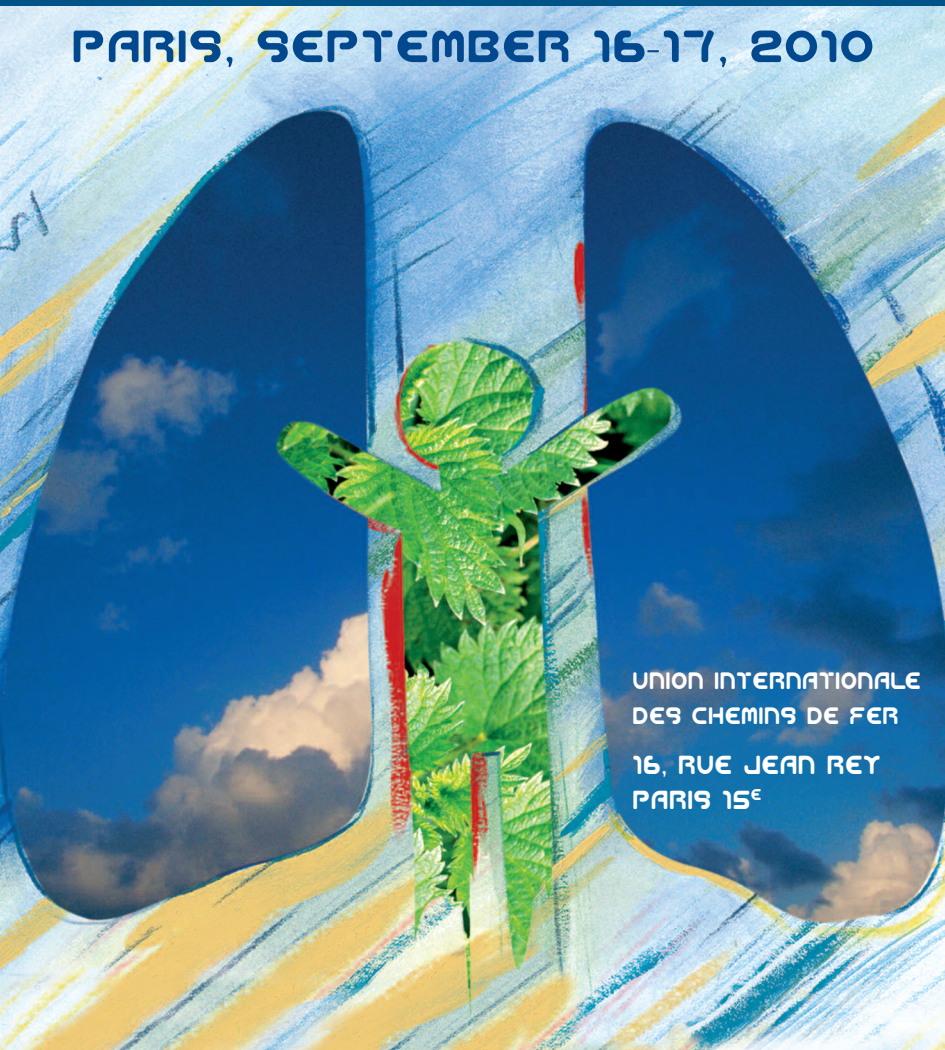
9TH INTERNATIONAL CONGRESS ON LUNG TRANSPLANTATION

PARIS, SEPTEMBER 16-17, 2010



UNION INTERNATIONALE
DES CHEMINS DE FER

16, RUE JEAN REY
PARIS 15E

9TH INTERNATIONAL CONGRESS ON LUNG TRANSPLANTATION

PARIS, SEPTEMBER 16-17, 2010

UNDER THE PATRONAGE OF

FONDATION FRANCO-AMÉRICAINE DU MARÉCHAL FOCH

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WELCOME ADDRESS

Dear Colleagues,

The 9th edition of the International Conference on Lung Transplantation will be headed by our two presidents : Dirk VAN RAEMDONCK from Leuven and Jonathan B. ORENS from Baltimore, eminent leaders of the two bestknown teams in the field of lung transplantation.

The scientific program will include new subjects in addition to classic topics.

Our hope is that the numerous lectures and debates will be fruitful and have a positive impact for the future activity of each participant.

Bien amicalement.

Docteur Alain BISSON

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✱ If you are a chairperson

You must be in your session room 10 minutes prior the beginning of the session.
Make sure that all speakers observe timing.
Participants should not speak without permission.
They should first clearly state their name, institution and country.

✱ If you are a speaker

Locate your session room in due time.
Speakers must go to the preview room and turn in their slide or computer assisted presentations that will be handed out to the session room. **Laptops will not be allowed in the meeting room**.
In the session room, strictly follow instructions from the chairperson, in particular those regarding the timing of your presentation.

✱ Administrative Secretariat

Office hours:
Thursday, September 16 7:30 a.m. - 6:30 p.m.
Friday, September 17 7:30 a.m. - 4:30 p.m.

After the Congress:

VBCE - Lung Transplantation
43, rue de l'Abbé Groult
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✱ Badges

For security and regulation reasons, all participants will be required to wear their badge at all time throughout the Congress.

✱ Certificate of attendance

A certificate of attendance for pre-registered participants is included in the documentation issued upon arrival. Participants who register on site should apply directly to the registration desk.

✱ Technical Exhibition

The technical exhibition is located close to the conference rooms. Please plan to visit the exhibits regularly, and especially during the breaks.

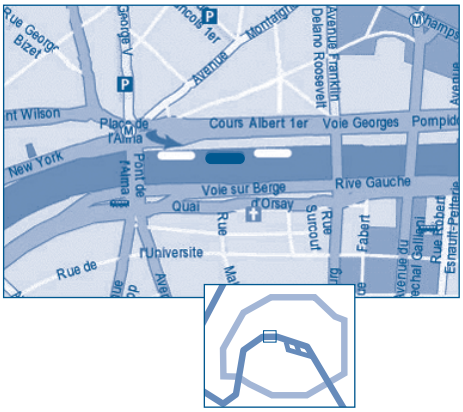
✱ Thursday, September 16

DINNER on "Les bateaux mouches"
Port de la Conférence
Pont de l'Alma
75008 Paris

8:00 p.m.

Price per person: 100 €
Reservation on site are possible upon availability.

What is more pleasant than having dinner while admiring the Eiffel Tower during a cruise on the Seine River ? The most beautiful buildings of the city will enchant you during your dinner.
You will embark for an unique journey of 2 hours in the middle of the magnificenses of Paris while savouring a refined meal.



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ACKNOWLEDGEMENTS

The Organizing Committee wishes to extend its thanks and appreciation to the following sponsors for their contribution:

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NOTES

SCIENTIFIC PROGRAM

NOTES

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10:20		Free communications p 17
12:30		
13:00	Long-term management of lung transplant patients Symposium Sponsored by Novartis p 19	
14:00	Antibody-mediated rejection p 20	
16:20		Impact of allocation practices p 22
18:00		
18:30		

FRIDAY 17

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10:00		
10:20		Immunosuppressive therapy in 2010 for lung transplantation p 26
12:30		
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8:30 → 8:45 **Room Louis Armand**

Opening

A. BISSON (France)
President of the Organizing Committee

J.B. ORENS (USA) **& D. VAN RAEMDONCK** (Belgium)
Presidents of the Congress

8:45 → 12:30 **Room Louis Armand**

Lung donors in 2010

Chairpersons: D. Van Raemdonck (Leuven, Belgium),
T. Waddell (Toronto, Canada)

Brain-dead donors

8:45 **Extended cadaveric donor criteria: impact on outcomes**
A. Fisher (Newcastle, UK)

9:05 **Optimizing donor Lung procurement**
T. Williams (Melbourne, Australia)

Non-heart-beating donors

9:25 **Controlled DCD lung donation: techniques**
J. Dark (Newcastle, UK)

9:45 **Uncontrolled DCD lung donation: techniques**
J. Moradiellos (Madrid, Spain)

10:05 Break

10:20 **How large is the DCD pool**
G. Nossent (Groningen, The Netherlands)

Ex-vivo lung reperfusion

10:40 **Lessons from a preclinical model of ex-vivo lung reperfusion**
T. Egan (Chapel Hill, USA)

11:00 **Ex-vivo lung reperfusion: will it help to improve outcome after lung transplantation?**
D. Van Raemdonck (Leuven, Belgium)

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11:20 **A porcine model of acute lung injury by gastric aspiration to study ex-vivo lung reperfusion** **01**
C.M.F. Meers, W. De Wever, E. Verbeken, S. Wauters, V. Mertens, S.I. De Vleeschauwer, R. Vos, B.M. Vanaudenaerde, G.M. Verleden, T.E. Lerut, D.E.M. Van Raemdonck (Leuven, Belgium)

11:35 **Ex-vivo lung recovery and lung repair**
T. Waddell (Toronto, Canada)

12:00 **Clinical results after ex-vivo reperfusion**
J. Moradiellos (Madrid, Spain)

10:20 → 12:30 **Room List**

Free communications

Chairpersons: C. Pison (Grenoble, France),
A. Shah (Baltimore, USA)

10:20 **Lung transplantation in developing countries** **02**
M. Awad Tag Eldin (Cairo, Egypt)

10:35 **Lung transplantation for cystic fibrosis: results from a single institution experience** **03**
G. Marulli, M. Schiavon, F. Calabrese, M. Loy, C. Breda, A. Zuin, S. Nicotra, A. Rebusso, F. Di Chiara, F. Rea (Padua, Italy)

10:50 **Clinical characteristics in patients with pulmonary fibrosis assessed for lung transplant** **04**
J. Ossés, R. Ahumada, G. Wagner, A. Bertolotti, J. Cáneva, R. Favaloro (Buenos Aires, Argentina)

11:05 **Is osteoporosis a real problem in patients referred for lung transplantation?** **05**
M. Ochman, D. Jastrzebski, S. Zeglen, J. Wojarski, D. Ziora, J. Kozielski (Zabrze, Poland)

11:20 **Unusual low incidence of acute rejection and BOS after lung transplantation: the impact of an only orally based standard immunosuppressive regimen for pre-operative introduction and maintenance therapy** **06**
M. Barten, H. Wirtz, W.F. Mohr, H.B. Bittner (Leipzig, Germany)

