Täiskasvanute astma käsitlus esmatasandil
Tõendusmaterjali kokkuvõte

Kliiniline küsimus nr 6

Kliinilise küsimuse tekst: Kas astma diagnoosiga püsiravi vajavatele patsientidele tuleks määrata ICS monoteraapiana *versus* ISC ja pikatoimeliste ß2-agonistide (LABA) kombineeritud teraapia? *Märkus: ravi alustamisel, mitte ülestiitrimisel, mis on kliiniline küsimus 7.*

Kokkuvõte, sh kriitiliste tulemusnäitajate kaupa:

Püsiravi alustamisel madalas annuses ICS (200-400 µg BUD-Eq/die) võrreldes samas annuses ICS ja LABA kombineeritud teraapiaga ravitulemustes suuri erinevusi ei ole: tulemusnäitajate osas olulisi erinevusi ei ole, v.a. kombineeritud ravi korral esineb mõnevõrra vähem päevaseid sümptomeid ja vajadus hooravi järgi on veidi väiksem. Ravi kõrvaltoimete osas olulisi erinevusi ei selgunud. Püsiravi alustamisel kõrgemas annuses ICS (800-1000 µg BUD-Eq/die) võrreldes kombineeritud teraapiaga (madalamas annuses ICS ja LABA), esineb kombinatsioonravi saanute hulgas rohkem suukaudset kortikosteroidravi vajavaid ägenemisi ja ravi katkestamisi. Kortikosteroidravi vajavaid ägenemisi esines vastavalt 11 ja 9 juhtu iga 100 vastavalt kombinatsioonravi või ICS monoteraapiat saava patsiendi kohta (ravi kestusega vähemalt 43 nädalat).

Andmed põhinevad Cochrane andmebaasi 2009. a avaldatud süstemaatilisel ülevaatel ja 22 kliinilise katse meta-analüüsil, mis hõlmab kuni 2008.a. läbi viidud uuringuid (Ni Chroinin 2009). Hiljem avaldatud 2 RCT metodoloogiline kvaliteet on madal.

Cochrane'i andmebaasi meta-analüüsi tulemusnäitajad olid täpsemalt järgmised:

Võrdlus 1: ISC+LABA vs ainult ICS samas annuses
LABA: salmeterool 50 µgx2 või formoterool 12 µgx2
ISC: 200-400 µg/die beklometasooni-Eq (vastavalt budesoniid 200-400 µg/die või flutikasoon 100-200 µg/die)

- Elukvaliteet – ei ole analüüsitud
- Astma ägenemiste esinemine, mis vajavad suukaudset kortikosteroidravi: OR 1.04 [0.73, 1.47] (statistiliselt mitteoluline)
- Suremus (astmast tingitud või olenemata põhjusest e all-cause mortality) - ei olnud surmajuhtusid
- Päevaste sümptomite esinemine: sümptomskoori muutus: -0.26 [-0.37, -0.14](statistiliselt oluline erinevus kombinatsioonravi kasuks); astmasümptomitega päevade osakaal (%) -0.18 [-4.47, 4.10](statistiliselt mitteoluline)
- Öösümptomid/unehäired: ärkamistega ööde osakaal (%): 0.60 [-1.39, 2.59]; astmasümptomitega ööde osakaal (%): 2.40 [-6.78, 11.58] (statistiliselt mitteolulised)
- Hooravi vajadus: hooravi vajaduse kordade muutus ööpäevas -0.41 [-0.73, -0.09](statistiliselt oluline erinevus kombinatsioonravi kasuks)
- Hospitaliseerimine (olenemata põhjusest) – ei ole andmeid, kuid on hospitaliseerimine astma ägenemiste tõttu: OR 0.38 [0.09, 1.65](statistiliselt mitteoluline)
- Ravi katkestamine kõrvaltoime tõttu 1.07 [0.67, 1.71] (statistiliselt mitteoluline)
- Füüsilise aktiivsuse piiratus – ei ole analüüsitud
- Ravikulu väiksem monoteraapia korral

Samadele järeldustele jõudis **ka Drug Class Review: Controller Medications for Asthma: Final Update 1 Report** [Internet].

