Immunosuppression protocol

Dr. E. Nemati

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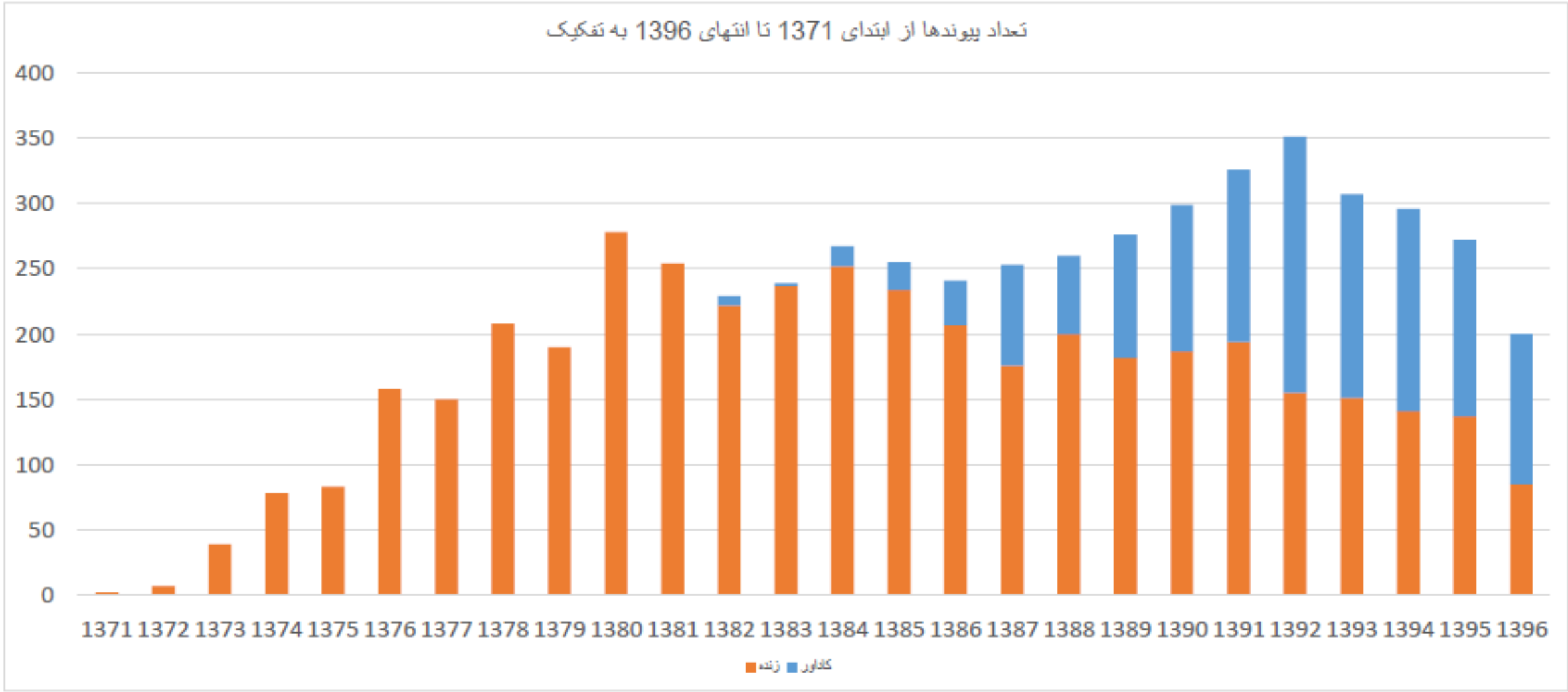
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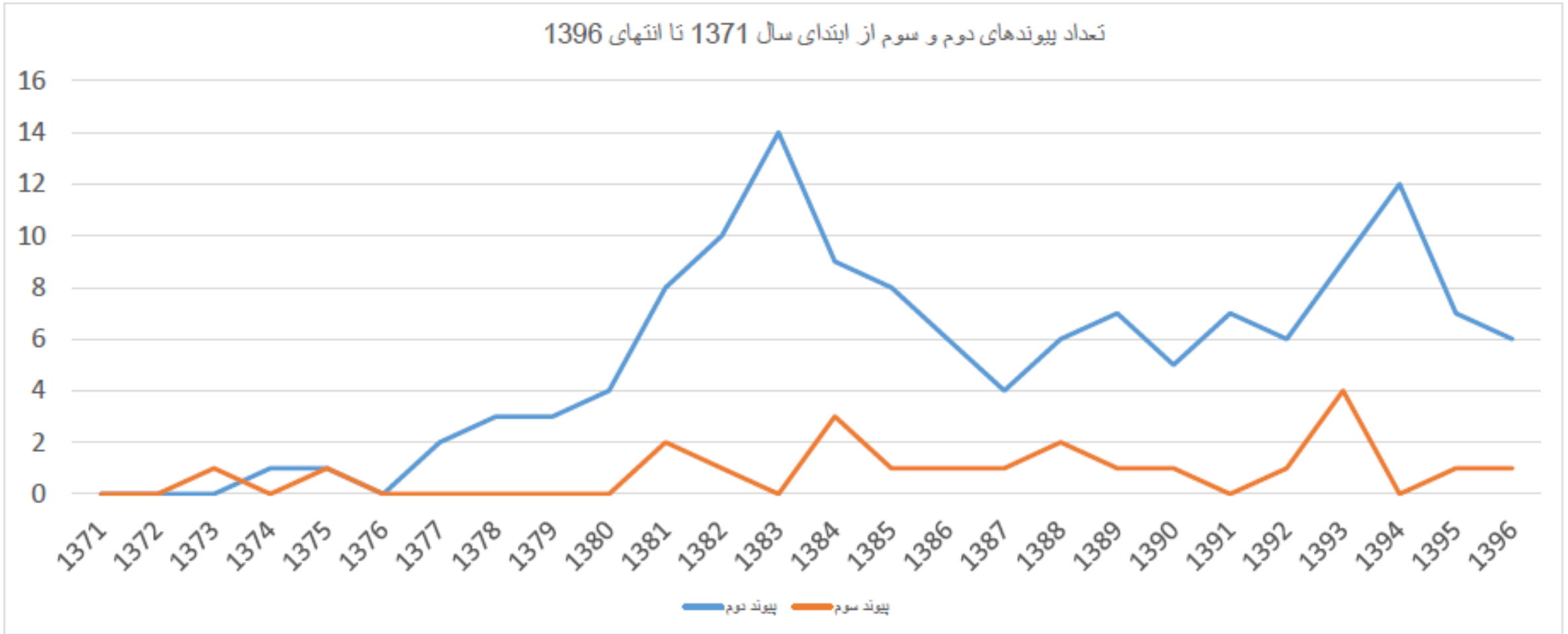
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Induction agents	Maintenance agents	Rescue agents
Polyclonal and monoclonal antibodies: ATG OKT3 Alemtuzumab Rituximab	Calcineurin inhibitors: Cyclosporine Tacrolimus	Mild to moderate cellular rejection: Corticosteroids
Interleukin-2 receptor antagonists: Basiliximab Daclizumab	Anti-metabolites: Azathioprine Mycophenolate mofetil	Moderate to severe cellular rejection: Polyclonal and monoclonal antibodies: ATG OKT3
Methylprednisolone	m-TOR inhibitors: Sirolimus Everolimus	Acute antibody-mediated rejection: Immunoglobulins Rituximab Bortezomib Eculizumab
	Newer agents: Co-stimulation blocker: Belatacept Protein kinase C inhibitor: Sotrastaurin JAK 3 inhibitor: Tofacitinib	

Classification of immunosuppressive agents according to clinical applications.

Induction Therapy

Definition

- Any potent immunosuppressive agent administered in the perioperative period to prevent immunologicaly mediated causes of graft loss ,or to modulate the response of effector-cells to the presence of antigens

Immunological Risk	Principles of risk stratification
Low	The absence of donor directed sensitization of HLA
Intermediate	Absence of historic DSA or presence of low level of DSA at the time of transplantation
High	Presence of high levels of circulating antibodies specific for mismatched donor HLA present at the time of transplantation

The process of stratifying of immunological risk of a patient into low, intermediate or high risk category.

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High risk characteristics (for acute rejection) in renal transplantation
• Young recipient age • Older donor age • Re-transplantation • Extended criteria donors • Deceased donors after cardiac death • Poor HLA match • Prolonger cold ischaemia • Preformed donor specific antibodies • Delayed graft function • African Americans

http://dx.doi.org/10.17352/acn.000024

Classification of induction agents

- Broadly fall into one of the following three categories:

1. Polyclonal antibody preparations
2. Monoclonal antibodies (MAbs),
3. Fusion proteins (engineered glycoprotein receptor-antibody hybrids).