11:35 **A murine model of brain death: an opportunity for future mechanistic studies on treatment for donor lung injury** **07**
S. Wauters, C. Meers, E. Verbeken, G. Verleden, J. Van Loon, T. Lerut, D. Van Raemdonck (Leuven, Belgium)

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11:50 **Plasma serum level of NT-proBNP as the strong and independent predictor of death in patients with end-stage lung diseases referred for lung transplantation** **O8**
M. Ochman, J. Nowak, P. Rozentryt, B. Hudzik, J.Wojarski, S. Zeglen, L. Polonski, M. Zembala (Zabrze, Poland)

12:05 **Improvement of post operative oxygenation and clinical outcome after sequential double lung transplantation using cardiopulmonary bypass during the second lung implantation** **O9**
H. Rozé, M. Thumerel, C. Dromer, L. Barandon, V. Perrier, J. Jougon, K. Nubret, L. Labrousse, F. Gomez, J.-F. Velly , A. Ouattara, G. Janvier (Bordeaux, France)

12:20 **Secondary pulmonary hypertension in IPF lung transplant recipients: the intraoperative right ventricle function as an early predictor of primary graft dysfunction** **O10**
A. Bertolotti, C. Gomez, D. Absi, J. Ossés, J. Caneva, R. Ahumada, G. Wagner, R.R. Favaloro (Buenos Aires, Argentina)

13:00 → 14:00 **Room Louis Armand**

Long-term management of lung transplant patients

Symposium Sponsored by Novartis

Chairpersons: M. Reynaud-Gaubert (Marseille, France),
M. Stern (Suresnes, France)

Renal dysfunction in lung transplant patients: perspectives
M. Hourmant (Nantes, France)

Bronchiolitis obliterants syndrome: breakthough in physiopathology
H. Mal (Paris, France)

14:00 → 18:00 **Room Louis Armand**

Antibody-mediated rejection

Chairpersons: C. Knoop (Brussels, Belgium),
T. Williams (Melbourne, Australia)

Management of the sensitized lung transplant candidates

14:00 **HLA antibodies: detection techniques?**
C. Suberbielle-Boissel (Paris, France)

14:20 **Necessity for screening transplant-relevant HLA- and MICA-antibodies after ventricular assist device support implantation** **011**
M.J. Barten, M.T. Dieterlen, S. Klein, J. Garbade, S. Dhein, F.W. Mohr, H.B. Bittner (Leipzig, Germany)

14:35 **Pretransplant therapeutic options for sensitized candidates**
K. McCurry (Cleveland, USA)

14:55 **Selection of donor: crossmatch and virtual crossmatch**
A. Shah (Baltimore, USA)

Antibody mediated rejection

15:15 **Biology of Ab mediated rejection**
T. Williams (Melbourne, Australia)

15:35 **Histology and immunohistochemistry of Ab mediated rejection**
M. Colombat (Paris, France)

16:00 Break

16:20 **Monitoring of anti-HLA Ab after lung transplantation**
F. Parquin (Suresnes, France)

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16:40 **Therapeutic options in acute antibody mediated rejection**
C. Knoop (Brussels, Belgium)

17:00 **Humoral immunity in chronic lung rejection**
S. Palmer (Durham, USA)

17:20 **Anti-HLA class I and anti-MICA antibodies: prognostic marker for transplant vasculopathy and post-transplant CMV-infection** **012**
M.J. Barten, M.T. Dieterlen, S. Klein, K. Eberhardt, S. Dhein, F.W. Mohr, H.B. Bittner (Leipzig, Germany)

16:20 → 18:30 **Room List**

Impact of allocation practices

Chairpersons: T. Egan (Chapel Hill, USA),
A. Fisher (Newcastle, UK)

16:20 **Lung allocation and practice in Europe**
J. Smits (Eurotransplant, The Netherlands)

16:45 **Lung allocation in United States. Impact on waitlist mortality and post transplant outcomes**
C. Merlo (Baltimore, USA)

17:10 **Who is being transplanted in the US and Europe and how do they differ?**
W. KLepetko (Vienna, Austria), T. Egan (Chapel Hill, USA)

17:50 **Lung allocation score: is there an application in the French context?**
G. Thabut (Paris, France)

18:15 **Proposals and refusals by French teams in lung procurement: a new way of improvement?** **013**
F.X. Lamy, C. Cantrelle, M. Stern, N. Santelmo, R. Dorent, M. Thuong, A. Atinault, French lung transplant teams (Saint Denis, France)

8:00 → 12:30 **Room Louis Armand**

Chronic lung dysfunction

Chairpersons: J. Orens (Baltimore, USA),
G. Verleden (Leuven, Belgium)

8:00 **Different types of chronic lung dysfunction besides BOS?**
G. Verleden (Leuven, Belgium)

Gastro-esophageal reflux

8:25 **Preoperative assessment of reflux**
C. Pison (Grenoble, France)

8:50 **Does reflux lead to chronic lung allograft dysfunction?**
A. Shah (Baltimore, USA)

9:15 **Does reflux lead to airway injury?**
S. Palmer (Durham, USA)

9:40 **The impact of air pollution on bronchiolitis obliterans syndrome and mortality after lung transplantation** **O14**
B.M. Vanaudenaerde, T.S. Nawrot, R. Vos, L. Jacobs, S.E. Verleden, C. Faes, P. Hoet, D.E. Van Raemdonck, L.J. Dupont , B. Nemery, G.M. Verleden (Leuven, Belgium)

9:55 Break

10:20 **Montelukast for bronchiolitis obliterans syndrome after lung transplantation** **O15**
S.E. Verleden, R. Vos, S.I. De Vleeschauwer, L.J. Dupont, D.E. Van Raemdonck, B.M. Vanaudenaerde, G.M. Verleden (Leuven, Belgium)

10:35 **A randomized placebo-controlled trial of azithromycin to prevent bronchiolitis obliterans syndrome after lung transplantation** **O16**
R. Vos, B.M. Vanaudenaerde, A. Schoonis, D.E. Van Raemdonck, L.J. Dupont, G.M. Verleden (Leuven, Belgium)

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10:50 **Place of azithromycine in chronic lung dysfunction**
J. Orens (Baltimore, USA)

11:15 **Long-term outcome of double lung and heart-lung transplantation for pulmonary hypertension: a comparative retrospective study of 210 patients** **017**
E. Fadel, O. Mercier, S. Mussot, D. Fabre, A. Chapelier, G. Simonneau, P. Dartevelle (Le Plessis Robinson, France)

11:30 **BAL neutrophilia**
G. Verleden (Leuven, Belgium)

11:55 **Cytokines and cells in BAL. What do they mean?**
J. McDyer (Baltimore, USA)

12:20 **The COLT study: French cohort in lung transplantation** **018**
M. Pain, I. Danner-Boucher, Y. Lacoeuille, A. Magnan, K. Botturi and the COLT investigators (Nantes, France)

8:00 → 10:00 **Room List**

Living with a lung transplant

Chairpersons: F. Dobbels (Leuven, Belgium),
F. Parquin (Suresnes, France)

8:00 **Quality of life after lung transplantation**
S. Bhorade (Chicago, USA)

8:20 **Psychological modifications after lung transplantation**
R. Farcy-Pauthe, S. Odie (Suresnes, France)

8:40 **Psychological adverse effects related to mycophenolate mofetil** **O19**
A. McDermott, M. McCurry, A. Apostolou, M. Carby (Harefield, UK)

8:55 **Adherence to the treatment: a key problem for long term survival**
F. Dobbels (Leuven, Belgium)

9:15 **Sport: a step further life after transplant**
M. Brechu (Association Etoiles des Neiges, France)

9:35 **Pregnancy after lung transplantation**
C. Knoop (Brussels, Belgium)

10:20 → 12:30 **Room List**

Immunosuppressive therapy in 2010 for lung transplantation

Chairpersons: S. Bhorade (Chicago, USA),
H. Reichenspurner (Hamburg, Germany)

10:20 **Induction therapy with alemtuzumab**
K. McCurry (Cleveland, USA)

10:40 **Inhaled cyclosporine provides high lung concentrations, low systemic exposure and is well tolerated: an interim report on the CYCLIST clinical trial** **O20**
S. Bhorade, B.A. Johnson, C. Johnson, W. Verret, T. Breen, R. Niven, J. Golden (Chicago, Pittsburg, Burlingame, San Francisco, USA)

10:55 **Tacrolimus: long term results of the international trial**
H. Reichenspurner (Hamburg, Germany)

11:15 **Evaluation of calcineurin activity as a biomarker of acute and chronic rejection after lung transplantation** **O21**
S. Sanquer, C. Amrein, D. Grenet, R. Guillemain, C. Lena, A. Diouf, R. Barouki, M. Stern (Paris, France)

11:30 **Results of recent trial MMF vs rapamycin**
S. Bhorade (Chicago, USA)

11:50 **Everolimus in lung transplantation**
M. Strueber (Hannover, Germany)

12:10 **Assistance of mTOR-inhibitor dosing after transplantation by pharmacodynamic monitoring of ribosomal protein S6 phosphorylation** **O22**
M.J. Barten, S. Klein, M.T. Dieterlen, J. Garbade, M. Vollroth, S. Dhein, F.W. Mohr, H.B. Bittner (Leipzig, Germany)

14:00 → 16:00 **Room Louis Armand**

Emergency lung transplantation

Chairpersons: E. Sage (Suresnes, France),
J. Gottlieb (Hannover, Germany)

14:00 **ECMO as a bridge to lung transplantation**
W. Klepetko (Vienna, Austria)

14:20 **Lung transplantation for recipient with invasive ventilation**
J. Gottlieb (Hannover, Germany)

14:40 **ECMO, an alternative to intubation in emergency for lung transplant candidates**
M. Strueber (Hannover, Germany)

15:00 **The impact of peri-operative extracorporeal membrane oxygenation or ECMO support on long-term survival in lung transplantation surgery** **023**
H.B. Bittner, S. Lehmann, C. Binner, A. Rastan, M. Barten, F.W. Mohr (Leipzig, Germany)

