

The effectiveness of intranasal corticosteroids in combined allergic rhinitis and asthma syndrome

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Summary

Background Allergic rhinitis (AR) and asthma often coexist and may represent two manifestations of the same disease recently named combined AR and asthma syndrome (CARAS).

Aim To review the common pathophysiology of combined AR and asthma and to investigate the efficacy of intranasal corticosteroids (INCS).

Methods Medline was used to identify articles relevant to mechanisms. A Cochrane systematic review was performed to assess the efficacy of INCS in CARAS.

Results There is cross-talk, evidence of a common inflammatory response in both sites, linked by a systemic component. The efficacy of anti-inflammatory INCS on asthma outcomes was assessed in a systematic review of 12 randomized controlled trials involving 425 subjects. After INCS there were non-significant trends for improvement in asthma symptom score (standardized mean difference (SMD) of 0.61; $P = 0.07$), forced expiratory volume in 1 s (SMD of 0.31; $P = 0.08$), and morning peak expiratory flow (weighted mean difference of 36.51; $P = 0.06$). There was no impact on methacholine airways responsiveness (SMD of -0.20 ; $P = 0.4$). The review identified two promising new treatment options in united airway disease such as INCS as monotherapy in rhinitis and mild asthma, and a combined intranasal and intrabronchial corticosteroid (IBCS) deposition technique.

Conclusion Common mucosal inflammatory responses occur in CARAS. This systematic review shows trends for a benefit of INCS in CARAS, but recognizes that more research is needed. At this stage, the current best practice is to treat asthma conventionally with IBCS with or without β_2 -agonist and to add INCS to improve specific rhinitis symptoms.

Keywords asthma, intranasal corticosteroid, randomized controlled trial, rhinitis

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Background

Allergic rhinitis (AR) and asthma are high-prevalence and high-cost diseases throughout the world [1]. Rhinitis and asthma commonly coexist. Nasal symptoms are experienced by as many as 30–99% of patients with allergic asthma [2], asthma is experienced by 13–43% of patients with rhinitis [3, 4], and up to 30% of AR patients, with no past history of asthma, will show bronchial hyper-reactivity (BHR) to methacholine [5]. The proposed mechanisms connecting upper and lower airways include a nasal–bronchial reflex, mouth breathing caused by nasal obstruction, pulmonary aspiration of nasal contents and common mucosal inflammatory processes. AR and asthma may therefore represent two manifestations of the same disease. To underline the strong link between upper and lower airways, new terminologies have been introduced such as united airway disease,

allergic rhinobronchitis or most recently combined AR and asthma syndrome (CARAS) [6].

Since AR and asthma are both mediated by similar allergic inflammatory mechanisms, the use of intranasal corticosteroids (INCS) may benefit asthma. Selective treatment of the nose could impact on the lungs by lowering systemic pro-inflammatory cytokines. Systemic absorption or bronchial deposition of INCS have also been advocated to explain the improvement of asthma parameters but this seems unlikely in the light of the moderate dosage of INCS used in most studies. In some clinical studies, INCS have additional benefit in controlling allergic seasonal asthma [7–9], whereas in others no effect of INCS on BHR was observed [10]. Patients with CARAS who were treated for AR had significantly fewer hospitalizations and emergency department visits for asthma than those who did not receive treatment [11]. Most narrative reviews support a positive effect of INCS [3, 5, 12–14], and the recent guidelines on rhinitis and asthma (ARIA), stated that optimal management of rhinitis may partly improve coexisting asthma [15]. Asthma guidelines are less clear on this topic [16, 17]. The purpose of this article is to review the pathophysiological mechanisms in CARAS, and to

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investigate the effects of INCS in CARAS via a systematic review of randomized controlled trials.

Pathophysiology of combined allergic rhinitis and asthma syndrome

The observation that AR often precedes the development of asthma has been confirmed by several recent studies [18–20]. The concept of a unified airway is now widely accepted, and as a consequence several specific terms have been proposed to define this entity, with CARAS appearing the most appropriate [6]. A new clinical instrument assessing health-related quality of life in rhinitis and asthma has also recently been validated [21]. Several mechanisms have been proposed to explain the interdependence of nasal and bronchial disease in CARAS. These include a common, systemically mediated inflammatory response, a nasal–bronchial reflex, mouth breathing caused by nasal obstruction and pulmonary aspiration of nasal contents. Common inflammatory processes appear to be the most important link in the cross-talk between the upper and lower airways.

