Program

12th International Congress on LUNG TRANSPLANTATION

Paris, september 15-16, 2016

Union Internationale des Chemins de Fer - 16, rue Jean Rey, Paris 15e

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FONDATION FOCH

12th International Congress on
LUNG TRANSPLANTATION

Paris, september 15-16, 2016

under the Patronage of

Marshal Foch Foundation
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Contents

Welcome Adress

Dear Colleagues,

The 12th edition of the International Congress on Lung Transplantation will be headed by our two presidents: Pr Geert M. VERLEDEN from Leuven and Pr Tom WADDELL from Toronto, eminent leaders of 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.

Best regards

Dr. Antoine ROUX,
Dr Edouard SAGE,
Dr. Marc STERN

Committees

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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.

General Information

✱ Administrative Secretariat

Office hours:
Thursday, September 15 8:30 a.m. - 6:30 p.m.
Friday, September 16 7:30 a.m. - 4:30 p.m.

After the Congress:

VBCE - Lung Transplantation
43, rue de l'Abbé Groult
75015 Paris
Phone: +33 (0) 1 45 33 60 46
Fax: +33 (0) 1 45 33 57 15
e-mail: secretariat-vbce@vbce.fr

✱ 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.

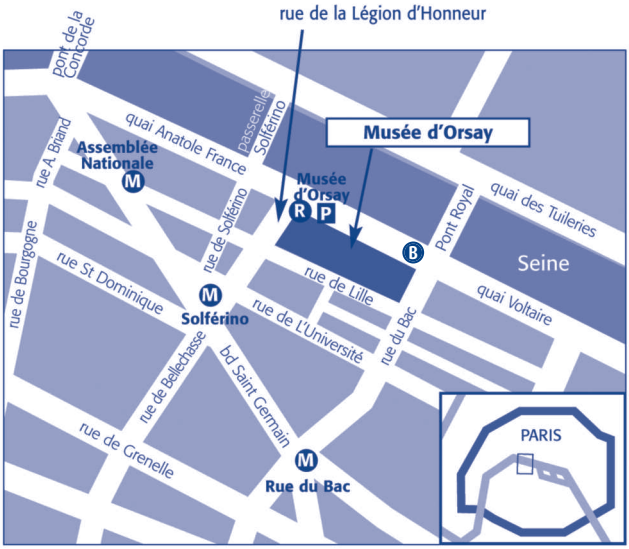
✱ Thursday, September 15

DINNER at the Musée d'Orsay
1 rue de la Légion d'Honneur
75007 Paris

8:00 p.m.

Price per person: 75 €
Reservation on site is possible upon availability.

Enjoy a dinner in the magnificient restaurant of the old station.
The dinner will be preceded by a free visit in the museum.



Ⓜ Métro Station: Solférino (line 12)

Ⓡ RER Station: Musée d'Orsay (line C)

Ⓑ Bus: lines 24, 63, 69, 83, 94

Exhibitors' List

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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

Scientific Program Thursday 15

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14:00	**Hot Topics in Lung Transplantation I** p 18	**Chronic Lung Allograft Dysfunction** 16:05-16:20 Break p 20
16:00	Break	
16:20	**Antimicrobials for Improving Outcomes** p 19	
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Scientific Program Friday 16

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9:00 → 12:30 **Room Louis Armand**

Update of Antibody Mediated Rejection

Chairpersons: Geert M. Verleden (Leuven, Belgium),
Tom Waddell (Toronto, Canada)

9:00 **Welcome**
Antoine Roux, Edouard Sage (Suresnes, France)

9:10 **AMR: A clinical consensus?**
Deborah J. Levine (San Antonio, USA)

9:40 **Pathology of AMR: a unified view?**
Fiorella Calabrese (Padova, Italy)

10:00 Coffee Break

10:20 **De novo DSA: What does it mean and what do we do?**
Jussi Tikkanen (Toronto, Canada)

10:45 **Intrapulmonary anti HLA donor specific antibodies (DSA): correlation with antibody mediated rejection (AMR) in lung transplantation** **O1**
S. Hirschi, J. Olagne, A. Essaydi, T. Degot, A. Schuller, S. Caillard Ohlmann, R. Kessler, A. Parissiadis, M.P. Chenard, F. Calabrese (Strasbourg, France)

10:57 **Persistence of de novo donor specific HLA-antibodies increases the risk of lung allograft dysfunction** **O2**
T. Kauke, M. Schmitzer, N. Kneidinger, C. Neurohr, V. Von Dossow, G. Preissler, R. Schramm, H. Winter (Munich, Germany)

11:09 **Anti HLA: What role in BOS and RAS development**
Robin Vos (Leuven, Belgium)

11:35 **Treatment of established AMR**
Antoine Roux (Suresnes, France)

10:20 → 12:30 **Room List**

Oral Communications

Chairpersons: Benoit Douvry (Suresnes, France),
Mark Greer (Hanover, Germany)

10:20 **Induction or no induction after lung transplantation? Vienna experience** **03**
A. Benazzo, S. Schwarz, G. Muraközy, C. Lambers, G. Lang, S. Taghavi, W. Klepetko, P. Jaksch (Vienna, Austria)

10:32 **Extracorporeal membrane oxygenation in lung transplantation: causes and complications** **04**
J. Fessler, M. Fischler, M. Le Guen (Suresnes, France)

10:44 **Ten-year experience with veno-arterial extracorporeal membrane oxygenation during double lung transplantation** **05**
L.J. Ceulemans, J. De Beule, A. Neyrinck, M. Schetz, W. Coosemans, H. Decaluwé, P. De Leyn, L. Depypere, P. Nafteux, H. Van Veer, B. Meyns, P. Herijgers, F. Rega, B. Meuris, R. Vos, L. Dupont, M. Delcroix, G.M. Verleden, D. Van Raemdonck (Leuven, Belgium)

10:56 **Veno-arterial ExtraCorporeal Life Support (ECLS) after bilateral lung and heart-lung transplantation for pulmonary hypertension** **06**
T. Kortchinsky, S. Mussot, S. Rezaiguia-Delclaux, M. Artiguanave, E. Fadel, F. Stephan (Le Plessis Robinson, France)

11:08 **Altered long term T-cell reactions in patients undergoing extracorporeal membrane oxygenation prior to lung transplantation** **07**
N. Strobl, H. Winter, G. Warnecke, E. Noessner, A. Knoefel, T. Kauke, R. Schramm, R. Hatz, A. Haverich, G. Preissler (Munich, Germany)

11:20 **Comparison of off-pump lung transplantation versus the use of cardiopulmonary bypass: a single centre experience** **08**
A. Page, T. Devine, S. Messer, C. Barbero, P. Catarino, J. Parmar (Cambridge, UK)

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11:32 **Increasing lung donor pool using Ex-Vivo Lung Perfusion (EVLP) technology should decrease the cost of lung transplantation** **09**
C. Keller, T. Gonwa, J. Naessens, L. While, M. Rucci, S. Visscher, R. Daly (Jacksonville, USA)

11:44 **Bilateral lung retrieval from a 6 weeks old baby: the youngest donor in the UK** **010**
E. Pavlushkov, N. Muthialu, H. Spencer, C. Ellis, B. Davis, S. Claydon, H. Garrido, M. Berman (Cambridge, UK)

11:56 **GvHD post-transplant pulmonary for histiocytosis** **011**
F. Garaix, C. Galambrun, N. Stremler, M. Tsimaratos (Marseille, France)

12:08 **Hyperthyroidism after heart transplantation** **012**
M. Barten, S. Schmidt, M. Rybczynski, F.M. Wagner, H. Reichenspurner (Hamburg, Germany)

12:45 → 13:45 **Room Louis Armand**

Antibody Mediated Rejection

symposium sponsored by One Lambda – A Thermo Fisher Scientific Brand

Chairpersons: Ramsey R. Hachem (Saint-Louis, USA),
Antoine Roux (Suresnes, France)

12:45 **Multidimensional approach of antibodies: where are we?**
Carmen Lefaucheur (Paris, France)

13:05 **Antibody Mediated Rejection ISHLT consensus: consequences for the future of LT research**
Ramsey R. Hachem (Saint-Louis, USA)

13:25 **Global risk stratification in solid organ transplantation**
Alexandre Loupy (Paris France)

14:00 → 16:00 **Room Louis Armand**

Hot Topics in Lung Transplantation I

Chairpersons: Peter Jaksch (Vienna, Austria),
Christiane Knoop (Brussels, Belgium)

14:00 **Biomarkers in PAH and timing of transplantation**
Laurent Savale (Le Kremlin-Bicêtre, France)

14:20 **New approaches of the perioperative management of lung transplant patients for PAH**
Olaf Mercier (Le Plessis Robinson, France)

14:40 **Cancer-related death after lung transplantation: the new first cause of mortality**
Tom Waddell (Toronto, Canada)

15:00 **How should we screen solid organ recipient for cancer?**
Jacques Dantal (Nantes, France)

15:20 **Retransplantation: Ethics and optimal management**
Shaf Keshavjee (Toronto, Canada)

16:20 → 18:00 **Room Louis Armand**

Antimicrobials for Improving Outcomes

Chairpersons: Jens Gottlieb (Hanover, Germany),
Clément Picard (Suresnes, France)

16:20 **Can we prevent CLAD with anti-infectives?**
Mark Greer (Hannover, Germany)

16:40 **Reducing CLAD with ALN-RSV01**
Jens Gottlieb (Hannover, Germany)

17:00 **Streptococcus pneumoniae in lung transplantation recipients: colonization, infection, vaccination** **013**
C. Picard, E. Farfour, L. Beaumont, AM. Hamid, B. Douvry, S. De Miranda, D. Grenet, G. Trebbia, F. Parquin, A. Roux (Suresnes, France)

17:12 **EBV lymphoproliferation**
Lionel Galicier (Paris, France)

17:32 **Anti-fungals in lung transplantation - State of the art**
Eliane Billaud (Paris, France)

14:00 → 18:00 **Room List**

Chronic Lung Allograft Dysfunction

Chairpersons: Andrew Fisher (Newcastle, UK),
Antoine Roux (Suresnes, France)

14:00 **The pathophysiology of CLAD development and the role of colonization**
Andrew Fisher (Newcastle, UK)

14:20 **The microbiome in CLAD: results from the Sysclad study**
John-David Aubert (Lausanne, Switzerland)

14:40 **Characterization of a B lymphocyte signature predictive of chronic lung allograft dysfunction: COLT study** **O14**
C. Brosseau, M. Durand, E. Durand, J. Loy, P. Lacoste, P. Royer, S. Brouard, A. Magnan (Nantes, France)

14:52 **What did we learn from the COLT/SysCLAD study?**
Adrien Tissot (Nantes, France)

15:12 **Transcriptome analysis in lung transplantation**
Pierre-Joseph Royer (Grenoble, France)

15:32 **Gastroesophageal reflux disease after lung transplantation: potential risk factors, aetiology and long term outcome** **O15**
B. Schmack, A. Sabashnikov, A. Padukone, A. Weymann, P. Mohite, M. Carby, A. Reed, A.R. Simon, A.F. Popov, S. Soresi (London, UK)

15:45 **Imaging in CLAD: what's new?**
Stijn E. Verleden (Leuven, Belgium)

16:05 Break

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16:20 **DEBATE - Azithromycin treatment after lung transplantation**
- **Prevention is the best option** – Robin Vos (Leuven, Belgium)
- **Treatment is the best option** – Paul Corris (Newcastle-upon-Tyne, UK)

16:50 **New therapies: extra corporeal photophoresis for CLAD**
Peter Jaksch (Vienna, Austria)

17:10 **New therapies: extra corporeal photophoresis for DSA**
Ramsey R. Hachem (Saint-Louis, USA)

17:30 **New therapies: anti-fibrotics**
Geert Verleden (Leuven, Belgium)

8:00 → 12:30 **Room Louis Armand**

Hot Topics in Lung Transplantation II – Focus on Recipient Selection

Chairpersons: Edward Cantu (Philadelphia, USA), Gabriel Thabut (Paris, France)

8:00 **Update on recipient selection guidelines**
John Dark (Newcastle, UK)

8:20 **Pediatric lung transplantation: 25 years of experience** **016**
R. Waseda, P. Jaksch, G. Muraközy, S. Gruber, C. Lambers, A. Benazzo, Z. Szepfalusi, E. Nachbauer, W. Klepetko (Vienna, Austria)

8:32 **Lung-first versus liver-first: a new dilemma in combined organ transplantation** **017**
L.J. Ceulemans, R. Vos, G.M. Verleden, J. Pirenne, A. Neyrinck, D. Van Raemdonck (Leuven, Belgium)

8:45 **Lung transplantation in patients over 70**
Edward Cantu (Philadelphia, USA)

9:05 **Scleroderma: to transplant or not?**
Jérôme Le Pavec (Le Plessis Robinson, France)

9:25 **Lung transplantation after stem cell transplantation**
Mark Greer (Hannover, Germany)

