A COMPARISON OF CLINICAL EFFICACY AND SAFETY OF CICLESONIDE WITH FLUTICASONE 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 fluticasone (FP) 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 fluticasone 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 FP.

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 fluticasone (FP)
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) • 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

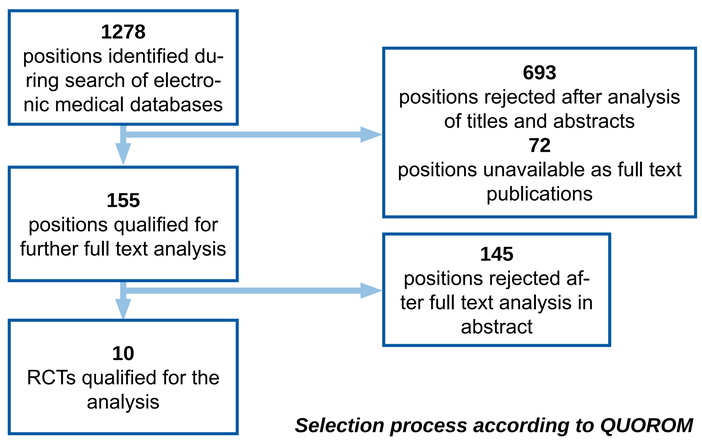
Characteristics of clinical trials

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 10 trials met predefined inclusion criteria and were suitable for further analysis:

- 10 RCTs comparing CIC with FP 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.

All patients in included studies were diagnosed with asthma. The severity of disease was not specified in seven studies but in three remaining trials all patient suffered from mild to moderate asthma. Ciclesonide was administered to patients in daily dose ranging from 100 mg up to 800 mg and the respective daily dose of fluticasone was in the range of 200 to 1000. Comparisons of both interventions in 1:1 and 1:2 dose ratios were assessed in 8 and 5 trials, respectively. Duration of treatment lasted from 8 to 24 weeks. Most of the included trials were of moderate and high quality (respectively: 3 and 4 points according to Jadad scale), however the quality of one study was assessed as low (2 points according to Jadad scale).



Selection process according to QUOROM

Table 2. Studies included in the analysis

Trial	Population	Number of participants	Dosing	Follow-up [weeks]	Jadad
Bateman 2008	asthma	CIC800: 255 FP750: 273	CIC400 bid FP375 bid	24	3/5
Boulet 2007	moderate asthma	CIC400: 234 FP400: 240	CIC400 od evening FP200 bid	12	4/5
Buhl 2006	asthma	CIC200: 266 PF200: 263	CIC200 od evening FP100 bid	12	4/5
BY9010/ M1-142	asthma	CIC100: 240 FP200: 240	CIC100 od evening FP100 bid	24	3/5
Dusser 2006	asthma	CIC800: 259 FP1000: 244	CIC400 bid FP500 bid	24	3/5
Hoshino 2010	asthma	CIC200: 14 FP200: 16	CIC200 od FP100 bid	8	2/5
Knox 2007	asthma	CIC200: 58 FP500: 53	CIC200 od evening FP250 bid	12	4/5
Lipworth 2005	mild and moderate asthma	CIC400: 40 CIC800: 42 FP1000: 41	CIC400 od evening CIC400 bid FP500 bid	12	3/5
Magnussen 2007	asthma	CIC100: 278 CIC200: 271 FP200: 259	CIC100 od evening CIC200 od evening FP100 bid	12	4/5
Zietkowski 2006	mild allergic asthma	CIC100: 12 CIC200: 12 FP200: 11	CIC100 od evening CIC200 od evening FP100 bid	12	3/5

Results

Efficacy

Efficacy of CIC was comparable to FP in both, 1:1 and 1:2 dose ratios with respect to reduction in risk of asthma exacerbations, improvement in proportion of symptoms-free days, rescue medication-free days and improvement in asthma symptoms. The quality of life was significantly improved in CIC group as compared do FF in 1:1 dose ratio (WMD = 0.12 [0.04, 0.019]). Moreover, no significant differences between treatment options in either dose range were observed as regards improvement in spirometric parameters. (Table 3 & Table 4)

