DM SEMINAR
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NEWER INHALED BRONCHODILATORS AND INHALED CORTICOSTEROIDS: REVIEW OF DEVELOPMENTS IN LAST FIVE YEARS

DR P SARAT SINGH
“THE GREAT THING IN THE WORLD IS NOT SO MUCH WHERE WE STAND, AS IN WHAT DIRECTION WE ARE MOVING”

OLIVER WENDELL HOLMES, SR.
PHYSICIAN AND POET
2006

• SMART (SALMETEROL MULTICENTRE ASTHMA RESEARCH TRIAL)
• RANDOMISED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL TO STUDY EFFECT OF ADDITION OF SALMETEROL TO USUAL ASTHMA PHARMACOTHERAPY
• LABA UNDER SCRUTINY, INCREASE IN RESPIRATORY AND ASTHMA RELATED DEATHS/LIFE THREATENING EXPERIENCES IN SALMETEROL TREATED VS PLACEBO SUBJECTS

* Chest 2006;129:15-26*
2006...

- LABA CONTROVERSY → GENETIC VARIATION OF BETA ADRENERGIC RECEPTOR (ADRβ2) STUDY
- Arg16Arg GENOTYPE ('RISK' GENOTYPE) - UNCERTAIN ROLE
- ICS/LABA (BUDESONIDE-FORMOTEROL) AS RELIEVER/CONTROLLER (UNSCHEDULED 'EXTRA PUFF' FOR ASTHMA SYMPTOMS) ALREADY TREATED WITH ICS/LABA GAINING ATTENTION

*Chest 2006;129:246-256*
2006..

- TORCH (TOWARDS A REVOLUTION IN COPD HEALTH), FIRST TRIAL WITH ICS/LABA FOR COPD MORTALITY
- EFFICACY OF COMBINATION THERAPY ON EXACERBATION, BENEFIT ON HEALTH STATUS ESTABLISHED, WITHOUT MORTALITY BENEFIT
- ADDITION OF ICS/LABA TO TIOTROPIUM IMPROVE LUNG FUNCTION, HEALTH STATUS, HOSPITALISATION RATE WITHOUT BENEFIT OF EXACERBATION
2007

- NAEPP (NATIONAL ASTHMA EDUCATION AND PREVENTION PROGRAMME) -- ASTHMA TREATMENT STEP 4 SPLIT TO 4-6 STEPS FOR LOGICAL ESCALATION OF STEROID DOSES
- 2ND CHANGE, RETRACTION OF PREFERANCE FOR LOW DOSE ICS/LABA OVER DOUBLING IN ICS DOSE
- BUT ‘GINA’ STILL PREFER LOW DOSE ICS/LABA OVER HIGHER DOSE OF ICS
- CONCERN FOR RISK OF LABA
2007...

- 2 STUDIES ON DE-ESCALATING TREATMENT FOR MILD PERSISTENT ASTHMA, ON LOW DOSE ICS CONTROL
- ALA-ACRC (AMERICAN LUNG ASSOCIATION ASTHMA CLINICAL RESEARCH CENTRES) FINDING-TWICE DAILY FLUTICASONE/SALMETEROL COULD BE STEPPED DOWN TO ONCE DAILY OF SAME COMBINATION, THEREBYHALVING ICS DOSE
- Pappi et al - BECLOMETHASONE/SALBUTAMOL, AS NEEDED LOW DOSE THERAPY, ABLE TO CONTROL MILD ASTHMA WITH FOUR-FOLD LOWER ICS REDUCTION

2007...

- CONTROVERSY OVER ICS TREATMENT CAUSING PNEUMONIA
- ISEEC (INHALED STEROIDS EFFECT EVALUATION IN COPD), POOLED STUDY OF SEVEN LONG TERM, RANDOMIZED, PLACEBO CONTROLLED ICS TRIAL, EACH OF >12 MONTHS DURATION
- ICS IMPROVE LUNG FUNCTION BETTER IN EX-SMOKER THAN CURRENT SMOKER,
- WOMEN RESPOND BETTER THAN MEN

*Chest 2007;131:682-689*
2008

- CHLOROFLUOROCARBON PROPELLED MDIs replaced by more eco friendly but costly hydrofluoroalkane counterpart
- LABA controversy continues but their role to stay in adults if given with ICS
- UPLIFT (understanding potential long-term impacts on function with tiotropium)-benefit in COPD exacerbation, hospitalisation but not FEV1 (tiotropium over placebo)
- Tiotropium also reduced respiratory and cardiac morbidity

