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REVIEW

Steroid-free and *steroid withdrawal* protocols in heart transplantation: the review of literature

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Summary

Corticosteroids (CSs) are still the mainstay of induction, rescue, and maintenance in heart transplantation (HTx). However, their use is associated with significant and well-documented side effects usually related to the dose administered and the duration of therapy. Moreover, CSs interfere with the recipient's quality of life and with the active process of graft tolerance. Physicians have been exploring ways to avoid or reduce CSs in association with other immunosuppressive drugs, minimizing side effects and costs. The regimens are classified as *steroid-free* or *steroid withdrawal* protocols. The studies analyzed in this review come to similar conclusions as benefits and adverse consequences: *steroid-free* protocols should be advisable and mandatory in pediatric patients, insulin-dependent diabetes mellitus (IDDM), presence of infection, familial metabolic disorders/obesity, severe osteoporosis, and in the elderly. On the other hand, *steroid withdrawal* can be successfully achieved in 50–80%, with late better than early withdrawal, no increase in rejection-related mortality, no adverse impact on survival, and probably a better quality of live. Safety and efficacy can certainly be improved by an individualized approach to the transplant recipient.

Introduction

Every year, about 4000 heart transplantations (HTx) are performed worldwide according to the ISHLT registry. Median survival is steadily improved from 8.5 years (1982–1992) to 10.9 years (1993–2002), and it is further improved since 2003 [1]. Acute rejection is now a fairly uncommon cause of death, being responsible for no more than 11% of deaths, whereas graft failure of different origin is the leading cause of death in the first 30 days after transplant and later. Even if the exact etiology of late graft failure is unknown, deaths are mainly due to cardiac allograft vasculopathy (CAV), an immunomediated process possibly worsened by other comorbidities as hypertension, diabetes mellitus, and hyperlipidemia. These deaths can at least in part be attributed to the effects of immunosuppressive therapies [1].

Calcineurin inhibitors (CNIs), mycophenolic acid (MPA), mammalian target of rapamycin inhibitors (mTOR), and corticosteroids therapy continue to be the dominant immunosuppressive choice after HTx [1]. CSs are a standard part of every phase of immunosuppression (induction, maintenance, rejection treatment). Their use is associated with significant and well-documented side effects usually related to the dose administered and the treatment duration [2,3]. The most frequent and distressing side effects of steroid association in transplant recipients are metabolic [4–8], skeletal [9–12], and vascular disorders [13], often combined with a higher susceptibility to infections [14].

The optimal immunosuppressive therapy is the combination of different drugs to enhance their immunosuppressive potential and decrease their toxic effects by

lowering the single dosage of each, also allowing the reduction or suppression of steroids. Thus, physicians have been exploring ways to avoid or eliminate the need for long-term steroid treatment, thereby minimizing side effects and costs. These regimens classified as *steroid-free* or *steroid withdrawal* protocols (early within the first 3–6 months after HTx or late between 6–12 months and beyond post-transplant) have been applied in several solid organ transplantations.

In the early 1980s, the European transplant community tried to withdraw from standard immunosuppression or avoid completely the use of CSs in organ transplantation, but the results were varied and might be not applicable to the actual therapies [15,16]. Instead, in a more recent analysis, Lerut [17] evaluated studies using more innovative drugs and concluded that results were satisfying in almost all types of solid organ transplants if steroid avoidance had been accomplished. Moreover, the same author reported that in clinical practice of liver transplantation, there was a tendency toward steroids minimization with their avoidance more favorable than their withdrawal [18]. CS minimization protocols and sparing have been applied even in kidney transplantation [19,20], and a meta-analysis of Knight SR *et al.* [21] revealed an increase in the risk of acute rejection (AR) with steroid avoidance or withdrawal protocol (RR 1.56, CI 1.31–1.87, $P < 0.0001$), but with no measurable effect on graft or patient survival, reporting at the same time significant benefits in cardiovascular risk profile. Steroid withdrawal in pancreas and islet transplantation, even if the success has been validated by several transplant centers, cannot currently be recommended because lacking in prospective randomized studies to verify the risk/benefit ratio [22,23].

The first to describe results with *steroid-free* immunosuppression in HTx was Yacoub *et al.* [24] in 1985, whereas the first experience with steroid withdrawal was reported by Pritzker *et al.* [25]. Moreover, this therapeutic approach was proven to be feasible also in pediatric HTx [26,27].

Experience with the *minimization* of CSs in heart transplantation is relatively poor and more heterogeneous when compared with other solid organs, and results are difficult to interpret. In fact, the clinical use of different CSs *minimization* protocols and different co-treatments in various clinical settings might make clinical outcomes difficult to compare. Thus, the purpose of this paper was to focus only on CSs-*free* and CSs-*withdrawal* protocols in HTx patients to evaluate the results achieved on survival, rejection and infection rate, or other drug side effects.

