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Original

On-demand Inhaled Corticosteroid and Fast-onset Beta-2 Agonist Combination Therapy Versus Conventional Treatment for Mild to Moderate Asthma : A Non-inferiority, Network Meta-analysis

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Abstract : The aim of this study was to assess the non-inferiority of on-demand (OD) inhaled corticosteroid (ICS) and fast-onset beta-2 agonist (FOBA) combination therapy. Although the guidelines recommend regular inhalation of ICS and long-acting beta-2 agonist (LABA), we investigated whether OD-ICS / FOBA is as effective as regular inhalation. A network meta-analysis of randomized controlled trials was conducted to inspect the non-inferiority of OD-ICS / FOBA efficacy compared with conventional best practice, i.e. regular low- to medium-dose ICS with or without LABA, plus OD short-acting beta-2 agonist (REG-ICS + OD-SABA or REG-ICS / LABA + OD-SABA) in patients with mild to moderate asthma. PubMed, the Cochrane library database, and Scopus were searched to identify relevant articles. Outcome measures were the incidence of asthma exacerbation or aggravation. A network meta-analysis was performed to estimate risk ratios (RRs) with 95% confidence intervals (CIs) and the probability of being the best treatment for the outcome. Four randomized controlled trials of treatment for mild to moderate asthma met the criteria and were included in the study. We could not demonstrate non-inferiority of OD-ICS / FOBA to REG-ICS + OD-SABA (RR, 1.17 ; 95% CI, 0.61 to 2.26) or to REG-ICS / LABA + OD-SABA (RR, 1.47 ; 95% CI, 0.79 to 2.71) for mild to moderate asthma. The probability of being the best treatment to reduce asthma exacerbation or aggravation was 10.5% for OD-ICS / FOBA, 10.3% for REG-ICS + OD-SABA, and 79.3% for REG-ICS / LABA + OD-SABA. Surface under the cumulative ranking (SUCRA) curves were 0.4, 0.2 and 0.9 for OD-ICS / FOBA, REG-ICS + OD-SABA, and REG-ICS / LABA + OD-SABA, respectively. Although non-inferiority of OD-ICS / FOBA to conventional best practice was not shown, SUCRA was higher for OD-ICS / FOBA than for REG-ICS + OD-SABA. From these results, we propose that OD-ICS / FOBA can be an effective alternative to REG-ICS + OD-SABA to reduce asthma exacerbation or aggravation in patients with mild to moderate asthma.

Key words : asthma, inhaled corticosteroid, fast-onset beta-2 agonist, network meta-analysis

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Introduction

The global use of inhaled corticosteroids (ICS) has contributed to a significant reduction in hospitalization for acute exacerbation or aggravation in patients with bronchial asthma[1]. The 2014 revision of Japanese Guideline for Adult asthma recommends regular treatment with ICS, regardless of asthma severity, because it is effective in suppressing airway inflammation and inhibiting asthma progression[2]. However, poor adherence to daily inhaled medication is a major obstacle in treating patients with asthma[3].

Randomized controlled trials (RCTs) have shown that on-demand use of an ICS and fast-onset beta-2 agonist (FOBA), such as a short-acting beta-2 agonist (SABA) or formoterol, without any regular treatment (OD-ICS / FOBA) is effective and might be an alternative therapy to regular ICS plus SABA (REG-ICS + OD-SABA) or regular ICS / LABA plus on-demand SABA (REG-ICS / LABA + OD-SABA) in patients with mild to moderate asthma[4, 5]. Another RCT showed the non-inferiority of on-demand use of beclomethasone in combination with albuterol without any regular treatment, relative to regular low-dose beclomethasone plus on-demand albuterol with or without regular albuterol[6]. This study also showed that on-demand use of beclomethasone with albuterol may be more effective for symptom relief than albuterol alone[6]. These results are biologically plausible because an ICS and beta-stimulant combination inhibits bronchoconstriction and suppresses airway inflammation[7].

