Successful steroid withdrawal in lung transplant recipients: result of a pilot study

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Summary

Objective: Corticosteroids play a key role in immunosuppression after transplantation. However, because chronic steroid treatment may cause significant morbidity and mortality, steroid-free immunosuppression remains a desirable goal. To the best of our knowledge, there are no reports on successful steroid withdrawal (SW) in lung transplant recipients.

Methods: The study group included 35 patients who underwent heart-lung, double-lung or single-lung transplantation. Criteria for initiation of SW were stable pulmonary function tests and absence of clinical or bronchoscopic evidence of acute or chronic rejection in the last 6 months. Pulmonary function, blood pressure and metabolic parameters were compared between the patients who underwent SW and those who did not.

Results: Eight patients (23\%) underwent SW. Median follow-up was 19 months (range 11–23 months). Compared to the non-withdrawal group, the withdrawal group was older (60±6 vs. 52±13 years, \( P = 0.01 \), \( r = 0.49 \)), had higher rates of emphysema (88\% vs. 18\%, \( P = 0.01 \)) and use of a cyclosporine-based regimen (62\% vs. 26\%, \( P = 0.0001 \)), and had longer time from transplantation to the withdrawal attempt (70±13 vs. 29±26 months, \( P = 0.0002 \)). The SW group showed no adverse effects in graft function and no deterioration on pulmonary function tests. SW had a beneficial metabolic effect, with a decrease in mean cholesterol level from 229±45 to 194±25 mg/dl (\( P = 0.02 \)) and no significant change in weight, systolic blood pressure or glucose level. In the non-withdrawal group, mean cholesterol levels increased from 175±34 to 209±57 mg/dl (\( P = 0.0005 \)), weight increased from 72±15 to 80±14 kg (\( P = 0.0001 \)), and systolic blood pressure increased from 125±15 to 139±16 mmHg (\( P = 0.001 \)); glucose levels did not change. There was a

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**KEYWORDS**
Steroid withdrawal; Transplantation; Pulmonary function

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**Abbreviations:** SW=Steroid withdrawal; FEV\textsubscript{1}=forced expiratory volume in 1 s; FEF\textsubscript{25–75}=forced expiratory flow at 25–75%; PFT=pulmonary function test

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significant correlation between total cholesterol level and weight in both groups ($P = 0.0006, r = -0.56$ and $P = 0.01, r = -0.46$, respectively).

**Conclusions:** Late SW is safe in stable patients after lung transplantation. There was no evidence of rejection or a deterioration in pulmonary function. Lipid profile improvement and blood pressure stabilization accompanied the termination of steroid therapy.

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**Introduction**

Corticosteroids have been available for more than 50 years and have played a key role in the evolution of successful organ transplantation. Most transplant physicians and surgeons agree, however, that side effects associated with these agents are responsible for a large number of long-term complications, including increased susceptibility to infections, dermatological problems, behavioral changes, cataracts and skeletal effects such as osteopenia and osteoporosis, aseptic necrosis and impaired growth.\(^1\)\(^-\)\(^6\) Moreover, steroid therapy may increase the risk of cardiovascular disease, an important cause of post-transplant morbidity and mortality.\(^7\)

The introduction of cyclosporine and tacrolimus (FK 506) has improved the results of transplantation and has allowed a reduction in the dosage of corticosteroids for maintenance therapy.\(^5\)\(^,\)\(^9\) Nevertheless, patients still develop steroid-related side effects, mainly diabetes, hypertension, hyperlipidemia and obesity.\(^10\) Steroid-induced diabetes has been associated with an increased incidence of infections and a decrease in patient and graft survival.\(^6\)\(^,\)\(^11\) Thus, the institution of a steroid-free immunosuppressive regimen is highly desirable. The benefits of eliminating steroids, however, must be weighed against the risk of promoting acute or chronic allograft rejection.\(^12\)\(^,\)\(^13\)

In the last few years, several attempts to withdraw steroids in transplant recipients of solid organs have been made.\(^14\)\(^-\)\(^22\) These reports found late withdrawal to be usually safe in the renal, liver, heart and pancreatic transplantation.\(^20\)\(^-\)\(^22\) To the best of our knowledge, there are no reports on steroid withdrawal SW following lung transplantation. We present our experience with SW in selected stable lung transplant recipients and compare the metabolic and pulmonary effects with patients in whom steroids were not withdrawn.

