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REVIEW

Minimization of steroids in liver transplantation

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Summary

Because of the markedly improved short-term results of liver transplantation (LT) and persistently high number of long-term complications, the attention of transplant physicians should be focused on minimizing immunosuppressive therapy as much as possible. Steroid-based immunosuppression is responsible for a substantial post-LT morbidity and mortality, hence, minimization of its use is of utmost importance to improve the quality of life of the successfully transplanted liver recipient. This literature review shows that LT can be performed safely with steroid-minimal immunosuppression without compromising graft and patient survival. The tendency in clinical practice is to move more and more from steroid withdrawal to steroid avoidance protocols.

Introduction

Because of the markedly improved results of organ transplantation in general and of liver transplantation (LT) in particular, the medical transplant community must pay more attention to long-term outcome of recipients [1]. The design of immunosuppressive protocols using combinations of different drugs that reduce their respective toxicities or protocols aimed at minimization or even withdrawal of immunosuppression (IS) are therefore most desirable [2–10]. From the very beginning of transplantation, steroids have been very popular as immunosuppressive drug. They are easy to handle and allow control of most rejections at a very low cost. They however interfere both with the recipient's quality of life and also with the active process of graft tolerance [1–6]. Systematic use of steroids should thus be avoided in view of their adverse effects on different organ systems which seriously compromise performance status and quality of life of the successfully transplanted liver recipient [2,6,10] (Table 1). Drug combinations minimizing or even avoiding steroids as well in induction as in maintenance IS protocols are therefore major steps to reduce post-transplant complications and to improve quality of life [11–14]. Steroid minimization protocols also have been proved to lower the yearly costs of transplantation by more than 5000$ [15,16]. It should also be noted that a majority of (renal) recipients prefer, because of the important side-effects, withdrawal of steroids over withdrawal of other immunosuppressive drugs [17].

Although steroid minimization (this means 'steroid-poor and steroid-free') IS schemes have already been used successfully for 25 years in renal, pancreatic, hepatic, heart and even intestinal transplantation, steroid-free IS still remains controversial due to the lack of evidence-based selection criteria, of well-conducted large clinical trials and of long-term follow-up studies looking at graft survival and chronic allograft rejection [18–29]. The results of the only available Canadian multicentre randomized prospective renal transplant long-term study showing that the adverse effect on renal allograft survival became clear only after 5 years of follow-up should be

Table 1. Side effects of glucocorticoid treatment.

Adverse effect on		
Cardiovascular risk factors	Diabetes mellitus	10% (3–17)
	Hypertension	15% (75–83)
	Lipid metabolism	36–68%
	Prothrombotic state	
Wound healing		
Septic ulcer disease		
Defense toward infection	CMV	15%
Tumor formation		
Linear growth		
Osteoarticular and muscular system	Osteopenia	
	Osteoporosis	
	Pathologic fractures	2% (1.1–5.5)
	Avascular necrosis	8% (10–15)
	Myopathy	
Cataract and glaucoma formation		10% (9–21)
Body figurement	Hirsutism	
	Cushing – obesity	
	Adrenal insufficiency	
Psychologic well being	Psychosis	
	Depression	
Increased risk of	Infection	
	Cancer	

Estimation of the incidence of adverse effects related to the use of steroids is difficult as many of them are also influenced or even reinforced by the use of other immunosuppressant drugs, i.e., CNI.

kept in mind (73% rejection rate in placebo group vs. 85% in low-dose steroid group – $P < 0.03$) [30].

As a consequence of all these arguments, steroids are still considered in many transplant centers to be the cornerstone of induction and maintenance [2–4,6,31,32].

Fortunately, the debate is easier to manage in the field of LT as it is well known from both experimental and clinical transplantation that the liver allograft has a immunoprivileged status, a condition that is beneficial for the development of IS minimization protocols [1–3,5,31,33]. This immunoprivilege is exemplified by the resistance of LT to positive cross-match, the irrelevance of HLA-matching, the reduced incidence of hyperacute rejection, the spontaneous recovery following severe rejection, the fact that a single rejection does not affect adversely graft outcome, the reduced incidence of chronic rejection and finally the reversal of chronic allograft rejection in up to 30% of cases [1]. The recent introduction of newer and more specific antibody induction therapies and of more powerful antimetabolite drugs has allowed to enlarge the implementation of steroid minimization protocols [6–8,11–13,34,35].

Steroid minimization can be achieved in many different ways using low-dose steroids from the moment of LT, early (within days or weeks) or late (within months) steroid withdrawal (STWD), use of alternating doses of steroids and finally, partial or complete avoidance of steroids (STAV) in induction as well as in maintenance therapy and/or in the treatment of rejection [3,4,6,31].

This review article aims at giving an overview of the actual status of steroid minimization protocols in the field of LT based on a detailed analysis of 51 peer and six non-peer-reviewed papers containing sufficient information to allow meaningful interpretation of results. The six non-peer-reviewed studies were published in *Transplantation Proceedings*; they were included in this review because their content was judged sufficient to draw adequate conclusions. For reasons of clarity, all important conclusions of the different scrutinized studies are represented in three synoptic tables (Tables 2–4). All significant advantageous differences are indicated in bold. The high variability of some data and results (i.e. in relation to frequency of rejection and reintroduction of steroids) reflects the different study designs, the lack of standardization of the pathology of acute rejection, the learning curve in relation to these newer immunosuppressive approaches and finally the continuously changing attitude of the transplant physicians adopted during a 15-year time span in relation to the treatment of liver recipients.