On-demand use may reduce the influence of poor adherence to daily inhaled medication and may improve control of asthma and reduce the requirement for regular use of ICS and beta-2 agonist[4–6]. However, the effects of OD-ICS / FOBA on symptom control in patients with mild to moderate asthma are unclear, and the ideal population of patients who may benefit from this treatment is undefined. Therefore, the aim of this study was to use a network meta-analysis and a well-established method for comparing treatments, to assess the non-inferiority of OD-ICS / FOBA compared to conventional treatments, such as REG-ICS + OD-SABA or REG-ICS / LABA + OD-SABA, in patients with mild to moderate asthma.

Methods

Publication search and inclusion criteria

We searched MEDLINE (PubMed), Scopus, and the Cochrane library database (up to August 2016). The search queries were as follows: asthma [title] AND (((inhaled corticosteroid [Title / Abstract] OR beta-2 agonist [Title / Abstract]) AND ((mild [All Fields] OR (mild [All Fields] AND moderate [All Fields])) OR moderate [All Fields])) AND ((on-demand [All Fields] OR symptom-driven [All Fields]) OR as-needed [All Fields])) AND (Randomized Controlled Trial [ptyp] AND "adult" [MeSH Terms]).

PubMed was mainly used for the publication search because it is an open access database that is suitable for a comprehensive literature search. Scopus was used to ensure that all eligible articles had been detected in PubMed. We also used the Cochrane library database to search for additional references. Embase was not used because it is unavailable at our institute, but

this is unlikely to have had a significant impact on the search results owing to the similarities between PubMed and Embase. The study was considered eligible if it met the following criteria : 1) a RCT that assessed the clinical efficacy of OD-ICS with a FOBA without any regular treatment, regular ICS plus OD-SABA, or regular ICS with LABA plus OD-SABA in mild or moderate asthma ; and 2) the study included the incidence of asthma exacerbation or aggravation in the outcome measures.

Data extraction and quality assessment

Case reports, non-English language studies, and single arm studies were excluded. Studies in children aged 18 years or younger were also excluded because the present analysis focused on adult asthma, rather than childhood asthma or pubertal asthma. The methodological quality of the included trials was evaluated using the Jadad score, which assesses studies on the basis of their description of randomization, blinding and dropout[8].

Data analysis

A network meta-analysis was performed to evaluate the effects of OD-ICS / FOBA, REG-ICS + OD-SABA, and REG-ICS / LABA + OD-SABA, using the statistical methods described previously[9, 10]. A traditional pairwise meta-analysis was also performed. The summary effect size is represented as the risk ratio (RR) with 95% confidential intervals (CIs). Non-inferiority for the incidence of asthma exacerbation or aggravation was defined as the upper 95% CI for the RR estimated in the network meta-analysis being no higher than 1.5, which was determined by reference to past non-inferiority trials[11]. Data analysis was performed using Revman 5 ver. 5.3 for Windows (Cochrane Corp., Oxford, UK) and STATA ver. 14.0 (Stata Corp., College Station, TX).

Ranking investigation

One of the advantages of a network meta-analysis is the ability to rank the treatments, which allows speculation on the probability of the best treatment and the possible ranks for each treatment. Moreover, the calculated probability can be used to identify the best treatment, second best, third best, etc.,[9, 10]. The surface under the cumulative ranking (SUCRA) curve, which is the ratio of the area under the cumulative ranking curve to the entire area in the plot, was also used to compare each treatment to an ideal treatment that is consistently the best without uncertainty. In this analysis, larger SUCRAs indicate more effective treatments[9, 10].

Inconsistency test

A network meta-analysis is carried out based on the assumption of consistency, which should be confirmed in a closed loop of evidence. The difference between direct and indirect evidence, which is expressed as an inconsistency factor, with 95% CIs and a *P*-value, was calculated by analyzing the equality of direct and indirect evidence. For loops in which the lower CI limit does not reach the zero line, a significant inconsistency is considered to be present[9, 10].

