Emerging Therapies for COPD

DM Seminar

17 Feb 06

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Introduction

- No present treatment reverses COPD
- Rational treatment
- Underlying cellular and molecular mechanisms
- Chronic inflammation
- Neutrophils, macrophages, CD 8 lymphocytes
- Fibrosis
- Destruction (neutrophil elastase, MMP)
- Asthma is different.

Newer interventions

- Smoking cessation
- New drugs
  - Bronchodilators
  - Mediator antagonists
  - Anti-inflammatory agents
  - Protease inhibitors
  - Remodelling agents
  - Drug delivery systems
- Bronchoscopic LVRS

Difficulties

- Molecular & cell biology still not understood
- Animal models lacking for early drug testing
- Long term studies (> 3 yrs), large no of pts.
- Surrogate markers- short term monitoring

Smoking Cessation

- Major cause for COPD
- Nicotine addiction
- Quit rates
  - Placebo 6%
  - NRT and behavioural therapy 9%
  - Bupropion (6-9 wks) 18% at 1 yr
  - ?? Nortryptilline
- Well tolerated, sleeplessness, epilepsy
- Better drugs may emerge.

New Bronchodilators

- Mainstay; need improvement
- LABA once daily ??
- Tiotropium recently introduced
- Slow diss from M1,M3 receptors
- Better than ipratropium QID
- Symptom control, QOL
- Decrease in exacerbations
- Additive effects with LABA
- Bronchodilator of choice in COPD

MEDIATOR ANTAGONISTS

- On going inflammation; even in ex-smokers
- Neutrophillic inflammation
- Reactive oxygen species
- Inhib of Leukotriene B4,chemokines, TNF,iNOS, anti-oxidants.

Leukotriene B4

- Potent chemoattractant of neutrophils
- Increased in sputum of COPD pts
- Synergy with IL-8
- BLT1(granulocyte monocyte)
- BLT2 (T lymphocytes)
- Antagonists eg LY29311 etc
- 5’ lipoxygenase inhibitors eg zileuton(synthesis)

Chemokine inhibitors

- IL-8 marked increase, disease severity
- Monoclonal Ab to IL-8 in clinical trials
- Block common receptor for CXC family
- CXCR1, CXCR2
- Monocyte chemotactic protein 1:CCR2

TNF alpha inhibitors

- TNF increased, increases IL-8 via NF-κB
- Severe wasting
- Infliximab (monoclonal Ab), etanerecept (soluble recep) may act.
- ? blocking Ab if long term
- ? Repeated injections inconvenient
- TNF conv enzyme (TACE) better target for inhibition with small molecules.

Anti oxidants

- Oxidative stress increases in COPD
- Reactive O2 sp aid pathology
- Anti-oxidants may help
- Oral NAC (small decrease in AE)
- Glutathione compounds
- Superoxide desmutase
- Selenium based drugs

iNOS inhibitors

- Increased NO release
- Peroxynitrite- potent radical: may nitrate proteins and alter fn.
- 3-nitrotyrosine (indicator) inc in COPD
- Selective inhibitors in development(inducible nitric oxide synthase)

New Anti-inflammatory Treatments

- Chronic inflammation
- Macrophages,neutrophils,CD8+ cells
- Airways and parenchyma
- Steroid resistance
  - Inhibitory effect of smoking (histone deacetylation)
  - New agents/unlocking steroid resistance

PDE4 inhibitors

- PDE4 predominant form expressed
- Selective inhibitors
- Cilomilast, roflumilast
- Limited by side effects (GIT)
- Isoenzyme subtype selective inhibitors may have less side effects

Nuclear Factor-KB inhibitors

- Regulates IL-8, TNF,MMP
- Several approaches
- Gene transfer of inhibitor
- Inhibition of NIK, IKK
- Hypoestoxide in African remedy for inflm
- Possibility of sepsis as a result

Adhesion molecule inhibitors

- Recruitment depends on adhesion mol.
- E-selectin (endothelial cells)
- Sialyl-Lewis (neutrophils)
- TBC1269 blocks selectins, neut adhesion
- Concerns about immunity/sepsis

IL-10

- Anti-inflammatory cytokine
- Inhibits TNF and IL-8
- Favours antiproteases (lowers MMP)
- Levels are low in COPD
- Tried in RA, psoriasis, IBD
- Daily injections over weeks
- Selective activator of IL-10 receptors

Mitogen activated protein kinase inhibitors

- p38 MAP kinase helps express Il8, TNF, MMP
- SB 203580 SB 239063
- Non peptide inhibitors
- Broad range of anti-inflammatory effects
- Toxicity?
- Limited by inhaled route?