9:45 **Telomerase mutations and lung transplantation**
Raphaël Borie (Paris, France)

10:05 Break

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10:20 **Role of adherence in lung transplantation**
Fabienne Dobbels (Leuven, Belgium)

10:40 **DEBATE - A lung allocation scoring system should be introduced in all countries?**
- **Pro** – Jens Gottlieb (Hannover, Germany)
- **Con** – Gabriel Thabut (Paris, France)

11:20 **Awake ECMO as bridge to lung transplant**
Alberto Benazzo (Vienna, Austria)

11:40 **Pulmonary fibrosis: why is that more difficult and what can we do about it**
Geert Verleden (Leuven, Belgium)

8:00 → 10:00 **Room List**

The Donor Pool: Making the most of what we've got till we get to the future

Chairpersons: François Parquin (Suresnes, France),
Dirk van Raemdonck (Leuven, Belgium)

8:00 **Management of the potential lung donor**
Eduardo Minambres (Santander, Spain)

8:25 **What is a marginal donor nowadays?**
Tom Waddell (Toronto, Canada)

8:50 **Lung transplantation from donors after previous cardiac surgery: ideal graft in marginal donor?** **018**
A. Palleschi, A. Mariolo, M. Montoli, P. Mendogni, D. Tosi, L. Morlacchi, P. Tarsia, F. Valenza, M. Nosotti (Milano, Italy)

9:02 **Lung donation after euthanasia**
Dirk van Raemdonck (Leuven, Belgium)

9:27 **Lung donation following hanging**
Edouard Sage (Suresnes, France)

10:20 → 12:30 **Room List**

Oral Communications

Chairpersons: Elise Cuquemelle (Suresnes, France),
Robin Vos (Leuven, Belgium)

10:20 **SCEDO-LUNG: International practice survey on Scedosporium colonization and infection in lung transplant recipients** **O19**
B. Rammaert, J. Le Pavec, O. Lortholary (Paris, France)

10:32 **Acute RSV infection in lung transplantation recipients: factors associated with a decrease in lung function** **O20**
H. Lafoeste, C. Picard, E. Farfour, L. Beaumont, L. Zemoura, B. Douvry, S. De Miranda, D. Grenet, AM. Hamid, A. Roux (Suresnes, France)

10:44 **Growth and pubertal onset after lung transplant in children with cystic fibrosis** **O21**
S. Abdelkefi, R. Guillemain, V. Boussaud, F. Barthes-Lepimpec, I. Sermet-Gaudelus (Paris, France)

10:56 **Lung retransplantation in Argentina: single center experience** **O22**
A. Bertolotti, R. Ahumada, J.M. Osses, G. Wagner, J. Caneva, G. Parrilla, M. Candioti, R.R. Favaloro (Buenos Aires, Argentina)

11:08 **Basiliximab for the treatment of acute cellular rejection after lung transplantation: a retrospective cohort study** **O23**
A.M. Rabain, A. Senechal, S. Sanchez, F. Thivolet-Bejui, J.F. Mornex (Lyon, France)

11:20 **Immunomodulatory effects of extracorporeal photopheresis are dependent on rejection status: a pilot study** **O24**
M. Barten, J. Garbade, H. Reichenspurner, F.W. Mohr, C. Oelschner, M.T. Dieterlen (Hamburg, Germany)

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11:32 **TGF-β1 in restrictive CLAD: is it important?** **025**
S. Verleden, A. Sacreas, H. Bellon, E. Vandermeulen, T. Heigl, D. Van Raemdonck, G. Verleden, R. Vos, B. Vanaudenaerde (Leuven, Belgium)

11:44 **Analysis of the regulatory T lymphocytes profile as predictive biomarker of the lung allograft chronic dysfunction in humans** **026**
M. Durand, P. Lacoste, C. Brosseau, E. Durand, J. Loy, S. Brouard, A. Magnan (Nantes, France)

11:56 **Security and usefulness of everolimus (ImTOR) associated with low tacrolimus dose to preserve kidney function in pediatrics lung** **027**
F. Garaix, E. Sampol, N. Stremler, M. Tsimaratos (Marseille, France)

12:08 **Autofluorescence bronchoscopy as innovative marker of airway complications after lung transplantation** **028**
L. Rosso, R. Carrinola, A. Palleschi, I. Righi, G. Invernici, M. Cattaneo, M. Pappalettera, F. Briganti, V. Rossetti, M. Nosotti (Milano, Italy)

12:20 **Novel approach for the treatment of GERD after lung transplantation: electrical stimulation of the lower esophageal sphincter** **029**
A. Bertolotti, A. Nieponice, R. Ahumada, A. Badaloni, J.M. Osses, C. Bilder, G. Wagner, R.R.Favaloro (Buenos Aires, Argentina)

14:00 → 16:30 **Room Louis Armand**

Therapeutic Approaches: Old, New and Future

Chairpersons: **Paul Corris** (Newcastle, UK),
Denis Glotz (Paris, France)

14:00 **Tolerance: definition and how to detect it?**
Sophie Brouard (Nantes, France)

14:20 **Complications with CNI and how to deal with them?**
Jussi Tikkanen (Toronto, Canada)

14:40 **Shifting tacrolimus from BID to OD**
- **A nephrologist view -** Dany Anglicheau (Paris, France)
- **A pulmonologist view -** Christiane Knoop (Brussels, Belgium)

15:10 **Review of induction therapy**
Paul Corris (Newcastle, UK)

15:30 **Anticomplement therapy in kidney transplantation**
Denis Glotz (Paris, France)

15:50 **Experience of adoptive Treg/Dendritic cells**
Julien Zuber (Paris, France)

14:00 → 16:05 **Room List**

EVLP: the end of PGD?

Chairpersons: Shaf Keshavjee (Toronto, Canada),
Edouard Sage (Suresnes, France)

14:00 **Pathophysiology and classification of PGD**
Edward Cantu (Philadelphia, USA)

14:20 **Logistical EVLP: the standard lung for transport and logistics**
Anne Olland (Strasbourg, France)

14:40 **EVLP to sterilize lungs**
Andrew J Fisher (Newcastle, UK)

15:00 **Drug treatment during EVLP to reduce PGD**
Dirk van Raemdonck (Leuven, Belgium)

15:20 **Cell-free hemoglobin: a new therapeutic target for prevention of primary graft dysfunction?** **O30**
C.M. Shaver, N. Wickersham, J.B. Mcneil, H. Nagata, J.L. Kuck, J.A. Bastarache, L.B. Ware (Nashville, USA)

15:32 **Association of long pentraxin-3 with pulmonary hypertension and primary graft dysfunction in lung transplant recipients** **O31**
J. Diamond, K. Ramphal, E. Cantu, M. Porteous, S. Palmer, P. Shah, M. Crespo, C. Hage, A. Weinacker, Y. Suzuki, V. Lama, K. Wille, L. Ware, S. Bhorade, L. Snyder, J. Orens, J. Christie, S. Kawut (Philadelphia, USA)

15:45 **Genetically modified lungs and the future of EVLP**
Shaf Keshavjee (Toronto, Canada)

P1 **Non-tuberculous mycobacteria infection and lung transplantation in cystic fibrosis: a worldwide survey of clinical practice**
A. Tissot, M. Thomas, P. Corris, M. Brodlie (Newcastle, UK)

P2 **Heart rate variability in bilateral lung transplant recipients**
T. Fontolliet, P. Gianella, V. Pichot, P.M. Soccal, G. Ferretti, F. Lador (Geneva, Switzerland)

P3 **Lung transplant projected commercial claim costs for 2016 in the United States**
S. George, A. Holland, S. Bentley, E. Claxton (Tampa, USA)

P4 **Conversion from tacrolimus twice-daily to tacrolimus once-daily in stable lung transplantation - Hungarian experiences**
N. Eszes, V. Müller, Z. Kováts, E. Csiszér, Z. Süttö, K. Czebe, G. Muraközi, G. Lang, G. Losonczy, A. Bohács (Budapest, Hungary)

P5 **Secondary pulmonary alveolar proteinosis after lung transplantation: A series with review of literature**
Q. Philippot, R. Borie, A. Cazes, M.P. Debray, D. Sroussi, C. Dupin, G. Dauriat, G. Jebrak, Y. Castier, P. Mordant, G. Thabut, H. Mal, O. Brugière (Paris, France)

Abstracts

INTRAPULMONARY ANTI HLA DONOR SPECIFIC ANTIBODIES (DSA): CORRELATION WITH ANTIBODY MEDIATED REJECTION (AMR) IN LUNG TRANSPLANTATION

S. Hirschi[4], J. Olagne[2], A. Essaydi[1], T. Degot[4], A. Schuller[4], S. Caillard Ohlmann[2], R. Kessler[4], A. Parissiadis[1], M.P. Chenard[3], F. Calabrese[5]

1- Department of Histocompatibility, 2- Department of Nephrology, 3- Department of Pathology, 4- Department of Respiratory Diseases, Strasbourg University Hospital, Strasbourg, France
5 Department of Pathology, Padova University Hospital, Padova, Italy

Aim of the study: Recent advances in diagnosis of AMR in lung transplantation have been made, emphasizing a multidisciplinary approach and defining the most frequent histological features. However, the absence of diagnostic tools with an acceptable level of confidence, the lack of sensitivity of C4d lung deposition and the presence of confounding factors are source of delayed diagnosis and impaired prognosis. We hypothesized that identification of DSA in pulmonary graft tissue (gDSA) might be correlated with AMR.

Methods: From January 2009 to April 2016, the patients from our cohort with circulating DSA who underwent transbronchial lung biopsies with frozen samples for clinical suspicion of AMR or systematic follow-up were retrospectively analyzed. Clinical history, histopathology, C4d and gDSA were studied. The gDSA were eluted from non-fixed frozen biopsies after washings to remove any contamination, as described in kidney transplantation. The DSA antibodies were identified using the Luminex technique (LSA, One Lambda). The diagnosis of AMR was reviewed by a committee of expert European pathologist panel and final diagnosis was made according to recent ISHLT consensus report. Patients were classified as probable AMR (graft dysfunction, circulating DSA, consistent histopathology and either C4d deposition or other disease excluded), possible AMR (graft dysfunction, circulating DSA, and consistent histopathology or other disease excluded), no AMR (circulating DSA, other diagnosis or absence of rejection). Then the presence of gDSA was analysed.

Results: Nine patients were included in the study. Circulating DSA at the time of biopsies had a class II specificity in 7 patients, class I and II specificities in 2 patients. Maximum intensity immunofluorescence ranged from 1000 to 16 000. Five patients, 3 cystic fibrosis, 1 pulmonary fibrosis and one chronic obstructive pulmonary disease, were classified as AMR (3 probable and 2 possible). All had positive gDSA. Four patients, 3 chronic obstructive pulmonary disease and 1 cystic fibrosis were classified as "no AMR". The first two had bronchiolitis obliterans syndrome (BOS) without any cellular infiltrate but presence of gDSA, 1 had a graft dysfunction with acute fibrinous organizing pneumonia without gDSA, and one had no graft dysfunction and no gDSA (systematic biopsy). It is not excluded that the 2 BOS cases with positive gDSA were "end stage" AMR. The specificities of gDSA were similar to the circulating DSA in all patients.

Conclusion: These results suggest a good correlation of gDSA with AMR, requiring however further confirmation by prospective studies on larger multicenter cohorts.

PERSISTENCE OF DE NOVO DONOR SPECIFIC HLA-ANTIBODIES INCREASES THE RISK OF LUNG ALLOGRAFT DYSFUNCTION

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Background: The impact of donor-specific (DSA) and non-donor-specific (nDSA) anti-HLA-antibodies diagnosed by solid-phase assays on outcome in patients after lung transplantation is still a matter of debate. We hypothesize that persistent as opposed to transient appearance of de novo DSA are associated with a dismal prognosis for survival following lung transplantation.

Methods: We investigated the clinical relevance of HLA-antibodies on lung allograft outcome prospectively in 72 recipients who were transplanted between 2013 and 2015. The presence of HLA-antibodies was analyzed regularly prior and after (3 weeks, 3 months, 6 months, 9 months, 12 months and 18 months) transplantation and in case of graft dysfunction. Lung function, survival of patients and risk factors for the development of DSA were assessed within a median follow-up of 21 months.

Results: The majority of recipients (83%) were non-immunized at the time of transplantation. Two patients (3%) were transplanted with preformed weak DSA. Twenty-three patients (32%) developed de novo DSA and 14 (19%) developed de novo nDSA. In 13 out of 23 patients (56%) DSA disappeared after a median of 114 days. Forty-four % (10/23) of the patients had persistent DSA post-transplant. Time to first DSA appearance was earlier in the case of transient DSA compared to persistent DSA (51.9 ± 62.1 vs. 177.3 ± 156.2 days, p=0,035). Risk factors for DSA development seem to be the concurrent existence of nDSA (p=0.001) and change in the immunosuppressive regime from Tacrolimus to Cyclosporine A in the first 3 months after transplantation (p=0.03). DSA impaired patient survival in comparison to controls (1-year patient survival 83% vs. 97%; p=0.078). Remarkably 1-year survival of patients with persistent antibodies was only 60%. Patients with persistent DSA had significantly reduced survival compared to those without DSA or with transient DSA (p=0,001).