**Statistical analysis**

Continuous variables are shown as means± standard deviations. Paired t-test was used to analyze statistically significant differences in mean continuous parameters before and after steroid withdrawal, and chi-square test in Fisher’s exact test was used to analyze statistically significant relationships between categorical variables. A $P$ value less than or equal to 0.05 was considered statistically significant.

**Results**

**Baseline characteristics**

Baseline characteristics of the SW and non-steroid-withdrawal (NSW) groups are shown in Table 1. SW
was completed successfully in eight patients (23%) and not done in 27. The NSW group included 22 males (81%); mean age was 52 ± 13 years compared to 60 ± 7 years in the SW group ($P = 0.01$, $r = 0.49$). Tacrolimus-based immunosuppression was administered to 20 patients (74%) in the NSW group and three (38%) in the SW group ($P = 0.001$, $r = 0.51$). In the NSW group, 20 patients (74%) underwent transplantation for pulmonary fibrosis, five for emphysema, one for primary pulmonary hypertension and one for cystic fibrosis. In the SW group, only one patient had fibrosis, six had emphysema and one had α-1-antitrypsin ($P = 0.01$). Mean time (± so) from transplantation to the SW attempt was 29 ± 26 months in the NSW group and 70 ± 13 months in the SW group ($P = 0.002$, $r = 0.60$). Reasons for nonperformance of SW were unstable PFT’s in 21 patients and bronchiolitis obliterans with poor lung function in six patients.

**Pulmonary function (Table 2)**

There was no change in either FEV$_1$ or FEF 25–75% after SW. The mean FEV$_1$ measured 67 ± 21% before withdrawal and 67 ± 17% after ($P = 0.50$); corresponding values for FEF 25–75% were 48 ± 36% and 55 ± 35% ($P = 0.13$). Pulmonary function in the NSW group included FEV$_1$: 62 ± 21% before follow-up and 54 ± 18% after; FEF 25–75%: 52 ± 31% before and 41 ± 29% after ($P = NS$).

**Metabolic effects and systolic blood pressure**

Lipid profile (cholesterol), mean weight, systolic blood pressure and glucose levels in the two groups are shown in Table 2. None of the patients in either group started treatment with statin. A significant improvement in lipid profile was noted after steroid
withdrawal, with cholesterol levels dropping from 229 ± 45 to 194 ± 25 mg/dl (P = 0.02). There were no statistically significant changes in the SW group in body weight (66 ± 13 vs. 65 ± 12.6 kg) or systolic blood pressure (141 ± 12 vs. 143 ± 11 mmHg). In contrast, the NSW group was characterized by a significant increase in cholesterol levels (from 175 ± 34 to 209 ± 57 mg/dl, P = 0.0005), weight (72 ± 15 to 80 ± 14 kg, P = 0.0001) and systolic blood pressure (125 ± 15 to 139 ± 16 mmHg, P = 0.001). No statistically significant changes were noted in glucose level.

Comparison of the changes between the groups (Table 2) yielded significant differences for total cholesterol and mean weight gain (P = 0.0006, r = −0.56 and P = 0.01, r = −0.46, respectively).

Discussion

Our review of the literature revealed that SW has been completed successfully in several types of organ transplantation.