The role of steroids in heart transplantation

CSs immunosuppressive action is multifactorial depending on the target cell type considered and their activation state: (i) synthesis of lipocortins which prevent arachidonic acid release from membrane-bound stores; (ii) blockade of selected elements of the signal transduction pathways that operate as a consequence of T-cell activation; (iii) inhibition of leukocyte adhesion molecule expression; and (iv) suppression of cytokine production and action [28]. To influence cellular function, CSs must enter the cell and bind to and activate intracellular receptors, named *glucocorticoid receptors* (GRs), type-I and type-II [29]. Type-II GRs, widely distributed in the immune system, affect all immune cells at an intermediate level in mature T and B cells and at very low level in neutrophils [30]. GRs density in peripheral T cells is a critical determinant of sensitivity, and despite the presence of functional GRs, clinical CSs resistance can arise [31]. It has been demonstrated that chronically CSs drug therapy may alter immune cell differentiation which may be of relevance in the induction of peripheral tolerance to allergenic stimuli [32–35].

The main CSs used to prevent and treat allograft rejection are *prednisolone* and *prednisone*. From a pharmacokinetic point of view, synthetic CSs present increased bioavailability, poor linkage to CS-binding globulin (CBG) and have much longer half-life than endogenous CSs (cortisol, corticosterone) [36,37]. CSs administration to humans results in rapid but transient lymphopenia (especially T cells) [38] and in a significant reduction in eosinophil and basophil numbers, whereas vice versa neutrophil exhibits a marked increase [39]. In clinical setting, beside the well-known effect on acute rejection, CSs could impact also on coronary allograft vasculopathy (CAV), present in 90% of patients within 10 years and considered one of the major cause of late death following HTx [40–43]. Etiology of CAV is mostly immunologic, but nonimmune pathways contribute to its development. Inflammatory cells and humoral injuries are present in evolving lesions [44]; cytokines and chemokines are known to mediate local and systemic immune responses and to recruit and activate inflammatory cells. Thus, CS minimization might accelerate the course of CAV being the disease for great part immunomediated. However, Ratkovec *et al.* [45] demonstrated that CSs minimization does not adversely affect the prevalence or progression of CAV during the first 2 years after HTx. Moreover, while cyclosporine and tacrolimus are not effective in preventing CAV [46], mychophenolate mofetil, sirolimus, and everolimus seem to impact on the appearance and progression of CAV, allowing a consistent reduction in CSs [47–49].

As it has been demonstrated that cumulative CSs dose in HTx recipients has been associated with hyperlipidemia and possibly with more diabetes and hypertension, CSs withdrawal or avoidance would decrease the incidence and progression of CAV [50].

Methods

This review is focusing on strategies to avoid CSs after HTx as a means to improve short- and long-term outcome. To analyze the impact of different CSs protocols, we searched the PubMed database up to June 2013 using the following keywords: *heart transplantation*, *corticosteroids*, *steroid-free*, *complete steroid avoidance*, *steroid withdrawal*, *steroid minimization, and steroid side effects.* Inclusion criteria specified any *prospective* or *retrospective* trial or observational study in adult and pediatric HTx recipients. This research was considering only studies that compared steroid groups (SG) versus steroid-free groups (SFG). Studies with steroid avoidance [steroid free = SF], with early steroid withdrawal (within the first 6 months) [early withdrawal in steroid, free maintenance immunosuppression = *ew*-SFM], and late steroid withdrawal (between 6 and 12 months and beyond post-HTx) [late withdrawal in steroid-free maintenance immunosuppression = *lw*-SFM] regimens, including pediatric experiences, were then analyzed separately.

Quality assessment was performed according to the Cochrane Collaboration Criteria for the evaluation of RCTs [51] and according to the GRACE principles for the evaluation of observational studies [52]. For the evaluation of RCTs, only internal validity criteria were computed for the final 10-points score (for each item, a yes/no/unclear evaluation was made; then, 1 point was assigned for each positive mark). For the evaluation of observational studies, an overall assessment was performed in accordance with GRACE principles, ranking studies as *low*, *medium,* or *high quality*. Considering the different quality levels, the variety in patients' characteristics, the fact that most studies had only one arm and that evaluation of the outcomes was different among studies, a meta-analysis was not attempted. Patients were divided in *steroid group* (SG) and *steroid-free (maintenance) group* (SFG). To compare the results of the studies, the following parameters were selected: *graft and patient survival*, *rejection* and *infection rate,* or *other complications*. Results of comparison among different drug therapy approaches and relative quality assessment results are reported in Tables 1–4. Finally, authors' conclusions were compared.

Results

Twenty-one studies were finally included in the review. Beyond what is shown in the tables, other findings will be highlighted in bold. Most studies were actually well conducted, but analyses were sometimes not appropriate for the outcome or conducted "as treated", so providing the reader with only the ideal efficacy of the treatment. Moreover, in only very few studies, a multivariable modeling was applied.

Steroid-free immunosuppression

There are few data on CSs avoidance in adult HTx, three prospective [53,54,56] and one retrospective [55] compared HTx results in SG versus SFG (Table 1). Only one paper was of high quality [55], and three were of low quality [53,54,56]. The reported 2-year survival was excellent either in SG and SFG without any significant differences (92% and 93% in the first study, 86% and 85% in the second, respectively) [53,54]. When evaluating prospective studies only, the incidence of acute rejection was found to be significantly higher in SFG versus SG in two studies [53,54] and lower in one [56]. On the contrary, the overall incidence of infections was significantly higher [53] or similar [54,56] in SG than SFG. The use of steroids was joined with increased antihypertensive drug use [54], vice versa reduction in bone loss and better cardiac function were recorded in the SFG [56]. Overall, it can be concluded that steroids-free therapies appear to be safe because of the good survival even in the presence of a higher rejection rate, with the incidence of infections being similar.

