

Recommendations for the Management and Treatment of Asthma in Argentina (RE.M.A)

A RAND/UCLA modified Delphi consensus Argentinian Association of allergy and clinical immunology and Argentinian association of respiratory Medicine

*Recomendaciones en el manejo y tratamiento del asma en la Argentina (REMA)
Consenso Delphi modificado RAND/UCLA de la Asociación Argentina de Alergia e Inmunología Clínica y Asociación Argentina de Medicina Respiratoria*

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ABSTRACT

Asthma is a common chronic airway disease in our country, although with high poor control. Some specialists of the Asociación de Alergia e Inmunología Clínica and Asociación Argentina de Medicina Respiratoria have made recommendations for management and treatment of asthma, using a RAND/UCLA modified Delphi consensus methodology, based on GRADE evidence.

This document provides recommendations based on specialist opinions about different strategies to improve adherence. Besides, it provides recommendations about critical issues of mild to severe asthma treatment.

It's recommended to improve adherence, personalized control-based management plan (1 °C), mobile devices (1B) and education (1 °C). Sublingual immunotherapy must be prescribed only in patients with allergic rhinitis, mite associated, and persistent symptoms although appropriate treatment with FEV₁ > 70 % (1B). Use of fast action bronchodilators associated with inhaled corticosteroids prn in mild asthma (GINA stage 2) has strong recommendation (1A). Use of triple inhaled therapy (long acting anticholinergics, long acting beta 2 agonists and inhaled corticosteroids) is recommended in severe asthma (1B). Biologics has strong recommendations severe asthma: in phenotype T2 with dupilumab (1A), in phenotype allergic T2 with omalizumab (1A) and phenotype eosinophilic T2 with benralizumab or mepolizumab with distinctive characteristic (1A).

Key word: Asthma; Adherence; Immunotherapy; Triple therapy; Biologics

RESUMEN

El asma es una enfermedad crónica de la vía aérea prevalente en nuestro país, con frecuente mal control. Algunos especialistas de la Asociación de Alergia e Inmunología Clínica y la Asociación Argentina de Medicina Respiratoria han realizado recomendaciones sobre el manejo y tratamiento del asma mediante la metodología de consenso RAND/UCLA Delphi modificada sobre la base de la evidencia científica (GRADE).

Este documento provee recomendaciones basadas en la opinión de especialistas y fundamentada en evidencia científica seleccionada en cuanto a la importancia de mejorar la adherencia al tratamiento y seguimiento a través de diferentes estrategias. Así mismo, provee recomendaciones actualizadas en aspectos críticos del tratamiento del asma leve al grave.

Se recomienda, para mejorar la adherencia, el uso de planes personalizados de manejo (1 °C), uso de herramientas a través de teléfonos móviles (1B) y educación (1 °C). Con respecto a la inmunoterapia sublingual solo debe ser indicada a pacientes con asociación con rinitis alérgica, asociada a ácaros y síntomas de asma a pesar del tratamiento adecuado con FEV₁ > 70 % (1B). Se recomienda fuertemente en el asma leve (escalón 2 GINA) el uso de broncodilatadores de acción rápida asociados a corticoides inhalados a demanda (1A). En asma grave, se recomienda el uso de la triple terapia inhalada con anticolinérgicos de acción prolongada, beta 2 de acción prolongada y corticoides inhaladas (1B). El uso de biológicos en asma grave está fuertemente indicado en fenotipo T2 con dupilumab (1A), T2 alérgico con omalizumab (1A) y en el T2 eosinofílico con benralizumab, o mepolizumab, con sus características distintivas (1A).

Palabras clave: Asma; Adherencia; Inmunoterapia; Triple terapia; Biológicos

INTRODUCTION

Asthma is a heterogeneous, inflammatory airway disease characterized by recurrent episodes of bronchospasm, bronchial hyperreactivity, and increased bronchial secretions.¹⁻³ It affects approximately 300 million people around the world; in Latin America, there is great heterogeneity regarding its prevalence depending on each country, ranging from 5 % to 24 %, as is the case in Costa Rica.⁴ In Argentina, it is estimated that between 6.4 % and 9.36 % of the population has asthma, according to different studies.⁵⁻⁶

The knowledge of the disease has made significant advancements in recent years, especially in terms of diagnosis and treatment. Paradoxically, even though morbidity and mortality and hospitalizations have been reduced through preventive anti-inflammatory treatment, there are still epidemiological indicators of poor control, and in some countries, there are still surprisingly high percentages of hospitalizations and mortality.^(1-3, 5, 7, 8)

This new knowledge also generates topics of discussion and points of interest that require local perspectives. There are already several recent international guidelines and one local guideline from a few years ago that cover the diagnosis and treatment of asthma broadly. The objective is to address key questions with the highest level of evidence, focusing on topics related to asthma management,

in order to create a practical and easily readable tool with recommendations that provide original contributions aimed at the interests of physicians dedicated to asthma.^(1-3, 9-10)

This document was prepared by a panel of specialists from the Association of Allergy and Clinical Immunology (AAAeIC) and the Argentinian Association of Respiratory Medicine (AAMR), with special emphasis on establishing scientific evidence-based recommendations for the diagnosis and treatment of asthma in adults, adapted to the local context.

MATERIALS AND METHODS

The convergence of both societies allowed for the analysis of common areas. Representatives with extensive experience in asthma management were selected from each society to choose questions that addressed common discussion points and were clinically relevant in our country regarding the diagnosis and treatment of asthma in adults. Twenty-eight specialists proposed twenty-two questions, assigning a score based on both conditions. These questions were then ranked from highest to lowest score, and the top 15 were analyzed (Table 1). For the purpose of preparing the manuscript, the questions were grouped based on the topics they covered (seven questions on adherence and eight on treatment), so that each question could be discussed and analyzed and the corresponding recommendations could be established (Figure 1).

Literature searches were conducted in the MEDLINE, EMBASE, Cochrane, SciELO, and Lilacs databases until October 31, 2022, using search terms relevant to the respective questions. WE used the GRADE system (*Grading of Recommendations, Assessment,*

TABLE 1. Summary of the questions

| Questions |
|--|
| <p><i>Adherence</i></p> <ol style="list-style-type: none"> 1. What is the efficacy of adding a written treatment plan to the routine care for adult outpatients with asthma? 2. Should remote electronic resources be used instead of the routine care for adult outpatients with asthma? 3. Should smartphone-based interventions be used instead of the routine care for adult patients with asthma? 4. Should education be used as an intervention to promote adherence instead of the routine care for adult outpatients with asthma? 5. Should pharmacist-led interventions be used to promote adherence instead of the routine care for adult outpatients with asthma? 6. Should personalized treatment be used as an intervention to promote adherence instead of the routine care for adult outpatients with asthma? <p><i>Treatment</i></p> <ol style="list-style-type: none"> 7. Should pharmacological treatment + sublingual immunotherapy (SL) be used instead of pharmacological treatment or placebo in adult patients diagnosed with allergic asthma? 8. Should a fast-acting bronchodilator (FABA) + inhaled corticosteroids (ICS) on demand be used instead of a short-acting beta-2 adrenergic bronchodilator (SABA) in adults with GINA Step 2 asthma? 9. Should long-acting anticholinergic bronchodilators (LAACs) + ICS + long-acting beta-2 adrenergic bronchodilator (LABA) be used instead of LABA + ICS for adult patients with severe uncontrolled asthma? 10. Is it safe to use LAAC+ICS+LABA in adult patients with severe uncontrolled asthma? 11. Should a LAAC+LABA+ICS be used according to the phenotype for adult patients with severe uncontrolled asthma? 12. Should omalizumab be used instead of placebo in patients with severe uncontrolled asthma with a T2 phenotype? 13. Should mepolizumab be used instead of placebo in adult patients with severe uncontrolled asthma with a T2 phenotype? 14. Should benralizumab be used instead of placebo in adult patients with severe uncontrolled asthma with a T2 phenotype? 15. Should dupilumab be used instead of placebo in patients with severe uncontrolled asthma with a T2 phenotype? |

Development, and Evaluation) of scientific evidence level of the publications of the American College of Chest Physicians (ACCP), and of the recently published level of recommendation.¹¹ The levels of scientific evidence were characterized as A (strong evidence), B (moderate evidence), and C (low or very low evidence) according to the study design, the consistency of the results, and the clarity of the evidence to answer clinical questions. This system was chosen for its simplicity, transparency, explicitness, and consistency with the current methodological approach for the development of evidence-based good clinical practice. The recommendations were labeled according to the balance between risk, benefit, social and epidemiological importance, and, in some cases, cost. Recommendations can be level 1 (mandatory) or level 2 (doubtful). For example, a 1A recommendation is a mandatory recommendation with strong scientific evidence, while a 2C recommendation is one with low scientific evidence, and is considered doubtful¹¹.

