

## Re-evolution of asthma management: dilemmas and new paradigms

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## Abstract

Asthma is one of the most common inflammatory diseases in the world, and the main treatment goal is to achieve the best level of control for each patient. Although every patient is different, there are several clinical practice guidelines that can help physicians to manage this respiratory condition. However, the recommendations made by the different guidelines are not always identical, and new data on different management strategies are being continuously released, which can mislead both patients and physicians.

Our aim with this article is to summarize the main controversies in terms of management and treatment recommendations in asthma guidelines, revise the most recent scientific evidence published so far and pinpoint some possible solution to these dilemmas. This review, however, does not aim to issue new recommendations or to challenge evidence-based guidelines.

As a conclusion of this article, the authors considered that more tools are necessary to reach and measure optimal asthma control, to better assess the impact of asthma in patients' lives. In addition, it would be of utmost importance to appraise more accurately the short-term and long-term effectiveness and safety of asthma therapies, and the possibilities of successful immunomodulation.

**Key Words:** asthma control, asthma management, dilemma, guidelines, inhaled corticosteroids, immunotherapy, paradoxes, treatment.

## Resumen

El asma es una de las enfermedades inflamatorias más comunes en el mundo, y el objetivo principal de su tratamiento es lograr el mejor nivel de control en cada paciente. Aunque cada enfermo es diferente, se han desarrollado guías de práctica clínica nacionales o internacionales, con el objeto de ayudar a los médicos a controlar la enfermedad, de acuerdo a la mejor evidencia científica disponible. No obstante, las recomendaciones formuladas por las diferentes guías no siempre son iguales, y continuamente se están publicando nuevos datos sobre diferentes y nuevas estrategias de manejo de la enfermedad. Todo ello, puede inducir a error tanto a los pacientes como a los médicos. Nuestro objetivo con este artículo es, en primer lugar, revisar las principales controversias o dilemas, en términos de manejo y recomendaciones de tratamiento, que generan las guías de manejo del asma más difundidas; en segundo lugar, revisar la evidencia científica más recientemente publicadas y finalmente señalar posibles soluciones a estos dilemas. Esta revisión, sin embargo, no tiene como objetivo emitir nuevas recomendaciones o cuestionar las directrices u recomendaciones basadas en la evidencia, definidas en las guías. Como conclusión de este artículo, los autores consideraron que se necesitan mejores herramientas para alcanzar y medir el control óptimo del asma y para evaluar mejor el impacto del asma en la vida de los pacientes. Además, sería de suma importancia conocer con mayor precisión la efectividad y seguridad a corto y largo plazo de las terapias para el asma, y las posibilidades de una inmunomodulación eficaz.

**Palabras clave:** control del asma, manejo del asma, dilema, guías, corticosteroides inhalados, inmunoterapia, paradojas, tratamiento.

## Introduction

Asthma is one of the most common inflammatory chronic diseases in the world, affects more than 330 million people worldwide, with a prevalence that is still growing in most countries (approximately around 1-18% of population worldwide). The prevalence varies from developed countries (e.g. 21% in Australia) to developing countries (e.g. 0.2% in China)[1,2].

As a chronic disease, the goal of asthma treatment is to achieve the best asthma control possible (minimise symptoms and limitations in daily activity, prevent exacerbations and improve lung function). However, every patient is different and treatment has to be adapted in different moments according to evolution of disease, and asthma control is not always easy to achieve. There are different asthma guidelines, such as the Global Initiative for Asthma (GINA)[3] or the most recent version of the Spanish Guidelines for Asthma management (GEMA)[4], aiming to help physicians to manage their patients. However, the recommendations issued by different guidelines are not always concordant among them. The majority of patients suffering from asthma can be categorized as having a mild severity disease. It is precisely in this step where there are more controversies in terms of management and treatment recommendations, which could be confusing for both patients and physicians.

In addition, there are a number of dilemmas in the management of asthma regarding other aspects such as the use of questionnaires, the indication of allergen immunotherapy, or the use of the combination of Inhaled Corticosteroids and Long Acting Bronchodilator Agonists (ICS/LABA) as reliever treatment[5].