Võrdlus 2: ISC+LABA vs ainult ICS, aga suuremas annuses
LABA: salmeterool 50 µgx2 või formoterool 12 µgx2
ISC 800-1000 µg/die beklometasooni-Eq (vastavalt budesoniid 800-1000 µg/die või flutikasoon 400-500 µg/die)

- Elukvaliteet – ei ole analüüsitud
- Astma ägenemiste esinemine, mis vajavad suukaudset kortikosteroidravi OR 1.24 [1.00, 1.53](statistiliselt oluline erinevus kombinatsioonravi kahjuks)
- Suremus (astmast tingitud või olenemata põhjusest e *all-cause mortality)* surmajuhtusid ei esinenud
- Päevaste sümptomite esinemine: astmasümptomitega päevade osakaal (%) -4.60 [-12.79, 3.59](statistiliselt mitteoluline)
- Öösümptomid/unehäired ärkamistega ööde osakaal (%): ei ole analüüsitud
- Hooravi vajadus: hooravi vajaduse kordade muutus ööpäevas 0.06 [-0.03, 0.15] (statistiliselt mitteoluline)
- Hospitaliseerimine (olenemata põhjusest) – ei ole toodud, kuid on hospitaliseerimine astma ägenemiste tõttu: 1.00 [0.31, 3.25](statistiliselt mitteoluline)
- Ravi katkestamine kõrvaltoime tõttu 1.00 [0.54, 1.84] (statistiliselt mitteoluline), kõik ravi katkestamised sõltumata põhjusest : OR 1.31 [1.07, 1.59] (statistiliselt oluline erinevus kombinatsioonravi kahjuks)
- Füüsilise aktiivsuse piiratus – ei ole analüüsitud
- Ravikulu – analüüsitud Haigekassa poolt

Ravijuhendid

Kokkuvõte ravijuhendites leiduvatest soovitustest: ravijuhendite soovitused on veidi erinevad, uuemad ravijuhised eelistavad püsiravi alustamisel alati ICS monoteraapiat:

- alustada püsiravi alati ICS monoteraapiaga; ei soovitata kombineeritud ravi ICS+LABA alustamist eelnevalt ICS mittekasutanud patsientidele (Canada 2010; ka SIGN 2012 samasisuline soovitus, küll mitte nii kategoorilises vormis)
- alustada püsiravi enamikul juhtudel madalas annuses ICS monoteraapiaga, erandina väga väljendunud sümptomite korral kohe keskmises/kõrges annuses ICS monoteraapiaga või kombineeritud raviga: madalas annuses ICS+LABA või vajadusel ICS kombinatsioonis teiste ravimitega (madalas annuses ICS+LTRA või madalas annuses ICS+ teofülliin retardpreparaat) (GINA 2012)
- alustada püsiravi sõltuvalt astma raskusastmest: püsiva kerge astma korral monoteraapia madalas annuses ICS-ga; püsiva mõõduka astma korral võrdsete valikutena kas madalas annuses ICS+LABA või keskmises annuses ISC monoteraapia (või vajadusel alternatiivid); raske astma korral koheselt kombinatsioonravi ICS+LABA (EPR-3 2007)
- GEMA-2009, VaDoD-2011 ja NVL-2011 juhendis soovitused ravi astmeliseks tõhustamiseks vastavalt raviga saavutatud astma kontrolli astmele

Süstemaatilised ülevaated
Otsistrateegia: "Adrenergic beta-Agonists"[Mesh] AND "Asthma"[Mesh] AND systematic[sb]

Kokkuvõte	Viide kirjandusallikale
BACKGROUND: Consensus statements recommend the addition of long-acting inhaled ss2-	Ni Chroinin M, Greenstone I, Lasserson T Ducharme FM.