The recommendations in response to each question were subjected to the agreement of a panel of nine specialists (four allergists and five pulmonologists) using the RAND/UCLA modified Delphi consensus methodology.¹²⁻¹³ Agreement on a recommendation was reached if a 75 % consensus was achieved. Each question and its recommendation were discussed in virtual meetings by the panel of specialists. If an agreement was not reached in the first round, a second round was conducted after a review of the literature and proposals one week later. All the recommendations reached a consensus exceeding 75 % within two rounds.

QUESTIONS AND RECOMMENDATIONS

About adherence

The World Health Organization (WHO) defines adherence as “the extent to which a patient’s

use of medication corresponds to the prescribed regimen”.¹⁴ Patient behavior regarding treatment adherence is complex and diverse. It is widely recognized that non-adherence is very common in patients with asthma (30-70 %) and is motivated by numerous factors.^{1-3,9-10} The concept of poor adherence primarily applies to the underutilization of daily preventive treatment.¹⁵⁻²¹ It is evident that poor adherence leads to an increase in morbidity, mortality, and use of healthcare resources. The psychosocial factors of the patient, inherent to the disease itself, the doctor-patient relationship, and access to medications have been extensively determined in the studies¹⁵⁻²¹. In the different definitions of “poorly controlled asthma,” assessing adherence problems and addressing them before labeling a patient as having severe asthma is a mandatory step in the recommendations of different international and national guidelines.^{1-3,8-10} In clinical studies, it is necessary to ensure treatment adherence more than 80 % of the time, and this is achieved not only through patient self-reporting of medication intake but also by counting the doses of the drugs under investigation and using electronic dosing devices during each visit or through telemedicine. Therefore, it is likely that better asthma control can be achieved in these patients solely by improving adherence.²¹

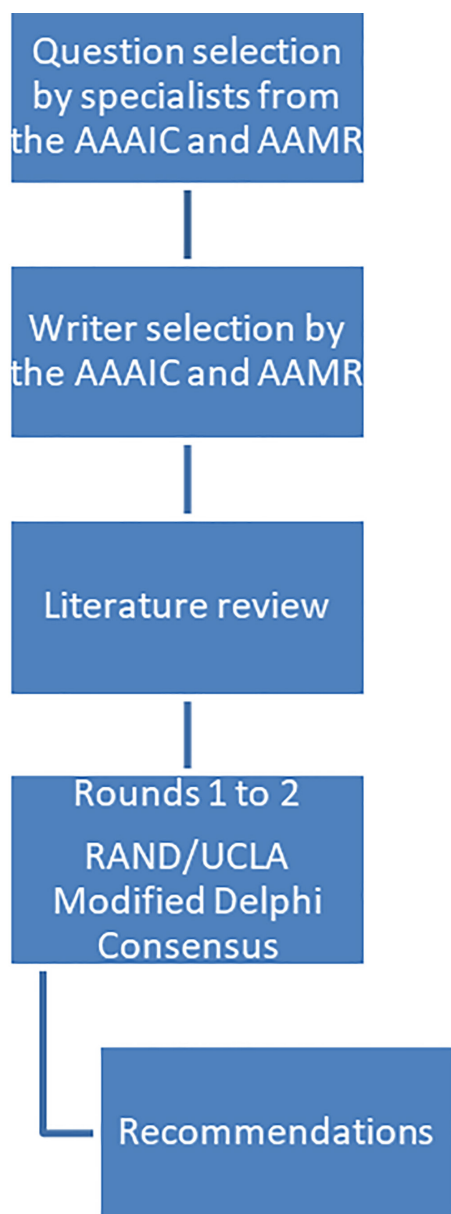


Figura 1. Design flow of the work
 AAAIC: Argentinian Association of Allergy and Clinical Immunology
 AAMR: Argentinian Association of Respiratory Medicine

Educating asthmatic patients is essential and recommended in every A evidence guideline as regards its benefits in reducing morbidity and improving adherence to treatment and follow-up.^{1-3,9,22-23}

Due to its relevance, the initial questions about different interventions to enhance adherence and their respective recommendations were grouped together.

1. Question: What is the efficacy of adding a written treatment plan to the routine care for adult outpatients with asthma?

Justification:

All the international and local guidelines agree on the need for providing an asthma patient with a written treatment plan, despite its challenging implementation^{1-3,8-9,22-23} and the limited scientific evidence regarding the positive effects of having this tool in asthma management.

On one hand, having a written plan contributes to the inclusion of the patient as an active participant in their treatment and as the central figure in their own condition. Thus, it is expected that knowledge of the treatment and action plan allows the patient to have better control over the disease, providing them with more tools to promptly request a consultation if necessary. Additionally, a written plan raises awareness of the disease among the patients, reducing the undesirable effects caused by the low risk perception associated with asthma. At this point, the importance of a written treatment plan is significant, as individuals diagnosed with asthma often underestimate their symptoms and the potentially fatal outcomes, especially in cases of poorly controlled asthma.⁶⁻⁸

On the other hand, the practical implementation of a written treatment plan is considered highly feasible due to its low cost, and is also beneficial for healthcare personnel involved with asthma patients and caregivers of high-risk asthmatic groups.^{1-3,8-9,22-24}

Lastly, a tool like the written treatment plan can help enhance adherence to asthma treatments, which is generally low, and its improvement is top priority.

Recommendation

The use of personalized management plans is recommended because of their low cost, although the benefits of using them in combination with standard treatment have an uncertain impact on exacerbations, asthma control, and improvement in quality of life (1C).