In this review we discuss some relevant controversies related to asthma treatment and some aspects of asthma management that can result paradoxical[6,7] (Table 1). Some doubts and myths about assessment of asthma control using questionnaires, immunotherapy, or benefits

of therapy with ICS/LABA as reliever, are also examined.

### **Dilemma number 1: DIFFICULTIES IN EVALUATING ASTHMA CONTROL**

Nowadays, the main goal of asthma management is the achievement and maintenance of optimal asthma control. Both the GINA[3] and GEMA 4.3[4] guidelines have defined the term *control* as effective management of the clinical characteristics of the disease, including symptoms, nocturnal awakening, reliever use, activity limitation and lung function, as well as future risk of adverse outcomes. Three levels of asthma control (well controlled, partially controlled and uncontrolled) have been established. Poor asthma control increases the future risk of exacerbations[8].

The most commonly used tools to assess asthma control are the Asthma Control Test (ACT) and the Asthma Control Questionnaire (ACQ), and both can be compared to the criteria used in GINA.

The ACT[9] and the ACQ[10] have been developed to assess the control of disease during 1 (ACQ) to 4 (ACT) weeks before consultation, and are used worldwide. These questionnaires are simple and easily completed by patients, and make it easy for clinical practitioners to assess how effectively asthma symptoms are controlled. Both of them have been adapted and validated in different languages, including Spanish. The scores in the ACT questionnaire range from 5 (worst control) to 25 (total control); it is easy to assess and was specifically designed for the use in clinical practise. The ACQ assesses 7 items, which include asking patients to recall their experiences in the previous week and to respond to questions about night-time waking, symptoms on waking, activity limitations, shortness of breath, wheezing, required use of short-acting b2-agonists (SABA) for rescue, and FEV<sub>1</sub> percent predicted before bronchodilator on a 7-point scale[5,8]. All these items are equally weighted. Shortened versions (ACQ5 and ACQ6) can also be used by eliminating the last 1-2 items.

In ACT questionnaire, one of the questions is the use of relief medication (salbutamol or terbutaline), but they do not mention the possible use of combination therapy with ICS/LABA as rescue medication, which in some circumstances has been proven to be more effective, both in adults and in children[11].

During the past few years, there have been numerous studies confirming the importance of exacerbations in the current control and prognosis of asthma. In fact, the presence of at least one exacerbation in the last year is considered to be one of the most important risk factors for new exacerbations; and the presence of exacerbations is considered to be the most important risk factor for the worsening of lung function[12]. All this previous factors would facilitate the presence of new exacerbations in a progressively growing vicious circle. However, the presence of moderate and severe exacerbations (an easy-to-obtain clinical data) is not included in any of the asthma control assessment questionnaires[9,10], while it is included in the guidelines[3,4]. The guidelines clearly state that the history of having presented an exacerbation during the last year is a sign of lack of control.

As time goes by, there is more and more interest in the e-health and computerized management, and maybe paper questionnaires are anachronistic tools. In some studies[13] an informatics approach of these questionnaires was contemplated. These studies have concluded that web-based management was feasible, safe, and preferred by patients, with no significant differences in clinical outcomes between the web-based and paper-based sequences.

Apart from considering all these instruments to assess control and adherence, there are no specific indications or suggestions of which of these questionnaires should be chosen in clinical practise.

And at this point, how reliable and successful are the clinical practice guidelines? This question arises because sometimes, even if recommendations of one clinical guide are carefully

followed, patients still remained uncontrolled. This was proven in the COAS study [14]. The aim of this study was to achieve control in patients with uncontrolled asthma, by following the recommendation of the GINA 2010. After treatment optimisation, most patients did not achieve optimal control according to GINA criteria. Risk factors identified were older age, higher body mass index, greater disease severity, longer disease evolution and worse lung function.