In the only retrospective study, rated as "high quality", dealing with 112 consecutive HTx patients initially immunosuppressed with CsA+AZA without CSs, Livi *et al.* [55] recorded good survival of discharged patients at 1 year and 2 years (95% and 94%, respectively), high incidence of acute rejection, and lower trend in hypertension incidence. The authors concluded that despite the more frequent occurrence of acute rejection, the excellent mid-term survival and the initial low incidence of both infection and chronic rejection justified a wider use of such treatment.

Beyond our primary end points, there are other aspects worthy to be considered. In a randomized prospective trial, Jones *et al.* compared the quality of life after HTx in patients treated with CsA+AZA (double therapy) versus CsA+AZA+CSs (triple therapy). Patients who received double therapy showed advantages in 10 of 11 measures of life quality with significant differences in score of anxiety, sexual activity, and physical well-being. Furthermore, patients who received double therapy reported a lower frequency of and less distress from the immunosuppression side effects with return to full-time employment and better weight control [57].

Steroid withdrawal immunosuppression

Experience with SFM protocol is large and highly variable depending on the dose, on the duration of CSs therapy, and on the other immunosuppressive drugs used. Based on this, it is not easy to compare different studies and clinical outcomes. In different publications, we found several protocols which can be simplified in *early withdrawal* (*ew*) and *late withdrawal* (*lw*) CSs protocols.

Table 1. Steroid-free regimen in adult heart transplantation recipients.

References	Study design	Participants and intervention	Survival	Rejection	Infections and other ADRs	Authors' conclusions	Quality assessment
[53]	Prospective RCT	*N* = 60. SG: 29 pts, mean age 42 years, M:F = 23:6; SFG: 31 pts, mean age 40 years, M:F = 25:5 SG: Cyc + AZA + CSs SFG: Cyc + AZA	SG: 2-year survival = 92%, SFG: 2-year survival = 93%. No patient died for transplant-related adverse events in both the groups	Higher overall incidence of rejection and at 1, 3, 6 and 12 months in the SFG (overall: 2.3 in SFG vs. 1.1 in SG, $P < 0.002$)	Overall incidence of infections: 1.6 in SG vs. 1.3 in SFG ($P > 0.05$). Similar occurrence of other ADRs, apart from obesity, being more common among SG pts (14/29 in SG vs. 9/31 in SFG)	The two protocols of therapy produce actuarial survival and morbidity rates comparable	3/10
[54]	Prospective RCT	*N* = 112 SG: 59 pts; SFG: 53 pts. Reported as well matched at randomization. SG: Cyc + AZA + CSs SFG: Cyc + AZA	Analyses were conducted "as treated". SG survival rates: 86% and 78% at 2 years and 5 years, respectively; SFG survival rates: 85% and 82% at 2 years and 5 years, respectively ($P > 0.05$)	Analyses were conducted "as treated". Higher incidence of rejection at 3 months in the SFG (2.3 episodes/100 patients vs. 1.5/100 patients in the SG, $P = 0.01$). No differences in rejection rates thereafter	Analyses were conducted "as treated". Similar total infection rates but increased antihypertensive drug use and cholesterol levels in SG. Steroid-related morbidity and coronary artery disease were comparable between the two groups	The rate of steroid-related morbidity (diabetes, bone complications, cataracts, and obesity) was low in both the groups and did not differ significantly	3/10
[55]	Retrospective, observational	Only SFG. *N* = 112, M:F = 92:20, median age 50 (1–68 years). All patients: Cyc + AZA	95% and 94% at 1 year and 2 years, respectively	Acute rejection was common (nearly 100%). Overall rejection rate: 1.7 ± 1.0 episodes per patient. Rejection-free survival rates: 20%, 10%, 7%, and 5% at 1, 6, 12, and 48 months. 21% of patients required steroid addition for persistent or repeated rejection	Infection rate was 0.1 ± 0.4 episode/patient. Freedom from infection survival rate was 85% at 2 years. Increasing trend in hypertension occurrence up to 57%. Lipid metabolism normal during follow-up	High incidence of acute rejection. Excellent medium-term survival and low incidence of both infection and chronic rejection	High quality
[56]	Prospective, open-label RCT	*N* = 32, 1:1 randomization. SG: mean age 49 years, M:F = 14:18. SFG: mean age 51 years, M:F = 13:19. SG: TC + MMF + Prednisone. SFG: TC + MMF + TMG. All patients received intra-operative TMG	One death per group (no further information)	Acute cellular rejections occurred in 69% of SG vs. 50% of SFG ($P = 0.29$). Mean number of acute cellular rejection episodes not significantly different between the two groups (1.07 in SG vs. 0.81 in SFG)	No difference in opportunistic infections incidence. Reduction in bone loss and augmented cardiac strength in the SFG. Four cases of skin cancers in the SFG group. No major bleedings, no lymphoproliferative disorders	With use of TMG, CSs avoidance seems to be safe with significant improvement in muscular strength and lower lost in bone density	4/10

AZA, azathioprine; CSs, corticosteroids; Cyc, cyclosporine; OKT3, muromonab-CD3; SFG, steroid-free group; SG, steroid group; MMF, mycophenolate mofetil; TC, tacrolimus; TMG, thymoglobulin.

