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REVIEW ARTICLE

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Avoiding steroids in solid organ transplantation

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Abstract The excellent results obtained today in solid-organ transplantation allow the envisaging of an improvement in long-term quality of life with a functioning graft. One way for this to be achieved is by the reduction, or even better, the avoidance, of steroid-based immunosuppression. Avoidance of steroids is indeed known to enhance the physical and psychological well being of the allograft recipient. This paper reviews the current status of steroid-free immunosuppression in renal, pancreatic, hepatic, intestinal, and cardiac transplantation.

Keywords Solid-organ transplantation · Immunosuppression · Steroid · Steroid withdrawal · Steroid avoidance

Introduction

Since the inception of organ transplantation, steroids have been a mainstay in both induction and maintenance immunosuppression (IS) [1]. Steroids are effective agents for reducing the incidence of allograft rejection. Their action is ubiquitous and begins at an early stage of the immunological cascade by influencing antigen presentation of the antigen-presenting cell and by inhibiting cytokine expression.

The addition of steroids to the immunosuppressive regimen affects the quality of life of the successful transplant patient. The adverse effects of steroids on the cardiovascular system—the development of diabetes mellitus, arterial hypertension, prothrombotic state and lipid metabolism dysregulation—are well documented, and they are responsible for osteo-articular and muscular problems, cataract formation, growth retardation, body disfiguration, and, last but not least, they interfere with the psychological well being of the recipient [2, 3, 4, 5, 6, 7] (Table 1). They may also play a role in the increased risk of infection and tumor formation in transplant patients [8], and there is evidence that they interfere with the tolerogenic pathway of organ acceptance [9, 10].

The excellent results that are obtained nowadays in solid-organ transplantation allow transplant physicians to focus their interest on the quality of life of the allograft recipient [11] and on the development of tolerogenic immunosuppressive strategies [12]. Newer and more-potent immunosuppressive drugs that have different mechanisms of action and different profiles of toxicity, allow more patient-friendly IS without compromising graft survival [13, 14, 15, 16, 17, 18, 19]. Clinical studies should thus strive to use well-balanced drug combinations with minimal toxicity and tailored, individualized IS that emphasizes the quality of life of the patient. Steroid-free induction and/or maintenance IS have to be seen in this context.

In the past, steroids have been deployed in many different ways. They have been administered at high or low doses from the very moment of transplantation; they have been withdrawn early (after 1 to 3 days, 1 to 2

Table 1 Side effects of glucocorticoid treatment

Side effect
Cardiovascular risk factors
Diabetes mellitus
Hypertension
Lipid metabolism
Prothrombotic state
Wound healing
Septic ulcer disease
Defense against infection
Tumor formation
Linear growth
Osteo-articular and muscular system
Osteopenia
Osteoporosis
Pathological fractures
Avascular necrosis
Myopathy
Cataract and glaucoma formation
Body disfigurement
Hirsutism
Cushing obesity
Adrenal insufficiency
Psychological well being
Psychosis
Depression

weeks or after 3 months) or later, the latter meaning 6 to 12 months post-transplantation or after establishment of stable graft function; they have been used alternatively, and, finally, they have been 'almost' or completely avoided, not only during induction IS, but also during maintenance IS, and even during treatment of rejection.

Steroid withdrawal (STWD) or avoidance in solid-organ transplantation raises numerous questions that demonstrate why steroid-free IS remains a controversial subject. What is the risk of acute or chronic rejection? Is there a sustained response? Are evidence-based selection criteria that justify STWD available? Is STWD advantageous in comparison with avoidance [2, 3, 17]? Is it feasible in children [7, 20, 21, 22] and in all types of solid-organ transplantation [17, 21, 23]? What is the effect on viral [24, 25, 26] and (de novo or recurrent) autoimmune allograft diseases [27]? What is its role in de novo or recurrent tumor formation? And finally, what role does STWD really play in the active process of organ tolerogenicity [10]? All these questions are difficult to answer as the number of randomized controlled studies is very limited [17]. Moreover, most studies lack long-term follow-up of sufficient duration and lack detailed analyses of the specific parameters that influence outcome; the clinical use of many new immunosuppressive drugs, furthermore, makes comparison of trials very difficult [10, 28].

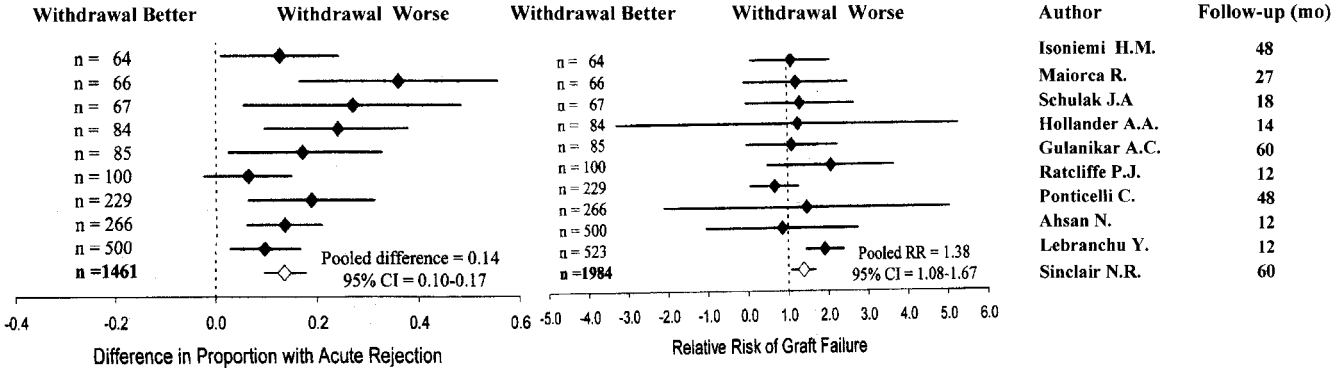
This paper presents a review of the use of steroid-avoiding IS in the clinical practice of kidney, pancreas, intestinal, heart, and liver transplantation. To date, data on steroid-avoiding IS in lung transplantation have not been published. Preliminary experience has, however, been recently collected in this field in Pittsburgh (Starzl, personal communication).

Renal transplantation

By 1982 (!), the European multicenter kidney transplant trial seemed to have answered, in part, the question of steroid-avoiding IS [29]. Indeed, 82% of patients underwent Cyclosporin A (CsA) (Sandimmun, Novartis, Basle, Switzerland) monotherapy IS, and 27% of patients never received steroids; 1-year graft survival was 73%.

Kasiske and colleagues' meta-analysis of STWD and renal transplantation indicated that the 'steroid question' is not easy to answer [17]. This analysis related to studies done before the advent of mycophenolate mofetil (MMF) (Cellcept, Roche, Basle, Switzerland) immunosuppression. Based on stringent criteria, i.e., publication in a peer-reviewed journal; clearly described randomization techniques and statistical methodology; double-blind, placebo-controlled, prospective study designs; description of study endpoints and intention-to-treat analyses, only ten, CsA-based, IS-studies could be considered (Table 2). This analysis showed that the risk of acute rejection (pooled mean difference between treatment and control was 0.14; $P < 0.001$) and renal graft failure (relative risk of failure was 1.4; $P < 0.01$) in homogeneous study material was significantly increased.

