Interactive CardioVascular and Thoracic Surgery 34 (2022) 250–254
doi:10.1093/icvts/ivab237 Advance Access publication 28 August 2021

BEST EVIDENCE TOPIC

Cite this article as: Zhu MZL, Huang JY, Liu DH, Snell GI. Does continuation of antifibrotics before lung transplantation influence post-transplant outcomes in patients with idiopathicpulmonary fibrosis? Interact CardioVasc Thorac Surg 2022;34:250–4.

Does continuation of antifibrotics before lung transplantation influence post-transplant outcomes in patients with idiopathic pulmonary fibrosis?

Michael Z.L. Zhu [†], Joanna Yilin Huang[†], David Hongwei Liu and Gregory I. Snell*

Lung Transplant Service, The Alfred Hospital, Melbourne, VIC, Australia

* Corresponding author. Lung Transplant Service, The Alfred Hospital, 55 Commercial Road, Melbourne, VIC 3004, Australia. Tel: +61-3-90762867; fax: +61-3-90763601; e-mail: g.snell@alfred.org.au (G.I. Snell).

Received 8 April 2021; received in revised form 26 July 2021; accepted 2 August 2021

Abstract

A best evidence topic was written according to a structured protocol. The question addressed was: 'Does continuation of antifibrotics before lung transplantation (LTx) influence post-transplant outcomes in patients with idiopathic pulmonary fibrosis (IPF) with regard to mortality, bronchial anastomotic dehiscence, reoperation for bleeding and wound complications, primary graft dysfunction or longer-term survival and allograft rejection?' A total of 261 articles were found using the reported search strategy, of which 7 represented the best evidence to answer the clinical question. Six out of 7 studies demonstrated equivalent post-transplant survival among IPF patients on antifibrotics before LTx compared with controls. Five out of 6 studies showed no increase in the risk of major bleeding, wound or bronchial anastomotic complications. One bi-institutional study found a higher incidence of early bronchial anastomotic dehiscence, but this difference was not statistically significant after longer term follow-up. In a study that only included IPF patients who underwent single LTx, a lower incidence of grade 3 primary graft dysfunction was reported in the antifibrotic group compared with controls. Overall, to date, only small ($N < 40$ in the antifibrotic group), non-risk-adjusted, retrospective observational studies have been published. Notwithstanding, the summation of available evidence suggests that, in IPF patients, continuation of antifibrotic therapy before LTx is likely safe, and the rates of perioperative bleeding, wound or bronchial anastomotic complications, as well as 30-day and 1-year survival, are similar to patients not on antifibrotics before LTx.

Keywords: Lung transplantation • Pulmonary fibrosis • Antifibrotics • Pirfenidone • Nintedanib

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the *ICVTS* [1].

THREE-PART QUESTION

In [patients with idiopathic pulmonary fibrosis (IPF)], does [continuation of antifibrotic therapy before and up to the time of lung transplantation (LTx)] influence post-transplant outcomes with regard to [mortality, bronchial anastomotic dehiscence, reoperation for bleeding and wound complications, primary graft dysfunction (PGD), or longer-term survival and allograft rejection]?

CLINICAL SCENARIO

A 60-year-old man with IPF has been wait-listed for LTx. He has been taking the antifibrotic drug pirfenidone for 12 months, but his pulmonary function continues to decline. The window of opportunity for LTx is now increasingly narrow and a compatible donor offer may present at any time. The transplant surgeon is concerned that antifibrotics may increase the risk of perioperative bleeding, wound or bronchial anastomotic complications. Antifibrotics inhibit fibroblast proliferation and may in theory impair tissue healing. The multidisciplinary transplant team is uncertain whether antifibrotics (pirfenidone and nintedanib) should be discontinued before LTx, to reduce the risk of surgical complications, or whether there is potential benefit in continuing antifibrotic therapy until transplantation. You search the literature for evidence.

SEARCH STRATEGY

Medline 1946 to 30 June 2021 using PubMed interface: [antifibrotic OR anti-fibrotic OR nintedanib OR pirfenidone] AND [idiopathic pulmonary fibrosis OR pulmonary fibrosis] AND [lung transplant OR lung transplantation]. The reference and citation lists of relevant articles were searched to identify potential articles not returned by the PubMed search.

[†]The first two authors contributed equally to this study.