Results of specific emergency lung transplantation programme

15:15 **In France. Evaluation of super emergencies in lung transplantation** **024**
F. Pessione, C. Cantrelle, R. Dorent, A. Atinault, French lung transplant teams (Saint-Denis, France)

15:30 **In Eurotransplant**
J. Smits (Eurotransplant, The Netherlands)

14:00 → 16:00 **Room List**

Current infections

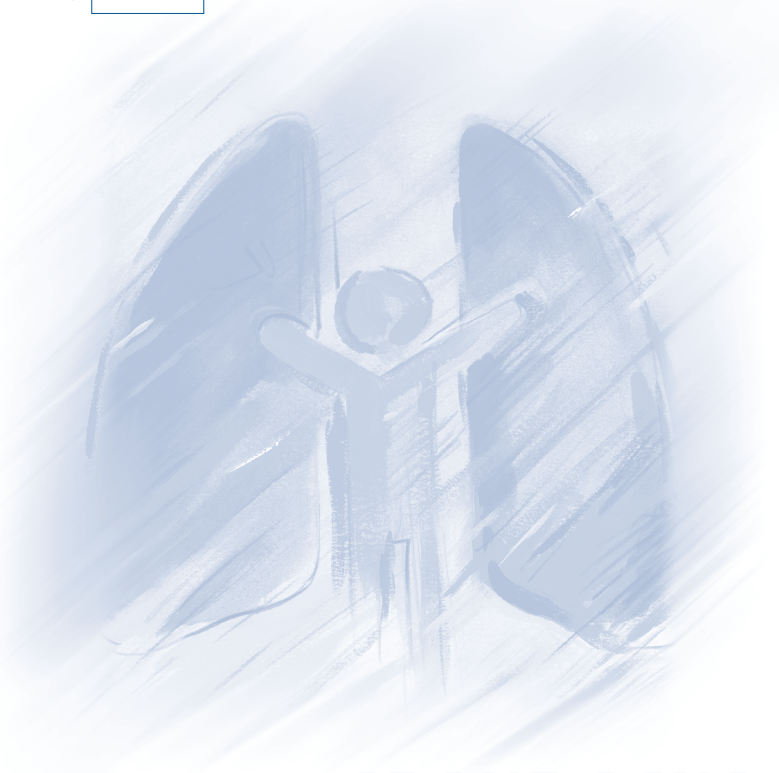
Chairpersons: J. McDyer (Baltimore, USA),
O. Lortholary (Paris, France)

14:00 **Emergent infectious agents**
O. Lortholary (Paris, France)

14:20 **CMV**
J. McDyer (Baltimore, USA)

14:40 **Pseudomonas aeruginosa: role of the inflammation**
A. Fisher (Newcastle, UK)

15:00 **Do we have to go on transplantating cystic fibrosis patients infected with Burkholderia cepacia genomovar III?** **025**
V. Boussaud, C. Amrein, R. Guillemain, F. Barthes le Pimpec, R. Souilamas, J.N. Fabiani (Paris, France)



ABSTRACTS

A PORCINE MODEL OF ACUTE LUNG INJURY BY GASTRIC ASPIRATION TO STUDY EX VIVO LUNG RESUSCITATION

Caroline MF Meers[1], Walter De Wever[2], Eric Verbeken[3], Shana Wauters[1], Veerle Mertens[4], Stéphanie I De Vleeschauwer[5], Robin Vos[5], Bart M Vanaudenaerde[5], Geert M Verleden[5], Toni E Lerut[6], Dirk EM Van Raemdonck[1,6]

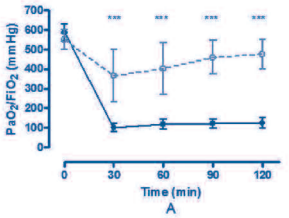
1- Laboratory of Experimental Thoracic Surgery, KU Leuven, Belgium; 2- Department of Radiology, UZ Leuven; 3- Department of Pathology, UZ Leuven; 4- Center for Gastroenterological Research, KU Leuven; 5- Laboratory of Pneumology, KU Leuven; 6- Department of Thoracic Surgery, UZ Leuven

Background. About 15% of donor lungs are declined because of evidence of aspiration contributing to current organ shortage. The aim of the study was to develop a porcine lung injury model through gastric juice (GJ) aspiration that can be used for future studies on pretransplant reconditioning through ex vivo lung perfusion.

Materials and methods. Pigs (n=6/group) were anesthetized and monitored. At T0 bronchial alveolar lavage (BAL) was performed followed by instillation of 4ml/kg GJ [GJ] or saline solution [SAL]. Before (T0) and after instillation (T30, T60, T90 and T120) hemodynamic and aerodynamic parameters and oxygenation were recorded and serum was collected. At T120 a second BAL was performed and lungs were flushed with cold Perfadex®. CT scans of explanted, inflated lungs were taken. Peripheral and central tissue samples were collected for histology. Wet/dry weight ratio was calculated. Pepsin and bile acids were measured in BAL. IL-8 was measured in serum and BAL.

Results. PO_2/FiO_2 ratio and lung compliance were significant lower (figure) and wet/dry weight ratio was significantly higher in [GJ] compared to [SAL] ($p<0.001$) at T120.
Neutrophils in BAL ($p<0.01$) and concentration of pepsin, bile acids and IL-8 ($p<0.05$) were higher in [GJ] at T120. More areas with consolidations were noticed on CT in [GJ] ($p<0.01$).
More haemorrhage, oedema and neutrophil inflammation were seen on histology in [GJ] ($p<0.01$, $p<0.001$, $p<0.001$; respectively).

Conclusion. Instillation of GJ in pig lungs caused acute lung injury with impaired oxygenation and increased inflammation in BAL, on histology and on imaging. This model can be helpful to study treatment strategies to recondition injured lungs through ex vivo perfusion prior to transplantation.



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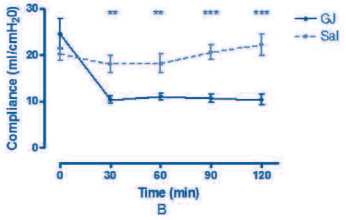

B

LUNG TRANSPLANTATION IN DEVELOPING COUNTRIES

Prof. Mohamed Awad Tag Eldin
Professor and Consultant of Thoracic Diseases, Ain Shams Faculty of Medicine, Abassia, Cairo, Egypt
Former Minister of Health and Population
Former President of Ain Shams University
President of the Egyptian Society of Chest Diseases and Tuberculosis

Lung transplantation is an accepted modality of treatment for advanced end stage lung diseases.

In the developing countries there is an increased need for lung transplantation due to the marked increase of the population numbers and age expectancy in such countries.

The increased prevalence of (COPD) as the expected prevalence of COPD is 10% of the population between the age of 40-65 years, end stage interstitial lung diseases and other congenital or acquired lung diseases in the developing countries.

Although the prevalence of *Schistosomiasis* have been markedly decreased but due to improvement in the life expectancy but we still have a high number of cases living with pulmonary and hepatic complications of *Schistosomiasis*. Increase the need for the presence of qualified centers for transplantation from living donors or calibers both for improving the life quality of patients and to decrease the mortality and morbidity of chronic pulmonary problems and also reducing the cost of long term treatment .

The progressive success in the fields of renal and liver transplantations is a good drive for implementation of lung transplantation.

Implementation of lung transplantation programs in developing countries is an essential need.

Co-operation between international organizations and eminent leaders in the field of lung transplantation and the national teams in developing countries is a vital step.

What about the future of double organ transplantation, e.g. patients with end stage liver cirrhosis complicated by end stage pulmonary disease!

LUNG TRANSPLANTATION FOR CYSTIC FIBROSIS: RESULTS FROM A SINGLE INSTITUTION EXPERIENCE

G. Marulli, M. Schiavon, F. Calabrese, M. Loy, C. Breda, A. Zuin, S. Nicotra, A. Rebusso, F. Di Chiara, F. Rea.

Department of Cardiac, Thoracic and Vascular Sciences. Thoracic Surgery Division. University of Padua, Medical School. Italy

Purpose of the study

Despite improvements in medical therapy allowed a better control of lung impairment in cystic fibrosis (CF), lung transplantation (LT) is still the most effective means of improving survival and quality of life in patients with end-stage CF. We reviewed our Institutional experience evaluating the outcome after bilateral LT.

Statement of the methods

Between 1998 and 2008, 86 patients with CF were included on waiting list (WL) for LT. 46 (53.4%) received LT, 20 (23.3%) died on WL and 20 (23.3%) are alive awaiting LT. Mean age at LT was 28.2±1.4 years and mean time on WL before LT was 10.7±1.3 months. Bacterial colonization before LT was seen in 67.4% (P. Aeruginosa 61%, S. Aureus 19.6%, B. Cepacia 4.3%). In 34.8% lungs from donor with extended criteria were used. In 9 (19.6%) patients a size reduced LT was performed.

Summary of the results

In hospital, mortality was 4.3%, postoperative overall complications were 67.4%. Mean intubation time was 5.8±2.1 days and discharge from hospital occurred after 32.9±2.4 days. Actuarial survival rates at 1, 3 and 5 years were 88%, 82% and 74% compared with 52% and 40% at 1 and 2 years for non transplanted patients (p=0.005). Nine (20.5%) patients developed BOS and 2 received a retransplantation.

Statement of the conclusion

LT for CF can be accomplished with a low mortality and acceptable morbidity rates. The significant survival benefit in this young and severely ill patients justifies their prioritization among patients awaiting LT.

CLINICAL CHARACTERISTICS IN PATIENTS WITH PULMONARY FIBROSIS ASSESSED FOR LUNG TRANSPLANT

Ossés J, Ahumada R, Wagner G, Bertolotti A, Cáneva J, Favaloro R
Intrathoracic Transplant Department, Favaloro Foundation, University Hospital. Buenos Aires. Argentina.

Objectives

To evaluate the characteristics of patients with pulmonary fibrosis (PF) assessed for lung transplant.

Materials and methods

Patients with a diagnosis of PF referred to our center for lung transplant were retrospectively assessed. Parameters of pulmonary function, gas exchange, co-morbidities and outcome were studied.

Results

118 patients studied between January 2000 and March 2008 were included : 67 males (57%), mean age 49 yrs., age range 10-69 yrs. Mean forced vital capacity at the time of assessment was 42% of the normal value, and diffusion lung carbon monoxide (DLCO) was 29%. Mean PCO_2 was 42 mmHg, and PO_2 was 56 mmHg.