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Depleting Antibodies	Polyclonal antibody: Horse or Rabbit ATG
	Mouse Monoclonal anti-CD3 antibody (Muromonab D3)
	Humanized Monoclonal anti-CD52 antibody (Alemtuzumab)
	Chimeric B cell depleting Monoclonal anti-CD20 antibody (Rituximab)
Non-depleting antibodies	Humanized Monoclonal anti-CD25antibody (Daclizumab)
	Chimeric Monoclonal anti-CD25antibody (Basiliximab)

Classification of ‘depleting’ antibodies and ‘non-depleting’ antibodies.

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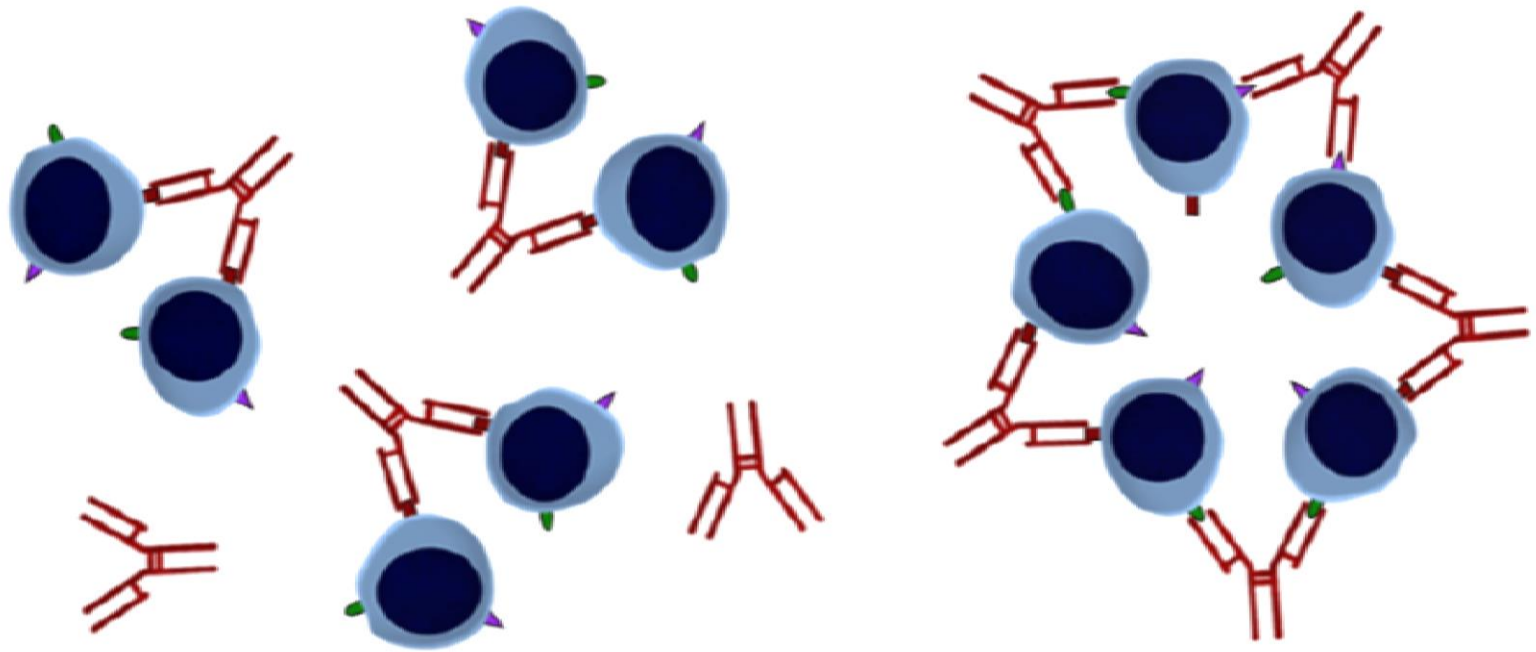
Characteristics of T cell depleting/ non-depleting induction agents.	
T cell depleting agents	**T cell non-depleting agents**
Causes actual lysis of T cells and their destruction	Inhibits the T cell activation pathway without their actual lysis
	Cytokine release does not occur and thereby minimal adverse
Cell lysis results in the release of cytokines and associated adverse reactions	reactions
Higher potency	Lower potency
	To be used in low immunological risk recipients
To be used in high immunological risk recipients	
Profound immunosuppression allows delayed introduction of CNI	CNI cannot be delayed
Higher incidence of infection and post-transplant malignancy	No significant increase in risk of infection or malignancy

http://dx.doi.org/10.17352/acn.000024

The commonly used induction agents.

Agent	Monoclonal/ polyclonal	Mechanism of action	Duration of effects	Adverse effect profile
Basiliximab	mAb	IL-2RA Binds to CD25 in activated T cells	Several weeks	No cytokine release effects No proven increase in incidence of infection / malignancy Rare hypersensitivity reactions (<1%)
rATG	pAb	Widespread inactivation and destruction of T cells	Months to years	Massive cytokine release effects Serum sickness like disease Thrombocytopaenia Infusion reactions
Alemtuzumab	mAb	Binds to CD52 on naïve T cells, some B cells, macrophages and natural killer cells	Months to years	Cytokine release effects Bone marrow suppression with pancytopaenia Infusion reaction

http://dx.doi.org/10.17352/acn.000024



Monoclonal versus Polyclonal Antibodies. Monoclonal antibodies are specific and bind a single antigen as shown on the left in the figure. Polyclonal antibodies are non-specific and bind multiple antigens as shown on the right in the figure.

Afaneh et al. J Transplant Technol Res 2011, S:4
http://dx.doi.org/10.4172/2161-0991.S4-001

Dosing schedule for induction

- They had following conclusions from their study:
- 1. The ultra-low total dose of 1.5mg/kg of r-ATG results in depletion of peripheral T and NK cells for at least one week.
- 2. A total dose of 3 mg/kg rTAG results in significantly lower T cells for one month, however at one-year the T cell count recovers to baseline values.
- 3. The T cell depleting effect of a total dose of 6 mg/kg of rATG lasts for almost one year.
- 4. The effect on B cell remains variable depending on the batch-to batch variability in the presence of B cell specific antibodies.

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Side-effect	Percentage
Fever	63%
Chills	57%
Headache	40%
Nausea	37%
Diarrhea	37%
Malaise	13%
Dizziness	9%
Pain	46%

Percentages of side effects associated with rATG.

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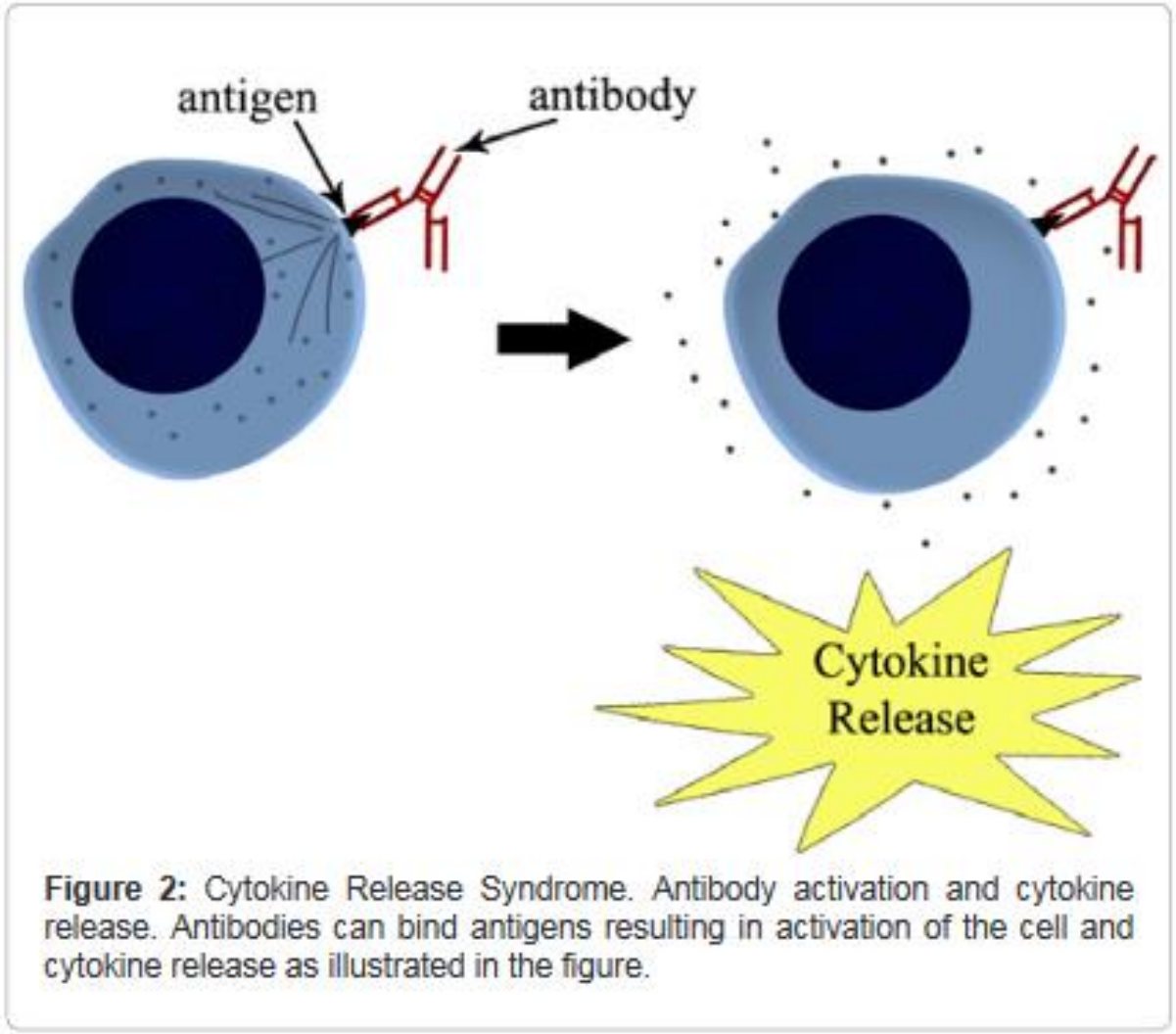