2009

- Tiotropium shown to protect from dynamic hyperinflation in COPD
- Benefit is independent of the extent of emphysema
- Dynamic hyperinflation related with reduced daily physical activity, exacerbations and mortality in COPD

2010

- LABA CONTROVERSY--RISK IN COMBINATION USE WITH ICS
  - BALANCE AGAINST ASTHMA SYMPTOMS
  - FDA WORKING FOR AN ANSWER

- ADRB2
  - DATA SUGGEST THAT HOMOZYGOTES FOR ARGININ ALLELE MAY BE AT GREATER RISK OF ASTHMA EXACERBATION WITH LABA WITHOUT ICS
INHALED BRONCHODILATORS

• BETA-2 ADRENERGIC AGONIST
  - SHORT ACTING (SABA) e.g. SALBUTAMOL (4-6 HRS) TERBUTALINE
  - LONG ACTING (LABA) e.g. (AR)FORMOTEROL (12 HRS) SALMETEROL
  - ULTRA LONG ACTING (ULABA) e.g. INDACATEROL (24 HRS) CARMOTEROL

• ANTICHOLINERGICS e.g. IPRATROPIUM BROMIDE
  (SHORT ACTING, 6-8 HRS)
  TIOTROPIUM BROMIDE
  ACLIDIUM BROMIDE
  (LONG ACTING, 24 HRS)
MOA INHALED BRONCHODILATOR

• BETA-2 AGONISTS:
  - G-PROTEIN—cAMP—ADENYLYL CYCLASE—MYOSIN LIGHT CHAIN KINASE PHOSPHORYLATION—K+ EFFLUX—HYPERPOLARISATION—AIRWAY MUSCLE
• ANTICHOLINERGICS(MOST EFFECTIVE BRONCHODILATORS)
  - ACT VIA M2,M3 MUSCARINIC RECEPTORS—PHOSPHOLIPASE C—IP3(INOSITOL PHOSPHATE),DAG(DIACYLGLYCEROL)
INDACATEROL

• INTRODUCED IN 2009, APPROVED BY EUROPEAN MEDICINES AGENCY FOR MAINTENANCE TREATMENT OF COPD AT 150 mcg, MAX. 300mcg OD

• PARTIAL BETA-2 AGONIST, HIGH INTRINSIC EFFICACY AT RECEPTOR LEVEL, NO ANTAGONIST BEHAVIOUR (‘NEAR FULL AGONIST’)

• RAPID (WITHIN 5 MTS), SUSTAINED ACTION (AT LEAST 24 HRS).

INDACATEROL...

• RCT PHASE III COPD TRIAL
• INDACATEROL 150 mcg OR 300mcg OD, UPTO 52 WEEK
• IMPROVEMENT OVER PLACEBO, FORMOTEROL SALMETEROL, ANTICHOLINERGIC Tiotropium
• PARAMETERS IMPROVED ARE TROUGH FEV1, SYMPTOM CONTROL, DYSPNEA, QUALITY OF LIFE, EXACERBATION

Chest. 2011 Feb24: (Epub ahead of publication)
INDACATEROL VS SALMETEROL

• COMPARED WITH SALMETEROL 50mcg BD, INDACATEROL 150 mcg OD

• SHOWED SUPERIORITY IN TROUGHS FEV1 AFTER 12 AND 26 WEEKS (+60ml AND +70 ml RESPECTIVELY, p<0.001)

• IMPROVED PARAMETERS INCLUDE QOL, DYSPNEA, NEED FOR ADDITIONAL RESCUE MEDICATION IN RANDOMIZED, DOUBLE BLIND, COMPARISON STUDY.

_Eur Respir J.2011;37:273-279_
INDACATEROL VS TIOTROPIUM

• IN A 26 WEEK RANDOMIZED COMPARISON TRIAL
• INDACATEROL 150 mcg AND 300 mcg OD COMPARED WITH PLACEBO AND OPEN-LABEL TIOTROPIUM 18mcg OD
• TROUGH FEV1 AT 12 WK INCREASED VS PLACEBO BY 180 ml WITH BOTH DOSING, AND BY 140 ml WITH TIOTROPIUM (ALL \( p < 0.001 \))
• AT 12, 26 WKS BOTH DOSING SHOWED (+40-50 ml) SUPERIORITY OVER TIOTROPIUM (\( p < 0.05 \), ALL COMPONENTS)

Am J Respir Crit Care Med 2010;182:155-162
INDACATEROL..