4 (3%) patients were in functional class (FC) II; 60 (51%) in FCIII, and 54 (46%) in FC IV. Forty patients (34%) had pulmonary hypertension, 19 of these had severely impaired systolic function of the right ventricle.

25 (21%) patients had hypertension; 22 (19%) ischemic cardiopathy, 17 (14%) depression, 15 (13%) osteoporosis, 9 (8%) diabetes mellitus, 7 (6%) cataracts.

25 patients underwent transplantation (24%), time on waiting list since assessment to transplant was 322 days, range: 3 to 1006 days. 15 (60%) patients underwent elective transplantation, 7 (28%) urgent transplantation and 3 (12%) emergency transplantation.

Survival while on waiting list at 12 months reached 43.2%, at 24 months, 17.3% and at 36 months, 10.8%.

Conclusions

Mortality while on waiting list among patients with PF is high, mainly due to the fact that these patients are referred for transplantation with already advanced lung disease. Referral should not be delayed while different therapeutic options are implemented.

IS OSTEOPOROSIS A REAL PROBLEM IN PATIENTS REFERRED FOR LUNG TRANSPLANTATION?

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Osteoporosis is well-recognized complication of lung transplantation that may significantly impair the final result of surgery.

We performed a study of bone mineral density (BMD) in 48 patients (35 men, 13 women, mean age 50.5±10.4) referred in 2006 – 2009 in Dpt. Of Lung Diseases in Zabrze for Lung transplantation (LT). Study group consisted of 12 pts with IPF, 15 pts with other form IIP, 5 pts with sarcoidosis and 16 pts with end-stage of COPD. The bone mineral density (BMD) of the lumbar spine (LS), total hip (TH) and femoral neck (FN) were measured. According to WHO standard (BMD T score < -2.5) patients were divided into group with osteoporosis (OG; 22 patients) and 26 patients without osteoporosis (WOG) with BMD T score ≥ -2.5. OG create 45.8% of study group. Age, BMI, duration of disease, steroid consumption, 6 minute walking test (6 MWT), lung function tests (FVC, FEV1) and results of blood gasses (PaO_2, $PaCO_2$, pH) were taken into consideration.

In OG the most affected was LS (mean T score -2.9±0.8), in WOG the most affected was FN (mean T score -1.3±0.6). In OG we observed significant ($p<0.05$) higher steroid consumption (13.3 mg/24 h vs 5 mg/24 h), lower distance in 6 MWT (284 m vs 322 m), lower FEV1%pred. (24 vs 39) and FVC%pred. (35 vs 45) and higher PaCO2 (49 mmHg vs 39 mmHg). We observed no differences in mean age, BMI, PaO2 and time of diagnosis between OG and WOG. We conclude that osteoporosis, which occur in almost half of patients referred for LT, influence on lung function and walking ability in patients with end-stage lung diseases referred for LT.

UNUSUAL LOW INCIDENCE OF ACUTE REJECTION AND BOS AFTER LUNG TRANSPLANTATION: THE IMPACT OF AN ONLY ORALLY BASED STANDARD IMMUNOSUPPRESSIVE REGIMEN FOR PRE-OPERATIVE INTRODUCTION AND MAINTENANCE THERAPY

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Purpose

Immunosuppression remains unsatisfactory with a high incidence of frequent acute rejection (AR) and early onset of bronchiolitis obliterans syndrom (BOS) in lung transplantation (LTX). Despite the introduction of many novel agents, the basis of currently applied protocols remains a CNI, i.e. cyclosporine/tacrolimus (tac). LTX is limited by the development BOS. The strongest risk factor for BOS is acute rejection .

Methods and materials

105 lung recipients received conventional immunosuppression with oral tac (3 mg) and oral Mycophenolate-mofetil (MMF 1.5 g) as induction 2 hours prior to skin incision. Intra-op,patients received methylprednisolone and IG-G 1ml/kg BW. Post-op oral tac/MMF was continued and trough levels monitored (target 8-12 ng/ml). Rapid steroid taper over 12 weeks for maintenance of 5-15 mg/d post-op. PFTs were performed frequently and daily after discharge by means of self-measuring device (daily FEV1). TBB were rarely performed.

Results

One patient had hyperacute rejection and died 6 weeks post re-LTX. Severe rejection (A4) in one patient. Early/one-year mortality (22%) was related to severe reperfusion injury and infections (Figure 1). The follow-up of the LTX patients and close monitoring of the immunosuppressive regimen and the medication response was 100% complete. The mean duration of observation per patient was 2.1 ± 1.7 years (median 1.4, range 0.0 – 6.8) and this study included 186.5 patient related years of follow-up. The one-three-and five-year survival following LTX was 70%, 60%, and 55%. Eight patients underwent high-dose IV bolus methylprednisolone treatment and taper for acute rejection. Three patients developed BOS more than 4 years following LTX. The AR and BOS related mortality was 0% within the 7-year interval of LTX. One patient required re-LTX 6 years post lung transplantation.

Conclusions

Our results suggest that oral pre-op introduction of conventional immunosuppression and oral maintenance protocols are very protective and reduce the incidence of chronic rejection. Acute rejection seems to be very rare following lung transplantation.

A MURINE MODEL OF BRAIN DEATH: AN OPPORTUNITY FOR FUTURE MECHANISTIC STUDIES ON TREATMENT FOR DONOR LUNG INJURY

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Introduction

Only 15-25% of brain death (BD) donors match the ideal donor criteria for lung transplantation. The mechanisms of BD-related lung injury are not fully understood justifying further research. A successful BD model in mice would help to further investigate mechanisms to attenuate lung injury at immunological level using knock-out animals.

Materials & methods

Mice (Balb/c, 28.6g ± 1.3) were anesthetized, tracheotomized and mechanically ventilated. Body temperature was kept constant at 36.5°C using a heating pad with temperature probe. BD was induced by rapid inflation of a subdural balloon catheter. Animals were randomly divided into 4 groups (n=3 each): 1h sham [SH1], 1h BD [BD1], 5h sham [SH5], 5h BD [BD5]. Heart rate (HR) and mean arterial pressure (MAP) were continuously monitored through a pressure transducer in the femoral artery. Cortical activity was monitored through electroencephalography (EEG) before and after balloon inflation. At the end of the experiment, bronchoalveolar lavage (BAL) was performed and biopsies were collected for histology. An average score (0-3) was given for neutrophilic infiltration, oedema, and congestion.

Results

BD was confirmed by pupil dilation and flat lined EEG. In both BD groups, MAP and HR increased significantly from 56.3 mmHg and 443.15 bpm (T0) to 83.8 mmHg and 471.9 bpm after balloon inflation ($p<0.05$) followed by hypotension after 10 minutes (46.4 mmHg). In the control groups, HR and MAP remained constant after balloon insertion.
A higher number in BAL neutrophils were seen in [BD5] (24.5%) compared to [BD1] (15.9%), [SH1] (2.9%), and [SH5] (14.0%); $p<0.05$. Alveolar oedema and congestion were seen on histology in [BD5] (1.3 and 1; respectively) compared to [BD1] (0 and 0.5; respectively) and controls (0 and 0; respectively).

Conclusions

The creation of a BD model in mice to study lung injury was successful facilitating further mechanistic studies for its treatment. A 5-hour period after BD is needed to observe significant inflammatory changes in BAL and on lung histology.

PLASMA SERUM LEVEL OF NT-PROBNP AS THE STRONG AND INDEPENDENT PREDICTOR OF DEATH IN PATIENTS WITH END-STAGE LUNG DISEASES REFERRED FOR LUNG TRANSPLANTATION

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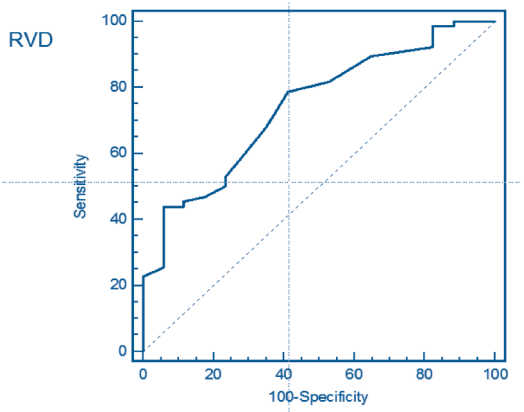
Purpose: Prognostic value NT-proBNP in patients with heart failure is well established. Little is know about its prognostic utility in patients with end-stage lung disease (ESLD). The aim of the study was to asses diagnostic value of NT-proBNP in predicting death in patients with end-stage lung disease listed for lung transplantation.

Methods: Thirty-five consecutive patients (30 M, 5 F; mean age 46.6±12 years) with ESLD and mild-to-moderate pulmonary hypertension listed for lung transplantation (LT) were assessed. Patients with heart and other diseases which might have caused right ventricular (RV) and left ventricular (LV) dysfunction were excluded. Transthoracic echocardiography was used for the evaluation of RV and LV systolic function. Plasma serum level of N-terminal-pro-B-type natriuretic peptide (NT-proBNP) and other biochemical parameters were determined in blood samples of 35 patients with ESLD.

Results: The patients were followed-up for 34.6±15 months. During this period 7 patients died. NT-proBNP level was the significant predictor of death in multivariate Cox-regression analysis (p=0.01). Receiver-operator characteristics analysis defined, both NT-proBNP cut-off 92.3 pg/ml and RV diameter > 32mm as optimal thresholds, yielding high sensitivity (64% for NT-pro BNP and 94%for RV diameter) and specificity (80% and 43% respectively) in prediction of death in patients with ESLD (AUC for NT-proBNP 0.74; 95% CI: 0.56-0.87; SE 0.09; p=0.007; positive predictive value – 100%, negative predictive value only 23%; AUC for RV: 0.7; 95% CI: 0.63-0.83; SE 0.06; p=0.002; positive predictive value - 97%, negative predictive value – 30%;). None of the other biochemical and echo-cardiographic parameters yielded significant results.

Conclusion: NT-pro BNP and right ventricular diameter may be helpful in predicting death in patients with end-stage lung diseases.



