



Liver transplantation: point of view of the Hepatologist

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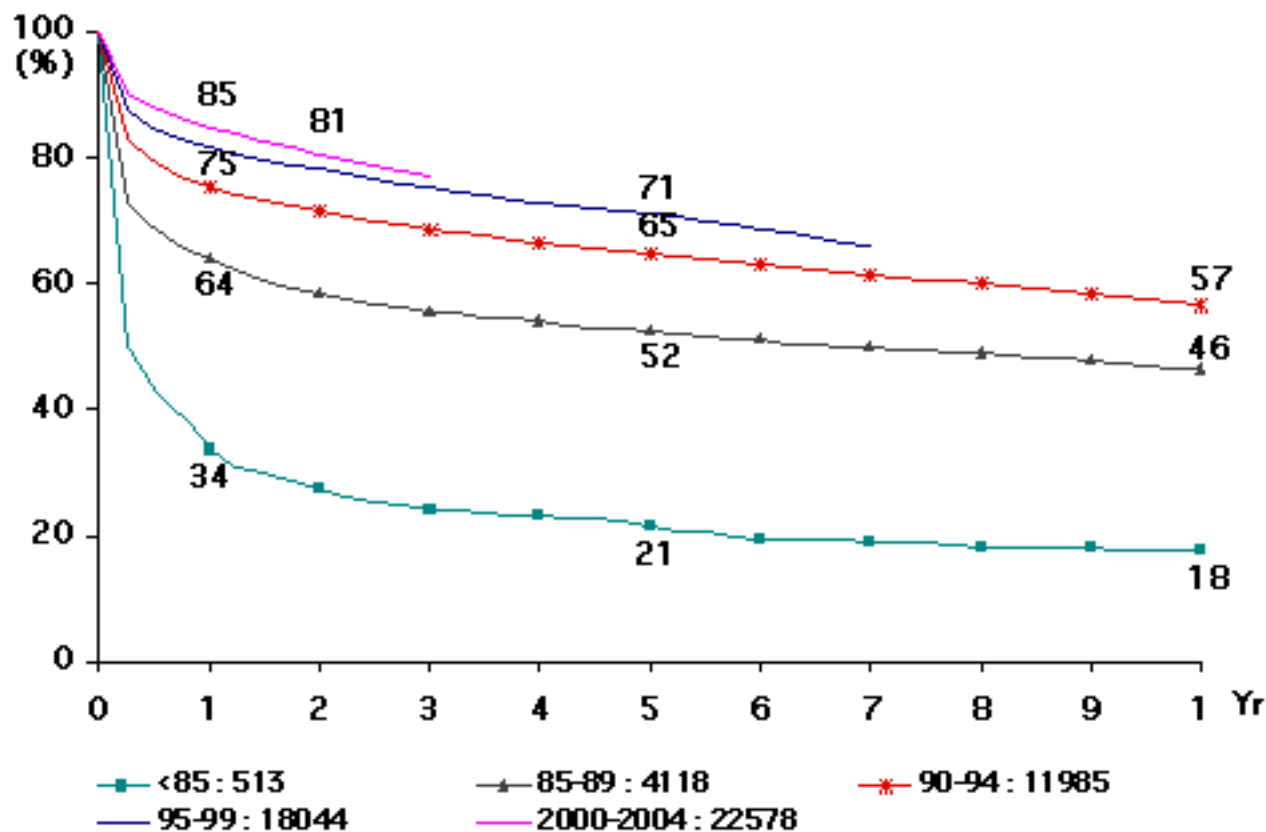
Journée du Président, SRBGE,
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Milestones in liver transplantation

- 1963: first human LTX (T. Starzl)
- 1980: introduction CyA
- 1983: NIH Consensus Development Conference

Patient Survival according to the Year of Liver Transplantation





Role transplant hepatologist

- Selection of patients for liver transplantation
- Management of patients with end-stage liver disease on the waiting list
- Immunosuppression
- Management cardiovascular risk factors
- Management of recurrence of disease after LTX



