Approach to immuno-suppression in immune mediated liver disease – does standard therapy apply?

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BTS British Transplantation Society
The Voice of Transplantation in the UK

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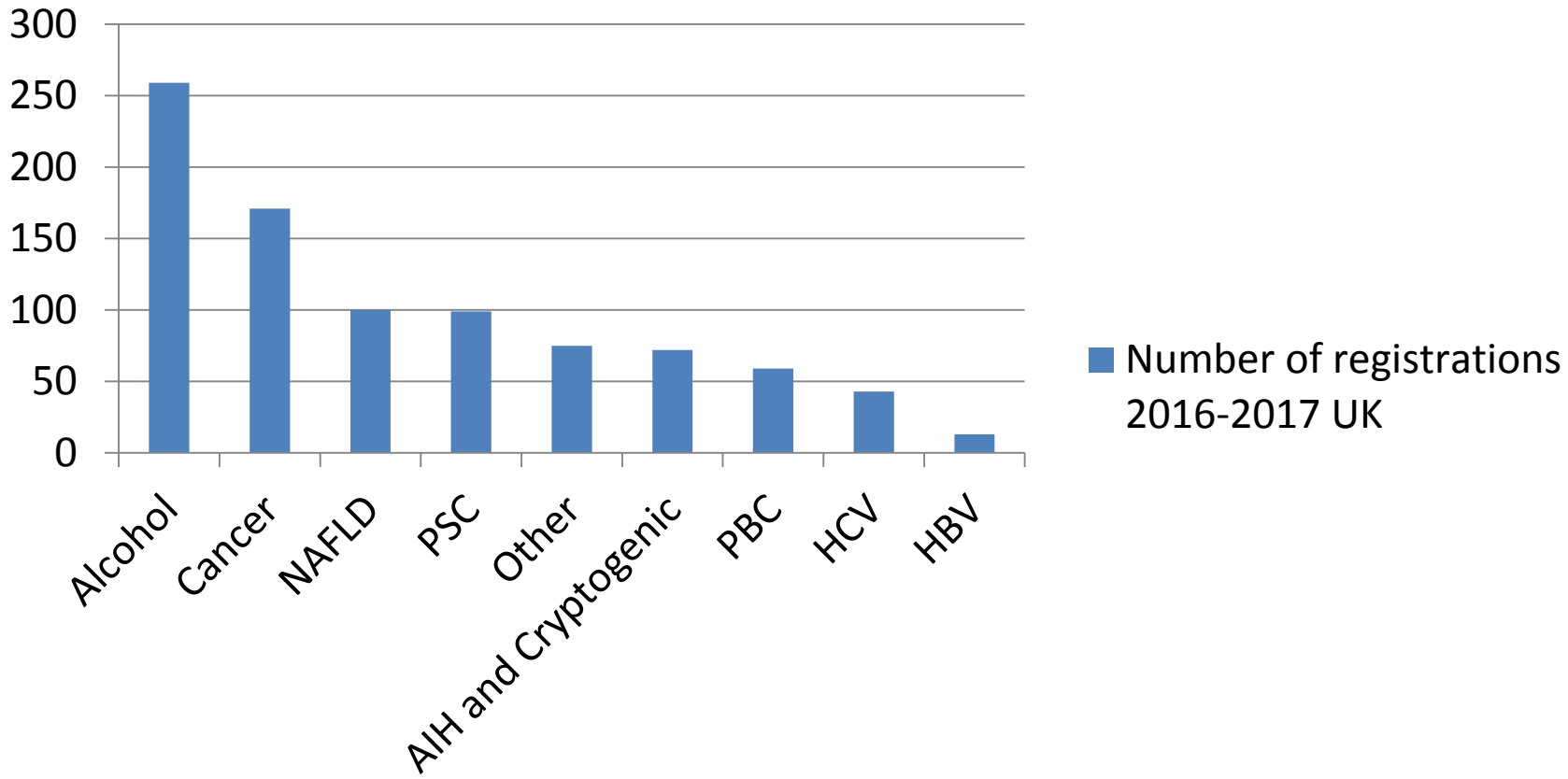
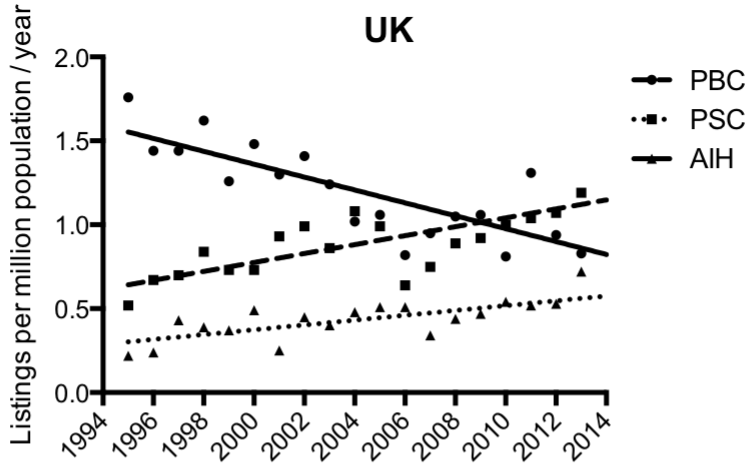
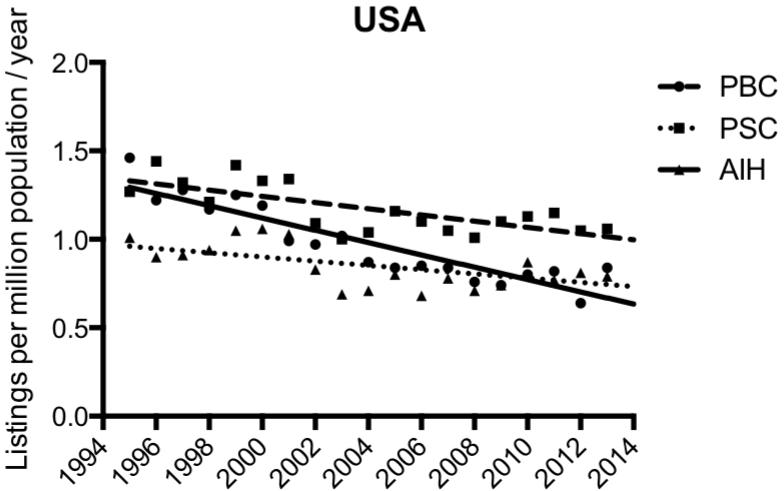