Table 2. *Early withdrawal* of steroid therapy in adult heart transplantation recipients.

References	Study design	Participants and intervention	Survival	Rejection	Infections and other ADRs	Authors' conclusions	Quality assessment
[25]	Observational prospective	SG: 32 patients, mean age 53 years, M:F = 30:0; SFM: 36 (29 on final analyses) patients, mean age 49 years, M:F = 20:9. **Therapeutic groups were defined by indication**. SG: Cyc + AZA + prednisone; SFM: as SG + prophylactic OKT3 and steroid withdrawal within 3 months	Survival in SG group: 94%, 94% and 81% at 1, 2, and 3 years; in SFM group: 100%, 100%, and 100% at 1, 2, and 3 years ($P = 0.171$ at 1 and 2 years, $P = 0.049$ at 3 years).	Rejection episodes' rates similar in both the groups (SG: 53% vs. SFM: 48%, $P = 0.910$), while rejection-free survival higher in SFM group (27 ± 17 days in SG vs. 205 ± 214 days in SFM, $P = 0.020$)	Significantly higher total cholesterol ($P = 0.003$) and LDL ($P = 0.013$) levels in SG at 1-year follow-up, but not at 2 years. Prevalence of hypertension similar in both the groups ($P = 0.242$) and weight gain/BMI increase slightly higher in SG ($P = 0.170$ and 0.108, respectively). Infectious complications similar in both the groups ($P = 0.091$)	Steroid-free maintenance immunotherapy is feasible and was attained in a high percentage of targeted patients (81%) with additionally lower lipid values, less hypertension, less weight gain, and similar infection rates	High quality
[58]	Retrospective	SG: 263 patients, mean age 49.4 years, M:F = 2018:45; SFM: 111 patients, mean age 48.4 years, M:F = 104:7. **Steroid withdrawal was attempted in the whole group. Analyses were then conducted "as treated"**. SG: Cyc or AZA + OKT3 + methylprednisolone/prednisone; SFM: as SG plus steroid withdrawal within 3 months	Analyses were conducted as treated. Ten-year survival was markedly better in SFM group ($P < 0.0001$). Independent predictors of mortality were as follows: total number of post-transplantation infections ($P < 0.001$), older age ($P = 0.001$), failed early corticosteroid withdrawal ($P = 0.006$), female gender ($P = 0.016$). Also allograft survival was better in SFM group	Rejection rates were lower in SFM group both during the first year (*P* not shown) and after the first year (0.07 episodes per pt/y in SFM vs. 0.15 episodes/pt/y in SG, $P = 0.0002$). Female recipients had more rejection episodes ($P = 0.054$)	Treated infections were more common in patients in which early corticosteroid weaning failed (*P* not shown). Severe allograft coronary artery diseases were lower in SFM group ($P = 0.10$)	Analyses not appropriate to evaluate outcome. Authors' statement: successful early corticosteroid withdrawal identifies a subgroup of "immunologically privileged" patients with a very low risk for long-term mortality and, when reached, is not associated with an increased prevalence of late rejection or clinically significant coronary artery disease	High quality

Table 2. continued

References	Study design	Participants and intervention	Survival	Rejection	Infections and other ADRs	Authors' conclusions	Quality assessment
[59]	Retrospective	SG: 46 patients, mean age 53.5 years, M:F = 41:5; SFM: 93 patients, mean age 52.9 years, M:F = 71:22. **Comparison of two different therapeutic approaches instituted at the hospital at different times (SG: 1988–1990, SFM: 1990 onward).** SG: Cyc + AZA + prednisone; SFM: as SG plus steroid withdrawal **within 6 months**	Overall survival in SFM group trended to be higher than in SG ($P = 0.06$). No differences regarding causes of death except for infections, more common in SG ($P = 0.06$)	Better freedom from rejection in SG ($P < 0.01$)	Overall freedom from infection similar in both the groups with a trend for higher incidence in SG ($P = 0.10$). Better overall freedom from malignancy in SFM group ($P < 0.01$), mainly because of fewer skin cancers ($P = 0.03$). Similar occurrence of other conditions (renal dysfunction, obesity, diabetes, coronary artery disease)	Steroid withdrawal is a possible and safe approach showing prolonged survival and lower/later occurrence of malignancies	High quality

AZA, azathioprine; Cyc, cyclosporine; CSs, corticosteroids; MMF, mycophenolate mofetil; OKT3, muromonab-CD3; SFM, steroid-free maintenance group; SG, steroid group; TC, tacrolimus; TMG, thymoglobulin.

The *ew*-CSs protocol was reported in one prospective [25] and two retrospective trials [58,59] (Table 2). All these studies were classified as high quality. The long-term survival in SFM group was significantly higher than SG in all the studies analyzed [25,58,59].

Comparing the groups about rejection episodes, results appear even more controversial. In fact, while some authors agreed that SG experienced better freedom from rejection ($P < 0.01$) [59], others showed that the *ew*-CSs protocols were associated with a lower incidence of rejection ($P = 0.0002$) in one study [58] or with similar results ($P = 0.910$) in the other [25].

