Effect of Liver Transplant on Pulmonary Functions in Adult Patients with Alpha 1 Antitrypsin Deficiency: 7 Cases

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Abstract

Objectives: **Alpha 1 antitrypsin (A1A) is a 52 kD glycoprotein that is mainly synthesized in the liver. As a major protease inhibitor, it binds to and neutralizes neutrophil elastase, thereby limiting the damage to the normal tissues after an inflammatory response.**

A deficiency in A1A leads to end-stage liver disease, both in children and in adults. In addition, the deficiency also has a detrimental effect in the lungs of the adult population. Alpha 1 antitrypsin deficiency is corrected with hepatic replacement; however, the changes in pulmonary functions have not been studied before and after liver transplant.

The purpose of this study was to observe the changes in the pulmonary functions of patients who underwent liver transplant for the treatment of A1A deficiency.

Materials and Methods: **Nine patients underwent liver transplant for A1A deficiency. Seven patients (5 men, 2 women; mean age, 49.95 ± 7.09 years) had their pulmonary function tests available before the liver transplant (mean, 5.6 ± 3.4; range, 0.9-10.1 months) and after the liver transplant (mean, 30.3 ± 18.4, range 7.8-48.1 months) for analysis.**

Results: **The mean, preliver, transplant, FEV1 was 2.69 ± 0.9 L, which was nearly unchanged after the liver transplant to a mean of 2.7 ± 1.2 L. During the mean total interval of nearly 3 years, an estimated decline of 250 mL in FEV1 was expected.**

Conclusions: **It appears from the results of our study that liver transplant probably prevented the progression of pulmonary disease in A1A-deficient patients. Further study and close, postliver, transplant follow-up is warranted to support our initial findings.**

Key words: *A1A, Liver transplantation, Pulmonary functions*

Alpha 1 antitrypsin (A1A) is a 52 kD glycoprotein that is mainly synthesized in the liver. Being a major protease inhibitor, it promotes the degradation of serine proteases, mainly neutrophil elastase, thereby limiting the damage to the normal tissues after an inflammatory response. Different alleles have been identified on chromosome 14 on which the gene for A1A is located (1-3). A deficiency in A1A affects 2 vital organs, the liver and the lungs, by distinctly different mechanisms (2, 4). Liver disease transpires by the deposition of globules in the hepatocytes, thereby inducing cirrhosis in early childhood or later, in the fourth or the fifth decade of life (1-3, 5-9). Destruction of alveoli within the lungs results in obstructive airway disease, with emphysematous changes manifesting in the fifth or the sixth decade of life (1, 2, 10).

While the use of human A1A infusion has some benefit in treating the pulmonary component (3, 10-17) that arises from A1A deficiency, such benefit has not been demonstrated in the hepatic component of the disease. In addition, there are several reports of successful liver transplant for the treatment of A1A deficiency (9, 18, 19). After liver transplant, A1A serum levels are restored to normal values (9, 20). However, the effects of this normalization on pulmonary functions after the liver transplant have

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not been studied. In this report, we examine the changes in pulmonary functions in patients who underwent successful liver transplant for the treatment of A1A deficiency.

Patients and Methods

Between May 1999 and June 2003, 9 patients (7 men, 2 women) with known A1A deficiency underwent a liver transplant at our institution. One patient (case No. 1) received a live-donor liver transplant, while the remaining 8 patients received a deceased-donor liver transplant. Pulmonary function tests were conducted preoperatively for all 9 patients. All values are presented as the mean ± standard deviation (Table 1).

For patient and graft survival analysis, Kaplan Meier estimates were done using SPSS software for Windows (Statistical Product and Service Solutions, version 16.0, SSPS Inc, Chicago, IL, USA).

Results

All patients in the study were followed until September 2008. Seven patients (5 men, 2 women; mean age, 49.95 ± 7.09 years), were available for evaluation; 2 patients were lost to follow-up. Mean follow-up was 72.3. ± 22.7 months.