In the study published by Olaguibel et al.[15], the objective was to evaluate which cut-off points from ACQ questionnaire best discriminate the level of asthma control according to GINA. Among 1,363 asthmatic patients, 13.6% were controlled, 34.2% partially controlled and 52.3% were uncontrolled. The ACQ cut-off points that better agreed with GINA-defined asthma control were:  $ACQ < 0.5$  for “controlled asthma” (sensitivity 74.1%, specificity 77.5%) and  $ACQ \geq 1$  for “uncontrolled asthma” (sensitivity 73%, specificity 88.2%)[15].

A meta-analysis [16] comparing efficacy of ACT and ACQ was published. Twenty-one studies (with 23,624 subjects) that examined the accuracy of the ACT, ACQ or both, in the assessment of asthma control were analysed. The results showed that ACT had good diagnostic accuracy for assessment of controlled and not well-controlled asthma, and the ACQ had good diagnostic accuracy for assessment of not well-controlled asthma at cut-off points specified above. The authors concluded that ACT is preferable to the ACQ in clinical practice, and the ACQ requires further cross-validation.

There are few agreements in terms of disease control between patients and physicians as well as among physicians and the validated questionnaires or established guidelines. This leads to an overestimation of well-controlled asthma among patients and physicians, indicating a too optimistic point of view, that can lead to wrong indications and wrong treatments[6,17].

Vennera et al.[18] performed a study to evaluate the agreement between the perception of disease control by both patients and physicians (according to GEMA guidelines). The results

showed that both physicians and patients overestimated control: 75.8% and 59.3%, respectively, had controlled asthma according to their opinions, but were not controlled according to GEMA. Only 10% of patients with severe asthma were controlled according to GEMA criteria.

But, what are the reasons of these different perceptions? According to the study published by Bidad et al.[19], patients' self-management is influenced by their perceptions of asthma and its treatments. Sometimes, symptoms indicative of poor control were often tolerated as part of living with asthma.

In conclusion, it is necessary to define which tool is the best to assess asthma control, because treatment relies very much on it. ACT is a validated questionnaire, very useful for clinical practice, but more studies are needed to finally settle down this one definitely.

### **Dilemma number 2: TREATMENT IN STEP 1: SABA OR SABA/ICS?**

Most patients suffering from asthma are categorised into mild severity (steps 1 and 2). And it is precisely in those steps where there are more controversies. The use of SABA as rescue treatment in mild asthma (step 1 and 2) is becoming a controversial issue.

All guidelines and most physicians usually recommend as-needed SABA as a quick relief of symptoms. However, it is well known that SABA does not reduce the risk of flare-ups and does not treat inflammation (the basis of asthma pathophysiology). Besides, regular use of SABA leads to rapid beta<sub>2</sub> receptor tolerance, rebound bronchoconstriction and even increases inflammation. And one important issue is that we do not have long-term safety data from SABA as the only treatment.

Inflammation is the basis of asthma, no matter which step we are in, and therefore, treating inflammation should be the main goal in all asthma steps, not only the severe ones. If we aim

to have good control from initial asthma steps, we could be much more effective from the beginning[5].

Although some recently published studies support the use of ICS/formoterol as needed as more effective to keep symptoms controlled in the initial asthma steps, the main guidelines have not changed the recommendations yet.

Although these studies have been carried on patients in step 2, some papers[5] suggests that ICS as needed could be used as well in step 1 of asthma. Adding ICS as needed in all patients with asthma, even in step 1, may help to reduce symptoms and exercise-induced bronchoconstriction, as well as to reduce risk of serious exacerbations and subsequent decline in lung function[5]. And due to the low adherence to ICS alone (because patients do not feel rapid relief), it has been proposed adding the combination of LABA and ICS from step 1[4,6,7].

Other study recently published[20] summarizes the new lines of treatment in step 1 of asthma. The authors explain that the recommendation of ICS at step 1 is an innovative, and evidence-based decision for different reasons: studies have shown ongoing airway inflammation and airway remodelling, elevated exhaled nitric oxide levels and bronchial biopsy evidence of airway inflammation have been found in patients with mild intermittent asthma, bronchoconstriction generates excessive mechanical forces within the airways that distort tissue cells, and this phenomenon might occur every time asthmatic subjects inhale SABA as needed.