- POOLED ANALYSIS, ATS 2010 MEET
- INDACATEROL 150 mcg or 300mcg OD OVER 3-6 MONTHS
- SIGNIFICANT IMPROVEMENT OF SYMPTOMS, HEALTH RELATED QOL, RESCUE USE, EXACERBATION IN MODERATE TO SEVERE COPD.
- BENEFITS INDEPENDENT OF AGE, CONCOMITANT ICS USE BASELINE BRONCHOCONSTRICTION REVERSIBILITY

*Am J Respir Crit Care Med 2010,181:A4439*
INDACATEROL..SAFETY

- COUGH COMMONEST S/E 17.1%, 10.3% IN 400mcg AND 200 mcg RESPECTIVELY
- SMALL CHANGE IN SER.K+, GLUCOSE AT HIGH DOSE 400-800 mcg IN ASTHMATICS
- 52 WK STUDY OF 150 mcg, 300mcg INDACATEROL, PLACEBO-ADVERSE EVENT 76%, 77%, 68%, SERIOUS EVENTS IN 10.4%, 12.3%, 10.5% RESPECTIVELY.
- INSIGNIFICANT QTc, K+, GLUCOSE LEVEL

_Chest 2011 Feb24;(Epub Ahead Of Print)_
INDACATEROL..SAFETY..

- WORTH et al..
  - CARDIO-/CEREBROVASCULAR EVENTS NOT SIGNIFICANTLY INCREASED AT 150mcg, 300mcg vs PLACEBO
  - QTc CHANGE (>60ms) LOW WITH BOTH DOSE
  - HOLTER MONITOR, NO RELEVANT EFFECT ON ARRHYTHMIA
  - MORTALITY LOWER WITH TREATMENT THAN WITH PLACEBO, 70% LOWER RR (p=0.054)
TIOTROPIUM

• APPROVED FOR COPD (FDA 04) NOT ASTHMA
• DISSOCIATES SLOWLY FROM M1 AND M3 (EXCITATORY RECEPTORS FOR ACH RELEASE) RECEPTORS (LASTING 24 HRS), RAPID FROM M2 (INHIBITORY RECEPTORS FOR ACH RELEASE)
• NOT ASSOCIATED WITH NEGATIVE CARDIOVASCULAR OUTCOME LIKE ACS, HF, DYSRHYTHMIAS AND CARDIOVASCULAR ASSOCIATED DEATHS (UNLIKE SHORT ACTING IPRATROPIUM)

*Expert Opin. Drug Saf. (2011) 10(5)*
TIOTROPIUM..

- IN A 3 WAY, DOUBLE BLIND, TRIPLE DUMMY CROSSOVER TRIAL, 210 PATIENTTS WITH ASTHMA
- ADDITION OF TIOTROPIUM (18 mcg) TO ICS, COMPARED WITH DOUBLING OF DOSE OF ICS (PRIMARY SUPERIORITY COMPARISON) OR ADDITION OF THE LABA SALMETEROL (2NDARY NONINFERIORITY COMPARISON)
- MEASURING MORNING PEF (PRIMARY OUTCOME), EVENING PEF, ASTHMA CONTROL DAYS, PREBRONCHODILATOR FEV1, DAILY SYMPTOM SCORES (2NDARY OUTCOMES) STUDIED
TIOTROPIUM...

- ADITION OF TIOTROPIUM TO ICS IMPROVED SYMPTOMS AND LUNG FUNCTIONS IN INADEQUATELY CONTROLLED ASTHMA
- EFFECTS BEING EQUIVALENT TO THOSE WITH THE ADDITION OF SALMETEROL

TIOTROPIUM..

- ACP, ACCP, ATS, ERS RECOMMENDATION FOR COPD-
- CLINICIANS TO PRESCRIBE MONOTHERAPY USING LONG ACTING INHALED CHOLINERGICS OR INHALED LABA
- FOR SYMPTOMATIC PATIENTS WITH COPD AND FEV1<60% PREDICTED (STRONG RECOMMENDATION, MODERATE QUALITY EVIDENCE)
- CHOICE BASED ON PATIENT PREFERANCE, COST, ADVERSE EFFECT PROFILE

TIOTROPIUM VS. SALMETEROL

• 1 YR RCT, DOUBLE BLIND, DOUBLE DUMMY, PARALLEL-GROUP TRIAL, 7376 PTS.
• 18mcg TIOTROPIUM OD VS. 50mcg SALMETEROL BD
• MODERATE TO SEVERE EXACERBATION OF COPD
• H/O EXACERBATION IN THE PRECEDING YEAR
TIOTROPIUM VS SALMETEROL...