Table 2 Steroid withdrawal and renal transplantation: the Kasiske meta-analysis including studies done during the period 1987–1999



Risk factors, such as ethnic origin, race, and major histocompatibility mismatching to determine the selection process of patients in whom STWD should be safe, could not be clearly identified [20]. There was also no significant difference between early and late STWD, and between rapid and slow steroid tapering; this was probably related to the small patient sample and the effectiveness of the remaining immunosuppressive agents. This latter point could not, however, be confirmed in two, large, multicenter, double-blind, randomized, prospective, studies that analyzed a combination of CsA microemulsion (Neoral, Novartis), steroids and MMF with or without antilymphocytic induction IS (ATG, Fresenius, Bad Homburg, Germany, or OKT3-Muromonab, Janssen-Cillag, Sollentuna, Sweden) [13, 30]. Both studies showed a significantly higher incidence of rejection at 12 months when steroids were stopped; these data led to the interruption of one trial [13]. The incidence of rejection was similar when antilymphocytic sera were used during induction IS [30]. STWD-patients had a significant benefit as regards blood pressure, lipid metabolism, and bone density. Other studies showed, for example, that steroids can be withdrawn safely in selected, stable, renal transplant patients on MMF treatment [31] or by the introduction of azathioprine when steroids were withdrawn [32]. The advent of new agents for induction IS (basiliximab (Simulect, Novartis), daclizumab (Zenapax, Roche) and maintenance IS (tacrolimus: Prograft, Fujisawa, Osaka, Japan; MMF; Rapamycine: sirolimus, Wyeth, Collegeville, Pennsylvania, USA) during the 1990s boosted the concept not only of withdrawing, but also of avoidance of steroids.

The greatest concern with regard to STWD is sustained allograft response. This is especially important in renal transplantation, as an acute rejection episode is a major risk factor for long-term graft loss. [33]. The only existing, randomized, double-blind, multicenter, long-term follow-up trial was conducted in Canada, with 523 CsA-treated renal patients. It showed that the adverse effect of STWD on allograft survival became *evident only after 5 years*. It should be noted that histological follow-up was not documented in this study. HLA-B mismatch, gender (male recipient), age and cause of death of the donor were all factors that had a negative impact on allograft survival [34]. Thiel et al. reported the need to switch to CsA-free treatment in 40% of patients in a 10-year follow-up of steroid-free renal transplants [35]. Both findings underline the necessity of long-term analysis before the real benefit of steroid-free IS can be judged in renal transplantation.

It has been assumed that results of STWD IS may be less favorable due to the conditioning of the recipient to steroids [2, 3, 9, 17]. The 'steroid-adapted immune system' is different from the 'steroid-free immune system'. Indeed a possible sensitization effect of prolonged steroid administration has been shown; lymphocytes exposed to prolonged steroids would be activated by steroid withdrawal [36]. Avoidance of steroid IS could be a better option, which, moreover, eliminates the potential side effects (late STWD will not prevent steroid-related complications) [2, 3, 37, 38] and dependency of the drug, and the need for steroid tapering with its inherent risk of outbreak of acute cellular rejection [17]. The Odense group in Denmark successfully applied this working hypothesis to clinical practice. In a retrospective study of 68 renal adult and pediatric patients on induction IS comprising ATG, MMF and Neoral, 97% 1-year-graft-and-patient survival rates were obtained. The rejection rate was 15% after a median follow-up of 188 days, and no patient was switched to steroids [8]. These results were confirmed in a 4-year follow-up study: 10% of patients had acute rejection and only 3% had chronic rejection [39]. The protocol was successfully applied to 14 pediatric kidney recipients [7]. Sarwal et al. also obtained 100% rejection-free graft survival in ten children, using daclizumab, MMF and tacrolimus (TAC) [40]. In both studies, no child received steroids at any time after transplantation. Because of the good short- and median-term graft survival rates, and because of the beneficial impact on growth development, steroid-avoidance protocols should become a priority in pediatric transplantation [2, 7].

In recent years, several 'steroid (almost) avoidance' IS trials have been reported in kidney transplantation. Initial results are good, with graft and patient survival rates of over 95%, and the incidence of acute rejection between 13% and 25%. Follow-up is too short, and IS too diverse to allow definitive conclusions to be drawn [8, 14, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48] (Table 3).

Pancreas transplantation

STWD was obtained by the Minneapolis group in 83% (10/12 patients) of stable simultaneous kidney–pancreas recipients under TAC–MMF steroid IS [49] and by the Pittsburgh group in 109 pancreas recipients under TAC–MMF or azathioprine (AZA)–steroid based IS [50] (Table 4). These results were confirmed in a prospective study comprising 11 simultaneous pancreas–kidney and 13 pancreas-after-kidney transplantations using TAC–MMF-steroid based IS [51]. Steroids were withdrawn ≥6 months after successful transplantation. Results were excellent in both groups (100% graft survival at 6 months). Similar results were obtained by Salazar et al. in seven simultaneous pancreas–kidney transplants in an IS scheme including Rapamycine (RAPA) [52]. All patients experienced better quality of life after STWD.

These excellent results fostered the development of rapid steroid-tapering and steroid-avoiding IS in simultaneous whole pancreas–kidney transplantation. After their early experience with successful STWD, reported in

Table 3 Steroid (almost) avoidance in renal transplantation (*LRKT* living related kidney transplantation)

Year	Author	Reference	Center	Induction IS	No. of patients	Follow-up (months)	Acute Rejection (%)	Graft survival (%)	Steroid Requirement (%)	Monotherapy (%)	Remarks
1998	Kupin et al.[a]	[41]	Detroit	CsA/MMF 3 Days steroids	26	11.4	4	100	4		LRKT
1999	Calne et al.	[14]	Cambridge	Campath 1H/Neoral	31	21	19.4	96.7	10	90	
2000	Landsberg et al.[a]	[42]	Canadian multicenter	Daclizumab/MMF/Neoral	57	12	25	89	26	NA	
2000	Kaufman et al.	[43]	Chicago	Anti-IL2 Rec Ab/MMF/TAC 3 Days steroids	54	12	13.2	100	NA	0	40 LRKT
2000	Short et al.[a]	[44]	Manchester	TAC	30	12	26.7	97	26.7	NA	
2000	Vincenti et al.	[18]	American multicenter	Basiliximab MMF/Neoral 4 Days steroids	83	6	20	100	20		45 LRKT
2000	Elias et al.	[46]	Australian multicenter	Neoral/AZA1 Day steroids	295	> 22	70	88/75 (1 year/5 years)	62	63	43 LRKT
2000	Buell et al.[a]	[47]	Cincinnati	MMF/TAC7 Days steroids	52	36	25	99 (3 years)			
2001	Weimar[a]	[48]	Rotterdam	Basiliximab MMF/TAC 3 Days/3 Months steroids	160	12	11	NA	NA	NA	
2001	Birkeland	[39]	Odense	ATG/MMF/CsA	100	54	13 (Chronic rejection 3)	82 (4 years)	0	NA	33 LRKT
1998	Birkeland et al.	[7]	Odense	ATG/MMF/CsA	14	38	21	85 (5 years)	0	50	10 pediatric LRKT
2001	Sarwal et al.	[40]	Palo Alto	Daclizumab/MMF/TAC	10	9	0	100	0	10	8 pediatric LRKT

[a]Published as abstract only

1991 [23], Cantarovich et al. from the Nantes group reported approximately 28 such transplantations implementing induction IS, consisting of steroid-avoiding-ATG, MMF and TAC or Neoral. Acute rejection rate of kidney and pancreas was remarkably low (7% and 10.7%, respectively), resulting in excellent kidney and pancreas survival rates (96.4% and 75%, respectively after ≥6 months) [53].