Graft function

Opelz23 reported that in renal transplant recipients initially prescribed triple therapy, the 5-year graft survival rate was significantly higher in patients switched to steroid-free immunosuppression (87%) than in patients who remained on triple therapy (76%) or in patients maintained on cyclosporine and corticosteroids (79%). SW did not lead to a deterioration in graft function in most cases. Accordingly, Matl et al.14 assessed the risk of rejection in 46 stable renal transplant recipients who underwent steroid withdrawal and 42 who continued triple-drug therapy. Graft rejection occurred in three patients in each group and leukopenia in one patient in the withdrawal group. There was no significant between-group difference in creatinine level at the 1-year follow-up.

However, the risk of rejection rises significantly if SW is initiated in the early post-transplant period. Ahsan et al.,20 in a study of renal transplant recipients who underwent steroid withdrawal 3 months after surgery, found that the rate of rejection and treatment failure (death, graft loss or refractory rejection) increased from 9.8% to 30.8%. In contrast, at 1 year after transplantation, there was no difference in patient or graft survival between those who underwent SW and those who did not. Ratcliffe et al.24 noted that although there were no cases of acute rejection after SW in stable renal transplant recipients, most of the patients showed an insidious increase in creatinine levels, which may or may not have been transient.

Everson et al.16 reviewed 16 reports on a total of 749 adults after liver transplantation. They found that early SW was not associated with future rejection or adverse effects on patient and graft survival. The same results were observed when withdrawal was done 1 year after transplantation.21 Different rejection rates were reported in two studies of heart transplant recipients,17,18 although both found similar or improved survival and graft function after SW. In our study, no rejection was noted in stable lung recipients who underwent SW.

Metabolic effects

SW was associated with beneficial metabolic effects, including decreased cholesterol level, in three relevant studies.14,20,24 and with lower blood pressure in two of them20,24 (Table 3). In the study of Everson et al.,16 in liver transplant recipients, early SW (less than 3 months) was associated with a reduced rate and better control of hypertension, reduced total cholesterol levels and improved control of diabetes. Gomez et al.21 found the same trend in stable liver transplant recipients who underwent SW more than 1 year after transplantation. Olivari et al.18 assessed the impact of SW 6 months after heart transplantation. The degree of weight gain, lipid abnormalities and incidence of hypertension was not modified by tapering prednisone, whereas the incidence of cataract and compression fracture was significantly reduced.

This improvement in metabolic parameters after SW can contribute to longer patient survival. Although our study was small and uncontrolled, to the best of our knowledge, it is the first to be conducted in stable lung transplant recipients after SW. Owing to the high incidence of rejection and infections in lung transplant recipients compared to recipients of other solid organs, we applied rigid inclusion criteria. The significant difference in mean duration from transplantation to the SW attempt between the two groups (70 ± 13 vs. 29 ± 26 months, P = 0.0002) reflects the time needed for the patients to stabilize. Most of the patients who underwent SW had emphysema, whereas most of those who did not had fibrosis. Although most of the emphysematous patients in our study were older and were still being treated with a cyclosporine-based regimen, SW did not affect graft function, and FEV₁ and FEF 25–75% remained stable during follow-up. SW also led to improvement in total cholesterol levels (P = 0.02).
and stabilization of systolic blood pressure. The markedly high pre-follow-up of cholesterol in the NSW group compared with the SW group (229 vs. 175 mg/dl) may be attributed to the long-term effect of steroids in these patients. Glucose level remained stable throughout follow-up in both groups, whereas weight, systolic blood pressure and cholesterol level increased significantly ($P = 0.0001, 0.001$ and $0.0005$, respectively) in the NSW group.

It should be mentioned, however, that data from renal transplant recipients have indicated that adverse effects of SW first appear only after 5 years. $^{23}$

We conclude that late withdrawal of steroids after lung transplantation is safe in stable patients. No increase in the number of rejections and no deterioration in pulmonary function was noted. There was a clear trend toward a reduction in cholesterol levels after 19 months. A longer-term randomized controlled study is needed to confirm our results. Further improvement is expected on longer follow-up in glucose metabolism and weight control and in other parameters such as bone density.

References