2. Question Should remote electronic resources be used instead of the routine care for adult outpatients with asthma?

TABLE 2. Summary of the recommendations

| Question | Grade |
|--|-----------|
| <i>Adherence</i> | |
| 1. The use of personalized management plans is recommended because of their low cost, although the benefits of their use together with standard treatment have an uncertain impact on exacerbations, asthma control, and quality of life improvement. | 1 C |
| 2. Broad implementation of remote electronic resources to enhance adherence in patients with asthma is not recommended. | 2B |
| 3. The implementation of smartphone-mediated tools is recommended, as they enhance adherence measured through electronic monitoring in asthma patients. Their effect is less evident when evaluated through self-report. | 1B |
| 4. The implementation of educational interventions is recommended because they have shown to be useful for enhancing adherence, measured by automatic counters on devices. | 1 C |
| 5. The use of pharmacist-led interventions is not recommended since there is no certainty regarding their effect on adherence enhancement evaluated through questionnaires. | 1 C |
| 6. The use of personalized treatments is not recommended, as there is no certainty regarding their effect on improving adherence measured through electronic monitoring. | 2B |
| <i>Treatment</i> | |
| 7. Sublingual immunotherapy is recommended for adult patients with asthma associated with allergic rhinitis who are sensitized to house dust mites and experience persistent asthma symptoms despite low to medium dose inhaled corticosteroid therapy, with a FEV ₁ of more than 70% of the predicted value (GINA 2), with limited impact on the decrease of exacerbations and the improvement of quality of life. | 1B |
| 8. The use of a FABA + ICS on demand is recommended instead of a SABA on demand in adults with GINA Step 2 asthma not receiving any other treatment, because it reduces the frequency of exacerbations requiring systemic corticosteroids and could reduce the number of visits to the emergency department. | 1A 1 C |
| 9. The addition of a LAAC to LABA+ICS is recommended in patients with severe uncontrolled asthma, as it provides a benefit in the improvement of lung function and has a modest effect on the decrease of exacerbations requiring SCS, as well as in asthma control. No benefit was found in the decrease of exacerbations that required hospitalization or the improvement of the quality of life. | 1B |
| 10. The addition of a LAAC to LABA+ICS is recommended in patients with severe uncontrolled asthma due to its safety, since it doesn't increase the cardiovascular risk. | 1B |
| 11. The addition of a LAAC to LABA+ICS is recommended in patients with severe uncontrolled asthma regardless of the phenotype. | 2B |
| 12. The use of omalizumab is recommended as additional maintenance treatment for severe uncontrolled asthma with an allergic T2 phenotype in children over 6 years and adults sensitized to perennial allergens, in order to reduce the rate of exacerbations, improve quality of life, and decrease the use of ICS, with no evidence of an increase in severe adverse effects. | 1B |
| 13. The use of mepolizumab is recommended in patients with severe uncontrolled patients aged 12 years or older as additional maintenance treatment for severe asthma with eosinophilic T2 phenotype, in order to reduce the rate of exacerbations, improve quality of life, decrease the use of SCS, and improve lung function, with no evidence of an increase in severe adverse effects. | 1A |
| 14. The use of benralizumab is recommended in adult patients with severe uncontrolled asthma as additional maintenance treatment for severe asthma with eosinophilic T2 phenotype, in order to reduce the rate of exacerbations, improve quality of life, decrease the use of SCS, and improve lung function, with no evidence of an increase in severe adverse effects. | 1A |
| 15. The use of dupilumab is recommended as additional maintenance treatment for severe uncontrolled asthma with a T2 phenotype in children aged 6 and older and adults, or associated with other T2 comorbidities (atopic dermatitis and chronic rhinosinusitis with nasal polyps), to reduce the exacerbation rate, improve quality of life, decrease the use of SCS, and improve lung function, with no evidence of an increase in severe adverse effects. | 1A |

FEV₁: forced expiratory volume in the first second

FABA: fast-acting bronchodilator

SABA: short-acting beta 2 adrenergic bronchodilator

ICS: inhaled corticosteroids

LAAC: long-acting anticholinergic bronchodilator

LABA: long-acting beta 2 adrenergic bronchodilator

SCS: systemic corticosteroids

Note: all the recommendations had 100% agreement after the second round.

Justification

There is significant variability in the scientific evidence regarding the use of remote electronic resources for enhancing treatment adherence in asthma patients. The uncertainty arises from methodological heterogeneity in the studied populations and measurement methods, both of which affect the variability of the effect size.²⁵

More specifically, there is high certainty for treatment adherence evaluated through electronic monitoring, low certainty for adherence evaluated through self-report²⁵, and very low certainty for the adherence evaluated through pharmacy aerosol refill. So, evidence results are inconsistent and inconclusive regarding the actual effectiveness of using remote electronic resources to enhance adherence to asthma treatment.

Recommendation

Broad implementation of remote electronic resources to enhance adherence in patients with asthma is not recommended (2B).

3. Question. Should smartphone-based interventions be used instead of the routine care for adult patients with asthma?

Justification

The certainty about the positive relationship between the use of mobile phone-mediated tools and the improvement in adherence is high. However, certainty is moderate for the adherence evaluated through self-report.²⁶

Recommendation

The implementation of mobile phone-mediated tools is recommended as they enhance adherence when measured through electronic monitoring in asthma patients. Their effect is less evident when evaluated through self-report (1B).

4. Question. Should education be used as an intervention to promote adherence instead of the routine care for adult outpatients with asthma?

Justification

As previously mentioned, education is essential in the treatment and follow-up of asthma patients.^{1-3,9,22-23,27} In fact, the set of educational content directly or indirectly favors adherence. Among the relevant content that should not be omitted, there is the correct diagnosis, guidelines for early

recognition of exacerbations and how to respond to them, tools to recognize different types of control and rescue pharmacological treatments, the importance of adherence, as well as the relevance of proper usage techniques, of reducing adverse events, seeking medical consultations promptly, and managing comorbidities correctly.^{1-3,9,22-23,27}

Recommendation

The implementation of educational interventions is recommended because they have shown to be useful for enhancing adherence, measured by automatic counters on devices (1C).

5. Question. Should pharmacist-led interventions be used to promote adherence instead of the routine care for adult outpatients with asthma?

Justification

Problems with adherence to treatment and follow-up are quite common in asthma patients, and this can be attributed to multiple factors, as mentioned earlier. Many studies have investigated various types of interventions of pharmaceutical personnel to evaluate the beneficial impact on adherence, but yielded inconclusive results. The certainty to improve adherence is very low for pharmacy aerosol refill and low for self-report.²⁸

Recommendation

The use of pharmacist-led interventions is not recommended, since there is no certainty regarding their effect on adherence enhancement evaluated through questionnaires (1C).

6. Question. Should personalized treatment be used as an intervention to promote adherence instead of the routine care for adult outpatients with asthma?

Justification

Due to contradictory published data regarding the use of mobile personalized action plans versus written action plans and the risk of bias, it is not clear at this time whether one format of action plan is superior to the other for both adolescents and adults.²⁷

Recommendation

The use of personalized treatments is not recommended, as there is no certainty regarding their effect on improving adher-

ence measured through electronic monitoring (2B).

About the treatment

7. Question Should pharmacological treatment + sublingual immunotherapy (SL) be used instead of pharmacological treatment or placebo in adult patients diagnosed with allergic asthma?

Justification

The latest edition of the Global Initiative for Asthma (GINA), states that specific immunotherapy (SIT) for allergens can be a treatment option where allergy plays a prominent role, including asthma with allergic rhinoconjunctivitis.¹ There are two forms of SIT: sublingual (SLIT) and subcutaneous (SCIT). While modest effects were identified in a systematic review of SLIT for asthma in adults and children, these effects are predominantly limited to oral and gastrointestinal symptoms.²⁹ As with any treatment, the potential benefits of SLIT for individual patients should be weighed against the risk of adverse effects and the cost for both the patient and the healthcare system.¹

On the other hand, in GEMA 2022, reference is made to SCIT with allergenic extracts as an effective treatment for well-controlled allergic asthma at low or moderate levels of treatment (therapeutic steps 2 to 4), provided that clinically relevant IgE-mediated sensitization to common aeroallergens has been demonstrated, well-characterized and standardized extracts are used, and the use of complex mixtures is avoided.^{1-2,30-33} However, many patients with mild intermittent asthma (step 1) concurrently suffer from moderate or severe allergic rhinitis, which justifies the prescription of immunotherapy.³⁴ SCIT should not be prescribed to patients with severe uncontrolled asthma, as its effectiveness is not well-documented and there is a high risk of suffering severe, even life-threatening adverse reactions.^{33,35} Therefore, it should be prescribed by specialized physicians with experience in this type of treatment and administered in facilities equipped with basic measures for the immediate treatment of a potential severe adverse reaction. The search for safer and more convenient alternatives for the patients has stimulated the study of the effectiveness of SLIT. Most clinical trials that demonstrated clinical efficacy have used well-characterized extracts at doses much higher than those typically used in SCIT. The tolerance

profile of sublingual immunotherapy is optimal, with no fatal reactions reported.^{34,36} When sublingual immunotherapy (SLIT) in oral lyophilized form for dust mites is added to the controlled maintenance pharmacological treatment, it is capable of reducing the number of moderate to severe exacerbations and improving disease control, with a very good safety profile.³⁷ Therefore, its use is recommended in adult patients with moderately controlled or partially controlled asthma.³⁴ If various immunotherapy alternatives are available, priority should be given to those that have the status of registered medicines with well-established efficacy, safety, and quality. At the moment, there are no comparative studies on the cost-effectiveness of immunotherapy versus conventional pharmacotherapy, and sure enough, such studies will not be conducted, as the complexity of their design makes them poorly viable. However, specific immunotherapy (SIT), in addition to controlling the manifestations of the disease, offers several additional advantages over pharmacotherapy. These include maintaining clinical benefits obtained until several years after treatment cessation, reducing the risk of developing asthma in patients with allergic rhinitis, or preventing the development of new sensitizations in mono-sensitive patients³⁸⁻⁴¹. Furthermore, allergen immunotherapy has a unique immunological justification, as it tailors the approach to an individual's specific IgE spectrum and modifies the natural course of the disease, with persistent efficacy after treatment completion. From this perspective, allergen immunotherapy (AIT) should currently be considered a prototype of Precision Medicine.⁴²

Recommendation

Sublingual immunotherapy is recommended for adult patients with asthma associated with allergic rhinitis who are sensitized to house dust mites and experience persistent asthma symptoms despite low to medium dose inhaled corticosteroid therapy, with a FEV₁ (forced expiratory volume in the first second) of more than 70 % of the predicted value (GINA 2), with limited impact on the decrease of exacerbations and the improvement of quality of life (1B).