agonists (LABA) only in asthmatic patients who are inadequately controlled on inhaled corticosteroids (ICS). It is not uncommon for some patients to be commenced on ICS and LABA together as initial therapy. OBJECTIVES: To compare the efficacy of combining inhaled corticosteroids with long-acting ss2-agonists (ICS+LABA) with inhaled corticosteroids alone (ICS alone) in steroid-naive children and adults with persistent asthma. We assessed two protocols: (1) LABA + ICS versus a similar dose of ICS (comparison 1) and (2) LABA + ICS versus a higher dose of ICS (comparison 2). SEARCH STRATEGY: RCT until May 2008. SELECTION CRITERIA: Randomised trials comparing ICS + LABA with ICS alone in children and adults with asthma who had no inhaled corticosteroids in the preceding 28 days prior to enrolment. MAIN RESULTS: Twenty-eight study comparisons drawn from 27 trials (22 adult; five paediatric) met the review entry criteria (8050 participants). Baseline data from the studies indicated that trial populations had moderate or mild airway obstruction (FEV1>/=65% predicted), and that they were symptomatic prior to randomisation. In comparison 1, the combination of ICS and LABA was not associated with a significantly lower risk of patients with exacerbations requiring oral corticosteroids (RR 1.04; 95% confidence interval (CI) 0.73 to 1.47) or requiring hospital admissions (RR 0.38; 95% CI 0.09 to 1.65) compared to a similar dose of ICS alone. The combination of LABA and ICS led to a significantly greater improvement from baseline in FEV1 (0.12 L/sec; 95% CI 0.07 to 0.17), in symptoms (SMD -0.26; 95% CI -0.37 to -0.14) and in rescue ss2-agonist use (-0.41 puffs/day; 95% CI -0.73 to -0.09) compared with a similar dose of ICS alone. There was no significant group difference in the risk of serious adverse events (RR 1.15; 95% CI 0.64 to 2.09), any adverse events (RR 1.02; 95% CI 0.96 to 1.09), study withdrawals (RR 0.95; 95% CI 0.82 to 1.11), or withdrawals due to poor asthma control (RR 0.94; 95% CI 0.63 to 1.41).In comparison 2, the combination of LABA and ICS was associated with a higher risk of patients requiring oral corticosteroids (RR 1.24; 95% CI 1 to 1.53) and study withdrawal (RR 1.31; 95% CI 1.07 to 1.59) than a higher dose of ICS alone. For every 100 patients treated over 43 weeks, nine patients using a higher dose ICS compared to 11 (95% CI 9 to 14) on LABA and ICS suffered one or more exacerbations requiring rescue oral corticosteroids. There was a high level of statistical heterogeneity for FEV1 and morning peak flow. There was no statistically significant group difference in the risk of serious adverse events. Due to insufficient data we could not aggregate results for hospital admission, symptoms and other outcomes. AUTHORS' CONCLUSIONS: In steroid-naive patients with mild to moderate airway obstruction, the combination of ICS and LABA does not significantly reduce the risk of patients with exacerbations requiring rescue oral corticosteroids over that achieved with a similar dose of ICS alone. However, it significantly improves lung function, reduces symptoms and marginally decreases rescue ss2-agonist use. Initiation of a higher dose of ICS is more effective at reducing the risk of exacerbations requiring rescue systemic corticosteroids, and of withdrawals, than combination therapy. Although	Addition of inhaled long-acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults and children. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD005307 Cochrane Database Syst Rev. 2009 Oct 7;(4):CD005307.

children appeared to respond similarly to adults, no firm conclusions can be drawn regarding combination therapy in steroid-naive children, given the small number of children contributing data.	
Lk 185-187 ICS+LABA compared with ICS (same dose) as first line therapy: Level of evidence: Moderate (≥ 12 years) Results from a good quality systematic review with meta-analysis and 8 RCTs found no difference in overall adverse events or withdrawals due to adverse events between subjects treated with ICSs plus LABAs and subjects treated with ICSs alone as first line therapy. Trials were 12-52 weeks in duration and were generally not designed to compare tolerability and adverse events. Indirect evidence from a recent systematic review that included a posthoc analysis of data from SMART suggests that the potential increased risk of asthmarelated death for those taking LABAs may be confined to patients not taking ICSs at baseline. Of note, ICS+LABA combination products are only indicated for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies.	Drug Class Review: Controller Medicatio for Asthma: Final Update 1 Report [Internet]. Jonas DE, Wines RCM, DelMonte M, Am HR, Wilkins TM, Einerson BD, Schuler CL Wynia BA, Shilliday BB. Portland (OR): Oregon Health & Science University; 2011 Apr. http://www.ncbi.nlm.nih.gov/books/NB 6695/pdf/TOC.pdf
"Asthma/drug therapy"[Mesh] AND "Adrenergic beta-Agonists"[Mesh] AND ("Steroids"[Mesh] OR "Adrenal Cortex Hormones"[Mesh]) AND (Meta-Analysis[ptyp] OR systematic[sb]) Vt ka: Kuigi rohkem küsimuse 7 kohta: http://www.ncbi.nlm.nih.gov/pubmed/22926172 - uuritavaks lapsed http://www.ncbi.nlm.nih.gov/pubmed/21463522 - 5 suure RCT *post hoc* analüüs	

Viited

Otsing (14.05.13): steroid-naive[All Fields] AND LABA[All Fields] annab 12 vastet, nendest 2 RCT.