AUC 0.74 (95%CI 0.63-0.83) p=0.002

IMPROVEMENT OF POST OPERATIVE OXYGENATION AND CLINICAL OUTCOME AFTER SEQUENTIAL DOUBLE LUNG TRANSPLANTATION USING CARDIOPULMONARY BYPASS DURING THE SECOND LUNG IMPLANTATION

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Background: The use of cardiopulmonary bypass (CPB) in bipulmonary transplantation remains controversial[1,2]. Previous studies have concluded that CPB is deleterious but these studies were confounded by the inclusion of more severe patients with elective or emergency use of bypass. During double lung transplantation, the newly implanted first lung has to accommodate the entire cardiac output during the implantation of the second lung. This can be responsible for an increased hydrostatic pressure with severe interstitial and alveolar oedema leading to catastrophic allograft dysfunction. We hypothesize that sequential double lung transplantation using CPB systematically during the second lung implantation improves post transplantation oxygenation and clinical outcome.

Method: A prospective study comparing 9 consecutive patients who underwent sequential double lung transplantation with CPB during the second lung implantation over 1 year to a control group of 10 consecutive patients who underwent sequential lung transplantation without CPB the year before. In order to avoid warm ischemia, CPB flow was adapted to End Tidal CO_2 in order to obtain values superior to 15 mmHg. At the same time, transoesophageal echocardiography was used to control the venous pulmonary blood flow in the pulmonary graft.

Results: The use of CPB during the implantation of the second lung improves post operative oxygenation.

CPB avoid the occurrence of severe pulmonary graft dysfunction with PaO_2/FiO_2 below 100 and extra corporeal membrane oxygenation requirement (0 patient with CPB and 3 patients without). The mean duration of CPB was short and blood transfusion was not different.

Variables	CPB n=9	Control group n=10	p-value
Age (years)	39 (13)	31 (14)	0.20
Donor PaO_2/FiO_2	407 (88)	421 (133)	0.99
CPB time (min)	111 (18)	NA	
Ischemic time (min)	395 (65)	432 (74)	0.21
Packed red blood cells (unit)	7 (3)	6 (3)	0.46
Lactates H+1 (mmol/l)	3.5 (2.7)	4.3 (4.3)	0.63
Post operative PaO_2/FiO_2 H+1	363 (51)	240 (113)	0.01
Post operative PaO_2/FiO_2 H+6	430 (111)	280 (103)	0.03
PGD ≥ 3	1 (11%)	3 (33%)	0.37
ECMO	0	3 (33%)	0.09
Mortality at 6 months	0	2 (20%)	0.18

Conclusions: Systematic CPB during the second lung implantation appears to have beneficial effect on early graft function and avoid the occurrence of unpredictable severe pulmonary oedema in the first transplanted lung.

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SECONDARY PULMONARY HYPERTENSION IN IPF LUNG TRANSPLANT RECIPIENTS: THE INTRAOPERATIVE RIGHT VENTRICLE FUNCTION AS AN EARLY PREDICTOR OF PRIMARY GRAFT DYSFUNCTION

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Introduction: Information on how to predict primary graft dysfunction (PGD) in patients with secondary pulmonary hypertension (SPH) as a consequence of idiopathic pulmonary fibrosis (IPF) is limited. We hypothesized that the intraoperative measurement of the right ventricle (RV) function during lung transplantation (LT) could be an early predictor of PGD in this subset of patients.

Objectives: To determine if changes in intraoperative RV function predict PGD in patients undergoing lung transplantation for IPF with SPH.

Population and Methods: The clinical records of all patients that had lung transplantation for IPF between April 1999 and April 2010 were reviewed. Patients with SPH (mPAP>25 mmHg) were further selected. Mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure (PCWP), transpulmonary gradient (TPG), pulmonary vascular resistance (PVR) and right ventricle stroke work index (RVSWI) were measured at baseline (b) and after reperfusion (p). All the hemodynamic parameters were obtained by right catheterization. The difference between bRVSWI-pRVSWI was defined as the change (Δ) in RVSWI. Preoperative, intraoperative and postoperative variables were also analyzed to identify factors that could predict severe PGD, 30 day and in-hospital mortality.

Results: Forty patients had LT for IPF. Out of 40 patients, 17 (42%) had SPH. One patient underwent bilateral LT, while 16 patients had single LT. Baseline and post reperfusion hemodynamic parameters are show in table 1. Six out of 17 patients (35%) developed grade 3 PGD; pmPAP and pTPG were greater in these patients with PGD (34±18 vs. 20±8, p= 0.03 and 18±10 vs. 8±6, p=0.04, respectively). The ΔRVSWI was 6±8. A ΔRVSWI < 10 correlated with the development of grade 3 PGD (p=0.04). The PaO_2/FiO_2 at 30 and 120 min. post reperfusion failed to predict severe PGD (p=NS).No other factor analyzed predicted PGD, 30-day or in-hospital mortality.

Conclusion: The decrease of RVWSI is an early indicator of RV function improvement after lung reperfusion in IPF patients with SPH undergoing lung transplantation. The magnitude of RVSWI decrease correlates with the development of postoperative grade 3 PGD.

	Baseline	Post reperfusion	*p* value
mPAP (mmHg)	45±17	25±14	0.001
PCWP (mmHg)	12±5	13±7	0.1
TPG (mmHg)	32±19	12±9	0.001
PVR (dyne-seg/cm^5)	617±420	210±127	0.002
RVSWI (gr-m/m^2)	13±1.3	7±1.2	0.006

NECESSITY FOR SCREENING TRANSPLANT-RELEVANT HLA- AND MICA-ANTIBODIES AFTER VENTRICULAR ASSIST DEVICE SUPPORT IMPLANTATION

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Objective

Patients that were bridged to transplantation with ventricular assist device (VAD) have a higher incidence for the development of antibodies directed against human leukocyte antigens (HLA) or against major histocompatibility complex class I related chain A (MICA). HLA- and MICA-antibodies have been associated with acute and chronic rejection leading to decreased survival after heart transplantation. Up to now, monitoring of these clinical relevant antibodies is not an established routine.

Methods

Sera of 15 patients who underwent VAD implantation were analyzed by Luminex® technology for anti-HLA class I, anti-HLA class II and anti-MICA antibodies. Blood transfusion history, gender, age and panel reactive antibody (PRA) level before VAD implantation were reviewed.

Results

The mean age was 51.1 ± 11.6 years and the group consist of 12 men. The 3 women were pre-operatively HLA I or II positive. Regarding age, gender and number of received blood transfusions no significant differences were obtained between HLA/MICA-positive and HLA/MICA-negative patients. Seven of 15 patients (47%) showed anti-HLA and/or anti-MICA antibodies after VAD implantation, whereas 3 patients (20%) developed *de novo* antibodies against HLA class I, HLA class II and/or MICA antigens.

Conclusions

Patients with implanted VADs prior to transplantation have a higher risk to develop alloreactive antibodies because of the necessity of high amount of blood transfusion, but also due to the VAD itself. Due to increasing numbers of VAD implantations in consequence of missing donor hearts antibody monitoring and pre-operative intervention may be useful for better transplantation outcome.

ANTI-HLA CLASS I AND ANTI-MICA ANTIBODIES: PROGNOSTIC MARKER FOR TRANSPLANT VASCULOPATHY AND POST-TRANSPLANT CMV-INFECTION

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Introduction

The causes of transplant vasculopathy after organ transplantation are not solved completely, but comprise immunologic as well as non-immunologic factors. Evidence suggests that antibodies against human leukocyte antigen (HLA) and major histocompatibility complex class I related chain A (MICA) play a key role in humoral response to alloantigens. Here, we described the appearance and allocation of HLA and MICA antibodies after heart transplantation (HTx).

Methods

Sera of 116 HTx patients were screened by Luminex xMAP® technology for anti-HLA class I and anti-MICA antibodies. For statistical analysis the gender, age, status of transplant vasculopathy, cytomegalovirus (CMV) infection and time from HTx to beginning of the study was documented for each patient.

Results

Twenty-four percent of all recipients (n=116) were positive for HLA and/or MICA antibodies. Data about gender, age, CMV infection and transplant vasculopathy were assorted in Table 1.

Table 1: Characteristics of HTx recipients (HTxR) with and without HLA and/or MICA antibodies.

	HLA and/or MICA positive HTxR (n=28)	HLA and MICA negative HTxR (n=88)
age, mean ± S.D.	55.5 ± 13.2 yr	56.3 ± 13.3 yr
recipient gender, % female	25.5 %	21.6 %
time from HTx to beginning of study, mean ± S.D.	75.5 ± 40.7 mo	87.0 ± 51.7 mo
CMV infection (count)	14.3 % (4) *	0.0 % (0)
cardiac transplant vasculopathy (count)	28,6 % (8)	15.9 % (14)

* P≤ 0.05

CMV-infection was confirmed at 16.7% of recipients with anti-MICA antibodies and 28.6% of recipients with anti-HLA class I antibodies. Furthermore, 50.0% of the recipients with transplant vasculopathy combined with positive antibody status were positive for MICA antibodies.

Conclusions

Our results showed that positive detection of MICA and HLA class I antibodies after HTx is related to a higher incidence for CMV-infection and transplant vasculopathy in recipients. Prospective studies will resolve if post transplant monitoring to both HLA and MICA antibodies will serve as a useful tool to identify humoral rejection and risks for allograft dysfunction and therefore serves as an important prognostic marker for rejection after organ transplantation.

PROPOSALS AND REFUSALS BY FRENCH TEAMS IN LUNG PROCUREMENT: A NEW WAY OF IMPROVEMENT?

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Introduction. The lung transplantation activity has suffered from a shortage which yielded a national debate and resulted in planned action of French transplant teams collaboration with the Agence de la biomédecine.
Since 2003, an increase in the number of potential lung donors and revision of the acceptance criteria led to doubling of the annual rate of lung transplantation.
The aim of this study was to explore new paths to increase the rate of lung transplantation activity by assessing the number of proposals by the Agence de la biomédecine to French teams and the refusals by the teams.

