

PULMONARY AND CRITICAL CARE BULLETIN

Vol. XI, No. 1, January 15, 2005
 Website : www.indiachest.org
 (p. 1-8)

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EDITORIAL COMMENT

Pulmonary hypertension is a relatively less often encountered problem by the respiratory physician when we exclude the secondary causes like corpulmonale. Primary pulmonary hypertension as such is a rare condition. However, better understanding of its pathogenesis has led to the development of newer treatment modalities that gives relief to these patients. Pulmonary arterial hypertension is now considered to be a vasoproliferative disorder rather than a vasoconstrictive disorder as believed earlier. Vasodilators, Prostanoids, Phosphodiesterase inhibitors and Nitric Oxide are some of the drugs that are helpful to treat this condition.

Published under the auspices of

Pulmonary C.M.E. Programme of
 The CHEST
 (Chest Health Care, Education & Research Trust)

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Annual : Rs. 100

Life Subscription : Rs. 700

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PULMONARY HYPERTENSION

Introduction

Pulmonary hypertension is a syndrome characterized by elevation of pulmonary arterial pressure with mean pulmonary artery pressure greater than 25mm of Hg at rest and greater than 30 mm of Hg on exercise.

Evian classification of pulmonary hypertension includes five categories based on biologic, etiologic, clinical and therapeutic characteristics. Minor changes have been made in the third world symposium on pulmonary hypertension held in Venice 2003.

A) PULMONARY ARTERIAL HYPERTENSION

1) Primary pulmonary hypertension/IPAH

2) Related to

Collagen vascular disease

Congenital systemic pulmonary shunts

Portal hypertension

Drugs/toxins/HIV

3) Pulmonary veno occlusive disease

4) Pulmonary capillary hemangiomatosis

B) PULMONARY VENOUS HYPERTENSION

- 1) Left sided heart disease
- 2) Fibrosing mediastinitis
- 3) Mediastinal tumors

C) PULMONARY HYPERTENSION ASSOCIATED WITH HYPOXEMIA

- 1) COPD
- 2) Interstitial lung disease
- 3) Sleep disordered breathing
- 4) High altitude

D) PULMONARY HYPERTENSION DUE TO CHRONIC THROMBOEMBOLIC DISEASE

E) MISCELLANEOUS

- 1) Sarcoidosis
- 2) Histiocytosis
- 3) Schistosomiasis

PATHOPHYSIOLOGY

Pulmonary arterial hypertension is now considered to be a vasoproliferative disorder rather than a vasoconstrictive disorder.

Pathologic hallmark is vascular remodeling (plexogenic arteriopathy) characterized by vasoconstriction, vascular smooth muscle hypertrophy, endothelial cell proliferation, extracellular matrix remodeling and in situ thrombosis. Genetic and environmental factors play a role in the pathobiology. Overexpression/activation vasoconstricting, mitogenic and prothrombotic factors (endothelin, thromboxane, serotonin) and impaired production of vasodilators and antiproliferative agents (prostacyclin, nitric oxide and heparin like substances) are responsible for the pathologic changes. Collagen vascular disease, HIV and anorectic agents produce a picture similar to that of primary pulmonary hypertension. Hypoxemia induced vasoconstriction, smooth muscle

hypertrophy and capillary obliteration are responsible for pulmonary hypertension secondary to lung diseases.

DIAGNOSIS

Pulmonary hypertension often presents with nonspecific symptoms such as dyspnoea, fatigue, progressive limitation of exercise tolerance and syncope. High index of suspicion, thorough history of potential risk factors, physical examination and stepwise evaluation are needed for accurate diagnosis. ECG, Chest X-ray and echocardiography are the initial screening tests. Further investigation (V/Q scan, lung functions, PSG, CT Chest, genetic screening) may be done to identify the etiology. Right heart catheterization provides the definite diagnosis of pulmonary hypertension and should be performed in all patients of pulmonary arterial hypertension before starting treatment.

