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BRN Rev. 2023;9(2):67-78

BRN Reviews

REVIEW ARTICLE

A New Therapeutic Approach Based on a Reinterpretation of Asthma Control

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ABSTRACT

The concept of asthma control is fundamental because it establishes a target for treatment, but despite the diversity of definitions, a high proportion of patients fail to achieve it. In this article, we highlight the shortcomings of the current concept of control by discussing aspects such as the differences between patient- and physician-perceived control and the limitations of the tools used to assess it. We also comment on the drawbacks of the stepwise approach to achieve control recommended by guidelines: the absence of conclusive evidence on the exclusive use of as-needed budesonide/formoterol in mild asthma, the lack of consideration of the different pharmacological properties of the currently available inhaled corticosteroids (ICS) and ignoring the existence of different asthma endotypes, some of which are resistant to these drugs. Other aspects, such as adherence to medication, the use of rescue medication, the influence of the inhalation device, the particle size, the pharmacological characteristics, and the lung deposition of ICS, are also mentioned. As an alternative to the guidelines´ recommendations, we propose a more customized approach based on the identification of therapeutic goals and treatable traits.

Keywords: Adherence. Asthma control. Inhaled corticosteroid. Inhaler device. Therapeutic index.

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Received: 04-07-2023
Accepted: 12-07-2023
DOI: 10.23866/BRNRev:2023-M0089
www.brnreviews.com

INTRODUCTION

Asthma is one of the most prevalent chronic respiratory diseases worldwide. In 2019, there were approximately 334 million asthmatics, and this number is expected to increase by a further 100 million by 2025[1,2]. In 2015, asthma caused around 400,000 deaths[1,3] and accounted for 1.1% of the global burden of disability-adjusted life years (DALYs)[1]. Current guidelines for the clinical management of asthma focus on disease control in two domains: symptom control and assessment of adverse outcomes[4].

Despite the efforts made to improve diagnosis, pharmacological treatments, non-pharmacological approaches, and patient education and empowerment, asthma is poorly controlled in 40%-60% of patients[5-11]. Poor asthma control increases the risk of exacerbations, reduces patient's quality of life (QoL), has a negative impact on work productivity and significantly increases healthcare costs[8,12,13].

In this article, we intend to show that shortcomings in the current concept of control (according to Global Initiative for Asthma Management (GINA) - Table 1-)[4] lead to ineffective or potentially iatrogenic therapeutic recommendations and propose rational alternatives that could avoid these risks.

ASTHMA CONTROL FROM THE PATIENTS' PERSPECTIVE

A recent study showed that 45%-65% of asthma patients perceived their disease to be completely controlled or well controlled[5], while other studies show that asthma control is not achieved in 40%-60% of cases[5-7], a rate that is more consistent with real-world evidence of excessive use of rescue medication and high symptom burden[5]. A recent survey[14] in 10,302 asthma patients from around the world showed that while 67% believed their asthma to be well-controlled, control was achieved only in 9% of the patients according to GINA's criteria[15], and the Expert Panel Report-3 (EPR-3) guidelines[16]. Moreover, ≥ 60% of the patients believe that short-acting β-antagonists (SABA) can be used daily as a symptom reliever, a practice not recommended in current guidelines[14]. All this shows that most patients underestimate their symptomatology and perceive their asthma to be under control when in fact, it is not[17,18], suggesting a widespread acceptance of the symptoms of their disease and the extent to which it limits their everyday life[8,10].

It is difficult for patients to adhere to the prescribed medication if they do not perceive the need for treatment. Adherence is only achieved in 50% of patients with chronic disorders, and this percentage could be even lower in those with respiratory disease[19]. Importantly, lack of adherence to maintenance (anti-inflammatory) medication results in uncontrolled airway inflammation and can lead to functional limitations, worsened QoL, and increased use of medical resources[20].

Good medication adherence has been shown in a meta-analysis to have a positive impact on reducing exacerbations[21]. Most patients with difficult-to-control asthma are non-adherent with their asthma medication. Patients showing poor adherence to inhaled corticosteroids (ICS) had a lower post-bronchodilator forced expiratory volume in one second (FEV_1)