The structure of airway mucosa presents similarities between the nose and the lungs. They both share the same pseudostratified epithelium with columnar, ciliated cells resting on a basement membrane. The submucosa of the nose and the bronchi feature vessels, mucous glands, nerves and inflammatory cells such as monocytes, lymphocytes and mast cells [22]. These clinical and morphologic findings emphasize strongly a linked immunopathogenesis in rhinitis and asthma. The nose and the lungs should therefore be considered as one entity, reason why an increasing number of authors have accepted the concept of ‘one airway one disease’. Important structural differences include a layer of smooth muscle surrounding the bronchi and an extensive submucosal vascular network in the nose.

Several recent studies emphasize common inflammatory processes in the nose and bronchi [23]. Non-asthmatic subjects with AR may have increased bronchial reactivity after conventional nasal allergen challenge. Challenge of the nose with allergens can also provoke an inflammatory response in the lower airways, manifest as an increase in eosinophils and in the expression of intracellular adhesion molecule-1, in both nasal and bronchial biopsies [24], and in induced sputum [25]. A recent study in a murine model also identified that nasal allergen challenge induced bronchial eosinophilic inflammation [26]. Another study in non-asthmatics with AR showed that bronchial inhalation of very low dose allergen challenge can induce an eosinophilic airway inflammation without inducing a clinical or spirometric response [27]. These data support the idea of linked pathogenesis in CARAS, and demonstrate that a nasal inflammatory stimulus can provoke lower airway inflammation, that may be present before the onset of bronchial hyper-responsiveness or clinical symptoms. This later study also demonstrated that the subjects with purely AR exhibited a different inflammatory pattern compared with those with CARAS. In the CARAS subgroup, the eosinophilic inflammation tended to increase progressively over the 4 days of the challenge while in the rhinitis only subgroup the bronchial eosinophilia only progressed initially before decreasing

subsequently. These two different types of inflammatory processes suggest an adaptation mechanism in rhinitis subjects that may protect against developing asthma [27].

The effect of bronchial provocation on nasal inflammation was examined in another study that performed segmental bronchoprovocation in non-asthmatic AR subjects. There was a reduction in nasal mast cell and basophils, as a result of enhanced degranulation. These two cell types and their mediators are important in the initiation of the early allergic response and these findings highlight from another perspective the united airway model. It was speculated that bronchial allergen challenge leads to a systemic effect through the whole respiratory system by the production of inflammatory mediators [28]. This is supported by the findings of increased plasma IL-5 after nasal allergen challenge in human [25] and animal studies [29], and by the link between the peak in serum IL-5 and bronchoalveolar lavage eosinophil influx [29]. Furthermore, a systemic blood eosinophilia can occur after nasal allergen challenge [30] and nasal allergen challenge can enhance cytokine release from peripheral blood inflammatory cells [31].

If a systemic inflammatory response is the link between nasal and lower airway disease in CARAS, then, bronchial inflammation should also provoke a systemic response with worsening of nasal symptoms. Indeed this is the case. Bronchial allergen challenge tends to increase circulatory eosinophils, basophils and their marrow-derived progenitor cells [32], and endobronchial allergen challenge provokes nasal inflammation with increases in nasal eosinophils and IL-2-positive cells [28]. Thus, there is considerable evidence supporting common inflammatory processes in CARAS with nasal and systemic responses leading to bronchial inflammation and asthma.

Other mechanisms linking nose and lower airway disease include route of breathing, a nasal bronchial reflex and pulmonary aspiration of nasal contents. AR results in nasal obstruction, which may promote mouth breathing. This bypasses the warming and humidifying effect of nasal breathing and can potentiate lower airway responses to irritants. For example, exercise-induced bronchospasm is potentiated by mouth breathing and blunted by nasal breathing [33]. The presence of nasal reflex proposes that nasal stimulation leads to reflex bronchoconstriction. This has recently been demonstrated with cold air stimulation in normals [34]. The significance of this mechanism in CARAS awaits confirmation. Aspiration of sinus contents in the bronchial tree has been a postulated but not confirmed mechanism in CARAS [35].

