器官移植與免疫抑制

王台欣藥師

2010/9/19

Outline

- 器官移植簡介
- 免疫抑制劑藥物個論
- 移植藥物交互作用及併發症
- 移植用藥衛教重點
- 施打疫苗的注意事項

器官移植的歷史

- Ancient history of organ transplantation
- Premodern era: 1900-1959
- Early immunosuppressive era of transplantation: 1960-1979
- The calcineurin era: cyclosporin and FK-506 (1983-present)

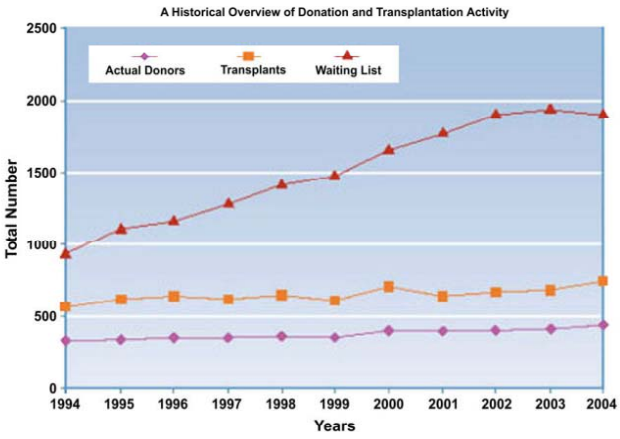


Fig. 3. United States organ transplant waiting list, transplants, and organ donors.

Crit Care Clin 25 (2009) 165–184

常見器官移植

- Solid Organ Transplantation
  - 腎臟移植
  - 肝臟移植
  - 心臟移植
  - 肺臟移植
  - 胰臟移植
  - 小腸移植
- Bone Marrow Transplantation (BMT)

Table I-5. Unadjusted One- and Five-Year Graft Survival by Organ

Organ Transplanted	One-Year Survival	Five-Year Survival
Kidney		
Deceased donor	90.4%	68.2%
Living donor	95.6%	80.7%
Pancreas alone	81.2%	51.3%
Pancreas after kidney	77.2%	53.6%
Kidney-pancreas (kidney)	92.8%	78.5%
Kidney-pancreas (pancreas)	86.0%	72.6%
Liver		
Deceased donor	82.4%	67.6%
Living donor	84.8%	70.9%
Intestine	68.3%	36.3%
Heart	87.2%	72.8%
Lung	82.2%	50.5%
Heart-lung	73.7%	45.2%

Source: *2008 OPTN/SRTR Annual Report*, Table 1.13.

Table I-4. Unadjusted One- and Five-Year Patient Survival by Organ

Organ Transplanted	One-Year Survival	Five-Year Survival
Kidney		
Deceased donor	95.0%	81.0%
Living donor	98.2%	90.6%
Pancreas alone	97.9%	88.7%
Pancreas after kidney	97.3%	83.9%
Kidney-pancreas	95.1%	86.6%
Liver		
Deceased donor	87.1%	73.3%
Living donor	89.9%	77.3%
Intestine	81.4%	56.2%
Heart	87.6%	73.9%
Lung	83.6%	53.4%
Heart-lung	73.8%	46.5%

Source: *2008 OPTN/SRTR Annual Report*, Table 1.13.

TABLE 92-7 Factors Negatively Affecting Allograft and Patient Survival

	Kidney	Liver	Heart
Donor factors	Decreased HLA matching Increased age Increased serum creatinine Cardiac instability Prolonged ischemia time History of hypertension	Size mismatch Age (youngest, oldest)	Size mismatch Increased age Prolonged ischemia time
Recipient factors	Age <15, >50 years Retransplantation African race Elevated PRA Multiparous women Poor drug compliance	Increased age Retransplantation African race ICU pretransplant ABO blood type Poor drug compliance	Age <5, >60 years ICU pretransplant Mechanical ventilation LVAD IABP Poor drug compliance