Conclusion: De novo DSA are associated with an increased risk for impaired graft function. Persistence of DSA in the first year after transplantation seems to be more harmful for lung allograft dysfunction than temporary DSA at an early stage. Further studies are needed to elucidate the difference between termporary and persisting DSA following lung transplantation.

INDUCTION OR NO INDUCTION AFTER LUNG TRANSPLANTATION? VIENNA EXPERIENCE

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Purpose

According to the Registry of ISHLT, about 50% of patients transplanted in the last 10 years received some type of induction therapy. The most used agents are IL2R Antagonists but interest for Alemtuzumab is increasing. In our study we reviewed all adult lung transplantations from 2007 to 2014 and we tried to understand the impact of induction immunosuppression on short-term and long-term outcomes.

Methods

Medical records of 780 patients were reviewed. The following outcomes were examined: patient survival, ACR, LB and CLAD incidence, malignancies, kidney function and diabetes. Infection incidence, perioperative outcomes and long-term comorbidities were also examined.

Results

446 Patients with a complete follow-up were included in our analysis. 231 received Alemtuzumab (51.80%), 50 Thymoglobulin (11.20%) and 165 didn't receive any induction (37%). Patients receiving this agent showed a better 5-years survival (62,9% for No induction, 70,7% for ATG and 77% for Alemtuzumab) (p=0,004, they had a greater freedom from ACR (p<0.001) and LB (p<0,01) and they showed a better freedom from CLAD compared to the other groups (p<001) (5-years freedom from CLAD is 50,6% for No induction, 84,7% for ATG and 72,4% for Alemtuzumab). Alemtuzumab group had the least rate of kidney insufficiency (no: 52.2%; ATG: 60%; Alemtuzumab: 36.6%; p=0.001) and in parallel, at a linear mixed model, no induction group (p<0.001) and ATG group (p=0.030) showed a significant increase of Creatinine in the long-term follow-up. ATG and No induction groups showed an higher infection rate in the first year (No: 35,3%; ATG: 36,2%; Alemtuzumab: 21,4%; p<0.001). At the multivariable analysis, independent from other covariates, Alemtuzumab improved survival (HR=0,619; CI=409-937; p=0,023) and along with ATG, it was protective against CLAD (ATG: HR=0,301, CI =0,144-631, p=0,001; Alemtuzumab: HR =0,556 CI=0,356-0,868 p=0,01).

Discussion

From our retrospective analysis, we deduce that any induction therapy improves long-term results and survival after transplantation. In particular Alemtuzumab seems to improve patient survival, ACR, LB and CLAD incidence independent from other factors. Moreover, in our cohort, Alemtuzumab with reduced maintenance IS was associated with better kidney function and less infections in the first year.

EXTRACORPOREAL MEMBRANE OXYGENATION IN LUNG TRANSPLANTATION: CAUSES AND COMPLICATIONS

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An intraoperative hemodynamic or respiratory acute event may require cardiopulmonary assistance during lung transplantation (LTx). Over the last years, Extracorporeal Membrane Oxygenation (ECMO) has widely replaced cardiopulmonary bypass in this setting (1, 2). ECMO, mostly femoro-femoral, can be withdrawn at the end of the surgical procedure, or it may need to be continued in the Intensive Care Unit (ICU). This study assesses the predictive factors of ECMO and its complications.

This monocenter cohort includes all patients undergoing a bilateral lung transplantation from January 2012 to July 2015, excluding those who had a preoperative ECMO. We defined three groups: patients without need of ECMO during surgery ("no ECMO"), patients with ECMO removed at the end of surgery ("short ECMO"), and patients with ECMO maintained in the ICU ("long ECMO"). Results are shown as number (percentage) or median [first and third quartiles] and compared with Fisher's exact test and Mann-Whitney test. Multivariate analysis was used to explore predictive factors for ECMO in LTx.

Among the 197 studied patients, 105 patients did not need ECMO, 55 a "short ECMO", and 37 a "long ECMO". Preoperative pulmonary hypertension was an independent factor for ECMO requirement, OR: 2.11; 95% CI: (1.13-3.94), whereas cystic fibrosis and emphysema were protective factors, respectively, OR: 0.20; 95% CI:(0.08-0.5) and OR: 0.12 95% CI: (0.04-0.33). The in-hospital length of stay was similar between "no ECMO" and "short ECMO" groups, but it was longer for the "long ECMO" group (29 [23-37], 30 [24-53], and 48 [31-73] respectively; p<0.001). Post-operative complications were similar between the "no ECMO" and "short ECMO" groups but was higher in the "long ECMO" group, particularly stage 3 primary graft dysfunction (PGD3) (Table 1). In-hospital mortality was similar between "no ECMO" and "short ECMO" groups, but was higher for "long ECMO" group (2 (2%), 2 (3.6%), and 6 (16%) respectively; p<0.001).

Short ECMO is safe and did not worsen patients' outcome; this suggests that we should not hesitate to resort to its implementation as soon as standard medical treatment fails to treat a hemodynamic or respiratory event. Maintenance of ECMO after the surgical procedure is associated to poorer outcome.

Table 1: Post-operative complications

	No ECMO	Short ECMO	Long ECMO	P-value
Hemorrhagic shock	4 (4%)	3 (5%)	10 (27%)	< 0.001†‡
Lower limb complications	2 (2%)	1 (2%)	6 (16%)	0.002†‡
Septic shock	13 (12%)	13 (23%)	16 (43%)	< 0.001†
Grade 3 of primary graft dysfunction	10 (10%)	15 (27%)	24 (65%)	< 0.001□†‡

□ : if difference between no ecmo and short ecmo groups
† : if difference between no ecmo and long ecmo groups
‡ : if difference between short ecmo and long ecmo groups

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TEN-YEAR EXPERIENCE WITH VENO-ARTERIAL EXTRACORPOREAL MEMBRANE OXYGENATION DURING DOUBLE LUNG TRANSPLANTATION

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Purpose: Over the last ten years, veno-arterial extracorporeal membrane oxygenation (ECMO) has replaced cardiopulmonary bypass (CPB) in our center for double lung transplant (DLTx) recipients requiring extracorporeal life support (ECLS). The aim of this single-center retrospective study was: 1/ to analyze our experience with intra-operative ECMO; and 2/ to compare the outcome with non-ECMO DLTx.

Methods: From 01/2005-01/2015, 498 DLTx were performed. Patients transplanted on veno-venous ECMO or CPB and combined-organ or lobar transplants were excluded. DLTx indications, demographics, complications, ICU/hospital stay, and 5-year patient survival were compared between the ECMO and non-ECMO group. The indication, timing and technique of ECMO were analysed. Results are reported as median.

Results: ECMO patients were slightly younger than non-ECMO patients (52y vs. 55y; $p<0.05$). Donor age and type of donor were similar between both groups. ECLS with ECMO was mostly indicated for pulmonary fibrosis (PF) (36% vs. 16% in non-ECMO group; $p<0.0001$) and idiopathic pulmonary arterial hypertension (IPAH) (15% vs. 0% in non-ECMO group; $p< 0.0001$). 59% of patients in the non-ECMO group were transplanted for emphysema (vs. 26% in the ECMO group). Patients after ECMO had more postoperative complications than non-ECMO group with a higher rate for tracheostomy (19% vs. 4%; $p<0.0001$) and re-intervention for hemothorax (22% vs. 8%; $p<0.001$). This higher complication rate in the ECMO group contributed to longer ICU (13d vs. 7d; $p<0.0001$) and hospital stay (35d vs. 27d; $p<0.0001$) than in the non-ECMO group. Overall 5-year survival was 78% (ECMO) versus 85% (non-ECMO); $p<0.01$. Timing of ECMO placement could be categorized in three groups: A/ pre-emptive, at start of DLTx (n=37: 41% PF; 38% IPAH); B/ first-lung implantation (n=28: 40% PF; 29% emphysema); C/ second-lung implantation (n=29: 41% emphysema; 31% PF). Central cannulation was performed in 80%.

Conclusions: Veno-arterial ECMO support is a valuable ECLS option used in 21% of DLTx, mostly indicated in patients with IPAH or PF. Although long-term outcome was very satisfactory, ECMO patients had a slightly inferior long-term survival than the non-ECMO group. This may be related to the specific indication for DLTx and complicated post-operative period in this patient cohort and will be further analysed in a multivariate analysis.

VENO-ARTERIAL EXTRACORPOREAL LIFE SUPPORT (ECLS) AFTER BILATERAL LUNG AND HEART-LUNG TRANSPLANTATION FOR PULMONARY HYPERTENSION

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Purpose

The postoperative course of bilateral lung and heart-lung transplantation for pulmonary hypertension could be complicated by circulatory failure and pulmonary graft dysfunction both associated with a high mortality rate. Extracorporeal life support (ECLS) is increasingly use in order to supply hemodynamic and oxygenation deficiencies. Results of lung transplanted patients treated with ECLS are promising but previous studies have included only few patients with pulmonary hypertension. The primary end-point was the survival rate at 30-day and 1-year in lung transplanted patients treated with veno-arterial ECLS in the post-operative period, compared with controls. The secondary end-points were the occurrence of nosocomial infections, bleeding and acute renal failure.

Methods

We retrospectively studied all lung transplanted patients for pulmonary hypertension between 2008-2013. Patients were divided into 2 groups according to the need of ECLS in the postoperative period. Mortality rates at 30-day and 1-year were recorded. Occurrence of nosocomial infections, bleeding and need of renal replacement therapy were also noted. Statistical analysis included survival after transplantation estimated by the Kaplan-Meier method, using the log-rank test.

Results

During the study period, 93 patients were transplanted for pulmonary hypertension (heart-lung=29, bilateral lung=64). 28 (30%) required ECLS in the postoperative period with a median delay of 0 [0-6 hours] days. Control patients had a better 30-day survival rate than ECLS patients (95.0% vs 78.5%); p=0.02) and also a better 1-year survival rate (83% vs 64%; p=0.005). Nosocomial infections was higher in ECLS patients (79% vs 48, p=0.0006) as the bleeding complications (43% vs 17%, p=0.008). There was no difference for need of renal replacement therapy between the two groups (11% vs 17%; p= 0.54).

Conclusion

Despite a better survival in control patients, veno-arterial ECLS is a useful and efficient treatment for pulmonary graft dysfunction associated with hemodynamic failure in heart-lung transplanted patients. However, ECLS patients suffered for more infectious and bleeding complications.

ALTERED LONG TERM T-CELL REACTIONS IN PATIENTS UNDERGOING EXTRACORPOREAL MEMBRANE OXYGENATION PRIOR TO LUNG TRANSPLANTATION

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Purpose: Extracorporeal membrane oxygenation (ECMO) represents a life-saving therapy in selected recipients waiting for lung transplantion (LTX). Although associated with strong inflammatory reactions, immunological consequences of perioperative ECMO-use in LTX have not been analyzed, so far. Hence, T-cell responses and rejection episodes were analyzed in LTX recipients supported by ECMO.

Methods: In total, 87 (m/f: 42/45, age: 53 ± 1y, LAS: 47 ± 2) patients were included in the study. Seven patients (age: 42 ± 6y, LAS: 77 ± 8) received ECMO-therapy in combination with mechanical ventilation before LTX (ECMO: 624 ± 216h; ventilation time (VT): 429 ± 187h) and during/after LTX (ECMO: 168 ± 79h; VT: 610 ± 171h), 33 patients (age: 56 ± 1y, LAS: 52 ± 3) were supported by ECMO-therapy after LTX (ECMO: 89h ± 39h; VT: 434 ± 101h), while 47 recipients (age: 50 ± 2y, LAS: 40 ± 1) were transplanted without ECMO (VT: 365 ± 125h), respectively. Blood samples for leukocytes, CRP and flow cytometry analysis of helper (Th: CD3+/CD4+; Th1: CD3+/CD4+/IFN-γ+; Th2: CD3+/CD4+/IL-4+), cytotoxic (CTL: CD3+/CD8+), and regulatory T-cells (Treg: CD3+/CD4+/CD25+/FoxP3+), were retrieved prior to LTX (day 0) and 7, 14, 21, 90, 180 and 365 days after LTX, respectively. Lung function tests were done in the same intervals. Patients treated with steroids due to a biopsy proven (A×1/ B×1) and/or clinical rejection episode (FEV1-loss) were defined positive for acute rejection (AR). Mean follow up time was 292 ± 12 days. Data are given as mean ± SEM.