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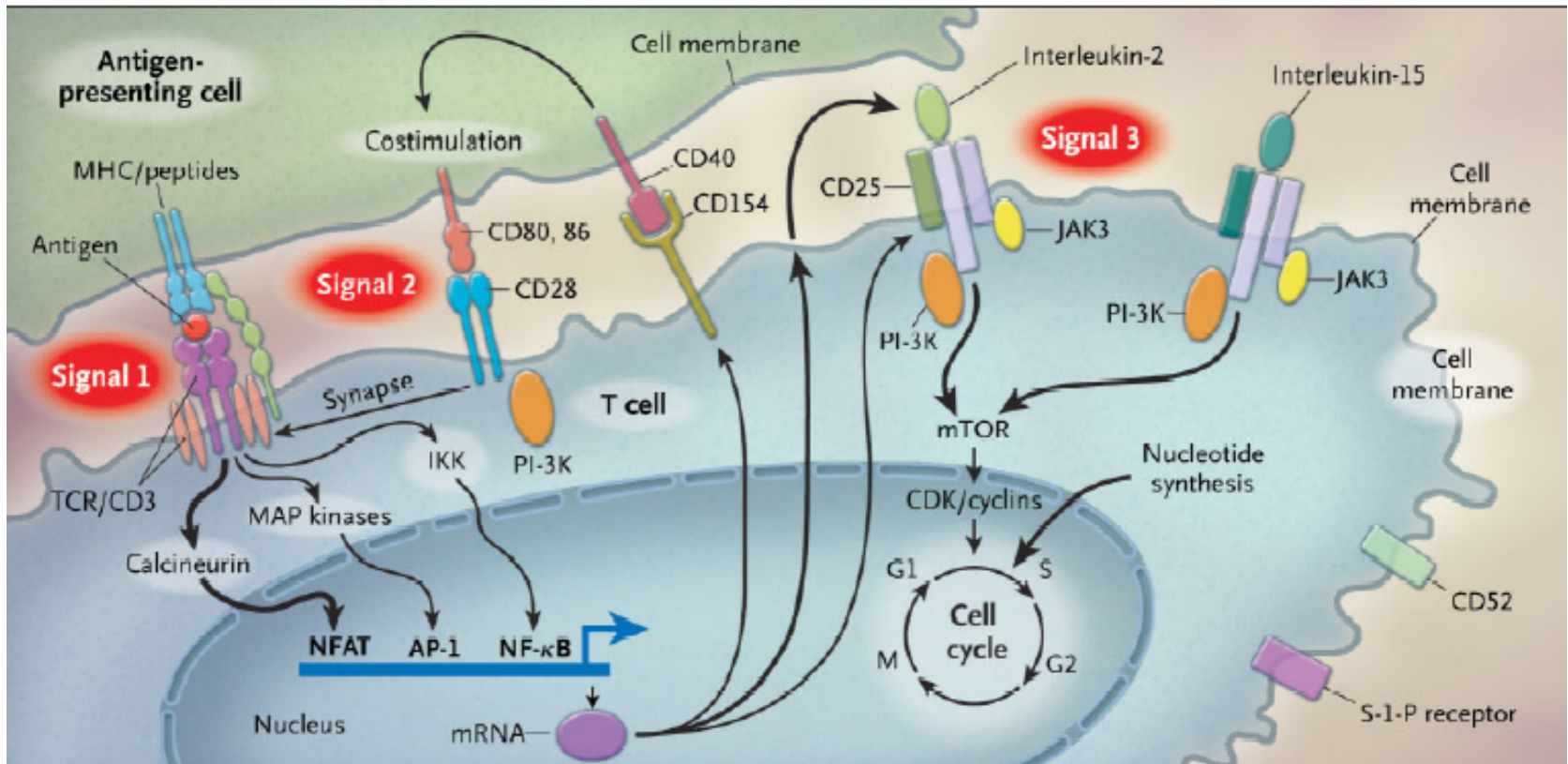


Immunosuppression in LTX History

- 1960s: corticosteroids, azathioprine
- Late 1970s: CyA
- Early 1990s: tacrolimus
- 2000s: adjunctive agents MMF and rapamycin (sirolimus)/everolimus