TREATMENT

Basic Therapy

Supplemental oxygen including ambulatory oxygen is indicated to maintain arterial oxygen saturation at a level greater than 90%. Low salt diet and diuretics may be used judiciously to decrease volume overload in right heart failure. Cardiac glycosides are most useful in pulmonary hypertension with concomitant left ventricular failure or atrial fibrillation. Oral warfarin is recommended with a target INR between 1.5-2.5.

Progress in the understanding of pathobiology of pulmonary hypertension has been paralleled by evolution of novel therapeutic agents. Treatment has evolved from vasodilators to antiproliferative agents.

VASODILATORS

Vasodilator testing (with IV adenosine / prostanoids / Nitric Oxide) is done in pulmonary arterial hypertension to delineate the subset (25%) of patients who may effectively be treated with oral

calcium channel blockers. 50% of the patients with acute vasodilatory responsiveness demonstrate long term hemodynamic and clinical response to calcium channel blockers. They have been never assessed in randomized controlled trials.

DRUGS THAT TARGET VASCULAR REMODELLING

Prostanoids

Prostanoids are vasodilators with antiplatelet, anti-inflammatory, antiproliferative, antifibrotic effects and may reverse the pulmonary vascular remodeling. They include prostacyclin (epoprostenol) and its analogues, treprostinil (IV or S/C), beraprost (oral, IV) and iloprost (oral, inhaled, or S/C). Prostacyclin analogues improve the pulmonary hemodynamics, functional capacity and quality of life in patients with pulmonary hypertension and class III/IV symptoms. Survival benefits of these drugs has not been addressed in most studies. Diarrhea, systemic vasodilation related hypotension, headache, jawpain, flushing, and complication of the drug delivery system have been the predominant side effects. Oral beraprost and inhaled iloprost appear promising even in patients with class II/III symptoms.

ENDOTHELIN RECEPTOR ANTAGONISTS

Bosentan is a dual endothelin (ET_A and ET_B) receptor antagonist while sitaxentan and ambrisentan are selective for ET_A . Bosentan in a dose of 125-250 mg twice a day for 16 weeks for studied in 213 patients (class III/IV). There was significant improvement in six minute walk distance, dyspnoea index, NYHA functional class and time to clinical worsening. Continuing bosentan for one year maintained the improvement in 6MWD, cardiac index and pulmonary vascular resistance in a preliminary study. Bosentan therapy is associated with transaminitis (upto 14%) which is dose related and transient. Monthly monitoring of liver functions is recommended.

PHOSPHODIESTERASE INHIBITORS

PDE_5 inhibition increases the levels of cyclicGMP, activating cyclicGMP kinase leading to potassium channel opening and vasorelaxation. Sildenafil is a potent and specific PDE_5 inhibitor. It blocks acute hypoxic pulmonary vasoconstriction, reduces mean pulmonary arterial pressure and pulmonary vascular resistance increasing 6MWD and cardiac index. It is a selective pulmonary vasodilator with advantage of oral administration. Combination therapy of sildenafil with iloprost, nitric oxide or prostacyclins has shown greater and more prolonged fall in mean pulmonary arterial pressures. Sildenafil has been tried in primary pulmonary hypertension, chronic thromboembolic pulmonary hypertension and pulmonary hypertension secondary to pulmonary fibrosis. Data on long term benefits is lacking.

NITRIC OXIDE

Nitric oxide increases cyclicGMP and causes selective pulmonary vasodilation. Benefits of nitric oxide is seen in pulmonary hypertension of new born, congenital heart disease, post operative pulmonary hypertension and ARDS. In chronic pulmonary arterial hypertension its use has been mainly in vasodilator reactivity testing and stabilization of patients during acute deterioration. Safety, effectiveness and feasibility of long term inhaled NO in ambulatory settings needs to be studied.

Choice of therapy depends on the functional class of the patient, clinicians experience, cost and patient preferences. Most of the studies have been done in PPH and pulmonary hypertension in collagen vascular diseases with class III/IV symptoms. Patients of moderate pulmonary hypertension (class I/II) not responding to vasodilators may be observed or given oral beraprost/bosentan. Patient in class III can be given prostacyclins or bosentan while class IV patients should be given IV prostacyclins. Combination therapy using drugs targeting the various pathways is an emerging option in pulmonary hypertension. Adjunctive therapy with sildenafil or bosentan has produced favourable outcomes in patients already on oral, inhaled or intravenous prostacyclins.