Treatment implications

The important pathophysiological link between the upper and lower airways has implications for the approach to treatment in CARAS. Therapy that could influence both the nose and the lung are allergen avoidance, specific immunotherapy, anti-IgE, oral antihistamines, oral leukotriene receptor antagonists and INCS. INCS have been the focus of most previous studies. Some data favour an additional benefit of INCS in controlling allergic seasonal asthma [7–9], whereas others failed to observe a reduction in BHR [10]. A recent

large retrospective cohort study has demonstrated that INCS confer significant protection against asthma leading to emergency department visits [36]. The ARIA guideline on rhinitis and asthma states that optimal management of rhinitis may help to control existing asthma. The assessment of efficacy of various drugs was based on an evidence-based medicine approach [37]. In this position paper, the panel of experts have listed the highest level of evidence available for each intervention by categorizing every trial from Ia to IV. The highest level of evidence for most interventions was Ib, which corresponds to the evidence of at least one randomized controlled trial. In particular there was Ib evidence for using INCS in seasonal rhinitis in children and adults as well as in perennial rhinitis in a paediatric and adult population. Although these studies have been properly assessed for relevance to the clinical question of interest, there has been no mention of quality assessment and potential biases.

Cochrane systematic review

We therefore performed a Cochrane systematic review of randomized controlled trials to determine whether treatment with INCS was effective on asthma outcomes, in patients suffering from rhinitis and asthma [38].

Eligible studies were identified in electronic databases as well as by hand searches. The following search terms were used: ([rhinitis or hayfever] AND [asthma OR wheeze OR hyper-responsiveness]) AND ([intranasal OR nasal] AND [steroid OR corticosteroid OR glucocorticoid OR beclomethasone OR fluticasone OR triamcinolone OR budesonide OR mometasone]). Statistical analysis for continuous data was done by weighted mean difference (WMD) or standardized mean difference (SMD).

Two independent reviewers retrieved initially 345 abstracts of which 19 were relevant. They finally excluded another seven articles (attempts to contact one author was unsuccessful, another author was unable to provide the required additional information and data were in an inadequate form for another five papers). Twelve randomized controlled trials involving 425 subjects were included in the review (Fig. 1). Quality assessment was done by using the Jadad score that was ranging from 2 to 3 and the allocation concealment that was quoted B for all studies. This indicates that study methodological quality was modest. There were eight studies in adults, three in children and one in a mixed age group (Table 1). There was a great variability in the number of reported asthma outcomes from one study to another making comparisons somewhat fragmented (Table 2). It was nevertheless possible to aggregate data from several studies and perform a meta-analysis for some outcomes. The absence of heterogeneity in three out of four meta-analyses and the mild heterogeneity in the asthma symptom score (ASS) meta-analysis ($P=0.05$) delineates the validity of these results. These meta-analyses showed a trend to improved asthma outcomes with INCS. ASSs showed a non-significant improvement after INCS with a SMD of 0.61 ($P=0.07$) (Fig. 2). Forced expiratory volume in 1 s (FEV_1) also increased non-significantly after INCS with a SMD of 0.31 ($P=0.08$) (Fig. 3). There was a similar trend towards efficacy

after INCS on morning peak expiratory flow (PEF) with a WMD of 36.51 ($P=0.06$) (Fig. 4). Methacholine airways responsiveness showed no improvement after INCS with a SMD of -0.20 ($P=0.4$) (Fig. 5).

We concluded that INCS as monotherapy in patients with rhinitis and mild asthma were well tolerated but failed to show a statistically significant effect on all analysed asthma outcomes.

The absence of statistically significant impact of INCS on FEV_1 , morning PEF and ASS and the absence of effect of these drugs on methacholine tests are disconcerting. These results do not sustain the ARIA guideline recommendations and seem to weaken most conclusions of previous narrative reviews. Some limitations of these meta-analyses are that only a limited number of studies, ranging from 2 to 5, could be aggregated and there was heterogeneity among the studies. Therefore, the addition of future studies might increase the statistical power and provide clearer evidence of benefits.

Inconclusive findings from a systematic review can occur because not enough outcomes can be synthesized into meta-analyses, because of the rigorous inclusion criteria inherent to the Cochrane methodology [47]. In addition, variable reporting of clinical trial outcomes diminishes the ability to pool data for meta-analyses. The usual implication of these systematic reviews is that more research should be done. Although not providing a definite answer this is in fact a very useful and evidence-based indicator of where to conduct further research. As a matter of fact, the 'Canadian Institute of Health Research' funding body goes one step further, by requiring that researchers justify in their grant application, the need for a new randomized controlled trial (RCT) in the light of conclusive/inconclusive systematic review(s).