Figure 2: Cytokine Release Syndrome. Antibody activation and cytokine release. Antibodies can bind antigens resulting in activation of the cell and cytokine release as illustrated in the figure.

Afaneh et al
J Transplant Technol Res 2011, S:4
http://dx.doi.org/10.4172/2161-0991.
S4-001

MAbs	Origin	Target protein
Muromonab (OKT3)	Murine	Anti-CD3
Daclizumab	Humanized	Anti-CD25 IgG1
Basiliximab	Chimeric mouse-human	Anti-CD25 IgG1
Alemtuzumab	Humanized	Anti-CD52
Rituximab	Chimeric	Anti-CD20

Classification of monoclonal antibodies based on the CD nomenclature.

Basiliximab

The main advantages of IL-2 receptor antagonist over rATG are:

- 1. These agents have highly favorable safety profile .
- 2. Therapy is not associated with cytokine release syndrome or serum sickness.
- 3. No increase in infectious complications or wound healing issues has been reported in clinical studies.
- 4. PTLD risk is more or less similar to no induction agent used
- 5. These agents have fixed dose, body-weight independent schedule so ease of administration.

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Basiliximab

- The disadvantages over rATG are as follows:

1. These agents have only a modest efficacy and cannot be used as rescue agents.
2. IL-2 receptor blocker induction is not that strong that it would allow CNI mono-therapy or CNI withdrawal/avoidance.

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Role of induction strategies in low-risk candidates

- A transplant clinician has three possible induction strategies in low-risk recipients:
- a. No Induction
- b. Induction with rATG
- c. Basiliximab induction

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Conclusions

- Low-risk patients, receiving triple immunosuppression (CNI, anti-proliferative agent and steroids) do not need ‘routine’ induction by antibody preparations.

- The patients in whom late initiation of CNI or early withdrawal of steroids is required such as those transplanted with kidney from extended criteria organ donors, either Campath or rATG induction is safe and efficacious.

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Considerations in Choosing a Maintenance Regimen

- ***There are several important factors to consider when choosing a maintenance immunosuppressive regimen for a particular patient.***
- The patient factor includes the immunologic risk,
- clinical characteristics and comorbidities.
- The medication factor may include the drug efficacy, specific side effect and financial cost.
- The ideal protocol should not only effectively prevent graft rejection (both acute and chronic), but also be affordable and tolerable, which can collectively provide better quality of life as well as superior graft and patient survival.

http://dx.doi.org/10.4236/ojots.2013.32005

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Classification of immunosuppressive agents according to clinical applications.

OVERVIEW OF OUR APPROACH TO INITIAL MAINTENANCE THERAPY

- maintenance immunosuppressive therapy is given to practically all recipients of renal allografts.

- Our approach — We and most transplant centers use a maintenance regimen consisting of triple immunosuppression therapy with the following agents:
- ●A calcineurin inhibitor (cyclosporine or tacrolimus).
- ●An antimetabolite (azathioprine, mycophenolate mofetil [MMF], or enteric-coated mycophenolate sodium [EC-MPS]).
- ●Prednisone.

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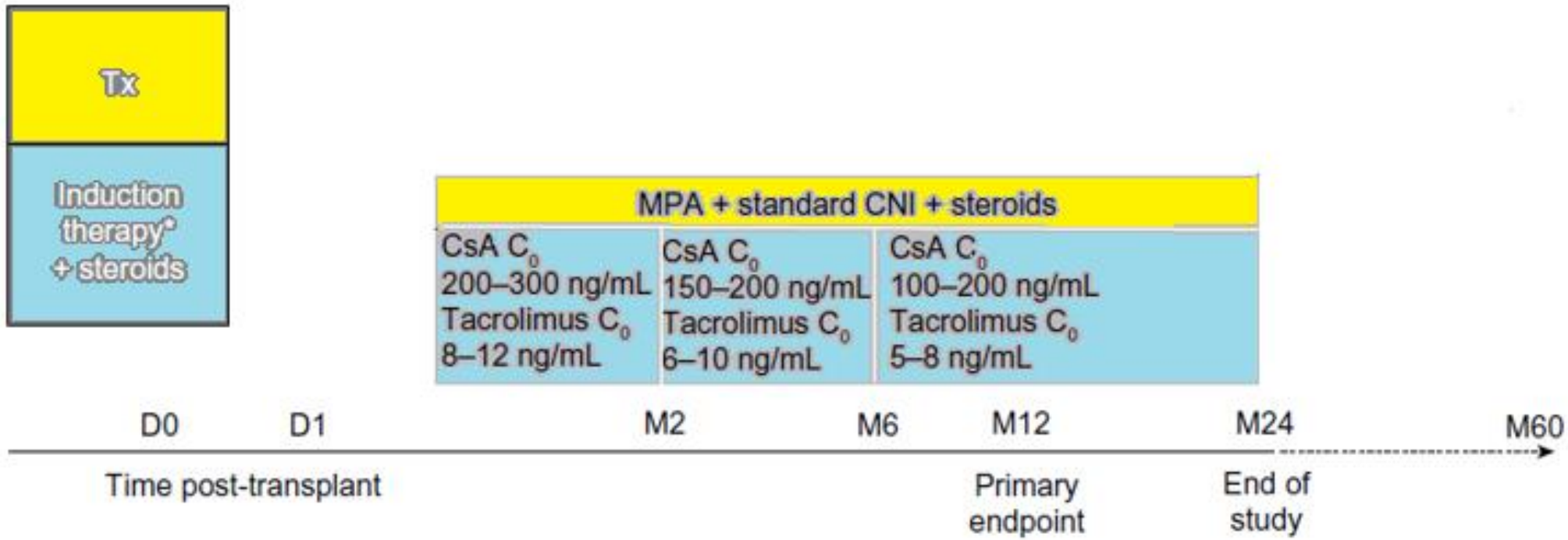


This article was published in the following Dove Press journal:
Open Access Journal of Clinical Trials
10 June 2014

Steroids

- Steroids are effective in preventing acute rejection.
- o 500mg iv given at induction
- Prednisolone

❑o 20mg from day 1

- At end of week 2, reduce prednisolone to 15mg/day
- At end of week 4, reduce prednisolone to 12.5mg/day
- At end of week 6, reduce prednisolone to 10mg/day
- From week 8 to week 12, reduce prednisolone down to a maintenance dose of a minimum of 5-7.5 mg/day, unless reason not to.

Kidney Transplant Guidelines v8.3/August 2016

Steroid withdrawal

- ***the KDOQI work group agreed that steroid therapy could be discontinued in low-risk patients after induction therapy .***

Azathioprine

- Azathioprine is metabolised in liver by TPMT to 6-MP , the active metabolite.
- ***inhibiting gene replication and T cell activation.***

DOSE AND ADMINISTRATION

- a maintenance adult dose of approximately 1.5 mg/kg/day PO is given once daily.
- Dosages are adjusted according to the white blood cell count.