Safety

Analysis of safety measures revealed that treatment with CIC, as compared to FP in 1:1 daily dose range, was associated with statistically significant risk reduction of adverse events possibly related to study medication (RR = 0.57 [0.39, 0.83]; NNT = 16.89 [10.24, 48.18]) and candidosis (RR = 0.31 [0.17, 0.56], NNT = 32.74 [22.23, 61.99]). The differences between groups with respect to AE related to study drug medication were not significant for 1:2 dose ratio. No significant difference was found as regard withdrawal from study due to adverse event and lack of efficacy. In both treatment groups there was similar frequency of upper respiratory tract infections (URTI), pharyngitis, rhinitis, pharyngo-laryngeal pain, and dysphonia. (Table 5)

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

Endpoint	CIC:FP dose ratio	Number of trials	Number of participants CIC/FP	WMD [95% CI]	Follow-up [weeks]
Change in FEV1 [L]	1:1	5	1030/1041	-0.02 [-0.06, 0.01]	12-24
	1:2	4	561/530	-0.04 [-0.09, 0.01]	12- 24
Change in FEV1 % predicted	1:1	3	259/266	-0.86 [-3.02, 1.30]	8–12
	1:2	1	12/11	-4.44 [-10.88, 2.00]	12
Change in morning PEF	1:1	3	740/765	2.23 [-4.31, 8.76]	12–24
	1:2	1	55/53	-6.96 [-26.74, 12.82]	12
	1:2	1	216/207	CIC non interior than FP	24
Change in evening PEF	1:1	1	233/239	3.90 [-6.63, 14.43]	12
	1:2	1	216/207	CIC non interior than FP	24
Change in FVC	1:1	4	1018/1030	-0.01 [-0.05, 0.04]	12
	1:2	2	333/312	0.06 [-0.03, 0.15]	12
	1:2	1	216/207	CIC non interior than FP	24
Change in MEF 25%	1:1	1	14/16	2.90 [-4.49, 10.29]	8
Change in MEF 50%	1:1	1	14/16	3.50 [-13.83, 20.83]	8
Chance in daytime ASS	1:1	5	1040/1016	NS difference in each trial	12–24
	1:2	6	1106/1069	NS difference in each trial	12–24
Change in nighttime ASS	1:1	5	1040/1016	NS difference in each trial	12–24
	1:2	2	290/270	NS difference in each trial	12–24
Asthma symptoms free days	1:1	4	1024/1034	NS difference in each trial	12- 24
	1:2	2	336/312	NS difference in each trial	12
Rescue medication use	1:1	6	1281/1279	NS difference in each trial	12-24
	1:2	2	290/270	NS difference in each trial	12
Improvement in QOL	1:1	3	734/741	**0,12 [0,04; 0,019]**	12
	1:2	1	240/240	CIC non interior than FP	12

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

Endpoint	CIC:FP dose ratio	Number of trials	Number of participants CIC/FP	RR [95% CI]	RD [95% CI]	Follow-up
Asthma exacerbation	1:1	5	1030/1026	0,86 [0,46; 1,61]	-0,003 [-0,01; 0,01]	12-24
	1:2	4	588/563	1,23 [0,47; 3,17]	0,003 [-0,01; 0,02]	12-24
Asthma worsening	1:1	4	1050/1039	0,76 [0,51; 1,15]	-0,002 [-0,02; 0,01]	12-24
	1:2	3	569/551	0,70 [0,36; 1,37]	-0,01 [-0,03; 0,007]	12