The effects of INCS were quite heterogeneous in the various studies included in the systematic review, for several potential reasons. Firstly, the increase of BHR during the pollen season is thought to be related to a certain threshold of allergen deposition in the lower airways. The effect of INCS on the lower respiratory tree might therefore also be dependent on the pollen load. Reliable comparisons of different studies in CARAS may therefore be accurate only when pollen counts are available. Secondly, the target population may need to be specified with more clarity. Are the patients who responded favourably to INCS on asthma outcomes a group that presented initially with more severe rhinitis? Thirdly, the specific drug, the duration, the dosage and specifically the mode of administration of INCS seem to be of great importance. These latter points are discussed below.

This systematic review has indeed been able to highlight two interesting future treatment options for CARAS. The intranasal inhalation technique was not specified in 10 studies, but it was assumed to be a standard intranasal inhalation technique. Two studies [9, 43] reported a slightly different technique where a pear-shaped, valved holding device equipped with a nozzle was added to the metered dose inhaler for drug delivery. Drug actuation was synchronized at commencement of a deep inspiration through each nostril and then a breath hold for 10 s. The aim of this technique was to achieve a combined intranasal and intrabronchial corticosteroid (IBCS) deposition.

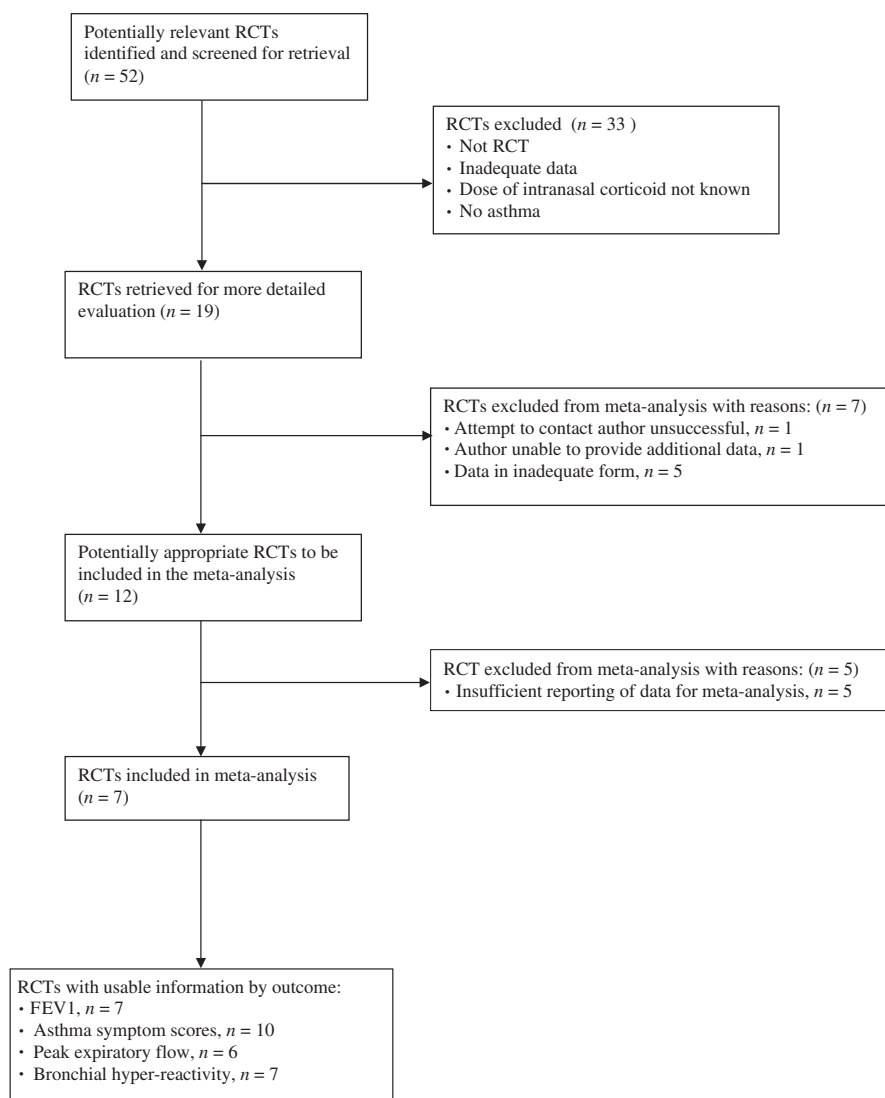


Fig. 1. Summary of a quorum flowchart for meta-analysis.