Literature review

Steroid withdrawal and LT

The Birmingham group under the lead of McMaster was the first to show in 1993 that LT without long-term steroid use was a beneficial undertaking [36]. By the end of 2007, 19 and 11 more STWD studies had been reported in adult [37–58] and in pediatric LT [54,59–66] (Tables 2 and 3).

The pediatric studies, usually dealing with late STWD (range from 3 to 201 months), showed that this attitude is possible without compromising as well patient (4–7% patient loss) as graft survival (0–13% graft loss). The only prospective evaluation of STWD in children was included in a larger adult study published by Mc Diarmid [54]. Four of the 11 studies were reported in a nonpeer-reviewed journal. Most pediatric studies were carried out in a Cyclosporine (CsA)-based IS population. Improvement in side effects was, as expected, poor due to the (too) late STWD.

The analysis of the adult experience is of greater interest as steroids were withdrawn after a usually shorter time period (ranging from 6 days to 24 months). Of nine prospective randomized controlled studies, only two were performed in a double-blind, placebo-controlled fashion [50,52]. In several studies, STWD was considered only after a stable graft function for a period of 6–12 months. CsA-based IS was part of IS protocol in 14 and tacrolimus (TAC)-based IS in eight studies. With follow-up

Table 2. Steroid withdrawal (STWD) in adult liver transplantation.

Year	Author	Ref	Center	Induction IS	No. pat.	Follow-up (months)	STWD time (months)	Success (%)	Rejection (%) Acute (CRR)	Rejection (%) Chronic	Advantages	Particularities	Graft Surv (%)
1993	Padbury Prospective	36	Birmingham, UK	CsA/AZA/STER CsA/STER.	197	28 med. (5–109)	≥3 (1–32)	85 → 71*	4.5	3.9	Art. hypertension Infection, Diabetes	Monotherapy CsA (47.2%)	94 GS PS 1 year
1995	Punch Selection†	37	Ann Arbor	CsA/STER/ATG or ALG	51	13.8 med. (4–36)	≥12 (stable >12 months rejection free; >6 months)	88	12	/	**Art. hypertens. Cholesterolemia** Weight loss		100 PS
1996‡	Tchervenkov Selection†	38	Montreal	CsA/STER/ATG/AZA	42	3–12	≥12 (stable, rejection free 6 months)	93	9	/	**Art. hypertens. Cholesterolemia Diabetes**	Monotherapy CsA (93%)	100 PS 1 year
1996	Fraser Retrospective	39	London, UK	CsA/AZA/STER ± ATG	114	27 ± 18.5	6.7 ± 3.9	84.2	8.3	3	Diabetes	Monotherapy CsA (29.2%)	(95.8)
1997	Stegall Prospective Selection: HBV patients	40	Denver	CsA/STER	28		>24	75	14.2	/	Art. hypertension Diabetes **Cholesterolemia**	Monotherapy CsA (75%)	(100)
1997	**Stegall Prosp. rand.**	41	Denver	NEORAL/STER/MMF	36	>6	14 days	100$	46	/		Monotherapy CsA/TAC (21.4%) at 6 months	91.7 GS 94 PS
	Open			TAC/STER/MMF	35		14 days	88.2	42.3		**Art. hypertens. Cholesterolemia**		85.7 GS 88.6 PS 6 months
1997‡	**Pichlmayr Prosp. rand.**	42	European MC	TAC/STER. CsA/AZA/STER ± ATG	264 265	36	36	80.3 68.1	45.4 55.1	2 6.9			70.6 65.3 3 years
1998	**Belli Prosp. rand.**	43 44¶	Milan	CsA/AZA/STER/R-ATG	54	41 mean	>3	98.5**	4	0	**Art. hypertens. Diabetes**		83 PS
					50	(4–68)	(4–5)		8	3	No difference HCV recurrene¶		82 PS 2 years
1998	**Tisone Prosp. rand.**	45	Rome	NEORAL/AZA/STER NEORAL/AZA	22	14 median	3	100	9.1	0	**Cholesterolemia Diabetes**		70.2
					23	(6–24)	0		8.7	0			78.3 2 years
1998	Gomez Prospective Selection†	46	Madrid	CsA/AZA/STER	86	23 mean (12–58)	>12 (stable graft > 12 months; 36 ± 18)	100	0	0	**Art. Hypertens. Cholesterolemia Body weight Bone disease** Diabetes	Monotherapy CsA if possible (83.5%)	100

