A COMPARISON OF CLINICAL EFFICACY AND SAFETY OF CICLESONIDE WITH BUDESONIDE IN 1:1 AND 1:2 DOSE RATIOS IN THE TREATEMENT OF BRONCHIAL ASTHMA

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*A study conducted by **HTA Consulting** **www.hta.pl***

Objective

The purpose of this study was to compare efficacy and safety of ciclesonide (CIC) with budesonide (BUD) in the treatment of bronchial asthma.

Introduction

Bronchial asthma is one of the most abundant chronic inflammatory disease of the airways, which is characterized by periodically recurrent attacks of breathlessness and wheezing. These symptoms vary in frequency and severity between individuals depending on stage of progression. Untreated asthma leads to an irreversible remodeling of the airways, which results in an airflow limitation.

The main aim of the asthma therapy is to control the disease preventing exacerbations, maintaining proper airflow and reducing the need of rescue therapies. The most effective and relatively safe drugs that are abundantly used in asthma controlling are inhaled corticosteroids. These drugs show anti-inflammatory, anti-allergic and immunosuppressive activity. Long-term administration of corticosteroids results in a gradual reduction in bronchial hyperactivity.

Ciclesonide and budesonide are two of four inhaled corticosteroids available in Europe for asthma control.

Methods

Comparison of efficacy and safety of analyzed drugs was based on randomized controlled trials (RCTs) identified by means of systematic review, carried out according to the Cochrane Collaboration guidelines and Agency for Technology Assessment in Poland. The most important medical databases (EMBASE, MEDLINE and CENTRAL) were searched. Two reviewers independently selected trials, assessed their quality and extracted data. Meta-analysis of head-to-head trials was performed to compare safety and efficacy of CIC with BUD.

The following databases were searched:

- MEDLINE,
- EMBASE,
- Biomed Central,
- Cochrane Library,
  - CENTRAL (The Cochrane Central Register of Controlled Trials),
  - The Cochrane Database of Systematic Reviews,
  - Center for Reviews and Dissemination (CRD),
- Governmental agencies websites (FDA, EMEA),
- Websites of agencies associated with INAHTA,
- AAAAI (American Academy of Allergy Asthma and Immunology)
- ATS (American Thoracic Society)
- PTA (*Polish Allergologic Society*)
- Scientific publications' references.

Databases were searched in January 2010.

Two authors independently assessed studies and extracted data. Critical appraisal of included studies was performed using the Jadad scale (5 point score).

Table 1. Methotdology of systematic review

Population	• Adults and adolescents (≥ 12 years of age) witch chronic bronchial asthma
Intervention	• Inhaled ciclesonide (CIC)
Comparator	• Inhaled budesonide (BUD)
Endpoints	• Changes in spirometric measures (FEV1, PEF, FVC), • Asthma exacerbations and worsening, • Changes in Asthma Symptom Score (ASS), • Asthma sympthoms-free days and nights, • Rescue medication use, • Quality of life (QOL) according to AQLQ questionnaire, • Withdrawals due to adverse events (AE) and lack of efficacy (LOE) • Adverse event (AE)
Design of clinical trials	• Randomized clinical trials, with or without blinding
Other inclusion criteria	• Studies published in Polish, English, French or German • Studies published as full texts or conference abstracts
Exclusion criteria	• <12 years of age • Treatment lasting ≤ 4 weeks • Inpatient treatment • Less than 10 patients • Non-randomized trials

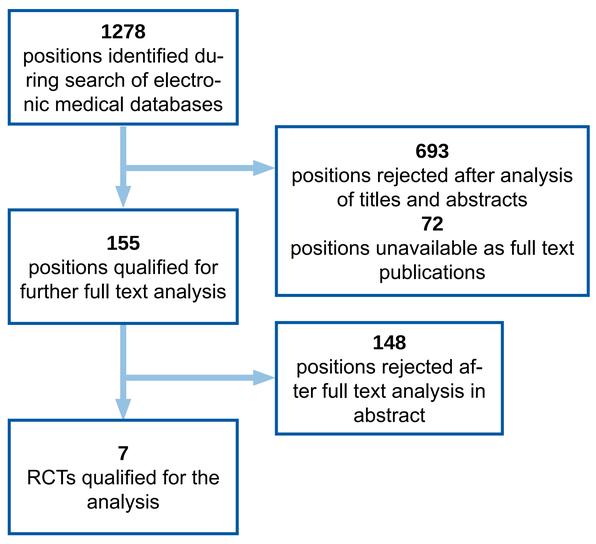
Characteristics of clinical trials

The search in medical databases resulted in total number of 1278 identified publications (including repeated titles). 155 positions were qualified for full text analysis. Finally 7 trials met predefined inclusion criteria and were suitable for further analysis:

- 7 RCTs comparing CIC with BUD in patients with mild to moderate bronchial asthma

All studies had apparel design. Methodological credibility of the trials included in the analysis was medium in most cases.