Atrial septostomy may be considered in severe pulmonary hypertension with recurrent syncope or progressive right heart failure on maximum medical treatment as a bridge to transplantation. Idiopathic pulmonary arterial hypertension is often progressive and fatal. Lung transplantation is an option in patients younger than 65 years not responding to medical treatment.

In pulmonary hypertension secondary to other diseases (chronic hypoxemia, sleep disorders, chronic thromboembolism, heart disease) early recognition and treatment of underlying cause is important. Thromboendarterectomy for accessible chronic thromboembolic disease is potential curable. Prostanoids, bosentan and sildenafil are being tried in pulmonary hypertension secondary to lung diseases and chronic thromboembolic pulmonary hypertension.

Right heart failure, NYHA class III/IV, elevated right atrial pressure, decreased cardiac output or low mixed venous oxygen saturation are poor prognostic factors in patients with pulmonary hypertension. Recent advances in the understanding of pathophysiological and molecular mechanisms in pulmonary hypertension have led to development of new therapies and renewed hope for these patients.

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EDITORIAL COMMENT

Sarcoidosis was considered to be a rare disease in this country. However, during the last few years it has been recognized as an important disease occurring in Indians. The disease has been reported from all parts of the country. It is a granulomatous disorder affecting multiple organ systems of the body, most notably the lungs. As tuberculosis is a common problem seen in this part of the world, sarcoidosis is most often confused with this disease. However, there are definite and certain differences in the clinical manifestation of the disease which differentiate the two. A number of immunological changes take part in this disease. Sarcoid granuloma is characterized by fibrinoid necrosis, rarely caseation. Sites of inflammation have activated T-cells and mononuclear phagocytes. These cells express pro-inflammatory cytokines & chemokines which are critical in granuloma formation and CMI. These are associated with dominant, polarized Th-1 immune response. Granulomatous inflammation is associated with oligoclonal T-cell population. As the disease can carry significant morbidity and mortality depending on the site of involvement the disease should be treated accordingly. Newer modalities of treatment are available now besides the time proven drug- prednisolone.

CURRENT CONTROVERSIES & UPDATE OF SARCOIDOSIS

SARCOIDOSIS

Multisystem granulomatous disorder of unknown origin characterized by activation of T-Lymphocytes and mononuclear phagocytes at sites of disease. It most commonly affects Lungs & Intra-thoracic lymph nodes. Diagnosis is securely established from compatible history, histology showing non-caseating granulomas in more than one organ & absence of competing Dx like TB\Fungal Disease\Malignancy.

PATHOGENESIS

Antigen Triggered : Sarcoidosis is antigen triggered, the evidence for which is suggested by T-cell Ag receptors (TCR) being monoclonal. There is ↑ in mRNA for TCR.

Genetic Susceptibility

In data from monozygotic twins who do not live in same environment, there is ↑ prevalence of disease in siblings of affected individual to suggest genetic involvement.

It is not a single gene disease. Multiple genes interact with one or more environmental triggers to provoke first phases of disease.

Further evidence is suggested by :

1. Racial Difference

Scandinavians with African - American have highest prevalence. Latin Americans have higher prevalence than white people.

2. Familial Sarcoidosis

RR for Sarcoidosis in siblings of affected

individual in one study was 36-73. Odds Ratio of familial disease from ACCESS study was 5.8.

INFERENCE

Familial sarcoidosis is present in majority of population. Family members of sarcoidosis cases have several fold increased, risk of disease compared with general population.

CAUSE OF SARCOIDOSIS

Sarcoid granulomas are formed in response to a persistent, poorly degradable antigenic stimulus. Non-infective agents implicated include Pine Pollen, Clay soil, talc, beryllium, zirconium. None of these theories have endured.

