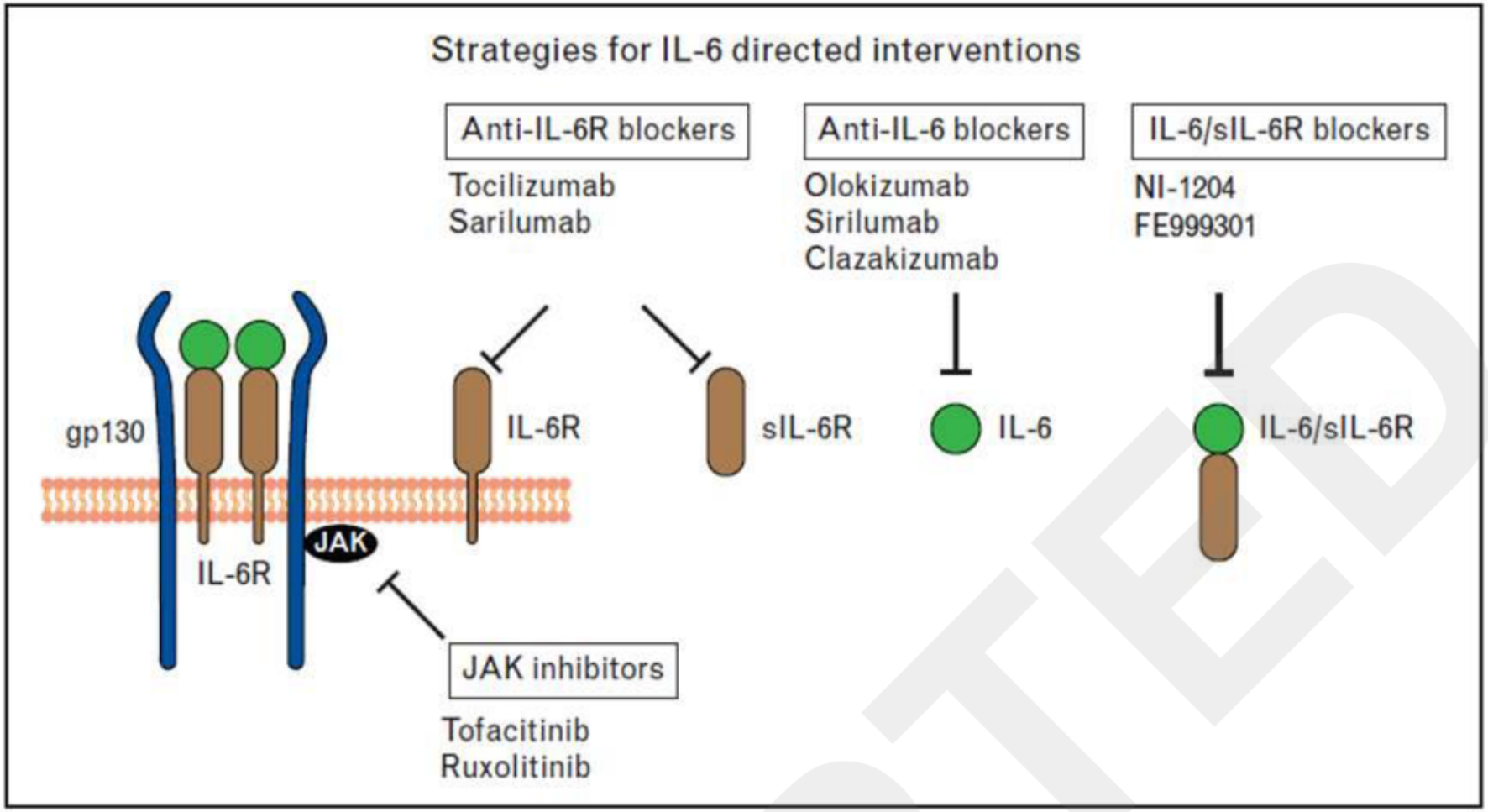
Background: IdeS, a proteinase from *Streptococcus pyogenes*, cleaves immunoglobulin (Ig)G antibodies with a unique degree of specificity. Pathogenic IgG antibodies constitute an important clinical problem contributing to the pathogenesis of a number of autoimmune conditions and acute transplant rejection.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

Anty - IL-6 strategies for treatment of antibodies mediated rejection

Figure 5



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Wiley Periodicals Inc.

doi: 10.1111/ajt.14228

Assessment of Tocilizumab (Anti–Interleukin-6 Receptor Monoclonal) as a Potential Treatment for Chronic Antibody-Mediated Rejection and Transplant Glomerulopathy in HLA-Sensitized Renal Allograft Recipients

