



***Blending the use of immunosuppressive
therapy into real-life practice:
How to minimize infectious complications?***

Siriorn Watcharananan, M.D.

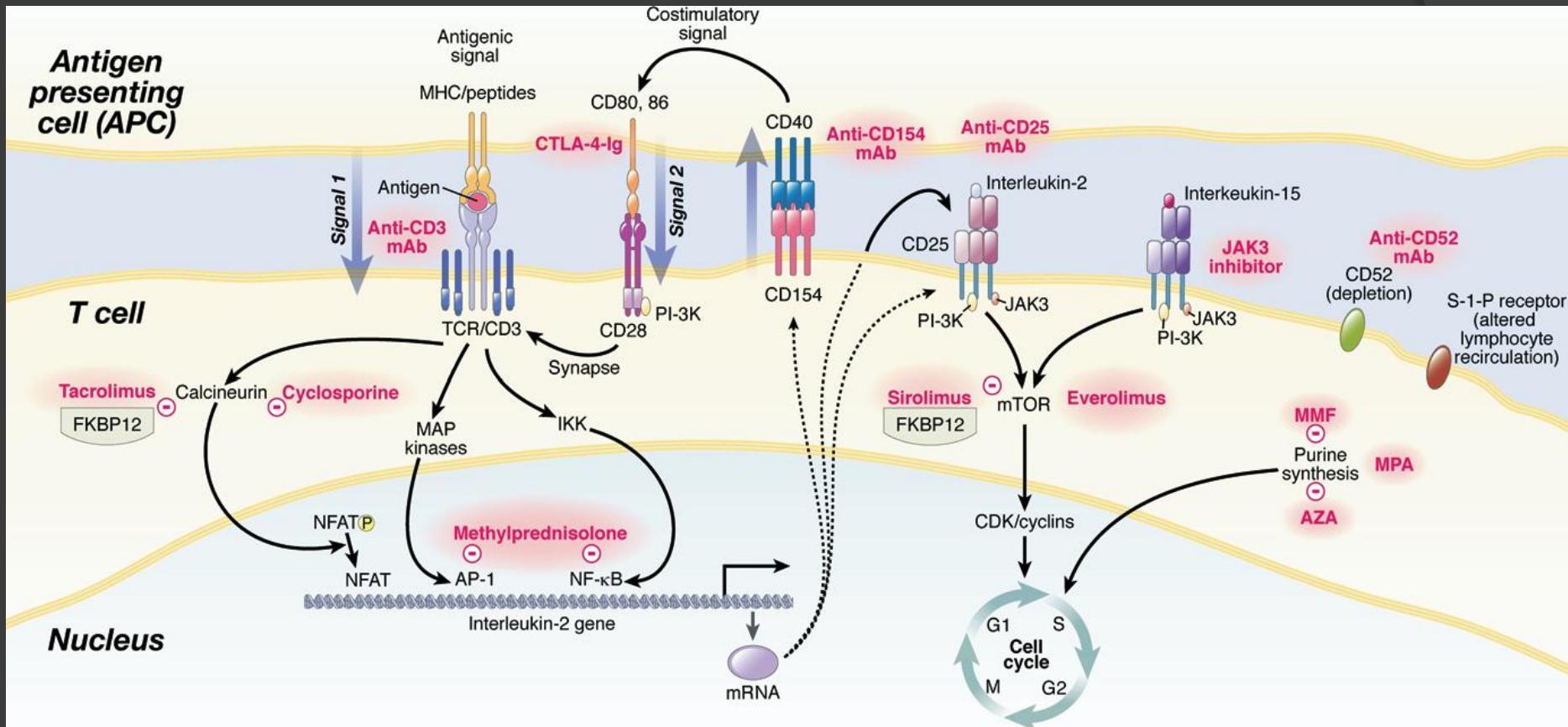
Assistant Professor

Division of Infectious Disease, Department of Medicine

Faculty of Medicine, Ramathibodi Hospital

Mahidol University

Immunosuppressive Agents in Transplantation and Site of Action



Rosen HR, GASTROENTEROLOGY 2008;134:1789–1801

Key changes in the US Practice of Immunosuppression in SOTs

Induction

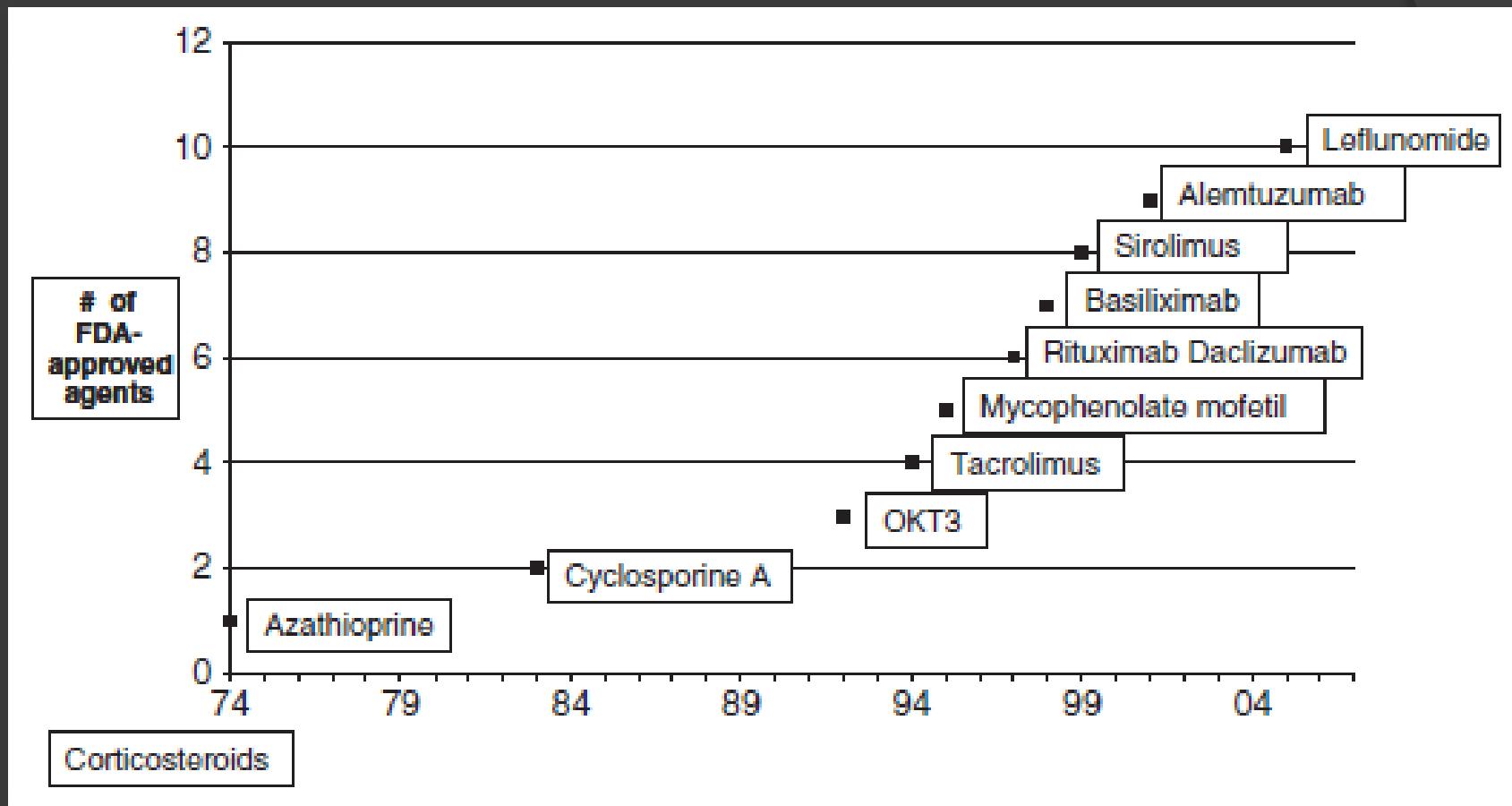
- The percentage of recipients with induction immunosuppression has increased throughout all transplanted organs, ranging from 20% to > 70%
- Anti-CD25-based therapies have reached a plateau
- Steady increase in use of depleting antibodies: thymoglobulin, alemtuzumab

Maintenance

- Mycophenolate mofetil/mycophenolic acid substituted for azathioprine
- Tacrolimus substituted for cyclosporine
- Since 2000, steady decrease in the use of corticosteroids

Mueller NJ, Transpl Infect Dis 2008;10:379-84

Timeline of US Food and Drug Administration (FDA)-approved agents used for immunosuppression in transplantation



Mueller NJ, Transpl Infect Dis 2008;10:379-84

Mycophenolate Mofetil

