DM SEMINAR

02-09-2011

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

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“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 (UNSCEDULED '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,THEREBY HALVING ICS DOSE
- Pappi et al- BECLOMETHASONE/SALBUTAMOL,AS NEEDED LOW DOSE THERAPY,ABLE TO CONTROL MILD ASTHMA WITH FOUR-FOLD LOWER ICS REDUCTION

N Engl J Med 2007;356:2040-2052

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 COUTERPART
- 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

N Engl J Med 2008;359:1543-1554

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

Pulm Phamacol Ther 2009;22:237-242

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 ALLELLE 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).

Int J Chron Obstruct Pulmon Dis.2011;6:237-243

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,INDACATEROL150 mcg OD
- SHOWED SUPERIORITY IN TROUGH 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 AT150mcg,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 PATIENTSTS WITH ASTHMA
- ADDITION OF TIOTROPIUM(18mcg)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

N Engl J Med 2010; 363:1715-26

TIOTROPIUM..

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

Ann Intern Med.2011;155:179-191

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

N Eng J Med 2011;364:1093-1103

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 110mcg(FF),200mcg(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</=50mg/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