Halloran, NEJM 2004;351:2715-29

T-cell activation through three signals



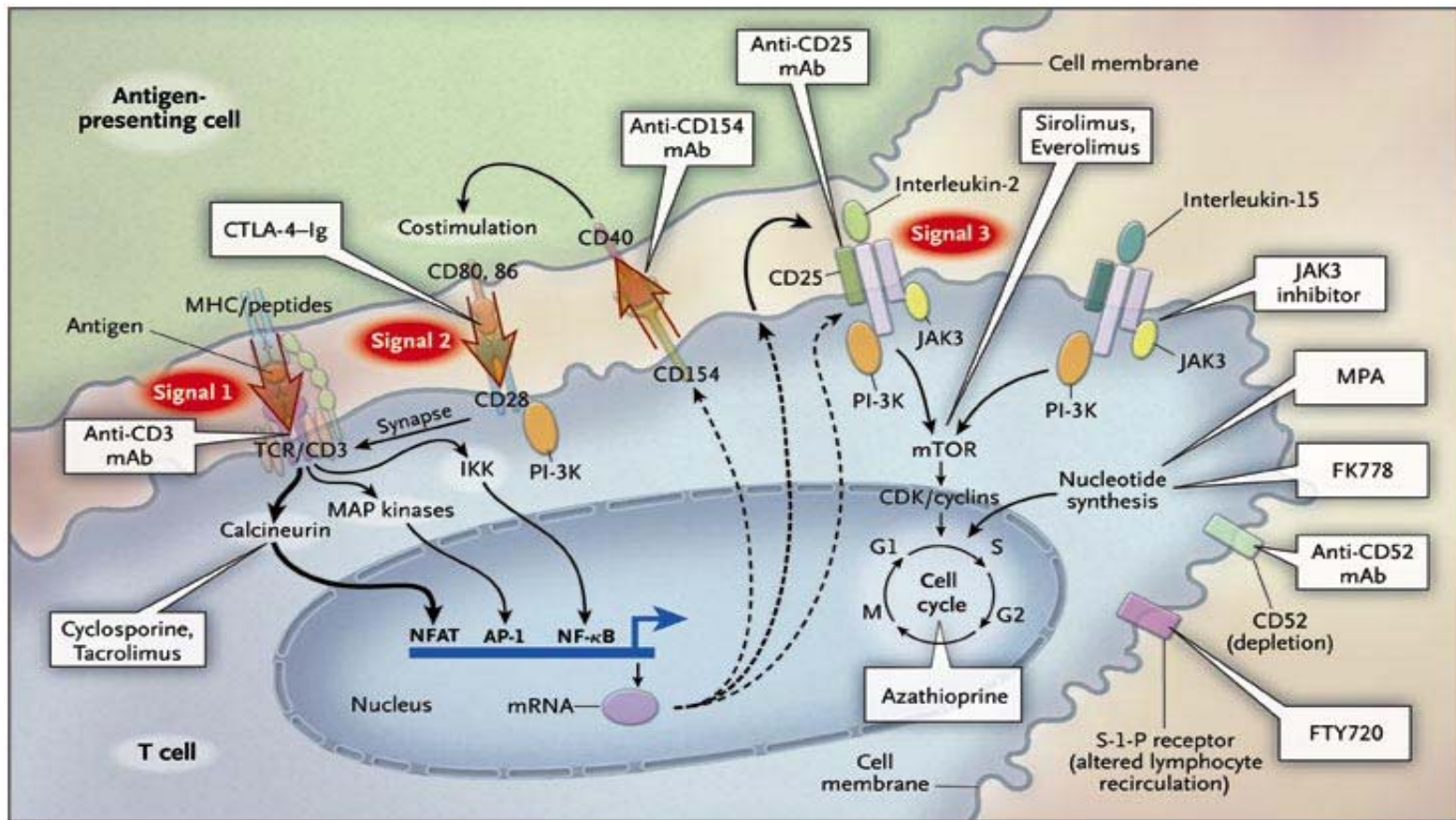


Mechanisms of allo-immunity



Individual immunosuppressive drugs and sites in the three-signal model

Halloran, NEJM 2004;351:2715-29





Overview of immunosuppressive agents

- Corticosteroids
 - Mechanisms of action:
 - Inhibition cytokine expression
 - Block ability macrophages to respond to lymphocyte-derived signals
 - Side effects
 - Hypertension
 - Hyperglycemia
 - Delayed wound healing
 - Risk of infection
 - Suppression pituitary-adrenal axis
 - Hyperlipidemia
 - Suppressed growth
 - Increased risk GI ulceration
 - Osteoporosis