8. Question. Should a fast-acting bronchodilator (FABA) + inhaled corticosteroids (ICS) on demand be used instead of a short-

acting beta-2 adrenergic bronchodilator (SABA) on demand in adults with GINA Step 2 asthma?

Justification

Based on new clinical information, in 2021 major international guidelines made changes to asthma treatment strategies.¹⁻² The recommendation for fixed-dose inhaled corticosteroids in GINA Step 2 is still the treatment of choice, as it allows for better disease control and has consistent accessibility within the healthcare system.¹ It's important to note that the controlled, prospective, double-blind studies that have been analyzed were conducted with the fixed-dose combination of budesonide-formoterol.⁴³⁻⁴⁸ This treatment strategy has shown a high level of evidence in the decrease of exacerbations that require the use of corticosteroids (CS). However, it does not have the same level of evidence for other variables such as emergency department visits, improved quality of life, asthma control, and improved lung function.⁴⁹

While the analyzed information may not strictly apply to patients included in GINA Step 1, it is understood that this strategy could be applied to such patients, with a lower level of evidence. As a strong recommendation in favor of using the budesonide-formoterol combination on demand, which is available in our country, the goal is to reduce the frequency of exacerbations that require systemic corticosteroids, likely leading to a decrease in the number of visits to the emergency department.

Recommendation

The use of a fast-acting bronchodilator + inhaled corticosteroids (FABA + ICS) on demand is recommended instead of a short-acting beta-2 adrenergic bronchodilator (SABA) on demand in adults with GINA Step 2 asthma not receiving any other treatment, because it reduces the frequency of exacerbations requiring systemic corticosteroids (1A), and could reduce the number of visits to the emergency department (1C).

9. Question. Should long-acting anticholinergic bronchodilators (LAACs) + ICS + long-acting beta-2 adrenergic bronchodilators (LABA) be used instead of LABA + ICS for adult patients with severe uncontrolled asthma?

Justification

Anticholinergic bronchodilators were among the first pharmacological groups used to treat asthma, as a natural component of *belladonna*. Beyond their bronchodilator action, long-acting anticholinergics have anti-inflammatory effects through both neuronal and non-neuronal route, acting on inflammatory cells and molecules.⁵⁰ Tiotropium is the LAAC with the largest amount of clinical information and has been studied in children, adolescents, and adults.⁵¹ Two other LAACs (glycopyrronium and umeclidinium) have been investigated in the CAPTAIN, IRIDIUM, TRIMERAN, TRIGGER, and ARGON studies, evaluating the clinical impact of the triple therapy in a single inhaler containing three pharmacological groups (LAAC, LABA, and inhaled corticosteroids) in patients with moderate and severe asthma not controlled with ICS/LABA.⁵²⁻⁵⁵ There are some differences in the evidence related to the duration of action of each drug, as well as the quantity and quality of available studies and the specific combinations of LABA+LAAC+ICS.

In an extensive review that included some studies with all three LAACs (11,894 children and adults; mean age: 52 years [range, 9-71 years]; 57.7 % women), the main objectives assessed were severe exacerbations, asthma control (measured by the Asthma Control Questionnaire, ACQ-7), quality of life (measured using the Asthma Quality of Life Questionnaire, AQLQ), mortality, and adverse events.⁵⁶ The results obtained demonstrated (with high certainty) that triple therapy versus dual therapy (LABA+ICS) in a single device once-daily was significantly associated with improved lung function (high certainty) and reduced risk of exacerbations requiring systemic corticosteroids (SCS) (moderate certainty), or hospitalization (low certainty).⁵⁶ There were no significant differences regarding the quality of life (high certainty of the evidence) or mortality (high certainty of the evidence) between dual and triple therapy.⁵⁶

Triple therapy was significantly associated with an increase in dry mouth and dysphonia, and for serious adverse events, there was no difference between the groups, including cardiovascular events (moderate certainty of the evidence).^{52-55,57-61}

One of the benefits of a fixed triple therapy *versus* an open one could be better treatment adherence, as it would reduce the number of inhalers

a patient needs to use, as well as the number of doses. Despite these results and other previous studies with another fixed triple therapy (TRIMARAN and TRIGGER), more studies are needed to confirm these improvements, especially with regard to exacerbations.⁵³⁻⁵⁵

Most safety studies were conducted in patients with COPD (higher mean age, and higher number of concomitant diseases of greater severity). In asthma, only one study on cardiovascular effects has moderate certainty of the evidence.⁶¹⁻⁶²

According to all asthma management guidelines, patients with severe asthma should be phenotyped.⁶³⁻⁶⁴ Regarding the therapeutic approach in this stage, the efficacy of the LAACs is independent of the asthma phenotype, irrespective of the eosinophilia degree and the fraction of exhaled nitric oxide (FeNO).⁶⁵⁻⁶⁶ The addition of LAACs could be considered for patients with persistent bronchial obstruction, symptomatic patients, and patients who are not frequent exacerbators (low certainty of the evidence).⁵²⁻⁵⁵

The GINA guideline recommends their use in patients who continue to have exacerbations despite intensive treatment with two controllers (inhaled corticosteroids and LABA), at step 4 or 5.¹ The GEMA (Guía Española para el Manejo del Asma) guideline suggests the use of LAACs from step 4 and 5 in combination with ICS and LABA.² The ATS/ERS (American Thoracic Society/European Respiratory Society) guideline recommends them in children, adolescents, and adults with severe uncontrolled asthma regardless of the GINA step 4/5 controller treatment.⁶³

Recommendation

The addition of a LAAC to LABA+ICS is recommended in patients with severe uncontrolled asthma, as it provides a benefit in the improvement of lung function and has an effect on the decrease of exacerbations requiring corticosteroids, as well as in asthma control. No benefit was found in the decrease of exacerbations requiring hospitalization or the improvement of quality of life (1B).

10. Question Is it safe to use LAAC+ICS+LABA in adult patients with severe uncontrolled asthma?

Justification

The rationale for this question is based on question 9.

Recommendation

The addition of a LAAC to LABA+ICS is recommended in patients with severe uncontrolled asthma due to its safety, since it doesn't increase the cardiovascular risk (1B).

11. Question Should LAAC+LABA+ICS be used according to the phenotype for adult patients with severe uncontrolled asthma?

Justification

The rationale for this question is based on question 9.

Recommendation

The addition of a LAAC to LABA+ICS is recommended in patients with uncontrolled severe asthma regardless of the phenotype (2B).