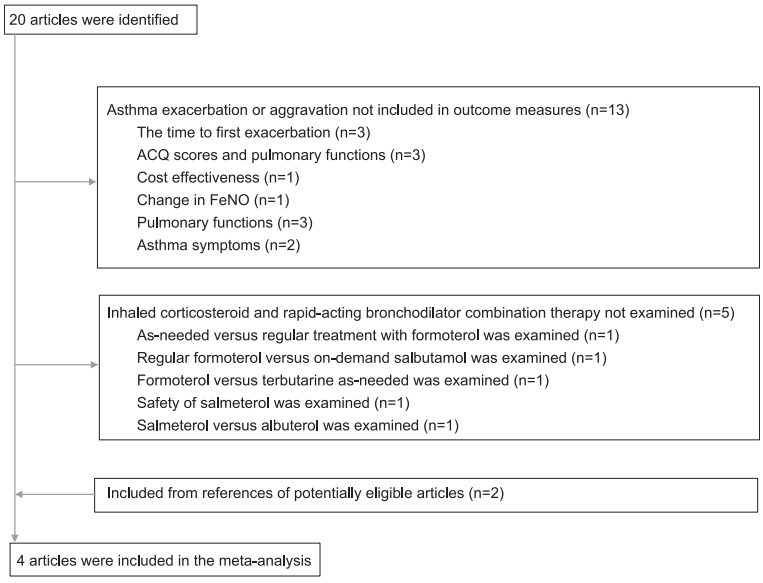

Fig. 1. Flow diagram of the study selection process. ACQ : asthma control questionnaire ; FeNO : fractional exhaled nitric oxide.

Comparison-adjusted funnel plot

A comparison-adjusted funnel plot is a scatter plot that reveals the association between study-specific effect sizes from the corresponding comparison-specific summary versus the inverted standard error. An asymmetrical funnel plot implies that there are small-study effects. We used comparison-adjusted funnel plots to assess differences in effectiveness between small and large studies (small-study effects)[9, 10].

Results

Search results and characteristics of included studies

The study selection process is shown in Fig. 1. Twenty citations were retrieved from the databases, of which 13 did not examine asthma exacerbation or aggravation, and 5 did not examine ICS and FOBA combination therapy. Two articles were identified from the reference lists of the retrieved studies, giving a total of 4 RCTs for inclusion in the network meta-analysis[4, 6, 12, 13]. All comparisons in the analysis are shown in Fig. 2. The characteristics of the 4 RCTs are shown in Table 1 and the interventions in these trials are described in Table 2. One trial compared OD-ICS / FOBA with REG-ICS / LABA + OD-SABA, 2 trials examined REG-ICS + OD-SABA and REG-ICS / LABA + OD-SABA, and 1 trial compared OD-ICS / FOBA with REG-ICS + OD-SABA. The mean age of the patients ranged from 36.8 to 45.8 years, and the study duration ranged from 12 weeks to 1 year. Two studies had Jadad scores of 4 because the dropout of patients was not documented, and two had scores of 5, indicating that the included studies were of high quality.