- A higher incidence of tissue-invasive CMV disease (but not asymptomatic CMV infection) has been documented in MMF-treated patients, particularly in those receiving 12 g of MMF per day
- Although the overall incidence of CMV disease was higher among renal transplant recipients who received azathioprine, CMV organ involvement occurred more frequently in patients who received MMF than in those who received azathioprine (58% vs. 18%; $P < .03$)

(Sarmiento JM, Clin Transplant 2000; 14:136–8)

- a higher incidence of CMV disease among KT patients who received 3 g of MMF per day, compared with patients who received smaller doses

(Transplantation 1996; 61:1029–37)

Calcineurin inhibitors

- “Fewer cytomegalovirus infections in tacrolimus, compared with cyclosporine A-containing regimens (Lancet 1994;343:423-8)
- “In the absence of induction therapy, the risk of developing PTLD was higher for KT recipients who received maintenance tacrolimus versus cyclosporine” (Am J Transpl 2004; 4: 87–93)
- Increase in the incidence of BK nephropathy following the use of novel, e.g. tacrolimus and MMF (Transplantation 1999; 67:918–922)
 - Higher risk in tacrolimus-combinations compared to cyclosporine or mTOR inhibitor-combinations (Am J Transpl 2009;9 (suppl 4):S136-46)