Results: ECMO-bridging was associated with a higher rate of AR (28.6%) compared to patients treated with ECMO perioperatively (21.2%) and non-ECMO patients (21.3%). This was accompanied by a sustained reduction of the CD4+/CD8+-ratio, significantly decreased already on day 0 when compared to perioperative and non-ECMO patients (1.2 ± 0.2 vs. 3 ± 0.7 and 2.6 ± 0.4), remaining suppressed until day 365 (1 ± 0.2 vs. 1.7 ± 0.4 and 2 ± 0.2). While group differences were absent in Tregs, bridged patients revealed a trend towards an increased Th1-cell frequency from day 180 to day 365 (+62.5% to +64.4% vs. perioperative ECMO and +30.9 to +74.6% vs. non-ECMO). Overall survival and graft function were not significantly different between the groups.

Conclusion: ECMO prior to LTX triggers an altered T-cell response, detectable as long as one year after LTX. Although the small sample size limits the explanatory power, the observed shift of the CD4+/CD8+-ratio in conjunction with a higher proportion of rejections indicated an augmented immune response. Interestingly, ECMO therapy starting at the time of LTX did not induce these changes, which might be related to the immunosuppressive therapy initiated simultaneously with the establishment of the extracorporeal circuit.

COMPARISON OF OFF-PUMP LUNG TRANSPLANTATION VERSUS THE USE OF CARDIOPULMONARY BYPASS: A SINGLE CENTRE EXPERIENCE

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Purpose of the study: To investigate the differences in outcomes following the elective use of cardiopulmonary bypass (CPB) versus off-pump when performing double lung transplantation (LTx) in a large volume single centre.

Methods: A total of 139 bilateral LTx were performed at our centre during the period September 2011 to February 2016 (CPB, n=42 and off-pump, n=97). A retrospective review of prospectively collected data was performed. Nearest neighbour 1:1 matching was used to identify a cohort of patients who were operated on off-pump that had matching donor and recipient characteristics to those patients that underwent bilateral LTx with CPB (n=42). All patients were analysed on an intention to treat basis. Normally distributed continuous variables were compared using an unpaired t-test and a Mann-Whitney U-test for non-normally distributed variables. Categorical variables were compared using Fisher's exact tests for analysis. Patient cohort survival was analysed with Kaplan-Meier assessment and a log-rank test was used to compare cumulative survival estimates.

Results: Pre-operative group demographics were sufficiently matched to ensure comparability between donor and recipient characteristics including recipient/donor age, sex, cause of donor death, donor smoking status, ischaemic time and recipient diagnosis.
Post-operatively, patients who underwent off-pump bilateral LTx had significantly less blood loss than those who utilised a CPB strategy – 778 mls vs. 1312 mls, (p=0.002). Both, total hospital stay and the length of time spent in the intensive care setting was markedly reduced in patients who underwent off-pump surgery – 27.2 days vs 35.6 days (p=0.005); 6.7 days vs. 16.1 days (p<0.001). This may be related to an increased period of ventilatory support that was required for patients who underwent surgery on CPB – 65.3 hrs vs. 126 hrs (p=0.017). There were no significant differences noted in rates of return to theatre, post-operative renal impairment, rejection episodes or airway complications.
Cumulative survival at 1 year and 5 years was significantly worse in patients who underwent bilateral LTx using CPB (p=0.0057, p=0.0163).

Conclusion: Our results suggest that in patients who require bilateral LTx, an off-pump strategy where appropriate may confer a significant survival advantage at 1 and 5 years following transplantation.
In our experience, off-pump bilateral LTx has been shown to be associated with decreased blood loss post-operatively, which may reduce the need for blood products. Furthermore, this treatment strategy is associated with a significantly decreased utilisation of intensive care resources with a shorter length of stay which may confer yet another cost advantage for opting for such a strategy in the appropriately selected patient.

INCREASING LUNG DONOR POOL USING EX-VIVO LUNG PERFUSION (EVLP) TECHNOLOGY SHOULD DECREASE THE COST OF LUNG TRANSPLANTATION

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Table 1	Period 1 05/05 - 8/08	Period 2 09/08 - 12/11	Period 3 01/12 - 04/15
Number Patients	152	186	148
LAS at LIsting	41 + 13	42 + 14	48 + 20
LAS at Transplant	45 + 17	51 + 19	58 + 22
Pre-Tx. ICU (%)	5%	12%	16%
LOS (days)	16 + 17	23 + 29	31 + 33
ICU days	5 + 7	12 + 18	17 + 25
Re-Admission Rate	34%	46%	48%

Purpose of the Study: Since introduction of the Lung Allocation Score (LAS) patients receiving lung transplantation have had increased serity of illness and increased resource utilization. EVLP can increase organ supply but adds increased cost. We analyzed the effect of LAS over time on costs of transplant to determine the financial effect that EVLP could have on the cost of transplantation.

Methods: 486 patients transplanted at Mayo Clinic (Florida and Minnesota) after institution of LAS were studied retrospectively. LAS, LOS (Lenght of Stay), transplant characteristics and cost for transplant hospitalization were studied during 3 different periods: Period 1: (5/05-8/08), Period 2: (9/08-12/11) and Period 3: (1/12-4/15). A regression model was utilized to correlate LAS with these factors and costs adjusted for time and inflation.

Results: From 5/2005 to 4/2015 there were 486 lung transplants Table 1 shows results of the analysis.
There was an increase of LAS at listing and transplant, number of patients transplant from the ICU, LOS, ICU days and readmission rate. All comparisons had $P<0.01$. LAS score was significantly correlated with all these changes. Statistical modeling demonstrated the correlation of LAS with cost of transplant adjusted for time and inflation. Analysis of this model demonstrated costs increased 9.5% for every 10 point increase of LAS at transplant.

Conclusions: In our center, LAS scores ae increasing, patients deteriorate significantly on the waiting list, and more are transplanted critically ill in ICU. This has increased LOS, ICU days post-transplant and 30-day readmission rate. These changes as well as cost are correlated with LAS.
EVLP has the potential to increase the number of lung donors available, which should allow patients to be transplanted earlier (lower LAS), and before suffering critical functional deterioration. Our model predicts cost-savings post transplant, which should overcome the added cost of EVLP.

BILATERAL LUNG RETRIEVAL FROM A 6 WEEKS OLD BABY: THE YOUNGEST DONOR IN THE UK

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Fourty-one-day-old male infant, (height 60 cm, weight 4 kg) died of cerebral oedema secondary to E.coli meningitis and bacteraemia. Presented on 13 post birth day with irritability, refusal to feed and oliguria. Cerebro-spinal fluid and positive blood cultures for E.Coli, Staph.epiderm and Stenotrophomonas maltophilia in tracheal aspirate. IV antibiotics (Cefatoxime, Amikacin, Meropenem) were commenced for 3 weeks. The patient was ventilated for 26 days in total.

The diagnosis of death by neurological criteria was made using the Academy of Medical Royal Colleges Code of Practice. In view of the immaturity of the newborn infant's respiratory system, the following precautionary measure should be considered regarding the apnoea test: a stronger hypercarbic stimulus is used to establish respiratory unresponsiveness. Specifically, there should be a clear rise in the arterial blood partial pressure of carbon dioxide (PaCO2) levels of >2.7 kPa (>20 mm Hg) above a baseline of at least 5.3 kPa (40 mm Hg) to >8.0 kPa (60 mm Hg) with no respiratory response at that level.

Preoperative assessment included the following: arterial gases; pO2 50.4 kPa, pCO2 4.9 kPa, on FiO2 100%, PEEP 5 cm H2O; fiberoptic bronchoscopy showed no secretions nor mucosal inflammation; CXR: clear lung fields and pleural spaces; normal ECG; transthoracic echocardiography did not demonstrate any major structural anomalies and showed good overall systolic function although high doses of inotropes (Adrenaline 0.18 and Noradrenaline 0.30 mcg/kg/min).

Both abdominal and cardiothoracic teams were involved. Due to the size of the donor, the dissection phase was performed consecutively: chest was open first. Inspection revealed dense adhesions in pericardial cavity, purulent left hemithorax effusion (negative Gram-stain), no consolidation in the lung. Good inflation/deflation test. Decision was made to retrieve the lungs. The heart was deemed not suitable for transplantation.

Following administration of Heparin and Epoprostenol, combined with numerous attempts to cannulate the abdominal aorta for kidney perfusion, haemodynamic instability ensued requiring cardiac massage to maintain cardiac output. Following decompression of the heart, antegrade pneumoplegia was administred. After cardiectomy, retrograde pneumoplegia and explantation of the lungs were carried out using standard technique. The following solutions were used for preservation: Heparin - 1500 Units, Perfadex - antegrade 300ml, retrograde 100mls, Epoprostenol - 50mcg bolus and 150mcg with Perfadex

The recipient, 4-month-old infant with alveolar capillary dysplasia. Severe pulmonary hypertension with supra-systemic RV pressures pre-op. Transplant done via bilateral thoraco-sternotomy on cardiopulmonary bypass, cooling to 30 degrees. Elective support post operativelly with nitric oxide. Over the following 48 hours, weaning of the nitirc oxide and inotropic support. Currentlly making good progress.

Lung procurement from a 6-week-donor with infectious complications and prolonged ventilation is a challenging undertaking but can be successful and should be attempted whenever possible given the paucity of organs available for paediatric recipients.

GvHD POSTTRANSPLANT PULMONARY FOR HISTIOCYTOSIS

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Introduction

We report the clinical case of a child who died after GvHD post-transplantation (TxP) in the context of histiocytosis.

Results

This is a 5 years old child, treated for severe pulmonary histiocytosis form by 4 monthly courses of 5 days Leustatine 5 mg/m2/day (total dose =97.3 mg/m2). Because of the isolated pulmonary form, the lack of response to chemotherapy, and the need for invasive ventilation, she's listed on TxP-waiting list and grafted four months after (two months after last leustatine cure) from a male donor. The initial outcome was favorable. At d+30 post-TxP, the child had fever, normal LBA. Gradually she developed severe diarrhea, erythrodermia and cholestasis. Diagnostic of acute GvHD was confirmed by mixed chimerism in total blood sample, digestive and skin biopsy. Despite corticosteroid (5 mg/kg/d), high level of cyclosporine, azathioprine and photophoresis, severe aGvH (Glucksberg grade III) progress with ophthalmic sicca syndrome and major exudative enteropathy. Mabthera couldn't contain EBV lymphoproliferation and the child died 44 days after the diagnosis of GvHD. All blood cell components had been irradiated and including those for the TxP's CEC.

Discussion

We suggest than profound lymphopenia related to cladribine before transplantation allowed stem cell engraftment of the donor and occurrence of severe GvH in context of HLA incompatibility. So it should be interesting to evaluate degree of immunodeficiency before TxP and wait when it is possible lymphocyte reconstitution.
As described in previous studies, the prognostic of post-transplant GvHD is fatal despite aggressive immunosuppressive treatment.

HYPERTHYROIDISM AFTER HEART TRANSPLANTATION

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Background

Hyperthyroidism is a common side effect after amiodarone therapy with varying clinical symptoms up to thyreoid crisis. Immunosuppressive drugs like tacrolimus and prednisolone are known to inhibit the pathogenesis of autoimmune disorders or are used to treat hyperthyroidism, respectively. However, here we report about a series of five patients who stopped amiodarone therapy pre-transplant but developed hyperthyroidism after heart transplantation (HTx) for the first time.

Case Reports

Five patients were diagnosed as amiodarone-induced hyperthyroidism although the last treatment with amiodarone was before HTx.
After HTx all patients were treated with an immunosuppressive drug regimen consisting out of tacrolimus (n=4) or cyclosporine (n=1) plus mycophenolate mofetil (2–3 g/day) and prednisolone (12.5-55 mg/day).
Four patients were treated with amiodarone till transplantation. Three of them developed a hyperthyroidism 1 to 3 months post-HTx, whereas one patient developed a late-onset hyperthyroidism after 11 months. Interestingly, one patient stopped amiodarone therapy 16 months before HTx but also developed a hyperthyroidism 3 months post-HTx.
Four of the patients presented with drug resistant symptoms of hyperthyroidism and, consequently, a (hemi-) thyroidectomy was performed. Only one patient could sufficiently treated with injection of dexamethasone into the thyroid combined with thyreostatic therapy.

Summary

Our study showed that patients with amiodarone therapy pre-HTx are at risk to develop hyperthyroidism after HTx. Although tacrolimus and prednisolone are known to reduce the risk for thyroid autoimmune disease, immunosuppression did not prevent progression to thyroid hyperactivity independent of time interval to last amiodarone treatment. Further studies are needed to investigate the potential role of the immunosuppressive drugs in patients treated with amiodarone pre-HTx.

STREPTOCOCCUS PNEUMONIAE IN LUNG TRANSPLANTATION RECIPIENTS : COLONIZATION, INFECTION, VACCINATION

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Background

Streptococcus pneumoniae (Sp) is the most frequent agent in community aquired pneumonia. Transplant recipients have an increased risk. We present an overview of Sp infection in LT recipients a single center.

