32nd Annual Meeting and Scientific Sessions
DAILY Links
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@ISHLT

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REVIEW: BOS Ain't BS

Bronchiolitis obliterans syndrome (BOS) limits long term outcomes after lung transplantation. During Thursday afternoon's **Concurrent Session 21, Therapeutics of Lung Transplantation**, researchers from around the world presented much awaited studies seeking to improve treatment of this syndrome.

Two studies on the effectiveness of everolimus were presented. Dr. Alan Glanville presented the CeMyLung Study. This three year study compared everolimus to mycophenolate as part of a three drug immunosuppression regimen that also included cyclosporine and corticosteroids. One hundred sixty five patients were included. No overall difference was seen between the two groups in the incidence or time to development of BOS on intention to treat analysis. With per protocol analysis, an increase in BOS was present in the everolimus group, but this was of lower grade than the mycophenolate group. Increased CMV antigenemia, diarrhea, and leukopenia were seen in the myophenolate group. Dr. Glanville stated that because this was an investigator driven and not pharmaceutical driven trial, financial considerations prevented increasing the number of subjects thus limiting this the power of the study. Dr. Martin presented "Everolimus versus MMF in Lung Transplant Recipients," with different results. In this single center randomized controlled trial (RCT), both drugs were compared as part of a three drug regimen including cyclosporin, and corticosteroids. While no difference in survival was seen, the everolimus group had improved BOS free survival at two years (90% vs 65%). Less CMV infection was seen in the everolimus group, although other infections were similar between the two groups. Side effects of everolimus included hemolytic uremic syndrome.

Dr. Johnson followed with the results of the CYCLIST trial which investigated the addition of cyclosporine inhaled solution to standard therapy compared to standard therapy alone. This multi-center RCT showed no difference in incidence of BOS between the two groups. However, the overall survival was superior to what was expected based on the ISHLT registry, partly because the inclusion criteria and tertiary as opposed to quaternary nature of the participating centers selected a healthier transplant population. This made it more difficult to show a difference between the two groups.

Dr. Corris presented "A Randomized Controlled Trial of Azithromycin Therapy in Bronchiolitis Obliterans Syndrome Post Lung Transplantation." This RCT evaluated the effect of azithromycin given to patients with established BOS. The adjusted increase in FEV1 after 12 weeks of azithromycin was 223 ml, which was statistically significant. In contrast to previous trials, there was no effect of azithromcyin on BAL neutrophila and no correlation of BAL neutrophilia with clinical response. Dr. Corris stated that this data showed a significant improvement in lung function even after BOS developed and thus suggested it was safe to wait, especially given the number of medications transplant patients are already on and the theoretical risk of fostering non-tuberculous mycobacterial infections.

Dr. Jaksch presented "Alemtuzumab Induction in Lung Transplant Recipients." This RCT compared alemtuzumab (Campath) vs ATG. In the alemtuzumab group, lower immunosuppressive targets were used (tacrolimus levels 10-12 and mycophenolate dose 1.5 grams per day) compared to the ATG group (tacrolimus levels 15-18 and mycophenolate dose 3 grams per day). While a significant decrease in the number of acute rejections (A2 or higher) was seen in the alemtuzumab group, no difference was seen in the incidence of lymphocytic bronchiolitis, morality, CMV infection, and renal failure.

Additionally, no significant difference in the incidence of BOS was seen though there was a trend towards early BOS in the alemtuzumab group. Leukopenia was more common in the alemtuzumab group, including one patient who died from invasive aspergillosis.

Lastly, Dr Chambers presented, "Mesenchymal Stromal Cell Therapy for Bronchiolitis Obliterans Syndrome – Preliminary Data in Humans." Mesenchymal stromal cells (MSC) are bone marrow derived cells that form the connective tissue scaffolding in the bone marrow and secrete cytokines, chemokines, and growth factors. Recently, MSC have been found in the lungs, and evidence exists for an immunosuppressive effect, including inducing CD4+ cells to express a regulatory phenotype. In this feasibility study, MSC were isolated from donors, grown in cell culture, and administered intravenously to four patients with BOS. No serious adverse effects were detected, and three of the four patients had stabilization of lung function.