Azathioprine

- ***Gradually azathioprine has been replaced with MMF in modern immunosuppressive protocols, but used during pregnancy due to reduced association with fetal malformations.***
- ***The cost differential between MMF and azathioprine was 10 fold to 15 fold***

Mycophenolate mofetil (MMF)

- ***MMF has been used extensively in all organ transplant recipients due to its good safety profile, efficacy, and ease of its administration without need of mandatory monitoring.***
- blocks both T and B lymphocyte proliferation .

Most Common Mycophenolic Acid Adverse Drug Reactions

Area of Affect	Adverse Effect
Gastrointestinal	Constipation** Diarrhea*refer to Management of Post -Transplant Diarrhea, page 45 Dyspepsia Nausea** Vomiting* Abdominal pain*
General	Edema Pain** Fever*
Hematologic	Bone marrow suppression Anemia*** Leukopenia**refer to Management of Post -Transplant Leukopenia, page 46
Infectious	Sepsis* Opportunistic (CMV) Urinary tract infection**
Nervous System Disorder	Insomnia* Tremor Headache

Mycophenolate mofetil (MMF)

- ***The use of MMF has allowed reduction of CNI exposure after 3 months***
- ***leading to improved creatinine clearance, uric acid, blood pressure and triglyceride values .***

KDIGO Recommendations

- We suggest that mycophenolate be the first-line antiproliferative agent.

Cyclosporine

- Cyclosporine was isolated in 1969 .
- Clinical trials of cyclosporine in renal transplantation began in Cambridge in 1978 and cyclosporine was introduced into immunosuppression regimen protocols world-wide in 1982.
- Blockade of IL2 gene transcription leads to failure of T cell clonal expansion and differentiation of precursor to mature cytotoxic T cells.

Cyclosporine

- trough level (C0) remains the standard despite inherent poor correlation with the outcomes.

- ***Evidence shows that the monitoring of cyclosporine at the (C2) is the most accurate single time point for assessment of cyclosporine absorption and immunosuppressive effect.***

Cyclosporine

- *that dosing of cyclosporine based on C2 levels (>1500 ng/mL in first 2 weeks after RT) reduced acute rejection significantly.*

Target Cyclosporine Blood Concentrations for Solid Organ Transplant Recipients

Time Post Transplant (Months)	Cyclosporine Trough Concentration (ng/mL) Tandem Mass Spectrometry Assay	Cyclosporine C_2 Concentration (ng/mL) Tandem Mass Spectrometry Assay
ADULT Kidney and Kidney Pancreas Transplant Recipients (Oct 2014)		
Less than 1	300 to 350	1300
1 to 2	250 to 300	1100
3 to 6	150 to 250	800 to 900
7 to 12	125 to 200	700
Greater than 12	75 to 125	450-600
PEDIATRIC Kidney Transplant* Recipients (Oct 2014)		
Less than 1	200 to 250	Not used
1 to 2	150 to 200	Not used
2 to 3	100 to 150	Not used
Greater than 3	80 to 100	Not used
as per Dr. Matsell November 1 2012		
ADULT Liver Transplant Recipients (Dec 2014)		
0 to 3	250 to 275	750 **
3 to 6	200 to 250	600 **
6 to 9	150 to 200	450 **
9 to 12	125 to 150	450 **
Greater than 12	100 to 125	450 **
** Cyclosporine C_2 is not routinely used in liver transplant recipients		
ADULT Lung Transplant Recipients (Nov 2014)		

Tacrolimus

- tacrolimus is a CNI, which was introduced in 1987. and was found to be 100 times more potent than cyclosporine.

- Tacrolimus binds to FK binding protein, leading to inhibition of IL-2 gene transcription and T-cell activation.

Target Tacrolimus Blood Concentrations for Solid Organ Transplant Recipients

Time Post-Transplant (Months)	Tacrolimus Trough Blood Concentration (ng/mL) 12 hours Post-Dose Tandem Mass Spectrometry Assay
ADULT Kidney and Kidney/Pancreas Transplant Recipients (Oct 2014)	
Less than 1	8 to 12
1 to 3	6 to 9
Greater than 3	4 to 8
PEDIATRIC Kidney Transplant Recipients (Oct 2014)	
Month 1	10 to 12
Month 2 and 3	8 to 10
Month 4, 5 and 6	6 to 8
After Month 6	4 to 6

❖*Over the last two decades, tacrolimus has gradually replaced cyclosporine because of superior results yielded by it.*

Tacrolimus

- *compared the efficacy and safety of tacrolimus with that of Sandimmune cyclosporine.*
- *At 1 year,*
- *there was significantly low incidence of acute rejection in tacrolimus group (30.7% vs. 46.4%; P=0.001), low incidence of moderate-to-severe rejection (10.8% vs. 26.5%).*

tacrolimus

- The incidence of post-transplant diabetes mellitus (PTDM) was 19.9% in the tacrolimus group and 4.0% in the cyclosporine group (P<0.001), and was reversible in some patient.

Target levels for calcineurin inhibitors

- ***In patients who receive rATG for induction therapy:***
- •7 to 10 ng/mL for the first month after transplantation
- •3 to 7 ng/mL for subsequent months

- ●***In patients who do not receive ATG for induction therapy:***
- •8 to 10 ng/mL for months 1 to 3 after transplantation
- •3 to 7 ng/mL for subsequent months

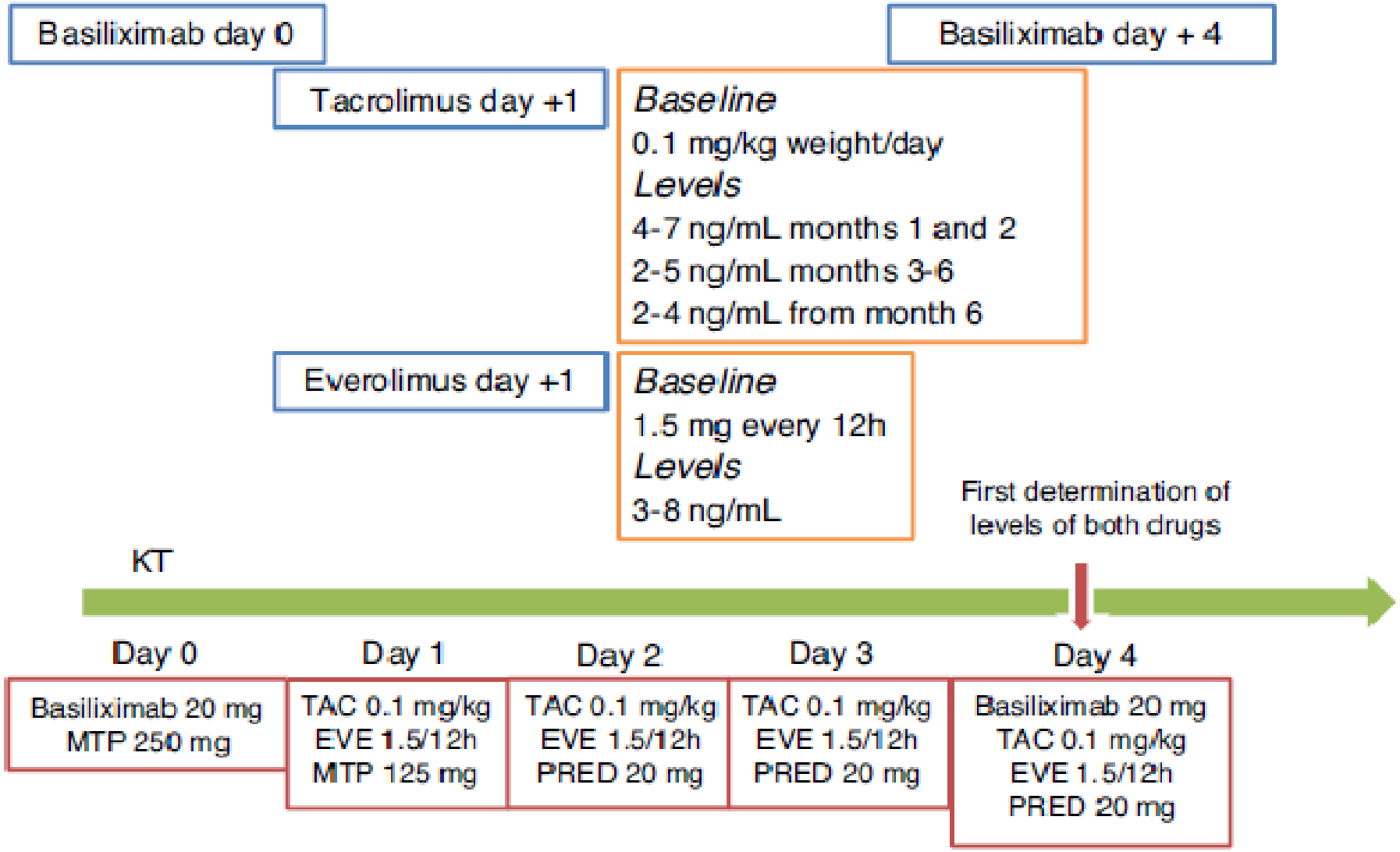
- ***cyclosporine, C0 target levels are the following:***
- ●200 to 300 ng/mL in months 1 to 3 after transplantation
- ●50 to 150 ng/mL for subsequent months
- ***Our C2 target levels are the following:***
- ●800 to 1000 ng/mL in months 1 to 3 after transplantation
- ●400 to 600 ng/mL for subsequent months

nonrenal toxicity with tacrolimus as compared with cyclosporine

- ●More prominent neurologic side effects such as tremor and headache
- ●More frequent incidence of NODAT
- ●More frequent diarrhea, dyspepsia, and vomiting
- ●More frequent alopecia
- ●Less frequent hirsutism, gingival hyperplasia, and hypertension
- In addition, tacrolimus but not cyclosporine has rarely been reported to induce a hypertrophic cardiomyopathy and severe neutropenia.