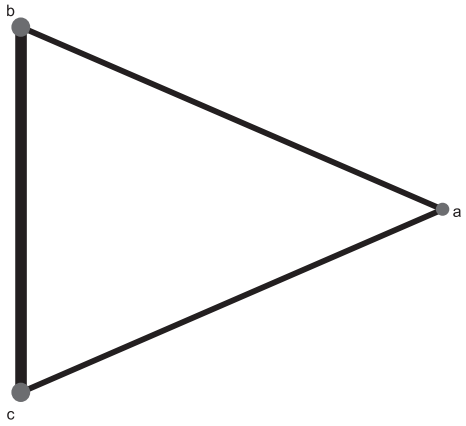

Fig. 2. Network of eligible comparisons in treatment efficacy network meta-analysis. The width of the lines represents the number of studies compared for each pair of treatments, and the size of balloons represents the total sample size of each treatment. a : on-demand inhaled corticosteroid and fast-onset beta-2 agonist combination without any regular treatment (OD-ICS / FOBA) ; b : regular inhaled corticosteroid plus on-demand short-acting beta-2 agonist (REG-ICS + OD-SABA) ; c : regular inhaled corticosteroid with long-acting beta-2 agonist combination plus on-demand short-acting beta-2 agonist (REG-ICS / LABA + OD-SABA).

Table 1. Characteristics of the studies included in the network meta-analysis

Reference	Study design	Group	Enrolled, n (M / F)	Average age, y	Severity of asthma	Study duration	Jadad score
Lalloo *et al* 2003[12]	RCT	REG-ICS + OD-SABA	237 (98 / 139)	40	mild to moderate	12 weeks after 2-week run-in period	4
		REG-ICS / LABA + OD-SABA	230 (102 / 128)	42			
Kuna *et al* 2006[13]	RCT	*REG-ICS / LABA + OD-SABA	202 (81 / 121)	45.8	mild to moderate	12 weeks after 2-week run-in period	4
		**REG-ICS / LABA + OD-SABA	207 (78 / 129)	43.9			
		REG-ICS + OD-SABA	207 (91 / 116)	45.1			
Papi *et al* 2007[6]	RCT	OD-FOBA	122 (50 / 72)	36.8	mild	6 months after 4-week run-in period	5
		OD-ICS / FOBA	118 (49 / 69)	40.6			
		REG-ICS + OD-SABA	106 (45 / 61)	45			
		REG-ICS / SABA + OD-SABA	109 (43 / 66)	43			
Papi *et al* 2015[4]	RCT	OD-ICS / FOBA	394 (153 / 241)	42.1	moderate	1 year after 6-week run-in period	5
		REG-ICS / LABA + OD-SABA	423 (185 / 238)	43.2			

RCT : randomized controlled trial ; REG-ICS + OD-SABA : regular inhaled corticosteroid plus on-demand short-acting beta-2 agonist ; REG-ICS / LABA + OD-SABA : regular inhaled corticosteroid and long-acting beta-2 agonist combination plus on-demand short-acting beta-2 agonist ; *REG-ICS / LABA + OD-SABA : two inhalations once-daily of 80 μg budesonide and 4.5 μg formoterol plus on-demand terbutaline or another preferred SABA ; **REG-ICS / LABA + OD-SABA : one inhalation twice-daily of 80 μg budesonide and 4.5 μg formoterol plus on-demand terbutaline or another preferred SABA ; OD-FOBA ; on-demand fast-onset beta-2 agonist without any regular treatment ; OD-ICS / FOBA : on-demand inhaled corticosteroid and fast-onset beta-2 agonist combination without any regular treatment ; REG-ICS / SABA + OD-SABA ; regular inhaled corticosteroid and short-acting beta-2 agonist combination plus on-demand short-acting beta-2 agonist.

Table 2. Details of the interventions in the studies included in the meta-analysis

Reference	Details of intervention
Lalloo *et al* 2003 [12]	• Twice-daily 200 μg budesonide plus on-demand terbutaline or salbutamol • Twice-daily 80 μg budesonide and 4.5 μg formoterol plus on-demand terbutaline or salbutamol
Kuna *et al* 2006 [13]	• Two inhalations once-daily of 80 μg budesonide and 4.5 μg formoterol plus on-demand terbutaline or another preferred SABA • One inhalation twice-daily of 80 μg budesonide and 4.5 μg formoterol plus on-demand terbutaline or another preferred SABA • One inhalation once-daily of 200 μg budesonide plus on-demand terbutaline or another preferred SABA
Papi *et al* 2007 [6]	• Placebo twice daily plus 100 μg of albuterol as needed • Placebo twice daily plus a combination of 250 μg beclomethasone and 100 μg albuterol in a single inhaler as needed • 250 μg beclomethasone twice daily plus 100 μg albuterol as needed • A combination of 250 μg beclomethasone and 100 μg albuterol in a single inhaler twice daily plus 100 μg of albuterol as needed
Papi *et al* 2015 [4]	• Placebo twice daily plus inhalation of a combination of 160 μg budesonide and 4.5 μg formoterol as needed • Twice-daily inhalation of a combination of 160 μg budesonide and 4.5 μg formoterol plus symptom-driven 500 μg terbutaline