Patient survival

All 7 patients, whose follow-up was available, were alive at the time of their last follow-up, yielding a 100% survival rate from 43.3 to 111.6 months (Figure 1).

Graft survival

One patient (case No. 2) underwent 2 retransplants, 5 months and 12 months after the initial liver transplant, owing to delayed, hepatic artery thrombosis on both occasions. He is alive 6 years after the second retransplant with an overall graft survival of 85.3% at 9 years (Figure 1).

Pulmonary function tests

Pulmonary function tests were performed at a mean time of 5.6 ± 3.4 months (median, 5.5; range, 0.9-10.1 months) before the liver transplant. They were repeated at 30.3 ± 18 months (median, 41.6 months; range, 7.8-48.1 months) after the liver transplant. Mean FEV1 before the liver transplant was 2.6 ± 0.9 L (median, 2.67 L; range, 1.7-3.9 L) with 7 ± 1.2 L (median, 2.7 L; range, 0.94-3.84 L) after the liver transplant. Case No. 4 had a 43.8% improvement in FEV1 at 45.5 months after the liver transplant, and case No. 5 had a 44.7% deterioration at 41.6 months after the liver transplant. Incidentally, case No. 4 was the youngest (age, 36.1 years), and case No. 5 was the oldest (age, 58.8 years) in the series. The remaining 5 patients (case Nos. 1, 2, 3, 6, and 7) experienced very little change after the liver transplant as compared to before the liver transplant. Overall, the mean percentage change in the after-liver transplant period was -0.8% ± 25.8%.

Details of pulmonary function tests with various parameters for individual patients before the liver transplant and after the liver transplant are given in (Table 1). Pulmonary function tests were performed 4

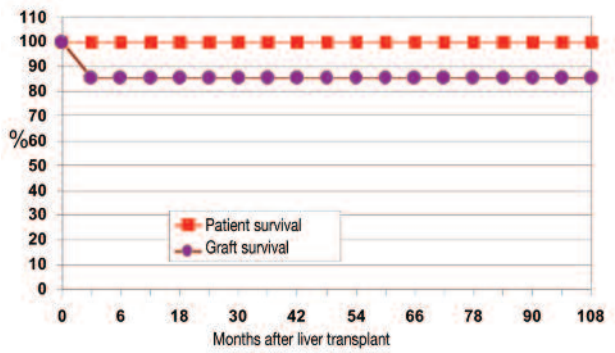

Figure 1. Patient and graft survival, in months, after the liver transplant.

Table 1. Pretransplant and posttransplant pulmonary function test

Case No.	Age (years)	A1A levels mg/dL	PFT months pre LTx	PreTx FVC liters	PreTx FVC %	PreTx FEV1 liters	PreTx FEV1 %	Pre Tx FEV1/FVC	PFT months post LTx	PostTx FVC liters	PostTx FVC %	PostTx FEV1 liters	PostTx FEV1 %	PostTx FEV1/FVC	PostTx % change in FEV1
1	55.3	86	3.6	2.21	71	1.71	73	77	48.1	na	na	1.58	63	na	-7.6
2	51.0	34	3.1	5.43	111	3.9	108	72	44.5	5.37	116	3.86	103	72	-1.0
3	49.5	22	5.5	3.9	74	2.14	51	55	12.4	3.09	59	2.23	54	72.2	4.2
4	36.1	66	9.2	3.77	78	2.67	70	71	45.5	5.6	115	3.84	99	69	43.8
5	58.8	70	7.2	2.15	72	1.7	74	79	41.6	1.23	51	0.94	51	76	-44.7
6	49.8	19	10.1	3.96	73	2.73	63	69	7.8	4.37	82	2.7	62	62	-1.1
7	49.1	52	0.9	5.11	88	3.54	85	69	12.0	5.39	93	3.57	86	66	0.8
Mean	49.9	49.9	5.6	3.8	81.0	2.6	74.9	70.3	30.3	4.2	86.0	2.7	74.0	69.5	-0.8
SD	7.1	25.7	3.4	1.3	14.4	0.9	18.0	7.8	18.4	1.7	27.4	1.2	21.6	5.0	25.8