Materials and methods. Deceased donors from which at least 1 organ was retrieved between 2006 and 2009 were included.
Donors were classified in 3 groups according to their medical characteristics:

- Optimal donors were non smokers aged of less than 56 years, with PaO2>400 mmHg, normal chest X ray and without inhalation.
- Extended criteria donors (ECD) were aged 56-70 years or with 200mmHg<PaO2 <400mmHg or with inhalation
- Marginal donors were aged of more than 70 years or with PaO2<200mmHg.

Results. In 2009, on the 1442 donors with one organ retrieved, 227 had at least 1 lung retrieved (16%).
However, the part of non proposed lungs by the regional allocation teams decreased (79% in 2006 and 77% in 2009).
As expected, the difference between proposed and retrieved donors increased with the degraded medical status of donors.
88% (61/69) of optimal donors were proposed, while the ECD donors were proposed in 28% of cases (249/884). An increase in the number proposed of marginal donors was also observed in recent years (0.8% in 1.9% between 2006 and 2009).
The main causes of non propositions were blood gazes, age and inhalation.
In the same time, the rate of refusal by transplant teams has decreased from 79% in 2006 to 69% in 2009.
The main causes of refusal were medical (59%) and logistic (21%) and depended on the teams.
The rate of refusal was different according to the type of donor: 7% for optimal donors, 28.5 for ECD and 78% for marginal donors.

Conclusion. The proportion of donors for which at least one lung was proposed by the regional allocation teams as well as the proportion of lungs accepted by transplant teams improved over time resulting in a gradual raise in the number of allocated lungs.
A potential donor pool in ECD was observed (which represents a fraction of nearly 600 donors).
This study led to broaden the ECD donor lung proposals and to decrease the refusals from transplant teams.

THE IMPACT OF AIR POLLUTION ON BRONCHIOLITIS OBLITERANS SYNDROME AND MORTALITY AFTER LUNG TRANSPLANTATION

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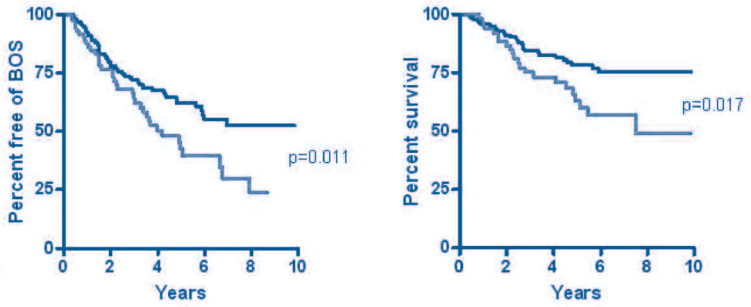
Bronchiolitis obliterans syndrome (BOS) has a prevalence of 30% and 50%, 3 and 5 years after lung transplantation, which is far more than after other solid organ transplantations. The direct contact with the environment, making the lung more susceptible for exposure to microbial specimens, toxic agents and other hazardous specimens, may offer a plausible explanation. Particulate matter (PM) is known to induce (neutrophilic) inflammation in the airways, which is the halmark of BOS.

In this epidemiological single center study we retrospectively investigated the effect of air pollution on the development of BOS and mortality in our lung transplant cohort (n=217). The incidence of chronic rejection was higher in those living close to major roads (<157 m), with an incidence of 14.7 per 100 person-years versus 9.0 per 100 person-years, respectively (p=0.011; figure). The corresponding data for mortality during follow-up were 10.7 deaths per 100 person-years in those living close to major roads and 3.1 per 100 person-years in those living further than 157 meters from a major traffic road (p=0.017, figure).

Figure: Incidence of BOS and death in transplant patients living close (<157 m, lowest tertile) and further away from major roads.



These results indicate a strong association between rejection/mortality in lung transplant patients and the role of road traffic fumes generated from motor vehicle exhaust as calculated by proximity to roads with high traffic density. This is independent of all other known risk factors for the development of BOS.

MONTELUKAST FOR BRONCHIOLITIS OBLITERANS SYNDROME AFTER LUNG TRANSPLANTATION

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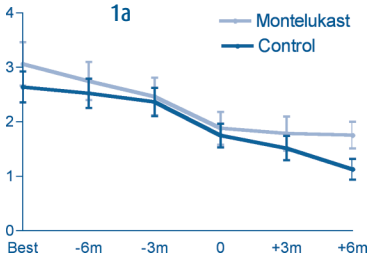
Purpose of the study. Bronchiolitis Obliterans Syndrome (BOS) remains a major cause of mortality after lung transplantation (LTx). We recently proposed the existence of a dichotomy within BOS (NRAD, neutrophilic reversible allograft dysfunction with bronchoalveolar lavage, BAL, neutrophilia >15%), versus fBOS (fibroproliferative BOS, BAL neutrophilia <15%). Whilst NRAD responds to azithromycin treatment, for fBOS, there is so far no effective therapy available. We investigated the potential of montelukast, a cysteinyl leukotriene receptor antagonist, also known as an antifibrotic agent, to treat fBOS.

Methods. Patients in early BOS (BOS stage ≤ 2), with a BAL neutrophilia <15%, were treated with additional oral montelukast (10 mg/day) and azithromycin. Montelukast was started shortly after diagnosis of BOS (i.e. < 6 weeks), and had to be taken for at least 6 months. We included a retrospective control group, which was in a comparable situation and only treated with azithromycin in addition to their current immunosuppressive regimen, but not with montelukast and which was otherwise left unchanged.

Results. The mean changes in FEV1 in both groups are shown in figure 1a. The decline in FEV1 (mL/month) in the montelukast group before the introduction of montelukast was 143.8 ± 29.5 mL/month and significantly decreased to 20.5 ± 17.2 mL/month during the 6 months of treatment (p=0.0083). In the control group, the decline in FEV_1 6 months before BOS was 128.6 ± 20.3 ml/month and remained unchanged during the following 6 months at 103.0 ± 28.8 ml/month (p=0.54) (figure 1b).

Conclusion. Montelukast may be a promising treatment for fBOS as it is able to arrest the progressive decline in FEV_1 in patients suffering from fBOS.



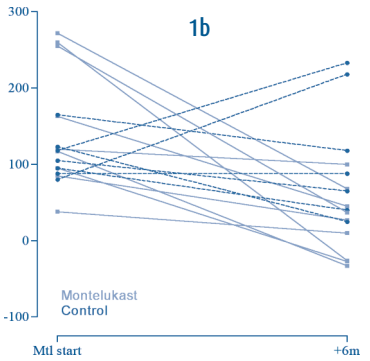


Figure 1a: The FEV1 evolution in the montelukast and control group. The FEV1 in the montelukast group stabilized (3 of 8 patients even experienced an increase in FEV1), while the control group further deteriorated.

Figure 1b: The FEV1 decline in the montelukast group is much less pronounced after 6 months of treatment with montelukast as the decline in all the patients decreased compared to the control group.

A RANDOMIZED PLACEBO-CONTROLLED TRIAL OF AZITHROMYCIN TO PREVENT BRONCHIOLITIS OBLITERANS SYNDROME AFTER LUNG TRANSPLANTATION

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Background

Azithromycin reduces airway inflammation and improves pulmonary function (FEV1) in chronic rejection, or its clinical correlate bronchiolitis obliterans syndrome (BOS), after lung transplantation. Prophylactic treatment with azithromycin might also prevent BOS.

Methods

A single-center, double-blind, placebo-controlled trial of oral azithromycin, initiated at discharge and given thrice-weekly for two years after lung transplantation, was performed from 2005 to 2009 at the Leuven University Hospital. Of the 119 patients transplanted during enrollment, 83 were randomly assigned to either placebo (n=43) or azithromycin (n=40). All included patients were analyzed according to the intention-to-treat principle and none were lost to follow-up.

Primary end-points were BOS-free and overall survival 2 years after transplantation, secondary end-points were acute rejection, lymphocytic bronchiolitis and pneumonitis rate, prevalence of pseudomonal airway colonization and gastroesophageal reflux and evolution of FEV_1, airway and systemic inflammation. Patients developing BOS were assessed for FEV_1-evolution after initiation of open-label azithromycin.

Findings

Chronic rejection occurred significantly less in the azithromycin treated group: 5 (12.5%) vs. 19 (44.2%) events (p=0.0017). BOS-free survival was better with azithromycin (hazard ratio 0.27; 95% CI 0.092-0.816, p=0.020) (Figure A). Survival was similar, with 6 deaths among patients receiving azithromycin and 8 deaths among patients receiving placebo (Figure B). Acute rejection, lymphocytic bronchiolitis, pneumonitis, colonization and reflux were comparable between groups. Patients receiving azithromycin had significantly better FEV_1 (p=0.028), lower airway neutrophilia (p=0.015) and systemic C-reactive protein levels (p=0.050) over time. Open-label treatment for BOS improved FEV_1 in 12 (52.2%) patients. No serious adverse events were noted.

Conclusions

Prophylactic treatment with azithromycin attenuates airway and systemic inflammation, improves FEV_1 and reduces chronic rejection two years after transplantation. Longer follow-up may be needed to confirm the durability of these observed effects.

Trial Registration:
ClinicalTrials.gov: number NCT01009619, ISRCTN-registry: number 36220396
Funding
Research Foundation-Flanders (FWO Grants 0643.08, 0723.10).

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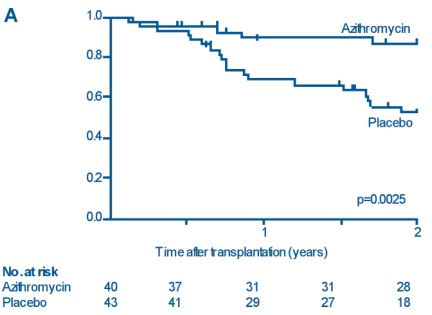
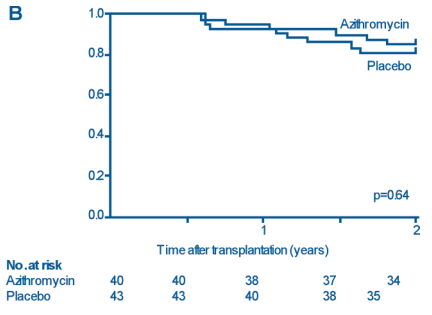
A. Freedom from BOS

The prevalence of BOS was lower in patients treated with azithromycin, with 19 events (44.2%) at 2 years after transplantation in the placebo group and 5 events (12.5%) in the azithromycin group (relative risk, 3.5; 95 percent confidence interval, 1.5 to 8.6; p=0.0015 by Chi square test). Multivariate time-to event analysis confirmed the better BOS-free survival of patients receiving azithromycin with a hazard ratio of 0.27 compared to placebo after adjustment for covariates (95 percent confidence interval, 0.092 to 0.816, p=0.020 by Cox-proportional hazards analysis).