The *32nd* Annual Meeting in *Numbers*
2,537 Registrants
48 Countries Represented

REVIEW: Extra, Extra Read All About It – RV Through Thick and Thin

RV failure is one of the greatest challenges in the management of advanced LV dysfunction. The **concurrent symposium 14: "Following the RV Through Thick and Thin"** session provided a thorough overview of the problem of RV dysfunction in patients with congestive heart failure due to LV diseases, with a pathophysiological overview of pulmonary hypertension secondary to LV dysfunction by Dr. Robert P. Frantz including pulmonary vascular resistance, pulmonary vasculopathy, impaired RV/LV interaction, arrhythmia, renal insufficiency and neurohumoral activation. Dr. Jean-Luc Vachiery described current approaches to medical therapy and discussed individual substances showing data that pulmonary hypertension is reversible with sildenafil in patients waiting for heart transplantation resulting in better hemodynamics in rest and exercise. New drugs are currently under investigation and prospective randomized trials are needed to gain more insights in understanding in pulmonary hypertension and improve treatment of these patients. Dr. Mauro Rinaldis' talk handled RV failure after LVAD implantation and after heart transplantation. Among others in this meeting, he highlighted that prevention is one of the major keys in these patients. Tricuspid valve regurgitation is a risk factor for RV failure. He presented a prospective trial of patients with heart transplantation and concomitant tricuspid valve repair (TVR). In the early phase there was a significant advantage for TVR, but in the long-term patient groups had comparable outcomes. The number of RV failure among LVAD patients is decreasing during the last years. However, it remains a major concern.

Excessive unloading of the LV increases tricuspid valve regurgitation by septal shift and should be avoided. He believes a low threshold for TVR during LVAD implantation is justified. But how is management of RV failure in LVAD patients to be monitored? Dr. Marc A. Simon discussed several methods from LV/RV ratio as proposed by the Berlin group, over free wall shortening to modified CT angiography and pulmonary arterial impedance measurements. Session closed with a discussion on different diagnostic and treatment modalities.

2012 Daily Links Editorial Staff

Front Row (L-R): Stuart Sweet, MD, PhD, Lisa de Leon, Stephen Chavez ,Vincent Valentine, MD
Rear Row (L-R): Susie Newton, Shiwan Shah, DO, Alexander Bernhardt, MD

Feeding the Future of ISHLT

Thursday`s **mentor lunch** was a great opportunity for young residents and fellows to meet with established specialists in heart and lung diseases. In small groups, fellows and attendings sat together having lunch and engaged in easy conversation. People from different countries and different specialties exchanged experiences, sorted out advantages of regional residency and fellow programs and discussed future directions of cardiac and lung medicine. This setting enabled questions that can usually not be asked during a meeting. Participants agreed that this lunch enhanced motivation for further meeting and networking.

Quotable Quotes

The art of medicine lies in the physician's ability to keep the patient entertained while the disease runs its inevitable course
- François Marie Arouet (Voltaire)

Surgeons must be very careful
When they take the knife!
Underneath their fine incisions
Stirs the Culprit - Life!
- Emily Dickinson

Diagnosis is not the end, but the beginning of practice.
- Martin H. Fischer

Medicine is the only profession that labours incessantly to destroy the reason for its own existence.
- James Bryce, 1914

A Short History of Medicine
2000 B.C. - "Here, eat this root."
1000 B.C. - "That root is heathen, say this prayer."
1850 A.D. - "That prayer is superstition, drink this potion."
1940 A.D. - "That potion is snake oil, swallow this pill."
1985 A.D. - "That pill is ineffective, take this antibiotic."
2000 A.D. - "That antibiotic is artificial. Here, eat this root."
- Author Unknown