Abbreviations: PFT, pulmonary function test; Tx, transplant; FVC, forced vital capacity; FEV1, forced expiratory volume in first second.

times in case No. 3 after the liver transplant at various time intervals ranging from 12 to 59 months after the liver transplant. There was very little change in any parameter after the liver transplant compared to before the liver transplant (Table 2).

Table 2. Serial PFTs case No. 3.

Months preTx	PreTx FVC liters	PreTx FVC %	PreTx FEV1 liters	PreTx FEV1 %	PreTx FEV1/FVC
5.20	3.9	74	2.14	51	55
Months postTx	**PostTx FVC liters**	**PostTx FVC %**	**PostTx FEV1 liters**	**PostTx FEV1 %**	**PostTx FEV1/FVC**
12.4	3.09	59	2.23	54	72.2
53.1	3.68	69	2.04	50	55
56.3	3.42	65	1.8	44	53
59.3	3.33	63	1.82	45	55

Abbreviations: FEV, forced expiratory volume; FVC, forced vital capacity; PFT, pulmonary function tests.

We then compared the impact of ascites, pleural effusion, and smoking with changes in pulmonary function tests (Table 4).

Effect of ascites/pleural effusion

Ascites was found in 4 out of 7 patients, roughly 57% (cases Nos. 3, 4, 5, and 6) of the before-liver transplant, whereas 1 patient (case No. 6) was found to have both ascites and pleural effusion after the liver transplant (Table 4). Of these 4 patients, half (case Nos. 3 and 4) demonstrated improvement, while the remaining 2 patients (case Nos. 5 and 6) experienced deterioration in FEV1.

Effect of smoking

Four out of 7 patients, roughly 57% (case Nos. 1, 4, 6, and 7) had a positive smoking history before having the liver transplant, whereas 43% (case Nos. 2, 3, and 5) reported that they had never smoked. Case No. 1 discontinued smoking completely after the liver transplant, and case Nos. 4 and 6 reduced the smoking considerably. Case No. 7 continued to smoke after the liver transplant period (Table 4).

Deterioration in FEV1 was seen in case No. 1, who discontinued smoking after the liver transplant. Out of the 2 patients who reportedly reduced smoking after the liver transplant, case No. 4, demonstrated an improvement in FEV1, whereas case No. 6 showed a deterioration. A mild improvement in FEV1 was seen 12 months after the liver transplant in case No. 7—the patient who smoked after the liver transplant. The remaining 3 patients did not smoke before or after the liver transplant. Of these patients, 1 patient (case No. 3) showed improvement in FEV1. Conversely, deterioration was seen in the remaining 2 patients (case Nos. 2 and 5) at 44 and 41 months after the liver transplant.

During the last follow-up, liver function, renal function, and immunosuppression tests were conducted, the results of which are shown in Table 3. Stable liver and satisfactory renal functions were seen in the majority of all the patients. All patients in this series are undergoing monotherapy with calcineurine

Table 3. Biochemistry and medications at last follow-up.

Case No.	Date	Total bilirubin μmol/L	AST U/L	ALT U/L	ALK PO4 U/L	GGTP U/L	BUN μmol/L	Creatinine μmol/L	Tacro dose mg/day	Tacro level ng/mL	Csa dose mg/day	Csa level ng/mL	Prednisolone mg/day
1	12/26/2008	20.5	39	37	100	152	7.8	68.6	6	6.5			0
2	1/21/2009	27.4	41	73	416	463	13.2	137.3			250	164	0
3	2/12/2009	20.5	27	34	115	120	8.9	83.9	2	5.5			0
4	9/25/2008	12	98	114	434	3705	6.1	83.9	6	7.5			0
5	2/14/2009	25.6	43	49	871	499	12.5	144.9			175	104	0
6	1/23/2009	13.7	21	20	111	104	19.3	213.5			150	100	5
7	2/2/2009	3.4	19	37	134	167	7.8	83.9	2	5.3			0
Mean		17.59	41	52	312	744	11	116.57	4.00	6.20	191.7	123	0.71
SD		8.42	27	32	287	1316	5	51.85	2.31	1.01	52.0	36	1.89