Therefore, early initiation of low-dose ICS leads to a greater improvement in lung function.

Moreover, treatment with LABA alone are expressly contraindicative even as reliever agents, the same argument could be applied to SABA.

Some studies in children were published about this topic. For example, Du et al.[8] presented in their meta-analysis, only the studies concerning symptoms in children. The conclusion indicated that 3 months of treatment with ICS significantly increased the number of children

without asthma symptoms compared with placebo. However, the same study showed that effects on lung function of ICS compared with placebo or LTRA (leukotriene receptor antagonists), were almost the same in terms of airway hyper-responsiveness, airway inflammation, symptom control and adverse effects (in patients with mild intermittent asthma).

The firsts ones to demonstrate that in mild asthma, treatment with intermittent on demand ICS was equally effective than continuous treatment with ICS or an antileukotriene, in terms of control of asthma exacerbations, were Boushey et al.[21] in 2005. Subsequently, Papi et al.[22] in 2007, demonstrated through a double blind placebo controlled study, that a combination of salbutamol and beclomethasone (250 mcg) in the same aerosol, depending on the symptomatic requirements of the patient was so effective (in terms of control of asthma exacerbations) that twice daily inhaled beclomethasone, despite the fact that the accumulative dose of ICS in the group of combined-on-demand treatment, was 4 times lower. Also in 2012, Calhoun et al.[23] did not find significant differences in the efficacy of treatment with intermittently ICS (at the same time the rescue SABA was used), compared with patients who used daily ICS, although the accumulative dose of ICS in the first group was also significantly lower.

It is accepted that asthma is a chronic and variable disease. The chronicity component of the disease is determined by the level of inflammation, while the component of variability is due to bronchospasm. Likewise, treatment for inflammation is practically concentrated in the use of ICS, while bronchospasm settles down in the use of SABA. Separating both treatments implies not assessing one of the physiopathological characteristics of asthma.

SABAs are short-acting drugs with a mechanism of action limited to bronchodilation. By recommending them as the only treatment in step 1 just when the symptoms appear, a message of asthma as an acute disease is being transmitted. This concept, rooted in patients,

will make it difficult for patients to correctly follow maintenance treatment in more serious stages of the disease.

As a conclusion, in step 1 of asthma treatment, the combination of ICS+LABA can be effective to use as needed treatment than SABA alone, because it helps to reduce inflammation and risk of exacerbations.

### **Dilemma number 3: STEP 2: CARRYING ON HABITS FROM STEP 1.**

This dilemma is very similar to the previous one, just continuing the same behaviour from step 1: the use of SABA as needed treatment in mild asthma (step 2) instead of using ICS/LABA. The use of SABA as reliever treatment promotes the belief that asthma has to be managed always with SABA as the only rescue treatment and not with ICS/LABA as needed. And this belief is difficult to eradicate later on in severe cases[4,7,24].

Moreover, as we mentioned previously, the adherence to ICS is very poor, in adults and children, estimated with an average dispensing cover less than 25% of days[25]. And this can be explained from the patient view that SABA is cheaper, with quicker more effective and safer (corticosteroid panic). And those qualities are enough for SABA to be patients' favourite treatment.

The fact that MART therapy is more effective than SABA-only treatment when suffering symptoms has been proven not only in adults but also in adolescents, with the same results[26]. Asthma is one of the most common chronic diseases in children and adolescents, and it is very variable during these years, leading to a difficult management. And in this concrete subgroup of people, poor adherence to ICS is even higher, with the increased risk of exacerbation. In the study presented by Jorup et al.[26], a clinical trial with 1847 adolescents (aged from 12 to 18 years-old), the results were that budesonide-formoterol as needed was similar than comparators for the primary end-point (time to first severe-exacerbation).