Table 1. Level of asthma control

A. Asthma symptom control			
In the past 4 weeks the patient had	**Well controlled**	**Partially controlled**	**Poorly controlled**
– Daytime asthma symptoms more than 2/w – Any night waking due to asthma – SABA use for symptoms more than 2/w – Activity limitation due to asthma	None of these	1-2 items	3-4 items
B. Risk factors for poor asthma control			
Assess risk factors at diagnosis and periodically, particularly for patients experiencing exacerbations. Measure FEV_1 at start of treatment, after 3–6 months of ICS-containing treatment to record the patient's personal best lung function, then periodically for ongoing risk assessment.			
a. Risk factors for exacerbations*			
Uncontrolled asthma symptoms (Having uncontrolled asthma symptoms is an important risk factor for exacerbations)			
Medications	High SABA use/Inadequate ICS		
Other medical conditions	Obesity, chronic rhinosinusitis, GERD, confirmed food allergy, pregnancy		
Exposures	Smoking, e-cigarettes, allergen exposure if sensitized, air pollution		
Psychological	Major psychological or socioeconomic problems		
Lung function	Major psychological or socioeconomic problems		
Type 2 inflammatory markers	Higher blood eosinophils, elevated FE_{NO} (in adults with allergic asthma taking ICS)		
Exacerbation history	Ever intubated or in intensive care unit for asthma, ≥1 severe exacerbation in last 12 months		
b. Risk factors for developing persistent airflow limitation			
History	Preterm birth, low birth weight and greater infant weight gain, chronic mucus hypersecretion		
Medications	Lack of ICS treatment in patient with history of severe exacerbation		
Exposures	Tobacco smoke, noxious chemicals; occupational or domestic exposures		
Investigation findings	Low initial FEV_1, sputum or blood eosinophilia		
c. Risk factors for medication side-effects			
Systemic	Frequent OCS, long-term, high-dose and/or potent ICS, P450 inhibitors		
Local	High-dose or potent ICS, poor inhaler technique		

FE_{NO}: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in one second; GERD: gastroesophageal reflux disease; ICS: inhaled corticosteroid; OCS: oral corticosteroid; SABA: short acting beta agonist; wk: week.
*Factors that increase the risk of exacerbations even if the patient has few asthma symptoms.
Adapted from Global Initiative for Asthma (GINA)[4,16,72].

(p=0.049). A poor inhalation technique also affects asthma control[22], and studies have shown that 66% of patients with asthma misuse the inhaler[23]. The Critikal study[24] found that 32%-38% of dry powder inhaler (DPI) users made an insufficient inspiratory effort which was associated with poor asthma control and increased risk of exacerbations. Khurana et al[23]. showed that correct inhalation technique increased FEV_1 from 2.0 to 2.15 l ($p < 0.001$) and improved the scores obtained in the asthma control test (ACT) from 18.0 to 20.75 ($p < 0.001$).

Patients with a poor inhalation technique must switch to another device they can use properly. DPI are the most widely used devices for

asthma treatment and can be grouped according to their intrinsic resistance[25]. Choosing a DPI with medium resistance has been associated with the highest mean airflow rates, while low rates were achieved with devices with low or high resistance[26].

Evidence shows that the selection of an effective inhaler device significantly influences the level of asthma control. Other factors affecting device performance are particle size and lung deposition. Particles should be 1 – 5 µm in diameter. Due to the peculiar lung anatomy, larger particles are likely to be deposited in the oropharynx space, while very small particles will either be deposited in the upper airway or exhaled[27], so ICSs should be formulated to optimize lung deposition[28]. Older inhalers presented lung deposition of 10% - 15%[29] and new inhalers 40% - 60%[30].

Simplifying the treatment regimen could promote adherence and improve asthma control[31,23.] Using an inhaler that is simple to handle and not reliant on the inhalation technique is also helpful[33,34], and the type of device prescribed should be revised in patients with poorly controlled disease, the "one-size-fits-all" notion is no longer applicable, and the inhaler should be chosen on the basis of the patient's specific characteristics and preferences[35].

The use of mHealth (mobile health, an umbrella general term for using mobile phones and other wireless technology in medical care) offers promising prospects for improving the management of asthma patients. Some studies have shown that mHealth can improve the quality of life of asthma patients compared to conventional monitoring. However, the cost-effectiveness results are conflicting, and more information is needed for these tools to be definitively incorporated into the educational plan of asthma patients[36].

ASTHMA CONTROL FROM THE CLINICIANS' PERSPECTIVE

Strategies to achieve control in the lower steps of asthma severity

The overuse of rescue inhaler therapy remains widespread, despite decades of guidelines and initiatives recommending the opposite. A survey of the habits of 3415 asthma patients showed that 74% used only SABA, despite having been prescribed maintenance therapy, and 51% presented poorly controlled asthma, as assessed by the asthma control questionnaire (ACQ). Moreover, patients classified as well-controlled presented an average of six exacerbations/year, and the most common response to symptom worsening is the use of SABA[8].