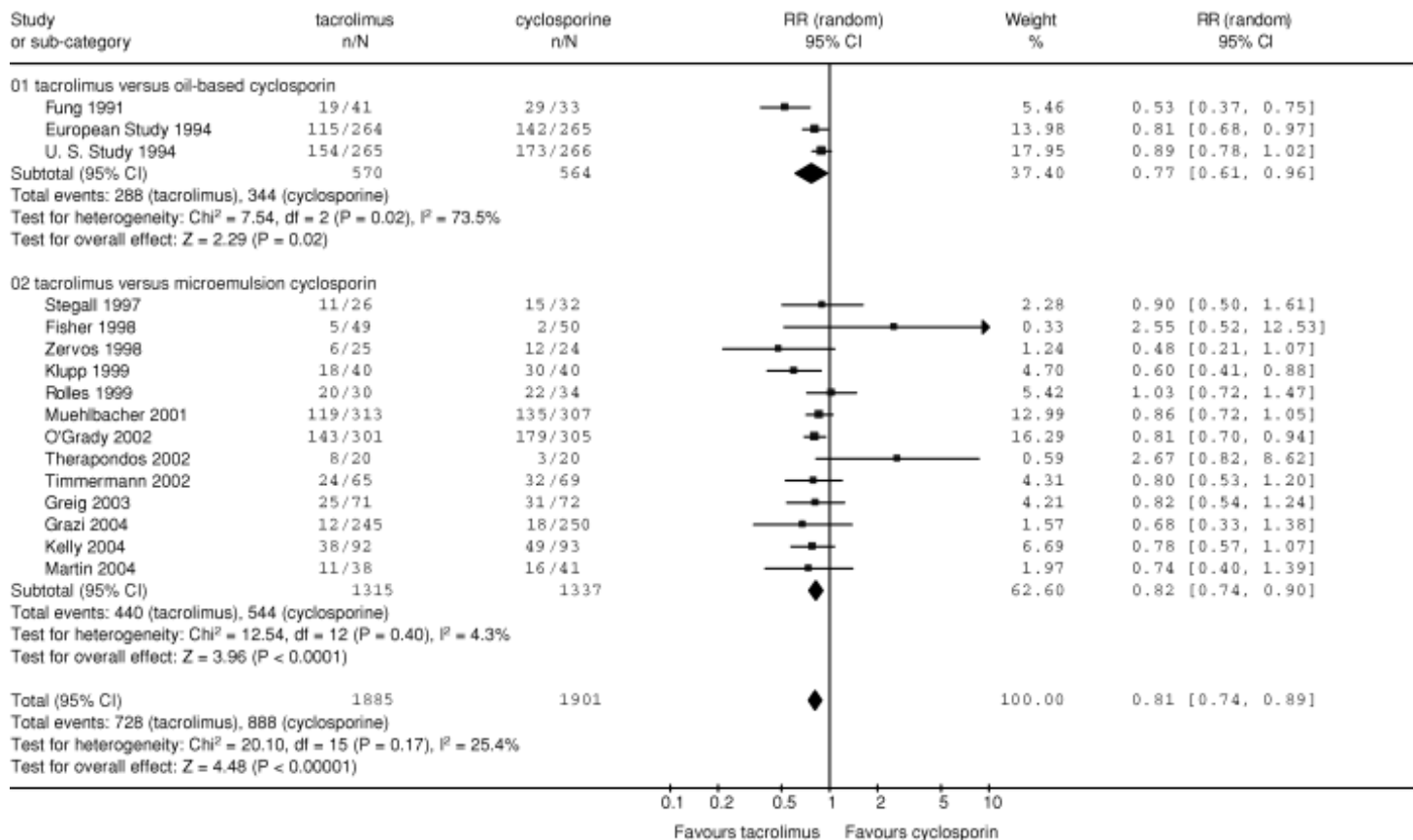
Overview of immunosuppressive agents

- Calcineurin-inhibitors: cyclosporin/tacrolimus
 - Mechanism of action: inhibition signal 1 pathway
 - Cyclosporin binds to cyclophilin, the complex binds to and inhibits calcineurin
 - Tacrolimus binds to FK-506 binding protein, blocking activation calcineurin
 - Side effects:
 - Nephrotoxicity
 - Neurotoxicity
 - Diabetogenic (TAC>CyA)
 - Increased susceptibility to opportunistic infections
 - *De novo* malignancies

Cyclosporin vs tacrolimus: acute rejection

McAlister, Am J Transpl 2006;6: 1578-85

Review: Cyclosporin versus tacrolimus for liver transplanted patients
 Comparison: 02 Stratified analysis, by cyclosporin formulation
 Outcome: 03 Acute rejection



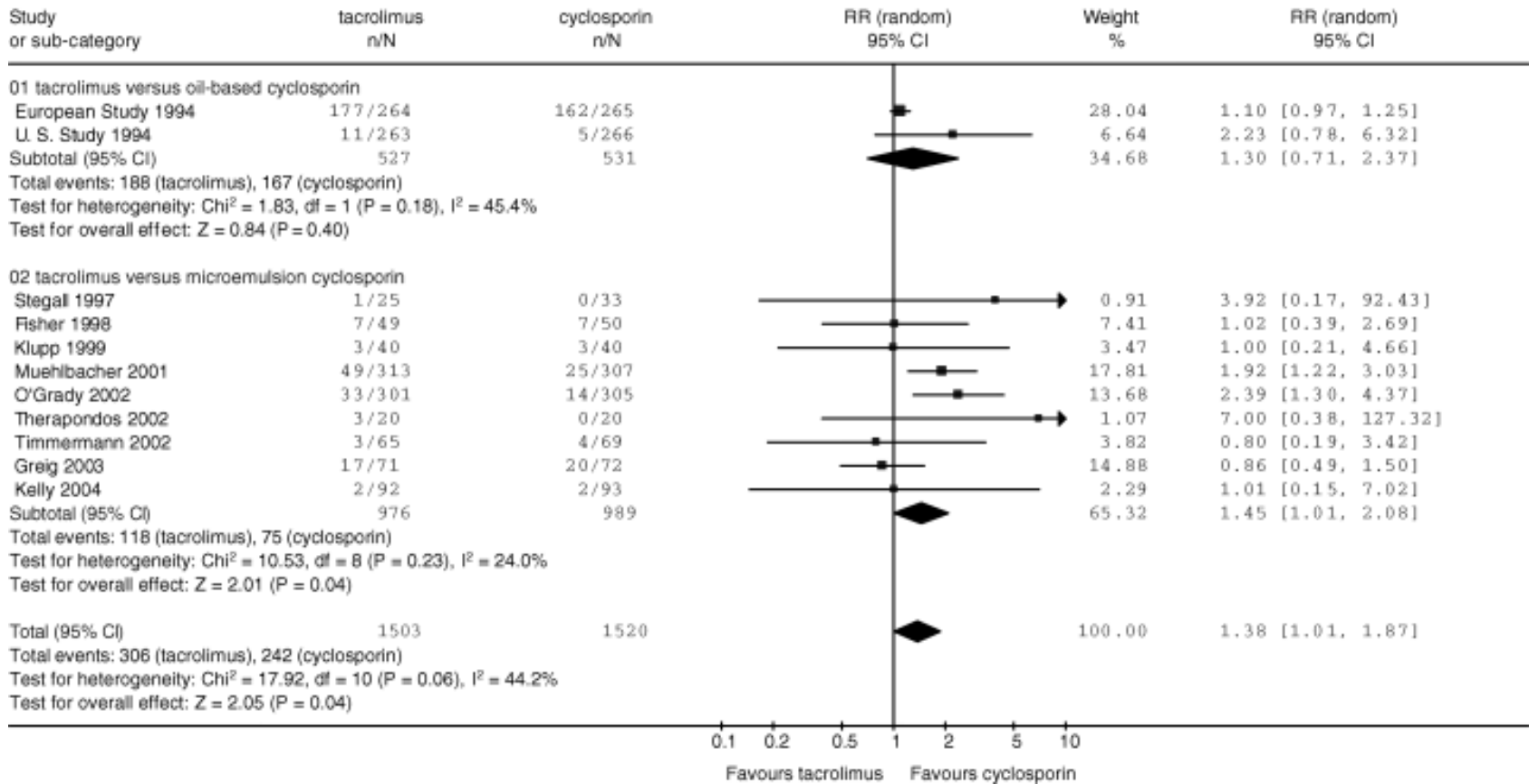


Cyclosporin vs tacrolimus: *de novo* diabetes

McAlister, Am J Transpl 2006;6: 1578-85



Review: Cyclosporin versus tacrolimus for liver transplanted patients
 Comparison: 02 Stratified analysis, by cyclosporin formulation
 Outcome: 06 Diabetes Mellitus: initially diagnosed after transplantation