Feasibility of pancreatico-renal transplantation using CsA-monotherapy was reported in 1994 by Ward et al. from the Liverpool group. The rejection rate was 38.9%; further information was, however, lacking in this report [54].

Kaufman reported approximately 40 such transplantations under IS consisting of ATG, TAC and MMF or RAPA and a 6-day steroid taper. Rejection rate was very low (2.5%), and 1-year pancreas- and kidney-graft survival rates were 100% [55]. The revival of islet transplantation using steroid-free IS will surely stimulate further steroid-avoidance trials in the field of whole-pancreas transplantation [56].

Intestinal transplantation

Transplantation of intestines has, for a long time, been considered as being forbidden. Development of more powerful IS allowed the introduction of intestinal transplantation in clinical practice during the 1990s; as a result, over-immunosuppression was often responsible for unfavorable outcomes [57]. Graft immuno-modulation with infusion of donor bone marrow and/or low-dose irradiation, and tolerance-enhancing strategies of pre-treating the recipient with ATG and minimal post-transplant IS, led to a marked improvement of results, even in steroid-avoiding protocols [58].

The Miami group reported 83% and 77% graft and patient survival in Campath 1H, a depleting, humanized anti-CD52 monoclonal antibody, TAC-based IS. Of 12 patients, six never received steroids, and the rejection rate was 33% [59].

The Pittsburgh group reached 90% graft survival under TAC-monotherapy IS preceded by high-dose ATG preconditioning; only two of ten patients developed rejection [57].

Heart transplantation

Groups in Sidney, Bad Oeynhausen, Minneapolis, and Chicago, showed that excellent long-term allograft function can be obtained when steroids are withdrawn after ATG- or OKT3-based induction IS and CsA-based maintenance IS [60, 61, 62, 63, 64, 65]. Despite the high incidence of rejection (from 35.8% to 93%), 53% to 79% of patients remained steroid free. Rejection usually occurred early after steroid taper or STWD [66]. Safety

Table 4 Steroid withdrawal and (almost) avoidance in pancreatic transplantation (*PTA* pancreas transplantation alone, *PAK* pancreas transplantation after kidney transplantation, *SPK* simultaneous pancreas kidney transplantation)

Year	Author	Reference	Center	Induction IS	No. of patients	Follow-up (months)	STWD time (months)	Acute rejection (%)	Graft Survival (%)	Steroid Requirement (%)	Steroid withdrawal (%)	Advantages
1991	Cantarovich et al.	[53]	Nantes	Anti-IL2-Rec Ab or ATG/A2A/ CsA/ster	37 SPK	30	1–1.5	32 Kidney 3 Pancreas	92 Kidney 80 Pancreas	25 at 2 years	75 at 2 years	Cholesterolemia Diabetes
1994	Ward et al.	[54]	Liverpool	CsA (?) avoidance study	30 SPK			38.9%	68 Kidney 69 Pancreas	38.9% at 1 year		
2000	Humar et al.	[49]	Minneapolis	ATG/TAC/ MMF/ster	12 SPK 2 PTA	18 (5–51)	21 (7–47)	14 (PTA)	93 Kidney 100 Pancreas	28 (MMF toxicity / rejection)	71	Cholesterolemia
2000	Jordan et al.[a]	[50]	Pittsburgh	TAC/MMF(59%) or AZA (51%)/ster	109 SPK	32 ± 13 (12–56)	> 4 15.2 ± 8 (4–40)	7.3 Kidney 1.8 Pancreas	91 Kidney 98 Pancreas (3 months)	53	47	Hgb A1 C[b] Renal function[b]
2001	Gruessner et al.[a]	[51]	Minneapolis	ATG/TAC MMF/ster	11 SPK 13 PAK	27 (10–50) 26 (8–49)	≥6 Months.	07.7 (PAK)	100 Kidney 100 Pancreas		100	Quality of life Cholesterolemia[b]
2001	Salazar et al.[a]	[52]	Halifax	ATG/TAC/ RAPA/ster	7 SPK	16 (6–26)	6	14	100 Kidney 100 Pancreas	14	100	Art. hypertension Cholesterolemia Renal function no insulin requirement
2000	Cantarovich et al.[a]	[23]	Nantes	ATG/CsA / TAC/MMF avoidance study	28 SPK	> 6 (4–24)		10.7 Kidney 7 Pancreas	96.4 Kidney 75 Pancreas	10.7 (MMF toxicity / rejection)		Art. hypertension[b] Cholesterolemia[b]
2002	Kaufman et al.[a]	[55]	Chicago	ATG/TAC/ RAPA/ster 6 daysATG/ TAC/MMF 6 days steroids "Almost avoidance" study	20 SPK 20 SPK	13.4 ± 2.9 12.7 ± 3.9	6 Days 6 Days	2.5	100 Kidney 100 Pancreas both groups	0		

[a]Prospective study
[b]Statistically significant improvement

Table 5 Steroid withdrawal in adult liver transplantation

Year Author	Reference	Center	Induction IS	No. of patients	Follow-up (months)	STWD time (months)	Success (%)	Acute rejection (%)	Chronic rejection (%)	Advantages	Particularities	Graft Survival (%)
1993 Padbury et al.	[75]	Birmingham, UK	CsA/AZA/ster CsA/ster	197	28 Med (5–109)	≥3 (1–32)	85 → 71[c]	4.5	3.9	Art. hypertension Infection Diabetes	Monotherapy CsA 47.2%	(98.1)
1995 Punch et al.	[77]	Ann Arbor	CsA/Ser/ATG or MALG	51	13 .8 Med (4–36)	≥12 Stable graft	88	12		Art. hypertension[b] Cholesterolemia[b]		(100)
1995 McDiarmid et al.[a,f]	[78]	Los Angeles	CsA/AZA/ster	33 (24 Adults)	23 Mean	≥12	94	6.5	0	Cholesterolemia		100
				31 (17 Adults)				6	0			
1996 Tchervenkov et al.	[79]	Montreal	CsA/ster/ATG/ AZA	42	3–12	≥12	93	9		Art. hypertension[b] Cholesterolemia[b] Diabetes[b]	Monotherapy CsA 93%	(100) 1 Year
1996 Fraser et al.	[80]	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 et al.	[81]	Denver	CsA/ster	28		> 24	75	14.2		Art. Hypertension Diabetes Cholesterolemia[b]	Monotherapy CsA 75%	(100)
1997 Stegall et al.[a]	[82]	Denver	CsA[g]/ster/MMF	71; 36	> 6	0.5	100[d]	46		Art. hypertension[b] Cholesterolemia[b] Diabetes[b]	MonotherapyCsA/ TAC at 6 months. 21.4%	94.4 88.6 (6 Months)
			TAC/ster/MMF	35		0.5	88.2	42.3				
1997 Pichlmayr et al.	[83]	European Multicenter	TAC/steroids	529; 264	36	36	80.3	45.4	2			70.6
			CsA/AZA/ster ± ATGG	265			68.1	55.1	6.9			65.3 3 Years
1998 Gomez et al.	[84]	Madrid	CsA/AZA/ster	86	23 Mean (12–58)	> 12 stable graft (36 ± 18)	100	0	0	Art. hypertension[b] Cholesterolemia[b] Diabetes Body weight[b] Bone disease[b]	Monotherapy CsA 83.5%	100
1998 Belli et al.[a]	[85]	Milan	CsA/AZA/ster/ ATG	104; 54	41 Mean (4–68)	> 3 (4–5)	98.5[e]	4	0	Art. hypertension[b]		8382
				50				8	3	Diabetes[b]		2 Years
1998 Tisone et al.[a]	[86]	Rome	CsA[g]/AZA/ster	45; 22	14 Median (6–24)	3	100	9.1	0	Cholesterolemia[b]		70.2
			CsA[g]/AZA	23				8.7	0	Diabetes[b]		78.3 2 Years
1999 Lerut et al.	[87]	Brussels-UCL	CsA/AZA/ster (Sandimmun)		≥60 (7.8–96)	7 (3–42)	97.1 → 88.6[c]	10	4.3	Art. hypertension Cholesterolemia Diabetes Bone disease	Monotherapy CsA at 60 months (66.6%)	74.3 5 Years