Several studies have shown that repeated incorrect exposure to SABA without ICS is associated with adverse effects (AE). For example, in a randomized comparison of terbutaline, budesonide, combined treatment, and matching placebo, Hancox et al.[37] observed a temporary increase in morning peak flows and a larger-than-expected increase in evening peak flows in the first two days of treatment with terbutaline, due to the development of tolerance to the bronchodilator effect (of tachyphylaxis). Moreover, morning peak flows decreased following treatment withdrawal, suggesting bronchoconstriction. These effects

are likely mediated by the downregulation of the β-receptor during treatment[37]. Similarly, in a retrospective chart study, Nwaru et al.[38] found that overuse of SABA (defined as ≥ 2 canisters/year compared to ≤ 2 canisters/year) without ICS was associated with an increased risk of exacerbation: 3 - 5 canisters hazard ratio (HR): 1.26 (95% CI = 1.24 - 1.28); 6 - 10 canisters HR: 1.44 (1.41 - 1.46); and ≥ 11 canisters HR: 1.77 (1.72 - 1.83). Moreover, the risk of mortality was also associated with the overuse of SABA compared to ≤ 2 canisters/year; 3 - 5 canisters HR: 1.26 (95% CI = 1.14 - 1.39); 6 - 10 canisters 1.67 (1.49 - 1.87); and ≥ 11 canisters 2.35 (2.02 - 2.72). Approximately 85% of asthma patients overusing SABA at baseline had continuous overuse during the study, whereas the proportion of patients not taking any ICSs more than doubled by the end of the study[38]. As mentioned, SABA use in these studies does not follow the indication found in asthma guidelines.

The maintenance and reliever therapy (MART) strategy was designed to improve control in patients already on maintenance therapy from GINA step 3 and beyond and has started to recommend using the combination ICS/formoterol (FOR) for steps 1 and 2[4], partly based on Symbicort Given as Needed in Mild Asthma (SYGMA) studies[39,40]. This approach relies on rapid as-needed adjustments in ICS/long-acting β-antagonist (LABA) when the patient would otherwise draw on SABA[41]. This strategy, described and recommended in GINA and a few more guidelines, merits analysis. For example, it is interesting to note that 9% - 29% of patients and 24% - 45% of physicians are unaware of this strategy, and among those who prescribed MART, 80% - 95% prescribed an additional (non-ICS) as-needed reliever[5], which is contrary to the original recommendation.

Studies evaluating the efficacy of MART therapy in mild asthma[39,40,42,43] have shown either no reduction[39,40] or modest reduction[43] in annual exacerbations. In contrast, maintenance ICS monotherapy measured by ACQ has demonstrated similar or better asthma control[40,42,43]. This comparison should be viewed with caution, because asthma severity varied in the foregoing studies. A critical appraisal found that only 17.1% of patients receiving ICS/FOR are controlled[44]. In seven trials lasting between six and twelve months, patients using this therapeutic approach were awoken by asthma symptoms once every seven-ten days (weighted average of 11.5%), suffered asthma symptoms more than half of the days (weighted average of 54.0%), and one in five patients had one severe exacerbation per year[44]. The long-term consequences of MART therapy have not been studied, although in one study, the use of MART for over one year was associated with a significant increase in sputum and biopsy eosinophilia[44]. The authors concluded that no evidence exists that better asthma treatment outcomes can be obtained with the as-needed use of ICS/LABA therapy compared with conventional maintenance ICS/LABA therapy. Airway eosinophils are a well-known symptom of inflammation in asthmatic patients[45]. A recent study[46] showed that in patients following MART therapy, the geometric mean percent sputum eosinophils remained unchanged (1.6% - 1.9%), whereas there was an increase in subepithelial eosinophils in biopsy specimens (6.2 cells/mm^2 - 12.3 cells/mm^2). These same parameters decreased with high fixed-dose treatment (2.2%

- 1.2%; 7.7 cells/mm^2 - 4.8 cells/mm^2, respectively), resulting in significant treatment differences of 0.7% (ratio, 1.8; 95% CI, 1.2 - 2.8; p = 0.0038) and 7.5 cells/mm^2 (ratio, 2.9; 95% CI, 1.6 - 5.3; p < 0.001), respectively, which remained within the range associated with stable clinical control. Other parameters, such as reticular basement membrane thickness, exhaled nitric oxide, exacerbation frequency, or FEV_1 remain unaltered[46].