Table 2. continued

Year	Author	Ref	Center	Induction IS	No. pat.	Follow-up (months)	STWD time (months)	Success (%)	Rejection (%) Acute (CRR)	Rejection (%) Chronic	Advantages	Particularities	Graft Surv (%)
1999	Lerut Retrospective	47	UCL – Brussels	CsA/AZA/STER (Sandimmun)	69	≥60 (7.8–96)	7 (3–42)	97.1 88.6	10	4.3	Art. hypertension Cholesterolemia Diabetes Bone disease	Monotherapy CsA 66. 6% at 60 months	74.3 5 years
2001	Mc Alister Prospective	48	Halifax	TAC/SRL/STER	56	23 med. (6–35)	3–12	91	14	/	Renal function Diabetes, Lipids		91 GS 93 PS
2003	**Greig** **Prosp. rand.**	49	Canadian MC	NEORAL/AZA/STER	72	3–12		75	43 (9.7)	0			**86 GS** **89 PS**
	Open label Selection: no rej <3 months prerandom. HBSAg+, renal failure			TAC/AZA/STER	71			63	35 (5.6)	0	No difference HCV recurrence		**97 GS** **97 PS**
2004	**Pageaux** **Prosp. rand.** **Double blind** **Plac. control.**	50	French MC	NEORAL/BAS /PLAC intraop. steroids 7 days	84	6	7 days	61.9	**38.1** (9.5) (39.3 at 1 year)	7.3	*De novo* diabetes	67.9% pts completed study	90.5 GS 91.7 PS
	Selection: high d 0–7, renal failure, graft dysfunction, surg complic. Ac rej. before random. at d7			NEORAL/BAS/STER intraop steroids. and steroid taper after 7 or 14 days	90				**24.4** (3.3) (25.6 at 1 year)	9.3	Less severe rejection No difference HCV recurrence	84.4% pts completed study	97.8 GS 97.8 PS at 6 months
2007	Ramirez Retrospective	51	Philadelphia	TAC/BAS/STER ± MMF (3 months) intraop. steroids 1gm	42	18.1 med (4.8–35.9)	>1 month	77 (10 months) 87 (last FU)	7.1 at 3 months			Monotherapy TAC. 77% at last follow-up	93 GS 93 PS 2 years
2007	**Moench** **Prosp. rand.** **Double blind** **Plac. control.**	52	Mainz	TAC/STER > PLAC	56		14 days	51.8	48.2 (0.9)	1.8	***De novo*** **diabetes** **Cholesterolemia** **Hypertriglycerid.** **at 6 months** CMV infection Art. hypertension	Majority of rej. <60 day 62.5% pts completing FU	85.7 GS 85.7 PS
				TAC/STER all intraop. steroids and steroid taper at d 14	54		6 months	64.8	35.2 (0)	0		66.7% pts completing FU	88.8 GS 88.8 PS

Table 2. continued

Year	Author	Ref	Center	Induction IS	No. pat.	Follow-up (months)	STWD time (months)	Success (%)	Rejection (%)		Advantages	Particularities	Graft Surv (%)
									Acute (CRR)	Chronic			
2008	**Chen Prosp. rand.**	53	Wuhan	TAC/MMF/STER	28	12	3		14.3		***De novo* diabetes Cholesterolemia HCCa recurrence (39.2% vs. 69.2%)**	All extended HCCa All adjuvant chemotherapy	64.2 PS
				TAC/MMF/STER	26				11.5				46.1 PS
HCV STUDIES													
2006	Berenguer Historical control	56	Valencia	NEORAL/TAC-STER	90		>6 months				Less severe recurrence Less graft loss		
				NEORAL/TAC-STER	52		<6 months						
2007	**Vivarelli Prosp. rand.**	57	Bologna Padova	TAC/STER Rapid taper	23	28 (4.3–45.9)	3		8.6				76.7 PS
	Selection: early graft, patient loss			TAC/STER Slow taper all intraop. steroids	16		24		25		**Less advanced fibrosis and cirrhosis at 1 yr (7.7 vs. 34.7%) More fibrosis-free survival (93.7% vs. 65.2%)** No difference HCV recurrence		80.8 PS 2 years
2007	**Humar** Prosp. historical control	58	Minneapolis	TAC/MMF/BAS STER 6 days	83	16.1	6 days		11		***De novo* diabetes at 6 months Histolgical HCV Recurrence (39% vs. 56%)**		86 GS 88 PS
	Selection: Autoimmune disease			TAC/MMF/STER	83	32			12				81 GS 81 PS
PEDIATRIC STUDIES													
1995	**Mc Diarmid Prosp. rand.**	54	Los Angeles	CsA/AZA/STER.	33	23 mean	≥12 (stable, rejection free	94	6.5	0	Cholesterolemia	24 (72.3%) adults!	100 GS
	Open label Selection†				31		> 6 months < 2 rej; autoimmune disease)		6	0		17 (54.8%) adults!	

Table 2. continued

Year	Author	Ref	Center	Induction IS	No. pat.	Follow-up (months)	STWD time (months)	Success (%)	Rejection (%)		Advantages	Particularities	Graft Surv (%)
									Acute (CRR)	Chronic			
2003	Vo Thi diem Retrospective Selection†	55	UCL-Brussels	CsA/STER NEORAL/STER	25 25	3.1 med 2.8 med	8.2 years 7.9 years		0 4	0 0	Advantage Growth especially if STWD < 2 years Art. Hypertension	34% of total pediatric population	
				TAC/STER	59	2.2 med 8.1 med (1.6–16.8) years	2.3 years (all stable graft)		0	0	**Renal function** **Cholesterolemia**	Three step STWD: Reduction > Alternate-day > Withdrawal	

All data in bold indicate statistically significant differences.

CsA, cyclopsorine; STER, steroids; AZA, azathioprine; SRL, sirolimus; TAC, tacrolimus; MMF, mycophenolate mofetil; PLAC, placebo; DAC, dacluzimab; BAS, basiliximab; STWD, steroid withdrawal; MC, multicentre; CRR, corticosteroid-resistant rejection; HCCa, hepatocellular cancer; PS, patient survival; GS, graft survival.