Table 1. Characteristics of included studies

Author	Design (quality score)	Enrolled (completed)	Age	R	A	INCS	Week
Armitage et al. [39]	Parallel (3)	20 (19)	Adult	SAR	Some	BDP 400 µg	12
Corren et al. [40]	Parallel (3)	22 (18)	Adult	SAR	All	BDP 336 µg	6
Foresi et al. [41]	Parallel (3)	50 (50)	Adult	SAR	No	FP 200 µg	6
Henriksen and Wenzel [42]	Parallel (3)	37 (36)	Child	PAR	All	BUD 400 µg	4
Pedersen et al. [43]	Cross-over (3)	30 (30)	Adult	SAR	All	BUD 800 µg	2
Pedersen et al. [9]	Cross-over (3)*	24 (23)	Child	PAR PNAR	All	BUD 1292 µg	3
Pelucchi et al. [44]	Parallel (3)	30 (26)	Adult	SAR	No	BDP 400 µg	6
Reed et al. [45]	Parallel (3)	60 (48)	Adult	SAR	Some	BDP 336 µg	8
Thio et al. [10]	Parallel (3)	25 (21)	Adult	SAR	All	FP 200 µg	6
Thio et al. [10]	Parallel (3)	72 (67)	Adult	SAR	All	BDP 400 µg, FP 200 µg	6
Watson et al. [8]	Cross-over (3)	28 (21)	Child	PAR	All	BDP 400 µg	4
Wood and Eggleston [46]	Cross-over (2)	12 (12)	Adult	PAR	Some	TA 440 µg	1
	Mean: (2.9)	Total: 410 (371)					Mean: 5.3

R, rhinitis; SAR, seasonal allergic rhinitis; PAR, perennial allergic rhinitis; A, asthma; PNAR, perennial non-allergic rhinitis; INCS, intranasal corticosteroid; BUD, budesonide; FP, fluticasone propionate; BDP, beclomethasone dipropionate; TA, triamcinolone acetonide. The quality score used was the Jadad scale with a maximum score of 5.

*This study also contributed data as a parallel study by extracting outcomes in the first treatment period only.

Table 2. Main asthma outcomes

Author	ASS	FEV ₁	PEF	BHR
Armitage et al. [39]	–	NR	+	–
Corren et al. [40]	–	–	–	+
Foresi et al. [41]	NR	–	NR	+
Henriksen and Wenzel [42]	–	–	–	NR
Pedersen et al. [43]	NR	NR	+	NR
Pedersen et al. [9]	+	NR	+	NR
Pelucchi et al. [44]	–	–	NR	+
Reed et al. [45]	+	NR	NR	NR
Thio et al. [10]	–	–	NR	–
Thio et al. [10]	–	–	NR	–
Watson et al. [8]	+	NR	–	+
Wood and Eggleston [46]	+	+	NR	NR

ASS, asthma symptom score; FEV₁, forced expiratory volume in 1 s; PEF, peak expiratory flow; BHR, bronchial hyper-reactivity; NR, not reported.

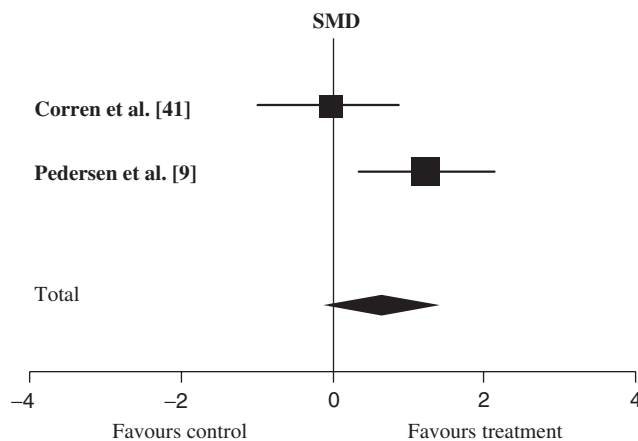


Fig. 2. Meta-analysis of the effects of INCS on Asthma symptom scores in CARAS. The effect size (shaded box) in standard deviation units is displayed with 95% CI. The overall effect size with 95% CI is shown as a shaded diamond. There was significant heterogeneity ($P = 0.05$). SMD, standardized mean difference; INCS, intranasal corticosteroids; CARAS, combined allergic rhinitis and asthma syndrome; CI, confidence interval.