Secondary end-point had also similar results (no superiority): total number of severe exacerbations, asthma symptoms scores, night-time awakenings, as-needed inhalators, FEV<sub>1</sub>, morning PEF and ACQ-5 score. With MART therapy, adolescents perceived benefits from the medication and this can help to improve adherence. So probably, this recommendation should be included in main clinical guidelines in the next few years.

Some of the most interesting articles regarding the use of ICS/LABA as needed in mild asthma (step 2), are the SYGMA (SYmbicort Given as needed in Mild Asthma) studies[7,24]. The conclusion of these articles was that in patients with mild-asthma (step 2), as-needed budesonide/formoterol provided superior asthma symptom control than as needed terbutaline, but was inferior to budesonide maintenance therapy. In addition, budesonide/formoterol used as needed resulted in substantially lower glucocorticoid exposure (less than one fifth) than budesonide maintenance treatment. Moreover, adverse effects were more frequent even in terbutaline group (42%) than in the budesonide/formoterol group (38%) or the budesonide maintenance group (39.9%). The results of this trial also suggest that the as needed use of budesonide/formoterol in mild asthma could address patients' concerns about the risks of treatment, another issue that causes overreliance on SABAs and poor adherence to maintenance treatment with ICS[24,27].

In the study presented by Bateman et al.[7], similar results were presented. They performed a double-blind, randomized, parallel-group, 52-week, phase 3 trial. With 4,215 patients, they were randomly assigned to receive twice-daily placebo plus budesonide/formoterol as needed or budesonide maintenance therapy with twice-daily budesonide plus terbutaline as needed. The results showed that in mild asthma, budesonide/formoterol used as needed was non-inferior to twice-daily budesonide with respect to the rate of severe asthma exacerbations; and this was achieved with less than one quarter of the total exposure to ICS. However, other

end points such as control of asthma symptoms, quality of life and FEV<sub>1</sub> were larger with budesonide maintenance therapy than with budesonide/formoterol used as needed[7].

Even though, not receiving ICS (because have not been prescribed, incorrect inhaler technique, or poor adherence) can be considered as a risk factor for adverse asthma outcomes (exacerbations, persistent airflow limitation, and medication side-effects). However, ICS do not improve symptom control[16,17].

In conclusion, ICS/LABA therapy has been proven to be more effective than SABA-only treatment for as needed treatment in step 2, improving as well adherence to ICS.

#### **Dilemma number 4: REDUCING SABA TO FEEL BETTER?**

Asthma management involves a personalised approach which includes self-management education. We need to be aware that indications are easy to understand not only for physicians, but also for patients. Although ICS/LABA as needed is more effective than SABA, also in step 1, (as explained in dilemma number 2), treatment with SABA alone, if permitted, should be done only in step 1. GINA recommends that SABA-only treatment should be restricted to patients who have symptoms less than twice per month, no waking due to asthma in the last month, and no risk factors for exacerbations[5,6]. In fact, regular SABA treatment leads to rapid beta2-receptor tolerance, rebound bronchoconstriction and even increased inflammation[5].

When a patient is not well-controlled and the physicians need to go up for the next step of treatment, a great contradiction is found. They have to adjust treatment by removing SABA from the maintenance drugs, precisely the drug that most reliefs the patient, when he is suffering from more and more important symptoms as we step up. From step 2 and forward, most important management guides recommend to cut down on the use of SABA (besides, it is

a criteria of control)[3,4]. However, from the beginning, we try to teach the patient to use SABA as needed.

SABA does not reduce the risk of flare-ups. Besides, there are no studies concerning the chronic use of SABA, adverse effects and even tolerance. But patients with mild asthma tend to suffer from some kind of "SABAphilia": they are addicted to SABA because they feel an instant relief without the need of chronic treatment [3,4,5]. They feel it is a familiar, safe and inexpensive treatment which controls their asthma. So when they start feeling symptoms of an exacerbation, they tend to use SABA instead of ICS. It makes them feel the wrong sensation that they are better than they really are, like being in a lower step. And this sensation is not only for patients, but also for physicians.