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SEARCH OUTCOME

A total of 261 articles were found using the reported strategy. Conference abstracts and studies with <10 patients in the antifibrotic group were excluded. Seven articles were identified as providing the best evidence to answer the clinical question (Table 1).

RESULTS

Leuschner *et al.* [2], from the Munich LTx group, compared 30 IPF patients who were on antifibrotic therapy [(P)irfenidone $n = 23$, (N)intedanib $n = 7$] in the 4 weeks before LTx to 32 patients not on antifibrotics during this pretransplant period [(C)ontrols]. Patients in the antifibrotic groups were significantly older (P: 59, N: 61, C: 55 years mean age, $P = 0.004$). The mean lung allocation score was, however, similar (P: 52, N: 50, C: 55; $P = 0.77$). The authors reported no difference in 30-day mortality (0%, all groups), rates of grade 3 PGD [P: 8.6% (2/23), N: 0% (0/7), C: 13% (4/32); $P = 1.0$], bronchial anastomotic complications [P: 4.3% (1/23), N: 14% (1/7), C: 22% (7/32); $P = 0.20$] or reoperation for bleeding or wound complications [P: 39% (9/23), N: 43% (3/7), C: 34% (11/32); $P = 0.87$]. Rates of chronic lung allograft dysfunction [P: 30% (7/23), N: 0% (0/7), C: 13% (4/32), $P = 0.14$] and 12-month Kaplan–Meier estimated survival were also similar (P: 77%, N: 100%, C: 91%, $P = 0.29$). The authors concluded that antifibrotic therapy continued before LTx did not increase bleeding, wound-healing complications or postoperative mortality after LTx.

In a bi-institutional study from the Vienna and Hannover LTx groups, Lambers *et al.* [3] compared 36 patients who continued antifibrotics in the 4 weeks before LTx to 96 patients not on antifibrotic therapy [$N = 72$ of whom were on cortico(S)teroids and $N = 24$ were not on corticosteroids]. Single LTx recipients were excluded. The authors demonstrated no difference in rates of bronchial anastomotic complications [P: 0%, N: 0%, S: 1.4% (1/72), C: 0%; $P = 0.84$], or reoperation for wound [P: 13% (3/23), N: 0% (0/13), S: 10% (7/72), C: 8% (2/24); $P = 0.76$] or bleeding [P: 13% (3/23), N: 0% (0/13), S: 10% (7/72), C: 4% (1/24); $P = 0.60$] complications. Estimated 1-year post-transplant survival was similar (P: 96%, N: 100%, S: 90%, C: 100%; $P = 0.32$). The authors concluded that continuation of antifibrotics before LTx did not increase the risk of bleeding and wound complications or impair post-LTx survival. Noticeably, the study included all patients with interstitial lung disease. In the antifibrotic groups, 92% (33/36) had IPF. In the non-antifibrotic comparison groups, only 47% (45/96) had IPF. This heterogeneity among comparative cohorts should be taken into account when interpreting the results of this study.

Mortensen *et al.* [4] from St Joseph's, Phoenix, evaluated 17 patients who were on pirfenidone in the 4 weeks before LTx against 13 IPF patients not on pirfenidone during this period. In the pirfenidone group, 82% (14/17) had stopped pirfenidone ≤1 day before LTx. One patient in the pirfenidone group developed postoperative wound dehiscence [P: 5.9% (1/17), C: 0% (0/13); $P = 1.0$]. No patients developed bronchial anastomotic dehiscence. Survival was 100% at 3 months mean follow-up. The authors concluded that patients who continued pirfenidone until LTx did not experience impaired wound healing.

In an Australian bi-institutional study, Mackintosh *et al.* [5] included 40 IPF patients in whom antifibrotics were continued until the day of LTx. When compared with 186 pulmonary fibrosis patients in the control group, the authors found a higher rate of early (<6 weeks) bronchial anastomotic dehiscence in the antifibrotic group [7.5% (3/40) vs 1.1% (2/186); $P = 0.01$], although the overall incidence after longer-term follow-up was not statistically different [7.5% (3/40) vs 2.2% (4/186); $P = 0.08$]. Rates of grade ≥2 PGD [30% (12/40) vs 26% (49/186); $P = 0.64$] and 30-day [100% vs 96% (179/186); $P = 0.21$] and 1-year [93% (27/29) vs 88% (147/167); $P = 0.42$] survival were similar. The comparisons were limited by the fact that patients in the antifibrotic group were significantly older (65 vs 59 years mean age, $P < 0.001$) and it was unclear what proportion of the 186 pulmonary fibrosis patients in the control group had IPF versus other types of interstitial lung disease. The authors concluded that antifibrotics can be safely continued before LTx and that the incidence of bronchial dehiscence is not significantly higher among IPF patients receiving antifibrotic therapy up to the time of LTx.