Impact of Immunosuppressive Agents on Major Infections after SOTs

Immunosuppressive agent	CMV	Other herpesviruses	HCV
Mycophenolate mofetil	Higher incidence of tissue-invasive CMV disease but not asymptomatic CMV infection [15]; potentiation of activity of ganciclovir against CMV [27, 28]	Higher rate of varicella-zoster virus infections [33]	Higher rate of acute cholestatic hepatitis due to HCV [34]; delayed allograft fibrosis due to HCV [39]
Rapamycin	No effect [62–66]	Higher rate of mucosal herpes simplex virus infections [65]	None reported
Monoclonal antibodies			
Basiliximab	No effect [90–92]	Lower rate of herpes simplex virus infections [91]	No data
Daclizumab	Lower incidence of CMV infection [96]	No effect [96–99]	No effect [100, 101]

Incidence of viral (primarily cytomegalovirus) infection lower in rapamycin as compared to mycophenolate mofetil

Hussain S. et al, Clin Infect Dis 2002;35:53–61

BKVAN and Type of Immunosuppression

	Patients with prior rejection	Prior anti-rejection		Immunosuppression at time of PAN diagnosis				Intervention and outcome (patients with stable function/ patients treated)		
		Steroids	ALG	CYC	TAC	AZA	MMF	SIR	Other	
Mackenzie et al 1978 ⁷⁸	1	1	0	0	0	1	0	0	1	red (1/1)
Mathur et al 1997 ⁷⁹	2	1	1	0	2	2	0	0	0	red (2/2)
Randhawa et al 1999 ⁴⁴	14	12	2	2	20	20	2	0	0	AR(4 /12), red (7/8) , no (0/2)
Howell et al 1999 ⁸⁰	2	2	1	5	1	0	6	0	1	AR+red (2/4), red (2/3)
Nickeleit et al. 2000 ⁸¹	9	8	3	0	8	0	9	0	0	AR (2/7), red (1/2)
Hurault de Ligny et al 2000 ⁷⁷	9	9	0	3	7	1	7	0	1	red (8/10)
Ahuja et al 2001 ⁸²	7	7	2	0	8	0	10	0	0	AR (0/10)
Barri et al 2001 ⁸³	6	6	1	1	7	0	8	0	0	AR+red (3/3), red (3/4)
Ramos et al 2002 ⁸⁰	8	8	1	6	61	2	65	0	1	AR+red (2/8), red (42/44), no (12/15)
Li et al 2002 ⁸⁴	na	na	na	0	6	0	3	3	0	AR (2/3), red (3/3)
Trofe et al 2002 ⁸⁵	5	5	0	0	9	1	7	1	0	red (10/10)
Trofe et al 2003 ⁸⁶	4	1	3	3	10	6	7	0	0	red(5/10)
Smith et al 2002 ⁸²	3	3	0	2	2	0	2	2	0	red (4/4)
Kang et al 2003 ⁸⁷	na	na	na	0	3	0	1	0	0	na
Rahaminov et al 2003 ⁸⁸	2	1	1	0	7	1	6	0	0	AR+red (6/7)
Buehrig et al 2003 ⁸⁷	5	3	4	0	18	0	16	1	0	red(11/18)
Mengel et al 2003 ⁸⁴	6	3	0	3	4	0	6	1	0	red(0/2)
Maiza et al 2002 ⁸⁹	2	2	na	1	1	na	1	0	0	AR+red (0/1) red (1/1)
Hirsch et al 2002 ⁷⁴	5	5	3	2	3	3	2	1	0	AR+red (4/4) red (1/1)

ret, retrospective; pro, prospective; n.a., not available; min, minimum; max, maximum; ALG, anti-lymphocyte globulin; CYC, cyclosporine; TAC, tacrolimus; AZA, azathioprine; MMF, mycophenolate, SIR, sirolimus; Pats, patients; AR, anti-rejection treatment; red, reduction of maintenance immunosuppression; no, no intervention.

Depleting Antibodies (e.g., ATG, OKT3, and alemtuzumab)

- Induction therapy with antithymocyte globulins is associated with a greater incidence of cytomegalovirus, Epstein-Barr virus, and BK polyomavirus infections, compared with therapy with interleukin (IL)-2a receptor antagonists
- The use of induction therapy in HCV-infected organ transplant recipients, especially in liver recipients, may increase HCV replication and accelerate progression to cirrhosis