INFECTIVE

Pointers of mycobacterial inf. Include histopathological appearance of granuloma, presence of mycobacterial disease existing coincidentally, succeeding or antedating sarcoidosis, finding of organisms in occ. granuloma together with occ. Caseation and transmissibility in animal expts. Points against mycobacterial infection include : absence of Caseation, Organisms are demonstrated rarely, absence of response to ATT, Tuberculin energy. Other organisms like propionibacteria, rickettsia helvetica, chlamydia pneumoniae, borrelia burgdorferi have also been implicated.

BASIC SCIENCE 'FACTS' OF SARCOIDOSIS'

Sarcoidosis is characterized by granuloma with fibrinoid necrosis, rarely caseation. Sites

of inflammation have activated T-cells and mono-nuclear phagocytes. These cells express pro-inflammatory cytokines & chemokines which are critical in granuloma formation and CMI. These are associated with dominant, polarized Th-1 immune response. Granulomatous inflammation is associated with oligoclonal T-cell population.

TREATMENT OF SARCOIDOSIS

General Principles From Clinical Observations: Granuloma formation dictates clinical course and therapeutic response. Therefore suppression of granuloma formation results in preservation of organ function and minimize long term fibrotic outcomes. Corticosteroids are effective in suppressing granuloma formation over both short term and long term. Non corticosteroid therapies are variably effective.

There is a threshold level of drug effect for most pts. below which there is progression of granuloma and above which there is suppression of granuloma. Kinetics of granuloma formation is variable : In some it progresses slowly while in others there is rapid progression resulting in organ dysfunction. Different tissues respond differently to drugs e.g. antimalarials are effective in skin & mucosal disease (Nasal sinus, URT) than pulmonary disease.

STRATEGIES FOR TREATMENT OF SARCOIDOSIS BASED ON STAGES OF INFLAMMATION IN DISEASE

- Step 1 : Inhibit Ag Presentation
(Anti-Malarial Drugs)
- Step 2 : Suppress Granuloma Formation
(Corticosteroids, Immunosuppressives, Anti TNF agents)
- Step 3 : Enhance Ag Clearance
? Peptide based therapy (future)
- Step 4 : Inhibit Fibrosis
(Corticosteroids, Immunosuppressives, Anti TNF agents)

1. Treatment to suppress initiation of granuloma formation :

Strategies include reduction of Ag deposition, enhancement of Ag clearance, inhibition of Ag processing and presentation.

A. Reduce Ag deposition by antibiotic therapy : Doxycycline, Minocycline are effective against

propionibacteria while Dapsone and Clofazimine have anti mycobacterial effects. Beneficial effects with these drugs are seen in a subset of sarcoidosis pts.

B. Inhibition of antigen processing and presentation by Chloroquin/Hydroxy Chloroquin : MoA includes inhibition of degradation of proteins by acid hydrolases within the lysosomes. They inhibit formation of MHC - peptide complexes thereby inhibiting Ag presentation to T-cells.

2. Treatment of Progressive granulomatous inflammation :

Corticosteroids : These have broad spectrum anti-inflammatory effects on multiple cells - T-cells/macrophages/granulocytes. They inhibit expression of pro-inflammatory cytokines and arachidonic acid metabolism. Overall they decrease cell activation and enhance apoptosis of activated T-cells.

Azathioprine : important mediator of immune suppression. It inhibits T-cell and B-cell proliferation and cytotoxic T-cell function.

Methotrexate : It is a folic acid analogue that inhibits dihydrofolate reductase and transmethylation reactions. The net effect is interference with purine metabolism and polyamine synthesis.

Cyclosporin : T-cell inhibition. They inhibit IL-2

TNF Inhibition : TNF plays a critical role in granuloma formation.

Pentoxifylline : It is a methylxanthine derivative which is a non-selective phosphodiesterase inhibitor. It inhibits TNF production by mononuclear cells including alveolar macrophages.

Thalidomide : Inhibits TNF production by mononuclear cells.

Etanercept : It is a biologic dimeric fusion protein which binds to TNF and related protein lymphotoxin- α and thus brings about its anti-TNF effect.

Infliximab : It is a humanized monoclonal antibody formed of human IgG1 Ab and protein segments from mouse monoclonal Ab. against human TNF. It blocks TNF.

None of these drugs classified as TNF inhibitors have been shown to be effective in sarcoidosis by rigorous studies. All these have a high cost & notable toxicities.

