Lung Transplantation in Patients with Cystic Fibrosis: The Israeli Experience

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Key words: cystic fibrosis, lung transplantation, pulmonary outcome

Abstract

Background: Lung transplantation is a well-established therapeutic option for end-stage lung disease in cystic fibrosis. Although it confers a clear survival advantage, outcome differs among centers according to local experience, patient selection, transplantation procedure, and postoperative care.

Objectives: To evaluate the national Israeli experience with lung transplantation in patients with CF.

Methods: We reviewed the medical charts of all CF patients who underwent lung transplantation between January 1996 and June 2005 at the two Israeli centers that perform this procedure.

Results: Eighteen transplantations were performed in 17 patients. Mean patient age at transplantation was 25.3 ± 9.1 years, and mean duration of follow-up in survivors (n=14) was 37.2 months (range 1–113 months). The actuarial survival rate was 88% at 1 year and 74% at 5 years. Pulmonary function, expressed as percent of predicted normal forced expiratory volume in 1 sec, improved from 22.4 ± 8.1% to 76 ± 16.8% at one year after transplantation. Bronchiolitis obliterans syndrome was diagnosed in 5 patients (29%), of whom 2 died and 2 are currently candidates for retransplantation. Median time to onset of BOS was 34.2 months (range 17–64 months).

Conclusion: In Israel, the early and intermediate-term results of lung transplantation for cystic fibrosis are encouraging. BOS remains a major complication that threatens long-term outcome.

IMAJ 2006;8:396–399

Lung disease associated with cystic fibrosis causes major morbidity, and it is the most common cause of death in CF patients [1]. Advances in its treatment have delayed the progression of the disease, but not arrested it. At present, lung transplantation is the only available treatment for end-stage respiratory insufficiency. According to the International Society for Heart and Lung Transplantation, CF is the single most common indication for bilateral lung transplantation, with a reported actuarial survival rate of 78.6% at 1 year and 52.9% at 5 years [2]. Although studies have shown that lung transplantation in patients with CF confers a clear survival advantage [3], outcome differs among centers according to local experience, patient selection, transplantation procedure and postoperative care. Lung transplantations have been performed in Israel since 1994, but the local experience with CF patients has not yet been reported.

The aim of the present study was to evaluate the short- and intermediate-term outcome of lung transplantation in CF patients in Israel.

Patients and Methods

We reviewed the files of all patients with CF who underwent lung transplantation from January 1996 to June 2005 at the two centers that performed these procedures in Israel from 1996 to 2001 – the Rabin Medical Center since 1997 and the Sheba Medical Center.

Recipient selection

As a rule, recipients were selected according to the international guidelines of the American Thoracic Society [4]. Colonization with multiresistant organisms or non-tuberculous mycobacteria was not considered a contraindication for transplantation. B*urkholderia cepacia* was not isolated in any of our patients.

Surgical details

Bilateral single lung transplantation was performed through a clamshell incision with a double-lumen endotracheal tube. One lung was extracted and implanted while the patient's contralateral lung was ventilated. The transplantation of the contralateral lung was done with support of the newly transplanted lung unless cardiopulmonary bypass was required to maintain adequate oxygenation and cardiac stability. If there was considerable size discrepancy between the transplanted lung and pleural cavity, volume reduction was performed *in situ* with mechanical staplers.

Infection prophylaxis

Post-transplantation prophylactic treatment at the Rabin Medical Center included broad-spectrum antibiotics (piperacillin-tazobactam and vancomycin) for 5 days. Thereafter, treatment was based

* Deceased

This paper is dedicated to the memory of Dr. Nira Reichart who devoted her life to pulmonary medicine.

CF = cystic fibrosis
BOS = bronchiolitis obliterans syndrome

on the results of the donor and recipient bacterial cultures. Cytomegalovirus prophylaxis consisted of intravenous ganciclovir for 7 days, followed by oral valganciclovir for 6 months in CMV-positive donors or recipients. Fungal prophylaxis with itraconazole was administered for the same period. Additional preventive treatments included sulfamethoxazole-trimethoprim and inhaled coliracin. Preoperative prophylactic antrostomy or drainage of the sinus cavities was not routinely performed in our patients.