Fishman J, et al, Clin Infect Dis 2009;48:772–86

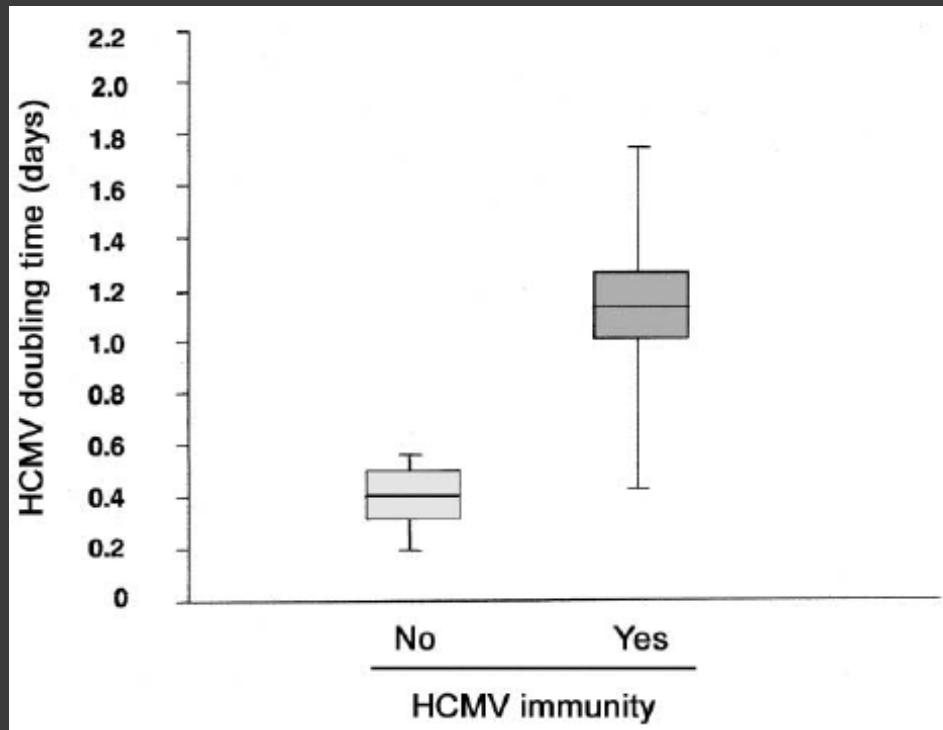


“Reduction of Immunosuppression is the Main Treatment of Transplant Related-Infection”



Cytomegalovirus as a model of Immunosuppression VS Control of the Infection Post Transplantation

CMV-Specific Host Defense in Normal Host



- Humoral response useful during viremia
- Cellular immunity key host defense
 - CD4+ T cells
 - Generation of antibody response
 - Stimulation of dendritic cells and subsequent cross-presentation of antigen
 - Primary, expansion, and maintenance of CD8+ CMV-specific CTL

Analysis of the CMV-specific CD4 T cells from long-term SOTs recipients

	Type of graft				p value of significance
	Controls n = 50	Kidney n = 68	Heart n = 14	Lung n = 24	
Age (years)	45.5 ± 16.8	52.7 ± 12.6	54.6 ± 10.3	48.9 ± 17.7	n.s.
CMV-specific CD4 T cells (%) median and range	1.22 (0.28–21.00)	1.48 (0.08–7.20)	0.90 (0.13–12.49)	0.60 (<0.08–1.98)	p = 0.0038
CMV specific CD4 T cells/ μ L Median and range	11.15 (0.19–22.30)†	8.21 (0.35–77.29)‡	2.31 (0.29–113.2)	2.19 (0.125–22.37)	p = 0.0002
Cyclosporine A (ng/mL) actual trough levels	n.a.	118 ± 35 n = 38	159 ± 35 n = 12	221 ± 54 n = 20	p < 0.0001
Tacrolimus (ng/ml) actual trough levels	n.a.	7.8 ± 3.9 n = 17	7.1 and 9.0 n = 7	12.5 ± 3.2 n = 4	p = 0.036

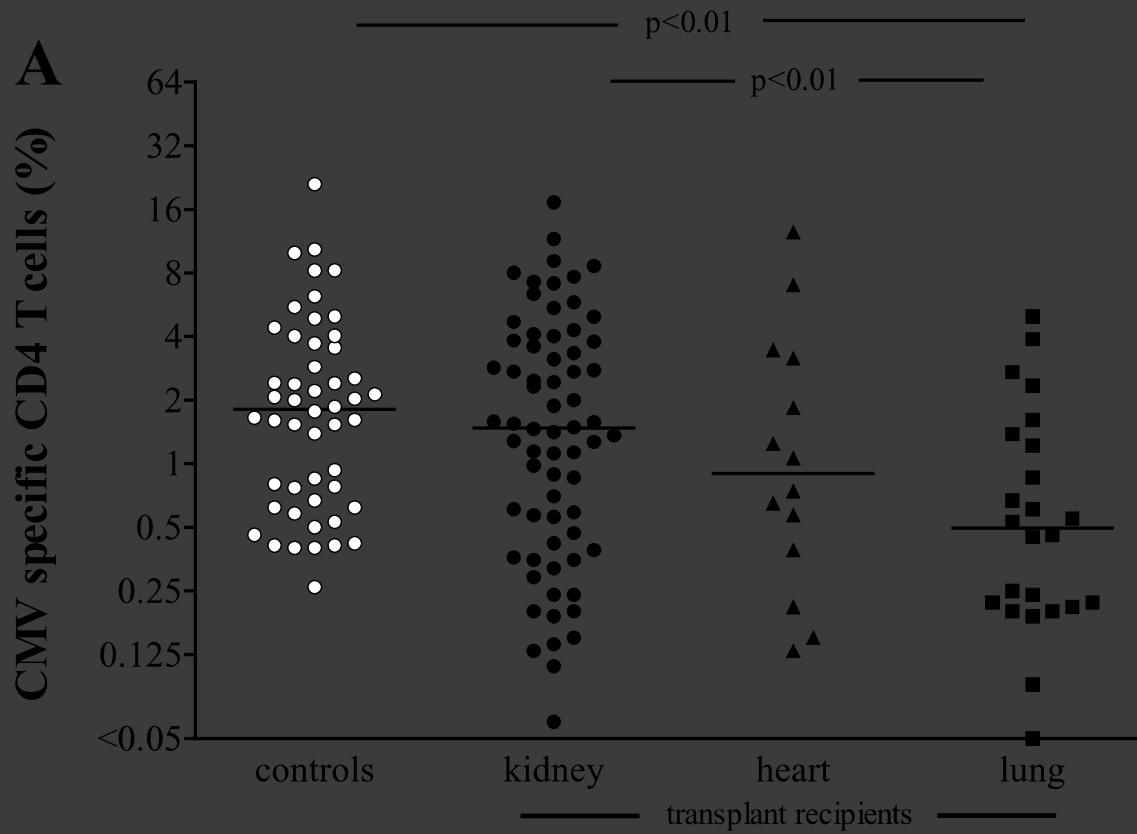
healthy individuals and long-term renal transplant recipients did not differ in the frequency of CMV-specific CD4 T cells