And as we mentioned before, it is very difficult for the patient to understand that SABA is not the correct treatment for them from step 2 and forward. Furthermore, as it happens with the treatment of almost every chronic disease, and as a probable consequence, some studies claimed that adherence to ICS is very poor in adults and children[25], with an average dispensing cover less than 25% of days. Some studies claimed that in adults and children, poor ICS adherence and over-reliance on SABA are associated to an increased risk of severe exacerbations and death[16,28].

From step 2 of treatment and forward, patients receive what appears to be a conflicting advice for the self-administration of SABA and LABA. The LABA, should never, under any circumstance, be used as monotherapy in asthma, but only in combination (preferably in a single-inhaler combination) with an ICS. However, patients are commonly told to use SABA as the only rescue medication. So far, there is evidence indicating that both SABA and LABA have serious risks as monotherapy, and no evidence suggests that there is any difference in the risks associated with regular "maintenance" use of either of them[4,6].

In conclusion, should SABA-only treatment be the initial treatment for asthma, even in step 1? Would it be easier to understand for the patient to use a combination of ICS-LABA on demand from the beginning? In that way we could prevent patients from feeling some kind of SABaphilia.

### **Dilemma number 5: COMBINATION ICS/LABA THERAPY AS RESCUE TREATMENT**

The use of the combination of LABA (formoterol) and ICS, delivered together, used as both Maintenance and Reliever Therapy is known as MART. Despite the fact that all guidelines recommend MART therapy (in steps 3-6 GEMA, steps 3-5 GINA), in the most important guidelines used nowadays continue appearing SABA as the preferred reliever drug as a rule. Even though it is known that MART therapy significantly reduces severe exacerbations and improves asthma control.

There is even evidence that administration of budesonide/formoterol (via Turbuhaler) as MART is more effective than the regimen comprising fixed-dose ICS/LABA maintenance with as needed SABA therapy in adults and children with chronic asthma. There is a meta-analysis summarising the benefits of MART therapy versus high dose of ICS/LABA, the odds-ratio for risk of exacerbations requiring hospitalization or visit to the emergency room was 0.72 (95% CI 0.57-0.90); while the odds ratio for exacerbations requiring oral corticosteroids was 0.75 (95% CI 0.65-0.87)[26,29,30,31].

The ability of the MART strategy to reduce the number of days without receiving ICS therapy and the number of days with overuse of SABA associated with delay in obtaining medical help, both of which have been demonstrated in adult asthma, and also in adolescents[32].

So from now on, the objective is that all this evidence will be reflected in all the international guidelines for asthma treatment.

On demand treatment according to severity of symptoms could be a problem for those patients having a low perception of dyspnoea or in alexithymics[33]. And in the other way round, could lead to an overtreatment such as in obese asthmatic patients, one of the most frequent comorbidities in asthma[34].

### **Dilemma number 6: CAN IMMUNOTHERAPY BE USED IN NOT WELL-CONTROLLED ASTHMA?**

Allergen-specific immunotherapy (AIT) is considered the only treatment capable of modifying the natural history of allergic respiratory disorders, and would be probably more useful for patients who suffer from more severe symptoms. It is a valuable therapeutic alternative in respiratory (rhinitis and/or asthma) allergic diseases, and its use is recognized and recommended in evidence-based practice parameters and international guidelines[3,4]. But so far, there have been problems with study quality and safety issues about subcutaneous immunotherapy (SCIT). In general, in all guidelines, allergen immunotherapy is not considered in patients with not-well controlled asthma, despite the fact that precisely in those patients, would be much more useful than in patients who are already controlled.