Considering the incidence of infections, Pritzker *et al.* [25] reported similar infective complication rates in both the groups ($P = 0.091$), whereas Taylor *et al.* revealed that treated infections were more common in patients in whom early CS weaning failed [58]. Similarly, Rosenbaum *et al.* [59] observed that freedom from infections did not differ between the two groups considered ($P = 0.10$). Moreover, the same authors observed better overall freedom from malignancy in SFM group (skin cancer, $P < 0.01$), while post-transplant morbidities (renal dysfunction, obesity, diabetes, CAV) were similar in both the groups. Also, Taylor observed that CAV was apparently lower in the SFM group, albeit not significant, ($P = 0.10$), and in other studies, SFM protocol seemed to be associated with lower lipid values, less hypertension, and better or similar weight control [25,59].

The *lw*-CSs protocol was reported in 10 papers, four prospective trials [61,64,65,69], and six retrospective [60,62,63,66–68] (Table 3). Five studies were of high quality and five of medium quality. Of the four prospective studies, only one was rated as "high quality" [64]; Opelz *et al.* [65] focused on mortality reporting 7-year survival rate significantly higher in SFM group ($P = 0.0008$). Rejection rate was similar in both the groups according to Delgado ($P = 0.825$) [61] and Opelz ($P = 0.148$) [65], whereas Mehra reported lower rate in SFM compared with SG ($P = 0.04$) [64]. The incidence of severe infections was similar in both the groups [61] or significantly more frequent in SG compared with SFM ($P < 0.001$) [64]. SFM groups experienced lower level of total cholesterol ($P = 0.008$) and a trend toward lower rate of hypertension [65].

In retrospective studies, the reported survival rates were higher according to Felkel (5 years: 93% in SFM group versus 77% in SG ($P < 0.0001$) [63], whereas it was similar between the two groups as reported by Teuteberg and Delgado ($P = 0.53$, $P = 0.34$, respectively) [66,67], and it was not analyzed by Crespo Leiro [68]. Episodes of rejection at 12 and 24 months were reported to be similar in both the groups [60,65,66], lower in the SFM group ($P < 0.0001$) [63], or not analyzed [67–69], as well as the incidence of infections [60] or other complications [61,68].

Table 3. Late-withdrawal of steroid therapy in adult heart transplantation recipients.

References	Study design	Participants and intervention	Survival	Rejection	Infections and other ADRs	Authors' conclusions	Quality assessment
[60]	Retrospective	SG: 27 patients, mean age 51 years, 89% of males. SFM: 37 patients, mean age 45 years, 81% males. **Steroid withdrawal was attempted in the whole group. Analyses were then conducted "as treated"**. SG: Cyc + AZA + prednisone; SFM: as SG plus steroid withdrawal within 1 year	Not analyzed	Rejection rates similar in both the groups, with a nonsignificant lower trend in the SFM group at 12- and 24-month follow-up	Incidence of infections similar in both the groups with a trend toward lower rates among SFM patients from 6 months on (P = ns). After transplantation, there was a significant weight gain in both the groups compared with baseline, but no direct comparison between the 2 groups was performed	There is a trend toward reduction of rejection incidence after 12 months with no increase in the number of infection episodes	High quality
[61]*	Observational prospective study	SG: 21 patients, mean age 44.5 years, 86% males; SFM group: 23 patients, mean age 45.6 years, 91% males. **Analyses were probably conducted as treated. Many patients were excluded from analysis**. SG: Cyc + AZA + prednisone; SFM: as SG plus steroid withdrawal within 1 year	Not analyzed	**End point analysis was performed at 1 year post-transplantation**. Rejection rates were similar in both the groups (SG: 18% vs. SFM: 23%, P = 0.825)	Similar proportion of overweight (P = 0.384), hypertension (P = 0.490), diabetes (P = 0.187) and severe infections (P = 0.592) in SG compared with SFM	The use of corticosteroids for more than 1 year is not likely to provide clinical benefit in orthotopic heart transplantation	Medium quality
[62]	Retrospective	Fifty-six patients discharged on triple-drug immunosuppression and on whom steroid withdrawal was attempted after 6 months. 12% (5/43) of patients were steroid-free at 1 year, and this proportion grew up to 75% (28/37) at 2 years. No data on demographic characteristics were shown. All patients: Cyc + AZA or MMF + Prednisone and steroid withdrawal attempted at 6 months	Analyses were conducted on the whole sample. 1-, 2-, 3-, 4-, and 5-year survival rates were 98%, 93%, 93%, 88% (one moment missing, not clear which)	On the whole sample, freedom from a first rejection episode was 71% at 1 month, 61% at 6 months, 61% at 12 months, 59% at 24 months, and 53% at 36 months	On the whole sample, freedom from infection was 85%, 79%, 77% 72% and 67% at 1, 6, 24 and 36 months, respectively	Despite the small number of patients in the series, the rate of infection, rejection, and transplant vasculopathy seemed not to be increased using a protocol that stressed steroid withdrawal	High quality