Immunosuppression

The immunosuppression regimen until 1998 was based on corticosteroids, cyclosporine and azathioprine. After 1998, corticosteroids, mycophenolate mofetil and tacrolimus were introduced. Patients under the old protocol were switched to the new regimen. Intravenous methylprednisolone 0.5 g was given before reperfusion of the allograft, then 0.5 mg/kg/day for 7 days, followed by oral prednisone with slow tapering to 0.1 mg/kg/day. Mycophenolate mofetil was started orally (1.5 g twice daily) prior to transplantation. Tacrolimus was given orally and blood levels were closely monitored; targeted trough levels were 10–15 mg/ml.

Follow-up

Routine flexible bronchoscopy was performed according to a pre-established schedule (3 days, 1 week, and 1 month) to assess anastomotic patency and to obtain transbronchial biopsy specimens. Additional biopsy studies and bronchoalveolar lavage were performed whenever clinically indicated.

Episodes of acute pulmonary rejection were treated with methylprednisolone 10 mg/kg/day for 3 days followed by tapered prednisone.

Statistical analysis

Continuous variables are expressed as mean ± SD or as median and range. For statistical comparisons of categorical variables, we used chi-square analysis or Fisher's exact test. Survival was analyzed by the Kaplan-Meier method.

Results

During the study period, 18 lung transplantations were performed in 17 patients (8 males) with CF: 10 at Rabin Medical Center and 8 at Sheba Medical Center. These included 14 bilateral sequential transplantations, 2 heart-lung transplantations, and 2 single lung transplantations (one patient who had a previous pneumonectomy and one for retransplantation). Cardiopulmonary bypass was used in 6 of the 18 transplantations (2 heart-lung, 2 single lung and 2 double lung). The mean patient age at transplantation was 25.3 ± 9.1 years (range 12.2–42), and the median time on the waiting list for patients treated at Rabin Medical Center was 18.8 months (range 3–56 months). Mean time to discharge from hospital was 21.2 ± 10 days.

The demographic and clinical characteristics of the patients in the pre-transplantation period are presented in Table 1.

CMV = cytomegalovirus

Table 1. Demographic and clinical characteristics of transplanted patients

Males/females	8/9
Age at transplantation (mean ± SD)	25.3 ± 9.1 yrs
Oxygen dependence	15/17 (88%)
BiPAP	6/17 (35%)
Gastrostomy	6/17 (35%)
Pancreatic insufficiency	14/17 (82%)
CFRD	11/17 (65%)
Body mass index (mean ± SD)	18.3 ± 2.3 kg/cm^2
FEV_1 (mean ± SD) (% predicted)	22.4 ± 8.1
Oxygen saturation (mean ± SD)	85.4% ± 6.9
PCO_2 (mean ± SD)	65.2 ± 21.4 mmHg

Values are n (%) unless otherwise indicated.
BiPAP = biphasic positive airway pressure, CFRD = cystic fibrosis-related diabetes, PCO_2 = partial carbon dioxide pressure.

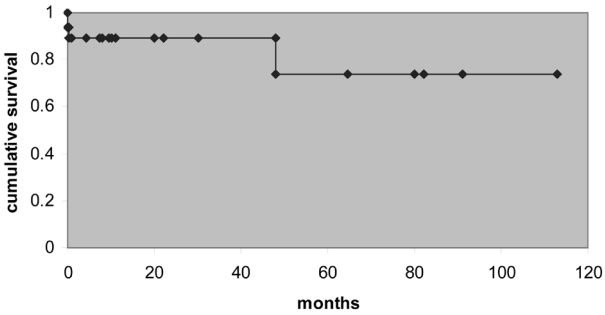

Figure 1. Actuarial survival (Kaplan-Meier) of CF patients after lung transplantation

Additional specific conditions included previous pneumonectomy followed by bronchocutaneous fistula, recurrent massive hemoptysis with several embolizations, and tracheostomy.