In another study from the Munich LTx group, Veit *et al.* [6] demonstrated, in a small cohort of single LTx recipients, that IPF patients on pirfenidone ($N = 17$) in the 2 weeks before LTx had similar 30-day survival [P: 6% (1/17), C: 8% (2/26); $P = 0.82$] and rates of bleeding and wound [P: 12% (2/17), C: 27% (7/26); $P = 0.23$] or bronchial anastomotic complications [P: 6% (1/17), C: 15% (4/26); $P = 0.34$] compared with IPF patients not on antifibrotics ($N = 26$). Patients in the pirfenidone group had a lower incidence of grade 3 PGD [0% vs 27% (7/26); $P = 0.019$] and postoperative mechanical ventilation time was shorter (mean: 38 vs 119 h; $P = 0.016$). The mean donor allograft ischaemic times were similar (7.4 vs 7.3 h). The authors concluded that pirfenidone was not associated with increased bleeding or wound complications in IPF patients undergoing single LTx. The authors also hypothesized that the observed reduction in rates of PGD may be due to the anti-inflammatory properties of pirfenidone, which may play a role in modulating lung allograft ischaemia–reperfusion injury.

Amor *et al.* [7] compared 14 IPF patients on antifibrotic treatment before LTx with 134 IPF patients not taking antifibrotics. At 20 months follow-up, survival in the antifibrotic group was 80% compared with 92% in the control group, $P < 0.05$. Perioperative bleeding, wound and airway complications were not reported. This study remains the only analysis to report reduced survival among IPF patients on pre-LTx antifibrotic therapy, compared with patients not on antifibrotics, although the authors did not provide an explanation for this observation. Whether antifibrotics were continued until LTx or discontinued earlier was not described. Comparison of baseline clinical characteristics between antifibrotic and non-antifibrotic groups was also lacking.

The LTx group from Melbourne [8] compared the early- and mid-term outcomes of 31 IPF patients, in whom antifibrotics were continued until the day of LTx, to 71 IPF patients not on antifibrotics before LTx. The authors reported no bronchial anastomotic complications in either group and no difference in rates of reoperation for wound or bleeding complications [antifibrotic: 13% (4/31), control: 8.4% (6/71); $P = 0.49$]. There was a trend towards fewer patients experiencing grade ≥2 PGD in the antifibrotic group [9.7% (3/31) vs 25% (18/71); $P = 0.11$]. Survival at 90 days, 1 year and 3 years was 97% at each of the 3 timepoints in the antifibrotic group and 97%, 93% and 81% in the non-antifibrotic group, $P = 0.08$. The authors commented that antifibrotic therapy continued up to the time of LTx was not associated with excess bleeding, wound or airway complications, although larger, risk-adjusted studies with longer-term follow-up are required.