CMV-Specific CD4+ T cells Posttransplant

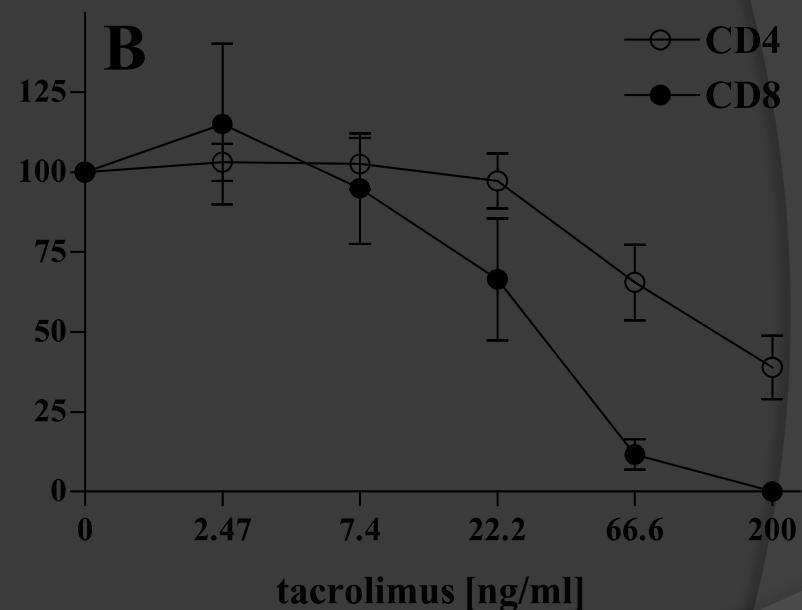
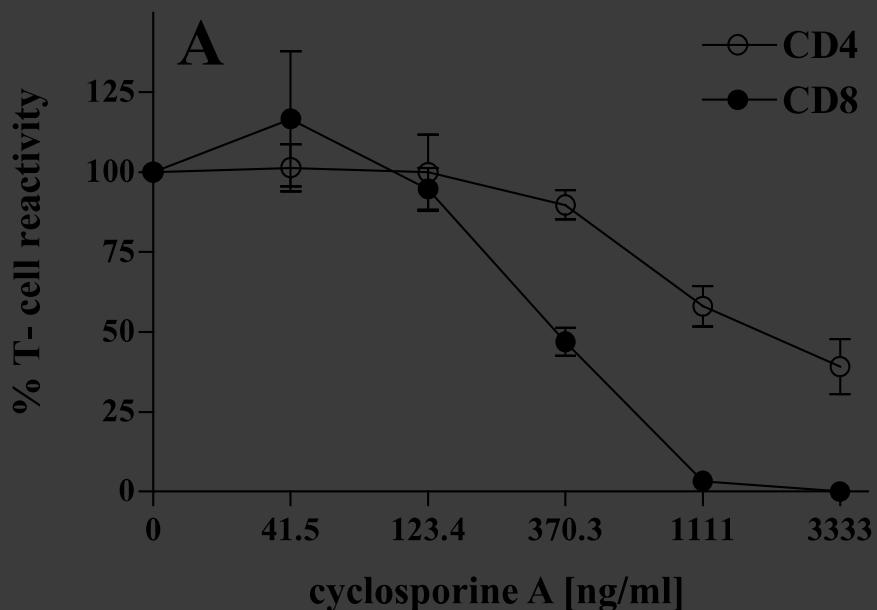
- Prolonged susceptibility to CMV by lung transplanted patients
 - Decreased CD4+ anti-CMV response
 - Dose related effects of calcineurin inhibition
- Level of CT4+ T-cell specific for CMV in all organ transplanted patients predictive of patient response

Sester U et al. *Am J Transplant.* 2005;5:1483-1489.