[a]Prospective randomized study
[b]Statistically significant improvement
[c]Steroid therapy restarted because of reasons other than rejection
[d]12.5% of patients were switched to TAC because of recurrent rejection
[e]Long-term therapy restarted because of intractable pruritus and severe cholestasis in one patient
[f]See also Table 6
[g]Micro-emulsionCsA

Table 6 Steroid withdrawal in pediatric liver transplantation

Year	Author	Reference	Center	Induction IS	No. of patients	STWD time (months)	Acute rejection (%)	Chronic rejection (%)	Graft loss (%)	Patient loss (%)
1989	Margarit et al.	[88]	Barcelona	CsA/ster	15	7	13	13	13	7
1993	Superina et al.	[89]	Toronto	CsA/AZA/ster	33	>12	–	–	–	–
1994	Murphy et al.	[90]	Birmingham	CsA/AZA/ster	135	3	27	10	6	3
1994	Dunn et al.	[91]	Philadelphia	CsA/AZA/ster	28	18	7	4	4	4
1995	McDiarmid et al.[a]	[78]	Los Angeles	CsA/AZA/ster	7	≥12	(6.5)	0	0	
1997	Martin et al.	[92]	Montreal	CsA/ster	55	58	11	–	–	–
1997	McKee et al.	[93]	Baltimore	TAC/ster	29	6	29	–	4.1	–
1998	Andrews et al.	[94]	Dallas	CsA/ster	53	54	13	–	–	–
1999	Jain et al.	[95]	Pittsburgh	TAC/ster	166	<12	21	–	0	0
2000	Reding	[20]	Brussels-UCL	TAC-CsA[b]/AZA/ster	78	8.4–164	8	0	0	0

[a]Prospective randomized study (see also Table 5)
[b]Micro-emulsion CsA

of STWD was correlated with stable graft function and CsA level. Another study showed that a trough level of less than 300–350 ng/ml correlated with a higher rejection rate. There was no negative impact of high CsA levels on serum creatinine [67]. The impact of induction therapy and the role of this HLA-B mismatch on the incidence of rejection were controversial [21], as was the impact of STWD on coronary artery allograft disease [68]. Similar results have been obtained in TAC-based adult heart transplantation [69]. Koerner et al. showed that CsA monotherapy is possible in selected adult and pediatric patients; indeed only 9% of 41 patients experienced steroid-sensitive rejection under CsA monotherapy [61].

The concept of STWD has been extended to pediatric heart transplantation under CsA, AZA, steroid-based IS [70, 71]. Almost half of children can remain steroid free without graft survival being compromised. The long-term safety of such an approach was confirmed by a detailed histological follow-up of 40 infants, showing that late rejection was a rare event after STWD [72].

Livi et al. from the Padova group promoted the concept of almost steroid-free IS after heart transplantation in a series of 112 adults under CsA, AZA and ATG or OKT3 induction IS and intra-operative steroid bolus administration. Cumulative incidence of rejection was very high (93% at 1 year), but 79% of patients could remain on CsA–AZA IS after a follow-up of 25±15 months with a 4-year actuarial survival rate of 94±3% [21]. This concept was extended to children. After a median (range) follow-up of 52 (3–132) months, 10% of 30 children suffered from rejection [73]; the 5-year actuarial survival rate was 76±6%. The drawback of this IS policy was a progressively rising creatinine level, adding to the observation made previously in the field of renal transplantation [35].

Most cardiac transplant studies showed that early STWD was beneficial regarding lipid profile [60, 74], arterial hypertension, thrombotic state [4], diabetes mellitus, graft atherosclerosis and osseous disease [21, 61, 69].

Liver transplantation

The immuno-privileged status of the liver allograft allows more aggressive withdrawal of immunosuppressive agents to be made, without compromising organ survival [27, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87]. It is no wonder that the concept of steroid-free IS has been developed farthest in the field of liver transplantation (LT). In 1993, the Birmingham group reported their large experience with steroid tapering and early STWD after LT. Acute or chronic rejection was rare, and metabolic benefits were important [75].

From 1993 to 2002, twelve studies on STWD after adult LT were reported [75, 77, 87]. Four [78, 82, 85, 86] were prospective, randomized, controlled trials, and all of them except for two were CsA-based. STWD was successful in 68.1–100% of patients after follow-ups ranging from 4 to 109 months. The incidence of acute and chronic rejection varied from 4.5% to 55.1% and from 0% to 6.9%, respectively. Use of antilymphocytic sera during induction IS did not have an impact on the results obtained. In seven studies, CsA monotherapy was obtained in 21.4% to 93% of patients. Graft survival rates were excellent, and metabolic benefits were significant in more than half of the studies (Table 5).

From 1989–2002, ten studies were reported in relation to STWD after pediatric LT [20, 78, 88, 89, 90, 91, 92, 93, 94, 95] (Table 6). Only one study was prospective and randomized, however two thirds of patients were adults [78]. IS was CsA based in seven studies and TAC based in two. STWD was successful in 64% to 89% of patients over a time range of 3 to 164 months. The incidence of acute and chronic rejection ranged from 7% to 27% and from 0% to 13%, respectively. Graft survival rates were excellent. Metabolic and growth benefits were seen, although, as expected, not significant, indicating too-long-a-delay between transplantation and time of STWD.