Lesions associated with calcineurin inhibitor use

- Acute CNI nephrotoxicity
- Acute arteriolopathy renal dysfunction without histological alterations
- Tubular vacuolization (isometric)
- Thrombotic microangiopathy (TMA)
- Chronic CNI nephrotoxicity Interstitial fibrosis and tubular atrophy (typically striped)
- Medial arteriolar hyalinosis
- Global glomerulosclerosis Pre-existing donor injury, aging, chronic glomerular ischemia.
- Focal segmental glomerulosclerosis (FSGS)
- Tubular microcalcifications



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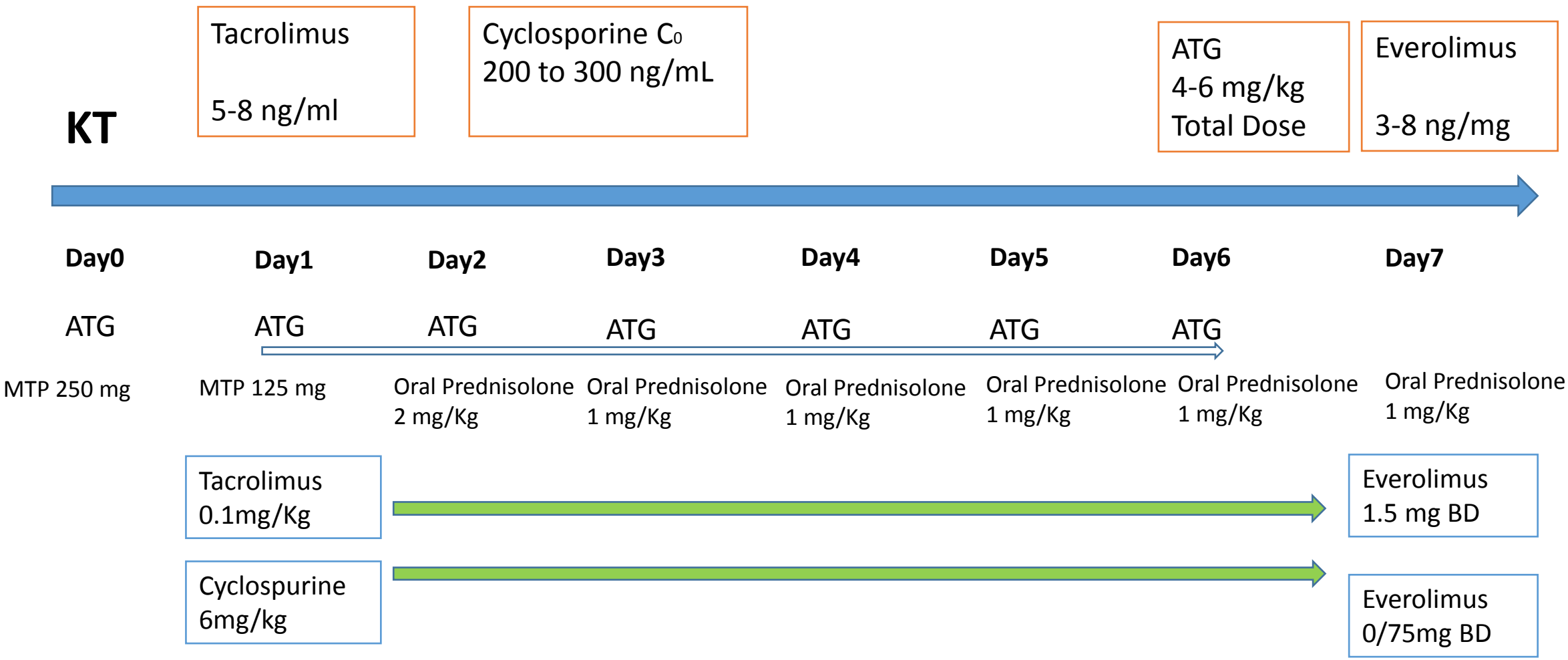
KT
Tacrolimus
5-8 ng/ml
Cyclosporine C0
200 to 300 ng/mL
ATG
4-6 mg/kg
Total Dose
Everolimus
3-8 ng/mg
Day0
Day1
Day2
Day3
Day4
Day5
Day6
Day7
ATG
ATG
ATG
ATG
ATG
ATG
MTP 250 mg
MTP 125 mg
Oral Prednisolone 2 mg/Kg
Oral Prednisolone 1 mg/Kg
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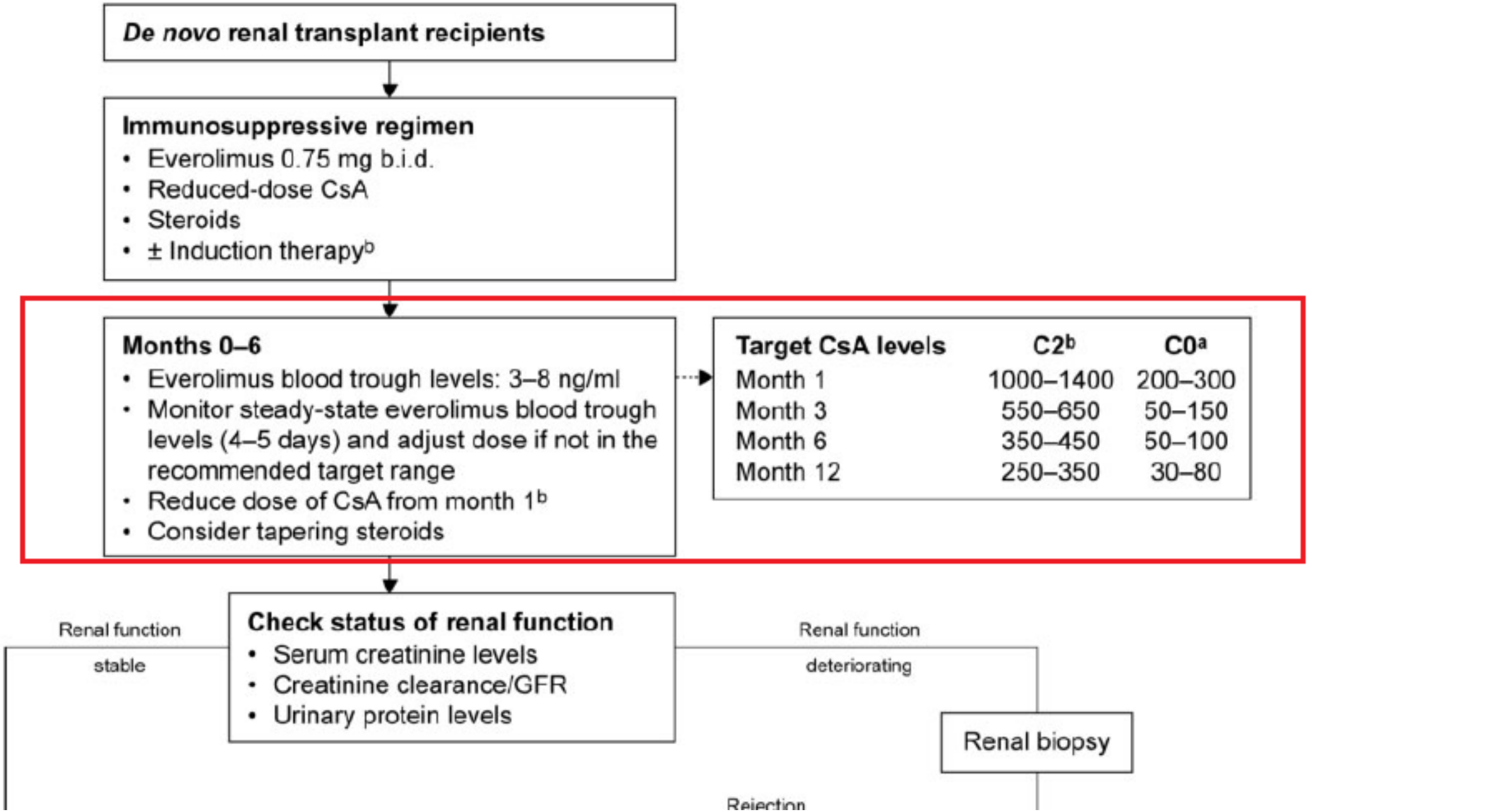
Oral Prednisolone 1 mg/Kg
Tacrolimus 0.1mg/Kg
Everolimus 1.5 mg BD
Cyclospurine 6mg/kg
Everolimus 0/75mg BD