J. Choi[1,*], O. Aubert[2], A. Vo[1], A. Loupy[2], M. Haas[3], D. Puliyanda[1], I. Kim[1], S. Louie[1], A. Kang[1], A. Peng[1], J. Kahwaji[1], N. Reinsmoen[3], M. Toyoda[4] and S. C. Jordan[1]

Abbreviations: AE, adverse event; AMR, antibody-mediated rejection; cAMR, chronic active antibody-mediated rejection; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; FDA, US Food and Drug Administration; iDSA, immunodomi-

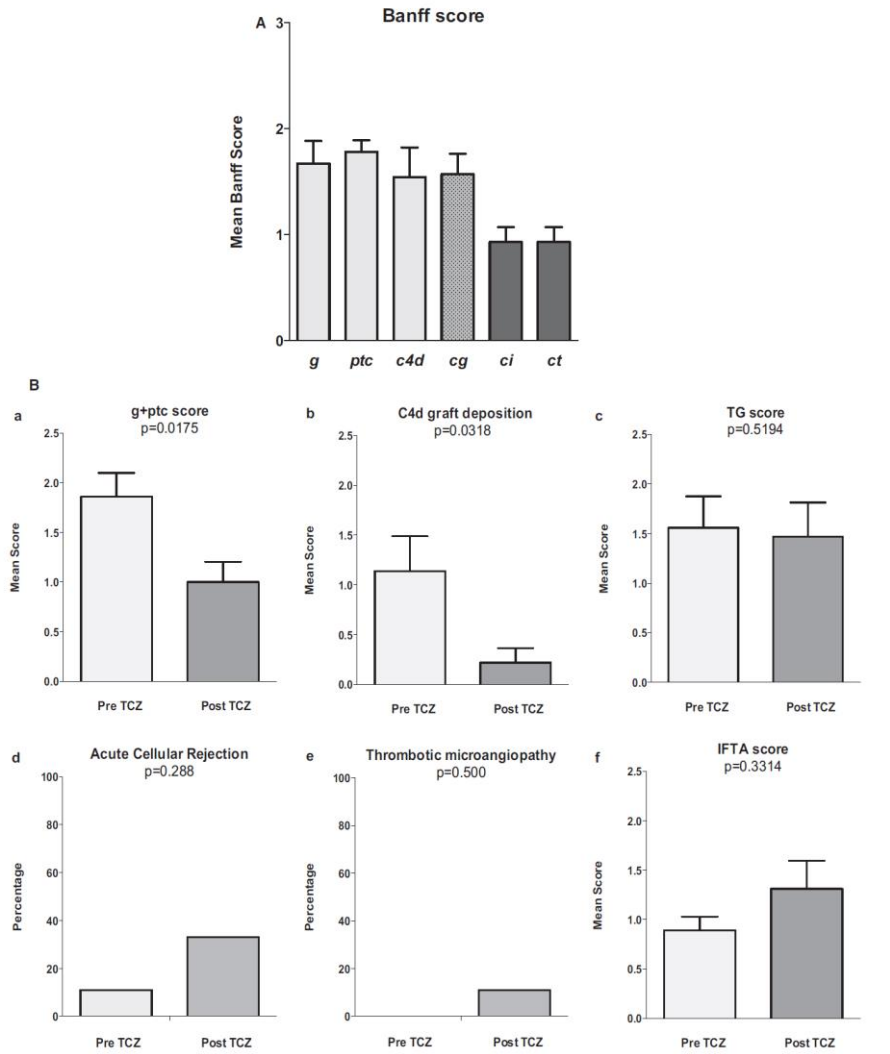


Figure 1: Index and 1 year post–tocilizumab allograft biopsies. (A) Kidney allograft index biopsy phenotypes at the initiation of tocilizumab treatment were obtained for 36 patients. All patients had significant glomerulitis (g), peritubular capilaritis (ptc), C4d positivity, and chronic changes in the glomerulus (cg), interstitium (ci), and tubules (ct). (B) This figure shows kidney allograft biopsy phenotypes before and after tocilizumab treatment (N = 9). Allograft biopsy specimens were obtained 1 year after tocilizumab treatment and compared with pretocilizumab chronic active antibody-mediated rejection biopsy specimens in nine patients. Significant reductions in g plus ptc scores and C4d deposition were seen with tocilizumab treatment. Other parameters were stable. TG, transplant glomerulopathy; IF/TA, Interstitial fibrosis/tubular atrophy.

TABLE 1.