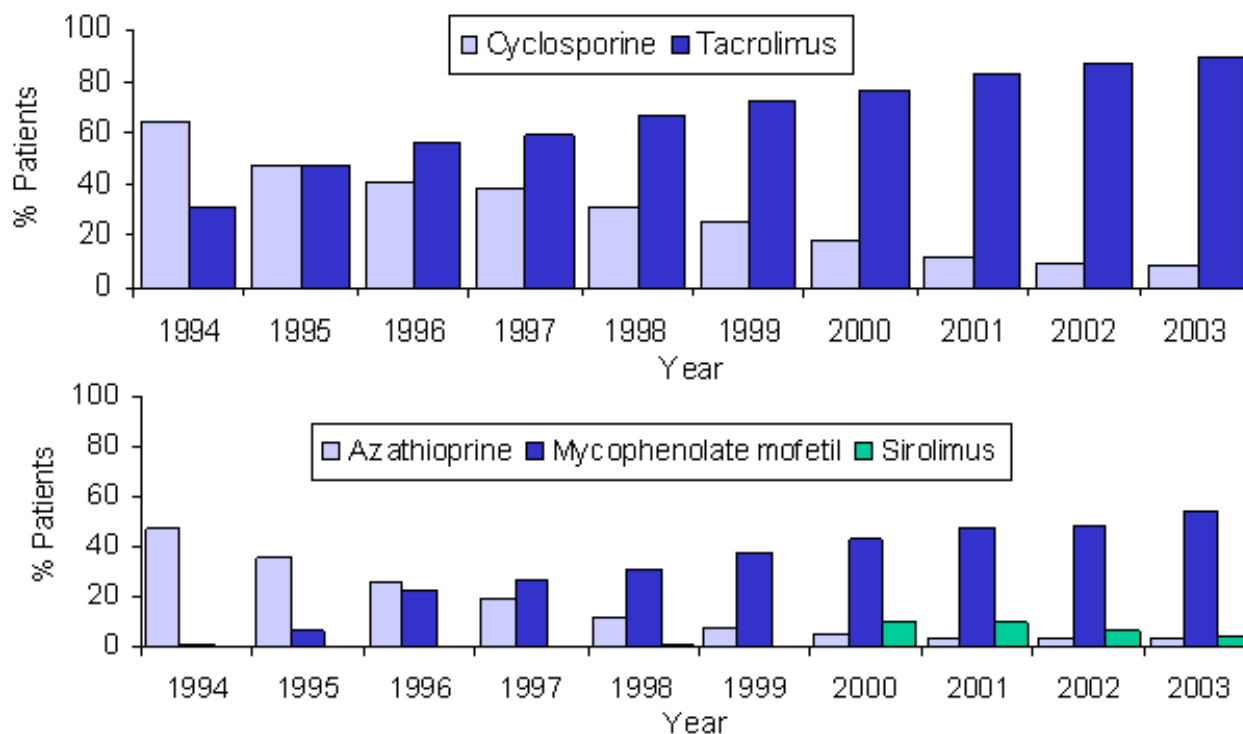
Cyclosporin vs tacrolimus

If you treat 100 patients with tacrolimus instead of cyclosporin, you will experience:

- 2 less deaths
- 5 less graft loss
- 9 less rejection
- 4 additional diabetes mellitus

Novel adjuvant immunosuppressive agents

Figure IV-13. Trends in Maintenance Immunosuppression Prior to Discharge for Liver Transplantation, 1994-2003



Source: 2004 OPTN/SRTR Annual Report, Table 9.6b.



Overview of immunosuppressive agents

- Mycophenolate mofetil
 - Mechanism of action: antimetabolite
Prodrug of mycophenolic acid. Inhibition of inosine monophosphate dehydrogenase, preventing formation GMP
 - Advantages:
 - No nephro- or neurotoxicity
 - Not associated with hypertension, hyperlipidemia, diabetes formation
 - Side effects
 - Gastrointestinal disturbances (dyspepsia, diarrhea)
 - Bone marrow suppression



MMF

- Monotherapy after CNI withdrawal: high rate ACR, steroid resistant rejection, ductopenic rejection
(Schlitt et al., Lancet 2001;357:587-91; Stewart et al., Lancet 2001; 357: 609-10)
- MMF+ TAC + S: lower TAC dosis, improvement liver function
(Fisher et al., Transplantation 1998;66:1616-21)
- Prospective RT of TAC + S vs TAC + S + MMF: fewer ACR, fewer S, improved GFR in MMF group, similar patient and graft survival.
(Jain et al., Transplantation 1998;66:1395-98)



Immunosuppression maintenance which includes MMF is associated with long-term preservation of native kidney function following primary liver transplantation

Ojo et al., Am J Transpl 2007; 7 (suppl 2), 270

- Group 1: CNI + MMF + S (n = 11,726)
- Group 2: CNI + S (n = 8,496)

Results at 3 months:

Risk development CRD 7% lower in MMF group

Kaplan-Meier Analysis and Cox Regression, MMF vs. no MMF and decline in GFR at 3 yrs. posttransplantation

Kaplan-Meier Analysis			Cox Regression*	
% without \geq 25% decline in GFR by 3 yr. post-tx				
CNI+MMF+S	CNI+S	p	HR	p
35.7%	31.3%	<.001	0.93	<.001