• Tiotropium increase time to first exacerbation (187 vs 145 days)
• 17% risk reduction (HR 0.83, 95% CI, 0.77-0.9, p<0.001)
• Increase time to first severe exacerbation (HR 0.72, 95% CI, 0.61-0.85, p<0.001)
• Also reduce annual no of moderate/severe exacerbation (0.64 vs. 0.72; RR, 0.89, 95% CI, 0.83 to 0.96, p=0.002)
• Adverse events, deaths comparable

ACLIDIUM BROMIDE

• SUBMITTED FOR EUROPEAN MARKETING AUTHORISATION JULY 2011 FOLLOWING SIMILAR SUBMISSION BY NDA TO FDA JUNE
• 400 mcg BD THROUGH NOVEL GENUAIR INHALER (MDPI, MULTIDOSE DRY POWDER INHALER). PHASE III DETAILS TO BE DISCUSSED AT ERS MEET SEPTEMBER 2011 AMSTERDAM
• FAST ONSET, MAY BE USEFUL FOR CONTROL
• RAPIDLY HYDROLYSED IN HUMAN PLASMA SO SYSTEMIC ANTICHOLINERGIC EFFECTS IN THE RANGE OF PLACEBO
• HEADACHE, NASOPHARYNGITIS COMMON S/E
INHALED CORTICOSTEROIDS (ICS)

• MOA: ANTI-INFLAMMATORY
  - GLUCOCORTICOID RECEPTOR COMPLEX---
    REGULATES GENE TRANSCRIPTION OF PROTEINS—INHIBIT PROINFLAMMATORY CYTOKINES
• HIGHLY LIPOPHILIC COMPOUNDS, GOOD BINDING TO RECEPTORS
• HIGH EFFICIENT FIRST PASS HEPATIC METABOLISM, LOWER SYSTEMIC ABSORPTION
ICS..

• ADVERSE EFFECTS:
  - COUGH, DYSPHONIA, ORAL CANDIDIASIS
  (USE OF CHAMBER DEVICE, MOUTH WASHING LESSEN THESE EFFECTS)
  - SYSTEMIC EFFECTS: ONLY IN HIGH DOSES-
    ADRENAL SUPPRESSION,
    OSTEOPOROSIS,
    GROWTH SUPPRESSION,
    SKIN THINNING
    EASY BRUISING
ICS...

- BECLOMETHASONE DIPROPIONATE
- BUDESONIDE
- MOMETASONE
- FLUNISOLIDE
- TRIAMCINOLONE ACETONIDE
- CICLESONIDE
- FLUTICASONE PROPIONATE
- FLUTICASONE FUROATE
FLUTICASONE FUROATE (FF) IS DIFFERENT FROM FLUTICASONE PROPIONATE (FP)

• ENHANCED AFFINITY OF FF TO TARGET RECEPTOR, SO DOSE LOWER 110 mcg (FF), 200 mcg (FP)
• ENHANCED LUNG RESIDENCY FOR FF VS FP, BD, MMT, SO OD DOSING
• CHANGE AT 17-α ESTER OF FP, NO COMMON METABOLITE WITH FP

Allergy Asthma Proc. 2009; 30: 84-.
FLUTICASONE FUROATE (FF)

- RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, 6 WAY CROSSOVER STUDY
- 24 ALLERGIC ASTHMA PATIENTS (MEAN AGE 38.2 YEARS, FEV1 >/= 70% PREDICTED, PC20 AMP</= 50 mg/ml), PC20 BEING CONCENTRATION OF ADENOSINE 5’ MONOPHOSPHATE CAUSING FEV1 TO DROP BY 20%.
- FF 1000 mcg OD, FP 1000 mcg, PLACEBO AT 2, 14, 26 H PRIOR TO AMP CHALLENGE AND eNO MEASUREMENT
FLUTICASONE FUROATE

- FF SIGNIFICANTLY IMPROVED PC20 AMP VS PLACEBO AT 2, 14, 26 HRS BUT FP VS PLACEBO SHOWED IMPROVEMENT ONLY UPTO 14 HRS
- THE NEW INHALED CORTICOSTEROID FF, BUT NOT FP, DEMONSTRATES PROLONGED PROTECTION UPTO 26 HRS AGAINST AHR TO AMP IN ASTMA PATIENTS
- FF WAS WELL TOLERATED AND THERE WERE NO SERIOUS ADVERSE EVENTS

Allergy 65(2010)1531-1535
SOME NEW DRUGS IN THE OFFING

• MABA-MUSCARINIC ANTAGONISTS BETA 2 AGONIST IN SINGLE FORMULATION
• ULTRA LABA-GSK 642444
• SOFT STEROIDS-TARGET SPECIFIC WITH VERY LITTLE SYSTEMIC EFFECTS