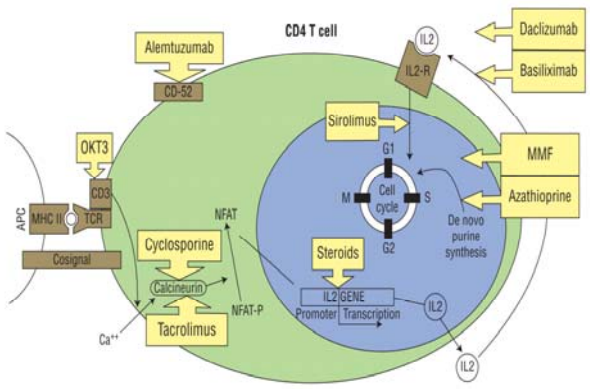
HLA, human leukocyte antigens; IABP, intraaortic balloon pump; LVAD, left ventricular assist device; PRA, panel of reactive antibodies.

免疫抑制劑的歷史

- 1962 Azathioprine (AZA)
- 1963 AZA + Corticosteroid
- 1978 Cyclosporine (CsA)
- 1981 Anti-thymocyte globulin
- 1983 Cyclosporine (FDA approval: Sandimmune)
- 1984 CsA, Steroids ± AZA
- 1986 Muromonab-CD3 (OKT3)
- 1990 CsA, Steroids, AZA ± OKT3 / ATG
- 1994 Tacrolimus (FK506)
- 1995 Mycophenolate Mofetil (MMF); Neoral
- 1998 Daclixumab (Zenapax)
- 1998 Basiliximab (Simulect)
- 1999 Sirolimus (Rapamycin)
- 2000 Gengraf
- 2004 Myfortic

免疫抑制劑藥物

- Induction therapy
  - Alemtuzumab
  - RATG (rabbit antithymocyte immunoglobulin)
  - IL2-RA (interleukin-2 receptor antagonist)
- Maintenance therapy
  - Calcineurin inhibitors: cyclosporine, tacrolimus
  - Corticosteroid
  - Antimetabolites: mycophenolate, azathioprine
  - Mammalian target of rapamycin (mTOR) inhibitors: sirolimus, everolimus