Biologics

Severe asthma constitutes 3 to 5 % of the population with asthma. It is characterized by the persistence of symptoms, higher number of visits to emergency rooms or unscheduled outpatient consultations, more hospitalizations, an increased use of rescue medication, systemic corticosteroids, antibiotics, and the resulting impact on the increased use of healthcare resources and increased mortality.⁶³⁻⁶⁴ Severe asthma represents a heterogeneous syndrome with multiple clinical variants. Over the past two decades, it has been intensely studied, and different phenotypes have been defined.⁶⁷⁻⁶⁹ Establishing the asthma phenotype in patients with severe uncontrolled asthma is part of the diagnosis and evaluation of these individuals, since it can lead to differential treatment and have prognostic implications.^{63-64,67-69} Two inflammatory phenotypic patterns have been defined: T2-high (present in allergic and eosinophilic asthma) and non-T2, also called T2-low. Both T2-high phenotypes often show some degree of overlapping. The fraction of exhaled nitric oxide, eosinophilia, and IgE are good biomarkers for the T2-high phenotype. Allergic T2 asthma represents 40-50 % of severe asthma and has an atopic basis orchestrated by the activation of T helper type 2 cells (Th2), the production of interleukins IL-4, IL-5, and IL-13, and isotype switching in B lymphocytes towards IgE production. Eosinophilic T2 asthma represents more than 25 % of severe asthma and is characterized by the presence of eosinophils in bronchial biopsies and sputum, even

in patients receiving high doses of glucocorticoids. It may be associated with chronic rhinosinusitis and nasal polyps.^{63-64,67-69}

The following questions and their respective recommendations are related to the use of biologics in severe asthma.

12. Question. Should omalizumab be used instead of placebo in patients with severe uncontrolled asthma with a T2 phenotype?

Justification

Omalizumab is a humanized monoclonal anti-IgE antibody (Mab) that binds to free IgE, preventing its attachment to mast cell and basophil receptors, and it can also reduce IgE receptors on effector cells.⁶³⁻⁶⁴

Omalizumab is indicated for type 2 allergic asthma with total IgE values between 30-1,500 IU. The dosage varies depending on the IgE level and body weight.⁶³⁻⁶⁴

The quality of the evidence is high, the magnitude of beneficial effects is moderate, and the magnitude of adverse events (AEs) is low. Therefore, the benefit-risk ratio favors the use of omalizumab.^{63-64,71-76}

The evidence is moderate regarding the decrease of exacerbations requiring SCS and the improvement of FEV₁.^{63-64,71-76} The evidence is low for the decrease of exacerbations requiring emergency care and hospitalization and for the improvement of the ACQ.^{63-64,71-76}

There are no cost-effectiveness studies in our country, but despite the high cost, most probably the benefit-risk ratio favors the use of the drug.

Recommendation

The use of omalizumab is recommended as additional maintenance treatment for severe uncontrolled asthma with an allergic T2 phenotype in children over 6 years and adults sensitized to perennial allergens, in order to reduce the rate of exacerbations, improve quality of life, and decrease the use of SCS, with no evidence of an increase in severe adverse effects (1B).

13. Question. Should mepolizumab be used instead of placebo in adult patients with severe uncontrolled asthma with a T2 phenotype?

Justification

Mepolizumab and reslizumab are both IL-5 inhibitors, but only mepolizumab is commercially available in our country.⁷⁰

The quality of the evidence is high, the magnitude of beneficial effects is moderate, and the magnitude of adverse events is low. Therefore, the benefit-risk ratio favors the use of mepolizumab.^{70,77-81}

The evidence is of high quality regarding the decrease of exacerbations requiring SCS and those requiring emergency care or hospitalization.^{70,77-81} The evidence is moderate regarding the improvement of the ACQ and the improvement of FEV₁.^{70,77-81}

There are no cost-effectiveness studies in our country, but despite the high cost, most probably the benefit-risk ratio favors the use of the drug.

Recommendation

The use of mepolizumab is recommended in patients with severe uncontrolled asthma aged 12 years or older as additional maintenance treatment for severe asthma with eosinophilic T2 phenotype, in order to reduce the rate of exacerbations, improve quality of life, decrease the use of SCS, and improve lung function, with no evidence of an increase in severe adverse effects (1A).

14. Question. Should benralizumab be used instead of placebo in adult patients with severe uncontrolled asthma with a T2 phenotype?

Justification

Benralizumab is an inhibitor of the IL-5 receptor α .⁷⁰ The quality of the evidence is high, the magnitude of beneficial effects is moderate, and the magnitude of adverse events is low.⁸²⁻⁸⁷ Therefore, the benefit-risk ratio favors the use of benralizumab.⁸²⁻⁸⁷

The evidence is high regarding the decrease of exacerbations requiring SCS and the improvement of FEV₁.⁸²⁻⁸⁷ The evidence is of high quality regarding the improvement of quality of life (ACQ) and the decrease of exacerbations requiring emergency care or hospitalization.⁸²⁻⁸⁷

There are no cost-effectiveness studies in our country, but despite the high cost, most probably the benefit-risk ratio favors the use of the drug.

Recommendation

The use of benralizumab is recommended in adult patients with severe uncontrolled asthma as additional maintenance treatment for severe asthma with eosinophilic T2 phenotype, in order to reduce the rate of exacerbations, improve quality of life, decrease the use of SCS, and improve lung function, with no evidence of an increase in severe adverse effects (1A).

15. Question. Should dupilumab be used instead of placebo in patients with severe uncontrolled asthma with a T2 phenotype?

Justification

Dupilumab is an inhibitor of the IL-4 receptor α subunit, which interferes with the action of both IL-4 and IL-13.⁸⁸

The quality of the evidence is high, the magnitude of beneficial effects is moderate, and the magnitude of adverse events is low.⁸⁸⁻⁹³ Therefore, the benefit-risk ratio favors the use of dupilumab.⁸⁸⁻⁹³

The evidence is of high quality regarding the decrease of exacerbations requiring SCS and those requiring emergency care or hospitalization, and also regarding the improvement in ACQ and the FEV₁.⁸⁸⁻⁹³

There are no cost-effectiveness studies in our country, but despite the high cost, most probably the benefit-risk ratio favors the use of the drug.

Recommendation

The use of dupilumab is recommended as additional maintenance treatment for severe uncontrolled asthma with a T2 phenotype in children aged 6 and older and adults, or associated with other T2 comorbidities (atopic dermatitis and chronic rhinosinusitis with nasal polyps, CRSw/NP), to reduce the exacerbation rate, improve quality of life, decrease the use of SCS, and improve lung function, with no evidence of an increase in serious adverse effects (1A).

GENERAL CONCLUSION REGARDING BIOLOGICS (TABLE 3)

Severe uncontrolled asthma is associated with a reduced quality of life, increased exacerbations, hospital admissions with frequent use of systemic corticosteroids, and elevated death risk.⁶³⁻⁶⁴ Phenotyping patients with severe uncontrolled asthma

(SUA) is necessary to prescribe the precise biologic therapy for each phenotype.⁶³⁻⁶⁴

Biologics targeting type 2 inflammation have shown improvement in disease control when used as additional therapy alongside maintenance treatment in patients with SUA (Step 5 according to GINA, Step 6 according to GEMA).^{1-2,63-64,94}

FINAL CONCEPTS

The modified Delphi methodology is a well-defined technique for reaching a consensus among specialists in areas of uncertainty, and it is particularly useful for making decisions in medical situations where scientific evidence is scarce or nonexistent.¹³⁻¹⁴ One of the strengths of this document is that it achieved 100 % agreement among the participants within two rounds. Another strength is that the specialists were selected by the two scientific societies for their expertise in the topics being discussed. The Delphi technique suggests that the participation of up to twelve specialists is sufficient and recommended.¹³⁻¹⁴ All authors had the opportunity to vote freely and express their opinions during discussion moments. This manuscript also has some limitations. The absence of participation from clinical physicians may, to some extent, limit the perspective regarding adherence or asthma management, especially in milder forms of the disease. Another limitation is that the specialists' opinions, as reflected in the selection of the supporting literature or their own experience in the field, may not encompass all the published evidence in the area. Furthermore, it has limited temporal validity and may change with the emergence of new scientific information. It should be interpreted rationally and complemented in the future with further research, especially within the context of areas of greater uncertainty.

In conclusion, this document provides recommendations based on expert opinion and grounded in scientific evidence with regard to the importance of enhancing adherence to treatment and follow-up through different asthma management strategies, especially given the frequent poor control of asthma in our country.⁷⁻⁸ It also provides updated recommendations on the critical aspects of the treatment of mild to severe asthma.