Material and methods

Retrospective study including all consecutive LT recipients with at least one isolate of Sp in a bacteriological sample (respiratory tract, hemoculture) and/or urinary antigen testing between 2010 january the first and 2016 may the first. In order to assess the efficiency of vaccination, the prevalence of isolates is analyzed depending with the prevalence of vaccination.

Results

Sp was identified in 85 samples from 59 patients during the study period. In 9 cases, isolates have been made during the immediate post-operative course. Pneumonia was present in 24 cases. Blood culture were positive in only 2 cases. ICU admission was required in 6 cases. Since 2013, 65% of the cohort of LT recipient of the center received the conjugate vaccine. A survey is ongoing tho asses the impact of vaccine on bacteriological isolates and clinical events.

Discussion and conclusion

Sp colonization and infection are frequent in LT recipients. Increased rate of vaccination could contribute to lower the incidence.

CHARACTERIZATION OF A B LYMPHOCYTE SIGNATURE PREDICTIVE OF CHRONIC LUNG ALLOGRAFT DYSFUNCTION: COLT STUDY

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The apparition of chronic lung allograft dysfunction (CLAD) is the main complication after lung transplantation (LT) and remains the most common cause of graft failure and death. Currently, the available immunosuppressive therapies cannot prevent the occurrence of CLAD in many patients (50% at 5 years). Conversely, some LT recipients, remain free of CLAD for a long time, and are considered as stable (STA). In kidney transplantation, we have already identified a predictive T-cell and B-cell signature of stability as well as allograft dysfunction. Our study aims to identify and validate predictive B lymphocyte signatures of CLAD in order to identify and lighten the risk of chronic allograft dysfunction and allow for early intervention before irreversible damages.

To this end, PBMCs from the COhort in Lung Transplanted patients (COLT) were immunophenotyped before LT, one month after LT, at the visit for which CLAD was diagnosed (V-CLAD), 6 months before and 6 months after V-CLAD, in order to have a longitudinal time course of the pathology. Blood from patients with long-term functional stability were also analyzed as control (STA) such as blood from healthy volunteers (HV). Cells will were stained for the "classical" B-cell markers CD19, CD27, CD38, CD138, CD22, CD24, IgD, and IgM to determine the percentage of B-cells, transitional, naive, plasmablast and memory. CD5, granzyme B and CD9 were also added to the mix to determine the percentage of regulatory B cells (Breg).

STA patients had twice less regulatory B cells CD24hi/CD38hi than HV (38% ± 7%) which can be explain by the use of immunosuppressive treatment. However, patients with CLAD had almost loss all their regulatory B cells (10% ± 5% compared to HV).

Regulatory T cells have long been the focus of all attention in the maintenance of tolerance, but recently a new subset of B cells have been identify as regulatory. Here we clearly show a defect in Breg in patients with allograft dysfunction which could explain (en partie) the lack of regulation of inflammation in these patients. An early prediction of CLAD based on principles of systems biology and personalized medicine would represent a major breakthrough and open a new area marked by early interventions based on risk stratification and personalized pathways modulation. Early recognition and specific intervention in patients at risk of CLAD would undoubtedly improve outcomes.

GASTROESOPHAGEAL REFLUX DISEASE AFTER LUNG TRANSPLANTATION: POTENTIAL RISK FACTORS, AETIOLOGY AND LONG TERM OUTCOME

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Introduction

The incidence of Gastroesophageal Reflux Disease (GORD) in lung transplant (LTx) recipients has been previously reported to be very high. GORD is a risk factor for the development of chronic lung allograft dysfunction (CLAD). Its high prevalence after surgery might be related to preoperative incidence, vagal damage during surgery and/or immunosuppression.
The aim of the study was to evaluate potential risk factors and aetiologies of GORD with particular focus on the impact of different transplant surgical techniques.

Methods

We retrospectively collected and analysed data from consecutive lung transplant recipients who underwent impedance study postoperatively in our institution. Patients were considered GORD positive when the number of total reflux episode was above 73 and or the total percentage time refluxing was above 2.1 at the impedance. Donor and recipients characteristic, peri- intra- and post-operative variables were considered in the analysis.

Results

Baseline characteristics (donor and recipient) did not differ between both groups. GORD was diagnosed in 107 patients (54.3%). Presence of GORD was associated with worse graft function in terms of lower FEV1 at 1 and 3 years (77.14±20.75% vs. 86.02±22.15%, p=0.03 and 70.87±22.26% vs. 85.1±21.15%, p=0.053) and more frequent episodes of at least grade A2 acute cellular rejection (n=20, 20.6% vs. 4, 4,8%; p=0.002). There was no difference observed in terms of the surgical approach (Clamshell vs. bilateral anterior thoracotomy).
The incidence of CLAD (defined as BOS) and the overall survival did not differ between both groups, however in both analysis, GORD positive patients showed a clear drop in their survival at 4 years after transplant.

Conclusion

Our study showed the high incidence of GORD in lung transplant recipients which is associated with significant reduction in lung function tests in the mid- and long term after transplantation. Patients with GORD showed also worse graft function and more frequent episodes of acute rejections. However no independent risk factor including different surgical approaches were observed for GORD.

PEDIATRIC LUNG TRANSPLANTATION: 25 YEARS OF EXPERIENCE

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Purpose

The value of lung transplantation in children and pediatric patients is frequently questioned, due to concerns about long term outcome. We reviewed our 25 years experience in this group of patients and compared it with results obtained in the adult population.

Methods

A retrospective analysis of all patients undergoing LuTX in our department with an age younger then 18 years was performed. All relevant data were retrieved from the institutional database. Patient survival, organ survival and freedom from BOS/CLAD were estimated by Kaplan-Meier curves.

Results

A total of 99 transplantations (82 primary transplants, 14 ReTX, 1 ReReTX and 1 ReReReTX) were performed in 82 patients in the time period 1989-2014. Mean age of the patients was 12.9 ±4.1 years (range 0.6-18). Indication for primary TX was CF (63%), IPH (12 %) and Eisenmenger (6%). Leading indication for retransplantation was CLAD in 80%.

Mean time from primary TX to first ReTX was 1135±964 days (range 39-2770).

Bilateral LuTX was performed in 95%, and single LuTX or combined HLTX was performed in 2,5 % each. In 60 % whole lungs were transplanted and in 40 % lobar Tx was performed. 5 children were transplanted using living donors.

Extracorporeal circulation was used in 78% of the transplantations (55 pats with ECMO, 9 with HLM). 1- and 5-yr patient survival rates were 78% and 64%, respectively. Analyzing different eras of transplantation (1990-2002 vs 2002-2014) suggests an improvement over the years with a 5-yr survival rate of 45.5% vs 71.16% in the second decade (p=0.002). A high rate of successful re-transplantations (5 years survival after first ReTX 62.3%) prolonged total patient survival. Freedom from CLAD at 5 years post-transplant was 71%.

Analysis of 1134 LuTX in adult patients in the same period of time (2002-2014) in our institution revealed a 1 and 5 year survival rate of 81 % and 70 %, and a freedom from CLAD of 72 % at 5 years.

Conclusion

Lung transplantation in children and pediatric patients in the recent decade provides results equal to those achieved in the adult population.

LUNG-FIRST VERSUS LIVER-FIRST: A NEW DILEMMA IN COMBINED ORGAN TRANSPLANTATION

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Purpose: Simultaneous lung/liver transplantation (LuLiTx) is a rare and complex procedure. Until now all reported LuLiTx were performed in the same sequence: lung prior to liver. With the advent of lung perfusion – prolonging tolerable ex-vivo lung preservation time – the traditional sequence could safely be inversed, resulting in several potential advantages. Herein we introduce our clinical experience with this liver-first principle.

Methods: All LuLiTx performed at our center (01/2000-04/2016) were reviewed for demographics, indications, ischemic/ex-vivo time, rejection, and patient survival. We discuss operative sequence and its (dis-)advantages. Results are reported as median (range).

Results: Ten patients underwent LuLiTx. Recipient age was 31 years (17-63 years). Indications were cystic fibrosis and liver cirrhosis (n=5), pulmonary fibrosis and liver cirrhosis (n=2), epithelioid hemangio-endothelioma of the lung and liver (n=2), and end-stage COPD with drug-induced acute liver failure (n=1). Three lung grafts developed late acute rejection and 1 chronic rejection was followed by re-transplant. One liver graft developed acute rejection and hepatic artery thrombosis, followed by re-transplant. Follow-up was 2.5 years (6 months-15.5 years). One patient died due to an intracranial bleeding.
In seven cases, lungs were transplanted first. In the case of acute hepatic failure, the liver was transplanted first to correct the coagulation disorder (INR>10) rendering LuTx safer. Due to expected longer preservation time, lungs were perfused normothermically (OCS™/Transmedics/Andover/USA). Following this success, we performed two other liver-first cases. Hypothetical advantages for this sequence are: (i) liver reperfusion-injury hits the native lungs instead of the new lungs, reducing lung edema; (ii) coagulation restoration might reduce the need for transfusion during LuTx; and (iii) shorter liver ischemia time, decreases biliary stricture rate.
In our third liver-first case (cystic fibrosis) it might have been preferable to transplant the lung first due to disturbed gas exchange during LiTx (pO2: 23 mmHg; pCO2: 59 mmHg; Lactate: 6.1 mmol/L). Therefore, the benefit of liver-first should always be outweighed against the medical need to transplant the sickest-organ (eg. lung) first.

Conclusion: LuLiTx is feasible with excellent outcome. Although hypothetical benefits are linked to the liver-first principle, the sickest-organ-first principle should be followed for patients with pre-transplant hepatic or pulmonary failure.

LUNG TRANSPLANTATION FROM DONORS AFTER PREVIOUS CARDIAC SURGERY: IDEAL GRAFT IN MARGINAL DONOR?

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Lung transplantation has clearly become the definitive therapeutic option for patient with end-stage lung disease but the number of available donor currently limits this option. Despite the efforts to expand donor criteria on different fields, previous cardio-thoracic surgery is still considered a contraindication from large part of transplant centres. Surely, a previous operation on the chest can be a real risk factor for poor quality of the graft. On the other hand, a donor who underwent a cardiac surgery can provide an ideal lung but high intraoperative risks and intrinsic technical challenges are expected.

The purpose of this study is to present four clinical cases of lung procurement from donors who had a previous major cardiac surgery.

One donor had aortic valve substitution, one had mitral valve substitution and two donors had coronary artery bypass. The others criteria of eligibility for organs allocation, such as donor age, ABO compatibility, PaO2/FiO2 ratio, absence of aspiration or sepsis were respected. In one of the cases with previous coronary bypass, the grafts were submitted under ex vivo lung perfusion (EVLP) evaluation, because the donor had extra-corporeal support (VA-ECMO).

We report the technical details of procurement and recipients' postoperative courses. All procurements were uneventful, without lung damages or waste of abdominal organs related to catastrophic events. All recipients had a successful clinical outcome.

In our experience, even if lung procurement from a redo chest can be technically challenging, it could be performed successfully by extensive experienced surgeons. We stress the cooperation among the teams involved in the procurement; the coordination of the abdominal team and the anaesthesiologist with the thoracic surgeon is vital for the safe procurement of abdominal as well as pulmonary grafts.

Even though the computed tomography (CT) is not mandatory in the routine setting, mainly for possible donor instability, a meticulous pre-operative planning with CT scan is mandatory in this donor subgroup. CT scan with contrast could anticipate potential catastrophic injury to cardiac structures and lungs due to extensive thoracic adhesions identification. Moreover, the availability of EVLP evaluation makes relevant the possibility to move forward the decision on suitability of graft.

We conclude that even such complicated situation might result in successful transplantation. We strongly believe that facing lung donor shortage, it is crucial to avoid the loss of any possible acceptable lungs; in particular, previous major cardiac surgery does not strictly imply a poor quality of lungs as well as unsustainable graft procurement.

SCEDO-LUNG: INTERNATIONAL PRACTICE SURVEY ON SCEDOSPORIUM COLONIZATION AND INFECTION IN LUNG TRANSPLANT RECIPIENTS

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Purpose

Scedosporium spp. are encountered in 3.5% of mold infections in lung and heart-lung (L/HL) transplant recipients, just after *Aspergillus* spp. The mortality is closed to 100% in disseminated infections. Confidence about the exact prevalence of prior fungal colonization with these molds in L/HL transplant candidates is limited, mainly by the lack of international culture standards and management guidelines. Additional issues need to be addressed including the passage from colonization to infection, and post-transplant outcome based on pre-transplant fungal colonization status.

Methods

On behalf of the ESCMID-EFISG, the SCEDO-LUNG practice survey aims at better understanding the daily practice of physicians dealing with *Scedosporium* colonization/infection in L/HL transplant candidates/recipients through an online questionnaire. The practice survey will be launched worldwide in L/HL transplantation centers in January 2017 and will last 3 months.