The influence of steroid-free IS on recurrent viral allograft disease in the allograft is of major concern in LT [24]. IS per se seems, however, to be responsible for a

Table 7 Steroid (almost) avoidance in adult liver transplantation

Year	Author	Reference	Center	Induction IS	No. of patients	Follow-up (Months)	STWD time (Months)	Steroid need (%)	Success (%)	Rejection		Advantages	Particularities	Graft Survival (%)
										Acute (%)	Chronic (%)			
1999	Tisone et al.[a,e]	[86]	Rome	Neoral/AZA/ster	22	14 Med (6–24)				9.1	0	Cushing Art. hypertension[b] Cholesterolemia Diabetes		70.2
				Neoral/AZA	23		3 No steroids			8.7	0			78.3 (2 Years pat. surv.)
1999	Rolles et al.[a]	[96]	Royal Free London	Neoral TAC	34	26 (19–33)	No steroids	+ 42		65			Monother. Neoral 64%	62
					30			+ 60		66			Monother. TAC 87%	73 (3 Years)
1999	Watson et al.[a]	[97]	Cambridge	SRL/Neoral/ster	4	4–27	3 (4–7)		100	0			Monother. RAPA 53%	66
				SRL/Neoral	7		3			28			Discontinuation RAPA 20%	
				SRL	4					1				
2001	Pirenne et al.	[98]	Leuven	TAC/AZA	21	12		+46		23	5	Cushing[b] Art. hypertension[b]	57% never steroids	100
				Neoral/AZA/ster (historical control)	21		3			23	5	Diabetesb		95 (1 Year)
2001	Eason et al.[a]	[99]	New Orleans	TAC/MMF/RATG	36	9 Med. (3–18)				20.5		Diabetes Less HCV recurrence	Monother. TAC 78%	89
				TAC/MMF/ster	35		3 (MMF stop 3)		20	32(6) [c]			Monother. TAC 63%	89 (1 Year)
2001	Ringe et al.	[100]	Gottingen	TAC/MMF Intraop. steroids	30	20 Med. (1.5–41)	No steroids		73	26			43% never steroids Monother. TAC 36.6%	83.9 (2 Years)
2001	Trotter et al.[a]	[101]	Denver	CsA/RAPA/ster 3 days.	22	4	3 Days	+ 21		36 (3)[c]		Cholesterolemia in TAC group	Discontinuation RAPA 21%	89
				TAC/RAPA/ster 3 days	17		3 Days							
				TAC/Neoral/MMF/ steroids 14 days (historical control)	191	14 Days	14 Days	+ 100		70 (37) [c]				89
2001	Kneteman	[102]	Edmonton	Daclizumab RAPA/TAC	26	3.6 ± 5	No steroids		/	26.9	/	Diabetes	Art. hypertension (30%); Hyperlipidemia (13%)	96.1 (1 Year)
2001	McAlister et al.	[103]	Halifax	TAC/RAPA/ster	56	23 Med. (6–35)	3–12		91	14		Renal function Diabetes	Hyperlipidemia	91
2001	Washburn et al.[a]	[104]	San Antonio	TAC/MMF/Daclizumab	15	> 6	15 days			6.7		Less HCV recurrence No art . hypertension and no diabetes		93
				TAC/MMF/ster/ Daclizumab	15	(15–21)	1 day			6.7				100
2001	Figueras[d]	[105]	Spanish multicenter	TAC/MMF/Daclizumab	66	3				9	/	Lipid Osteomuscular		97
2002	Lerut et al.[a/d]	[106]	Brussels-UCL	TAC/placebo	20	> 12	No steroids		100	5	0	Art. hypertension; cholesterolemia; diabetes	Monother. TAC 100%	90
				TAC/ster	20	(12–18)	2			25	20		Monother. TAC 84.2%	95 (1 Year)

[a]Prospective randomized study
[b]Statistically significant improvement
[c]Cortico resistant rejection
[d]Published as abstract only
[e]see also Table 5

Table 8 Preliminary results of prospective, blind, placebo-controlled, randomized study comparing TAC-short-term and low-dose steroids and TAC-placebo

Parameter		TAC-placebo (%)	TAC-steroid[a] (%)
Patient survival	3 Months	100	95.2
	1 Year	89.5	85.7
Graft survival	3 Months	100	95.2
	1 Year	84.2	85.7
Rejection	Banff ≥6	36.8	52.4
	Treatment at day 7 during first year	0	10
		10.5	38.1 ($P=0.04$)
	VBDS at 1 year	0	14.3[a] ($P=0.08$)
Monotherapy TAC	At 1 year	100	80 ($P=0.04$)
De novo	At 1 year		
	Insulin-dependant diabetes	5.9	15.5
	Arterial hypertension[b] (pressure >140/100 mmHg)	11.8	0
	Renal insufficiency (creat. >1.5 mg/dl)	17.6	16.6
	Hypercholesterolemia (>220 mg/dl)	5.9	5.6
Karnofsky score >80%	At 1 year	100	100

[a]Steroids were withdrawn in all patients at 64 post-LT days
[b]Monodrug therapy

more-aggressive allograft recurrence, as the few studies related to hepatitis C showed that incidence and severity of allograft re-infection were identical, with or without STWD [25, 26].

Since the feasibility and long-term safety of STWD has been shown in both adult and pediatric LT, the use of steroids becomes controversial, not only in maintenance-IS after LT, but also in induction-IS. Thirteen studies, on steroid avoidance or almost avoidance IS protocols, have already been reported during the period 1999–2002 [26, 86, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106]. Nine were prospective, randomized, controlled studies [26, 86, 96, 97, 99, 101, 104, 105, 106]. IS was TAC based in 11 studies (Table 7). Because of the use of several drug combinations, interpretation of the results is difficult. After a short follow-up (from 1.5 to 41 months), acute and chronic rejection occurred in 5% to 66% and 0% to 6% of patients, respectively; steroids needed to be re-introduced in 0% to 60% of patients. In five studies, TAC monotherapy was obtained in 36.6% to 100% of patients. The 1-year graft survival rate was excellent (≥90%), and metabolic benefits were clear.

A prospective, blind, placebo-controlled, randomized study performed in this institution in 2000 shows that steroids can almost completely be avoided without any penalty in terms of patient and graft survival (Table 8). In a series of 40 consecutive adults, receiving 1,000 g of hydrocortisone peri-operatively, 1-year graft and patient survival rates were almost identical in TAC-short-term steroid (64 days) and TAC-placebo patient groups. TAC monotherapy was obtained in 100% of TAC-placebo patients and in 80% of TAC-steroid patients ($P=0.04$). Incidence of de novo diabetes mellitus, arterial hypertension, hyperuricemia, hypercholesterolemia, and renal insufficiency were identical in both patient groups. There was a significant difference in relation to the incidence of treated rejection during the first year (10.5% in TAC-placebo vs 38.1% in TAC-steroid groups, $P=0.04$); two TAC-steroid patients had vanishing bile duct syndrome. This study has now been extended to 120 adults; preliminary results seem to be similar to those obtained in the first patient cohort [106].

Conclusion

The avoidance of steroids in immunosuppression has been shown to be feasible and safe in heart, liver, kidney, pancreas, and more recently, even intestinal transplantation, in children and in adults. Up to now, success has been greatest in liver transplantation. Avoidance of steroids is probably better than their withdrawal, as it eliminates the risk of rejection and potential steroid-related side effects. The safety of such immunosuppressive protocols can be improved by the use of other drug combinations. In order to judge safety and efficacy, more prospective, randomized, blind, placebo-controlled, clinical, *pluricentric*, investigator-driven studies using internationally accepted histological scoring systems, are necessary.