De novo renal transplant recipients
Immunosuppressive regimen
• Everolimus 0.75 mg b.i.d.
• Reduced-dose CsA
• Steroids
• ± Induction therapy[b]
Months 0–6
• Everolimus blood trough levels: 3–8 ng/ml
• Monitor steady-state everolimus blood trough levels (4–5 days) and adjust dose if not in the recommended target range
• Reduce dose of CsA from month 1[b]
• Consider tapering steroids
Target CsA levels | C2[b] | C0[a]
Month 1 | 1000–1400 | 200–300
Month 3 | 550–650 | 50–150
Month 6 | 350–450 | 50–100
Month 12 | 250–350 | 30–80
Check status of renal function
• Serum creatinine levels
• Creatinine clearance/GFR
• Urinary protein levels
Renal function stable
Renal function deteriorating
Renal biopsy
Rejection

immunosuppressive effect, mTOR inhibitors have a number of characteristics that make them attractive for the use in KT:

a) **reduction of glomerular hypertrophy and pro-inflammatory and pro-fibrotic cytokines,**
b) Reduction of angiogenesis;
c) Reduction of tumour growth and in de novo neoplasms;
d) Cardioprotective effects;
e) Reduction of viral infections

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Optimizing everolimus exposure when combined with calcineurin inhibitors in solid organ transplantation

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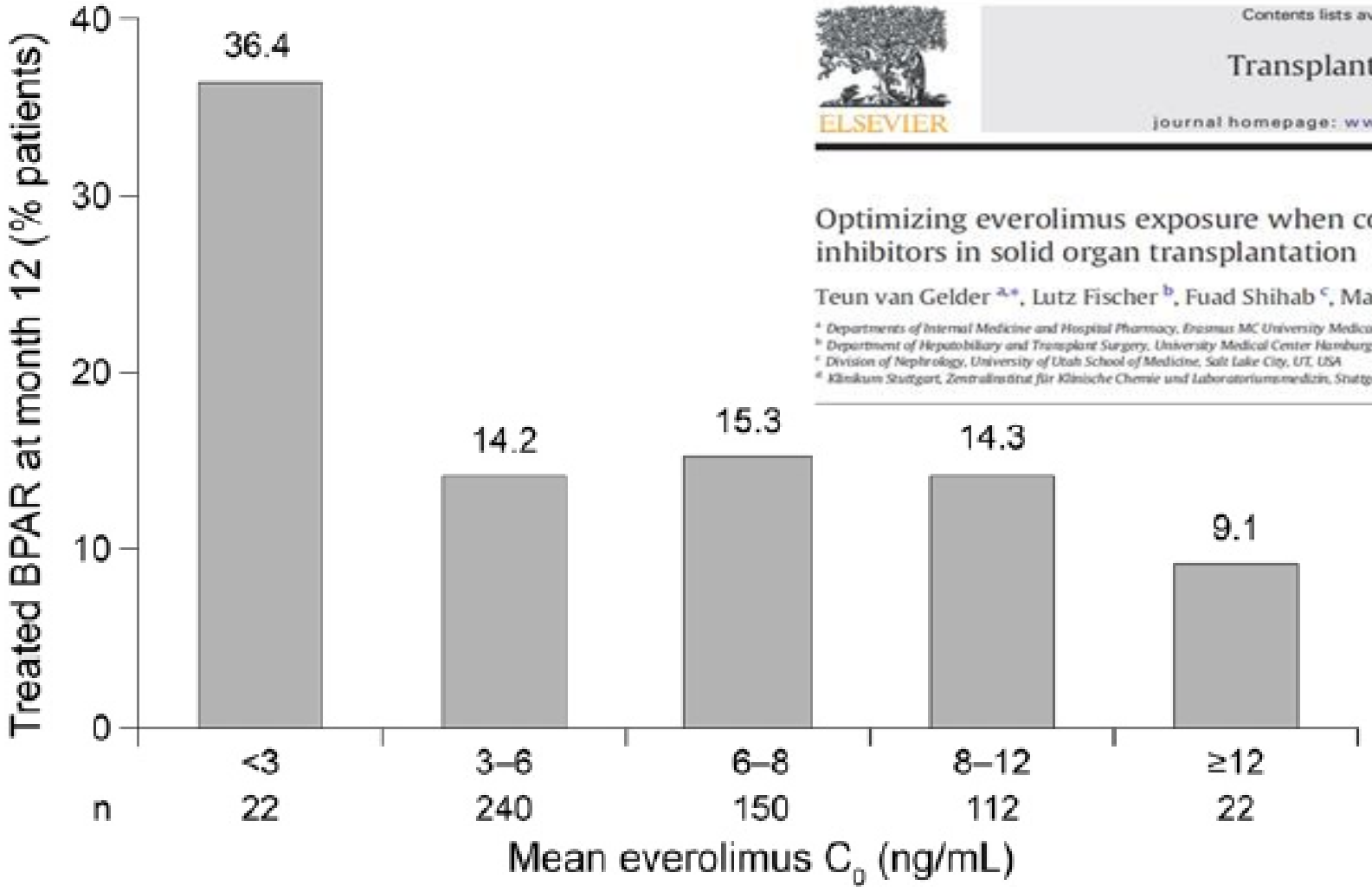
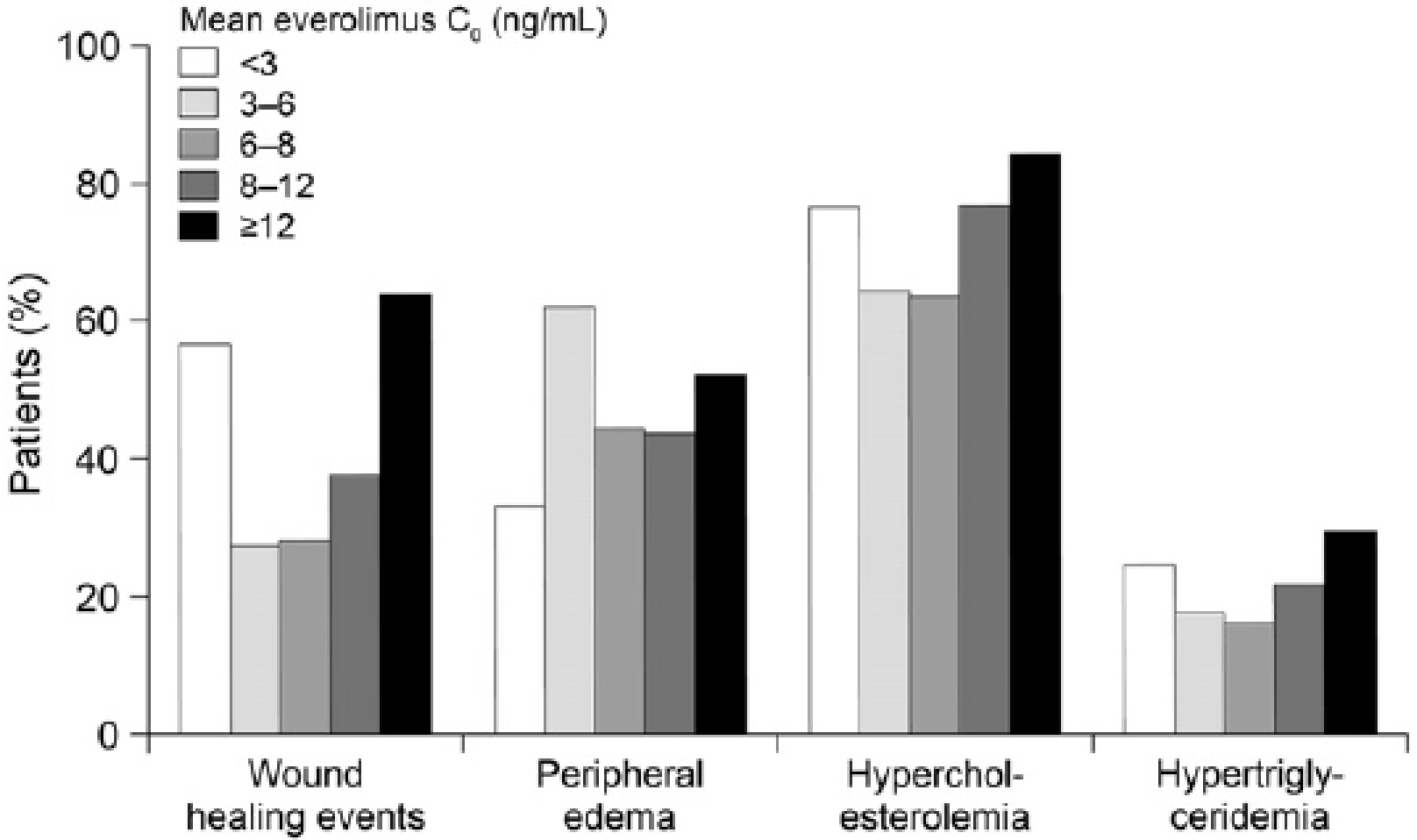