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TABLE 3. Orientation in the selection of the biologics

| Characteristics | Anti-IgE | Anti-IL4 R α | Anti-IL5/IL5 R α |
|-----------------------------|--|---|--|
| Indication | Severe allergic asthma | Type 2 severe asthma | Severe eosinophilic asthma |
| Age group | Children, adolescents and young adults | Children, adolescents and adults | Adults |
| Start | Childhood | Childhood or adulthood | Adulthood |
| Allergy | Pre-requisite | Independent from allergy | Independent from allergy |
| Dominant biomarkers | Total serum IgE | FeNO | Blood eosinophilia |
| Total serum ige | IgE and weight to calculate dose | Independent from IgE | Independent from total IgE |
| Blood eosinophil count | Slightly elevated; responds with increased count | ≥ 150 $\geq 1500/\mu\text{L}$ | Prerequisite: increased frequency, ≥ 150 to $300/\mu\text{L}$ |
| Feno | Slight improvement with increased FeNO | Better response if FeNO is $> 25\text{ppb}$ | Independent from FeNO |
| Co-existing conditions | AR, CRS w/NP and chronic hives | DA, CRS w/NP | CRS w/NP |
| Previous year exacerbations | > 2 exacerbations | > 2 exacerbations | ≥ 2 exacerbations |

Adapted from Brusselle GG, Koppelman GH. Biologic Therapies for Severe Asthma. *N Engl J Med.* 2022;386:157-71.

IgE: immunoglobulin E

FeNO: fraction of exhaled nitric oxide

AR: allergic rhinitis

CRSwNP: chronic rhinosinusitis with nasal polyps

Conflict of interest

This manuscript was not funded by any pharmaceutical company, but rather was a peer education project initiated by both sponsoring scientific societies.

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Anahí Yañez: clinical research investigator for GSK, AstraZeneca, Sanofi Chiesi, Novartis, MDS, Roche, Faes, TEVA, Avillon, Bayer, Sanofi Gynzene. Medical advisor for GSK, AstraZeneca, Eurofarma, Sanofi Genzyme, Novartis. Continuing medical education activities for Sanofi Genzyme and GSK.

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Gabriel Gattolin: speaker and clinical research investigator for AstraZeneca, Sanofi, Novartis, GSK, AbbVie, Roche, Amgen, Lilly, Pfizer, TEVA Pharma, Chiesi, and Takeda.

Walter Mattarucco: speaker in continuing medical education activities for AstraZeneca. Researcher in asthma for Novartis, Sanofi, AstraZeneca.

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KEY POINTS

Current knowledge

Despite the advances in asthma management and preventive treatment that improve quality of life and reduce morbidity and mortality, our country still has poor asthma control and an unacceptable rate of hospitalizations and mortality.

Contributions of the article to current knowledge:

Specialists from two medical societies committed to taking actions to improve asthma control in our country have made locally adapted recommendations in various critical aspects of asthma management and treatment.

REFERENCES

1. Global Initiative for Asthma. Difficult to treat & Severe Asthma in adolescent and adult patients: Diagnosis and Treatment. 2022. Acceso el 2 de febrero de 2023 en www.ginasthma.org.
2. Alobid I, Álvarez Rodríguez C, Blanco Aparicio M, et al. GEMA 5.2. Guía Española para el manejo del asma. ISBN: 978-84-19069-13-9. Acceso el 2 de febrero de 2023 en www.gema.com.
3. British Thoracic Society. Sign 158: British Guideline on the management of asthma. 2019.
4. Forno E, Gogna M, Cepeda A, et al. Asthma in Latin America. *Thorax* 2015;70:898-905. <https://doi.org/10.1136/thoraxjnl-2015-207199>
5. Arias S, Neffen H, Bossio JC, et al. Prevalence and features of asthma in young adults in urban areas of Argentina. *Arch*

- Bronconeumol 2018;54:134-9. <https://doi.org/10.1016/j.arbres.2017.08.021>
6. Neffen H, Fritscher C, Cuevas Schacht F, et al. Asthma control in Latin America: the Asthma Insights and Reality in Latin America (AIRLA) Survey. *Rev Panam Salud Publica* 2005;17:191-7. <https://doi.org/10.1590/S1020-49892005000300007>
 7. Maspero JF, Jardim JR, Aranda A, et al. Insights, attitudes and perceptions about asthma and its treatment: findings from a multinational survey of patients from Latin America. *World Allergy J* 2013;6:19. <https://doi.org/10.1186/1939-4551-6-19>
 8. Colodenco D, Neffen H, Baena-Cagnani C, et al. Recomendaciones para el diagnóstico y tratamiento del asma de difícil control (ADC). *Rev Am Med Resp* 2006:15-36.
 9. Yang CL, Hicks EA, Mitchell P, et al. Canadian Thoracic Society 2021 Guideline update: diagnosis and management of asthma in preschoolers, children and adults. *Can J Respir Crit Care Sleep Med* 2021;5:348-61. <https://doi.org/10.1080/24745332.2021.1945887>
 10. Programa Nacional de prevención y control de las enfermedades respiratorias crónicas. Protocolo de Orientación para el diagnóstico y manejo del asma en adultos. Ministerio de Salud de Nación. Dirección de Promoción de Salud y Enfermedades No Transmisibles. 2015.
 11. Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians Task Force. *Chest*. 2006;129:174-81. <https://doi.org/10.1378/chest.129.1.174>
 12. The Delphi Method. Techniques and Applications Edited by Harold A. Linstone. Portland State University Murray Turoff. New Jersey Institute of Technology 2002 Murray Turoff and Harold A. Linstone.
 13. Fitch K, Bernstein SJ, Aguilar MD, et al. The RAND/UCLA appropriateness method user's manual. Acceso el 13 de julio de 2023 en: https://www.rand.org/content/dam/rand/pubs/monograph_reports/2011/MR1269.pdf
 14. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005; 353:487-97. <https://doi.org/10.1056/NEJMr050100>
 15. Gillissen A. Patient's adherence in asthma. *J Physiol Pharmacol* 2007;58: 205-222.
 16. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2008:CD000011. <https://doi.org/10.1002/14651858.CD000011.pub3>
 17. Bosley CM, Parry DT, Cochrane GM. Patient compliance with inhaled medication: does combining beta-agonists with corticosteroids improve compliance? *Eur Respir J* 1994;7:504-9. <https://doi.org/10.1183/09031936.94.07030504>
 18. Sackett DL, Snow JC. The magnitude of compliance and non-compliance. In: Haynes RB, Taylor WD, Sackett DL, editors. *Compliance in health care*. Baltimore: Johns Hopkins University Press; 1979. pp. 11-22.
 19. Gamble J, Stevenson M, McClean E, Heaney LG. The prevalence of nonadherence in difficult asthma. *Am J Respir Crit Care Med* 2009;180:817-22. <https://doi.org/10.1164/rccm.200902-0166OC>
 20. Boslev Barnes C, Suppli Ulrik C. Asthma and adherence to inhaled corticosteroids: current status and future perspectives. *Respir Care* 2015;60:455-68. <https://doi.org/10.4187/respcare.03200>
 21. Costello RW, Cushen B. Looking back to go forward: adherence to inhaled therapy before biologic therapy in severe asthma *Eur Respir J* 2020;55:20000954. <https://doi.org/10.1183/13993003.00954-2020>
 22. Gibson PG, Powell H, Coughlan J, et al. Limited (information only) patient education programs for adults with asthma. *Cochrane Database Syst Rev* 2002:CD001005. <https://doi.org/10.1002/14651858.CD001005>
 23. Powell H, Gibson PG. Options for self-management education for adults with asthma. *Cochrane Database Syst Rev* 2003:CD004107. <https://doi.org/10.1002/14651858.CD004107>
 24. Gatheral TL, Rushton A, Evans DJ, Mulvaney CA, Halcovitch NR, Whiteley G, Eccles FJ, Spencer S. Personalized asthma action plans for adults with asthma. *Cochrane Database Syst Rev* 2017:CD011859. <https://doi.org/10.1002/14651858.CD011859.pub2>
 25. Jeminiwa R, Hohmann L, Qian J, Garza K, Hansen R, Fox BI. Impact of eHealth on medication adherence among patients with asthma: A systematic review and meta-analysis. *Respiratory Medicine* 2019;149:59-68. <https://doi.org/10.1016/j.rmed.2019.02.011>
 26. Murphy JA, Heisser JM, Montgomery M. Evidence-Based Review of Smartphone Versus Paper Asthma Action Plans on Asthma Control. *J Pharm Technol* 2019;35:126-34. <https://doi.org/10.1177/8755122519830446>
 27. Normansell R, Kew KM, Stovold E. Interventions to improve adherence to inhaled steroids for asthma (Review). *Cochrane Database of Systematic Reviews*; 2017:CD012226. <https://doi.org/10.1002/14651858.CD012226.pub2>
 28. Jia X. Effect of pharmacist-led interventions on medication adherence and inhalation technique in adult patients with asthma or COPD: A systematic review and meta-analysis. *J Clin Pharm Ther*. 2020;45:904-7. <https://doi.org/10.1111/jcpt.13126>
 29. Fortescue R, Kew KM, Leung ST, Shiu T. Sublingual immunotherapy for asthma. *Cochr Database Syst Rev* 2020;9:CD011293. <https://doi.org/10.1002/14651858.CD011293.pub3>
 30. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev*. 2010;(8):CD001186. <https://doi.org/10.1002/14651858.CD001186.pub2>
 31. Dhami S, Kakourou A, Asamoah F, et al. Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis. *Allergy*. 2017;72:1825-48. <https://doi.org/10.1111/all.13208>
 32. Adkinson NF Jr, Eggleston PA, Eney D, al. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med*. 1997;336:324-31. <https://doi.org/10.1056/NEJM199701303360502>
 33. Pitsios C, Demoly P, Bilo MB, et al. Clinical contraindications to allergen immunotherapy: an EAACI position paper. *Allergy* 2015;70:897-909. <https://doi.org/10.1111/all.12638>
 34. Agache I, Lau S, Akdis CA, et al. EAACI Guidelines on Allergen Immunotherapy: House dust mite-driven allergic asthma. *Allergy* 2019;74:855-73. <https://doi.org/10.1111/all.13749>
 35. Bernstein DI, Wanner M, Borish L, Liss GM, Immunotherapy Committee, American Academy of Allergy, Asthma and Immunology. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. *J Allergy Clin Immunol* 2004;113:1129-36. <https://doi.org/10.1016/j.jaci.2004.02.006>