B. Overall survival

Survival between both groups was similar at 2 years after transplantation. There were 8 deaths (18.6%) in the placebo group, as compared with 6 deaths (15.0%) in the azithromycin group (p=0.64 by log-rank analysis). Multivariate time-to event analysis showed a hazard ratio 0.25 for azithromycin compared to placebo after adjustment for covariates (95 percent confidence interval, 0.05 to 1.38, p=0.11 by Cox-proportional hazards analysis, survival not censored for retransplantation or study-drug discontinuation).



LONG-TERM OUTCOME OF DOUBLE LUNG AND HEART-LUNG TRANSPLANTATION FOR PULMONARY HYPERTENSION: A COMPARATIVE RETROSPECTIVE STUDY OF 210 PATIENTS

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Objectives

There is controversy as to whether double-lung (DLT) or heartlung transplantation (HLT) provides the best outcome for patients with pulmonary hypertension (PH). At our institution, patients with severe right ventricular dysfunction or with congenital systemic-to-pulmonary shunt (CSPS) were treated preferably with HLT. We reviewed retrospectively our experience in order to determine whether our policy is still justified.

Methods

Between 1986 and 2007, 210 patients (of whom 27 had CSPS) underwent either a DLT (n=62) or HLT (n=148) for end-stage PH.

Results

When compared to the HLT group, patients who underwent a DLT had preoperatively a higher cardiac index (2.5±0.7 vs. 2.0±0.6; P=0.008), lower NYHA functional class (3.5±0.5 vs. 3.8±0.4; P=0.0009), lower kidney (34% vs. 66%; P=0.002) and liver failure rates (14% vs. 38%; P=0.007) and preoperative inotropic support was less frequently (11% vs. 24%; P=0.04).
The 1, 5 and 10-year survival was 69, 49 and 38% in the HLT group and 79, 49 and 41% in the DLT group, respectively (P=NS). Freedom from obliterative bronchiolitis-related death was 100% at 1 year, 83% at 5 years and 75% at 10 years in HLT patients and 98% at 1 year, 68% at 5 years and 57% at 10 years in DLT patients (P=0.03).

Conclusions

In patients with end-stage PH, good long-term survival can be obtained either by DLT or HLT. However, to achieve these results, HLT should be chosen in PH patients with right heart failure or with CSPS. Obliterative bronchiolitis-related death occurs less frequently in HLT than in DLT.

THE COLT STUDY: FRENCH COHORT IN LUNG TRANSPLANTATION

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Purpose of the study: Lung transplantation remains the last therapeutic option for selected patients with end stage pulmonary disorders. However its long-term prognosis is still limited by the onset of Obliterative Bronchiolitis (OB), considered as the manifestation of chronic lung allograft rejection. Despite standard three-drug calcineurin inhibitor-based immuno-suppression regimen, OB occurs in 35% of patients at 5 years after surgery, with a mortality rate of 45% at 5 years. At the tissue level, injury to the bronchiolar structure is the primary event which triggers an invasion of various inflammatory cells and an increase in pro-inflammatory and chemotactic mediators within the bronchiolar wall. As the process evolves, an uncontrolled repair process, with sub-mucosal fibrous tissue proliferation leads to obstructive airway scarring. This mechanism involves mesenchymal cell and fibroblast replication, together with connective-tissue deposition in response to profibrotic cytokines and growth factors released within the local tissue. Facing the complexity of OB mechanisms, the discovery of a unique biomarker predictive for OB is unlikely.The aim of this study is to detect predictive risk factors of OB through a national multicentric cohort of 500 newly transplanted recipients (COLT).

Methods: Our work will approach 4 research axes. Two of them concern the study of biomarkers already identified by comparing OB to non OB patients in small cohorts of lung transplanted patients that need to be validated longitudinally in a large cohort. The last two axes stand upstream, and propose the potential identification of new biomarkers and/or therapeutic targets in a longitudinal approach:

- Role of Treg cells and DC maturation stage in graft tolerance.
- Genomic study of cytokine polymorphisms expressed by healthy and OB recipients.
- Microarray analysis of RNA from healthy and OB recipients.
- Proteomic analysis of *in situ* samples (BALF, IS, plasma) from healthy and OB recipients.

Main results: Enrolment of patients for this study started in September 2009, reaching actually 244 patients among which 75 newly lung transplant recipients. For each patient enrolled, cells, DNA, RNA and *in situ* samples are stored in a bio-collection in Nantes.
The COLT study has also permitted the creation and dissemination of COLT database in all participating centres. Concerning research axes, the blood study with evaluation of Treg populations and DC maturation stage and the proteomic analysis from *in situ* samples had started.

Conclusion: This longitudinal cohort, by aggregating around the same patients, various fields of biology and immunology, will allow both approaching reliable diagnostic indices and relevant therapeutic pathways. Beyond this first series of research, COLT will be perpetuated and extended above the 500 first patients, in order to offer in the long term the opportunity for new discoveries to be tested as diagnostic and/or therapeutic purposes.

PSYCHOLOGICAL ADVERSE EFFECTS RELATED TO MYCOPHENOLATE MOFETIL

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Introduction: Mycophenolate Mofetil (MMF) has a number of recognised side effects. Depression and mood changes are cited in the product information as possible side effects but little has been published regarding these adverse effects. In our institution a number of patients have developed a temporally related clinically significant mood disturbance, which resolved after the cessation of MMF.

Case 1: 45 year old male, who underwent a heart & lung transplant for Eisenmengers Syndrome in 1996. Initial immunosuppressants included Cyclosporin, Azathioprine & Prednisolone (standard protocol). Due to a number of rejection episodes Azathioprine was discontinued and MMF was commenced in January 2006. In November 2006 the patient reported marked lability of mood, with symptoms alternating between depression, anxiety & anger. This effect became more notable as the dose of MMF was increased. Anti-depressants were commenced and after 6 weeks there was a minor improvement in mood. However, two weeks later the patient took an intentional overdose of multiple prescribed medications. MMF was discontinued. The patient reported immediate improvement in mood and complete resolution of psychological symptoms within 6 months. He was discharged from psychiatric follow-up.

Case 2: 50 year old male who underwent a heart & lung transplant for cystic fibrosis in 1991. Initial immunosuppressants followed standard protocol. In 2001, following repeated episodes of rejection, MMF was commenced. In 2003 the patient reported marital difficulties, anger management problems resulting in uncharacteristic violence directed towards his wife. The patient reported that these mood/behaviour changes had appeared since commencing MMF. MMF was immediately discontinued and at the following clinic review the patient reported a cessation of symptoms.

Case 3: 35 year old female who underwent a heart & lung transplant for congenital heart disease in 1988. MMF was commenced in 2006 due to impaired renal function caused by cyclosporine therapy. Four weeks following commencement of MMF the patient reported low mood and tearfulness. MMF was discontinued and the patient reported improvement within one week of discontinuation.

Discussion: Our experiences indicate that in some patients there is a correlation between the commencement of MMF and onset of mood disturbance, with resolution of symptoms on discontinuation of therapy. None of the patients discussed had a previously known or diagnosed affect/anxiety/behaviour disorder.

Conclusion: Mood disorders can be detrimental to both the patient and their family and may result in reduced quality of life. Evidence in the literature supports a correlation between low mood and increased morbidity and mortality. Therefore, it is important for physicians/nurses to be aware that use of MMF is related to mood deterioration in some patients and, where appropriate, consideration should be given to alteration of the immunosuppressant therapies used.

INHALED CYCLOSPORINE PROVIDES HIGH LUNG CONCENTRATIONS, LOW SYSTEMIC EXPOSURE AND IS WELL TOLERATED: AN INTERIM REPORT ON THE CYCLIST CLINICAL TRIAL

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Purpose

The CYCLIST study is a randomized-controlled trial to determine the effect of inhaled cyclosporine (CIS) on bronchiolitis obliterans syndrome-free survival in recipients of a lung transplant.

Methods and Materials

Subjects are randomized to CIS plus standard of care or standard of care alone. CIS, comprised of cyclosporine dissolved in propylene glycol and aerosolized via a compressor and nebulizer, has the potential to cause mild airway irritation. In subjects randomized to active drug, CIS is initiated at a dose of 100 mg following pretreatment with aerosolized lidocaine and albuterol. The dose is increased in increments of 50mg to a maximum of 300 mg over up to 10 days. At the end of the titration period, subjects are treated with the maximum dose achieved three times per week.

Results

288 subjects have been enrolled in the study. Demographic characteristics of the subjects are similar to that reported in the 2009 ISHLT registry. Of the 133 subjects randomized to CIS, 117 subjects (88%) achieved the target dose of at least 250 mg. The mean number of days to reach this dose was 5 (median 4 days). Subjects with a single lung transplant, an FEV1 $\leq$ 2 liters took longer to reach the target dose (median 5 days). The majority of subjects have not required pretreatment after the titration period. Most subjects have continued to tolerate the aerosol three times a week during maintenance treatment. 5 of 10 subjects have completed a pharmacokinetic, scintigraphy sub study. In these subjects deposition varied from 13.2 to 51.4mg CIS (mean 29.2). The data are consistent with earlier data from Burckart[1] et al and confirm that dosing three times a week is sufficient to maintain lung CIS levels in the therapeutic range.

Conclusions

Aerosolized cyclosporine appears to be well tolerated in recent recipients of single and double lung transplants.