Otsing: "Asthma/drug therapy"[Mesh] AND "Adrenergic beta-Agonists"[Mesh] AND ("Steroids"[Mesh] OR "Adrenal Cortex Hormones"[Mesh]) AND (Randomized Controlled Trial[ptyp] AND ("2008/05/01"[PDAT] : "3000/12/31"[PDAT])), n=58, asjakohaseid:

Kokkuvõte (abstrakt või kokkuvõtlikum info)	Viide kirjandusallikale
Combinations of inhaled corticosteroids (ICS) and inhaled long-acting beta(2)-agonists (LABA) have become widely used for the initiation of maintenance treatment for asthma. However, it has not been fully elucidated whether ICS/LABA alters the time-course of different control outcome measures in steroid-naive patients with asthma compared to the treatment with ICS alone. We compared the time-response in Asthma Control Questionnaire (ACQ), forced expiratory volume in 1 s (FEV1), exhaled nitric oxide fraction (FE(NO)), and airway responsiveness to methacholine (PD(200)) between budesonide 160 mcg (BUD) and budesonide/formoterol 160/4,5 mcg (BUD/FM). BUD/FM therapy significantly improved the ACQ score at week 2 and week 4 ($p < 0.01$ and $p < 0.05$), and increased FEV1 and the methacholine threshold at week 8 and week 24 (all $p < 0.05$) compared to BUD alone. A logistic function model showed that the BUD/FM combination significantly improved ACQ, FEV1, FE(NO) and PD(200) at a faster rate than BUD over 24 weeks	Matsunaga K, Kawabata H, Hirano T, Sugiura H, Minakata Y, Ichinose M. Difference in time-course of improvement in asthma control measures between budesonide and budesonide/formoterol . Pulm Pharmacol Ther. 2013 Apr;26(2):189-94. http://www.ncbi.nlm.ni h.gov/pubmed/231239

(p < 0.001 for ACQ, FEV1, PD(200), and p < 0.05 for FE(NO), z-test). A significant variance in the time-response was also found in the outcomes of the two treatment groups (FE(NO) and ACQ > FEV1 and PD(200), p < 0.001, z-test).	25 RCT, väga väikesemahuline uuring (36 uuritavat), kestus 24 nädalat, tulemusnäitajaks surrogaatmarker (FeNO2), FVC, FEV1, ka küsimustik ACQ. High risk of bias. Budesoniidi annus madal (160 µg), ka formoterooli annus madal
Objective of this study was to compare the efficacy of initial controller therapy with fluticasone propionate (FP) 100 microg twice daily to the efficacy of fluticasone propionate/salmeterol xinafoate (FSC) 100/50 microg twice daily in patients with persistent asthma symptoms while using as-needed SABA alone. METHODS: This randomized, double-blind, parallel-group study was conducted at 45 general practice and 15 specialist centers. A total of 526 adult patients were randomized to receive FP or FSC for 24 weeks. The primary efficacy endpoint was change in morning peak expiratory flow (PEF) from baseline. Secondary efficacy endpoints included symptom- and rescue-free days; asthma exacerbation rate; asthma-related health-care utilization; and the onset of effect. Safety was assessed by monitoring adverse events. RESULTS: Mean morning PEF was significantly greater in the FSC versus the FP group (P<0.001); this greater effect was evident as early as the first week of treatment (P<0.001). The percentages of symptom-free days and rescue-free days in the FSC group were 7.7% (P=0.009) and 8.4% (P=0.001) higher than the FP group, respectively. Trends toward lower exacerbation-related health care-utilization for FSC versus FP were not statistically significant and exacerbation rates were not significantly different. The incidence of adverse events was low with both treatments. This study was funded and sponsored by GlaxoSmithKline Inc., Mississauga, Canada	Renzi PM, Howard LA, Ortega HG, Ahmad FF, Chapman KR. Low-dose fluticasone propionate with and without salmeterol in steroid-naïve patients with mild, uncontrolled asthma. Respir Med. 2010 Apr;104(4):510-7. http://www.ncbi.nlm.nih.gov/pubmed/19944581 Esmane tulemusnäitaja on surrogaatmarker. Teisesed tulemusnäitajad: sümptomivabade ja rescue –med vabade päevade muutus toodud relatiivsena, aga absoluutne muutus? Neid andmeid artiklis üldse pole! GRADE: • Design: RCT, • High risk of bias - eelkõige: selective outcome reporting bias (primary outcome =surrogate marker, PEF

	muutuse % võrreldes algtasemega, absoluutse efekti kohta andmed täielikult puuduvad), drop-out 21% study group , 18% control group • no serious inconsistency • no serious indirectness • no serious imprecision • other considerations: väga suur hulk uuringukeskusi (vähem kui 10 püsiva kerge astmaga patsienti keskuse kohta, kuidas suudeti tagada uuringu kvaliteet igas keskuses?), uuring toimus GSK finantseerimisel 2002-2004, publitseeriti 2010. • Effect: vaid suhteline efekt: vt abstrakt • Quality: low