*adjusted for recipient, donor & transplant characteristics



Overview of immunosuppressive agents

- Rapamycin (Sirolimus)/Everolimus
 - Mechanism of action: blocks signal transduced from IL-2 receptor to the nucleus by blocking key protein 'mammalian target of rapamycin' (mTOR): signal 3 transduction
 - Advantages:
 - No nephro- or neurotoxicity
 - Side effects
 - Gastrointestinal disturbances
 - Bone marrow suppression
 - Oral ulcerations
 - Elevated cholesterol and triglycerides
 - Impaired wound healing



mTOR inhibitoren in LTX

- 2 phase II/III trials of RAPA (Wyeth Study 211 and 220)
- Several single-center reports
- RCT with everolimus (Novartis Study)

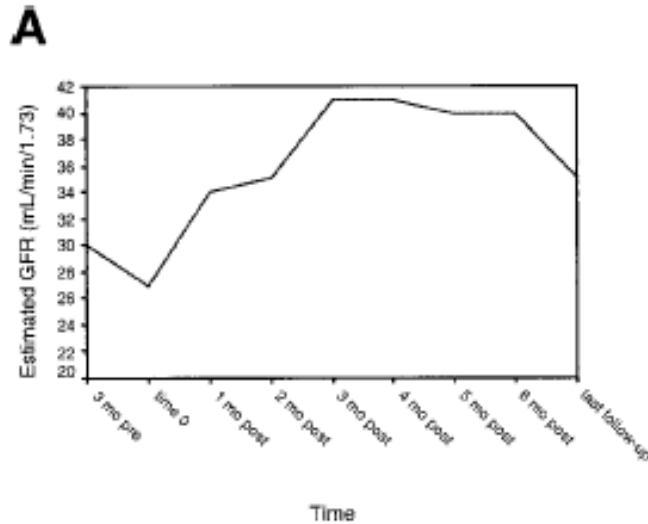


Sirolimus in liver transplantation: thrombosis VP/AH

Fung & Marcos, Liver Transplantation 2003;9:469-72

Table 5. Adverse Events in TAC Versus RAPA/TAC in Liver Transplant Trial			
	TAC (n = 112) No. (%)	RAPA/TAC (n = 110) No. (%)	<i>P</i> Value
Deaths	6 (5.4%)	16 (14.5%)	.025
Graft Loss	4 (3.6%)	11 (10.0%)	.07
Combined	10 (8.9%)	25 (22.7%)	.006
HAT/PVT	2 (1.8%)	9 (8.2%)	.03

Abbreviations: TAC, tacrolimus; RAPA, rapamycin; HAT, hepatic artery thrombosis; PVT, portal vein thrombosis.



Renal function after switching from CNI to sirolimus
 Fairbanks et al., Liver Transpl 2003;9:1079-85

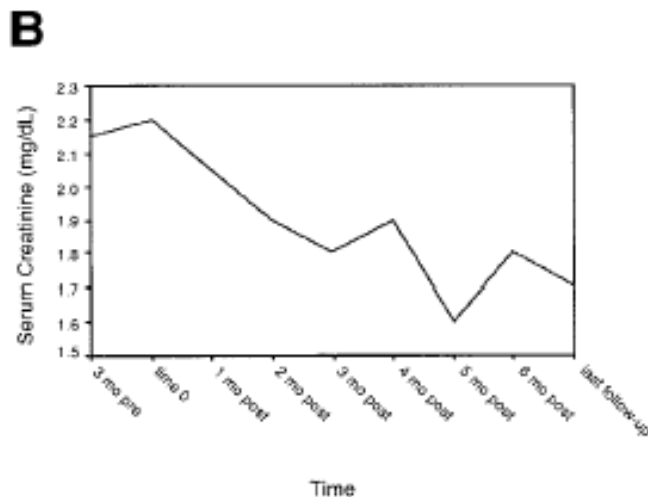


Figure 2. Change in median (A) eGFR and (B) serum creatinine level before and after conversion to sirolimus.



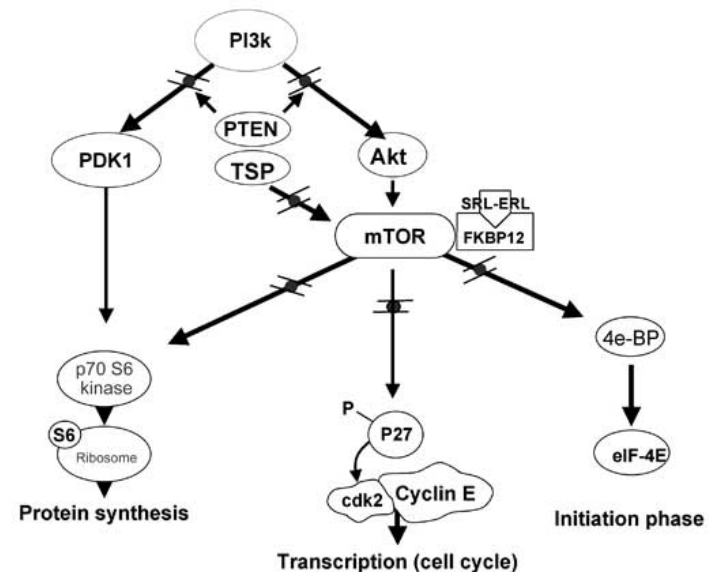
Early (< 90 d) versus late SRL conversion

Rogers et al. WTC 2006, abst # 493

	Early conversion (n=24)	Late conversion (n=12)	CNI based IS (n=27)	P value
MELD	24	20	19	ns
Mean time LT to conversion (days)	44	301	NA	0.004
eGFR at LTx	62	51	78	0.09
eGFR at F/U (> 1 y)	77	39	58	0.03

Antiproliferative effect mTOR-inhibitors

- Multiple oncoproteins result from hyperactivation kinase pathway modulated by mTOR
- Theoretical antineoplastic function of mTOR inhibitors
- Anti-angiogenic properties demonstrated
- Rapamycin inhibits growth multiple cell lines
 - Tumours CNS, breast ca, colon ca
 - HCC, melanoma...
- Sirolimus and everolimus have an antiproliferative effect on transformed B cells in vitro and in mice, suggesting a possible role in prevention and treatment of lymphoproliferative syndrome.