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; Alk PO4, alkaline phosphatase; GGTP, gamma gluatamyl transpeptidase; Csa, cyclosporine; Tacro, tacrolimus.

Table 4. Comparison of change of FEV1 in preLTx and postLTx and factors influencing it.

	PreLTx				PostLTx		
No.	Age (y)	Smoker	Ascites	Pleural effusion	△ FEV1	Smoking	Comments
1	62	yes	no	no	▼130 mL	no	No improvement in FEV1 despite the absence of pleural effusion, ascites and smoking cessation.
2	58	no	no	no	▼40 mL	no	No improvement in FEV1
3	55	no	yes	no	▲90 mL	no	Improvement in FEV1
4	42	yes	yes	no	▲1210 mL	reduced	Deterioration in FEV1
5	63	no	yes	no	▼760 mL	no	Deterioration in FEV1
6	54	yes	yes	yes	▼40 mL	reduced	Deterioration in FEV1
7	59	yes	no	no	▲30 mL	yes	Improvement in FEV1

Abbreviations: FEV, forced expiratory volume.

inhibitor, with the exception of case No. 6, who is on 5 mg daily prednisolone.

Discussion

Alpha 1 antitrypsin deficiency leading to end-stage liver disease both in children and in adults is well-described in the literature; currently, liver transplant remains the only option for the failing liver in this subset of patients (9, 18, 19, 21-23). However, while successful liver transplant restores the A1A serum levels, the genetic defect continues (1, 9).

Liver disease due to A1A deficiency can affect in early childhood and the middle-aged population, while lung involvement appears to occur solely among middle-aged individuals. The pulmonary component of this condition is unknown or is not reported in the childhood population (10). Several reports exist on postliver transplant survival outcomes of patients with A1A deficiency. Kemmer and associates (19) described 567 cases from the UNOS database who received liver transplants in response to A1A deficiency, while Vennarecci (9) reported 35 cases (13 children, 22 adults). Albeit in these publications, no attempts were made to study the pulmonary functions in the postliver transplant period.

In our extensive literature search, we could not find any such study that documented changes in pulmonary function tests after correction of A1A serum levels after liver transplant. This report is the first to address pulmonary function test results in the after-liver transplant period in the adult population. In patients who underwent liver transplant for A1A deficiency, we were surprised to have 100% survival in up to 9 years of postoperative follow-up. From our observation, it appears that the restoration of A1A levels after the liver transplant aids in the stabilization of pulmonary disease but does not cause any improvement in pulmonary function tests.

The registry of the patients with severe deficiency of A1A, an NHLB1-sponsored multicenter study of over 1129 patients, found an annual FEV1 decline of 54 mL/year based on high-quality, sequential, pulmonary function measurements (24). The rate of decline among the participants who were not receiving augmentation therapy was higher (84 mL/year) with FEV1 between 50% and 79% of the predicted value. Seven patients we described are in the latter group. For these 7 patients, the time interval between before liver and after liver transplant spirometry averaged 35.9 months, or almost 3 years. One would expect these untreated patients to have a reduction of FEV1 by 84 mL/year, which would represent a loss of 251.3 mL over this time. The fact that these 7 patients had no further deterioration of FEV1, as determined by pulmonary function tests over a period of 3 years, is quite remarkable. When we examined the factors that could potentially affect the pulmonary function tests in our population, in terms of presence of ascites and/or pleural effusion, there was no clear relation in the study population. However, one would imagine that with the improvement in ascites and/or pleural effusion after the liver transplant, there would be some improvement in overall pulmonary function tests. In addition, when we compared these 2 patients who had discontinued smoking after the liver transplant with the other 2 patients who reduced the amount of smoking, we noted mixed results, which were similar to those patients who never smoked.