It is accepted that immunotherapy (sublingual and subcutaneous) is recommended in mild-to-moderate allergic asthma patients, improving control and reducing exacerbations and maintenance medication. However, recent studies have shown that sublingual immunotherapy (SLIT) with house dust mite (HDM) extract is safe and effective in patients with persistent asthma not well-controlled with medium to high ICS dose[27,35,36]. SCIT/SLIT proved to significantly improve symptom and medication scores versus placebo or active comparators in respiratory allergy, with various adverse effects. Although current evidence extracted from meta-analyses and systematic reviews support AIT as an effective, relatively safe, and well

tolerated treatment in some allergic diseases, heterogeneity and some methodological inconsistencies may affect the validity and applicability of their results, especially in the context of individual, real-life settings.

One of the most interesting studies was recently published in JAMA[37]. In this paper, the authors treat patients with moderate persistent (400-1,200 µg budesonide; approximately 40% of the participants used 800 µg to 1200 µg of budesonide per day at randomization) and not well-controlled asthma (ACQ score between 1 and 1.5) with HDM SLIT. According to GINA classification, 72% of participants had partly controlled asthma and 28% of participants had uncontrolled asthma at randomization. With this therapy, daily ICS use was reduced to 50% for 3 months and subsequently withdrawn completely for participants who did not experience an asthma exacerbation. The conclusions were: among adults with HDM allergy-related asthma not well controlled by ICS, the addition of HDM SLIT to maintenance medications improved time to first moderate or severe asthma exacerbation during ICS reduction. However, so far there are no indications in relation to immunotherapy for patients with not well controlled asthma in both GINA[3] and GEMA[4].

The possible (although usually mild) adverse events related to AIT have, until now, limited its use to mild-to-moderate and controlled asthma. However, two different situations need further studies to assess the potential efficacy and safety of AIT in other situations: in severe well controlled patients and maybe in severe partially-controlled patients after receiving (pre- or concomitant administration) treatment with biologic drugs (such as omalizumab, mepolizumab...)[38].

AIT/omalizumab combination has been explored in a few trials on asthma patients[39] and also in other allergic disorders, such as rhinitis, hymenoptera systemic reaction and food allergy[40,41] with significant and positive results.

## **Dilemma number 7: ALLERGIC VERSUS NON-ALLERGIC ASTHMA**

Finally, the differences between allergic and non-allergic asthma should be considered. Important asthma guidelines, such as GINA, do not distinguish between allergic and non-allergic types[3]. The concept of “Allergic Respiratory Disease” is not even mentioned. This fact should be taken into consideration because the management across different levels of severity may differ in some relevant aspects (allergen avoidance, AIT, anti-IgE therapy...), both in children and adults[11, 32].

Moreover, it has been reported that the patterns of sensitization can lead to different presentations of respiratory disease[32,43,44] and quality of life in patients with respiratory disease is influenced by the clinical sensitization profiles[45].

Two consecutive descriptive, non-intervention multicentre studies were carried out (PERFILAR I and II). In those studies, the results were evaluated according to ACG-5 test for disease control and Mini-AQLQ and SPRINT-15 to assess quality of life. In this paper, the conclusions were that different aeroallergens produce different sensitization profiles with different symptoms and different levels of severity and different quality of life[43-45]. And this is crucial in order to establish correct treatment and predict possible evolution. Thus, the causative allergen must play a greater role in decisions on diagnosis and therapy, since the duration and severity of the disease are determined to a large extent by the allergen.

Thus, it is very important to ascertain the relevant causal agents in allergic respiratory disease, in order to apply avoidance measures, to consider the indication of AIT, to assess the start and duration of drug treatment, the potential impact in quality of life, and to assess the future risk according to the characteristics of the culprit allergen(s) and expected exposure.

## **CONCLUSIONS**

Asthma management is based on standardised protocols which are recognized as “best practice”, as reflected in clinical guidelines. However, as recently acknowledged in an opinion paper by several experts in the field: “when considering asthma treatment clinicians usually focus on established asthma, rather than the fundamental underlying causes”[42]. This may have led to overlook important etiopathogenic aspects of the disorder, as well as the recognition of the different variants that encompasses the broad term “asthma”.