OPTN/SRTR 2008 Annual Report

Immunosuppression Use by Organ in 2006 and 2007

	Organ								
	Heart-Lung	Heart	Intestine	Kidney	KP	Liver	Lung	PAK	PTA
Transplants (2007)	29	2,207	198	16,623	862	6,489	1,471	261	208
Tx With Immunosuppression Info at Discharge	27	2,135	194	16,114	840	6,207	1,404	247	197
Induction Drug Reported	81.5%	53.9%	49.0%	78.0%	78.0%	25.8%	62.3%	88.2%	67.0%
Induction Drugs									
Atgam/NRATG/NRATS	33.3%	4.2%	0.5%	1.1%	1.8%	1.2%	5.8%	1.2%	1.0%
OKT3	7.4%	3.2%	17.5%	1.2%	1.2%	2.9%	1.0%	0.4%	7.6%
Thymoglobulin	0.0%	19.2%	23.7%	43.8%	52.0%	9.6%	4.3%	61.9%	42.1%
Zenapax	11.1%	12.7%	9.8%	10.8%	6.5%	8.2%	16.2%	2.0%	7.1%
Simulect	25.9%	14.2%	2.1%	16.6%	5.7%	5.6%	25.9%	4.0%	3.6%
Campath	18.5%	2.8%	13.4%	9.5%	13.2%	1.4%	9.8%	12.1%	13.7%
Tx With Immunosuppression Info and Functioning Graft at Discharge	26	2,044	166	15,884	826	5,902	1,325	228	182
Maintenance at Discharge									
Corticosteroids Use	100.0%	88.7%	77.1%	65.9%	65.4%	75.9%	95.3%	58.3%	58.2%
Steroids	100.0%	88.7%	77.1%	65.9%	65.4%	75.9%	95.3%	58.3%	58.2%
Calcineurin Inhibitor Use	100.0%	97.9%	97.0%	95.6%	98.3%	97.9%	97.6%	97.8%	97.3%
Cyclosporine	3.8%	33.0%	0.0%	10.1%	4.5%	7.2%	10.1%	4.8%	2.2%
Tacrolimus	96.2%	64.9%	97.0%	85.4%	93.8%	90.7%	87.5%	93.0%	95.1%
Antimetabolite Use	84.6%	91.9%	22.9%	92.1%	91.2%	72.8%	92.3%	94.3%	59.3%
Mycophenolate Mofetil	65.4%	85.6%	21.1%	75.0%	73.2%	67.2%	54.3%	83.8%	52.2%
Mycophenolate Sodium	3.8%	3.4%	0.0%	16.4%	17.2%	4.9%	6.4%	9.2%	5.5%
Azathioprine	15.4%	2.8%	1.8%	0.6%	0.7%	0.6%	31.5%	1.3%	1.6%
Leflunomide	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
mTOR Inhibitor Use	0.0%	4.5%	9.0%	5.2%	10.5%	2.5%	0.2%	7.9%	17.0%
Sirolimus	0.0%	1.2%	9.0%	4.8%	10.5%	2.5%	0.2%	7.9%	17.0%
Everolimus	0.0%	3.3%	0.0%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%
Transplants (2006)	31	2,193	175	17,091	924	6,650	1,406	293	173
Tx With Maintenance Use at 1yr PostTx	20	1,879	120	15,092	803	5,245	1,141	218	122
Maintenance at 1yr PostTx									
Corticosteroids Use	100.0%	68.4%	60.8%	65.8%	67.6%	39.6%	97.4%	67.4%	48.4%
Steroids	100.0%	68.4%	60.8%	65.8%	67.6%	39.6%	97.4%	67.4%	48.4%
Calcineurin Inhibitor Use	95.0%	96.5%	99.2%	91.7%	96.4%	92.7%	96.8%	95.0%	99.2%
Cyclosporine	5.0%	32.0%	1.7%	11.2%	6.2%	8.3%	11.2%	6.9%	2.5%
Tacrolimus	90.0%	64.5%	97.5%	80.6%	90.2%	84.5%	85.5%	88.1%	96.7%
Antimetabolite Use	85.0%	87.1%	6.7%	86.7%	83.8%	49.3%	84.6%	83.0%	50.0%
Mycophenolate Mofetil	60.0%	76.7%	5.8%	67.7%	57.7%	44.1%	51.3%	67.4%	35.2%
Mycophenolate Sodium	0.0%	5.1%	0.0%	16.9%	24.4%	4.7%	4.6%	13.3%	13.9%
Azathioprine	25.0%	5.2%	0.8%	1.4%	1.0%	0.6%	28.7%	1.4%	0.8%
Leflunomide	0.0%	0.2%	0.0%	0.8%	0.7%	0.0%	0.0%	0.9%	0.0%
mTOR Inhibitor Use	0.0%	9.3%	12.5%	11.3%	16.1%	9.4%	6.1%	16.1%	22.1%
Sirolimus	0.0%	7.6%	12.5%	10.8%	16.1%	9.4%	6.1%	16.1%	22.1%
Everolimus	0.0%	1.6%	0.0%	0.5%	0.0%	0.0%	0.0%	0.0%	0.0%

OPTN/SRTR 2008 Annual Report

Immunosuppression Use by Organ
Maintenance Regimen at Discharge, 2007 Transplants