Expected results

The main points that will be highlighted include: screening of pre and post-transplantation fungal colonization of the lower respiratory tract, management of *Scedosporium-Pseudallescheria complex/Lomentospora prolificans* colonization/infection before and after lung transplantation, and the feasibility of further multicentric studies on scedosporiosis in L/HL transplantation setting, by the transplant centers.

Conclusion

Developing a network of physicians and laboratory well aware of *Scedosporium* issues in L/HL transplantation could improve both knowledge and patients' management of these devastating infections.

ACUTE RSV INFECTION IN LUNG TRANSPLANTATION RECIPIENTS: FACTORS ASSOCIATED WITH A DECREASE IN LUNG FUNCTION

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Background

Chronic Lung Allograft Dysfunction (CLAD) is the main cause of mortality after lung transplantation (LT). Repeated episodes of viral infection of the respiratory tract have been associated with the occurrence of CLAD. The mechanism leading from viral infection to CLAD remains unclear. Therefore we analyzed a series of LT recipient with acute Respiratory Syncytial Virus (RSV) infection.

Material and Method

This observational retrospective study included every consecutive LT recipient who had a positive RSV-PCR in BAL or nasal swab, between January 2013 and February 2016. In order to identify factors associated with lung injury, decliners patients, defined as having a loss of > 10% of their basal FEV1, were compared with non-decliners. The further occurrence of CLAD at 6 months is also reported.

Results

Forty-tree episodes of RSV were documented in 42 patients. There were 29 decliners (69%). The comparison of decliners to non-decliners showed no significant difference between the two groups regarding the presence of Donor Specific Antibodies (DSA), occurrence of cellular rejection or co existing bacterial or fungal infections. BOS appeared or aggravated at 6 months in 10 patients (25%). Further results will be presented on September 2016.

Conclusion

In this small series, acute RSV was frequent in LT recipients. This infection was often associated with acute decline of lung function. No association with rejection has been documented. Everything happens as if the viral infection by itself was harmful.

GROWTH AND PUBERTAL ONSET AFTER LUNG TRANSPLANT IN CHILDREN WITH CYSTIC FIBROSIS

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Background: One of the ultimate goals of successful lung transplantation in Cystic Fibrosis (CF) pediatric recipients is attaining an optimal final adult height. There are no studies about growth after lung transplantation in CF children. The aim of our study was to review growth and puberty after lung transplant in children with CF.
Methods: We reviewed history of all Children with CF, who received lung transplant before the age of 16 years from 01/01/2000 to 21/12/2014 in lung transplant unit of Georges Pompidou European hospital in Paris. We included pre or per pubertal children at the time of transplant (Tanner stage 1 or 2). Anthropometric data, expressed as weight, height and BMI z-score and growth velocity were assessed one year before and during 5 years after lung transplant .Impact of different factors that may interact with growth such as graft function, post-transplant complications, cumulative doses of corticosteroids and pubertal status were considered.
Results: We enrolled 29 children with CF (9 boys and 20 girls) aged 7.5 to 15.7 years (median 13.7 years).Thirteen children died with an average survival time after transplantation of 4.05 years [1.17; 10.35]. Weight, height and BMI z-score did not improve after lung transplant in the whole population.Thirty one percent of children (n=9) had not started their puberty at the moment of transplant (4 boys)). Among those prepubertal children, growth peak appeared between the 3rd and 5th year after transplant , and maximized at 5.87 cm/year in boys and 7.25 cm / year in girls. This was correlated to onset of puberty (14.62 years for boys and 14.66 for girls). In perpubertal patients, growth velocity increased significantly during the 2 first years of transplant from 1.7cm/year in boys and 1.96 cm/year in girls before lung transplant to respectively 5.3 cm/year and 2.53 cm/year after 2 years of transplantation. Altogether, in both prepubertal and perpubertal children, peak velocity was delayed and insufficient, explaining the absence of height catch-up. Height z-score change was significantly correlated to duration of steroid treatment ,children who had the longer duration of steroid treatment had the least height z-score change.
Bone mineral density was investigated in 19 children and showed at latest post transplant evaluation a mean z score of 2.25 [-4;-1.2] at spine and -2.47 [-3.8;-1.1] at hip. There was no significant difference compared to value before transplant. Vitamin D level was below the target level at 20.3 ng/ml.
Conclusion: Neither growth nor bone mineralization were improved after lung transplant in our cohort. Those defects are linked to factors which can be amended such as pubertal delay, and post transplant steroid treatment duration. It is of paramount important to pay attention to those parameters and to treat them to get the best conditions for achieving the target adult size and maximize quality of life in pediatric lung recipients.

LUNG RETRANSPLANTATION IN ARGENTINA: SINGLE CENTER EXPERIENCE

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Introduction: Lung ReTransplantation (LRTx) is a valid therapeutic option for a selected group of lung transplant recipients with severe graft disfunction due to different etiologies. Although ethic considerations of redo transplant in a context of lack of organs, the increasing number of recipients facing this situation is a challenge for the lung transplant team.

Objectives: To analyze the outcomes of LRTx at a single center.

Material and methods: Descriptive and retrospective analysis of all LRTx performed at a single center in Argentina. Demographic characteristics, clinical status at re-transplant, time to LRTx, postoperative complications and survival were analyze.

Results: Since 2/1993 to 12/2015, 322 lung transplant (LTx) were performed to 310 recipients. Twelve patients (3.7%) received LRTx. The first LRTx was performed in 2004, 11 years after the beginning of the lung transplant program. Mean age was 43±16 years (16-65) and 7 (58%) were female. First transplant indication was COPD: 6 (all Single LTx); CF: 3 (Bilateral LTx); IPF: 1 (Single LTx); PPH: 1 (Bilateral LTx) and Eisenmenger Syndrome with Congenital Heart Disease: 1 (Heart-Lung Tx). Causes of retransplantation were CLAD: 8 recipients; post-viral pneumonitis fibrosis: 3 recipients (2 CMV, 1 HVS), PGD grade 3: 1 recipient. All LRTx recipients were on NYHA FC IV, 1 ventilated and 1 on VV ECMO. Eight recipients were in Emergency (High Priority) and 4 in Urgency at transplant. Bilateral LRTx was performed in 10 recipients and single LRTx in 2 (2 left side, 1 right pneumonectomy). Median time to LRTx was 1114 days (32-3202). In-hospital mortality was 41% (5 recipients) due to septic shock (4 patients) and PGD Grade 3 (1 p). Seven over 12 p (59%) were discharged after LRTx: mean time on ventilator was 26h (11-41); 1p required postoperative VV ECMO (13 days) due to PGD Grade 3; 3p developed PGD Grade 2 and 2p were surgically explored due to postoperative bleeding. During the long term follow-up, 1p died at 6.5 years and the remaining 6 are alive on NYHA FC I.

Conclusion: In this cohort, LRTx was a valid option for a selected group of lung transplant recipients. Otherwise, early mortality was high. Complications post retransplantation were similar to those observed in the first lung transplant. Candidate selection is a challenge for lung transplant programs and early mortality risk factors should be identify.

BASILIXIMAB FOR THE TREATMENT OF ACUTE CELLULAR REJECTION AFTER LUNG TRANSPLANTATION : A RETROSPECTIVE COHORT STUDY

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Purpose of the study

Despite improvements in early survival after lung transplantation, long-term survival is only 53% at 5 years post-transplant. Chronic allograft dysfunction remain the main factor limiting long term transplant. Acute cellular rejection episodes (and steroid resistant rejection (SRR)) are one of the CLAD's risk factor. Therapy for SRR is not well established. Basiliximab is a monoclonal antibody targeting the interleukin 2 receptor currently used as induction therapy for lung transplant.

The aim of our study is to evaluated the effectiveness and safety of Basiliximab for the treatment of ACR and SRR in lung transplant.

Statements of the methods

This was a retrospective analysis data collected from the first January of 2008 and the first august of 2014. The inclusions criteria were the occurrence of ACR from grade 1 to 4. The exclusion criteria were the age under eighteen at the transplant. Persistence of rejection, time to next ACR, occurrence of diabetes, neoplasia, infections, cytokine released syndrome, death were analyzed

Summary of the results

Eighty one had an episode of ACR, sixteen were minor at the time of the transplant. 19/65 patients received once Basiliximab for the treatment of ACR or SRR. 0/7 patients treated with Basiliximab for the first ACR had rejection on the trans-bronchial biopsy (Tbb), 11/45 patients treated without Basiliximab had rejection on the Tbb. The occurrence of a new ACR after the first resolved episode of rejection was lower in the Basiliximab group than in the no Basiliximab group respectively 65% and 83% p=0.25. No cytokine released syndrome have been described.

Statements of the conclusion

Basiliximab is an effective and safe treatment for ACR and SRR. Prospective studies are now needed to evaluated the use of Basiliximab as first line therapy for ACR or SRR in lung transplant.

IMMUNOMODULATORY EFFECTS OF EXTRACORPOREAL PHOTOPHERESIS ARE DEPENDENT ON REJECTION STATUS – A PILOT STUDY

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Purpose

No clear consensus consist on how to use ECP after heart transplantation (HTx). The clinical use of extracorporeal photopheresis (ECP) is based on its ability to induce cell-mediated immune tolerance towards foreign and self antigens. In this pilot study, we evaluated the stimulatory effects of ECP on immune cells in HTx patients.

Methods

HTx patients received ECP therapy as prophylaxis of rejection (PRX; n=7) or to treat acute cellular rejection (ACR, n=5) or chronic allograft vasculopathy (CAV; n=3). ECP was performed according to a specific treatment protocol for each group. Blood samples were taken before, after the third ECP cycle and two months after the last ECP cycle. Blood samples were analyzed for the tolerance-inducing cell subsets regulatory T cells (Tregs), myeloid and plasmacytoid dendritic cells (m and pDCs). The stimulatory effect was calculated from the baseline value without ECP treatment compared to the values after the third ECP treatment and 2 months thereafter.

Results

Our pilot study gave first hints that the response profile between ECP-treated patients with PRX, ACR and CAV differed regarding the cellular parameters mDCs, pDCs and Tregs. A high stimulatory effect for pDCs and mDCs was detected for patients of the PRX (pDCs: 11.1fold increase; mDCs: 1.7fold increase) and the ACR group (pDCs: 3.7fold increase; mDCs: 1.4fold increase) two months after the last ECP cycle. ECP-treated patients with CAV showed a lower stimulatory effect two months after ECP treatment for pDCs (1.6fold increase) and no effect for mDCs. Treg profile analysis revealed a high stimulatory effect in the CAV and the PRX group (both 1.2fold increase) and a moderate reduction in the ACR group (0.9fold) two months after ECP treatment.

Conclusion

In our pilot study, we showed different stimulatory effects of ECP on DCs and Tregs between prophylactic and preemptive ECP therapy after HTx. Immunological monitoring could be valuable to develop an individual ECP therapy strategy in patients without, acute or chronic rejection.

TGF-β1 IN RESTRICTIVE CLAD: IS IT IMPORTANT?

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Restrictive chronic lung allograft dysfunction (rCLAD) has recently been identified as a novel manifestation of CLAD characterized by restrictive pulmonary physiology, persistent parenchymal infiltrates, pleural thickening and a worse survival compared to obstructive CLAD (BOS). The pathophysiological mechanisms remain elusive.

We investigated the role of TGF-β1 by ELISA measurement in broncho-alveolar lavage (BAL) fluid (BAL) of patients with BOS, rCLAD and stable patients. Subsequently, we assessed if TGF-β1 stimulation of a pleural cell line (MET-5a, ATCC) could elicit mesothelial mesenchymal transition (MMT), assessed by a decrease in E-cadherin and an increase in fibronectin by western blot. Lastly, we wanted to assess if current therapeutic strategies for CLAD could inhibit MMT.

We demonstrated a significant increase in BAL TGF-β1 in rCLAD patients (n=26) compared to stable patients (n=20), while there was no difference in stable vs. BOS patients (n=23) ($p<0.05$). rCLAD patients with a TGF-β1 concentration above the median, had a significantly worse prognosis compared to those with a lower level ($p=0.033$). Stimulation of a pleural cell line with TGB-β1 induced transition to a mesenchymal (fibroblast-like) phenotype (increase in fibronectin and decrease in E-Cadherin; $p<0.0003$). Dexamethasone, azithromycin, pirfenidone or montelukast could not inhibit MMT.

In conclusion, we showed that TGF-β1 could play an important role in the pathophysiological mechanisms of rCLAD which needs further investigation and validation.

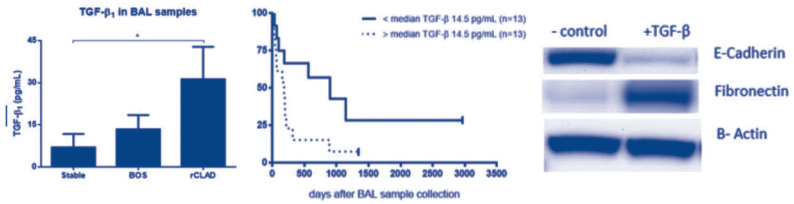

Figure legend: Left. TGF-β1 concentrations as measured by sandwich ELISA. ANOVA analysis showed significant differences between groups ($p=0.043$) with the highest concentrations present in RAS. Middle. Survival analysis divided based on the median TGF-β1 concentration as measured in BAL at the moment of diagnosis showed an inferior survival in patients with a high TGF-β1 concentration. Right. Western blot showing increased expression of fibronectin and decreased expression of E-Cadherin after TGF- β1 stimulation, B-actin is shown as control.