*Steroid therapy restarted because of reasons other than rejection.

†Selection mostly based on graft stability (>6 to 12 months) and absence of recent rejection.

‡Papers published in nonpeer-reviewed journal (*Transplantation Proceedings*).

$12.5% of patients switched to TAC because of recurrent rejection.

¶Reported later on in separate report dealing with same patient cohort.

**Long-term therapy restarted because of intractable pruritus and severe cholestasis in one patient.

Table 3. Steroid withdrawal in pediatric liver transplantation.

Year	Author	Ref.	Center	Induction IS	No. pat.	STWD time (months)	Acute rejection (%)	Chronic rejection (%)	Graft loss (%)	Patient loss (%)
1989*	Margarit	59	Barcelona	CsA/STER	15	7	13	13	13	7
1993*	Superina	60	Toronto	CsA/AZA/STER	33	>12	–	–	–	–
1994	Murphy	61	Birmingham	CsA/AZA/STER	135	3	27	10	6	3
1994	Dunn	62	Philadelphia	CsA/AZA/STER	28	18	7	4	4	4
1995	**Mc Diarmid Prosp. rand**.	54	Los Angeles	CsA/AZA/STER	7	≥12	(6.5)	0	0	
1997*	Martin	63	Montreal	CsA/STER	55	58	11	–	–	–
1997	Mc Kee	64	Baltimore	TAC/STER	29	6	29	–	4.1	–
1998*	Andrews	65	Dallas	CsA/STER	53	54	13	–	–	–
1999	Jain	66	Pittsburgh	TAC/STER	166	<12	21	–	0	0
2000	Reding	31	UCL-Brussels	TAC-Neoral/AZA/STER	78	8.4–164	8	0	0	0
2003	Vo Thi diem	56	UCL-Brussels	CsA-Neoral-TAC/STER	119	1.6–16.8 years	3.4	0	0	0

*Papers published in nonpeer-reviewed journal.

ranging from 3 to 109 months, STWD was obtained in 61.9–100% of patients. The incidences of acute and chronic rejection varied from 4.5% to 55.1% and from 0% to 9.3%, respectively. In seven studies, CsA monotherapy was achieved in 29.4–83.5% of patients and in one study TAC monotherapy was achieved in 77% of patients. Graft- and patient-survival rates were excellent. Ten studies showed significant benefits in relation to diabetes, lipid metabolism, arterial hypertension and sometimes in relation to bone disease. Our group showed that STWD was successful in 91.7% of patients even when using the old formulation of CsA (Sandimmun®; Novartis, Basel, Switzerland); in this study, 66.6% of patients reached CsA monotherapy at 5 years [47].

The prospective randomized, double-blind, placebo-controlled French multicenter and Mainz studies are of particular interest. Pageaux *et al.* [50] showed that the incidence of acute rejection was significantly higher in the STWD group (38.1% vs. 24.4%). Moench *et al.* [52] showed, however, that the short-term STWD group had significantly less diabetes and hypercholesterolemia.

Chen *et al.* [53] showed that early STWD could be of benefit in relation to the incidence of recurrence of advanced hepatocellular cancers.

Three studies were carried out to analyze the impact of STWD on hepatitis C virus (HCV) allograft recurrence. Berenguer *et al.* [56] and Vivarelli *et al.* [57] indicated that late STWD (after more than 6 months) and slow steroid taper (over a period of 24 months) were associated with less severe HCV recurrence. Humar *et al.* [58] showed, however, in a historical control study that histologic recurrence was significantly lower after rapid discontinuation of steroids.

In several studies, steroids had to be re-introduced for extrahepatic manifestations of the liver disease, autoimmune phenomena and renal impairment [44,67]. Steroid minimization protocols in autoimmune liver diseases, such as primary biliary cirrhosis and sclerosing cholangitis are, although feasible, still under discussion (Jabbour N, personal communication). All these observations indicate that steroid minimization protocols have to be individualized taking into account as well the original liver disease as, i.e., *de novo* autoimmune manifestations after LT.

It should be underlined that STWD significantly increases the exposure to (CsA and) TAC because of the reduced metabolism of these calcineurin inhibitors (CNI) [68]. Careful monitoring of CNI is mandatory when applying such IS scheme.

In conclusion, the great majority of studies show that STWD is safe in terms of patient and graft survival and that incidence of especially chronic rejection after STWD is of much less concern in liver than in renal transplantation. Further long-term follow-up of these patients is mandatory to confirm these findings. STWD is beneficial in relation to metabolic effects. If steroids are used, slow STWD is probably the better option in HCV-positive patients.

Steroid avoidance and LT

Based on the STWD experience, STAV-IS protocols were launched in 1999 (Table 4). The theoretical advantage of STAV is based on four major observations derived from experimental and clinical experience with STWD protocols: (i) absence of steroid dependence in a patient not exposed to steroids, (ii) elimination of all potential side effects from the moment of LT onwards, (iii) absence of steroid taper with its inherent risk of breakthrough rejection, and (iv) finally absence of interaction with the active process of tolerance induction. It has become clear that the steroid-adapted immune system behaves in a different way to the one that has not been exposed to steroids [2,69–72].

Table 4. Steroid (almost = period up to 3 days) avoidance in liver transplantation.