DIFFERENT STRATEGIES FOR DIFFERENT STAGES OF SARCOIDOSIS, ROLE OF TH-1 RESPONSE :

In early stages, Th-1 driven granulomatous response is effective in clearing granuloma inducing Ag while in chronic sarcoidosis, the ongoing Th-1 immune response results in impaired organ function. Therefore it would be apt to minimize immune suppression early in the disease while in chronic stages focus should be on minimizing granulomatous inflammation.

TREATMENT OF PROGRESSIVE PULMONARY FIBROSIS

Persistent granulomatous inflammation results in fibrosis. Probably, there is a switch to Th-2 response in late stages resulting in elaboration of pro-fibrotic cytokines like IL-4. There is no data to support the use of anti-fibrotic agents such as colchicine / perfenidone in fibrocystic sarcoidosis. For now, anti-inflammatory drug therapy that inhibit granuloma formation would retard/prevent progressive fibrosis.

DIFFICULT TREATMENT ISSUES IN SARCOIDOSIS²

Management Issues :

When to start therapy : Specific conditions requiring therapy include. Cardiac involvement, neurologic involvement, hypercalcemia and ocular diseases not controlled by topical therapy. Pulmonary involvement per se does not require therapy. For Pulmonary disease, symptomatic pts. and worsening lung function warranty treatment.

CORTICOSTEROID THERAPY IN PULMONARY SARCOIDOSIS³

In an analysis of 8 RCT of the role of steroids i.e. oral/inhaled or both in outcome of sarcoidosis it was found that treatment of pulmonary sarcoidosis with oral steroids for a period of 6-24 mths. improved CXR findings. Pts. not treated with steroids had more chances of deterioration compared with those receiving prednisolone. Results from these RCT confirm that stage I do not require Treatment with OCS but those with ILD (stage II/III) may show radiologic improvement. Trials of ICS were small and results too inconsistent to make firm conclusions concerning efficacy of this mode of corticosteroid delivery.

APPROACH TO TREAT PULMONARY SARCOIDOSIS WITH CORTICOSTEROIDS⁴

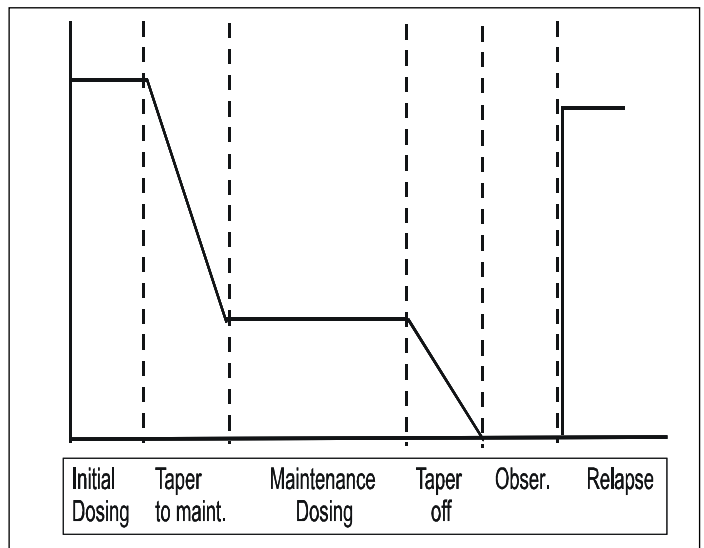
AC. pulmonary sarcoidosis is defined as pt. with sarcoidosis who present early and have symptoms of short duration.

Chronic pulmonary sarcoidosis are those cases who have symptoms persisting for > 2 yrs.