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

Endpoint	CIC:FP dose ratio	Number of trials	Number of participants CIC/FP	RR [95% CI]	RD [95% CI]	Follow-up
Total AE	1:1	5	1283/1278	0.96 [0.88, 1.04]	-0.02 [-0.06, 0.02]	12-24
	1:2	3	576/552	1.03 [0.89, 1.21]	0.01 [-0.04, 0.07]	12- 24
Serious AE	1:1	4	1028/1005	0.89 [0.42, 1.89]	-0.001 [-0.01, 0.01]	12-24
	1:2	3	576/552	1.29 [0.43, 3.88]	0.003 [-0.01, 0.02]	12–24
Severe AE	1:1	1	259/244	1.41 [0.65, 3.09]	1.44 [0.63, 3.27]	24
Treatment-related AE	1:1	2	492/483	**0.57 [0.39, 0.83]**	-0.06 [-0.10, -0.02]	12-24
	1:2	2	298/293	0.59 [0.30, 1.14]	-0.03 [-0.07, 0.01]	12-24
Candidiosis	1:1	4	1013/1019	**0.31 [0.17, 0.56]**	-0.03 [-0.04, -0.02]	12-24
Withdrawal (AE)	1:1	4	1028/1005	0.90 [0.52, 1.56]	-0.003 [-0.02, 0.01]	12-24
	1:2	3	576/552	0.72 [0.30, 1.73]	-0.01 [-0.02, 0.01]	12- 24
Withdrawal (LOE)	1:1	2	536/522	3.58 [0.59, 21.56]	0.01 [-0.002, 0.02]	12
	1:2	1	278/259	1.86 [0.17, 20.43]	0.003 [-0.01, 0.02]	12
Pharyngitis	1:1	2	536/522	1.57 [0.72, 3.42]	0.01 [-0.01, 0.03]	12
	1:2	1	278/259	2.17 [0.57, 8.32]	0.01 [-0.01, 0.04]	12
Nasopharyngitis	1:1	4	1017/1015	0.97 [0.70, 1.34]	-0.002 [-0.02, 0.02]	12-24
	1:2	3	576/552	0.77 [0.50, 1.19]	-0.02 [-0.05, 0.01]	12-24
URTI	1:1	3	780/780	1.08 [0.74, 1.59]	0.005 [-0.02, 0.03]	12–24
	1:2	1	58/53	0.37 [0.07, 1.80]	-0.06 [-0.15, 0.03]	12
Rhinitis	1:1	3	791/795	0.92 [0.51, 1.67]	-0.002 [-0.02, 0.01]	12–24
	1:2	2	336/312	0.71 [0.26, 1.95]	-0.01 [-0.03, 0.02]	12
Dysphonia	1:1	3	747/756	0.63 [0.40, 1.001]	-0.02 [-0.04, 0.001]	12–24
Pharyngolaryngeal pain	1:1	2	488/512	1.25 [0.65, 2.41]	0.01 [-0.01, 0.03]	12–24
	1:2	1	58/53	0.91 [0.13, 6.26]	-0.003 [-0.07, 0.07]	12

Limitations

Limitations of the analysis were related to differences in methodology between studies. The main differences concerned the length of treatment period, dosage of investigated drugs and the method of drug application. However the conclusion was based on best available evidences about relative efficacy and safety of treatment options and the discrepancies may reflect various treatment schemes used in treatment of heterogeneous population of people suffering from asthma.

Conclusions

Ciclesonide is a therapeutic option for patients with bronchial asthma showing comparable efficacy to fluticasone in both 1:1 and 1:2 dose with regard to clinically significant endpoints as well as improvement in spirometric parameters. Cicleconide, as compared to fluticasone in 1:1 daily dose ratio, provides concomitant improvement in the quality of life measured according to AQLQ questionnaire and reduces the risk of adverse events related to medication as well as candidosis.

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
CIC	Ciclesonide
CRD	Center for Reviews and Dissemination
EMA	European Medicines Agency
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 second
FP	Fluticasone
FVC	Forced Vital Capacity
INAHTA	International Network of Agencies for Health Technology Assessment
LOE	Lack of Efficacy
NNT	Number Needed to Treat
NS	Non-signifficant
od	Once Daily
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