1- Pharmaceutical Research 20:2;2003

EVALUATION OF CALCINEURIN ACTIVITY AS A BIOMARKER OF ACUTE AND CHRONIC REJECTION AFTER LUNG TRANSPLANTATION

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Introduction

Anti-calcineurin immunosuppressive drugs have been the standard for rejection prophylaxis after lung transplantation (LT) for the last 20 years. To date, there are no robust biomarkers that could predict the efficacy of immunosuppressants, which may partially account for the frequent failure of rejection prophylaxis, since more than 50% of the recipients developed acute rejection after LT. Moreover, acute rejection is considered as a significant factor in the development of bronchiolitis obliterans syndrome (BOS), a major complication after LT that affects more than 40% of the recipients during the first 5 years following transplantation. We have conducted a study in order to evaluate the efficiency of calcineurin activity (CN-a) to predict rejection during 4 years following LT.

Methods

107 patients entered the study from March 2004 to August 2008. CN-a was measured once a month during the first 6 months after LT. CN-a was determined in mononuclear cells isolated from whole blood by quantifying by HPLC the dephosphorylation of a phospho-RII peptide. Episodes of acute rejection were diagnosed on the basis of lung function and biopsy results. Pulmonary function was estimated according to the spirometric data FEV1 and FEF_{25-75}, and the slopes between 2 consecutive values at 1 month-interval were calculated. The relationship between CN-a levels at a given month and the level of the FEV1- and/or FEF_{25-75} slopes calculated the following month was evaluated. Finally, the relationship between CN-a levels and the occurrence of BOS was determined.

Results

CN-a was significantly increased in patients treated for acute rejection during the first month following transplantation. An inverse correlation was found between CN-a and FEV1-slope, and patients with CN-a levels higher than 100 pmol/mg/min were those who displayed the lowest FEV1-slope (i.e. in favor with a stability of FEV1 values). Similarly, an inverse correlation was found between CN-a and FEF_{25-75}-slope, and patients with both CN-a levels lower than 10 pmol/mg/min and higher than 29 pmol/mg/min were those who displayed a negative FEF_{25-75}–slope (i.e. in favor with an alteration of FEF_{25-75} values). Finally, we found an association between CN-a levels and the risk of developing BOS. Indeed, CN-a levels lower than 100 pmol/mg/min during the first 6 months following LT allow to predict with 92% specificity (p=0.038, Fisher's test) the absence of BOS during the first 4 years after transplantation.

Conclusion

These results show that CN-a could be a tool to estimate the efficiency of immunosuppressive drugs after LT. Furthermore, these results suggest that CN-a could be useful in identifying patients who are at risk to develop BOS.

ASSISTANCE OF MTOR-INHIBITOR DOSING AFTER TRANSPLANTATION BY PHARMACODYNAMIC MONITORING OF RIBOSOMAL PROTEIN S6 PHOSPHORYLATION

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Objective

Therapeutic drug monitoring (TDM) of immunosuppressive drugs after transplantation (Tx) like the mTOR-inhibitors sirolimus (SRL) or everolimus (ERL) is based on measuring blood levels alone. But this often results in under- or over-immunosuppression leading to rejection or infection, respectively. Earlier studies have shown the potential value of measuring pharmacodynamic drug effects for TDM. Therefore we developed an assay to measure drug effects on the mTOR-pathway.

Methods

Blood from five healthy volunteers was incubated with five to six different clinical relevant concentrations of SRL (0.9-91.4µg/L), cyclosporine A (CsA, 75.1-1202µg/L), mycophenolate acid (MPA, 0.08-3.2mg/L) or Dexamethasone (DEX, 0.5-200ng/mL). Following activation whole-blood was analyzed by flow cytometry to measure phospho-S6 in T-cells, a downstream product of the mTOR-pathway. For validation we determined coefficient of variation for inter-assay and intra-assay variability.

Results

Phospho-flow analysis revealed that addition of SRL suppressed phosphorylation of ribosomal-protein S6 in human T-cells, whereas CsA, MPA and DEX as known from their mechanism of action did not inhibit mTOR-related S6-phosphorylation. We determined the assay-specific IC_{50} for SRL at 23.5nM. The maximum inhibitory effect (I_{max}%) of SRL on S6 phosphorylation in T-cells was obtained at 89%. Inter-assay and intra-assay coefficients of variation ranged from 0.12 to 0.25 and 0.03 to 0.05 respectively.

Conclusions

In this study, we established a specific whole-blood assay to assess drug effects on the mTOR-pathway. Future studies on transplanted recipients will show if such an assay has the potential to dose mTOR-inhibitors SRL or ERL in combination with either CsA, MPA or DEX more safely without loosing the efficacy.

THE IMPACT OF PERI-OPERATIVE EXTRACORPOREAL MEMBRANE OXYGENATION OR ECMO SUPPORT ON LONG-TERM SURVIVAL IN LUNG TRANSPLANTATION SURGERY

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Purpose

Extracorporeal membrane oxygenation (ECMO) is usually the last resort treatment of patients with global respiratory dysfunction and graft failure following lung transplantation (LTX) operations. We report our experiences of pre-intra- and post-op ECMO support for cardiopulmonary failure and its outcome in LTX.

Methods

From 2003 until the end of 2009 one hundred-eight patients underwent LTX through limited access muscle-sparing thoracotomies without sternum-transection. All patients underwent femoral artery and vein exposure for extracorporeal circulatory support connections. Notably, the majority of patients presented with IPF (53%) and markedly elevated pulmonary artery pressure (sPAP > 60 mm Hg 45%). Statistics: t-tests, chi2, Kaplan-Meier survival analysis and log-rank test, *=p<0.05.

Results

Twenty-seven or 25% of patients required (4 pre-op) peri-op ECMO (age 49± 12, double-LTX 63%*, female 48%, 54% IPF with PAP>60 mm Hg) vs. 81 patients without ECMO (age 53± 112, double-LTX 40%, female 33%, 35% IPF with PAP>60 mm Hg). There were no significant differences in ischemic-times, end-stage lung diseases, ischemia-reperfusion injury. The 30-day, 90-day, and 1-year survival was 80%, 78%, and 71% in the no-ECMO patients compared to 42%, 38%, and 33% in the ECMO-group. Factors for significantly reduced survival rates are, in addition to ECMO support, red blood cell and FFP transfusion requirements.

Conclusions

ECMO-supported patients represent the sickest patient group of an already very high-risk population with end-stage cardiopulmonary disease. A patient group for statistical comparison analysis does not exist. Although ECMO therapy is a significant risk factor for mortality in LTX, its impact is still favorable in an otherwise unsalvageable group of patients with near 100% mortality and lack of alternative support strategies.

EVALUATION OF SUPER EMERGENCIES IN LUNG TRANSPLANTATION IN FRANCE

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Introduction. In 2007, the French Lung transplant task force implemented new rules, Super Urgencies (SU), to allocate lungs preferentially to the patients who are at high-risk of dying, with deteriorating medical conditions and having as indications:

- cystic fibrosis or bronchiectasis;
- Idiopathic or secondary pulmonary fibrosis;
- pulmonary vascular disease.

The objective of these new rules was to decrease deaths on the lung waiting list by favouring the patients who had the worse medical status while, in the same time, not penalizing the other patients.

We reviewed the first 2 years of its use and the impact on the lung transplantation waiting list and 1 year post transplantation survival.

Materials & methods. Patients registered on the waiting list between 2007 and 2009 were included for the descriptive analysis.

For survival comparisons according to period (before and after SU) we considered 4 periods 2000-2003, 2004- June 2006, July 2006 - June 2007 and July 2007 - June 2008.

All requests for SU registered in the national database (Cristal) were analyzed.

Kaplan Meier curves were used to analyse access to transplantation and patient post transplantation survival.

Results. One hundred and eight SU demands were made for 104 patients. The criteria of SU were well defined and no expert refused a demand.

Analysis of the impact of SU in lung transplantation is difficult because these new rules were associated to an increase in the number of patients registered on the waiting list (from 257 in 2006 to 273 in 2009).

Despite an increase in shortage indicators, we didn't observe an increase in the number of deaths on the waiting list.

Period	% death on the waiting list	Median time to transplant (month)	1 year survival rate (%)
2000-2003	22,5	12,3	69
2004-jun06	13,4	4,1	75
jul06-jul07	12,7	4,5	77
jul07-jun08	10,7	4,2	71

We observed a diminution of 1 year post transplantation survival (71% for July 07 - June 07 and 75% for 2004 - June 06) and it mainly related to the patients with the worse medical status (survival for patients with the worse medical status: 75% in 2004 - June 06 versus 73% in July 07 - June 08 while survival for not at risk patients: 67% in 2004 - June 06 versus 56% in July 07 - June 08).

Conclusion. Since the creation of the SU, the access on the waiting list of patients who were at high-risk of dying improved. The study didn't show a negative impact on the non urgent patients. The survival was decreased but it concerned mainly high risk patients.

The analysis will be continued and deepened with more hindsight.

DO WE HAVE TO GO ON TRANSPLANTATING CYSTIC FIBROSIS PATIENTS INFECTED WITH BURKHOLDERIA CEPACIA GENOMOVAR III?

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Burkholderia cepacia complex (Bcc) colonisation is associated with poor outcome among Cystic Fibrosis (CF), patients especially concerning Genomovar III: Cenocepacia. This chronique infection may be an exclusion criteria for Lung Transplantation (LT) in some centers because of the very bad prognosis.

Methods

Between 1993 and 2010, 201 CF patients received LT (n=164) or combined Lung-Liver Transplantation (LLT) (n=37). There were 13 retransplantations. Twenty two patients were colonised with Bcc (11%): 9 men and 13 women of wich 8 were infected with Bcc genomovar III cenocepacia. Median age was 22 (8 to 34 yoa). Twenty patients received bilateral LT and two LLT.

Results

Survival for Bcc non cenocepacia patients was 85% at 3 months, 77% at one year, 60% at 5 years and 37% at 10 years. Survival for cenocepacia patients was 58% at 3 months, 29% at one year and 14% at 3 years.

Seven patients out of 8 infected with Bcc cenocepacia died: six were colonised with Pan resistant strains and died within 5 months of uncontrollable cepacia syndrome. Two had Sensible strain and died of Bronchiolitis Obliterans Syndrome at 2,2 years and 9,8 years after LT.

Conclusion

Mortality among CF patients colonised Bcc Genomovar III is extremely hight and may be a matter of discussion before giving access to a transplantation list. Our results suggest that cenocepacia colonisation with Pan resistant strains might reasonably be kept out LT program due to their short term life expectancy after transplantation.

NOTES

AUTHORS' INDEX

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