SABA : short-acting beta-2 agonist

Treatment comparison for exacerbation or aggravation of asthma.

The RRs of OD-ICS / FOBA vs. REG-ICS + OD-SABA and OD-ICS / FOBA vs. REG-ICS / LABA + OD-SABA for the incidence of asthma exacerbation or aggravation were 1.17 (95% CI, 0.61 to 2.26) and 1.47 (95% CI, 0.79 to 2.71), respectively (Table 3). Because the upper 95% CIs for RR extended beyond the non-inferiority margin, we concluded that we failed to demonstrate non-inferiority of OD-ICS / FOBA to REG-ICS + OD-SABA or REG-ICS / LABA + OD-SABA in the meta-analysis.

Analysis of ranking probability

Rankings for OD-ICS / FOBA, REG-ICS + OD-SABA, and REG-ICS / LABA + OD-SABA are shown in Table 4. The respective probabilities were 10.5%, 10.3%, and 79.3% for being the best treatment, 58.1%, 23.4%, and 18.5% for being the second best, and 31.4%, 66.3%, and 2.2% for being the third best treatment. SUCRAs for the incidence of asthma exacerbation or aggravation were 0.4, 0.2, and 0.9 for OD-ICS / FOBA, REG-ICS + OD-SABA, and REG-ICS / LABA + OD-SABA, respectively (Fig. 3, Table 4).

Inconsistency test

A funnel plot (Fig. 4) showed symmetry to the line, which suggests that there is no small-

Table 3. Results from pair-wise meta-analysis (direct comparison) and network meta-analysis (mixed comparison)

Treatment comparison	Direct comparison	Mixed comparison
OD-ICS / FOBA vs. REG-ICS + OD-SABA	1.25 (0.84, 1.86)	1.17 (0.61, 2.26)
OD-ICS / FOBA vs. REG-ICS / LABA + OD-SABA	0.87 (0.29, 2.61)	1.47 (0.79, 2.71)
REG-ICS + OD-SABA vs. REG-ICS / LABA + OD-SABA	1.48 (0.29, 2.61)	1.25 (0.86, 1.84)

Results are expressed as risk ratios with 95% confidence intervals for the incidence of asthma exacerbation or aggravation with the first treatment compared to the reference second treatment. OD-ICS / FOBA : on-demand inhaled corticosteroid and fast-onset beta-2 agonist combination without any regular treatment. REG-ICS + OD-SABA : regular inhaled corticosteroid plus on-demand short-acting beta-2 agonist. REG-ICS / LABA + OD-SABA : regular inhaled corticosteroid plus long-acting beta-2 agonist and on-demand short-acting beta-2 agonist.