Phosphoinositide-3 kinase inhibitors

- PI-3K enzymes promote lipid 2nd messengers
- PI-3Kγ neutrophil recruitment, activation
- Selective inhibitors may help COPD

PROTEASE INHIBITORS

- Protease- Antiprotease imbalance.
- Proteases digest elastin.
- Anti-proteases protect
- Inhibiting proteases/Increasing anti-proteases.
- Progress in identification of these.

Endogenous antiproteases

- Supply endogenous antiproteases
- Recombinant form/Viral vector gene delivery
- Poor efficacy/ Not cost effective
- Gene delivery inadequate protein

Protease inhibitors

- More promising
- Small molecule inhibitors of proteinases
- ONO-5046, FR901277
- Inhibit elastase induced injury
- Neutrophil elastase,MMP-9,cathepsins

REMODELLING AGENTS

- Retinoic acid reverses histo/physio changes in rats (Increases alveoli)
- Activates receptors
- Growth/diffrentiation genes
- Extrapolation to humans?
- Trial of ATRA in emphysema underway

Drug Delivery

- MDI/DPI
- Low mass median diameter
- Deposition in periphery
- Targetting specific cell types eg macrophages
- Prodrugs activated by elastases to concentrate drug at site of disease activity and reduce systemic exposure.

Genetic factors

- 10-20% of smokers have COPD.
- Identification of genes predisposing to COPD may identify new approaches to therapy

Surrogate markers

- Predicting clinical usefulness of drugs
- Large studies over 2 yrs
- Sputum parameters/ Exhaled condensates
- Cells/mediators/enzymes/cytokines/lipid mediators
- Improved imaging emphysema vs small airway disease

LVRS

- Established palliative therapy in emphysema
- Improves lung fn,ex.capacity, QOL.
- Significant mortality and morbidity
- Offset benefits of the procedure
- Attempts at technique modification.
- Plication,stapling without removal
- Faster, less post-op air leak.

Bronchoscopic LVRS

- Ingenito et al
- Sheep model of emphysema
- FOB glue application
- Creation of absorption atelectasis
- ?? Sterile abscesses
- Toma mechanical plug/occluded stent
- Less invasive, reduced cost, more eligible

Bronchoscopic LVRS

Chest 2003;124;1073-1080

- Implanting multiple bronchial prostheses in segmental airways of pts with emphysema.
- 10 pts severe upper lobe emphysema
- Emphasys endobronchial prostheses
- Placed under GA, over guide wire
- Antibiotics and bronchodilators given.

Procedure

- Time 1 h 55 min avg
- No post op rehab
- No deconditioning
- 1 pneumonia, 2 AE, 1 Ptx
- No migration,excess coughing, hyperinflation

Respiratory fn

- No change in FEV1, FVC, TLC, ABG,MRC
- CT- Little atelectasis
- Perfusion to upper lobes decreased

BLVRS

- Safe and technically feasible
- Glues, plugs, stents, valves
- No radiological atelectasis achieved
- Perf/ventilation decreased
- Perivalv leak,incompetence, net gas prod, collateral vent channels, tensile forces from lower lobes

Promoting collapse

- More valves
- Adhesive substance through valve
- Active aspiration
- Percutaneous catheter and suction

Benefit without collapse

- Exercise capacity improved
- Dynamic hyperinflation with exercise minimized
- Reduction in dead space
- ? Recruitment of collapsed capill bed

Conclusion

- Improved smoking cessation techniques
- New drugs/Modes of delivery based on underlying mechanisms of inflammation,fibrosis, alveolar destruction
- Brochoscopic LVRS