ANALYSIS OF THE REGULATORY T LYMPHOCYTES PROFILE AS PREDICTIVE BIOMARKER OF THE LUNG ALLOGRAFT CHRONIC DYSFUNCTION IN HUMANS

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In lung transplantation (TP), although acute rejection is today well controlled thanks to immunosuppressive drugs improvement in the last decades, the chronic allograft dysfunction (CLAD) remains a therapeutic challenge for the long-term graft survival. Regardless of Bronchiolitis Obliterans Syndrome (BOS) or Restrictive Allograft Syndrome (RAS), both immune mechanisms involved and predictive biomarkers have to be better defined.

The COLT Cohort (Cohort in Lung Transplantation) was initiated in 2009 in order to understand the physiopathology of CLAD in a longitudinal prospective long-term monitoring of lung-transplant patients. This biocollection gave us the opportunity to immunomonitor the patients from the transplantation to the CLAD occurrence.

On 40 lung-transplant stable patients (STA), 38 develop a CLAD whose 20 patients with a BO Syndrome and 18 with a RA Syndrome. Patients who will report a BOS in the 3 years post-TP show an increase in FoxP3+ regulatory T cells (Tregs) proportion 1 year post-TP. Even though Tregs are commonly described as predictor of good clinical outcomes in different solid-organ transplantation, we consider this circulating Tregs population could be induced in response to successive inflammatory phenomenon leading to CLAD. An extent analysis of the memory (mTregs) and naïve (nTregs) regulatory T cell subset denotes only mTregs are increased in BOS patients compared to STA.

In the light of their first results we are currently exploring the kinetics of the Tregs response from the transplantation to the CLAD in STA, BOS and RAS patients including new makers and functional analysis.

In conclusion, we lead to identify Regulatory T cells as new potential predictive biomarkers of the CLAD including both phenotypical and functional modalities in humans.

SECURITY AND USEFULNESS OF EVEROLIMUS (IMTOR) ASSOCIATED WITH LOW TACROLIMUS DOSE TO PRESERVE KIDNEY FUNCTION IN PEDIATRICS LUNG TRANSPLANTATION, ABOUT A CASE

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Introduction

Alteration of renal function after lung post-transplant (TxP) is well known, and unlike cardiac or renal adult transplantation, pediatrics' use of ImTOR in TxP is little reported.

Results

We report the case of an 11 years old boy who received a TxP for cystic fibrosis. At time of transplantation, renal function was subnormal. Because of immunological complications with a steroid-resistant rejection the first year post-transplant and recurrent infections requiring antibiotics, like aminoglycoside high doses, a progressive decline in kidney function is observed. Thus, 3 years after the transplantation, (51)Cr EDTA clearance was 53 ml/min/1,73 m^2 (IRC stage III) with a rapid renal function decline. To preserve the renal capital, everolimus is introduced with a 5-7 µg/l rate achieved very gradually in 3 months. The doses required to achieve this objective were 0.08 mg/kg twice a day. In parallel, tacrolimus is decreased with a target of 4-5 µg/l rate. Treatment was well tolerated, without adverse clinical or biological effect reported, growth remains perfect. No episode of rejection is found on the systematic annual biopsies carried out. The ACALS remain negative. (51)Cr EDTA clearance one year after the introduction of the treatment significantly improved to 72 ml/min/1,73 m^2.

Discussion

This case shows that the introduction of ImTOR can preserve renal function and, when it is associated with tacrolimus low dose, can prevent lung rejection. A slow introduction and close monitoring of rates to minimize the occurrence of side effects is required. A larger use of ImTOR can be offered in pediatric lung transplant provided close monitoring.

AUTOFLUORESCENCE BRONCHOSCOPY AS INNOVATIVE MARKER OF AIRWAY COMPLICATIONS AFTER LUNG TRANSPLANTATION

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Airway complications after lung transplantation lead to significant morbidity and mortality, typically in the first two years. The pathogenesis of post-operative bronchial stenosis is associated to peri-anastomotic ischemia related to multiple and controversial risk factors. Moreover, a technique to predict the stenosis onset is still lacking. The auto-fluorescence bronchoscopy (AFB) is currently used in oncology: the different blood supply of healthy mucosa from the pathological can identify precancerous lesions due to the different capacity of absorption of ultraviolet light. The increase in thickness of the precancerous mucosa prevent the absorption of frequencies of the red light by hemoglobin, and therefore the mucosa presents a bright red color as opposed to the "normal" green color. A similar result is obtained when ultraviolet light hits an ischemic or infected mucosa.

Aim of this prospective study was to find a relationship between the degree of bronchial vascularization and the onset of airway stenosis with AFB and investigate its possible role as pre-clinical marker.

From February 2014 and October 2015, we enrolled all consecutive patients transplanted. Exclusion criteria were < 18 years old, intensive care unit stay > 7 days, postoperative survival < 6 months.

Rejection surveillance by transbronchial pulmonary biopsies was scheduled as usual. All procedures were performed with AFB (Olympus EVIS Lucera Spectrum AFI) weekly during the first month and next quarterly up to the first year of follow-up. All procedures were recorded on a USB storage device. The degree of fluorescence was measured using a histogram. The magenta color identifies the ischemic mucosa and the green color the normal vascularized mucosa. Results, in terms of intensity ratio (R/G ratio), were correlated with graft cold ischemic time and with the onset of complications of airways.

Twenty-three patients resulted eligible for the study. We examined 39 bronchial anastomosis and we considered each as a unit for statistical purpose. We observed 8 bronchial stenoses from 6 subjects. After logistic regression, R/G ratio at 45 days, 3 and 6 months, and 1 year correlated with stenosis onset (p=0,0417; 0,0231; 0,0036; 0,0027 respectively).

The AFB allows the assessment of the vascularization of the graft bronchial mucosa and provides a valuable tool as preclinical marker of airway complications in lung transplantation.

NOVEL APPROACH FOR THE TREATMENT OF GERD AFTER LUNG TRANSPLANTATION: ELECTRICAL STIMULATION OF THE LOWER ESOPHAGEAL SPHINCTER

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Gastroesophageal reflux disease (GERD) had been associated to the development of chronic lung injury after lung transplantation. Electrical stimulation of the lower esophageal sphincter (LES) (LES-EST) has emerged as a new alternative for the treatment of GERD. Briefly, the technology involves a laparoscopically implantable neurostimulator with two electrodes implanted at the LES that provide programmed electrical stimuli to improve LES function.

Objective: To present a novel approach to the management of GERD in lung transplant recipients.

Clinical Case: Male, 46 years-old, diagnosis of idiopathic pulmonary arterial hypertension who underwent an emergent bilateral lung transplantation. Extubated after 8 days due to delirium and bilateral diaphragmatic paresis. Discharged at postoperative day 16. Evolves with improvement of NYHA FC and normalization of spirometric values at first year post transplant: FVC 1.49 (94%), $FEV_1$3.20 (82%), FEV_1/FVC 66. At month 22th presented cough, dyspnea on FC II-III and sustained drop of spirometric values: FVC 3.27 L (66%), FEV_1 1.92 (49%), FE_1/FVC 59% without evidence of AR, airway or bronchial anastomosis complication, or infection (bacterial pneumonia, viral pneumonitis or opportunistic infection). CT Scan showed pathologic changes compatibles with CLAD. Anamnesis revealed 1 month history of reflux. Esophageal Impedance Manometry and Ph Manometry showed GERD. The LES Stimulation system (EndoStim, BV, The Hague, The Netherlands)was implanted using standard laparoscopic technique (SurgEndosc. 2013;27:1083-92) and stimulation was delivered in 12, 30 minute sessions of5mA, 215 usec, at 20Hz.. After the procedure, the patient evolved with impairment of GER symptoms. Spirometric test: FVC 4.13 (89%); FEV_1 2.91 (77%) FEV_1/FVC 70.

Conclusion: The utilization of electrical stimulation of the LES with minimal invasive approach showed efficacy for the treatment of GERD post lung . Early diagnosis and treatment of GERD after lung transplantation is necessary to avoid severe lung injury and lost of the graft.

CELL-FREE HEMOGLOBIN: A NEW THERAPEUTIC TARGET FOR PREVENTION OF PRIMARY GRAFT DYSFUNCTION?

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Purpose of the Study: Extracellular hemoglobin can be released into the circulation in a variety of clinical settings including chronic hemolytic states such as sickle cell disease and acute hemolytic states such as extracorporeal circulation or sepsis. When liberated from the reducing environment of the red blood cell, cell-free hemoglobin (CFH) is a potent oxidant that can oxidize lipid membranes and other substrates leading to vascular injury and organ dysfunction including acute lung injury. We reported that pre-operative plasma CFH levels are elevated in patients with end-stage lung disease and are independently associated with primary graft dysfunction (PGD) after lung transplantation (JHLT 2013;32:S42-3). We also found that acetaminophen, a specific hemoprotein reductant, can abrogate CFH-mediated oxidative injury and organ dysfunction in patients with severe sepsis (CCM 2015;43:534-4). The purpose of the current study was to test the effect of CFH on vascular permeability in the ex vivo human lung and to determine whether acetaminophen could limit these effects.
Methods: Human lungs declined for transplantation were perfused with DMEM with 5% albumin at a flow rate to maintain PAP of 8-12 mmHg with CPAP 10cmH2O. After steady state was achieved, CFH (100 mg/dL) was added to the perfusate with or without acetaminophen (15 µg/mL, a level within the therapeutic range). Lung vascular permeability was measured gravimetrically by continuous monitoring of lung weight and by extravasation of Evans blue dye-labeled albumin (EBD) from the vasculature into BAL. To test the mechanism of increased permeability, human pulmonary microvascular endothelial cells (hPMVECs) were exposed to CFH (0.5 mg/mL) ± acetaminophen (160 µM) for 24 h and permeability assessed by electrical cell-substrate impedance sensing.
Results: In the ex vivo human lung, CFH increased lung vascular permeability over 2 h compared to control (12% vs. 2% weight gain from baseline, p=0.03). Increased vascular permeability was confirmed by a 4.8-fold increase in EBD in the airspace compared to control. Addition of clinically relevant doses of acetaminophen to the perfusate prevented lung weight gain (p=0.06 vs. CFH). In hPMVECs, CFH increased monolayer paracellular permeability as measured by a fall in monolayer resistance (p=0.03 vs. control). This effect was attenuated by acetaminophen (p=0.045 vs. CFH).
Conclusions: Circulating CFH is a potent inducer of vascular permeability in the ex vivo human lung, an effect that may be mediated by increased paracellular permeability of the microvascular endothelium. These findings help to explain the mechanism by which elevated CFH levels are associated with PGD after lung transplantation. The hemoprotein reductant acetaminophen attenuates the effects of CFH on lung vascular permeability and could have utility for the prevention and treatment of PGD after lung transplantation.

Funded by: NIH HL126176

ASSOCIATION OF LONG PENTRAXIN-3 WITH PULMONARY HYPERTENSION AND PRIMARY GRAFT DYSFUNCTION IN LUNG TRANSPLANT RECIPIENTS

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Purpose of the study: Lung transplantation remains the only available therapeutic option for pulmonary arterial hypertension (PAH) that is refractory to treatment and severe WHO Group 3 pulmonary hypertension (PH). PH related to either PAH or parenchymal lung disease significantly increases the risk of post-lung transplant primary graft dysfunction (PGD). Despite the enormous adverse impact of PH on transplant, there is poor understanding of the biochemical mechanisms linking PH to PGD. Elevated levels of the secreted innate immune mediator long pentraxin 3 (PTX3) have been associated with both PAH and increased risk of PGD. We therefore evaluated the association of PTX3 plasma level with PH in lung transplant candidates and the effect of PTX3 concentration on the association of PH with PGD after lung transplantation.

Methods: We performed a cohort study using patients enrolled in the prospective, multicenter Lung Transplant Outcomes Group Cohort (LTOG) study between 2003 and 2010. Plasma PTX3 levels were measured in samples collected from a cohort of 164 patients with plasma samples available from prior to lung transplantation using a commercially available ELISA. PGD was defined as grade 3 PGD present at 48 or 72 hours after transplant using standard ISHLT criteria. Pre-transplant PH was defined as a mean pulmonary arterial pressure (mPAP)×40 mmHg based on previous PGD risk factor studies demonstrating moderate PH as a significant risk factor for PGD. PH was also assessed as a continuous variable. The cutoff for PTX3 plasma level was selected based on the distribution of plasma levels in the overall cohort and to ensure an adequate sample size in each subgroup.