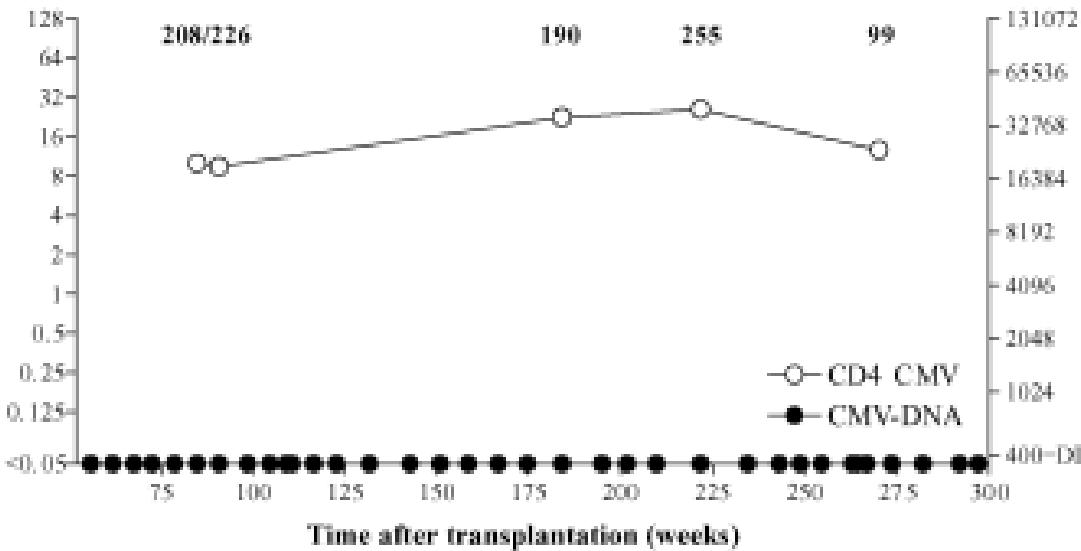
Lung transplant recipients had significantly lower frequencies of specific CD4 T cells than controls or renal transplant recipients ($p < 0.01$)



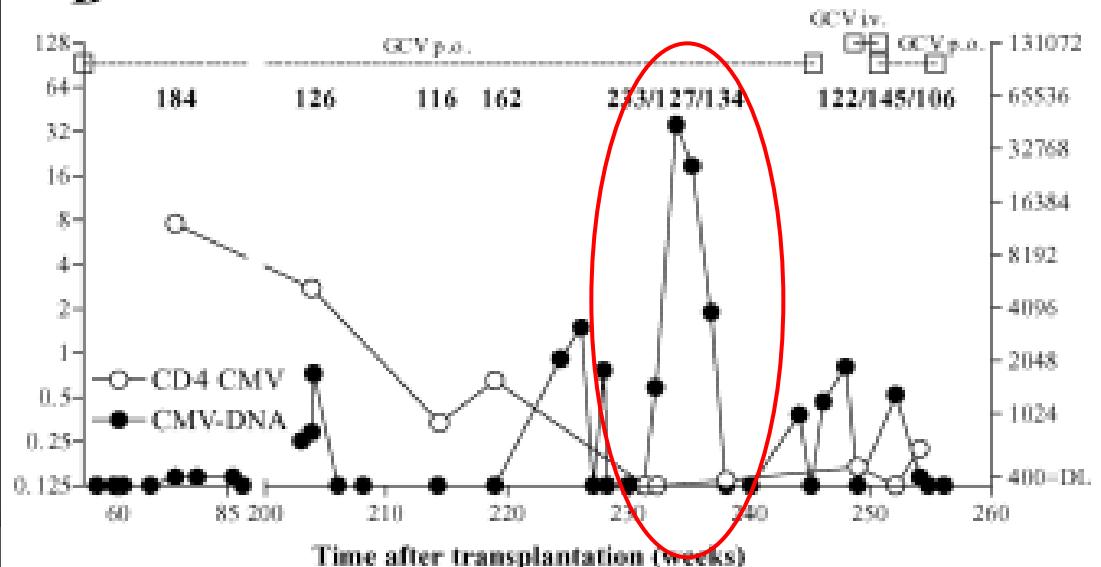
The suppressive effect of increasing doses of CNIs (A) cyclosporine A or (B) tacrolimus on CMV-specific CD4 and CD8 T cells was analyzed in vitro from whole blood of three healthy individuals



Calcineurin inhibitors decrease CMV-specific T-cell reactivity in a dose-dependent manner

C**lung transplant recipient**

Stable level of CMV-specific CD4 T cell correlate with no CMV infection

D**lung transplant recipient**

Recurrent CMV replication and dynamic changes in CMV-specific T-cell numbers

Treatment of CMV Disease

The antiviral drugs for treating CMV disease are intravenous ganciclovir and valganciclovir (Table 2; Ref. 68). Oral ganciclovir should NOT be used for treatment of CMV disease because its poor oral bioavailability will lead to insufficient systemic levels. Cautious reduction in the degree of immunosuppression should be considered in SOT patients presenting with CMV disease, especially if the disease is moderate to severe.



Practice of reducing immunosuppression during the infection: how low is low enough?