Survival

Actuarial survival (Kaplan-Meier) was 88% at 1 and 3 years, and 74% at 5 years [Figure 1]. The mean follow-up time was 37.2 months (median 20, range 1–113 months). The perioperative mortality rate (< 30 days) was 11.1%: 2 patients died of acute graft failure at 3 and 6 days after surgery. Another patient died 4 years after surgery from bronchiolitis obliterans syndrome.

Pulmonary function

Pulmonary function, expressed as percent predicted of normal forced expiratory volume in 1 sec, improved from 22.4 ± 8.1% preoperatively to 74.2 ± 20.6% after 6 months, 76 ± 16.9% after 1 year, and 71 ± 24.3% after 2 years [Figure 2].

Bronchial stenosis

Three patients presented with five bronchial stenoses. The granulation tissue was eliminated by laser in three cases, and two were treated by endobronchial stent insertion [Figure 3].

Infection

Eighty-eight percent of the patients displayed signs of lower respiratory tract infection, at a rate of 2.6 episodes per patient. A single bacterial pathogen was identified in 14 events (38%) (*Pseudomonas aeruginosa* 64%, methicillin-resistant *Staphylococcus aureus* 7%, and other gram-negative bacilli 29%); in the others, multi-organism infection (due to aspiration) or clinical pneumonia was diagnosed. In five events, Aspergillus infection was detected by bronchoalveolar lavage. Three cases of cytomegalovirus pneumonitis (diagnosed by transbronchial biopsy or positive blood antigen) were treated with intravenous ganciclovir.

Infections at sites other than the respiratory tract included Aspergillus endophthalmitis (treated with voriconazole for 6 months), cutaneous *Mycobacterium abscessus* (treated with multiple drugs over a long term), reactivation of hepatitis B virus, and Candida endocarditis (which required vegetation resection).

Acute rejection

There were 11 episodes of acute rejection in 6 patients. Most were observed in the first postoperative year. In 80% of affected patients, the first episode occurred within the first 6 months of transplantation. All episodes were managed with methylprednisolone 10 mg/kg/day for 3 days followed by tapered prednisone.

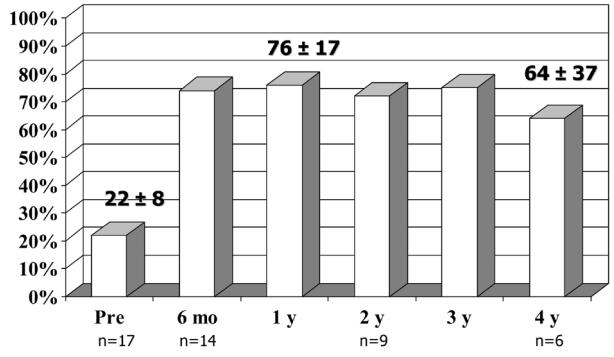

Figure 2. Mean FEV_1 before and after lung transplantation

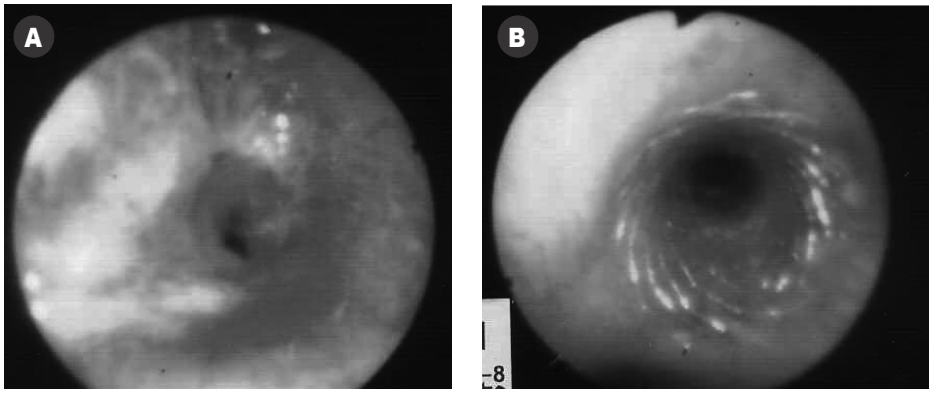

Figure 3. Stenotic anastomosis **[A]** before and **[B]** after endobronchial stent insertion.