36. Lin SY, Erekosima N, Kim JM, Ramanathan M, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: A systematic review. *JAMA* 2013;309:1278-88. <https://doi.org/10.1001/jama.2013.2049>
37. Virchow JC, Backer V, Kuna P, et al. Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma: A randomized clinical trial. *JAMA*. 2016;315:1715-25. <https://doi.org/10.1001/jama.2016.3964>
38. Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med*. 1999;341:468-75. <https://doi.org/10.1056/NEJM199908123410702>
39. Jacobsen L, Niggemann B, Dreborg S, et al. The PAT investigator group. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy*. 2007;62:943-8. <https://doi.org/10.1111/j.1398-9995.2007.01451.x>
40. Kristiansen M, Dhami S, Netuveli G, et al. Allergen immunotherapy for the prevention of allergy: A systematic review and meta-analysis. *Pediatr Allergy Immunol*. 2017;28:18-29. <https://doi.org/10.1111/pai.12661>
41. Pajno GB, Barberio G, de Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy* 2001;31:1392-7. <https://doi.org/10.1046/j.1365-2222.2001.01161.x>
42. Canonica GW, Bachert C, Hellings P, Ryan D, Valovirta E, Wickman M, De Beaumont O, Bousquet J. Allergen Immunotherapy (AIT): a prototype of Precision Medicine. *World Allergy Organ J*. 2015;8:31. <https://doi.org/10.1186/s40413-015-0079-7>
43. O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. *N Engl J Med* 2018;378:1865-76. <https://doi.org/10.1056/NEJMoa1715274>
44. Bateman ED, Reddel HK, O'Byrne PM, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. *N Engl J Med* 2018;378:1877-87. <https://doi.org/10.1056/NEJMoa1715275>
45. Beasley R, Holliday M, Reddel HK, et al. Controlled trial of budesonide-formoterol as needed for mild asthma. *N Engl J Med* 2019;380:2020-30. <https://doi.org/10.1056/NEJMoa1901963>
46. Hardy J, Baggott C, Fingleton J, et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicenter, superiority, randomized controlled trial. *Lancet* 2019;394:919-28. [https://doi.org/10.1016/S0140-6736\(19\)31948-8](https://doi.org/10.1016/S0140-6736(19)31948-8)
47. Tanaka A, Ohta S, Yamamoto M, et al. Tolerability of as-needed treatment with budesonide and formoterol combination in adult patients with mild asthma. *Am J Resp Crit Care Med* 2017;195:A3199.
48. Haahtela T, Tamminen K, Malmberg LP, et al. Formoterol as needed with or without budesonide in patients with intermittent asthma and raised NO levels in exhaled air: A SOMA study. *Eur Resp J* 2006;28:748-55. <https://doi.org/10.1183/09031936.06.00128005>
49. Crossingham I, Turner S, Ramakrishnan S, et al. Combination fixed-dose beta agonist and steroid inhaler as required for adults or children with mild asthma (Review). *Cochrane Database of Systematic Reviews*; 2021:CD13518. <https://doi.org/10.1002/14651858.CD013518.pub2>
50. Wessler I, Kirkpatrick CJ. Acetylcholine beyond neurons: the non-neuronal cholinergic system in humans. *Brit J Pharmacol* 2008; 154:1558-71. <https://doi.org/10.1038/bjp.2008.185>
51. Halpin D. Tiotropium in asthma: what is the evidence and how does it fit in? *World Allergy Org J* 2016;9:29. <https://doi.org/10.1186/s40413-016-0119-y>
52. Lee LA, Bailes Z, Barnes N, et al. Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomized, phase 3A trial. *Lancet Respir Med* 2021;9:69-84. [https://doi.org/10.1016/S2213-2600\(20\)30389-1](https://doi.org/10.1016/S2213-2600(20)30389-1)
53. Kerstjens HAM, Maspero J, Chapman KR, et al. Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomized, double-blind, controlled phase 3 study. *Lancet Respir Med* 2020;8:1000-12. [https://doi.org/10.1016/S2213-2600\(20\)30190-9](https://doi.org/10.1016/S2213-2600(20)30190-9)
54. Virchow JC, Kuna P, Paggiaro P, et al. Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomized, controlled phase 3 trials. *Lancet* 2019; 394:1737-49. [https://doi.org/10.1016/S0140-6736\(19\)32215-9](https://doi.org/10.1016/S0140-6736(19)32215-9)
55. Gessner C, Kornmann O, Maspero J, et al. Fixed dose combination of indacaterol/glycopyrronium/mometasone furoate once-daily versus salmeterol/fluticasone twice-daily plus tiotropium once-daily in patients with uncontrolled asthma: A randomized, Phase IIIb, non-inferiority study (ARGON). *Respir Med* 2020;170:106021. <https://doi.org/10.1016/j.rmed.2020.106021>
56. Oba Y, Anwer S, Maduke T, Patel T, Dias S. Effectiveness and tolerability of dual and triple combination inhaler therapies compared with each other and varying doses of inhaled corticosteroids in adolescents and adults with asthma: a systematic review and network meta-analysis. *Cochrane Database Syst Rev* 2022:CD013799. <https://doi.org/10.1002/14651858.CD013799.pub2>
57. Peters SP, Kunselman SJ, Icitovic N, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med* 2010;363:1715-26. <https://doi.org/10.1056/NEJMoa1008770>
58. Tan LD, Alismail A, Ariue B. Asthma guidelines: comparison of the National Heart, Lung, and Blood Institute Expert Panel Report 4 with Global Initiative for Asthma 2021. *Curr Op Pulm Med* 2022;28:234-44. <https://doi.org/10.1097/MCP.0000000000000867>
59. Kew KM, Dahri K. Long-acting muscarinic antagonists (LAMA) added to combination long acting beta2-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma. *Cochrane Database Sys Rev* 2016:CD 011721. <https://doi.org/10.1002/14651858.CD011721>
60. Tian JW, Chen JW, Chen R, Chen X. Tiotropium versus placebo for inadequately controlled asthma: A meta-analysis. *Respir Care* 2014;59:654-66. <https://doi.org/10.4187/respcare.02703>
61. Kerstjens HA, Engel M, Dahl R, et al. Tiotropium in asthma