Selection process according to QUOROM



All patients in included studies were diagnosed with asthma. The severity of disease was not specified in all studies included except for one trial in which recruited patient suffered from mild to moderate asthma. Ciclesonide was administered to patients in daily dose ranging from 200 mg up to 400 mg and the respective daily dose of budesonide was in the range of 400 to 800. Comparisons of both interventions in 1:1 and 1:2 dose ratios were assessed in 3 and 4 trials, respectively. Duration of treatment was equal in the studies and lasted 12 weeks. All of included trials were of moderate and high quality (respectively: 3 and 4 points according to Jadad scale).

Table 2. Studies included in the analysis

Trial	Population	Number of participants	Dosing	Follow-up [weeks]	Jadad
Boulet 2006	asthma	CIC400: 179 CIC400: 180	CIC400 od morning BUD400 od morning	12	4
BY9010/M1-136	asthma	CIC200: 124 CIC400: 125	CIC200 od evening BUD400 od evening	12	3
BY9010/M1-137	asthma	CIC200: 64 CIC400: 61	CIC200 od evening BUD400 od evening	12	3
Hansel 2006	mild and moderate asthma	CIC400: 195 BUD400: 177	CIC400 od morning BUD200 bid	12	3
Niphadkar 2005	asthma	CIC200: 270 BUD400: 134	CIC200 od morning CIC200 od evening BUD200 bid	12	3
Ukena 2007	asthma	CIC400: 198 BUD400: 201	CIC400 od evening BUD400 od evening	12	4
Vermeulen 2007	asthma	CIC400: 272 BUD800: 131	CIC400 od evening BUD800 od evening	12	4

Results

Efficacy

CIC as compared with BUD in 1:1 dose ratio was associated with significant improvement in forced vital capacity (FVC) and peak expiratory flow (PEF) by spirometry (WMD=0.09 [0.03; 0.14] and WMD=19.00 [2.37; 35.63], respectively) as well as reduction in proportion of symptom-free days (p=0.018). Equivocal results were obtained for comparison of CIC with BUD in 1:1 dose ratio with respect to frequency of rescue medication use. While one of included studies showed significant difference in favor of CIC (p=0.026), the other revealed similar results for both treatment groups. Efficacy analysis of both therapeutic options in 1:2 dose ratio showed no significant difference between groups in asthma exacerbation, days free from symptoms of asthma and spirometric measurements (Table 3 & Table 4).

Safety

CIC-treated patients experienced less upper respiratory tract infections (URTI) than those treated with BUD in 1:1 dose ratio, however the difference was on the border of statistical significance (RR = 0.65 [0.43; 0.99], NNT not significant). There were no statistically significant differences between CIC and BUD in either dose ratio with respect to risk of total and treatment-related adverse events, serious and severe adverse events. No significant difference was found as regard withdrawal from study due to adverse event and lack of efficacy. In both treatment groups there were similar frequencies of pharyngitis, rhinitis, pharyngo-laryngeal pain, and dysphonia. (Table 5)

Table 3. Results of the efficacy analysis for the comparison of CIC vs BUD – continuous measures

Endpoint	CIC:BUD dose ratio	Number of trials	Number of participants CIC/BUD	WMD [95% CI]	Follow-up [weeks]
Change in FEV1 [L]	1:1	3	561/548	0.02 [-0.08, 0.12]	12
	1:2	4	698/427	-0.04 [-0.08, 0.01]	12
Change in FEV1 % predicted	1:2	1	249/126	NS	12
Change in PEF by spirometry [L/min]	1:1	1	198/201	**19.00 [2.37, 35.63]**	12
	1:2	1	270/130	3.00 [-14.80, 20.80]	12
Change in morning PEF [L/min]	1:1	3	565/552	5.11 [-1.12, 11.35]	12
	1:2	2	537/263	2.52 [-4.52, 9.56]	12
	1:2	2	158/164	CIC non inferior than BUD	12
Change in evening PEF [L/min]	1:1	2	377/381	4.32 [-2.41, 11.06]	12
	1:2	2	537/263	2.65 [-2.55, 7.85]	12
	1:2	2	158/164	CIC non inferior than BUD	12
Change in FVC	1:1	2	377/381	**0.09 [0.03, 0.14]**	12
	1:2	2	540/263	-0.001 [-0.04, 0.04]	12
	1:2	1	107/114	CIC non inferior than BUD	12
	1:2	1	51/50	Non-inferiority CIC vs BUD not fulfilled	12
Change in daytime ASS	1:1	2	377/366	NS difference in each trial	12
Change in nighttime ASS	1:1	2	377/366	NS difference in each trial	12
Asthma symptoms free days	1:1	1	179/180	**CIC significantly better (p = 0.018)**	12
	1:2	2	188/186	NS difference in each trial	12
Rescue medication use	1:1	1	179/180	**CIC significantly better (p = 0,026)**	12
	1:1	1	198/201	NS	12
	1:2	2	188/186	NS difference in each trial	12
Improvement in QOL	1:1	2	377/366	NS difference in each trial	12