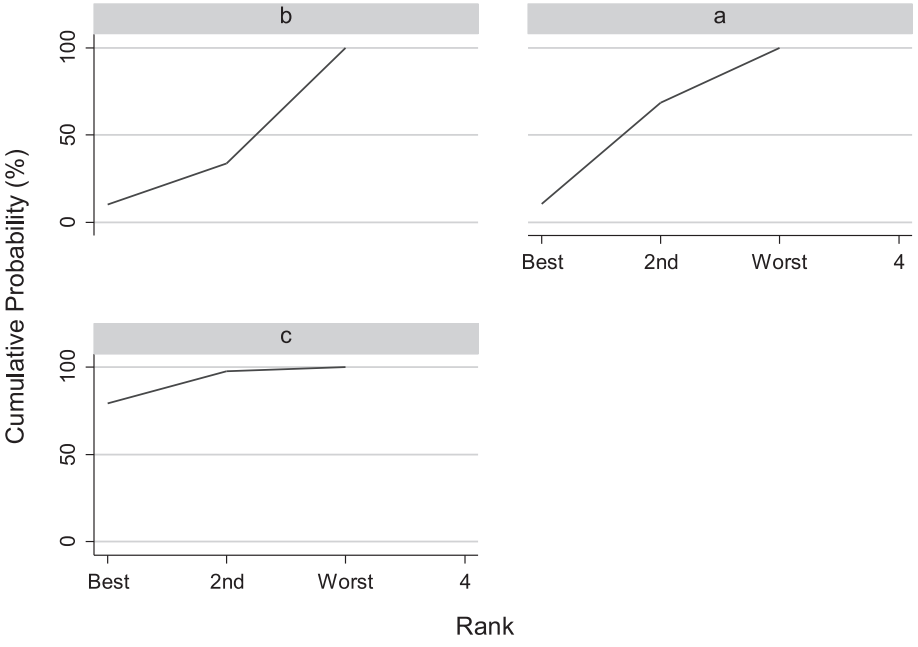

Fig. 3. Surface under the cumulative ranking curves for asthma exacerbation or aggravation. a : on-demand inhaled corticosteroid and fast-onset beta-2 agonist combination without any regular treatment (OD-ICS / FOBA) ; b : regular inhaled corticosteroid plus on-demand short-acting beta-2 agonist (REG-ICS + OD-SABA) ; c : regular inhaled corticosteroid with long-acting beta-2 agonist combination plus on-demand short-acting beta-2 agonist (REG-ICS / LABA + OD-SABA).

study effect in the network meta-analysis. An inconsistency plot (Fig. 5) suggested that there was no significant inconsistency of results between direct and indirect comparisons because the corresponding CIs included zero.

Table 4. Ranking probabilities and surface under the cumulative ranking (SUCRA) curve values

Treatment	Best	2nd	3rd	Mean rank	SUCRA
OD-ICS / FOBA	10.5	58.1	31.4	2.2	0.4
REG-ICS + OD-SABA	10.3	23.4	66.3	2.6	0.2
REG-ICS / LABA + OD-SABA	79.3	18.5	2.2	0.9	0.9

Probability (expressed as a %) of being the best, second best, or third best treatment, and SUCRA values, for asthma exacerbation or aggravation, calculated from the network meta-analysis.

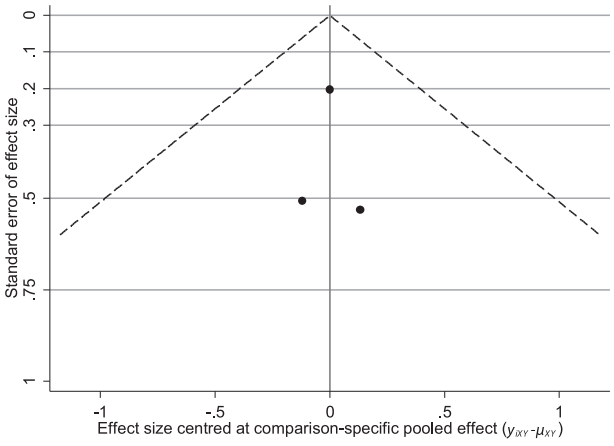

Fig. 4. Comparison-adjusted funnel plot for the network meta-analysis.

