Emerging Therapies for COPD

DM Seminar
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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), etanercept (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 inflammation
- 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
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• 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
- Bronchoscopic LVRS