300
250
200
150
100
50
0
Alcohol
Cancer
NAFLD
PSC
Other
AIH and Cryptogenic
PBC
HCV
HBV
Number of registrations 2016-2017 UK





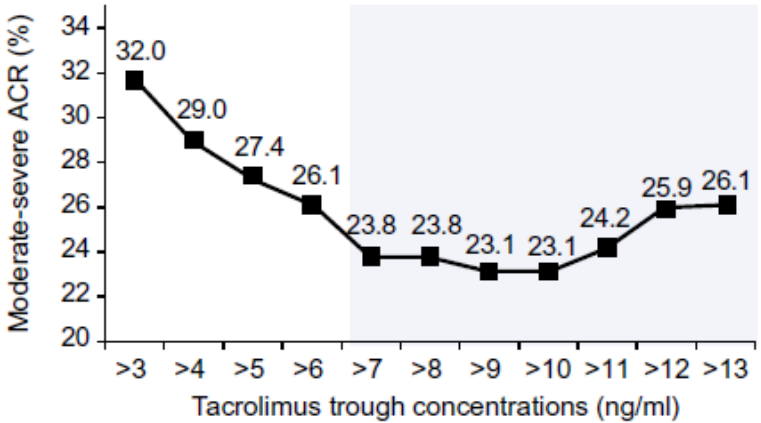
Webb G et al Clin Gastroenterol Hepatol 2018 Feb

Are patients with autoimmune liver disease at greater risk of ACR?