- poorly controlled with standard combination therapy. *N Engl J Med* 2012;367:1198-207. <https://doi.org/10.1056/NEJMoa1208606>
62. Scosyrev E, van Zyl-Smit R, Kerstjens H, et al. Cardiovascular safety of mometasone/indacaterol and mometasone/indacaterol/glycopyrronium once-daily fixed-dose combinations in asthma: pooled analysis of phase 3 trials. *Respir Med* 2021;180:106311. <https://doi.org/10.1016/j.rmed.2021.106311>
 63. Holguin F, Cardet JC, Chung KF, et al. Management of severe asthma: an European Respiratory Society/American Thoracic Society guideline. *Eur Respir J* 2020;55:1900588. <https://doi.org/10.1183/13993003.00588-2019>
 64. Global Initiative for Asthma. Difficult to treat & severe asthma in adolescent and adult patients: diagnosis and management. 2018. Acceso el 14 de febrero de 2023 en www.ginasthma.org.
 65. Iwamoto H, Yokoyama A, Shiota N, et al. Tiotropium bromide is effective for severe asthma with noneosinophilic phenotype. *Eur Respir J* 2008;31:1379-82. <https://doi.org/10.1183/09031936.00014108>
 66. Szeffler SJ, Vogelber C, Bernstein JA et al. Tiotropium Is Efficacious in 6-to 17-Year-Olds with Asthma. Independent of T2 Phenotype. *J Allergy Clin Immunol Pract* 2019;7:2286-95. <https://doi.org/10.1016/j.jaip.2019.03.019>
 67. Wenzel S. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med* 2012;18:716-25. <https://doi.org/10.1038/nm.2678>
 68. Agache IO. From phenotypes to endotypes to asthma treatment. *Curr Opin Allergy Clin Immunol* 2013;13: 249-56. <https://doi.org/10.1097/ACI.0b013e32836093dd>
 69. Fitzpatrick AM, Moore WC. Severe asthma phenotypes - How should they guide evaluation and treatment? *J Allergy Clin Immunol Pract* 2017;5:901-8. <https://doi.org/10.1016/j.jaip.2017.05.015>
 70. Farne HA, Wilson A, Powell C, et al. Anti-IL5 therapies for asthma. *Cochr Database Syst Rev* 2017;9:CD010834. <https://doi.org/10.1002/14651858.CD010834.pub3>
 71. Normansell R, Walker S, Milan SJ, et al. Omalizumab for asthma in adults and children (Review). *Cochrane Database Syst Rev* 2014:CD003559. <https://doi.org/10.1002/14651858.CD003559.pub4>
 72. Solèr M, Matz J, Townley R, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001;18:254-61. <https://doi.org/10.1183/09031936.01.00092101>
 73. Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001;108:184-90. <https://doi.org/10.1067/mai.2001.117880>
 74. Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: A randomized trial. *Ann Int Med* 2011;154:573-82. <https://doi.org/10.7326/0003-4819-154-9-201105030-00002>
 75. Humbert M, Taillé C, Mala L, Le Gros V, Just J, Molimard M. Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophilic count: The STELLAIR study *Eur Respir J*. 2018;51:1702523. <https://doi.org/10.1183/13993003.02523-2017>
 76. Casale TB, Luskin AT, Busse W, et al. Omalizumab effectiveness by biomarker status in patients with asthma: Evidence from PROSPERO, a prospective real-world study. *J Allergy Clin Immunol Pract*. 2019;7:156-64. <https://doi.org/10.1016/j.jaip.2018.04.043>
 77. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651-59. [https://doi.org/10.1016/S0140-6736\(12\)60988-X](https://doi.org/10.1016/S0140-6736(12)60988-X)
 78. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma. *N Engl J Med* 2014;371:1198-207. <https://doi.org/10.1056/NEJMoa1403290>
 79. Bel EH, Wenzel SE, Thompson PJ, et al. Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma. *N Engl J Med* 2014;371:1189-97. <https://doi.org/10.1056/NEJMoa1403291>
 80. Khurana S, Brusselle GG, Bel EH, et al. Long-term Safety and Clinical Benefit of Mepolizumab in Patients With the Most Severe Eosinophilic Asthma: The COSMEX Study. *Clinical Therapeutics*; 2019;41:2041-56. <https://doi.org/10.1016/j.clinthera.2019.07.007>
 81. Harrison T, Canonica GW, Chupp G, et al. Real-world mepolizumab in the prospective severe asthma REALTI-A study: initial analysis. *Eur Respir J* 2020; 56: 2000151. <https://doi.org/10.1183/13993003.00151-2020>
 82. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomized, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016;388:2128-41. [https://doi.org/10.1016/S0140-6736\(16\)31322-8](https://doi.org/10.1016/S0140-6736(16)31322-8)
 83. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2 -agonists (SIROCCO): a randomized, multicentre, placebo-controlled phase 3 trial. *Lancet Respir Med* 2016;388:2115-27. [https://doi.org/10.1016/S0140-6736\(16\)31324-1](https://doi.org/10.1016/S0140-6736(16)31324-1)
 84. FitzGerald JM, Bleecker ER, Menzies-Gow A, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. *Lancet Respir Med* 2018;6:51-64. [https://doi.org/10.1016/S2213-2600\(17\)30344-2](https://doi.org/10.1016/S2213-2600(17)30344-2)
 85. Busse WW, Bleecker ER, FitzGerald JM, et al. Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. *Lancet Respir Med* 2019;7:46-59. [https://doi.org/10.1016/S2213-2600\(18\)30406-5](https://doi.org/10.1016/S2213-2600(18)30406-5)
 86. Nair P, Wenzel S, Rabe KF et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. *N Engl J Med* 2017;376:2448-58. <https://doi.org/10.1056/NEJMoa1703501>
 87. Korn S, MDa, Bourdin A, Chupp G, et al. Integrated Safety and Efficacy Among Patients Receiving Benralizumab for Up to 5 Years. *J Allergy Clin Immunol Pract* 2021;9:4381-92. <https://doi.org/10.1016/j.jaip.2021.07.058>
 88. Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 2013;368:2455-66. <https://doi.org/10.1056/NEJMoa1304048>
 89. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting B2 agonist: a randomized double-blind placebo-controlled pivotal phase 2b dose-ranging trial.

- Lancet 2016;388:31-44. [https://doi.org/10.1016/S0140-6736\(16\)30307-5](https://doi.org/10.1016/S0140-6736(16)30307-5)
90. Castro M, Corren J, Pavord ID, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. *N Engl J Med*. 2018;378:2486-96. <https://doi.org/10.1056/NEJMoa1804092>
91. Rabe KF, Nair P, Brusselle G, et al. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. *N Engl J Med*. 2018;378:2475-85. <https://doi.org/10.1056/NEJMoa1804093>
92. Zayed Y, Kheiri B, Banifadel M, et al. Dupilumab safety and efficacy in uncontrolled asthma: a systematic review and meta-analysis of randomized clinical trials. *J Asthma*. 2018;1:1-10. <https://doi.org/10.1056/NEJMoa1804093>
93. Bacharier LB, Maspero JF, Katelaris CH, Fiocchi AG, Gagnon R, de Mir I. Dupilumab in Children with Uncontrolled Moderate-to-Severe Asthma. *N Engl J Med* 2021;385:2230-40. <https://doi.org/10.1056/NEJMoa2106567>
94. Agache I, Beltran J, Akdis C, Akdis M, Canelo-Aybar C. Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the EAACI Guidelines - recommendations on the use of biologicals in severe asthma. *Allergy*. 2020;75:1023-42. <https://doi.org/10.1111/all.14221>