These studies are necessary, as it is clear that the goal of solid-organ transplantation is no longer patient and/or graft survival, but morbidity and, even more importantly, cost, and quality of life of the recipient. This goal can be achieved by an individualized approach to the transplant recipient, which, on one hand combines, at specific times post-transplantation, different drugs with specific side effects and toxicities, and eliminates, on the other hand, drugs such as steroids, which have been shown in thousands of cases to be detrimental to the physical and psychological well being of transplant recipients. The way from steroid-withdrawing IS to steroid-avoiding IS is open and very promising. It is very probable that these strategies will finally open the door to minimization and tolerogenic immunosuppression protocols [12, 27, 58, 107].

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References

1. Starzl TE, Marchioro TL, Waddel WR (1963) The reversal of rejection in human renal homograft with subsequent development of homograft tolerance. Surg Gynecol Obstet 117:385–395
2. Hricik DE, O'Toole MA, Schulak JA, Herson J (1993) Steroid-free immunosuppression in cyclosporine-treated renal transplant patients—a metaanalysis. J Am Soc Nephrol 4:1300–1305
3. Schulak JA, Hricik DE (1994) Steroid withdrawal after renal transplantation. Clin Transplant 8:211–216
4. Sartori TM, Maurizio PG, Sara P, et al. (1999) Relation between long-term steroid treatment after heart transplantation, hypofibrinolysis and myocardial microthrombi generation. J Heart Lung Transplant 18:693–700
5. Kobashigawa JA, Kasiske B (1997) Hyperlipidemia in solid organ transplantation. Transplantation 63:331–338
6. Grotz WH, Rump LC, Niessen A, et al. (1998) Treatment of osteopenia and osteoporosis after kidney transplantation. Transplantation 66:1004–1008
7. Birkeland SA, Larsen KE, Rohr N (1998) Pediatric renal transplantation without steroids. Pediatr Nephrol 12:87–92
8. Birkeland SA, Andersen HK, Hamilton-Dutoit SJ (1999) Preventing acute rejection, Epstein–Barr virus infection, and posttransplant lymphoproliferative disorders after kidney transplantation : use of acyclovir and mycophenolate mofetil in a steroid-free immunosuppressive protocol. Transplantation 67:1209–1214
9. Qian S, Lu L, Fu F, et al. (1997) Apoptosis within spontaneously accepted mouse liver allografts : evidence for deletion of cytotoxic T cells and implications for tolerance induction. J Immunol 158:4654–4661
10. Wang C, Sun J, Sheil AGR, McCaughan GW, Bishop GA (2001) A short course of methylprednisolone immunosuppression inhibits both rejection and spontaneous acceptance of rat liver allografts. Transplantation 72:44–51
11. Hilbrands LB, Hoitsma AJ, Koene RAP (1995) The effect of immunosuppressive drugs on quality of life after renal transplantation. Transplantation 59:1263–1270
12. Starzl TE, Demetris AJ, Trucco M (1993) Cell migration and chimerism after whole-organ transplantation : the basis of graft acceptance. Hepatology 17:1127–1152
13. Ahsan N, Hricik D, Matas A, et al. (1999) Prednisone withdrawal in kidney transplant recipients on cyclosporine and mycophenolate mofetil—a prospective randomized study. Steroid withdrawal study group. Transplantation 68:1865–1874
14. Calne R, Moffatt SD, Friend PJ, et al. (1999) Campath 1H allows low-dose cyclosporine monotherapy in 31 cadaveric renal allograft recipients. Transplantation 68:1613–1616
15. Nashan B, Moore R, Amlot P, Schmidt AG, Abeywickrama K, Soublon JP (1997) Randomized trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. Lancet 350:1193–1198
16. Kreis H, Cisterne J, Land W, et al. (2000) Sirolimus in association with mycophenolate mofetil induction for the prevention of acute graft rejection in renal allograft recipients. Transplantation 69:1252–1260
17. Kasiske BL, Chakkera HA, Louis TA, Ma JZ (2000) A meta-analysis of immunosuppression withdrawal trials in renal transplantation. J Am Soc Nephrol 11:1910–1917
18. Vincenti F, Ramos E, Brattstrom C, et al. (2001) Multicenter trial exploring calcineurin inhibitors avoidance in renal transplantation. Transplantation 71:1282–1287
19. Mahalati K, Kahan BD (2001) Sirolimus permits steroid withdrawal from a cyclosporine regimen. Transplant Proc 33:1270
20. Reding R (2000) Steroid withdrawal in liver transplantation. Transplantation 70:405–410
21. Livi U, Luciani GB, Boffa GM, et al. (1993) Clinical results of steroid-free induction immunosuppression after heart transplantation. Ann Thorac Surg 55:1160–1165
22. Chakrabarti P, Wong HY, Scantlebury VP, et al. (2000) Outcome after steroid withdrawal in pediatric renal transplant patients receiving tacrolimus-based immunosuppression. Transplantation 70:760–764
23. Cantarovich D, Giral-Classe M, Hourmant M, et al. (2000) Low incidence of kidney rejection after simultaneous kidney–pancreas transplantation after antithymocyte globulin induction and in the absence of corticosteroids : results of a prospective pilot study in 28 consecutive cases. Transplantation 69:1505–1508
24. McMillan JS, Shaw T, Angus PW, Locarnini SA (1995) Effect of immunosuppression and artificial agents on hepatitis B virus replication in vitro. Hepatology 22:36–43
25. Belli LS, Alberti AB, Rondinara GF, et al. (2001) Early ribavirin treatment and avoidance of corticosteroids in hepatitis C virus (HCV)-positive liver transplant recipients : interim report of a prospective randomized trial. Transplant Proc 33:1353–1354
26. Bilbao I, Pou L, Castells L, et al. (2000) Tacrolimus monotherapy in liver transplantation: comparison with dual regimen of tacrolimus with steroids. Hepatology 32:598A
27. Mazariegos GV, Reyes J, Marino I, et al. (1997) Weaning of immunosuppression in liver transplantation recipients. Transplantation 63:243–249
28. Braun F, Lorf T, Ringe B (1998) Update of current immunosuppressive drugs used in clinical organ transplantation. Transpl Int 11:77–81
29. European Multicentre Trial (1982) Cyclosporine A as sole immunosuppressive agent in recipients of kidney allografts from cadaver donors. Lancet 2:57–60
30. Vanrenterghem Y, Lebranchu Y, Hené R, Oppenheimer F, Ekberg H (2000) Double-blind comparison of two corticosteroid regimens plus mycophenolate mofetil and cyclosporine for prevention of acute renal allograft rejection. Transplantation 70:1352–1359
31. Grinyo JM, Gil-Vernet S, Seron D, et al. (1997) Steroid withdrawal in mycophenolate mofetil-treated renal allograft recipients. Transplantation 63:1688–1690
32. Sandrini S, Maiorca R, Scolari F, et al. (2000) A prospective randomized trial on azathioprine addition to cyclosporine versus cyclosporine monotherapy at steroid withdrawal, 6 months after renal transplantation. Transplantation 69:1861–1867
33. Matas AJ (1998) Risk factors for chronic rejection—a clinical perspective. Transpl Immunol 6:1–11
34. Sinclair NR (1992) Low-dose steroid therapy in cyclosporine treated renal transplant recipients with well-functioning graft. Can Med Assoc J 147:645–657
35. Thiel G, Block A, Spondlin M, et al. (1994) Long-term benefits and risks of cyclosporin A (Sandimmun)—An analysis at 10 years. Transplant Proc 26:2493–2498