In this systematic review the two studies [9, 43] that used the combined intranasal and intrabronchial inhalation technique, both showed a positive impact on nearly all measured asthma outcomes such as a statistically significant improvement of ASS and a non-statistically significant increase in morning and evening PEF. The use of average higher doses of budesonide ranging from 800 to 1292 µg/day could be partly related to the apparent efficacy of this technique in these two studies [9, 43]. This specific glucocorticoid deposition in two locations of the naso-bronchial airway is possibly of great importance and has not been sufficiently studied. There are only very few clinical trials focusing on this technique and no radiolabelled studies have been performed so far. The potential advantages of this combined inhalation techniques include greater corticosteroid deposition in the airway without an increase of total steroid dose, control of nasal symptoms, potential reduction of oral candidosis and therefore an improvement in compliance. The optimal steroid dose for this combined naso-bronchial deposition is not yet defined. Further studies will have to perform radiolabelled studies to measure the amount of corticosteroid deposition in the nose and in the lungs. A new large RCT will also need to

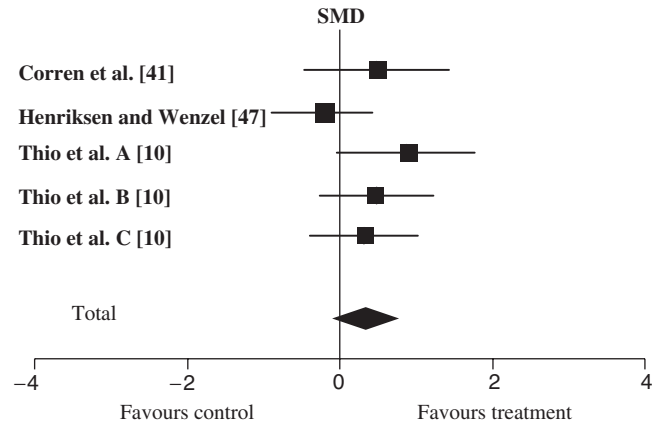


Fig. 3. Meta-analysis of the effect of INCS on FEV₁ in asthmatics with rhinitis. The effect size (shaded box) in standard deviation units is displayed with 95% CI. The overall effect size with 95% CI is shown as a shaded diamond. There was significant heterogeneity ($P = 0.36$). SMD, standardized mean difference; FEV₁, forced expiratory volume in 1 s; INCS, intranasal corticosteroids; CI, confidence interval.

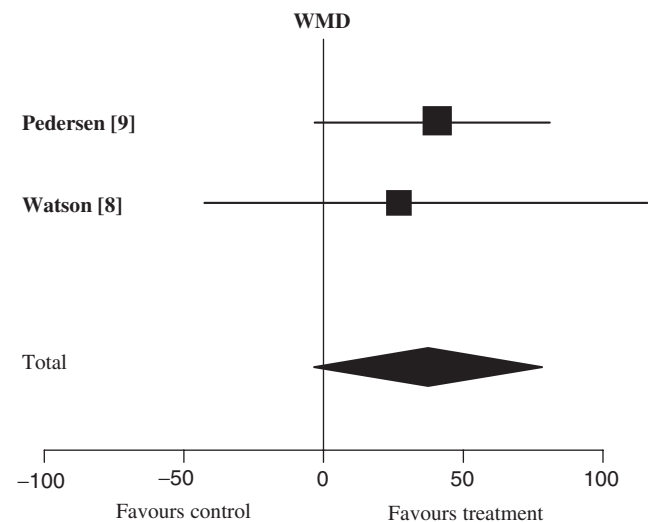


Fig. 4. Meta-analysis of the effect of INCS on morning PEF in CARAS. Results expressed as mean difference (squares) and summarized as WMD (diamond) with 95% CI. INCS, intranasal corticosteroids; PEF, peak expiratory flow; CARAS, combined allergic rhinitis and asthma syndrome; CI, confidence interval; WMD, weighted mean difference; CI, confidence interval.

assess if the suggested advantages of the combined inhalation technique are indeed better than the addition of INCS plus IBCS.