Table 4. Results of the efficacy analysis for the comparison of CIC vs BUD – dichotomous measures

Endpoint	CIC:BUD dose ratio	Number of trials	Number of participants CIC/BUD	RR [95% CI]	RD [95% CI]	Follow-up
Asthma exacerbation	1:1	1	179/180	3,02 [0,12; 73,56]	0,01 [-0,01; 0,02]	12
	1:2	2	336/192	1,57 [0,37; 6,63]	0,01 [-0,01; 0,03]	12
Asthma worsening	1:1	2	375/357	0,97 [0,59; 1,60]	0,01 [-0,03; 0,04]	12
	1:2	4	731/450	1,20 [0,76; 1,90]	0,01 [-0,02; 0,04]	12

Table 5 Results of the safety analysis for the comparison of CIC vs BUD

Endpoint	CIC:BUD dose ratio	Number of trials	Number of participants CIC/BUD	RR [95% CI]	RD [95% CI]	Follow-up
Total AE	1:1	3	573/558	0,99 [0,77; 1,27]	-0,005 [-0,10; 0,09]	12
	1:2	4	731/450	1,17 [0,98; 1,40]	0,05 [-0,01; 0,10]	12
Serious AE	1:1	1	179/180	0,50 [0,05; 5,50]	-0,01 [-0,02; 0,01]	12
	1:2	3	458/319	1,43 [0,49; 4,14]	0,01 [-0,01; 0,03]	12
Severe AE	1:2	1	124/125	1,76 [0,53; 5,88]	0,02 [-0,03; 0,08]	12
Treatment-related AE	1:2	3	460/320	1,51 [0,54; 4,25]	0,01 [-0,01; 0,03]	12
Candidiosis	1:1	2	377/381	0,51 [0,05; 5,56]	-0,002 [-0,01; 0,01]	12
	1:2	2	336/192	0,69 [0,04; 10,49]	-0,002 [-0,01; 0,01]	
Withdrawal (AE)	1:1	2	393/378	1,33 [0,43; 4,15]	0,004 [-0,01; 0,02]	12
	1:2	3	458/322	2,27 [0,88; 5,86]	0,02 [-0,003; 0,04]	12
Withdrawal (LOE)	1:1	2	374/357	0,82 [0,54; 1,25]	0,002 [-0,06; 0,02]	12
	1:2	1	270/133	1,97 [0,42; 9,15]	0,01 [-0,01; 0,04]	12
Pharyngitis	1:1	1	179/180	1,21 [0,38; 3,88]	0,01 [-0,03; 0,04]	12
	1:2	1	272/131	1,54 [0,58; 4,12]	0,02 [-0,02; 0,06]	12
Nasopharyngitis	1:1	1	272/131	3,37 [0,42; 27,12]	0,02 [-0,01; 0,04]	12-24
URTI	1:1	2	375/357	**0,65 [0,43; 0,99]**	-0,05 [-0,09; 0,002]	12–24
	1:2	4	731/450	1,27 [0,86; 1,88]	0,02 [-0,01; 0,05]	12
Rhinitis	1:1	2	375/357	0,74 [0,34; 1,61]	-0,01 [-0,04; 0,02]	12–24
	1:2	1	271/133	0,37 [0,08; 1,62]	-0,02 [-0,05; 0,01]	12
Dysphonia	1:2	1	64/61	0,95 [0,02; 47,33]	-0,0004 [-0,03; 0,03]	12–24
Pharyngolaryngeal pain	1:1	1	179/180	1,51 [0,26; 8,92]	0,01 [-0,02; 0,03]	12–24

Limitations

Limitations of the analysis were related to different approach to assessing and reporting of drug efficacy between included trials what precluded metaanalyses. However, the conclusion was based on best available evidences, which took into account all studies showing different results.

Conclusions

Ciclesonide provides an improvement in spirometric parameters and reduction of asthma symptom-free days as compared to budesonide in 1:1 dose ratio, while no differences were noticed between CIC and BUD in 1:2 dose ratio. Cicleconide, as compared to budesonide in 1:1 daily dose ratio, provides concomitant risk reduction of upper respiratory tract infections.

Abbreviations

AAAAI	American Academy of Allergy Asthma and Immunology
AE	Adverse Event
AQLQ	Asthma Quality of Life Questionnaire
ASS	Asthma Symptom Score
ATS	American Thoracic Society
bid	Twice Daily
BUD	Budesonide
CIC	Ciclesonide
CRD	Center for Reviews and Dissemination
EMA	European Medicines Agency
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
INAHTA	International Network of Agencies for Health Technology Assessment
LOE	Lack of Efficacy
od	Once Daily
NNT	Number Needed to Treat
NS	Non-signifficant
PEF	Peak Expiratory Flow
PTA	Polish Allergologic Society
QOL	Quality of Life
RCT	Randomized Controlled Trial
RR	Relative Risk
URTI	Upper Respiratory Tract Infections
WMD	Weighted Mean Difference