	Organ								
	Heart-Lung	Heart	Intest-ine	Kidney	KP	Liver	Lung	PAK	PTA
Functioning Graft at Discharge	27	2,070	166	16,252	841	6,005	1,361	240	187
With Immunosuppression Info	26	2,044	166	15,884	826	5,902	1,325	228	182
Maintenance Regimen									
CyA	0.0%	0.0%	0.0%	0.1%	0.0%	0.1%	0.0%	0.0%	0.0%
Tac	0.0%	0.6%	11.4%	1.5%	1.1%	4.7%	0.5%	2.6%	6.0%
--- + MMF/MPA	0.0%	0.1%	0.0%	0.5%	0.0%	0.3%	0.1%	0.9%	0.0%
CyA + MMF/MPA	0.0%	2.3%	0.0%	1.9%	0.4%	1.2%	0.0%	0.9%	1.1%
Tac + MMF/MPA	0.0%	7.1%	11.4%	27.6%	24.1%	15.7%	1.6%	28.9%	20.3%
--- + OtherAntimet	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%	0.0%
CyA + OtherAntimet	0.0%	0.1%	0.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%
Tac + OtherAntimet	0.0%	0.2%	0.0%	0.1%	0.0%	0.2%	2.0%	0.0%	0.0%
Tac + MMF/MPA + OtherAntimet	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%	0.0%
--- + Siro/Evero	0.0%	0.0%	0.0%	0.1%	0.1%	0.1%	0.0%	0.0%	0.0%
CyA + Siro/Evero	0.0%	0.1%	0.0%	0.9%	2.3%	0.5%	0.0%	0.4%	0.0%
Tac + Siro/Evero	0.0%	0.2%	0.0%	0.6%	1.2%	0.1%	0.0%	0.0%	1.6%
--- + MMF/MPA + Siro/Evero	0.0%	0.0%	0.0%	0.2%	0.2%	0.2%	0.0%	0.4%	0.0%
CyA + MMF/MPA + Siro/Evero	0.0%	0.1%	0.0%	0.0%	0.0%	0.1%	0.0%	0.0%	0.5%
Tac + MMF/MPA + Siro/Evero	0.0%	0.0%	0.0%	0.3%	4.6%	0.1%	0.0%	7.0%	12.1%
--- + Steroids	0.0%	0.4%	1.8%	0.4%	0.1%	0.8%	0.9%	0.0%	1.6%
CyA + Steroids	0.0%	0.9%	0.0%	0.3%	0.0%	0.7%	0.6%	0.4%	0.0%
Tac + Steroids	15.4%	2.3%	56.0%	2.0%	1.5%	19.2%	5.1%	1.8%	28.6%
--- + MMF/MPA + Steroids	0.0%	1.4%	0.0%	2.4%	0.7%	1.1%	0.7%	1.3%	1.1%
CyA + MMF/MPA + Steroids	3.8%	24.3%	0.0%	5.6%	1.2%	3.0%	2.0%	1.8%	0.5%
Tac + MMF/MPA + Steroids	65.4%	52.4%	8.4%	51.4%	59.0%	48.6%	55.9%	51.3%	22.0%
--- + OtherAntimet + Steroids	0.0%	0.1%	0.0%	0.0%	0.0%	0.0%	0.9%	0.0%	0.0%
CyA + OtherAntimet + Steroids	0.0%	1.3%	0.0%	0.1%	0.0%	0.1%	6.8%	0.4%	0.0%
Tac + OtherAntimet + Steroids	11.5%	0.8%	1.8%	0.2%	0.4%	0.2%	21.5%	0.4%	1.1%
--- + Siro/Evero + Steroids	0.0%	0.1%	1.2%	0.1%	0.1%	0.2%	0.0%	0.0%	0.0%
CyA + Siro/Evero + Steroids	0.0%	2.8%	0.0%	0.9%	0.4%	0.1%	0.0%	0.0%	0.0%
Tac + Siro/Evero + Steroids	0.0%	0.1%	6.6%	0.9%	1.3%	0.4%	0.1%	0.0%	2.7%
Other Regimen	3.8%	1.9%	1.2%	2.0%	1.3%	2.3%	1.3%	1.3%	0.5%

Cyclosporine

- History: approved by FDA in 1983, Neoral approved by FDA in 1995
- Chemistry:
  - Fungal metabolite
  - Cyclic polypeptide (11 amino acids)
  - Neutral and hydrophobic (nonpolar) product
- Indication: prophylaxis and treatment of allograft rejection in conjunction with other immnosuppressive agents
- Pharmacokinetics:
  - Absorption : slow, variable and incomplete (30%), peak at 2-4 hrs
  - Distribution: widely distributed throughout the body primarily in liver, pancreas, and lung, highly protein bound (mainly RBC), not dialyzed
  - Metabolism: extensively metabolized by the liver (CYP 450 enzyme)
  - Elimination: primarily excreted via biliary
- Dosage:
  - Oral: 5-18 mg/kg/day initially in 1-2 doses
  - IV: 2-6 mg /kg/day over 2-6 hrs infusion (IV dose = 1/3 oral dose)
  - Adjust dosage based on renal function & cyclosporine level