In conclusion, further studies are needed to reach appropriate conclusions regarding the convenience of therapy in steps 1 and 2 of GINA guidelines as concluded in other recent works[47].

Problems with the stepwise strategy

The step-up approach recommends increasing the ICS dose to achieve asthma control in patients failing to achieve control at the current dose[48]. However, it has been shown that 80% - 90% of the maximum benefit is normally obtained with low doses of ICS (100 - 200 µg of fluticasone propionate or equivalent), and higher doses expose the patient to a significantly higher risk of systemic AE with no clear clinical benefit[49,50]. Similarly, a recent meta-analysis comparing low, moderate, and high starting doses of ICS in monotherapy or combination with a LABA found that all doses were comparable with respect to nighttime rescue medication, symptom burden and FEV_1 improvement. The authors concluded that high starting doses of ICS did not confer significant benefits compared to lower doses and could potentially present more safety concerns[51].

The dose escalation strategy recommended in guidelines is based on equivalence/equipotency tables[52]. GINA recently published an update that is based on a limited number of studies and product information[4]. Traditionally, however, the potency of topical corticosteroids has been estimated using McKenzie's indirect method[53], a test based on the skin-bleaching properties of corticosteroids[53] caused by vasoconstriction. It should be noted that McKenzie's study did not consider that the therapeutical effects of ICS in asthma patients are mainly due to their genomic effect on the airway[54]. This is important, because the step-up approach in asthma management leads to an increase in the ICS dose in patients with poor asthma control[4,55] without considering the pharmacological properties of each available alternative. There is a widespread belief, possibly promoted by asthma treatment guidelines, that all ICSs have the same pharmacological properties[29]. These, however, are determined by the molecular structure, which in turn affects important aspects such as drug potency, lipophilicity, and by the pharmacokinetic and pharmacodynamic characteristics, which determine efficacy and systemic exposure to ICS and cause the main adverse effects. The relationship between these two key factors is clearly expressed by the therapeutic index (TI), insofar as a high TI means that the desired clinical effect will be achieved with a low risk of adverse effects. A simple classification of ICS into low, medium, and high doses does not reflect their pharmacological characteristics, as shown in table 2.

It is also essential to consider that high ICS doses are associated with a significant risk of systemic AEs[50] that include cataracts, bone density abnormalities, increased risk of diabetes,

Table 2. Pharmacological properties and therapeutic index of some inhaled corticosteroids

ICS/dose form	Relative glucocorticoid receptor binding affinity	Lipophilicity (log P)	Plasmatic protein binding (%)	Bioavailability F (%)	Therapeutic index
Fluticasone furoate DPI	2989	4.17	99.7	15DPI 1oral	18.6
Fluticasone propionate DPI	1775	3.89	99.3	16 DPI 1oral	1.84
Budesonide DPI	935	2.32	91.4	39 DPI 11oral	1.31

DPI: dry powder inhaler; the therapeutic index is calculated as ED50 = dose at which 50% of the maximum effect is achieved/AMP PC20 = provocative concentration of adenosine-5′-monophosphate causing a ≥ 20% decline in forced expiratory volume in one second.
Adapted from Daley-Yates et al.[29,73].

and suppression of the adrenal function[56]. A recent systematic review found that the few studies that assess the systemic effects of ICSs present conflicting findings, multiple biases, and residual confounding[56] A meta-analysis showed that 6.8% of asthma patients on average presented adrenal insufficiency. The risk of this AE varied according to the dose used: 1.5% with low-dose ICS (95% CI: 0.2 - 9.4), 5.4% with medium-dose ICS (95% CI: 2.7 - 10.4) and 18.5% with high-dose ICS (95% CI: 8.7 - 35.2)[57]. Another critical issue is that medication is not usually stepped down[58,59], for example, a study found that step-down was only attempted in 6% of patients, even though 60% had achieved asthma control[59].

The stepwise strategy can result in ICS overtreatment and iatrogenic side effects. Although, as stated above, ICSs are pharmacologically different, guidelines only marginally consider switching between them, probably due to the lack of studies evaluating this possibility[4,55]. Theoretically, switching the ICS could help to improve asthma control by widening the TI, thus favouring lower doses with higher receptor affinity binding and lower systemic exposure[29]. Although in another type of obstructive lung disease, the Global Initiative for Obstructive Lung Disease (GOLD)[60] suggests that changing the drug, the device, or both, should be considered before stepping up treatment in patients with poor control.