DECISION TO TREAT WITH CORTICOSTEROIDS IN AC. PUL. SARCOIDOSIS

Patient Subgroup	Decision
1. Asymptomatic Pts.	No treatment
2. Mild Pulmonary Dysfunction	Observation
3. Pts. With excellent prognosis	Observation, Palliative (Erthema nodosum) therapy.
4. Mild-Mod. Pul. Dysfunction	Observation, treat if deteriorates.
Mild-Mod. Fun. Limitation	Treat if no improvement after 6 mths. of therapy.
5. Severe Pul. Dysfunction	Severe Functional Limitation

There is no long term benefit from corticosteroid therapy in asymptomatic pts., regardless of CXR stage. Asymptomatic pts. with (n) PFT should not be treated because of radiographic abnormality alone. The different phases of treatment of acute sarcoidosis is represented in the graphic format below :



Decision to taper steroids should be based on stabilization or improvement in symptoms/PFT findings. Sarcoidosis pts. with stable PFT should not have their treatment plan adjusted on the basis of Lab. evidence (S. ACE level, BAL cell count differentials, Ga Scans) of 'active disease'. Maintenance period of 6 mths. - 1 yr. is ass. with few relapses. Pulmonary symptoms and spirometry are most useful parameters to monitor when deciding if corticosteroid therapy should be re-instituted. > 20% relapses occur > 1 yr. after steroid cessation while 10% relapses occur after 2 yrs. Observation period for post steroid cessation should be atleast 2 yrs. Relapses occur in 20-50% of pts. in whom steroids are stopped. In case of relapse reinstitute high dose steroids for 2-6 wks. and then it should be followed by a tapering scheme. Some authors believe in increasing the maintenance dose or in increasing the maintenance period after a relapse.

CHRONIC PULMONARY SARCOIDOSIS

Three fourth of these pts. who require >5yrs. of steroids relapse when steroids are withdrawn. Almost all relapses occur within 1-2 mths. of withdrawal. Therefore oral steroids should be weaned very slowly with close monitoring of symptoms, spirometry and CXR findings. In chronic pulmonary sarcoidosis even asymptomatic radiographic infiltrates with/without pulmonary dysfunction, smaller steroid "bursts" should be given. If pt. cannot be completely weaned off steroids then continue lowest maintenance dose. Corticosteroid dependence in chronic sarcoidosis should not be considered as corticosteroid failure. Low dose steroids may be superior to alternative therapies, or to no therapy at all.

ALTERNATIVES TO CORTICOSTEROIDS AND WHEN SHOULD THEY BE USED⁵

1. **Methotrexate** : Used in chronic sarcoidosis. Appears to take 6 mths. to become effective. Protocol for its use should be to start with dose of 10 mg/wk and then progress to 15 mg/wk (max dose). The dose adjustment should be based on neutropenia or nausea. CBC, Renal parameters should be monitored every 8 wks. Folic acid 1 mg/day may be used to avoid GI toxicity. Toxicity includes GI, Hepatotoxicity, Pulmonary and BM affections. Efficacy is 60-80%.
2. **Anti-Malarial Agents** : These have been shown to be steroid sparing in RCT of chr. pul. sarcoidosis. Dose is chloroquin 500mg/day

(~300 mg base drug) or hydroxychloroquin 200-400 mg/day. S/E include GI toxicity and ocular toxicity (Eye exam. yearly). Efficacy is 30-50%.

3. **Azathioprine** :
Efficacy similar to methotrexate. Usual dose : 50-200 mg/day. Monitoring: CBC, LFT should be done every 2 mths. Toxicity includes nausea, abd. pain pancytopenia. Efficacy is 50-80%
4. **Cyclophosphamide** :
Used for refractory disease esp. neurological disease. Dose : 50-150mg/day PO. S/E include BM depression, nausea, haemorrhagic cystitis, bladder cancer. Efficacy is 80%.
5. **Thalidomide** :
Dose is 100-200mg/day. S/E include sedation constipation & painless peripheral neuropathy.
6. **Infliximab** :
Anti-TNF Ab. Dose is 5mg/kg which should be given every 4-6 wks. Toxicity includes- risk of infection.

In chronic/refractory sarcoidosis use of combination therapy is recommended. Monitoring should be done, as there is increased risk of toxicity.

CONCLUSION

Therapy need not be given to all pts of sarcoidosis. Once initiated, atleast 1 yr. of treatment is required. In high risk cases of chronic disease frequent monitoring should be done if corticosteroids are discontinued. Steroid sparing agents are useful for chronic pts. of sarcoidosis .

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