Variables		
Age (yr)		48 ± 11
MELD		18.3 ± 9
Gender	Male	308 (62.5%)
	Female	185 (37.5%)
Aetiology	Hepatitis C	116 (23.6%)
	Alcoholic liver disease	119 (24.1%)
	Hepatocellular carcinoma	60 (12.2%)
	Autoimmune*	112 (22.7%)
	Acute liver failure	43 (8.7%)
	Others	43 (8.7%)
Immunosuppression protocol	Tac monotherapy	237 (48.1%)
	Tac + steroids	39 (7.9%)
	Tac + azathioprine	17 (3.4%)
	Tac + azathioprine + steroids	145 (29.4%)
	Tac + mycophenolate	33 (6.7%)
	Tac + mycophenolate + steroids	22 (4.5%)
Protocol biopsy-histological rejection	No rejection	101 (20.5%)
	Mild rejection	216 (43.8%)
	Moderate rejection	157 (31.8%)
	Severe rejection	19 (3.9%)

Rodriguez-Peralvarez et al J Hep 2013

- Patients with autoimmune disease (primary biliary cirrhosis, primary sclerosing cholangitis and autoimmune hepatitis) had moderate/severe ACR in 42.9% compared to 33.6% of cases in other indications



Rodriguez-Peralvarez et al J Hep 2013

Does it matter?

- No association with ACR and recurrent AIH

  Wright et al Transplantation 1992

- ACR is not a major cause of graft loss

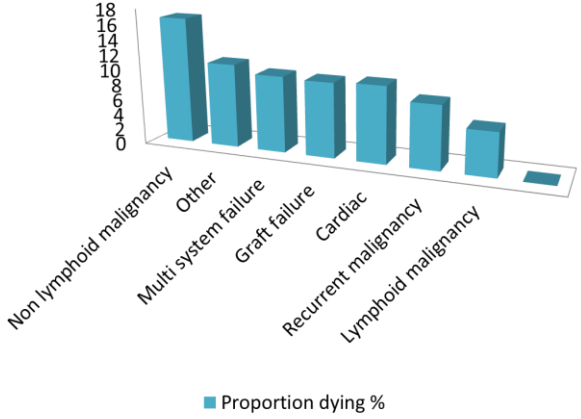
- Sepsis a common problem early on in patients transplanted for AIH given prior history of Immunosuppression

  Duclos-Vallee et al Gut 2003

- Late acute rejection after liver transplantation impacts patient survival

Uemura et al Clin Transplant 2008

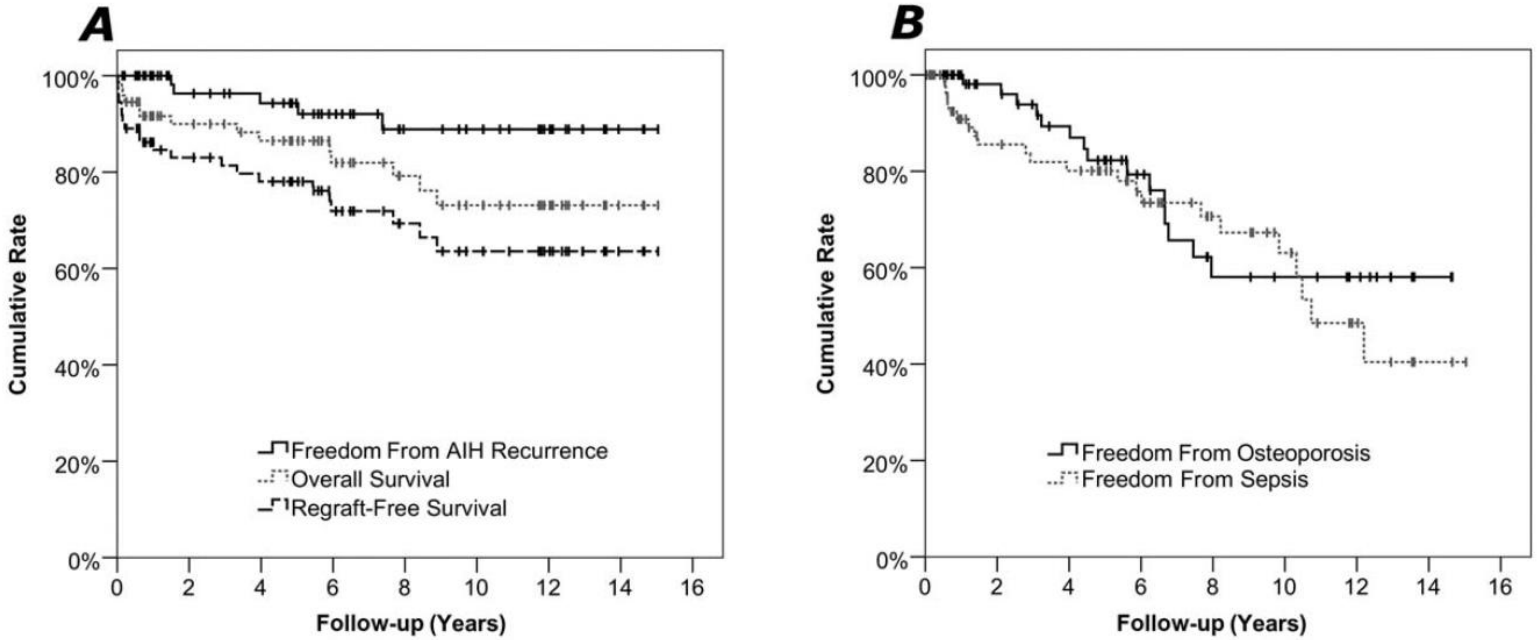
- Late acute rejection is more common in patients with PBC, AIH and PSC