On the individual basis, 1 patient (case No. 4; age, 36 years) who was the youngest in the series, had 43.8% improvement in FEV1 at 45.5 months after the liver transplant, whereas the oldest patient in the series (case No. 5; age, 58.8 years), who was a nonsmoker, had the largest deterioration in FEV1 at 41.6 months after the liver transplant. This is most likely a coincidental observation, but it makes one think whether the patient's age could be a factor in improvement. If liver transplant is performed early, the damage to the lung may be reversible when compared with when it is performed at a later stage in life, when the damage has established permanency. Such dramatic changes may be mechanical in nature (ie, related to ascites or other factors); however, this did not have any expected improvement.

In case No. 3 (age, 49.5 years), sequential pulmonary function tests at 4 time points after the liver transplant showed a stable FEV1 from 12 to 59 months after the liver transplant period. Although only abnormal Protease inhibitor alleles ZZ is associated with the disease, it is well-known that there are several different alleles that are responsible for A1A production (1-3). The possibility exists that there may be genetic differences between those with predominant lung disease and others with predominant liver disease.

Alpha 1 antitrypsin-deficient individuals who escape severe liver disease in childhood, generally are

free of clinical liver disease until later in life. From age 20-40, the incidence of liver disease in the A1A-deficient population is 2%. Between 41-50 years of age, the incidence increases to approximately 5%, which increases further to 15% in the age group 51 to 60 years (2). A1A augmentation therapy slows the annual decline in FEV1 in patients with severe hereditary A1A deficiency (3, 11-17, 25), whereas no such benefits of A1A infusion on the liver component are presently known (1-3). It may be possible that the effectiveness of restoring A1A ± serum concentration by liver transplant may not be as significant in improving lung disease compared with liver disease due to differences in genetic composition. The literature comparing the pulmonary functions of patients with A1A deficiency before and after liver transplant has yet to be reported. Although the number of patients is smaller in the present study, these findings suggest that augmentation of A1A levels, via a liver transplant, stabilizes lung function, as was observed in the patients documented in the A1A infusion registry (14).

Certainly, further longitudinal studies with frequent monitoring of pulmonary function tests after the liver transplant may provide us with a more concise picture.

Conclusions

Liver transplant remains the only option for liver failure in patients with A1A deficiency by providing substantial, long-term survival. Most importantly, this modality can only be expected to arrest the pulmonary deterioration resulting from A1A deficiency without reversing the damage to the lungs already caused by the disease.