Table 1: Best evidence articles

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Leuschner *et al.* (2017), J Heart Lung Transplant, Germany [2] Retrospective cohort (level III)	P: 23 (37%) N: 7 (11%) C: 32 (52%) Inclusion: antifibrotics ≤4 weeks before LTx Bilateral LTx: P: 13/23 (57%), N: 1/7 (14%), C: 20/32 (63%); *P* = 0.21	PRBC (units), mean ± SD	Intraoperative: P: 3.2 ± 5.2, N: 4.3 ± 3.7, C: 5.7 ± 8.2; *P* = 0.40 Postoperative: P: 4.2 ± 5.7, N: 7.2 ± 8.1, C: 9.3 ± 14.7; *P* = 0.54	High proportion of single LTx, especially in antifibrotic group Patients in antifibrotic group were older (P: 59, N: 61, C: 55 years; *P* = 0.004), and more had coronary artery disease (37% vs 13%; *P* = 0.029). LAS was similar (P: 52, N: 50, C: 54; *P* = 0.77) Post-LTx follow-up: P: 25.4 ± 17.8, N: 9.3 ± 5.0, C: 26.3 ± 15.0 months
		PGD (grade 3) at 72 h	P: 2/23 (8.6%), N: 0/7 (0%), C: 4/32 (12.5%); *P* = 1.0[a]	
		Bronchial anastomotic complications, total / requiring intervention	P: 1/23 (4.3%) / 0/23 (0%), N: 1/7 (14%) / 0/7 (0%), C: 7/32 (22%) / 2/32 (6.3%); *p* = 0.20[a] / *P* = 0.61[a]	
		Reoperation for bleeding or wound complication	P: 9/23 (39%), N: 3/7 (43%), C: 11/32, (34%); *P* = 0.87	
		30-Day survival	100% (all groups)	
		ACR grade ≥A1	P: 3/23 (13%), N: 1/7 (14%), C: 1/32 (3.1%); *P* = 0.28[a]	
		Chronic lung allograft dysfunction	P: 7/23 (30%), N: 0/7 (0%), C: 4/32 (13%); *P* = 0.14[a]	
		1- and 2-year Kaplan–Meier estimated survival	P: 77% / 77%, N: 100% / not available, C: 91% / 82%; *P* = 0.29 / *P* = 0.52	
Lambers *et al.* (2018), Eur Respir J, Austria/ Germany [3] Retrospective cohort, multicentre (level III)	P: 23 (17%) N: 13 (9.8%) Steroids only: 72 (55%) C (no steroids or antifibrotics): 24 (18%) Inclusion: antifibrotics ≤4 weeks before LTx Exclusion: Single LTx All ILD patients included IPF: 59% (78/132) Other ILD: 41% (54/132) Proportion of IPF patients: P: 23/23 (100%), N: 10/13 (77%), Non-antifibrotic: 45/96 (47%)	Bronchial anastomotic complications	P: 0/23 (0%), N: 0/13 (0%), Steroids: 1/72 (1.4%), C: 0/24 (0%); *P* = 0.84	Median post-LTx follow-up: 21 months (IQR: 13–29)
		PRBC (units), median (IQR)	P: 2.0 (0–5.0), N: 1.5 (0–3.0), Steroids: 2.0 (0–4.0), C: 2.0 (0–4.0); *P* = 0.83	
		Ventilation (days), median (IQR)	P: 1.0 (0.5–1.5), N: 1.0 (0.5–1.5), Steroids: 1.0 (0.5–1.5), C: 2.0 (1.5–2.5); *P* = 0.63	
		Reoperation for haemothorax	P: 3/23 (13%), N: 0/13 (0%), Steroids: 7/72 (10%), C: 1/24 (4%); *P* = 0.60	
		Wound infection requiring vacuum-assisted closure	P: 3/23 (13%), N: 0/13 (0%), Steroids: 7/72 (10%), C: 2/24 (8%); *P* = 0.76	
		1-Year Kaplan–Meier estimated survival	P: 96%, N: 100%, Steroids: 90%, C: 100%; *P* = 0.32	