Incidence of biopsy-proven acute rejection (BPAR) according to everolimus mean trough concentration (C_0) in de novo kidney transplant patients receiving everolimus with reduced-exposure cyclosporine

T. van Gelder et al. / Transplantation Reviews xxx (2017) xxx–xxx



Incidence of selected adverse events according to everolimus mean trough concentration (C_0) at month 12 after kidney transplantation in 556 de novo kidney transplant patients receiving everolimus with reduced-exposure cyclosporine

T. van Gelder et al. / Transplantation Reviews xxx (2017) xxx–xxx

Clinical factors influencing everolimus trough concentration (C_0).

Factor	Effect on everolimus C_0
Hepatic dysfunction	⇧⇧⇧
CYP3A4/ABCB1 inhibitors	⇧⇧
CYP3A4/ABCB1 inducers	⇩⇩
CNI therapy	
CsA dose increase	⇧⇧
CsA dose decrease	⇩⇩
Switch from CsA to tacrolimus	⇩⇩⇩
Switch to dispersible tablet form	⇩
Non-adherence	⇩⇩⇩
High-dose steroid therapy	⇩?
Immunoassay cross-reactivity	⇧

T. van Gelder et al. / Transplantation Reviews xxx (2017) xxx–xxx

Factors that appeared to predict response included:

- Proteinuria
- Histological grade of allograft nephropathy
- Grade of vascular intimal thickening
- Number of acute rejections before conversion (all $P<0.05$).

Table 4 – Relative contraindications to the use of everolimus in *de novo* KT and reasons for advising against it.

Relative contraindication	Reason
Interstitial lung disease or severe chronic obstructive pulmonary disease	To avoid exposure to the drug in recipients susceptible to suffering mTOR-inhibitor-associated pneumonitis
Obesity with a body mass index greater than 35 kg/m^2	To avoid exposure to the drug in subjects with a greater tendency to suffer surgical wound complications and lymphoceles due to their obesity
Primary focal segmental glomerulosclerosis as underlying nephropathy	Potential of the drug to cause proteinuria by podocyte damage and development of focal segmental sclerosis
Atypical haemolytic–uraemic syndrome	Since the aetiopathogenic association of mycophenolate with thrombotic microangiopathy syndromes has not been described, its combination with CNIs is considered more advisable in *de novo* kidney transplantation
Complex vascular surgeries (*e.g.* renal artery anastomosis to a Gore-Tex iliac stent)	To avoid high risk of suture dehiscence
Need for use of high doses and elevated levels of CNI, such as for example, those with a very high immunological risk	To avoid nephrotoxicity with maximisation of the CNI

CNI: calcineurin inhibitor.

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Delayed graft function

- Early studies with sirolimus did not show a higher frequency of DGF; even in the Symphony study, the sirolimus group presented the lowest DGF (21.1% vs. 35.7% in the tacrolimus/MMF group).

- No clinical study comparing CNI-everolimus and CNI-MPA has shown differences in the onset of DGF.

Table 2 – Main complications considered to be a impediment to *de novo* use of an mTOR inhibitor and their incidence in various clinical trials.

	A2309 (CsA) EVE vs. MPA[16,17]		US09 (tacrolimus)[15]		ASSET (tacrolimus)[14]		Symphony[2,56]	
	EVE (1.5 mg/d)	MPA	EVE (1.5 mg/d) + low tacrolimus	EVE (1.5 mg/d) + standard tacrolimus	EVE (1.5 mg/d) + very low tacrolimus	EVE (1.5 mg/d) + low tacrolimus	Tacrolimus-MMF	Sirolimus-MMF
Delayed graft function	10.2	9.2	0	2	NA	NA	35.7	21.1
Lymphocele	6.6	5.1	4.1	2.3	7.3	10.9	4	11.6
Surgical wound	1.8	1.1	4.1	2.3	18.3	14.3	2.5	2.4
Incisional hernia	1.5	1.5	2	4.7	3.7	1.7	NA	NA
Acute rejection	16.2	17	14	14	18.7	7.7	15.4	39

Data (%).
EVE: everolimus; MMF: mycophenolate mofetil; MPA: enteric-coated mycophenolic acid; NA: not available.

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Reduced Incidence of Cytomegalovirus Infection in Kidney Transplant Recipients Receiving Everolimus and Reduced Tacrolimus Doses

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diet in renal disease; MPS, mycophenolate sodium; mTORI, mammalian target of rapamycin inhibitors; r-ATG, rabbit antithymocyte globulin; TAC, tacrolimus

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Review Article

Everolimus and Malignancy after Solid Organ Transplantation: A Clinical Update

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- CNI therapy has been shown to increase the risk of malignancy after kidney , liver , and heart transplantation in a dose-dependent manner.
- CNI therapy or to specific CNI-related effects which promote oncogenesis, such as stimulation of transforming growth factor beta (TGF-β) and increased production of proangiogenic vascular endothelial growth factor (VEGF) .
- In contrast, the mammalian target of rapamycin (mTOR) inhibitor class exerts various anti oncogenic effects.

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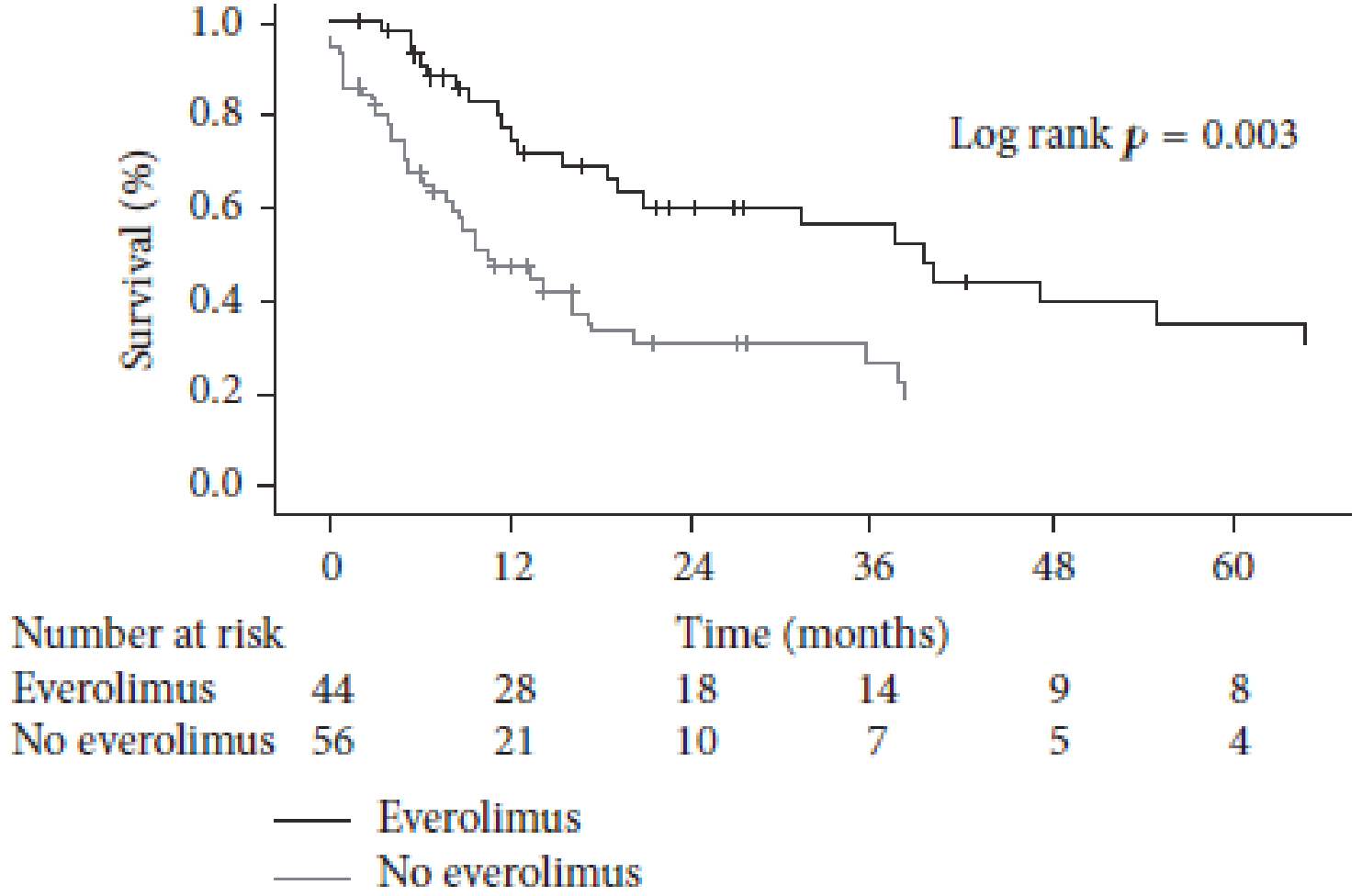