Bronchiolitis obliterans syndrome

BOS, defined as irreversible loss of FEV_1 to ≤ 80% of the postoperative baseline, was observed in five patients. The median time of onset was 34.2 months (range 17–64 months). Two patients died: one 6 days after retransplantation and one 1 year after BOS onset. Two additional patients are currently candidates for retransplantation.

Distal intestinal obstruction syndrome

Six of the 17 patients experienced at least one episode of distal intestinal obstruction syndrome, 4 of them within the first month after transplantation, 1 with a previous history of meconium ileus. Three patients recovered after treatment with fluoroscopic gastrografin (one of them while on mechanical ventilation). In one patient, the obstruction was opened by colonoscopic lavage with gastrografin, and another required laparotomy, bowel resection, and ileostomy that was closed after 15 months. In 2003, we started prophylactic treatment with polyethylene glycol immediately after transplantation, and no DIOS has occurred since.

Other complications

Other complications included convulsions (two patients), sinus infection treated by functional endoscopic sinus surgery (three patients), gastroparesis, recurrent aspiration pneumonia treated by fundoplication and pyloroplasty, and pulmonary artery stenosis treated by extracorporeal membrane oxygenation for 3 days and re-operation.

Discussion

In this national study, we present the early and intermediate outcome of lung transplantation for patients with cystic fibrosis in Israel. The 1 and 5 year survival rates (88% and 74%, respectively) and the clear improvement in pulmonary function tests (increase in FEV_1 from 22.4% to 76% at 1 year postoperatively) clearly justify the referral of patients with end-stage CF lung disease to lung transplantation. Our data confirm the benefits of transplantation in patients with CF reported in previous studies [5-10].

The actuarial survival curve in the present study is in line with other reports from even larger established centers. The ISHLT statistics showed 1 and 5 year survival rates of 78.6% and 52.9%, respectively [2], and in Toronto, the 5 year survival for patients negative for *Burkholderia cepacia* was 76% [8].

The findings on pulmonary function tests following bilateral lung transplant are encouraging as well. Similar to previous reports, $\%FEV_1$ in

FEV_1 = forced expiratory volume in 1 sec
DIOS = distal intestinal obstruction syndrome
ISHLT = International Society for Heart and Lung Transplantation

the present series increased to a plateau within 6 months after transplantation. Our results for pulmonary function are lower than those reported by others [6,7], but they still represent a great improvement compared to baseline (pre-transplantation).

DIOS is a known complication in patients with CF. A serious course of DIOS occurred in two of our patients. One of them required repeated surgery and ileostomy. Prompted by a previous report [11], we instituted prophylactic treatment with polyethylene glycol, which seems to be protective. In patients with DIOS in whom preventive steps are useless, a high index of suspicion and early intervention are imperative for a good outcome.

Even in our relatively "young" program, BOS was a threat to long-term morbidity. The incidence of BOS is expected to rise with the increase in follow-up time. A better understanding of the pathophysiology of this condition, in association with new therapeutic trials like those recently published [12-15], are needed to improve long-term outcome.

The first lung transplantation in a patient with CF was performed in Israel in 1994. Unfortunately, the patient died 6 weeks later from disseminated aspergillosis [16]. There has been only a slight increase with time in the number of procedures performed, mainly because of a scarcity of donors. There is currently an 18 month waiting time between listing and receipt of a lung transplant. Nevertheless, we expect donor supply to improve with the introduction of a massive campaign promoting organ donation and the establishment of in-hospital transplant coordinator teams.