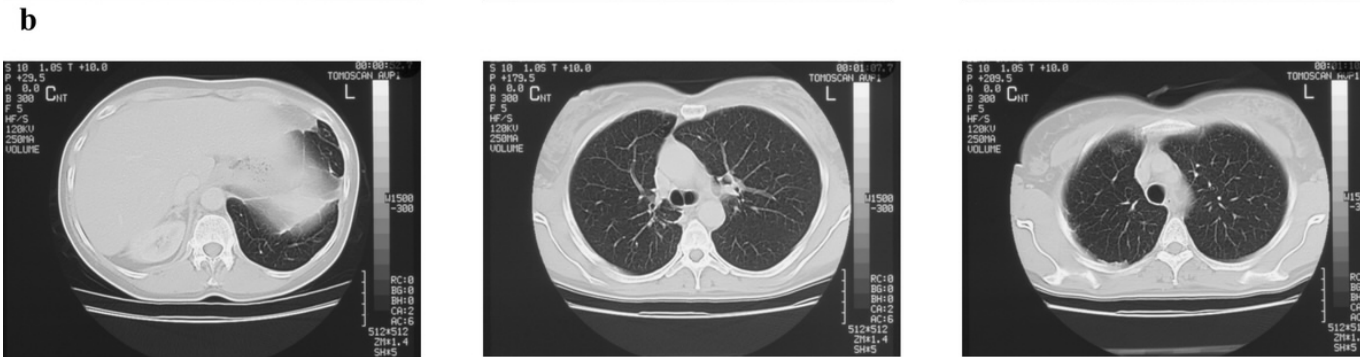
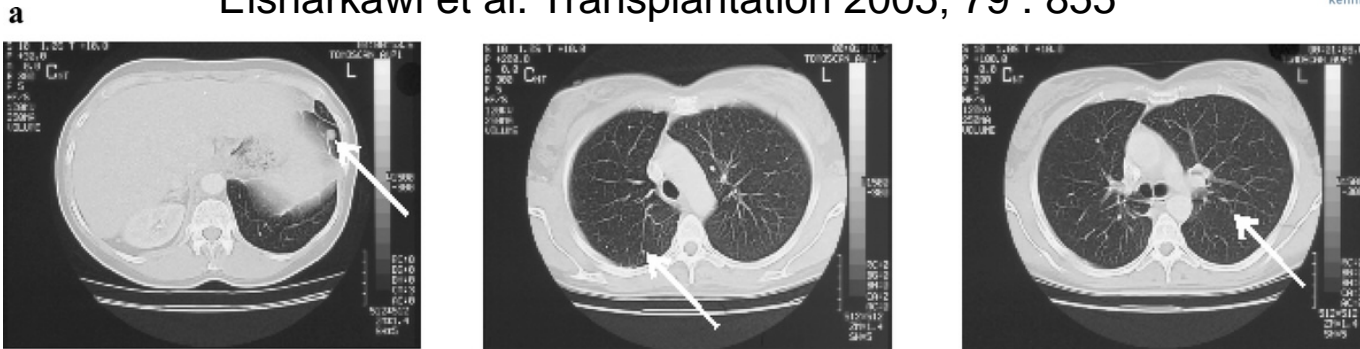


Complete Remission of Posttransplant Lung Metastases from Hepatocellular Carcinoma under Therapy with Sirolimus and Mycophenolate Mofetil



Elsharkawi et al. Transplantation 2005; 79 : 855

Baseline





Role transplant hepatologist

- Selection of patients for liver transplantation
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- **Immunosuppression**
- **Management cardiovascular risk factors**
- **Management of recurrence of disease after LTX**



Risk factors for atherosclerotic cardiovascular disease

- Age
- Male gender
- Smoking
- Arterial hypertension
- Diabetes mellitus
- Physical inactivity
- Obesity
- Excessive alcohol intake
- Elevated LDL cholesterol
- Low HDL cholesterol
- Elevated triglycerides



Dyslipidemia



- Total cholesterol/HDL cholesterol
 - Desirable: < 3
 - Increased risk: > 5
- Pathogenic factors in LTX: corticosteroids, dietary habits, genetic factors, mTOR inhibitors
- Treatment:
 - Diet:
 - Cholesterol intake $< 200-300$ mg/d
 - Restriction total fat 25-30% of daily calories
 - Saturated fats $< 70\%$ of total calories
 - Increased intake soluble dietary fibers
 - If insufficient: statins (pravastatin drug of choice, other statins may interfere with CNI metabolism)



Diabetes mellitus

- Prevalence:
 - 10-30% of LTX candidates
 - De novo diabetes in 20-40%
- Etiology
 - Pre-existing IGT
 - Corticosteroids
 - CNI (CyA > Tac)
 - NAFLD in transplant liver
- Management
 - Yearly screening LTX patients
 - Treatment as in nontransplant setting
 - Diet
 - Insulin-sensitizing agents (metformin/glitazones)