Table 3. continued

References	Study design	Participants and intervention	Survival	Rejection	Infections and other ADRs	Authors' conclusions	Quality assessment
[63]	Retrospective	SG: 65 patients, mean age 47 years, M:F = 48:17. SFM: 72 patients, mean age 48.4 years, M:F = 60:12. **Steroid withdrawal was attempted in the whole group**. SG: Cyc + AZA + prednisone; SFM: as SG plus steroid withdrawal within 1 year. **Analyses were conducted on patients still alive at 1 year after transplantation, and groups were defined "as treated"**	At 5 years, estimated survival was 93% in SFM group vs. 77% in SG ($P = 0.0001$). Independent predictors of better survival were being a white patient in both SMF and SG groups, while group per se had no significant impact on survival	Rejection rates were lower in SFM group (1.3 episode/pt in SFM vs. 2.3 episodes/pt in SG, $P < 0.0001$) However, no difference in severity was observed ($P = 0.158$ for year 1 and $P = 0.930$ for subsequent years)	Not analyzed	In the context of tailoring immunosuppressive treatment, the results of this study support the approach of attempting to wean steroids in white recipients of heart transplantation.	High quality
[64]	Observational prospective study	SG: 16 patients, mean age 54 years, 71% males. SFM group: 25 patients, mean age 52 years, 58% males. **Steroid withdrawal was attempted in the whole group. Analyses were then conducted "as treated"**. SG: MMF + TC+ Corticosteroids SFM: as SG plus steroid withdrawal within 1 year matched	Not analyzed	Outcomes were assessed after 1 year following steroids' discontinuation. SFM group had significantly lower rejection rates compared with SG (0.22 vs. 0.82 episodes/pt/year, $P = 0.04$)	Serious late infections were significantly more frequent in SG compared with SFM group (0.60 vs. 0 infections/pt/year, $P < 0.001$). No significant differences with respect to blood pressure, hyperglycemia, body mass index, cholesterol and LDL levels were observed between the two groups, but almost all patients were also receiving statins	Unlike metabolic benefits of steroid withdrawal with Cyc, heart transplant recipients treated with TC and MMF demonstrated no incremental metabolic benefits, but instead experienced benefits of decreased serious late infections	High quality

Table 3. continued

References	Study design	Participants and intervention	Survival	Rejection	Infections and other ADRs	Authors' conclusions	Quality assessment
[65]	Observational prospective study with retrospective controls	SG: 1260 patients retrospectively reviewed, mean age 48.8 years, 82.7% males. SFM: 420 patients followed prospectively, mean age 48 years, 82.9% males. Most patients (>90%) received Cyc-based immunosuppression. Steroid withdrawal was attempted in the SFM group at 6 months after transplantation. No further details are provided	Seven-year survival rates were significantly higher in SFM group (76% in SFM vs. 66.9% in SG, $P = 0.0008$)	The rate of patients requiring treatment for rejection at 5 years was similar in the two groups (35% in SFM vs. 30.6% in SG, $P = 0.148$)	SFM group experienced lower high cholesterol cases (total cholesterol >300 mg/dL: 5.3% in SFM vs. 8.4 in SG, $P = 0.007$) and a trend toward lower high pressure cases (SBP >150 mmHg: 22.1% in SFM vs. 25.9 in SG, $P = 0.063$). No significant differences were found regarding any other secondary end point (hypertension treatment rates, osteonecrosis, osteoporosis, cataracts)	Good long-term outcomes and no worsening of allograft function after steroid withdrawal in low-risk cardiac transplant recipients on Cyc-based immunosuppression	Medium quality
[66]	Retrospective	SG: 82 patients transplanted between 1999 and 2001, mean age 51 years, 78% males. SFM: 83 patients transplanted between 2002 and 2004, mean age 53 years, 66% males. **Comparison of two different therapeutic approaches instituted at the hospital in different times (SG: 1999–2001, SFM: 2002–2004)**. SG: Cyc or TAC + MMF or AZA + Prednisone. SFM: as SG plus steroid withdrawal starting at 1 year	No difference in estimated survival rates between the two groups ($P = 0.53$)	No statistically significant differences in the rates of significant rejections at 1 year (40% in SG vs. 49% in SFM, $P = 0.24$) nor at 2 years (7.4% in SG vs. 9.2% in SFM, $P = 0.70$)	Data on lipids and HgA1c not comparable between the two groups because of different dyslipidemia treatment regimen or not routine testing of HgA1c until 2001	With an aggressive steroid-weaning strategy, it seems to be possible to have almost all patients steroid-free by 1 year post-transplant	High quality
[67]	Retrospective	Comparison of 4 groups of patients >50 years, 82% males, **as treated**. SG: continuation of steroids for 5 years after HT (A: CS <5 mg/d, B: CS>5 mg/d); SFM: steroid discontinuation after at least 1 years (C: with subsequent CS reintroduction, D: complete steroid withdrawal)	No differences in the estimated survival rates between the four groups ($P = 0.34$)	Not analyzed	Not described	Late steroid withdrawal was not associated with an increased mortality. Patients from whom CSs are withdrawn must be monitored to detect the need for reintroduction	Medium quality

