MD Seminar

Management of IPF

Idiopathic pulmonary fibrosis

- Also known as CFA
  - Chronic scarring illness limited to lungs & characterized by
    - Progressive dyspnea
    - Restrictive pulmonary physiology
    - Radiographically diffuse lung disease
    - Occurs in adults, manifesting beyond 5th and 6th decade
- Until recently, diagnosis and management was difficult because
  - Vague case definition
  - Clinical features overlapped with other chronic interstitial pneumonias

Epidemiology

- IPF is most common diagnosis among all IIPs
- Usually affects older adults and men
- Risk factors
  - Familial IPF- 3% of cases, suggests genetic predisposition may interact with environmental factors
  - Environmental factors
    - Smoking
    - Inhalation of organic and inorganic dust
    - Exposure to dust (pinewood)
    - Use of tricyclic antidepressants
    - Gastroesophageal reflux
  - No connection between IPF and an infective agent

Pathophysiology

- Current hypothesis

Recurrent, unknown injury (extrinsic or intrinsic)
To distal pulmonary parenchyma

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Repeated epithelial injury

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Abnormal wound healing,
Mediated by fibroblasts and fibroblast-like cells
Or myofibroblasts

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Progressive fibrosis

Natural history of IPF

- Fatal illness –
  - progressive impairment of lung compliance and gas exchange
  - Inexorable course
  - usually death because of hypoxic respiratory failure, associated with pulmonary hypertension & cor pulmonale
  - Increased risk of bronchogenic carcinoma
- Median survival – 80 months from the time of onset of symptoms (King et al.)
- Acute exacerbations may occur in absence of infection
  - Fulminant decline in oxygenation
  - Rapidly progressive respiratory failure

Diagnosis

- Clinical evaluation- based on CRP
  - **History –**
    - subacute course of progressive symptoms (SOB & Cough) over months to years
    - Past, family and environmental history to rule out other types of ILDs (HP, occupational ILD, CT-ILD)
  - **Examination –**
    - Fine end inspiratory crackles at lung bases
    - Pulmonary hypertension & right heart failure late in disease
    - Clubbing in majority

- **Radiological –**
  - **CXR-** Useful initial visual perception of overall lung involvement
    - Low lung volumes
    - Bilateral reticular opacities- most severely involving periphery and bases of lungs
    - Features of heart failure
    - Features are not specific but demonstrate disease extent & progression & cardiopulmonary status

- **HRCT-** necessary step in diagnostic evaluation
  - First may illustrate characteristic features of UIP-
    - patchy, predominantly peripheral, sub pleural, bibasal reticular abnormalities
    - Traction bronchiectasis &/or sub pleural honeycombing
    - May enable clinical diagnosis without need for biopsy
  - Secondly
    - clinical diagnosis of new onset IPF can be made accurately if classic clinical & HRCT features are present
    - If typical findings not present may identify other disease processes
  - Thirdly
    - May assist in decision of whether or not to biopsy & the sample site(s)
    - If extensive fibrosis & honeycombing present, disease likely is end stage

- **Pulmonary function test-** Initial PFT useful for gauging global physiological severity of disease
  - Restrictive impairment (reduced VC & TLC) by body plethysmography
  - **D**Lco corrected for Hb is reduced frequently
  - Resting ABG- normal or hypoxemia & respiratory alkalosis (these abnormalities accentuated by exercise)
- **Bronchoscopy –** can make a definitive diagnosis in few ILDs but not in IPF
  - It is done to detect BAL cellular or histologic patterns atypical for IPF
  - Significant increase in lymphocytes & granulomas is not a feature of IPF

- **Surgical lung biopsy –** open or thoracoscopic
  - Final diagnostic step
  - Decision to proceed must be individualized for each patient
  - Optimal location and number of biopsy sites is important
    - Location based on radiological appearance on HRCT
      - Optimal sites- visibly abnormal areas as well as normal appearing lung adjacent to abnormal areas
    - Biopsy from more than one lobe is helpful
      - NSIP and UIP may be present in different lobes in same lung
  - UIP is the pathological abnormality essential to diagnosis of IPF
    - Heterogenous appearance with alternative areas of normal lung, interstitial inflammation, fibrosis & honeycomb change affecting the peripheral sub pleural parenchyma most severely

Treatment

- **Conventional therapy**
  - Corticosteroids alone- ineffective and associated with significant side effects
  - Corticosteroids + immunosuppressives
    - Limited efficacy in slowing the progressive deterioration in lung function
    - Slightly superior to corticosteroids alone, when initiated for new onset IPF
    - Low dose prednisone + azathioprine- frequently used initial treatment in IPF
    - Alternative -Prednisone + cyclophosphamide