36. Almawi WY, Hess DA, Chudzik DM, Rieder MJ (1999) Pretreatment with glucocorticoids enhances T-cell effector function : possible implication for immune rebound accompanying glucocorticoid withdrawal. Cell Transplant 8:637–647
37. Sivaraman P, Nussbaumer G, Landsberg D (2001) Lack of long-term benefits of steroid withdrawal in renal transplant recipients. Am J Kidney Dis 37:1162–1169
38. Matas A, Ramcharan T, Paraskevas S, et al. (2001) Rapid discontinuation of steroids in living donor kidney transplantation : a pilot study. Am J Transplant 1:278–283
39. Birkeland SA (2001) Steroid-free immunosuppression in renal transplantation. Transplantation 71:1089–1090
40. Sarwal MM, Yorgin PD, Alexander S, et al. (2001) Promising early outcomes with a novel, complete steroid avoidance immunosuppression protocol in pediatric renal transplantation. Transplantation 72:13–21
41. Kupin W, Verkat KK, Goggins M, et al. (1998) Transplantation without steroids in 1-haptotype and 2-haptotype matched living related renal transplant recipients treated with mycophenolate (abstract). International Transplantation Society
42. Landsberg D, Cole E, Russell D, et al. (2000) Renal transplantation without steroids—one-year results of a multicentre Canadian pilot study. Transplantation 69: S134
43. Kaufman DB, Leventhal JR, Fryer JP, Abecassis MI, Stuart FP (2000) Kidney transplantation without prednisolone. Transplantation 69: S133
44. Short CD, Johnson RWG, Roberts IDS (2000) Two years of tacrolimus monotherapy following renal transplantation. Fourth International Conference on New Trends in Clinical and Experimental Immunosuppression. Geneva Abstract 154
45. Vincenti F, Monaco A, Grinyo J, et al. (2001) Rapid steroid withdrawal versus standard steroid therapy in patients treated with basiliximab, cyclosporine, and mycophenolate mofetil for the prevention of acute rejection in renal transplantation. Transplant Proc 33:1011–1012
46. Elias TJ, Bannister KM, Clarkson AR, et al. (2000) Excellent long-term graft survival in low risk, primary renal allografts treated with prednisolone-avoidance immunosuppression. Clin Transplant 14:157–161
47. Buell JF, Kulkarni S, Grewal HP (2000) Early corticosteroid cessation at 1 week following kidney transplant under tacrolimus and mycophenolate mofetil (MMF) immunosuppression, three-year follow-up. Transplantation 69: S134
48. Weimar W (2001) Anti-CD25 prophylaxis allows steroid-free transplantation. A transplant Odyssey (abstract), Istanbul S2.1:1693
49. Humar A, Parr E, Drangstveit MB, Kandaswamy R, Gruessner AC, Sutherland DER (2000) Steroid withdrawal in pancreas transplant recipients. Clin Transplant 14:75–78
50. Jordan ML, Chakrabarti P, Luke P, et al. (2000) Results of pancreas transplantation after steroid withdrawal under tacrolimus immunosuppression. Transplantation 69:265–271
51. Gruessner RWG, Sutherland DER, Parr E, Humar A, Gruessner AC (2001) A prospective, randomized, open-label study of steroid withdrawal in pancreas transplantation. A preliminary report with 6-month follow-up. Transplant Proc 33:1663–1664
52. Salazar A, McAlister VC, Kiberd BA, Bitter-Suermann H, Al-Kerithy MF, MacDonald AS (2001) Sirolimus–tacrolimus combination for combined kidney–pancreas transplantation : effect on renal function. Transplant Proc 33:1038–1039
53. Cantarovich D, Paineau J, Karam G, et al. (1991) Definitive corticosteroid withdrawal following simultaneous pancreas and kidney transplantation. Transplant Proc 23:1583–1584
54. Ward RG, Gecim E, Bone JM, Bakran A, Sells RA (1994) Cyclosporin monotherapy in pancreaticorenal transplantation. Transplant Proc 26:548
55. Kaufman DB, Leventhal JR, Koffron AJ, et al. (2002) A prospective study on rapid corticosteroid elimination in simultaneous pancreas–kidney transplantation. Transplantation 73:169–177
56. Shapiro AMJ, Lakey J, Ryan EA, et al. (2000) Islet transplantation in seven patients with type I diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med 343:230–238
57. Abu-Elmagd KM, Bond GJ, Murase N, et al. (2002) Graft immunomodulation and tolerance enhancing strategy for intestinal transplantation (abstract). Am J Transplant 2:350
58. Starzl TE (2002) A tolerogenic strategy for organ transplantation (abstract) Transplantation 74:147
59. Tzakis AG, Kato T, Nishida S, et al. (2002) Campath 1H combined with tacrolimus in intestinal and multivisceral transplantation (abstract). Am J Transplant 2:350
60. Keogh A, Mc Donald P, Harvison A, Richens D, Mundy J, Spratt P (1992) Initial steroid free versus steroid based maintenance therapy and steroid withdrawal after heart transplantation : two views of the steroid question. Transplant 11:421–427
61. Koerner NM, Posival H, Tenderich G, et al. (1994) Long-term results with cyclosporine monotherapy after heart transplantation. Transplant Proc 26:2718–2720
62. Price GD, Olsen SL, Taylor DO, O'Connell JB, Bristow MR, Renlund DG (1992) Corticosteroid free maintenance immunosuppression after heart transplantation : feasibility and beneficial effects. J Heart Lung Transplant 11:403–415
63. Prieto M, Lake KD, Pritzker MR, et al. (1991) OKT3 induction and steroid-free maintenance immunosuppression for treatment of high-risk heart transplant recipients. J Heart Lung Transplant 10:901–911
64. Bolman RM (1993) Steroid-free heart transplantation: an analysis. Ann Thorac Surg 55:1069–1070
65. Miller LW, Wolford T, McBride LR, Peigh P, Pennington DG (1992) Successful withdrawal of corticosteroids in heart transplantation. J Heart Lung Transplant 11:431–434
66. Pritzker MR, Lake KD, Reutzel TJ, et al. (1992) Steroid-free maintenance immunotherapy: Minneapolis Heart Institute experience. J Heart Lung Transplant 11:415–420
67. Nohria A, Ehtisham J, Ramahi TM (1998) Optimum maintenance through levels of cyclosporine in heart transplant recipients given corticosteroid-free regimen. J Heart Lung Transplant 17: 849–853
68. Newell KA, Alonso EM, Whitington PF, et al. (1996) Posttransplant lymphoproliferative disease in pediatric liver transplantation. Transplantation 62:370–375
69. Baran DA, Segura L, Kushwaha S, et al. (2001) Tacrolimus monotherapy in adult cardiac transplant recipients: intermediate-term results. J Heart Lung Transplant 20:59–70
70. Bailey LL, Gundry SR, Razzouk AJ, Wang N, Sciolaro CM, Chiavarelli M (1993) Bless the babies: one hundred fifteen late survivors of heart transplantation during the first year of life. J Thorac Cardiovasc Surg 105:805–814