Table 3. continued

References	Study design	Participants and intervention	Survival	Rejection	Infections and other ADRs	Authors' conclusions	Quality assessment
[68]	Retrospective	Comparison of 3 groups of patients >50 years, 82% males, **as treated**. SGs: continuation of steroids for 5 years after HT (A: CS <5 mg/d, B: CS>5 mg/d); SFM: steroid discontinuation after at least 1 year	Not analyzed	Not described	The incidence of hypertension increased with the increasing CS dosage. No difference were observed regarding incidence of diabetes and of bone fractures	Maintaining steroid therapy beyond the first year significantly increased their risk of becoming hypertensive over the following 2 years. Any effect on diabetes or liability to bone fracture must in general show a slower evolution; therefore, conclusions cannot be drawn	Medium quality
[69]	One-arm prospective trial	One arm: 40 patients, 82.5% males, mean age 56.5, 13 ± 3 years after HT. Steroid withdrawal and Cyc reduction attempted in the whole group with the introduction of MMF	Not analyzed. One patient died of miocardial infarction	Suspected rejections occurred in 8% of patients (one case for noncompliance)	Significant improvement of most cardiovascular risk factors, of blood pressure and of renal function. Quality of life decreased rapidly after steroid withdrawal. Dropouts occurred for 42% of patients. Of these, 36% were attributable to steroid withdrawal syndrome	Better focusing on patients under CS for no longer than 2 years. In these patients, the cardiovascular risk will probably improve without the side effect of CS-withdrawal syndrome	6/10

AZA, azathioprine; Cyc, cyclosporine; CSs, corticosteroids; MMF, mycophenolate mofetil; OKT3, muromonab-CD3; SFM, steroid-free maintenance group; SG, steroid group; TC, tacrolimus; TMG, thymoglobulin.

*Delgado *et al.* report *P*-values not adequate to the frequencies indicated. Here are reported re-computed *P*-values from the chi-squares proposed in the original paper.

Table 4. Pediatric experiences on different steroid regimens in young heart transplantation recipients.

References	Study design and steroid regimen	Participants and Intervention	Survival	Rejection	Infections and other ADRs	Authors' conclusions	Quality assessment
[70]	Observational prospective study Late withdrawal	21 pediatric patients surviving 6 months after transplantation, mostly <6 months old (only 3 patients >1 year old), M:F = 14:7 All patients: Cyc + AZA + prednisone without any induction therapy plus steroid withdrawal starting at 6 months after transplantation	Only one patient in the entire group suddenly died, 18 months after transplantation	Four patients (24%) experienced treatment for rejection; among these, one experienced complicated rejection with congestive heart failure. One other patient experienced mild rejection without requiring any treatment	In total, 17 (81%) patients were successfully steroid-free at the end of the study period. Only one case of coronary arteriopathy was observed	Steroid withdrawal is feasible in most, but not all, infant or young children heart transplant recipients initially treated with triple-drug immunosuppression	High quality
[26]	Retrospective Steroid-free	30 patients, 20 (66.7%) males, mean age 9, all <18 years. Intra-and perioperative deaths were excluded. All patients: Cyc + AZA	Intra-and perioperative mortality was 14%. Long-term overall survival was 80%, 76% and 76% at 1, 5, and 10 years, respectively, with a median follow-up time of 52 months (range 3 to 132)	Rejection rate was 1.2 episode/patient	Frequency of major infections was 0.2 episode/patient. There were 3 (10%) cases of lymphoproliferative disease, 1 (3%) primitive brain tumor, 3 (10%) systemic arterial hypertension cases. No cases of diabetes, of hepatic or renal failure, of coronary disease were found	Data lend further evidence in support of steroid-free immunosuppression in the pediatric group	Medium quality
[71]	Retrospective Early withdrawal	77 patients, age < 16 years, median age at transplant 3.9 years (0.1–15.6). Median time to death or follow-up 4.5 years. All patients: Cyc + AZA + prednisone with induction therapy (ATG and methylprednisolone) plus steroid withdrawal starting at 6 weeks after transplantation	Estimated survival was 88%, 85%, and 70% at 1, 5, and 10 years	Overall rejection rate was 0.17 episodes/patient or 0.03 episodes/patient/year	Three children (4.2%) experienced coronary disease, and 2 of these died. Four children (5.6%) developed lymphoma, all EBV-related. Two of these died. Four children (5.6%) experienced severe renal failure. All the others experienced mild to moderate renal impairment. There was a nonquantified tendency toward pneumococcal infections with ear and respiratory infections. Five children (6.5%) failed to gain weight, but 4 of them well recovered after food supplements	Treatment regimen has resulted in very good rejection-free survival	High quality

Table 4. continued

References	Study design and steroid regimen	Participants and Intervention	Survival	Rejection	Infections and other ADRs	Authors' conclusions	Quality assessment
[72]	Retrospective Steroid-free	55 patients, median age 7.1 years (2 weeks to 22 years), 27 males (40.9%). All patients: TMG+TC+MMF	Post-transplant survival in the whole group was 91% at 6 months and 88% at both 12 and 24 months	Steroid-free immunosuppression was achieved in 40 (72.7%) patients. Rejection episodes occurred in 8 patients. Freedom from first rejection was 92% at 6 months, 87% at 1 year, 81% at 2 years. Freedom from first cellular rejection was 97% at 6 months, 95% at 1 year, 95% at 2 years	Eleven (20%) patients experienced CMV infection (10 from donor), in 8 (14.5%) EBV viremia was found. One developed diabetes mellitus and one glucose intolerance. Antihypertensive treatment was continued beyond 3 months post-transplant in 31 (56.4%) of patients and beyond 1 year in 17 (30.9%) patients	Low incidence of rejection during the first year after transplant was found. A minority of patients were initiated on maintenance steroids	High quality

AZA, azathioprine; Cyc, cyclosporine; MMF, mycophenolate mofetil; TC, tacrolimus; TMG, thymoglobulin.