Year	Author	Ref	Center	Induction IS	No. pat.	Follow-up (months)	STWD time (months)	Steroid need (%)	Success (%)	Rejection (%) Acute (CRR)	Rejection (%) Chronic	Advantages	Particularities	Graft Surv (%)
Adult studies														
1999	**Tisone Prosp. rand.**	45	Roma	NEORAL/AZA/STER	22	14 med.	3			9.1	0	Cushing Higher HCV-RNA load		70.2
				NEORAL/AZA	23	(6–24)	0			8.7	0	**Cholesterolemia** **Diabetes**		78.3 PS GS 2 years
1999	**Rolles Prosp. rand.**	73	Royal Free London	NEORAL	34	26 (19–33)	0	+42		65	/		Monother. Neoral (64%)	62 GS 78 PS
				TAC	30			+60		66			Monother. TAC (87%)	73 GS 85 PS 3 years
1999	**Watson Prosp. rand.**	74	Cambridge	SRL/NEORAL/STER SRL/NEORAL SRL	4 7 4	4–27	3 (4–7) 3		100	0 28 75	/		Monotherapy SRL 53% Discontinuation SRL 20% Lipidemia	66
2001	Trotter Prosp. historical control -open	75	Denver	NEORAL/SRL/STER. TAC/SRL/STER	22 17	4	3 days 3 days	+21		**36** (**3**)		Cholesterolemia TAC group **Less acute and CRR rejection**	Discontinuation SRL (21%) Exclusion from study (34%)	89
				TAC/NEORAL/MMF	191		14 days	+100		**70** (**37**)				89 GS/PS
2001	**Washburn Prosp. rand.** Open label	76	San Antonio	TAC/MMF/DAC/STER TAC/MMF/DAC all intraop. steroids	15 15	>6 (15–21)	12 months 1 day			6.7 25 (6.7 treated)	/	**Cholesterolemia** Bone density No influence on HCV recurrence		93 100
2001	**Eason Prosp. rand.**	77	New Orleans	TAC/MMF/R-ATG (no steroids)	36	9 med. (3–18)	0			20.5 (**0**)		Diabetes Less HCV recurrence (50 vs.71%) Less CMV infection	Monother. TAC78%	89 GS 91 PS
				TAC/MMF/STER intraop. steroids	35		3 days (MMF stop 3 months)		20	32 **(18.9)**		No difference in HCV recurrence	Monother TAC 63% SRL in 4 pts neurotox.	89 GS 91 PS 12 months
2001	Pirenne Prospective	78	Leuven	TAC/AZA no intraop. steroids	21	40 med	0	+ 48		23.5 (4.7)	4.7	**Cushing** **Art. hypertension** **Diabetes**	52% never steroids	95 GS 100 PS 3 years

Table 4. continued

Year	Author	Ref	Center	Induction IS	No. pat.	Follow-up (months)	STWD time (months)	Steroid need (%)	Success (%)	Rejection (%) Acute (CRR)	Rejection (%) Chronic	Advantages	Particularities	Graft Surv (%)
2001	Ringe Prosp. open	79	Gottingen	TAC/MMF intraop. steroids	30	20 med. (1.5–41)	0		73	26	/		Monother. TAC 36.6% 43% never steroids	83.9 2 years
2001	Kneteman Prospective	80	Edmonton	DAC/SRL/TAC	26	3.6 ± 5	0		/	26.9	/	Diabetes	Art. Hypertension 30% Hyperlipidemia 13%	96.1 1 year
2003	Starzl Prospective	5	Pittsburgh	TAC + R-ATG (thymoglobulin)	17	18	0	45				Spaced monotherapy 78.6% at 12 months	Weaning IS after 60 days Donor bone marrow, infusion in 4 pts	82.4 PS
2003	**Eason**	81	New	TAC/MMF/STER			3	50		31	0			80 GS
	Prosp. rand.	82*	Orleans	Phase I	35				88.6				Monother. TAC 88.5%	85 PS
	Phase I MMF 3 months			Phase II	24				75				Monother. TAC 75%	96 GS
	Phase II MMF 3 weeks			TAC/MMF/R-ATG Phase I Phase II	36 24	18.5 mean (6–33)	0	6.6	83.3 75	25	0	**CMV infection** ***De novo* diabetes** **Less rejection** HCV severity	Monother. TAC 83.3% Monother. TAC 75% SRL in nephrotoxic pts	82 GS 85 PS
2004	Liu Prosp, open label, Historical control	83	Hong Kong	TAC/BAS/MMF	31	10.8 med (1.6–16.6)	0	6	94	**6**	NA	***De novo* diabetes** **CMV antigenemia** Cholesterolemia Viral HBV breakthrough	94% HBV pts 61% LDLT	94
				TAC/STER intraop. steroid + 1 day	49	21.6 med. (3.9–30.6)	>6			**27**	NA		84% HBV pts 67% LDLT	94
2005	**Boillot** **Prosp. rand.** Open label Selection: bioartificial liver	84	European MC	TAC/DAC (study completion 74%)	356	3	0			25.4 (**2.8**) (3 months)	NA NA	***De novo* diabetes,** **CMV infection** **Hepatitis** Cholesterolemia	Monother. TAC 98.9%	89.7 GS 94.5 PS 91.9 GS
	MASTER-study			TAC/STER (study completion 81%) intraop. steroids	352		>3			26.5 (**6.3**) (3 months)				93.7 PS 3 months
2006	Figueras Prosp, open label. Selection: renal failure	85	Spanish MC	TAC/MMF/DAC intraop. steroids	102	6	0			9.8 (0) (6 months) 11.8% (1) (12 months)	/	Similar rejection rate in 35 HCV pts **More adverse** **events in HCV pts** Art. hypertension Diabetes, Cholesterolemia	84% pts completed the study	95 GS 96 PS 12 months