Obesity

- Prevalence
 - Pre-LTX: 20-30% of patients with ESLD
 - Post-LTX: 30-70%
- Pathogenesis
 - Genetic factors
 - Decreased physical activity
 - Side effects of immunosuppression
 - Diabetes
 - Dietary habits
- Management



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- Prevalence
 - Pre-LTX: 20-30% of patients with ESLD
 - Post-LTX: 30-70%
- Pathogenesis
 - Genetic factors
 - Decreased physical activity
 - Side effects of immunosuppression
 - Diabetes
 - Dietary habits
- Management
 - Diet
 - Pharmacotherapy: not sufficiently evaluated
 - Bariatric surgery:
 - Not formally evaluated
 - Cave GI absorption immunosuppressive drugs!



Arterial hypertension



- Frequent after LTX
- Target BP < 140/90 mm Hg; < 130/80 if other risk factors
- Mechanisms
 - Corticosteroids
 - CNI
- Therapy
 - General:
 - Weight reduction
 - Sodium restriction
 - Smoking cessation
 - Aerobic exercise
 - Alcohol restriction
 - Medication
 - Calcium blocker + thiazide diuretic
 - Betablocker + thiazide diuretic
 - ACEI and spironolactone less appropriate (hyperkalemia)



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Table 1. Disease Recurrence After OLT

Etiology of Disease	Recurrence Rate	Five-yr Survival (CI)	Five-yr Graft Survival (CI)
Hepatitis C	>90%	70% (67–72%)	57% (54–59%)
Hepatitis B	<5% with prophylaxis	79% (74–83%)	68% (61–75%)
Hepatocellular carcinoma	8–15%	52% (35–67%)	46% (31–60%)
Primary biliary cirrhosis	11–23%	86% (83–89%)	73% (71–76%)
Primary sclerosing cholangitis	9–47%	86% (83–89%)	73% (71–76%)
Autoimmune hepatitis	16–46%	77% (71–82%)	68% (63–75%)
Alcohol-induced cirrhosis	<5%	72% (68–76%)	65% (61–68%)
Nonalcoholic steatohepatitis	11–38%	73% (68–77%)	66% (61–70%)

CI = 95% confidence interval.

Recurrence rate data from sources quoted in text. Five-yr patient and graft survival (N = 11,791) from Forman *et al.* (5).

Kotlyar DS et al. Am J Gastroenterol 2006;101:1370-78



Hepatocellular carcinoma

- Predictors recurrence
 - Tumour size
 - # tumours
 - Vascular invasion
 - Poor differentiation
 - Satellite lesions
 - Tumour rupture
 - Lymph node involvement



Hepatocellular carcinoma

- Milan criteria (Mazzaferro et al. NEJM 1996;334:693-9):
 - 1 single tumour ≤ 5 cm
 - ≤ 3 tumours each ≤ 3 cm
 - Absence of vascular invasion

Prognosis after LTX similar as without HCC

Is now SE in Eurotransplant (15% initial exceptional MELD)

- UCSF criteria (Yao et al. Hepatology 2001;33:1394-1403)
 - 1 single tumour ≤ 6.5 cm
 - ≤ 3 tumours (largest ≤ 4.5 cm)
 - Maximal total tumour size ≤ 8 cm
- 1 y survival 90%, 5 y survival 75%



Hepatocellular carcinoma and LTX

AASLD Practice Guidelines, Hepatology 2005;42:1208-36

Recommendations

14. Liver transplantation is an effective option for patients with HCC corresponding to the Milan criteria: solitary tumor ≤ 5 cm or up to three nodules < 3 cm (level II). Living donor transplantation can be offered for HCC if the waiting time is long enough to allow tumor progression leading to exclusion from the waiting list (level II)./

15. No recommendation can be made regarding expanding the listing criteria beyond the standard Milan Criteria (level III).

16. Preoperative therapy can be considered if the waiting list exceeds 6 months (level II).



AIH

- Recurrence rate: 16-46%
- DD: acute, chronic rejection, viral hepatitis
- Timing of recurrence poorly studied
- Treatment: as pre-LTX
- Prevention: maintenance patients with AIH on corticosteroids and/or higher IS to prevent rejection and recurrence (?)



PBC

- Recurrence rate 11-23% in 3-6.6 y, mostly slow progression
- Diagnosis: pathology (granulomatous bile duct destruction, plasma cell infiltration)
- Treatment: UDCA (?)



PSC

- Recurrence rate 9-47%
- DD: ischemic or infectious bile duct strictures
- Treatment: UDCA (?)



ALD

- Prevalence:
 - Death due to recurrence ALD rare (5%)
 - Dependent on definition
- Predictors:
 - Duration abstinence pre-LTX
 - Daily dose of drinking pre-LTX
- ALD returning to drinking worsened mortality not to graft failure ut to comorbidities



NASH

- Prevalence: 11-38% (in small series)
- Progression from NAFLD to NASH post LTX documented in small serial biopsies in some patients



Liver transplantation: the Hepatologists point of view Summary



- In LTX, CNI remain the backbone of immunosuppressive protocols.
- The availability of a number of immunosuppressive medications with variable potencies and side effect profile allows for tailoring the regimen to the individual patient.
- The transplant hepatologist should be aware of management common risk factors for atherosclerotic cardiovascular disease and recurrence of diseases after LTX.