- **Newer therapies-** required because of ineffectiveness and side effects of conventional therapy
  - Immuno modulators
    - Interferon γ - inhibitory effect on fibroblasts
  - Antifibrotic agents
    - Colchicine
    - D-penicillamine
    - Pirfenidone
    - ACE inhibitors
    - Statins
  - Anti-oxidants
    - N-acetylcysteine

- Endothelial receptor-1 antagonist
  - Bosentan
- Tumor necrosis factor-α blocker
  - Etanercept
- Imatinib mesylate - cAbl tyrosine kinase inhibitor + PDGF receptor antgonist
- CTGF blocker
  - FG-3019
- Rapamycin
- Antileukotriene drugs
  - Zileuton

Prognosis

- Indicators of longer survival
  - Younger age (<50 years)
  - Female
  - Shorter symptomatic period (< 1 year) with less dyspnea, relatively preserved lung function
  - Ground glass and reticular opacities on HRCT
  - Increased lymphocytes (20 – 25%) in BAL
  - Beneficial response or stable disease 3-6 months after initial therapy

Monitoring clinical course of IPF

- Parameters used are
  - Assessment of dyspnea
  - Physiologic testing
    - Lung volumes
    - **D**Lco
    - Resting ABG
    - Cardiopulmonary exercise testing with measurement of gas exchange
  - HRCT

Approach to treatment

- Therapy is not indicated for all patients
  - Age >70 years
  - Extreme obesity
  - Concomitant major illness
  - Severe impairment in pulmonary function
  - End stage honeycomb on radiology
- Treatment should be started
  - At the first identification of clinical or physiological evidence of impairment of lung function
  - Early in the course of the disease before irreversible fibrosis has developed

- Combination therapy is a reasonable approach
  - Corticosteroid (prednisone or equivalent)
    - 0.5mg/kg/day orally X 4 weeks
    - 0.25 mg/kg/day X 8 weeks
    - 0.125 mg/kg/day as initial therapy
  - Azathioprine at
    - 2-3 mg/kg/day to maximum dose of 150mg/day orally
    - Begin at 25-50 mg/day
    - Increase by 25 mg increments every 7-14 days
- Or
  - Cyclophosphamide

- Length of therapy –
  - objective response may take >3 months of therapy
  - Combined therapy should be continued for at least 6 months in absence of complications
- Monitoring of therapy
  - At 6 month
    - If patient worse – therapy stop or changed
    - If patient improved or stable - therapy continued at same doses
  - At 12 months
    - If patient worse - therapy stop or changed
    - If patient improved or stable - therapy continued at same doses
  - At 18 month or more
    - Therapy continued indefinitely only in individuals with evidence of continued improvement or stabilization

- Favorable (or improved) response to therapy- Decrease in symptoms (SOB, cough)
  - Reduction of CXR/ HRCT findings
  - Physiologic improvement
    - ≥ 10% increase in TLC or VC (or at least ≥200-ml change)
    - ≥15% increase in single breath **D**Lco
    - Improvement or normalization of O_2 saturation
- 2 or more, on 2 consecutive visits over a 3- to 6- month period

- Stable response
  - 10% change in TLC or VC (or <200- ml change)
  - <15% change in DLC
  - No change in O_2 saturation

- 2 or more, on 2 consecutive visits over a 3- to 6- month period

- Failure to respond to therapy- (after 6 month of therapy)
  - Increase in symptoms
  - Increase in opacities, honeycombing, PHT
  - Deterioration in lung function
    - ≥10% decrease in TLC or VC (or ≥200-ml change)
    - ≥15% decrease in single breath **D**Lco
    - Worsening of O_2 saturation

Monitoring for adverse effects

- Corticosteroids
- Azathioprine & cyclophosphamide
  - Hematological
  - Hepatic
  - Oncogenic potential
  - Hemorrhagic cystitis
- Also monitor for
  - Opportunistic lung infection
  - Pneumonia
  - Pulmonary emboli
  - Secondary pulmonary hypertension
  - Heart failure
  - Neoplasm

Lung transplantation

- Considered for progressive physiologic deterioration despite therapy and who meet established criteria
  - Severe functional impairment
  - Oxygen dependency
  - Deteriorating course
  - <60 year age
- Early listing important because long waiting period
- 5 year survival- 50-60%

Summary

- IPF has evolved into a well defined clinical pathological syndrome characterized by UIP on HRCT & lung biopsy
- Diagnosis is straight forward in advanced cases, SLB is required if atypical features are present
- Gold standard of diagnosis rests on an interactive discussions among pulmonologists, radiologists and pathologists

Summary

- For treatment, until an efficacious regimen is developed patients should be treated with combined prednisone and azathioprine (as recommended by ATS) for at least 6 months
- Patient should be encouraged to enroll in ongoing clinical trials for development of novel therapies
- Patient should be monitored during therapy for response, adverse effects and other complications