Results: The incidence of PH in this cohort was 18.3% and the incidence of PGD was 11%. The median plasma concentration of PTX3 was significantly higher in patients with mPAP×40 compared to those with mPAP<40 (4.4 ng/ml vs. 2.7 ng/ml, p=0.03). The result was similar when excluding the 6 subjects transplanted for PAH (4.6 ng/ml vs. 2.7 ng/ml, p=0.03). PH was strongly associated with PGD in the overall cohort (OR=1.8 per 10mmHg increase in mPAP, 95%CI=1.2, 2.6, p=0.004) when controlling for pre-transplant diagnosis. The relationship between PH and PGD appears to be impacted by plasma PTX3 level. In patients with PTX3 level <7.5ng/ml (n=123), the relationship of PH with PGD was attenuated (OR=1.5 per 10mmHg increase in mPAP, 95%CI=0.9, 2.4, p=0.09). Among patients with PTX3 level>7.5ng/ml (n=41), the relationship between PH and PGD remained significant (OR=7.6 per 10mmHg increase in mPAP, 95%CI=1.4, 39.5, p=0.02).

Conclusion: Levels of the innate immune mediator PTX3 in lung transplant candidates with at least moderate PH are significantly higher than in patients with lower PA pressures. Additionally, PTX3 plasma level may modify the relationship of PH with PGD with higher PTX3 plasma concentrations magnifying the association of PH with PGD. Future study should focus on the role of innate immunity in PH and the impact of innate immune regulation on the PH-PGD relationship.

NON-TUBERCULOUS MYCOBACTERIA INFECTION AND LUNG TRANSPLANTATION IN CYSTIC FIBROSIS: A WORLDWIDE SURVEY OF CLINICAL PRACTICE

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Purpose: Non-Tuberculous Mycobacteria (NTM) infection in Cystic Fibrosis (CF) is of increasing concern and prevalence. Optimal treatment usually requires multiple antibiotics for a period of more than 12 months. When considering lung transplantation for patients with NTM the clinician has to consider the risk of an uncontrolled infection post-transplant and severe toxic effects of treatment against the potential benefits of the procedure. It appears that there are different approaches in the lung transplantation community towards this challenging clinical issue. Recent international recommendations largely leave decision-making open to the individual centre/clinician. In this survey we assessed the current international practice with regard to assessing and listing patients with CF for lung transplantation who have NTM infection.

Methods: We designed a short YES/NO questionnaire enquiring about local practice regarding screening for NTM infection, specific contra-indications to transplantation, management and segregation of patients pre and post-transplant. The survey was sent via e-mail to 31 paediatric and adult centres across Europe, North America and Australia.

Results: We gathered complete questionnaires from 19 centres (61% response rate). All centres screen specifically CF patients for NTM infection but very few (26%) have a clear written policy regarding this issue. Thirteen centres require molecular identification of species and main samples accepted as relevant are sputum and broncho-alveolar lavage (100% and 94% respectively). Only 4 centers would consider infection with Mycobacterium abscessus Complex in itself a contra-indication for listing. Opinions are more heterogeneous when considering either NTM infection with persisting positive cultures despite optimal treatment or association with another relative contra-indications where more than half of centres would not consider lung transplantation. Eighty-nine percent require treatment pre-transplant and all centres decide a peri-transplant treatment cocktail at the time of listing. Finally, there were no clear policies identified regarding segration (e.g in the waiting room) of patients pre and post-transplant depending on their NTM status.

Conclusions: The issue of NTM infection in CF patients requiring lung transplantation is well recognized among the lung transplantation community. However, official guidance is sparse and although suspected sub-optimal outcomes following transplantation in patients with NTM, most centres do not consider it as an absolute contra-indication unless associated with other comorbidities or in the absence of a suitable cocktail for antimicrobial therapy.

HEART RATE VARIABILITY IN BILATERAL LUNG TRANSPLANT RECIPIENTS

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Introduction

Bilateral lung transplantation (BLT) implies complete lung denervation. It is an excellent model for testing cardiovascular regulation in absence of modulation of heart activity by lung afferents. The high frequency (HF) component of heart rate variability (HRV) is synchronous with breathing frequency (BF). If this comes from neural modulation of the heart beat by BF, HF of HRV should disappear after BLT. The aim of this study was to analyse HRV and baroreflex sensitivity (BRS) in BLT as compared with healthy controls (C).

Methods

Eleven BLT (6 women and 5 men), aged 49.0±14.5 years and eleven sex- and age-matched C, aged 47.3±14.5, were studied. We continuously recorded heart rate (HR, by electrocardiography), arterial blood pressure (Portapres) and BF (ultrasonic device) during 10 min of free breathing at rest, 10 min of cadenced breathing (0.25Hz) (CB) at rest and 5 min with handgrip (HG), in supine posture. We evaluated spontaneous variability of R-R interval (RR), systolic, diastolic and mean pressure (SAP, DAP and MAP respectively), by power spectral analysis, and BRS, by the sequence method, using the BRSanalysis® software. 2-way ANOVA and Tukey post-hoc test were used.

Results

BLT, compared to C, had higher HR in all conditions, higher DAP and MAP in CB and HG conditions and the same SAP in all conditions. BF was higher in BLT than in C during free breathing. BLT showed lower BRS, total power (PTOT), low-frequency peak (LF) and HF, in all conditions. The LF/HF ratio was higher in BLT than in C. In normalised units, BLT had higher LF (LFnu) and lower HF (HFnu) than C. Concerning blood pressure, BLT had higher PTOT, LF and HF powers for SAP; higher HF and lower LF/HF for DAP; lower LF/HF for MAP, than C.

Discussion

Lung denervation carried along a remarkable reduction of HRV. The higher LF/HF ratio implies that the PTOT drop was mostly due to the HF component. The reverse was the case for SAP. Thus, the results of this study are compatible with the hypothesis that a neural modulation from lung afferents contributes to the HF component of HRV.

LUNG TRANSPLANT PROJECTED COMMERCIAL CLAIM COSTS FOR 2016 IN THE UNITED STATES

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Purpose: Lung transplantation is generally considered to be a costly procedure that improves survival and quality of life in patients who have severe lung disease. Publications on lung transplant costs in the pre- and post-operative periods is lacking. In this commercial claims analysis, we report the average allowed cost (AAC) per lung transplant and associated pre- and post- lung transplant AAC at 180 days.

Methods: Using standardized procedure codes, we identified patients who had a lung transplant from the 2011-14 Truven MarketScan commercial claim databases. The occurrence of a lung transplant procedure code during an inpatient claim and all activities (i.e., facility, professional, drug) were categorized as an event. Patients were excluded if: they were under 15 years old, there was a pharmacy claim for an immunosuppressive drug within 3 months prior to the index claim, or there was an occurrence of a heart-lung transplant procedure code during the study timeframe. Any second lung transplant cost for the same patient was also excluded. Using commercial allowed cost trends, we projected the AAC to July 2016 from event service date. Event costs are reported separately as are pre- (PRE) and post- (POST) transplant costs that are within a 180 day timeframe.

Results: A total of 620 patients met the study criteria. The AAC per event was $482,000 representing an inpatient average length of stay (ALOS) of 31 days. In total, 79% of patients received a bi-lateral lung transplant which accounted for 83% of event cost. For the event, 84% of patients (n=523) had an AAC per patient of less than $750,000 (average = $343,000) while eight patients had an AAC of $2.6 million. In the PRE timeframe, 455 patients (165 were not eligible at day 180) were identified with an AAC cost of $104,000 per patient of which the lowest 92% (n=418) of patients had an AAC of $70,000. In the POST timeframe, 409 eligible patients were identified with an AAC of $177,000 per patient of which the lowest 85% (n=348) of patients had an AAC of $118,000. The largest cost driver for the PRE timeframe was due to inpatient admissions at $46,000 per patient (396 inpatient admissions and ALOS=10 days). Similarly, inpatient cost was the highest cost driver in the POST timeframe at $66,000 per patient (497 inpatient admissions and ALOS=8 days).

Conclusion: This study provides an updated analysis of commercial claim costs for payers. While this study does not consider the impact of payer coverage determination criteria, it could involve both the pre- and post-transplant metrics i.e., cost, clinical, patient quality of life. Our projected cost could be impacted by changes in transplant selection criteria (e.g., lung allocation scores), sample size, or with advances in technology.

CONVERSION FROM TACROLIMUS TWICE-DAILY TO TACROLIMUS ONCE-DAILY IN STABLE LUNG TRANSPLANTATION: HUNGARIAN EXPERIENCES

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Purpose of the study

Prolonged-release tacrolimus (TAC) was developed to provide a more convenient twice-daily (BID) dosing that could improve patient adherence after solid organ transplantation. The aim of this study was to evaluate clinical effects of switching on tacrolimus twice daily (TAC BID) to tacrolimus once daily (TAC OD) in stable lung transplant (LT) Hungarian recipients.

Methods

Study subjects were post-lungtransplant patients with stable lung function, on stable doses of TAC BID and who were candidates to switch to TAC OD. Fifteen LT patients were included in the retrospective analysis. Lung function parameters, serum creatinin level and rejection rate was observed before and after the conversion.

Results

Causes of LT were cystic fibrosis (n=4), chronic obstructive lung disease (COPD) (n=4), pulmonary fibrosis (n=3), silicatosis (n=2), primer pulmonary hypertension (n=2). No significant (ns) differences were observed in the serum creatinine levels (µmol/L; mean (SD)) before and two and three years after the conversion (111.5 (25.28) vs. 115.1 (26.34) vs. 118.1 (41.71) µmol/L, p=0.686;). The forced vital capacity (L; mean (SD)), and the maximal expiratory flow rate at 50% of vital capacity (percentage of the predicted values given in median and interquartile range) were similar before and after conversion (3.55 (1.01) vs 3.51 (0.98) vs 3.61 (0.88) L, p=0.632; and 52 (40-100) vs 53 (39-118) vs 52 (41-114) %, p=0.944).

Conclusion

Our results indicate TAC BID can be safely switched to the more convenient OD formulation in LT patients.

SECONDARY PULMONARY ALVEOLAR PROTEINOSIS AFTER LUNG TRANSPLANTATION: A SERIES WITH REVIEW OF LITERATURE

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Pulmonary alveolar proteinosis (PAP) is a rare disease in which lipoproteinaceous material accumulates within alveoli, related to alveolar macrophage dysfunction. Very few cases of secondary PAP have been reported in solid-organ transplant recipients. Amongst them, only 4 cases of PAP occurred in lung transplantation (LTx) recipients. We report here a series of 4 new cases of PAP in LTx recipients, which occurred during a four-year period in our center, with death attributed to PAP in all cases.

The four recipients (3 male/1 female) had undergone single (n=2) or double (n=2) LTx for idiopathic lung fibrosis (n=3) or emphysema (n=1). Immunosuppressive therapy included tacrolimus or cyclosporine/azathioprine or MMF/steroids, without induction therapy. PAP onset occurred within the first three months (post-operative day [POD] 72,33,32 and 69). The native lungs from the 2 single LTx recipients were not involved by PAP disease. A delay ranging from 20 to 53 days was observed between the onset of graft lesions retrospectively attributed to PAP and the diagnosis of PAP in 3 patients, whereas a post-mortem diagnosis was made in the last patient. Indeed, diagnosis of PAP was initially confused with an atypical acute rejection episode (AR) in three cases, which led to steroid boluses administration. Re-examination of biopsies and CT-scan ultimately allowed diagnosis of PAP. Diagnosis were performed in all cases on a typical CT-scan pattern including a crazy-paving aspect associated with characteristic histological features of PAP on transbronchial biopsies (n=4) and/or bronchoalveolar lavage (n=2). Other causes of acute lung injury were excluded including graft infection (viral, bacteriological, parasitic and mycological infection), cellular or antibody-mediated rejection, and left ventricular failure. Only in 1 patient, an AR initially co-existed with PAP, before resolution of the AR episode and persistence of PAP. Consistent with the diagnosis of secondary PAP, anti-GM-CSF anti-bodies were measured and found negative in three patients. We also studied GM-CSF pathway in one LTx recipient with PAP and 3 stable LTx recipients used as controls. Interestingly, functional tests found a selective impairment of GM-CSF pathway in blood neutrophils from the LTx recipient affected by PAP whereas tests were normal in stable LTx recipient.

Outcome of our four patients were unfavorable despite treatment with GM-CSF therapy (n=2 patients), therapeutic lobar lavages (n=1) and minimizing of immunosuppression (n=2).

In conclusion, physicians should be aware of this rare but fatal post-LTx complication, which can mimic atypical AR. In the opposite with AR treatment, the diagnosis of PAP in the context of LTx may necessitate a reduction of immunosuppression, associated with other specific therapies. In this series, the initial misdiagnosis and/or diagnosis delay were most often associated with increased immunosuppression for suspected AR. This probably has favored a significant worsening of PAP and fatal outcome in these cases.

Notes

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