Summarizing the authors' conclusions, the use of CSs for more than 1 year after transplantation seems unlikely to provide clinical benefit [61]; moreover, in SFM group, good long-term outcomes and no worsening of allograft function were observed [65], with a trend toward reduction in rejection incidence, number of infection episodes [60], and hypertension rate [68].

Pediatric experiences

There are four studies on pediatric experiences, one prospective [70] and three retrospectives [26,71,72] (Table 4). Three studies were classified as high quality [70–72], and only one was of medium quality [26]. Two retrospective publications on *steroid-free* protocols come to similar conclusions [26,72]. Livi *et al.* [26] reported their experience on 30 pediatric HTx patients receiving CsA/AZA alone, observing 1-, 5-, and 10-year overall patient survival at 80%, 76%, and 76%, respectively, a rejection rate of 1.2 episodes per patient, and an infection frequency of 0.2 episodes per patient. Singh *et al.* [72] reported the outcome of 55 HTx pediatric recipients with a post-transplant survival of 91% at 6 months and 88% at 12 and 24 months, whereas freedom from first rejection was still over 80% at 2 years.

Two publications reported early and late *steroid withdrawal*. Canter *et al.* [70] prospectively evaluated the feasibility of steroids withdrawing at 6 to 12 months after HTx in 21 pediatric patients. Four of 21 patients (24%) had rejection after steroid withdrawal, and survival rate was 88% at 6 months. Similar results were obtained in a retrospective study by Leonard *et al.* [71] who reported in 77 HTx pediatric patients a survival of 88, 85, and 70% at 1, 5, and 10years, respectively, with an overall rejection rate of 0.03 episodes/patient/year. The author concluded that this regimen presented a very good rejection-free survival.

In conclusion, experience in pediatric HTx has been shown in many centers to have excellent outcomes by *complete steroid avoidance*. Thus today, the "one size fits all" approach to immunosuppressive therapy in pediatric patients is an obsolete concept, and the ultimate target should be to tailor immunosuppression for any single case [73].

Limitations

Despite the application of the Cochrane and GRACE criteria, the real quality of studies was sometimes difficult to evaluate. Most studies were retrospectives, and their design or analysis seems to be not always appropriate to evaluate outcomes, and moreover, those have been conducted "as treated" demonstrating only the feasibility and the efficacy of the new therapy. This means that in most cases, where SG was compared with SF/SFM groups, the SFG/SFM was

defined as group of patients in whom steroid avoidance or withdrawal was finally achieved. Also, multivariable modeling was applied only in few studies and so probably a immunologically privileged group in which steroids could be effectively withdrawn was compared to the rest of the study group.

Conclusions

Many of the cited studies showing good results of steroid weaning were those where steroid withdrawal was attempted in all patients, and then, 30–50% of weaned patients were compared with the patient cohort in which weaning was not successful. The conclusion coming from different studies that steroid weaning could be advantageous is a leap of faith as usually two different patient populations were compared. For example, the Yamani study [56] included only patients that were thought to be immunologically at low risk (PRA < 10%, virtual and actual cross-match negative).

In addition to all the studies reported in this review, other trials, not focusing specifically on steroids, provide important information about efficacy of steroid withdrawal. For instance, in the TICTAC study where steroids were discontinued after 8 weeks in all patients (150 patients), the long-term outcome was excellent [74].

In recent guidelines reported by the International Society of Heart and Lung Transplantation (ISHLT) [75], CS avoidance, early CS weaning, or very low-dose maintenance CS therapy are all acceptable therapeutic approaches with level of evidence B. In the present review, the studies analyzed came overall to similar conclusions in terms of benefits and adverse consequences of both CS-*free* and CS-*withdrawal* protocols after HTx: 1) good mid- and long-term graft/patient survival; 2) higher incidence of acute rejection in CS-*free* approach; 3) a variable incidence of infection episodes; 4) lower serum cholesterol levels; 5) possibly lower hypertension rate; 6) amelioration of weight control; and 7) slightly lower risk of diabetes and bone loss. Accordingly, CS-*free* therapy should be advisable and sometimes mandatory in pediatric age, in cases of active infection, IDDM, familial metabolic disorders/obesity, severe osteoporosis, and in elderly patients. In all HTx patients, CS *withdrawal* seems to be *feasible* (any age, sex, and race; at present, a success rate of 50–80%) and *safe* (does not increase rejection-related mortality and has no adverse impact on survival) and maybe more practicable when combined with the new drugs. Defining what is better, whether *early* or *late* withdrawal, does not seem currently possible because the number of published trials is still limited. Anyhow, *early steroid withdrawal* should be used in recipients with a lower propensity to rejection, also in the long term.

The very critical aspect is that many of the cited studies were reporting a successful attempt of steroid withdrawal in more than 50% of patients treated and those compared with patients in which steroids weaning was not successfully achieved. This incorrect methodology can favor erroneous interpretation of the results, as the feasibility and efficacy of steroids avoidance or withdrawal reflect probably an immune-privileged subset of patients.

In conclusion, a prospective randomized trial should be carried out to verify whether CS *withdrawal* or CS-*free* maintenance improve long-term outcome following HTx and impact significantly on quality of life by reducing complications and immunosuppression side effects.

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