Does long term steroid use reduce the rate of recurrent disease in AIH?

Author	Cohort size	Median follow up (months)	Recurrence rate (%)	Median time to recurrence (months)	Diagnostic criteria
Milkiewicz et al	47	50	28	29	Biochemical / Histological
Reich et al	32	27	25	15	Biochemical/ Histological
Gonzalez-Koch et al	41	72	17	52	Histological

Steroid use and prevention of rec AIH

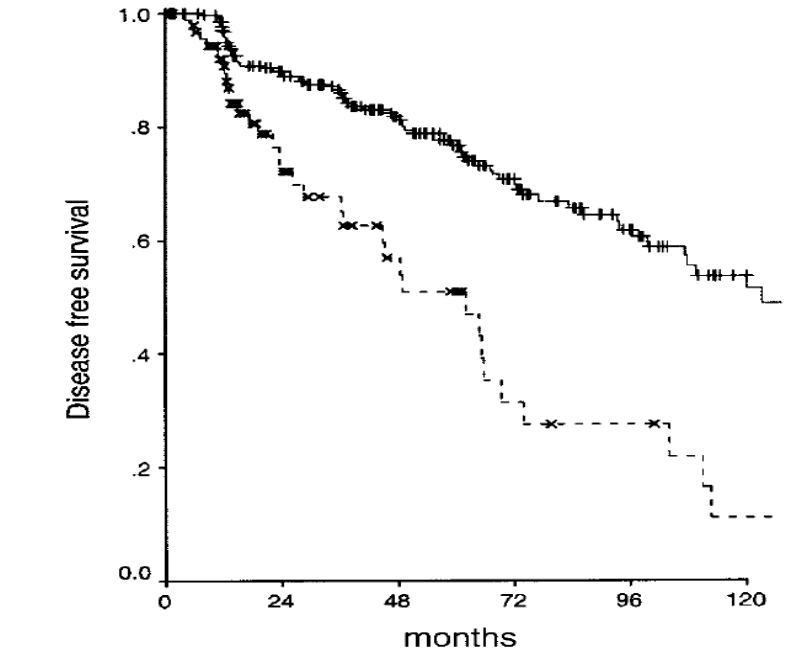


Krishnamoorthy et al Liver Transpl 2016

Cyclosporin vs Tacrolimus in PBC

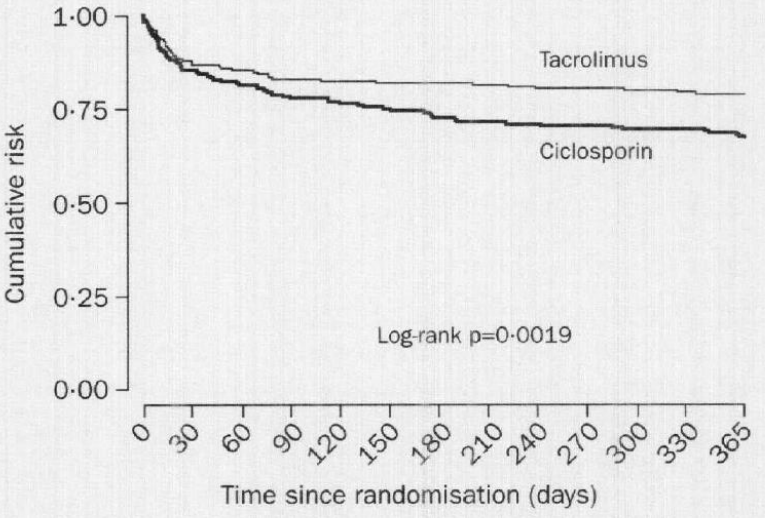
Author	Cohort size	Median follow up (months)	Recurrence rate (%)	Median time to recurrence (months)	Diagnostic criteria
Sanchez et al 2003	156	72	13	50	Histological
Neuberger et al 2004	485	79	23	123 (Cyc) 62 (Tac)	Histological
Jacob et al 2006	100	118	14	61	Histological

Cyclosporin vs Tacrolimus in PBC



Neuberger et al Liver Transpl 2004

Is recurrent PBC important enough to change TAC?



Number of patients at risk

Tacrolimus	301	262	258	251	250	247*	246	245	242	241*	239	238	237
Ciclosporin	305	261	247*	236†	230	226	219	215	213	212	210	209	204

Figure 2: **Survival plot showing freedom from primary endpoint (combined treatment failure, retransplantation, or death)**

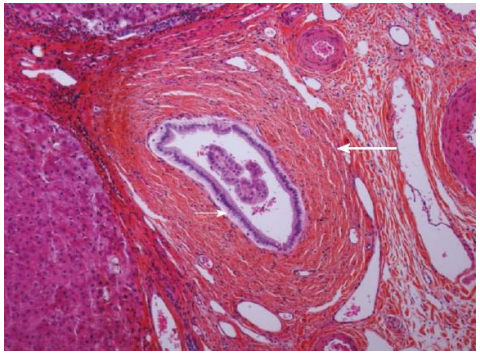
Preventing recurrent PSC

Authors	Cohort size	Median follow up range (months)	Recurrence rate (%)	Median time to recurrence (months)	Diagnostic criteria
Graziadel et al 2002	150	55	27	46	Radiology/ Histology
Vera et al	152	53	37	36	Radiology/ Histology
Campsen et al	130	66	17	NA	Radiology/ Histology
Alabraba et al	230	83	23	55	Radiology/ Histology

Immunosuppression and recurrent PSC

- No evidence of a link between ACR and recurrent PSC
- The choice of Immunosuppression seems to have no influence on the incidence or progression to recurrent PSC

Fosby et al WJG 2012



IBD and risk of ACR
Immunosuppression and IBD/PSC

- the incidence of moderate or severe rejection in patients with IBD was 70% vs 36% in PSC patients without IBD, and 37 % in a matched control group

Narumi et al Hepatology 1995

- Young age at diagnosis of IBD and dual treatment with tacrolimus and mycophenolate mofetil were significant risk factors for increased IBD activity after transplantation, whereas combination treatment with cyclosporin A and azathioprine had protective effects

Jorgensen et al Clin Gastroenterol 2013

Summary

- Increased risk of ACR and late acute rejection in patients with autoimmune liver disease
- Some evidence to suggest that long term steroid use protects against recurrent AIH
- Cyclosporin is associated with less recurrent PBC; however in practice tacrolimus is still used due to its clinical benefits
- No link between immunosuppression choice and recurrent PSC