71. LeBidois J, Kachaner J, Vouhe P, Sidi D, Tamisier D (1992) Heart transplantation in children: mid-term results and quality of life. Eur J Pediatr 151 S1:59–64
72. Leonard HC, O'Sullivan JJ, Dark JM (2000) Long-term follow-up of pediatric cardiac transplant recipients on a steroid-free regime : the role of endomyocardial biopsy. J Heart Lung Transplant 19:469
73. Livi U, Caforio AL, Gambino A, et al. (1998) Cyclosporine based steroid-free therapy in pediatric heart transplantation : long-term results. Transplant Proc 30:1975–1976
74. Lake KD, Reutzel TJ, Pritzker MR, Jorgensen CR, Emery RW (1993) The impact of steroid withdrawal on the development of lipid abnormalities and obesity in heart transplant recipients. J Heart Lung Transplant 12:580–590
75. Padbury RTA, Gunson BK, Dousset B, et al. (1993) Steroid withdrawal from long-term immunosuppression in liver allograft recipients. Transplantation 55:789–794
76. Padbury R, Toogood G, McMaster P (1998) Withdrawal of immunosuppression in liver allograft recipients. Liver Transpl Surg 4:242–248
77. Punch JD, Shieck VL, Campbell DA, Bromberg JS, Turcotte JG, Merion RM (1995) Corticosteroid withdrawal after liver transplantation. Surgery 118: 783–788
78. McDiarmid SV, Farmer D, Goldstein L, et al. (1995) A randomized prospective trial of steroid withdrawal after liver transplantation. Transplantation 60:1443–1450
79. Tchervenkov JI, Tector AJ, Cantarovich M, et al. (1996) Maintenance immunosuppression using cyclosporine monotherapy in adult orthotopic liver transplant recipients. Transplant Proc 28:2247–2249
80. Fraser GM, Grammoustianos K, Reddy J, et al. (1996) Long-term immunosuppression without corticosteroids after orthotopic liver transplantation: a positive therapeutic aim. Liver Transpl Surg 2:411–417
81. Stegall MD, Everson GT, Schroter G, et al. (1997) Prednisolone withdrawal late after adult liver transplantation reduces diabetes, hypertension, and hypercholesterolemia without causing graft loss. Hepatology 25:173
82. Stegall MD, Wachs M, Everson FT, et al. (1997) Prednisone withdrawal 14 days after liver transplantation with mycophenolate. Transplantation 64:1755–1760
83. Pichlmayr R, Winkler M, Neuhaus P, et al. (1997) Three-year follow-up of the European multicenter tacrolimus liver study. Transplant Proc 29:2499–2502
84. Gomez R, Moreno E, Colina F, et al. (1998) Steroid withdrawal is safe and beneficial in stable cyclosporine-treated liver transplant patients. J Hepatol 28:150–156
85. Belli L, Decarlis L, Rondinara G, et al. (1998) Early cyclosporine monotherapy in liver transplantation: a 5-year follow-up of a prospective randomized trial. Hepatology 27:1524–1529
86. Tisone G, Angelico M, Palmieri G, et al. (1999) A pilot study on the safety and effectiveness of immunosuppression without prednisone after liver transplantation. Transplantation 10: 1308–1313
87. Lerut JP, Ciccarelli O, Mauel E, et al. (2001) Adult liver transplantation and steroid–azathioprine withdrawal in cyclosporine (Sandimmun)-based immunosuppression—5 year results of a prospective study. Transpl Int 14:420–428
88. Margarit C, Martinez-Ibanez V, Tormo R, Infante D, Iglesias H (1989) Maintenance immunosuppression without steroids in pediatric liver transplantation. Transplant Proc 21:2230–2231
89. Superina R, Acal L, Bilir B, Zaki A (1993) Growth in children after liver transplantation on cyclosporine alone or in combination with low-dose azathioprine. Transplant Proc 25:2580
90. Murphy MS, Harrison R, Davies P, et al. (1996) Risk factors for liver rejection: evidence to suggest enhanced allograft tolerance in infancy. Arch Dis Child 75:502–506
91. Dunn S, Falkenstein K, Lawrence JP, et al. (1994) Monotherapy with cyclosporine for chronic immunosuppression in pediatric liver transplantation recipients. Transplantation 57:544–547
92. Martin SR, Paradis K, Alvarez F (1998) Cyclosporine monotherapy in long-term pediatric liver transplant recipients. Transplant Proc 30:1424–1426
93. McKee, Mattei P, Schwarz K, Wise B, Colombani B (1997) Steroid withdrawal in tacrolimus treated pediatric liver transplant recipients. J Pediatr Surg 32:973–975
94. Andrews WS, Shimaoka S, Sommerauer J, Moore P, Hudgins P (1994) Steroid withdrawal after pediatric liver transplantation. Transplant Proc 26:159–160
95. Jain A, Mazarriegos G, Iurlano K, Fung J, Reyes J, Starzl TE (1999) Why some children are still on steroid beyond five years post liver transplantation under tacrolimus. Transplantation 67:5231
96. Rolles K, Davidson BR, Burroughs AK (1999) A pilot study of immunosuppressive monotherapy in liver transplantation. Transplantation 68:1195–1209
97. Watson CJE, Friend PJ, Jamieson NV, et al. (1999) A potent new immunosuppressant for liver transplantation. Transplantation 67:505–509
98. Pirenne J, Aerts R, Koshiba T, et al. (2001) Standard cyclosporine A-based versus completely steroid-free FK506-based immunosuppression after liver transplantation. Transplant Proc 33:1505
99. Eason JD, Loss GE, Blazek J, Nair S, Mason AL (2001) Steroid-free liver transplantation using rabbit antithymocyte globulin induction: results of a prospective randomized trial. Liver Transplant 7:693–697
100. Ringe B, Braun F, Schutz E (2001) A novel management strategy of steroid-free immunosuppression after liver transplantation: efficacy and safety of tacrolimus and mycophenolate mofetil. Transplantation 71:508–515
101. Trotter JF, Wachs M, Bak T (2001) Liver transplantation using sirolimus and minimal corticosteroids (3-day taper). Liver Transplant 7:343–351
102. Kneteman NM (2001) Steroid-free immunosuppression: balancing efficacy and toxicity. Liver Transplant 7:698–700
103. McAlister VC, Gao Z, Peltekian K, Domingues J, Mahalati K, MacDonald AS (2000) Sirolimus–tacrolimus combination immunosuppression. Lancet 355:376–377
104. Washburn K, Speeg KV, Esterl R (2001) Steroid elimination 24 hours after liver transplantation using daclizumab, tacrolimus and mycophenolate mofetil. Transplantation 72:1675–1679
105. Figueras J (2001) Steroid-free regime with daclizumab, mycophenolate mofetil, and tacrolimus in liver transplant recipients (abstract). Second International Congress on Immunosuppression, San Diego, 2001 p 81
106. Lerut J, Ciccarelli O, Talpe S (2002) Tacrolimus monotherapy in adult liver transplantation: preliminary results of a prospective, randomized, double-blind, placebo-controlled, single center study (abstract). Am J Transplant 2:371
107. Takatsuki M, Uemoto SH, Inomata Y, et al. (2001) Weaning of immunosuppression in living donor liver transplant recipients. Transplantation 72:449–454