Tacrolimus (FK-506)

- History:
  - Discovered in Tsukuba, Japan in 1984
  - Approved by FDA in 1994
- Chemistry:
  - Fungal metabolite (isolated from strptomyces tsulubaensis)
  - Macrolide antibiotics
  - Lipophilic
  - Structurally different from cyclosporine
  - Structurally similar to rapamycin
- Indication: immunosuppressant in combination with steroid in solid organ transplantation
- Pharmacology: similar to cyclosporine, 50-100 times as potent as cyclosporine on a weight to weight basis
- Pharmacokinetics:
  - Absorption : incomplete, bioavailability 27% (6-57%), onset 1-4 hrs
  - Distribution: widely distributed in heart, lung, spleen, kidney and pancreas, not dialyzed
  - Metabolism: 98% metabolized by the liver (CYP 450 enzyme)
  - Elimination: < 2% excreted as uncharged drug, primarily excreted via bile, half-life:8.7 hrs
- Dosage:
  - IV continuous infusion: 0.05-0.1 mg/kg(ABW)/day
  - Oral: 0.075-0.15 mg /kg(ABW) q12h (with empty stomach)
  - Dosage adjustment in renal or hepatic failure patients

Corticosteroid (Prednisone)

- Chemistry:
  - Synthetic glucocorticoid
- Indication: immunosuppression, anti-inflammation
- Pharmacokinetics:
  - Absorption : rapidly and completely, peak at 1-3 hrs
  - Distribution: protein binding 75-90%
  - Metabolism & elimination: rapidly converted to prednisolone (active form) in the liver
- Dosage:
  - Initially 0.5-2 mg/kg/day than tapper to minimum effect MD (0.1-0.2 mg/kg/day) ASAP
  - Take single dose prior to 9 AM (minimize adrenal supp.)
- Parameters to monitor:
  - BW, edema, serum K+, glucose, BP

Mycophenolate (MMF)

- History: first clinical trial reported in 1992, approved by FDA in 1995
- Chemistry:
  - Synthesized prodrug of mycophenolic acid (MPA) to improve bioavailability
  - MMFL morpholinoethyl ester of MPA
  - MPA: a fermentation product of several Penicillium species
- Indication: as an adjunct to cyclosporine and corticosteroids for the prevention of renal allograft rejection
- Pharmacokinetics:
  - MMF → MPA (active metabolite) → MPAG (inactive metabolite)
  - Absorption : rapidly absorbed and hydrolyzed to form MPA, Tmax= 1-1.3 hrs, bioavailability 94%
  - Distribution: MPA 97% protein bound, MPAG 82% protein bound , not dialyzed
  - Metabolism: enterohepatic recirculation (2^{nd} peak: 6-12 hr post dose)
  - Elimination: <1% excreted as MPA, 87% excreted as MPAG, half-life= 16-18 hrs
- Dosage:
  - 1 g po bid with empty stomach, adjust dose based on WBC count and episodes of diarrhea
  - Over 1000 mg twice daily: GI side effects ↑
  - GFR < 25 ml/min/1.73 m2: < 1000 mg twice daily

Azathioprine (AZA)

- Chemistry: purine analog, prodrug of 6-mercaptoprine (6-MP)
- Indication:
  - Immnosuppression
  - Reumatoid arthritis
- Pharmacokinetics:
  - Absorption: rapidly, onset 1 hr
  - Distribution: partially dialyzed, cross placenta
  - Metabolism & elimination: rapidly converted into 6-MP in liver & RBCs
    - AZA (inactive, t1/2=50 min) → 6-MP (active metabolite, t1/2=74 min) → 6-TU (inactive metabolite) → urine
- Dosage:
  - Initially 1-2 mg /kg qd then taper to 0.5-1.0 mg/kg/day, adjust dose based on WBC and platelet counts
  - Take with empty stomach unless GI upset occurs
- Parameters to monitor:
  - CBC and platelet counts
  - LFTs and bilirubin monthly