Survival after diagnosis of nonskin malignancy in 39 liver transplant patients according to treatment with everolimus or no everolimus.

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Improvement in the cardiovascular profile

The everolimus-CNI combination improves the cardiovascular profile through two mechanisms:

- 1) adequate minimization of the CNI allows better blood pressure control and a reduction in the number of anti-hypertensive agents,
- 2) a direct beneficial effect of everolimus on the atherosclerotic plaque, observed in animal models of transplantation and in heart transplants, in which there is a ***reduction in***:
- Allograft vasculopathy,
- Peripheral vascular disease
- Left ventricular hypertrophy.

PTDM

- In regimens with everolimus, the incidence of (PTDM) ranges between 11.5% and 14% if it is combined with CsA, or 12.8% and 24% if combined with tacrolimus, this similar to that observed in the Symphony study .
- There is no evidence that minimised CNI-everolimus regimen is associated with more frequent or more severe PTDM than with use of CNI-MPA regimens.

Table 3 – Incidence of the main adverse events classically related to mTOR inhibitors.

	A2309 (CsA) Eve vs. MPA[16,17]		US09 (tacrolimus)[15]		ASSET (tacrolimus)[14]		Symphony[2,56]	
	EVE (1.5 mg/d)	MPA	EVE (1.5 mg/d) + low tacrolimus	EVE (1.5 mg/d) + standard tacrolimus	EVE (1.5 mg/d) + very low tacrolimus	EVE (1.5 mg/d) + low tacrolimus	Tacrolimus-MMF	Sirolimus-MMF
Oedema (%)	2.6	1.4	9.3	10.2	9.2	10.9	12	32
Hyperlipidaemia (%)	21	16	10.2	9.3	26	21	9.9	15.8
Proteinuria [>0.5 g/24 h (%)]	9.1	7.3	0	2.3	7	11	5.3	5
Diabetes (%)	14	16	24	38	15.1	12.8	10.6	7.8

EVE: everolimus; MMF: mycophenolate mofetil; MPA: enteric-coated mycophenolic acid.

Management of adverse events

Dyslipidemia

One common adverse event occurring with sirolimus and everolimus treatment is hyperlipidemia, with increased serum cholesterol and triglyceride levels occurring in 30–50% of the patients .

- In renal-transplant recipients, ***sirolimus*** induces ***dose-dependent hyperlipidemia***, including
- hypertriglyceridemia,
- increased low-density lipoprotein (LDL)-cholesterol
- increased Apo lipoprotein B 100 and Apo lipoprotein C circulating levels.
- A similar increase in serum cholesterol and triglyceride levels has also been reported in renal transplant recipients receiving ***everolimus***.

Proteinuria

proteinuria may occur in patients who receive de novo sirolimus. Less data are available about everolimus,

The onset of abundant urinary protein excretion is of importance because ***proteinuria is a marker for the risk of progressive decline in renal function,and is an important predictor of renal dysfunction*** following conversion from a CNI- to a PSI-based regimen.

Development of proteinuria

- The mechanism by which mTOR inhibitors may cause proteinuria in the KT recipient is not well understood.
- They may produce proteinuria by inhibiting VEGF, which alters endothelial and podocyte function.
- The incidence of everolimus associated proteinuria reported in the Symphony study was 12% vs. 8% in the tacrolimus-MMF group.

Peripheral edema

The mechanism responsible for edema

- increased vascular permeability that may be related to an increase in prostacyclin and a decrease in VEGF.
- Current studies combining everolimus with CsA report an incidence of oedema between 2.6% and 32%.
- combination everolimus and tacrolimus, the incidence of oedema is 10%, similar to that reported in the Symphony study.
- ***After ruling out other causes of oedema, mTOR inhibitor dose adjustment is recommended and, if CsA is combined with everolimus,adjust CsA to the lowest dose, since CsA increases tissue exposure to everolimus.***

Anemia

- An increased incidence of microcytic anemia has been observed in studies with sirolimus compared with either CsA or MMF .
- in a 12 month comparative study of everolimus and MMF, the incidence of anemia was similar with both agents (29–34%).
- A dose reduction in PSI or MPA-based therapy may be sufficient to resolve anemia, although severe anemia should be treated with erythropoietin .

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ORIGINAL ARTICLE

Interstitial pneumonitis caused by everolimus: a case–cohort study in renal transplant recipients

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Wound healing

Due to the antiproliferative action of PSIs, concerns have been

raised over possible effects on tissue-regeneration processes.

the antiproliferative action of everolimus can reduce the healing of lymphatic channels that are divided during transplant surgery, which may lead to lymphatic leakage and the formation of a lymphocele.

Everolimus studies showed that the overall incidence and severity

of wound-healing-associated complications following renal transplantation were comparable for MMF- and everolimus-based immunosuppressive regimens.

Mouth ulcers

- Mouth ulcers appear to result of a ***direct toxic mechanism*** of mTOR inhibitors on the oral and nasal mucous membranes.
- They usually appear at the ***beginning of the therapy*** , approximately ***after one week of exposure***, and are usually ***dose-dependent.***
- ***the incidence is much lower*** if the drug is used de novo rather than in conversion.
- ***Ulcers usually begin to heal after the dose adjustment of the mTOR inhibitor or topical corticosteroid treatment.***

Table 1: Most common adverse events in mTOR-I-treated renal transplant recipients.

Adverse events	Rate of occurrence (%)	References
Pulmonary toxicity	2–11	[20, 21, 24, 33]
Hematopoietic adverse effects		
Anemia	13–58	[6, 36, 44–47, 50, 56, 57, 70, 72, 135, 147]
Leukopenia	5–39	[6, 45, 46, 56, 66, 117, 121, 147]
Thrombocytopenia	4–45	[6, 45–47, 56, 66, 70, 117, 118, 121, 122, 147]
Metabolic disorders		
Hyperlipidemia	8–87	[6, 45–47, 57, 66, 70–72, 115, 117, 118, 121, 135, 147]
Posttransplantation diabetes	3–33	[56, 70, 72, 78, 80, 115, 121, 138, 147]
Hypophosphatemia	15–20	[45, 46, 57]
Lymphedema	<5	[99–102]
Cardiovascular disease	1–6	[80, 100, 117, 122, 124, 128]
Hypertension	8–58	[46, 57, 70, 72, 115, 117, 121, 122, 135]
Cutaneous adverse effects		
Acne, folliculitis	9–25	[6, 57, 70, 116–118, 135, 147]
Stomatitis and mucous membrane disorders	9–64	[6, 118, 138, 147]
Edema	2–70	[6, 56, 57, 70, 121, 122, 135, 147]
Nail and hair pathologies	74	[116]
Gonadal complications	<5	[123–126]
Surgical wound complication	2–20	[56, 70, 72, 133–136]
Infections	2–60	[6, 72, 117, 122, 136]
Gastrointestinal complication	2–51	[6, 46, 47, 56, 57, 70, 72, 117, 118, 121, 135, 147]

Management of complications:

the timing to reduce the dose and when to discontinue the drug