As discussed above, the effectiveness of chronic disease management is affected by difficulties in achieving optimal compliance. In the case of asthma, a disease defined by the great variability of its clinical expression, patients may choose to match medication to symptoms. To avoid this, emphasis needs to be placed on a good education program[7,61].

The inflammatory endotype is not considered in asthma treatment guidelines

Therapeutic recommendations found in asthma guidelines do not consider the inflammatory characteristics of asthma patients (endotypes) and their clinical manifestations (phenotypes)[62]. Studies have shown that patients with low sputum eosinophils may not respond to glucocorticoids[63]. Moreover, it has been found that a majority (73%) of patients with mild persistent asthma have low sputum eosinophil

Table 3. Therapeutic goals and treatable traits

Therapeutic Goals	Treatable Traits	Biomarkers Associated with Therapeutic Traits
Improved symptoms: – Dyspnoea – Night awakenings – Health-related QoL	Bronchial obstruction	FEV_1
	Non-adherence	Questionnaires (TAI)
	Aggravating factors (allergens, environmental pollution, etc.)	Environmental levels
	Smoking	COHb
	Comorbidities	Patient variability
	Mucus hypersecretion	CT scan
	Lung hyperinflation	Inspiratory capacity
Reduced risk of: – Mortality – Disease progression – Exacerbations – Adverse effects of medication	Eosinophilia	Eosinophils in Peripheral blood or airway
	Chronic infection	Germ isolation
	Adrenal insufficiency	Cortisol
	Chronic bronchitis	Chronic bronchitis
	Chronic hypoxemia	PaO_2/SaO_2

AT: anti-trypsin; COHb: carboxyhemoglobin; FEV_1: forced expiratory volume in one second; Pa: partial pressure; QoL: quality of life; TAI: test of adherence to inhalers.
Adapted from Pérez de Llano et al.[65].

levels and no significant difference in their response to an ICS (mometasone) or long-acting muscarinic antagonist (tiotropium) compared with placebo[64]. While it would be ideal to prescribe treatment according to each patient's endotype, we must acknowledge that the biomarkers available for clinical practice still have many limitations.

In an attempt to overcome these drawbacks, some authors suggest an asthma management strategy based on identifying patient-specific therapeutic goals (the objectives set to improve the clinical condition of the patient) and treatable traits (characteristics that can be targeted by treatment)[65]. The therapeutic goals, treatable traits, and associated biomarkers are shown in table 3[65].

This approach requires further evidence before it can be recommended in guidelines.

Shortcomings of tools to estimate control

Guidelines recommend the use of numerical questionnaires (Table 4) to assess the level of control in asthma patients[4,55]. A moderate correlation was found between ACT scores and outcomes such as rescue medication use, exacerbations, sleep quality, and work and productivity, but a poor correlation between general health-related QoL, use of healthcare resources, and costs[66]. ACQ is significantly associated with asthma-related QoL[67] but is a poor predictor of lung function and exacerbations[68]. These tools do not consider the presence of exacerbations in the preceding 12 months, which is known to be an important prognostic factor for future exacerbations[69]. The recently developed Asthma Impairment and Risk Questionnaire (AIRQ) predicts exacerbation risk over 12 months

Table 4. Asthma control assessment tools

	#items	Age	Symptom frequency	Reliever use	Activity limitation	Nocturnal symptoms	Exacerbations	Additional measures
Asthma Control Test (ACT)[75]	5	>12	Yes	Yes	Yes	Yes	No	Self-perception of control
Childhood ACT (cACT)[76]	7	4-11	Yes	No	Yes	Yes	No	Self-perception of control
Asthma Control Questionnaire (ACQ)[77]	6	>12	Yes	Yes	Yes	Yes	No	FEV1
Asthma Therapy Assessment Questionnaire (ATAQ)[78]	4	≥18	No	Yes	Yes	Yes	No	Self-perception of control
Lara Asthma Symptom Scale (LASS)[79]	8	>3	Yes	No	No	Yes	Yes	Parent perception of control
Asthma Impairment and Risk Questionnaire (AIRQ)	10	>12	Yes	Yes	Yes	Yes	Yes	Self-perception of control

This table displays the questions asked to the patients, the age to which the test has been validated and some clinical specific information.
Adapted from Alzahrani and Becker[74].

and the probability of time to first exacerbation[70].