References

1. Anthony S. Fauci DLK, Dan L. Longo, et al. Harrison Priciples of Internal Medicine. 17th ed. New York: McGraw-Hill Companies, Inc.; 2008.
2. RNM MacSween, BC Portmann, KG Ishak, PJ Scheuer, PP Anthony. Pathology of the Liver. 4th ed. London: Churchill Livingstone; 2002.
3. Stoller JK, Aboussouan LS. Alpha1-antitrypsin deficiency. Lancet. 2005;365(9478):2225-2236.
4. van Steenbergen W. Alpha 1-antitrypsin deficiency: an overview. Acta Clin Belg. 1993;48(3):171-189.
5. Lomas DA, Evans DL, Finch JT, Carrell RW. The mechanism of Z alpha 1-antitrypsin accumulation in the liver. Nature. 1992;357(6379):605-607.
6. Perlmutter DH. The cellular basis for liver injury in alpha 1-antitrypsin deficiency. Hepatology. 1991;13(1):172-185.
7. Perlmutter DH. Clinical manifestations of alpha 1-antitrypsin deficiency. Gastroenterol Clin North Am. 1995;24(1):27-43.
8. Sveger T. The natural history of liver disease in alpha 1-antitrypsin deficient children. Acta Paediatr Scand. 1988;77(6):847-851.
9. Vennarecci G, Gunson BK, Ismail T, et al. Transplantation for end stage liver disease related to alpha 1 antitrypsin. Transplantation. 1996;61(10):1488-1495.
10. Piitulainen E, Sveger T. Respiratory symptoms and lung function in young adults with severe alpha(1)-antitrypsin deficiency (PiZZ). Thorax. 2002;57(8):705-708.
11. Abboud RT, Ford GT, Chapman KR. Alpha1-antitrypsin deficiency: a position statement of the Canadian Thoracic Society. Can Respir J. 2001;8(2):81-88.
12. Abboud RT, Ford GT, Chapman KR. Emphysema in alpha1-antitrypsin deficiency: does replacement therapy affect outcome? Treat Respir Med. 2005;4(1):1-8.
13. Pierce JA. Alpha1-antitrypsin augmentation therapy. Chest. 1997;112(4):872-874.
14. Stockley RA, Bayley DL, Unsal I, Dowson LJ. The effect of augmentation therapy on bronchial inflammation in alpha1-antitrypsin deficiency. Am J Respir Crit Care Med. 2002;165(11):1494-1498.
15. Stoller JK, Fallat R, Schluchter MD, et al. Augmentation therapy with alpha1-antitrypsin: patterns of use and adverse events. Chest. 2003;123(5):1425-1434.
16. Vidal Pla R, Padulles Zamora N, Sala Pinol F, Jardi Margaleff R, Rodriguez Frias F, Montoro Ronsano JB. Pharmacokinetics of alpha1-antitrypsin replacement therapy in severe congenital emphysema. Arch Bronconeumol. 2006;42(10):553-556.
17. Ward AC, Keogh BA. Intravenous alpha-1-antitrypsin replacement therapy: case report after one year of treatment. Ir J Med Sci. 1997;166(1):7-9.
18. Esquivel CO, Vicente E, Van Thiel D, et al. Orthotopic liver transplantation for alpha-1-antitrypsin deficiency: an experience in 29 children and ten adults. Transplant Proc. 1987;19(5):3798-3802.
19. Kemmer N, Kaiser T, Zacharias V, Neff GW. Alpha-1-antitrypsin deficiency: outcomes after liver transplantation. Transplant Proc. 2008;40(5):1492-1494.
20. Putnam CW, Porter KA, Peters RL, Ashcavai M, Redeker AG, Starzl TE. Liver replacement for alpha1-antitrypsin deficiency. Surgery. 1977;81(3):258-261.
21. De Roover A, Detry O, Honore P, et al. Alpha-1-antitrypsin deficiency. An indication for pediatric liver transplantation (French). Rev Med Liege. 2001;56(11):753-758.
22. Filipponi F, Soubrane O, Labrousse F, et al. Liver transplantation for end-stage liver disease associated with alpha-1-antitrypsin deficiency in children: pretransplant natural history, timing and results of transplantation. J Hepatol. 1994;20(1):72-78.
23. Prachalias AA, Kalife M, Francavilla R, et al. Liver transplantation for alpha-1-antitrypsin deficiency in children. Transpl Int. 2000;13(3):207-210.
24. The Alpha-1-Antitrypsin Deficiency Registry Study Group. Survival and FEV1 decline in individuals with severe deficiency of alpha1-antitrypsin. Am J Respir Crit Care Med. 1998;158(1):49-59.
25. Seersholm N, Wencker M, Banik N, et al. Does alpha1-antitrypsin augmentation therapy slow the annual decline in FEV1 in patients with severe hereditary alpha1-antitrypsin deficiency? Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL) alpha1-AT study group. Eur Respir J. 1997;10(10):2260-2263.