Immunosuppression should be reduced in kidney transplant patients with PyVAN

Aim to improve BKV-specific immunity

Strategies:

1. First dose reduction of the calcineurin inhibitor by 25%–50%; followed by reducing the antiproliferative drug by 50%; followed by discontinuing the latter if necessary
 2. First reducing the antiproliferative drug by 50% followed by reducing calcineurin inhibitors by 25%–50% followed by discontinuing the antiproliferative drug if necessary
- Oral prednisone is typically tapered to 10 mg or less daily dose
 - Immunosuppression is further adapted according to the course of serum creatinine concentration and the plasma viral loads, but responses may require several weeks

No accurate tool to measure and counterbalance between “infection” and “rejection”

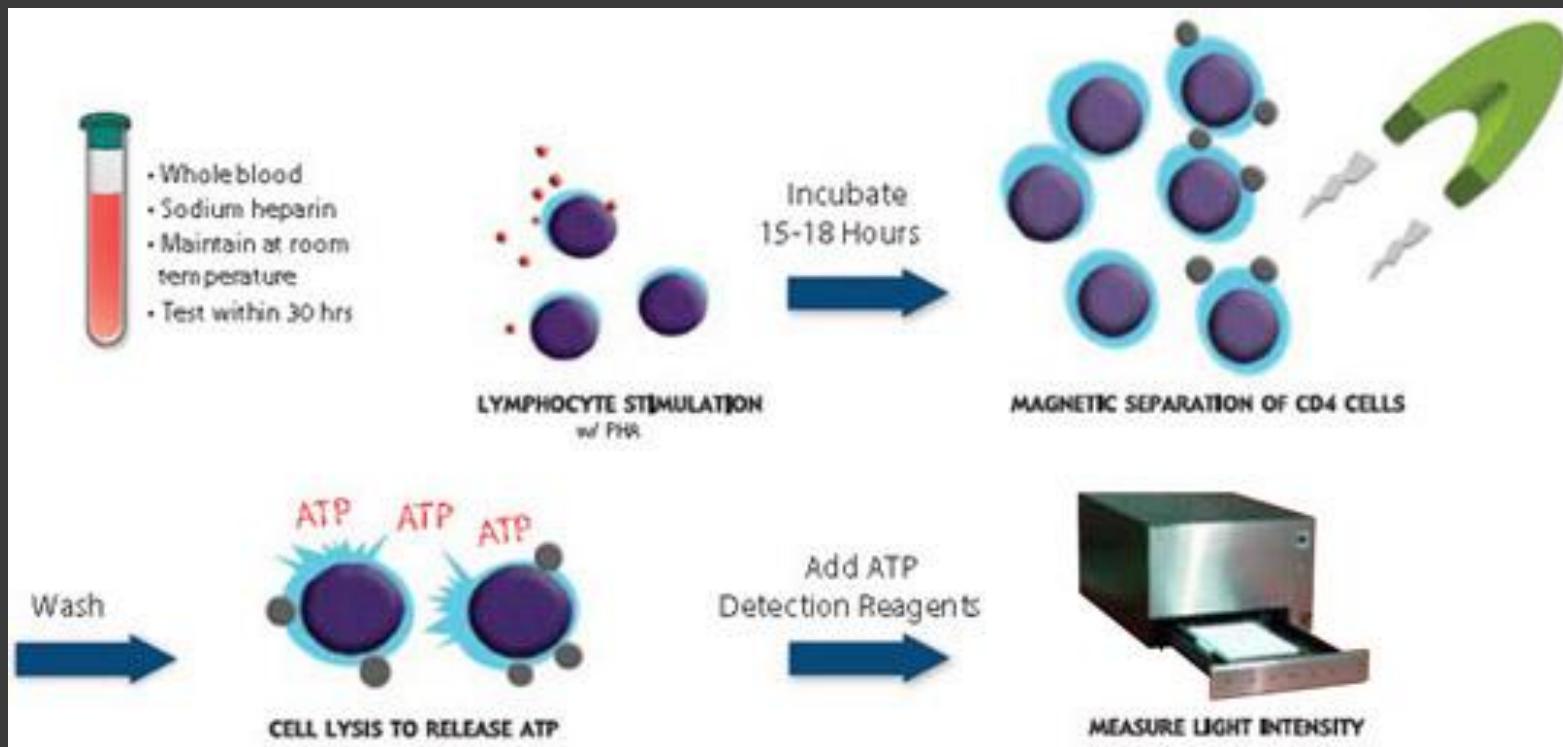
Viral Dynamic using Blood viral load as a marker for viral disease progression

Rationale: faster viral growth rates (ie, a shorter viral doubling time) and slower viral clearance rates (ie, a longer viral half-life) were associated with a higher likelihood of viral disease