The main limitations of our study were the small number of patients and the short follow-up period. However, our promising short and intermediate-term outcomes in terms of survival and pulmonary function should serve as an incentive for small transplantation programs worldwide to improve the survival and quality of life of CF patients with progressive irreversible lung disease.

Conclusions

Lung transplantation for CF patients is a viable therapeutic option in Israel. The satisfactory short and intermediate-term outcomes indicate that we are well beyond the learning curve. We hope to overcome the long waiting time for organ receipt by increasing public awareness. In the future, living-related transplantation may be considered an alternative therapeutic option in Israel as well.

Addendum: Since the submission of this manuscript, four additional CF patients were successfully transplanted; all received a double lung.

Acknowledgment. The authors thank all Cystic Fibrosis Centers in Israel for their devoted care of their patients.

References

1. Egan TM, Detterbeck FC, Mill MR, et al. Long-term results of lung transplantation for cystic fibrosis. *Eur J Cardiothorac Surg* 2002;22:602–9.
2. International Society for Heart Lung Transplantation website: http://www.ishlt.org/registries/ June 2005.
3. Aurora P, Whitehead B, Wade A, et al. Lung transplantation and life extension in children with cystic fibrosis. *Lancet* 1999;354:1591–3.
4. American Society for Transplantation Physicians, American Thoracic Society, European Respiratory Society, and International Society for Heart and Lung Transplantation. International Guidelines for the selection of lung transplant candidates. *Am J Respir Crit Care Med* 1998;158:335–9.
5. Yankaskas JR, Mallory GB Jr, Consensus Committee. Lung transplantation in cystic fibrosis. Consensus Conference Statement. *Chest* 1998;113:217–26.
6. Bech B, Pressler T, Iversen M, et al. Long-term outcome of lung transplantation for cystic fibrosis – Danish results. *Eur J Cardiothorac Surg* 2004;26:1180–6.
7. Vricella LA, Karamichalis JM, Ahmad S, Robbins RC, White RI, Reitz BA. Lung and heart-lung transplantation in patients with end-stage cystic fibrosis: The Stanford experience. *Ann Thorac Surg* 2002;74:13–18.
8. de Perrot M, Chaparro C, McRai K, et al. Twenty-year experience of lung transplantation at a single center: influence of recipient diagnosis on long-term survival. *J Thorac Cardiovasc Surg* 2004;127:1493–501.
9. Ganesh JS, Rogers CA, Bonser RS, Bannder NR; for the steering group of the UK Cardiothoracic Transplant Audit. Outcome of heart-lung and bilateral sequential lung transplantation for cystic fibrosis: a UK national study. *Eur Respir J* 2005;25:964–9.
10. Wiebe K, Wahlers TH, Harringer W, vd Hardt H, Fabel H, Haverich A. Lung transplantation for cystic fibrosis – a single center experience over 8 years. *Eur J Cardiothorac Surg* 1998;14:191–6.
11. Minkes RK, Langer JC, Skinner MA, et al. Intestinal obstruction after lung transplantation in children with cystic fibrosis. *J Pediatr Surg* 1999;34:1489–93.
12. Gerhardt SG, McDyer JF, Girgis RE, Conte JV, Yang S, Orens JB. Maintenance azithromycin therapy for bronchiolitis obliterans syndrome. *Am J Respir Crit Care Med* 2003;168:121–5.
13. Verleden GM, Dupont LJ. Azithromycin therapy for patients with bornchiolitis obilerans syndrome after lung transplantation. *Transplantation* 2004;77:1465–7.
14. Young LR, Hadjiliadis D, Davis RD, Palmer SM. Lung transplantation exacerbates gastroesophageal reflux disease. *Chest* 2003;124:1689–93.
15. Hadjiliadis D, Duane Davis R, Steele MP, et al. Gastroesophageal reflux disease in lung transplant recipients. *Clin Transplant* 2003;17:363–8.
16. Anteby I, Kramer M, Rahav G, Benezra D. Necrotizing choroiditis-retinitis as presenting symptom of disseminated aspergillosis after lung transplantation. *Eur J Ophthalmol* 1997;7:294–6.

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