Validated tools are available to assess the degree of symptom control in each patient, and others are being developed that estimate the risk of exacerbations. However, the concept of "future risk" needs to be defined more rigorously. It is not yet possible to clearly identify which patients will develop long-term fixed obstruction and which will develop an exacerbation. The latter has been the most widely researched risk to date, but it remains unclear to what extent factors such as eosinophilia and high fractional exhaled nitric oxide (FE_{NO}) are in themselves predictors of exacerbations; a more precise identification of future risk is needed before it can be translated into specific therapeutic strategies. In this sense, a prototype scale (OxfoRd Asthma attaCk risk ScaLE [ORACLE]) based on biomarkers of type 2 inflammation has shown feasibility and potential to predict asthma attacks that might be prevented by treatment[71]. More initiatives like this one are needed to bridge the gap between current control and future risk.

DISCUSSION/CONCLUSIONS

Despite the efforts made over the years to achieve asthma control, it is still an issue for many patients. Lack of adherence to medication or treatment guidelines, poor inhalation technique, and incorrect use of SABA without ICS as rescue therapy negatively affect control. GINA and a limited number of scientific societies presently recommend this strategy has shown little to no improvement in asthma control compared to regular ICS/LABA. The step-up approach recommended by asthma guidelines does not consider the different pharmacologic profiles of available ICSs. It is also important to bear in mind that not all patients will respond to anti-inflammatory treatment, especially those who do not present

bronchial eosinophilic inflammation. High-dose ICS increases the risk of iatrogenic injury and has no clear therapeutic benefit for the patient. Besides, it is still essential to verify treatment adherence and inhalation technique in patients with poor asthma control, and if necessary, consider switching to a drug with different characteristics to achieve control without the need for high doses of ICS. The concept of control needs to be further defined, and new tools that estimate future risk would enable clinicians to make more accurate therapeutic decisions. In the meantime, a strategy based on identifying therapeutic goals and treatable traits would facilitate a more personalized treatment.

CONFLICTS OF INTEREST

LPLl has received grants, personal fees, and non-financial support from AstraZeneca, Teva, Sanofi; personal fees and non-financial support from GSK, Novartis, Chiesi, personal fees from MSD, Techdow Pharma, Leo-Pharma, Gebro, Gilead; grants and non-financial support from Faes Farma.

LME has received payment for lectures, including service on speaker's bureaus from AstraZeneca, Böehringer Ingelheim, Chiesi, GSK, Faes Farma, Menarini, MSD, Novartis, Pfizer, Sanofi and Teva; for a consultancy from AstraZeneca, GSK, MSD and Sanofi.

IC has received payment for lectures, from GSK, Boehringer Ingelheim, and Chiesi; for a consultancy from Sanofi.

ID has received payment for lectures, including service on speaker's bureaus from Allergy Therapeutics, AstraZeneca, Chiesi, Diater, GSK, Leti, Novartis, Sanofi; for a consultancy from Allergy Therapeutics, ALK-Abello, AstraZeneca, GSK, Merck, MSD, Novartis, Sanofi; and grants for Thermofisher Diagnostics.

CA has received payment for lectures, including service on speaker's bureaus from AstraZeneca, Chiesi, GSK, Novartis, Boehringer Ingelheim, Sanofi; for a consultancy from ALK-Abello, AstraZeneca, GSK, MSD, Novartis, Sanofi; and grants from GSK.

BAB has received payment for lectures, including service on speaker's bureaus from AstraZeneca, Chiesi, GSK, Novartis, Faes-Farma, Sanofi.

JM has received payment for lectures, including service on speaker's bureaus from AstraZeneca, Chiesi, Menarini, Diater, GSK, Novartis, Faes-Farma, Sanofi, ALK-Abelló and for a consultancy from Sanofi and Chiesi.

AIS has received payment for lectures, including service on speaker's bureaus from AstraZeneca, ALK-Abelló, Immunotek, Chiesi, Diater, GSK, Faes Farma, Menarini, MSD, Novartis, Pfizer, Roxall, Sanofi and Teva.

CD has received payment for lectures and travel expenses from ALK, Allergy Therapeutics, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Esteve, GSK, HAL Allergy, Inmunotek, Menarini, Novartis, Pfizer, Sanofi, Stallergenes Greer, Takeda, Teva

AUTHOR CONTRIBUTIONS

LPLl, LME and CD collaboratively designed the conceptual outline of the review and

contributed to all sections. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

Alfonsina Trento, Ph.D., Blanca Piedrafita, Ph.D. and Antoni Torres-Collado, Ph.D. provided assistance during the development of the project and editorial assistance in writing the manuscript

FAES Farma provided an unrestrictive grant for this project but was not involved in the study.

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