Table 4. continued

Year	Author	Ref	Center	Induction IS	No. pat.	Follow-up (months)	STWD time (months)	Steroid need (%)	Success (%)	Rejection (%) Acute (CRR)	Rejection (%) Chronic	Advantages	Particularities	Graft Surv (%)
2006	**Llado Prosp. rand.** open label Selection: acute failure THOSIN-study	86	Spanish MC	NEORAL/BAS	96	6	0			18 (4) **24 HCVneg**	3	**Art. hypertens** ***De novo*** **diabetes at 1 month Lipids at 3 months Infection in diabetic pts. at 6 months**	45% HCV pts	90 GS 94 PS
				NEORAL/BAS/STER. All intraop. steroids + MMF if renal failure in 109 pts	102	6	3 months			13 (4) **10 HCVneg**	1	No difference HCV recurrence		88 GS 89 PS (6 months)
2007	**Tan** Prospective	87	Pittsburgh	TAC/ Alemtuzumab	47	24.3 ± 10.9	0		75.6	10.3 at 12m			All LDLT Multidrug IS in 24.4%	91.4 GS 93.6 PS
2008 (in press)	**Lerut Prosp. rand. Double blind Placebo controlled** Selection: none	88	UCL-Brussels	TAC +¨PLAC	78	12	0			23 (**12.8**) (8.8)°	1.2	**Less severe evolution HCV (fibrosis and cirrhosis : 0% vs. 23.8%)**	Monother. TAC 78.2% (91% of survivors)	83.3 GS 85.9 PS
				TAC + STER	78		2			19.2 (**3.9**) (3.9)°	5.1	**Less CRR if all pts included.** °If renal failure pts excluded no difference	Monother. TAC 82% (80.5% of survivors)	92.3 GS 93.6 PS
HCV-STUDIES														
2004	**Filipponi Prosp. rand. Double blind Placebo controlled** Selection: high risk, renal failure	89	Italian MC	NEORAL/AZA (6 months)/ BAS/STER intraop. steroids	74	12	3		NA	29.7	4	**Lower histologic rejection**	70% (99 pts) only had histologic control at 12 months	84.8 GS 89 PS
				NEORAL/AZA (6 months)/ BAS/PLAC	66	12	0	37.9	NA	37.9	0	**Lower treatment failure** (death, graft loss, withdrawal, adverse events) No advantage HCV recurrence		73 GS 81.5 PS

Table 4. continued

Year	Author	Ref	Center	Induction IS	No. pat.	Follow-up (months)	STWD time (months)	Steroid need (%)	Success (%)	Rejection (%)		Advantages	Particularities	Graft Surv (%)
										Acute (CRR)	Chronic			
2004	Marcos Retrospective	90	Pittsburgh	TAC/Alemtuzumab	76	14–22				10	0	Lower acute rejection rate in HCV pts (6% vs.30%)	38 HCV pts. Progressive reduction TAC after 4 months Monother. TAC 82.2%	79 GS 84 PS
				TAC/STER ± MMF all intraop. steroids 1gm	84		>2			20	0	Lower HCV-RNA load	TAC spacing (62%) similar HCV pos/neg pts	71 GS 80 PS
2005	**Margarit Prosp. rand.** Selection: high risk, renal failure	91	Vall'Hebron Barcelona	TAC intraop. steroids	28	44 mean	0	60	90	39 (14)	0	Art hypertension *De novo* diabetes Lower HCV-RNA load Milder HCV evolution **Fibrosis score; cirrhosis: 9% vs. 45%**		85–81 GS 85–81 PS
				TAC/STER	32		3	100	90	32 (9)	0			75–60GS 81–78 PS 1–3 years
2005	Marubashi Retrospective historical control	92	Osaka	TAC or CsA (5)/ MMF 3 months/ DAC (8)-BAS (1)	9	12.1	0	22.1	77.9	22.2	NA	Art. Hypertension Diabetes Infection Renal impairment	All HBV-HCV viral pts All living donor LT	100
				TAC or CsA (1)/ STER/MMF/DAC (2)-BAS (2) intraop. steroids.	13	17	>3			23.1	NA	Lower HCV-RNA load in steroid group		74.1 PS-GS
2005	De Ruvo Retrospective historical control	93	Bologna	TAC/R-ATG (thymoglobulin)	22	12	0	36		36.4 (4.5)	NA	**Lower HCV-RNA level HCV recurrence time shorter**	Weaning TAC (54.5%) TAC mono. 100%	72.7 GS 86 PS
				TAC/STER all intraop. steroids	30	12	3	100		40 (3.3)	NA	No difference HCV recurrence		90 GS 93 PS