Viral kinetics in transplant and non-transplant settings

	Intracellular delay	Transplant patients			Non-transplant patients			Viral generation time	References used to calculate kinetic estimates
		Doubling time	Half-life	R_0^*	Doubling time	Half-life	R_0^*		
Cytomegalovirus	Approximately 18 h (reference 22)	1·3 days	1–20 days	0·83–1·5	2 days	17 h to 3 days	0·5–1·3	≥3 days	23–26
Epstein-Barr virus	Not well defined	7 h to 3 days	16 h to 3 days	>1–1·4	..	1·7–2·6 h	27–30
Human herpesviruses 6	5–6 h	≤10 h	21 h	1·5	≤16 h	31
Human herpesviruses 7	5–6 h	≤22 h	1·8 days	1·2	≤30 h	31
Hepatitis C virus	≥6 h (reference 32)	7–35 h	0·2–10 h	>2·2	..	1·5–4·6 h	>15	≥8 h	9, 32–35
GB virus C	2·5–18 days	36
Polyomavirus type BK	2 days (reference 37)	18 h to 37 days	1–6 h	0·86–2·6	2–3 days	36
Adenovirus	≥16 h (reference 38)	1·3 days	0·05 h	1·4	≥16 h	39, 40
HIV-1	Approximately 1 day (reference 41)	0·5 h	2–20	1–2 days	6, 16, 32, 42

Immuknow Cylex: Commercialized Immune Monitoring Kit



ORIGINAL ARTICLE

ImmunoKnow as a Diagnostic Tool for Predicting Infection and Acute Rejection in Adult Liver Transplant Recipients: A Systematic Review and Meta-Analysis

Emilio Rodrigo,¹ Marcos López-Hoyos,² Mario Corral,³ Emilio Fábrega,⁴ Gema Fernández-Fresnedo,¹ David San Segundo,² Celestino Piñera,¹ and Manuel Arias¹

¹Nephrology Service, ²Immunology Service, ³Marquesa de Pelayo Library, and ⁴Gastroenterology and Hepatology Unit, Marqués de Valdecilla University Hospital, University of Cantabria, Institute for Training and Research of the Marqués de Valdecilla Foundation, Santander, Spain

Immunoknow assay as a Predictor of Infection VS. Rejection

TABLE 1. Characteristics of the Studies Included in the Infection Meta-Analysis

Study	Country	Study Type	Mean Age (Years)	Male Sex (%)	Posttransplant Follow-Up (Months)	Mean Testing to Diagnosis (Days)	Maximum ImmunKnow		True Positives (n)	False Positives (n)	False Negatives (n)	True Negatives (n)	AUC-ROC
							Cutoff (µg/l)	n					
Cheng et al. ³¹ (2011)	China	Retrospective	48	86	3	0	200	84	59	22	177	0.812	
Mizuno et al. ¹⁹ (2011)	Japan	Not reported	50	73	50.7	Not reported	225	6	7	0	27	Not reported	
Hashimoto et al. ¹⁸ (2010)	United States	Retrospective	52	76	7.9	0	225	23	7	3	16	0.930	
Xue et al. ¹⁷ (2010)	China	Retrospective	49	78	Not reported	Not reported	126	69	23	12	74	Not reported	
Cabrera et al. ¹⁶ (2009)	United States	Prospective	51	71	Not reported	0	225	15	7	0	20	Not reported	

Immunoknow assay as a Predictor of Infection VS. Rejection

TABLE 2. Characteristics of the Studies Included in the Acute Rejection Meta-Analysis

Study	Country	Study Type	Mean Age (Years)	Male (%)	Posttransplant Follow-Up (Months)	Maximum Time from Immunoknow Testing to Diagnosis (Days)	Cutoff (ng/ml)	True				False				True Negatives (n)	AUC-ROC		
								Immunoknow		Positives (n)	True Positives (n)	False Positives (n)	False Negatives (n)						
								Mean	SD										
Cheng et al. ²¹ (2011)	China	Retrospective	48	80	3	0	304	43	68	11	220	0.806							
Mizuno et al. ¹⁹ (2011)	Japan	Not reported	50	73	50.7	Not reported	525	1	2	1	36	Not reported							
Dong et al. ²⁰ (2011)	China	Not reported	43	64	<1	Not reported	407	12	11	9	45	0.869							
Hashimoto et al. ¹⁸ (2010)	United States	Retrospective	52	76	7.9	0	525	1	0	10	38	0.930							
Cabrera et al. ¹⁶ (2009)	United States	Prospective	51	71	Not reported	0	325	4	7	8	23	Not reported							

Immunoknow assay as a Predictor of Infection VS. Rejection

TABLE 3. Pooled Results for the Diagnostic Role of ImmuKnow in Predicting Infection or Acute Rejection in Adult Solid Organ Recipients

	Sensitivity*	Specificity*	DOR*	Summary		SROC†
				Positive	Negative	
Infection	83.8% (78.5%-88.3%, 23.1%)	75.3% (70.8%-79.4%, 0.0%)	14.6 (9.6-22.3, 0.0%)	3.3 (2.8-4.0, 0.0%)	0.824 - 0.034	
Acute Rejection	65.6% (55.0%-75.1%, 86.2%)	80.4% (76.4%-83.9%, 82.2%)	8.8 (3.1-24.8, 47%)	3.4 (2.4-4.7, 16.5%)	0.835 - 0.060	

*The 95% CIs and χ^2 values are presented in parentheses.

†The data are presented as means and SEs.

Practice in Thailand: open
for discussion