Continued

Table 1: Continued

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Mortensen *et al.* (2018), Multidiscip Respir Med, USA [4] Retrospective cohort (level III)	P: 17 (57%) C: 13 (43%) Inclusion: pirfenidone ≤1 month before LTx. 14/17 (82%) stopped pirfenidone ≤1 day before LTx Bilateral LTx: P: 14/17 (82%) C: 13/13 (100%)	Wound dehiscence Bronchial anastomotic dehiscence Survival, mean follow-up: 94 days (range: 84–127)	P: 1/17 (5.9%), C: 0/13 (0%), $P = 1.0$[a] Nil 100% (both groups)	
Mackintosh *et al.* (2019), J Heart Lung Transplant, Australia [5] Retrospective cohort, multicentre (level III)	P: 29 (13%) N: 11 (4.9%) C: 186 (82%) Inclusion: antifibrotics continued until day of LTx Bilateral LTx: P/N: 34/40 (85%) C: 159/186 (86%) DCD: P/N: 8/40 (20%) C: 40/186 (22%)	Early (<6 weeks) bronchial anastomotic dehiscence Overall bronchial anastomotic dehiscence PGD (≥grade 2) at 72 h 30-Day survival 1-Year survival	P/N: 3/40 (7.5%), C: 2/186 (1.1%); $P = 0.01$ P/N: 3/40 (7.5%), C: 4/186 (2.2%); $P = 0.08$ P/N: 12/40 (30%), C: 49/186 (26%); $P = 0.64$ P/N: 40/40 (100%), C: 179/182 (96%); $P = 0.21$ P/N: 27/29 (93%), C: 147/167 (88%); $P = 0.42$	Largest study to date Control group ($n = 186$) included all ILD patients Antifibrotic group older (65 vs 59 years old, $P < 0.001$) and fewer were on long-term preoperative corticosteroids [30% (12/40) vs 53% (98/186), $P = 0.01$] compared with control group
Veit *et al.* (2019), Am J Transplant, Germany [6] Retrospective cohort (level III)	P: 17 (40%) C: 26 (60%) Inclusion: pirfenidone ≤2 weeks before LTx Exclusion: Bilateral LTx, Nintedanib	Bronchial anastomotic complication Reoperation for bleeding or wound complication PGD (grade 3) at 72 h Ventilation (h), mean ± SD ACR (grade ≥A1) at 30 days 30-Day mortality	P: 1/17 (5.9%), C: 4/26 (15%); $P = 0.34$ P: 2/17 (12%), C: 7/26 (27%); $P = 0.23$ P: 0/17 (0%), C: 7/26 (27%); $P = 0.019$ P: 37.5 ± 34.8, C: 119 ± 151; $P = 0.016$ P: 0/17 (0%), C: 5/26 (19%); $P = 0.054$ P: 1/17 (5.9%), C: 2/26 (7.7%); $P = 0.82$	Likely some overlap in the patients include in this study and Leuschner *et al.* [2]
Amor *et al.* (2020), Isr Med Assoc J, Israel [7] Retrospective cohort (level III)	P: 5 (3.4%) N: 9 (6.1%) C: 134 (91%) Unclear whether antifibrotics continued until LTx or discontinued earlier	Survival, 20 months maximum follow-up	P: 80%, C: 92%; $P = 0.01$ N: 80%, C: 92%; $P = 0.03$	Only 9.4% (14/148) in antifibrotic group No comparison of baseline characteristics between antifibrotic versus control group
Zhu *et al.* (2021), Transplantation, Australia [8] Retrospective cohort (level III)	P: 23 (22.5%) N: 8 (7.8%) C: 71 (69.6%) Antifibrotics continued until day of LTx Bilateral LTx: P/N: 22/31 (71%) C: 54/71 (76%) DCD: P/N: 4/31 (13%) C: 16/71 (23%)	Early reoperation for bleeding or wound complication Bronchial anastomotic complication PGD (grade ≥ 2) at 72 h Ventilation (h), median (IQR) 90-Day, 1-, 3- and 5-year retransplant-free survival	P/N: 4/31 (13%), C: 6/71 (8.4%), $P = 0.49$[a] Nil (both groups) P/N: 3/31 (9.7%) C: 18/71 (25%); $P = 0.11$[a] P: 39.9 (16.4–66.1) C: 29.5 (16.0–85.0); $P = 0.87$ P/N: 97%, 97%, 97%, 97%, C: 97%, 93%, 81%, 67%; $P = 0.08$	Longest follow-up published to date Median post-LTx follow-up: P/N: 1.9 (IQR: 1.3–3.0), C: 3.0 (1.8–4.4) years Antifibrotic group significantly older than control group (66 vs 61 years, $P < 0.001$)

[a]Fisher's exact test.

ACR: acute cellular rejection; C: control; DCD: donation after circulatory-determined death; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis; IQR: interquartile range; LAS: lung allocation score; LTx: lung transplantation; N: nintedanib; P: pirfenidone; PGD: primary graft dysfunction; PRBC: packed red blood cells; SD: standard deviation.

CLINICAL BOTTOM LINE

Studies that have evaluated the outcomes of LTx among IPF patients treated with antifibrotic therapy before LTx compared with on antifibrotics have so far been limited to small, non-risk-adjusted, retrospective observational studies with relatively short-term follow-up. Notwithstanding, the summation of available evidence suggests that, in patients with IPF, the continuation of antifibrotic therapy before and up to the time of LTx is unlikely to be associated with increased perioperative bleeding, postoperative surgical wound or bronchial anastomotic complications, or an increased risk of early or longer-term mortality. Whether the continuation of antifibrotic therapy prior to LTx may have beneficial effects such as reducing the incidence of primary graft dysfunction or allograft rejection also warrants further investigation.

Conflict of interest: none declared.

Reviewer information

Interactive CardioVascular and Thoracic Surgery thanks Markus Kamler and Shekar L.C. Reddy for their contribution to the peer review process of this article.

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