Table 4. continued

Year	Author	Ref	Center	Induction IS	No. pat.	Follow-up (months)	STWD time (months)	Steroid need (%)	Success (%)	Rejection (%) Acute (CRR)	Rejection (%) Chronic	Advantages	Particularities	Graft Surv (%)
2006	**Samonakis Prosp. rand.** Selection	94	London Royal Free	TAC	27					70 (7)	0	Fewer rejection episodes Fewer moder. rejection		70.3 GS 77.7 PS
					22	(3–54)						No difference HCV recurrence No difference HCV-RNA load		
				TAC/AZA/STER	29		3–4			86 (7) (at 3 months)	3.4			86 GS 96.7 PS 12 months
2007	**Kato Prosp. rand.** Open label	95	Miami	TAC/DAC	50	12				47		**Wound infection**	Pre-emptive antiviral treatment	No diff GS and PS (±95)
				TAC/DAC/MMF						**19**		**Diabetes** Art. hypertension	from d14 to 12 mo Significantly less rejection in MMF groups	
				TAC/STER	50		3			56		No difference in		
				TAC/MMF/STER						**35**		HCV fibrosis stage but **severity of HCV related to treatment of rejection**		
2007	**Klintmalm Prosp. rand.**	96	US MC	TAC/STER	80		>3–12			**18.1 (severe 10.5)**		No difference HCV RNA-load		84.8 GS 89.5 PS
	Open label Selection: ICU pts, renal failure			TAC/MMF/STER	79	12	>3–12					No difference HCV recurrence		88.1 GS 89.4 PS
				TAC/DAC/STER	153					**7 (severe 0)**		De novo diabetes Cholesterolemia		89.9 GS 92.5 PS
PEDIATRIC STUDIES														
2003	Reding Retrospective historical match control Selection: high	97	UCL-Brussels	TAC/BAS/MMF (+MMF 9 pts)	20	12	0	15	85	**25**	0	**Growth** Art. Hypertension Cholesterolemia		100 PS
				TAC/STER all intraop. steroids	20		>12	100	0	**50**	0			95 PS
2006	**Spada Prosp. rand.** Open label	98	Palermo	TAC/BAS	36	12	>3–6 months			**12.3** (0)	NA	**Infection** Art. hypertension	Monotherapy TAC 87.5 at 2 years	80 GS 86.6 PS
	Selection: renal failure			TAC/STER all intraop. steroids	36	12				**32.3** (0)	NA		75.8 at 2 years	85.5 GS 91.4 PS

All data in bold indicate statistically significant differences.

STWD, steroid withdrawal; CRR, corticosteroid-resistant rejection; CsA, cyclosporine; STER, steroids; AZA, azathioprine; SRL, sirolimus; TAC, tacrolimus; MMF, mofetil mycophenolate; PLAC, placebo; DAC, dacluzimab; BAS, basiliximab.

*Reported later on in separate report about same patient cohort.

Steroid avoidance-IS has been investigated in LT using various drug combinations [4]. STAV-IS protocols are defined as those in which no steroids at all were used or those in which steroids were administered only in the immediate (<3 days) peri-operative period (almost steroid avoidance).

From 1999 to December 2007, 26 STAV studies were reported; only two were carried out in children [2,73–98]. Fourteen studies were prospective, randomized and controlled; only two studies were carried out in a double-blind, placebo-controlled fashion [87,88]. In contrast to the STWD protocols, STAV protocols were mainly made (22 studies) using the CNI TAC. The more potent properties of this drug, confirmed in the TMC trial performed by O'Grady and in a recent meta-analysis performed by Mc Allister, apparently gave more confidence to the clinicians to develop such protocols.[99–101]. Despite this 'advantage', all but six STAV studies were carried out using a heavily reinforced IS. In 20 studies, induction IS included the use of anti-lymphocytic sera, anti-IL-2 monoclonal antibodies or m-TOR inhibitor: TAC monotherapy induction IS was used in two centers only [73,91,94].

Conclusions from this review are somewhat more difficult to draw because of the very different study designs, the heterogeneous patient populations and the frequently inadequate duration of follow-up (range from 3 to 54 months). Acute and chronic rejections were observed in 6–70% and in 0–4.7%, respectively. The incidence of rejection was significantly higher in STAV-IS in one adult study only [75]; in one study, the incidence of rejection was significantly higher in steroid-free HCV-negative recipients [86]. In studies in which steroids are replaced by other IS agent(s), the incidence of rejection seems to be lower. Steroids needed to be introduced in 6–100% of patients. In eight studies, TAC monotherapy was used in 63–100% of patients. One-year graft survival ranged from 79% to 100% in all TAC-based studies. Metabolic benefits were significant in eight of 24 adult studies. Significant infectious advantages were observed in two adult studies and in one pediatric study. One should stress that all these results were mostly obtained at the price of a much heavier induction IS.

Eight STAV studies were specifically carried out in relation to outcome of LT in HCV patients [89–96]; only one study was carried out in a placebo-controlled and double-blind fashion [89]. The influence on post-transplant HCV-RNA load was variable (two times each higher, lower or stable). There was no clear difference in relation to viral allograft re-infection in six studies. In one of these STAV studies, post-transplant HCV-recurrence was significantly milder in the steroid-free group [90]. These variable findings seem to indicate that the total IS load is probably more dominant factor than the use of steroids.