REVIEW: When the Fontan Fails to Fix

Concurrent Syposium 11: Management of the Failing Fontan Across the Age Spectrum

The Fontan procedure has represented a significant advance for treatment of children born with congenital heart disease with single ventricle physiology. However, failure of the Fontan procedure often occurs over time. During Friday's Concurrent Symposium 11, Management of the Failing Fontan Patient Across the Age Spectrum, this challenging issue was addressed. Dr. Anne Dipchand detailed reasons for failure of the Fontan procedure, including pathway obstruction, arrhythmias, poor hemodynamics of the atriopulmonary Fontan, elevated pulmonary vascular resistance, ventricular systolic dysfunction, ventricular diastolic dysfunction, atrioventricular valvular regurgitation, and protein losing enteropathy. She emphasized that diastolic dysfunction is particularly difficult to diagnose by echocardiography. When a Fontan fails, several options are available. With failure due to an arrhythmia or pathway obstruction, Dr. Carl Backer suggested that Fontan conversion be considered. During this procedure, the atriopulmonary Fontan is taken down, the enlarged right atrium is resected, and a cavo-pulmonary anastamosis is created.

A MAZE procedure is often done to address the atrial fibrillation/flutter, and a permanent dual chamber pacemaker is inserted. This procedure is not useful for other causes of failure including pump dysfunction. In these cases, heart transplantation should be considered. Dr. Asif Hasan noted that transplantation for a failing Fontan is complicated by the “abnormal plumbing.” As a result, Dr. Steven Zangwill noted that these patients have a higher operative mortality. Post-operative complications, as detailed by Dr. Jane Cassidy, include early bleeding, right heart failure, pulmonary hypertension, and vasoplegia. Part of the increased post-operative mortality may be related to the severity of illness prior to transplantation. As a result, Dr. Bernstein discussed the importance of listing these patients when signs of worsening first occur, but prior to full decompenseated disease and protein losing enteropathy. Despite the complications and higher operative mortality, conditional mortality after the initial post-operative period is excellent compared to transplantation performed for other diseases. Lastly, during the panel discussion, the issue of ventricular assist device (VAD) as bridge to transplant was discussed. While data is lacking, VAD may stabilize symptoms and improve the protein losing enteropathy allowing for a more stable patient for transplantation. VAD would be primarily useful in patients with systolic ventricular dysfunction. In addition, VAD destination therapy may allow for symptom control and improved quality of life in patients with a failed Fontan who are not candidates for heart transplantation.

REVIEW: Under Pressure

This mornings Concurrent Abstract Session 40 was about diagnostic and medical therapy for Secondary (Non-PAH) Pulmonary Hypertension. Dr. Guglin compared multiple vasodilators for reversibility of pulmonary hypertension in a meta- analysis. Because reversibility of pulmonary hypertension in pre-heart transplant patients is mostly determined by vasoconstriction, prostaglandins, especially prostacyclin, appeared to be the drugs of choice in acute reversibility testing. Transpulmonary gradients are defined by the difference of mean pulmonary artery pressure and mean wedge pressure. By contrast pulmonary vascular gradients (PVG) are the difference between invasive diastolic pulmonary artery pressure and mean wedge pressure.

Dr. Gerges tested the prognostic value of PVG in 3107 patients. He identified a threshold of 7mmHg as out-of-proportion pulmonary hypertension associated with adverse outcome believing that PVG may be useful for clinical drug trials. A possible medical treatment strategy for secondary PH is the use of PDE inhibitors.

Dr. Reichenbach presented a matched case-control study in heart

transplant candidates to compare clinical and hemodynamic outcome in patients with advanced heart failure and severe pre-capillary PH with or without administration of sildenafil. Long-term survival as well as clinical and hemodynamic outcome was better with sildenafil. In addition, he found that sildenafil prevents weight loss.

Dr. Molina evaluated echo-Doppler profiles of poor RV function and high afterload in patients treated with sildenafil concluding that the echo-Doppler profile of both a low TAPSE and Doppler-RVOT notching was highly prevalent. Session continued with Dr. Cogswell's talk about the REVEAL prediction model. REVEAL score was designed to predict one-year survival in patients with pulmonary hypertension. It can be applied for different reasons for PH and has a well matched predicted to observed survival. Pulmonary vascular findings are well characterized in pulmonary hypertension.