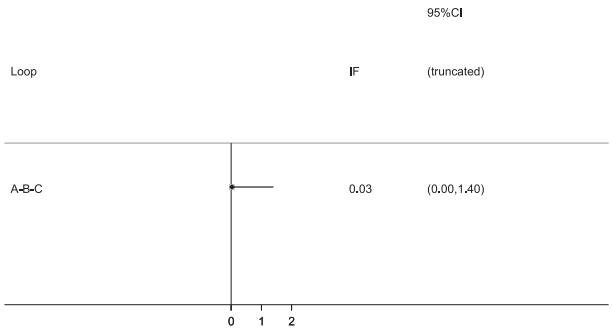

Fig. 5. Inconsistency plot for the network meta-analysis. IF : inconsistency factor ; CI : confidence interval.

Discussion

In this meta-analysis, we assessed the non-inferiority of OD-ICS / FOBA for the incidence of asthma exacerbation and aggravation compared to conventional best practice treatments for mild to moderate asthma. Four RCTs were included in the network meta-analysis. We could not demonstrate non-inferiority of OD-ICS / FOBA to REG-ICS + OD-SABA or REG-ICS / LABA + OD-SABA, but the same ranking probability of being the best treatment was found for OD-ICS / FOBA and REG-ICS + OD-SABA. Moreover, SUCRA was higher for OD-ICS / FOBA than REG-ICS + OD-SABA. As expected, the best-ranked treatment probability and highest SUCRA were obtained for REG-ICS / LABA + OD-SABA.

Several previous RCTs have assessed the efficacy of OD-ICS / FOBA compared with conventional best practice in patients with mild or moderate asthma[4-6]. One RCT demonstrated the non-inferiority of on-demand beclomethasone with albuterol without any regular treatment relative to regular beclomethasone plus on-demand albuterol in mild asthma[6]. Another RCT found inferiority of on-demand budesonide and formoterol without any regular treatment relative to regular budesonide and formoterol plus on-demand terbutaline, but also showed that the dif-

ferences in asthma control were small and the level of control remained above that of partially controlled asthma, indicating that OD-ICS / FOBA can be considered in individual cases[4].

To our knowledge, this is the first study using a network meta-analysis to assess the non-inferiority of OD-ICS / FOBA relative to conventional best practice treatment in mild to moderate asthma. SUCRA was higher for OD-ICS / FOBA than for REG-ICS + OD-SABA. This result suggests that OD-ICS / FOBA is effective and might be an alternative therapy to REG-ICS + OD-SABA in patients with mild to moderate asthma. The ideal population of patients who may benefit from this treatment remains undefined.

Conventional regular treatment can generally be recommended for patients who have a high risk of deterioration of asthma control with on-demand combination treatment, such as females or patients with a history of heavy smoking. In contrast, patients for whom it is difficult to maintain asthma control using a regular treatment due to lower adherence may benefit from on-demand treatment because it is convenient and requires a significantly lower total amount of drugs.

Several limitations of this study should be acknowledged. First, only published studies were included, and some publication bias may thus be present. Second, a meta-analysis is a form of retrospective research that is subject to the metrological deficiencies of the studies included in the analysis. Finally, only four articles were used in each analysis, which may affect statistical power.

In summary, we assessed the non-inferiority of OD-ICS / FOBA using the incidence of asthma exacerbation and aggravation relative to conventional best practice therapy, such as REG-ICS + OD-SABA or REG-ICS / LABA + OD-SABA, in patients with mild to moderate asthma, using a network meta-analysis. We failed to demonstrate non-inferiority of OD-ICS / FOBA to REG-ICS + OD-SABA or REG-ICS / LABA + OD-SABA, but SUCRA was higher in OD-ICS / FOBA than REG-ICS + OD-SABA. These results suggest that OD-ICS / FOBA is effective as an alternative therapy to REG-ICS + OD-SABA for patients with mild to moderate asthma, especially for patients whose adherence to regular treatment is low. Considering the limitations of this meta-analysis, there is a need for further research to confirm the efficacy of treatment using OD-ICS / FOBA.

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Conflict of interest disclosure

None of the authors have a conflict of interest to declare.

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