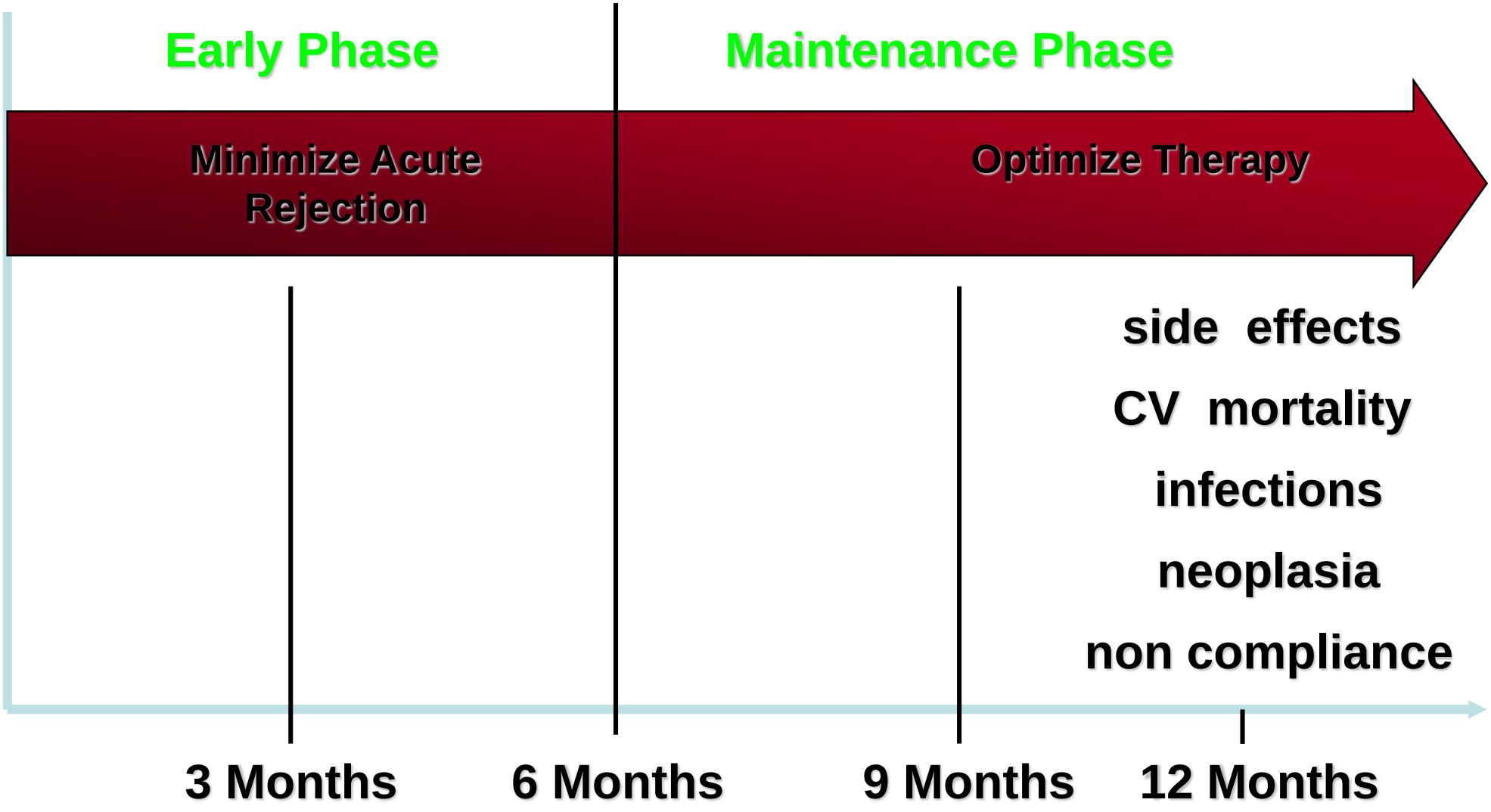
Application of nanotechnology in transplantation

Applications in transplantation	Platforms	Description
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.

Metabolic toxicities of immunosuppressive drugs

Complication	CsA	Tac	Ster	AZA	SRL/ EVL	MMF
Nephrotoxicity	+	+	-	-	-	-
Hypertension	++	+	+	-	-	-
Hyperlipidaemia	++	+	+	-	+++	-
Diabetes	+	++	++	-	+	-
Haematologic toxicity	-	-	-	+	+	+

Emerging Clinical Objectives



Conclusions

- **There are no specific, effective and safe new immunosuppressive drugs**
- **CNI remain fundamental IS drugs**
- **GS and CNI sparing strategies at *de novo* renal allograft recipients require induction therapy with mono or policlonal anty-T antibodies**
- **GS or CNI withdrawal at early period after kTx is combined with increased risk of AR, the impact of these strategies on long-term results is unknown?**
- **AMR does not respond to conventional therapy with GS, and needs an alternative therapy**
- **Individualization of immunosuppressive therapy provides improvement of patient and graft survival**
- **Future:**
  - **More detailed TDM monitoring**
  - **Tolerogenic immunosuppression**