Co-Chair of this session, Dr Carlsen analyzed pulmonary vascular lesions in explanted lungs from 64 COPD patients for lung transplantation, lungs from 18 patients with idiopathic PH served as control group. The severity of pulmonary vascular lesions in COPD correlated with the severity of PH and lesions only rarely include plexiform lesions, the hallmark of idiopathic PH.

REVIEW: Alphabet Soup

During Saturday morning's **Concurrent Abstract Session 38, From BOS to CLAD and Beyond**, six groups presented emerging data on chronic lung allograft dysfunction (CLAD). Dr. Vos and colleagues started off the session with follow up data from their previous study that showed azithromycin begun after lung transplantation (LT) improved BOS free survival. Today, they showed that this improvement was durable up to six years. Interestingly, patients in the original placebo group had a shift to an increased FEV1/FVC ratio towards the end of the follow up period suggesting restrictive allograft syndrome (RAS). Graft survival was similar between the two groups, likely due to open label use of azithromycin in the original placebo group among those who developed BOS.

Dr. Sato and colleagues evaluated the effect of timing of onset of CLAD on mortality. In their study of 98 bilateral LT recipients, although development of CLAD was associated with increased mortality, RAS was more strongly so than BOS. Specifically, patients with onset of BOS more than 36 months after transplant did not have increased mortality, suggesting a more benign phenotype. However, as Dr. Glanville pointed out during the discussion, it is possible these patients may not have had the disease long enough for mortality to manifest.

Dr. Westall and colleagues reported that in a study of 245 lung transplant recipients followed at least one year, nonobstructive phenotypes of CLAD, including those with mixed or restrictive spirometry, were associated with radiographic infiltrates and fibrinous organizing pneumonia on pathology. No antibodies were seen on immunohistochemisty. Survival in this subgroup was worse than those with an obstructive phenotype.

Dr. Bhorade presented on behalf of the AIRSAC investigators and reported results of a survey evaluating the concordance of BOS diagnosis. During the AIRSAC study, three separate reviewers evaluated for the presence of BOS using established criteria, and discordance was present in 35 of the 181 subjects (19%). Five of these discordant cases were randomly selected and sent to the ISHLT pulmonary council members via electronic mail. There was discrepancy in diagnosis of BOS 30% of the time. Even for those cases in which there was an agreement on the diagnosis of BOS, there was only 41% agreement on the time of onset of BOS. Possible reasons include some variability in establishing an endpoint, difficulty in evaluating individual time points as opposed to a FEV1 trajectory, and complexity in incorporating of concomitant events. In addition, even though most of the respondents stated they were very familiar with the BOS guidelines, they may have used a clinical gestalt rather than strictly adhering to the guidelines. This provocative research highlights the difficulties of performing studies in which BOS is an end point and suggests that better education, revision of the guidelines, or addition of other criteria, including clinical and radiological criteria may be needed to improve consistency in diagnosis.

Dr. Bhinder and colleagues presented data that suggested air pollution may contribute to development of BOS. Evaluation of 421 transplant patients revealed that a higher density of roadways in a 300 meter radius of the patient's house was

associated with increased development of BOS and all cause mortality. Exposure to pollutants based on measurements at the nearest fixed site station was also evaluated and particulate matter was associated with an increased incidence of BOS although not mortality. No association existed between ozone or nitrogen dioxide exposure and BOS/mortality. Furthermore, in patients with established BOS, no association was seen between pollutants and increased mortality.

Lastly, Dr. Saito and colleagues presented data that BOS and RAS patients may have different cytokine profiles on bronchoalveolar lavage (BAL). Comparing 5 BOS patients, 3 RAS patients, and 8 LT patients without CLAD, the researchers found that the cytokines CCXL1, 8, 9, 12, and HGF were increased in patients with CLAD. Increased lymphotoxin alpha levels characterized BOS while increased IL-6/IL-10 ratio and RANTES levels characterized RAS.

Prague Castle

See you all next year …

April 24-27, 2013
33rd Annual Meeting and Scientific Sessions
Palais des Congrés de Montréal
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