INCS as monotherapy in rhinitis and mild asthma did not improve significantly any asthma outcomes despite the fact that there was a strong trend for FEV₁, morning PEF and ASS. The absence of significant effect of INCS on objective lung functions measurement such as morning PEF and FEV₁ may partly be related to the fact that these techniques are potentially not sensitive enough to allow subtle detection of airway calibre modifications in mild or intermittent asthma. Surprisingly there was no effect of INCS on bronchial reactivity despite the fact that this technique is more sensitive than spirometry. Lung flows and volumes and methacholine hyper-reactivity measures do closely reflect airway calibre but correlate poorly with lung inflammation. There is now

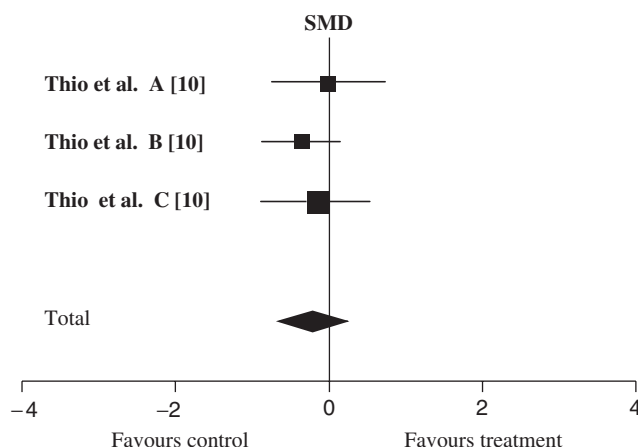


Fig. 5. Meta-analysis of the effects of INCS on methacholine airways responsiveness in CARAS. The effect size (shaded box) in standard deviation units is displayed with 95% CI. The overall effect size with 95% CI is shown as a shaded diamond. There was significant heterogeneity ($P = 0.05$). SMD, standardized mean difference; INCS, intranasal corticosteroids; CARAS, combined allergic rhinitis and asthma syndrome; CI, confidence interval.

sufficient evidence to show that indirect challenge test with adenosine 5-monophosphate (AMP) reflects much closer to the allergic inflammatory process than BHR to methacholine [48], which can be rather disconnected from the lung functions in mild asthma. Likewise exhaled nitric oxide (NO) [49] and induced sputum [50] are two other markers of inflammation that are better indicators of treatment impact than spirometry in mild asthma. Another possible explanation for the absence of effect of INCS on bronchial reactivity is again that the statistical power of this meta-analysis, done with only three outcomes extracted from two studies, was too low.

INCS as monotherapy might still be a promising alternative to treat rhinitis and mild asthma once more research is done on this topic and when future meta-analyses with greater statistical power will provide a new perspective. There is also a need to start research on the effect of INCS in rhinitis and moderate-to-severe asthma in the absence of currently available data.

Conclusion

The common immunopathogenesis linking the upper and lower airways are progressively better understood and support a common mucosal inflammation response linked by a systematic cytokine release. This forms the rationale for using INCS to treat patients suffering from rhinitis and asthma. This systematic review shows trends for a benefit of INCS in CARAS, but recognizes that more research is needed. At this stage, the best current practice is to treat asthma conventionally with IBCS or IBCS plus β_2 -agonist and to add INCS only to improve specific rhinitis symptoms.

This Cochrane systematic review has nevertheless highlighted that INCS, as monotherapy may be a promising alternative treatment in people with coexisting rhinitis and mild asthma, once more research is done on the topic. Future

studies will also have to assess the impact of INCS on more sensitive outcomes reflecting bronchial inflammation such as exhaled NO, sputum induction and AMP indirect bronchial challenges. The issue of adding an INCS to an ongoing IBCS will have to be addressed in coming trials in order to assess effectiveness and reduction in asthma exacerbation over a long period. The combined intranasal and IBCS deposition technique also appeared to be interesting and would represent a new treatment alternative that could simplify the management of CARAS. Further studies are needed to confirm the amelioration of asthma outcomes, the reduction of oral candidosis and the subsequent improvement of compliance, which is a key feature in the long-term management of asthma.

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