Asthma treatment involves both a personalized and a global approach: every patient is different, and various aspects need to be taken into account, such as self-management, a written action plan, management of comorbidities, modifiable risk factors, etc. This complexity and the lack of precise information on several aspects of the disease make it difficult to generalize the recommendations and at the same time try to personalize treatment. It is perhaps unavoidable that some contradictions and dilemmas arise pertaining different aspects of the diagnosis, management and prognosis of the different “asthmas”.

In this review article we have presented our opinion on some controversies and discordances that we may have to face when treating patients that many physicians manage every day. We consider that more and better tools are needed to reach an optimal control, and these probably would be computerized or web-based tools. In addition, more studies are needed to clarify and define whether ICS/LABA therapy should replace SABA as reliever treatment, and whether SABA should be always associated with ICS in every patient to treat inflammation from step 1.

In addition, more studies are needed to establish the safety and utility of using allergen immunotherapy in not well-controlled asthma.

We understand that these issues are not ready, at this moment, to be included in evidence-based asthma guidelines, but at least they should fuel the discussion on how to improve

asthma management and to consider new paradigms to confront this complex respiratory disorder.

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JMO has served as a consultant to AstraZeneca, and GSK, and has received lecture fees by, Leti, AstraZeneca, Mundipharma and Astra Zeneca.

JD has been received speaker's honoraria from AstraZeneca, TEVA, Chiesi, Mundipharma, Pfizer, Leti and Merck.

VP in the last three years received honoraria for speaking at sponsored meetings from Astrazeneca, Chiesi, GSK and Novartis. Received help assistance to meeting travel from Chiesi and Novartis. Act as a consultant for ALK, Astrazeneca, Boehringer, MundiPharma and Sanofi. And received funding/grant support for research projects from a variety of Government agencies and not-for-profit foundations, as well as AstraZeneca, Chiesi and Menarini.

FJAG has been received financial support for attending congresses, lecture's fees and has served as consultant for Alk-Abello, Astra/Zeneca,Bial, Boheringer-Ingelheim, Chiesi, Menarini, Mundipharma, GSK, Novartis, Pfizer and TEVA

JMP has received lecture's fees from Astra Zeneca, Boehringer-Ingelheim, GlaxoSmithKline, Menarini, y Roche in the last 3 years. He has received financial support for Research projects from governmental agencies, scientific societies and Boehringer-Ingelheim.

EMB has received lecture's fees and has served as consultant Almirall, Astra-Zeneca, Boehringer Ingelheim, Chiesi, Gebro, GlaxoSmithKline, Intermune, Mundipharma, Novartis, Pfizer, Roche, Rovi y Teva.

SQ has served as a consultant to AstraZeneca, Novartis, Sanofi, Gennetech, Teva, ALK, Mundipharma, and GSK, and has received lecture fees by Chiesi, Novartis, GSK, Leti, AstraZeneca, Mundipharma and GSK.

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Table 1. Main dilemmas in asthma management.

DILEMMA	DESCRIPTION
1	It is necessary to define which tool is the best to assess asthma control, because treatment relies on it. ACT is a validated questionnaire, very useful for clinical practice, but more studies are needed to finally settle down this one definitely.
2	In step 1 of treatment, the use of SABA associated with inhaled corticosteroids (ICS) can be more effective and safe, despite the fact that the recommendation still nowadays is the use of SABA alone.
3	ICS/LABA therapy has been proven to be more effective than SABA-only treatment for as needed treatment in step 2, improving adherence to ICS.
4	From step 2 and forward, it is recommended to reduce the use of short-acting $\beta$ 2 agonist (SABA), precisely the one that reliefs the most to the patient.
5	There are many studies proving that MART therapy is safe and more effective. However, guidelines still have SABA alone as preferred relief treatment.
6	Immunotherapy is only considered accepted in mild-moderate asthma patients. However, there are some studies that support the safety and effectiveness of immunotherapy in not well-controlled asthma patients.
7	Allergic and non-allergic asthma differ in aetiology as well as in some treatment and management aspects. However, international guidelines, do not differentiate the two types.