Sirolimus

- History:
  - Isolated from soil samples in the 1970s as an antifungal agent against Candida albicans and immunosuppressive properties as well
  - Approved by FDA in 1999
- Chemistry:
  - Macrocyclic lactone (a macrolide) produced by Streptomyces hygroscopicus
  - Structurally similar to FK506
- Indication: prophylaxis of organ rejection in patients receiving renal transplants, used in a regimen with cyclosporine and corticosteroids
- Pharmacokinetics:
  - Absorption : incomplete, bioavailability 14% (oral solution), 27% (tablet)
  - Distribution: extensively bound (92%) to human plasma proteins
  - Metabolism: substrate for both CYP450 3A4 and P-glycoprotein
  - Elimination: excreted in the feces (91%) and urine (2.2%), half-life elimination mean time: 62 hrs
- Dosage:
  - Maintenance dose: 2 mg/day
- Parameters to monitor:
  - Cholesterol , TG, CBC, platelet, wound infection, and SCr

TABLE 92-4 Comparison of Common Adverse Effects of Maintenance Immunosuppressants

AZA	MMF	SIR	Steroids	CSA	TAC
Nausea, vomiting	Diarrhea, nausea	Hyperlipidemia	GI bleeding	Hyperlipidemia	Diarrhea, nausea
Thrombocytopenia	Leukopenia	Thrombocytopenia	Hyperlipidemia	Nephrotoxicity	Hepatotoxicity
Leukopenia		Leukopenia	Leukocytosis	Tremor	Nephrotoxicity
			Hypertension	Hypertension	Tremor, headache
			Hyperglycemia	Hyperglycemia	Hypertension
			Weight gain	Gingival hyperplasia	Hyperglycemia
			Mood changes	Hirsutism	Hyperkalemia, hypomagnesemia

AZA, azathioprine; CSA, cyclosporine; MMF, mycophenolate mofetil; SIR, sirolimus; TAC, tacrolimus.

藥物交互作用

TABLE 92-5 Effect of Concomitant Drug Administration on Cyclosporine, Tacrolimus, and Sirolimus

Cyclosporine Levels		Tacrolimus Levels		Sirolimus Levels	
Increase	***Decrease***	***Increase***	***Decrease***	***Increase***	***Decrease***
Ketoconazole	Rifampicin	Ketoconazole	Rifampin	Ketoconazole	Rifampin
Fluconazole	Phenytoin	Fluconazole	Dexamethasone	Fluconazole	Phenytoin
Itraconazole	Phenobarbital	Itraconazole	Phenytoin	Itraconazole	
Voriconazole	Carbamazepine	Voriconazole		Voriconazole	
Erythromycin	Sulfadimidine	Erythromycin		Erythromycin	
Levofloxacin	Trimethoprim	Levofloxacin		Clarithromycin	
Diltiazem		Diltiazem		Diltiazem	
Verapamil		Verapamil		Verapamil	
Danazol		Danazol		Atorvastatin	
Nicardipine		Cimetidine		Cyclosporine	
Metoclopramide		Omeprazole		Protease inhibitors	
Methylprednisolone		Clotrimazole			
Norethisterone		Nefazodone			
Sirolimus		Corticosteroids			
Tacrolimus		Cyclosporine			
Protease inhibitors		Basiliximab			
		Protease inhibitors			

併發症

- Hypertension
- Hyperlipidemia
- Post-transplantation diabetes mellitus
- Infection
- Osteoporosis
- Malignancy

衛教

- 不可擅自停藥或調藥
- 了解所服用藥物的名稱、用途、服藥時間、副作用、注意事項及保存方法
- 應經常測量並記錄血壓、血糖及體重變化 (體重每日一次，血壓、血糖一日兩次)
- 健康的飲食、休息及規律的生活作息
- 由於服用抗排斥藥物的關係，因此，不應食用含高鹽及高鉀之食物；高鈣飲食對類固醇引起之骨質疏鬆有所助益

疫苗施打

- When possible, vaccinate pre-transplant
- When giving live vaccines pre-transplant (eg MMR, varicella, zoster), wait 4 wks to do transplant
- Wait at least 3-6 months post-transplant to start immunization series (stable immnosuppression)
- Generally, no live vaccines post-transplant