Similar findings were present in the recently reported almost steroid avoidance and TAC monotherapy IS study carried out in Brussels [88; paper will be published in December 2008]. In this prospective, randomized, double-blind, placebo-controlled study, TAC-placebo (PL) was compared to TAC low-dosage, short-term (64 days) steroid (ST) IS. This study is unique because of the fact that it is a large sample (156 adults), investigator-driven, single-center study including primary liver transplant recipients irrespective of their medical, viral and immunologic status at the time of grafting. Infectious, tumor and metabolic complications and performance status were similar in both groups. The incidence of advanced (fibrosis and cirrhosis) HCV graft re-infection was significantly less in the placebo group [0/14 TAC-PL vs. 5/21 (23.8%) TAC-ST patients, $P = 0.03$].

Three- and 12-month patient-survival rates were 93.6% and 85.9% in the TAC-PL group and 98.7% and 93.6% in TAC-ST group ($P = 0.09$ and 0.11, respectively). Three- and 12-month graft-survival rates were 92.3% and 83.3% in the TAC-PL group vs. 97.4% and 92.3% in the TAC-ST group ($P = 0.14$ and 0.09, respectively). By 1 year, 78.2% (61/78) of TAC-PL patients and 82% (64/78) of TAC-ST patients were on TAC monotherapy ($P = 0.54$). When considering the 67 TAC-PL and 74 TAC-ST survivors, these rates of monotherapy were 91% (61 patients) and 86.5% (64 patients), respectively ($P = 0.39$). At 1 year 62.5% (42/67 patients) of TAC-PL survivors and 64.9 (48/74 patients) of TAC-ST survivors were on low-dosage (<6 ng/ml) TAC monotherapy ($P = 0.79$).

The immunologic results of this study are of interest. The number of patients treated for rejection at 3 (16 patients – 20.5% vs. 10 patients – 12.5%; $P = 0.19$) and 12 (18 patients –23% vs. 15 patients – 19.2%; $P = 0.54$) months was not significantly different between the TAC-PL and TAC-ST groups. Corticosteroid-resistant rejection (CRR) (defined as non-response to five doses of 200 mg methylprednisolone) at 3 and 12 months was significantly higher in the TAC-PL (STAV) group [12.8% (10/78 patients) of TAC-PL patients vs. 3.8% (3/78 patients) of TAC-ST patients – $P = 0.04$]. When analyzing separately the 145 patients transplanted without artificial renal support at moment of transplantation, the differences in relation to CRR at 3 and 12 months [8.8% (6/68 patients) of TAC-PL patients vs. 3.9% (3/77 patients) of TAC-St patients] became nonsignificant ($P = 0.22$). Vanishing bile duct syndrome was diagnosed in one (1.2%) TAC-PL patient and four (5.1%) TAC-ST patients ($P = 0.17$). The Banff scores of the day-7 protocol biopsies were identical in both groups, an observation that was also made previ-

ously in an open-labeled study conducted by the group at the Royal Free Hospital in London [102].

This study has indicated in a placebo-controlled and, more importantly, in a blinded fashion that TAC monotherapy, and thus steroid avoidance, is a feasible and safe induction as well as maintenance IS in adult LT. The major drawback of such minimization IS protocol and surely of calcineurin inhibition monotherapy induction IS relates to the fact that the recipient management is more difficult if serious liver and/or renal and/or neurologic dysfunctions are present at, or immediately after, LT. Lowering of IS to spare renal function explains the higher risk to develop a severe rejection. IS must therefore be refined and individually tailored to the peri-transplant condition of the recipient during induction and maintenance periods. The combination of TAC with other non-neurotoxic or nephrotoxic drug regimens may be more appropriate to overcome the potentially more complex post-transplant course of such recipients. Feasibility and benefits of such approaches using mycophenolate mofetil, single dose rabbit anti-thymocyte globulin or humanized anti-CD52 monoclonal antibody (alemtuzumab) as induction therapy in conjunction with TAC have been shown by the New Orleans, Pittsburgh and Miami groups [5,81,90,103–105].

Because of the elimination of their tolerance breaking effects, steroid minimization IS protocols are theoretically superior to multiple tolerizing drug cocktails [103–107]. Minimization IS seems to be a most logic and pragmatic way to optimize interaction between donor and recipient immune systems allowing even complete IS withdrawal [5]. Early minimal peri-transplant IS is a prerequisite to avoid erosion of the seminal tolerance mechanism of clonal exhaustion–deletion described by Starzl *et al.* [5,108]. By doing so, it can be anticipated that even complete IS withdrawal may be obtained more frequently in well-selected cases [4,5,109–111]. Larger prospective, placebo-controlled and blinded pluricentric studies avoiding particularly the use of steroids are warranted to confirm such hypotheses.

Conclusion

This literature review indicates that STWD and STAV protocols are safe immunosuppressive protocols in LT. Steroid-free status can be obtained after transplantation even without reinforcement of the induction IS. Graft and patient survival are not jeopardized and metabolic benefits are clear. Long-term follow-up including regular liver biopsies of steroid-free liver recipients is warranted to consolidate this IS approach. The ideal 'steroid' immunosuppressive strategy for HCV patients is not yet determined as demonstrated by the contradictory results of different studies. Slow steroid taper or steroid avoidance seem to be the better strategies to avoid aggressive HCV allograft recurrence. The results of HCV recipients will probably only improve substantially by the introduction of better antiviral therapies and by manipulating different as well donor as recipient variables [112–114]. Further prospective randomized placebo-controlled studies will be necessary to identify for the best possible IS especially in high-risk and viral-infected recipients.

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