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American Review of Respiratory Medicine
Revista Americana de Medicina Respiratoria

SPECIAL ARTICLE

ISSN 1852-236X

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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Recived 08/07/2023
Accepted: 10/21/2023

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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 (1C), mobile devices (1B) and education (1C). Sublingual immunotherapy must be prescribed only in patients with allergic rhinitis, mite associated, and persistent symptoms although appropriate treatment with FEV_1> 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).

Rev Am Med Resp 2023;23:277-292
https://doi.org./10.56538/ramr.KYEH5462

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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 (1C), uso de herramientas a través de teléfonos móviles (1B) y educación (1C). 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 $FEV_1 > 70$ % (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
Adherence
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?
Treatment
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 (LAMA) + 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 LAMA+ICS+LABA in adult patients with severe uncontrolled asthma?
11. Should a LAMA+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 doubtful[11].

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 studies[15-21]. 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]

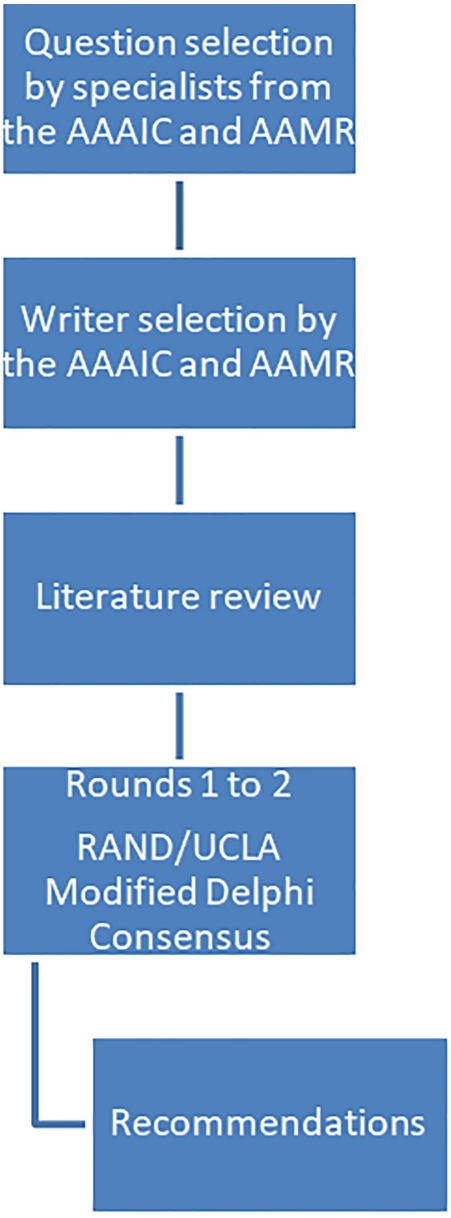

Figura 1. Design flow of the work
AAAIC: Argentinian Association of Allergy and Clinical Immunology
AAMR: Argentinian Association of Respiratory Medicine

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
Adherence	
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
Treatment	
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 FEV1 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 LAMA 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 LAMA 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 LAMA 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-report[25], 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 patients [38-41]. 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 FEV_1 (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 (LAMA) + 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 LAMA with the largest amount of clinical information and has been studied in children, adolescents, and adults.[51] Two other LAMA (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 (LAMA, 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+LAMA+ICS.

In an extensive review that included some studies with all three LAMA (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 LAMA is independent of the asthma phenotype, irrespective of the eosinophilia degree and the fraction of exhaled nitric oxide (FeNO).[65-66] The addition of LAMA 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 LAMA 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 LAMA 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 LAMA+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 LAMA 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 LAMA+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 LAMA 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 FEV_1.[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 FEV_1.[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 FEV_1.[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 FEV_1.[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.

Acknowledgement

The authors thank the collaboration of Dr. Alejandro Videla and Damián Silva and Vanesa Kirchuk as methodological advisors.

TABLE 3. Orientation in the selection of the biologics

Caracteristics	Anti-IgE	Anti-IL4 Rα	Anti-IL5/IL5 Rα
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 <1500/µL	Prerequisite: increased frequency, 150 to 300/µL
Feno	Slight improvement with increased FeNO	Better response if FeNO is > 25ppb	Independent from FeNO
Co-existing conditions	AR, CRS w/NP and chronic hives	RA, 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.

Pablo Moreno: no conflict of interest.

Susana Lühning: no conflict of interest.

Anahí Yañez: clinical research investigator for GSK, AstraZeneca, Sanofi Chiessi, 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.

Ana Stock: clinical research investigator for AstraZeneca, Sanofi, GSK, Novartis, Chiesi, Zambón, Bristol, Bayer, MSD, and Roche. Continuing medical education activities for AstraZeneca Sanofi, GSK, ELEA Phenix, Novartis. Medical advisor for GSK, AstraZeneca, Sanofi and ELEA Phoenix.

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

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

Martin Maillo: clinical research investigator for: GSK, Novartis, Astra-Zéneca, Forrest, Pearl, Chiesi, Sanofi, Roche, Janssen, TRI, Insmed and Zambon. Has received fees as a speaker or advisor from: GSK, AstraZeneca, Novartis, and Sanofi/Genzyme.

Marcos Hernández: continuing medical education activities for ELEA, Boehringer Ingelheim, AstraZeneca, GSK, Tuteur.

Martín Sivori: continuing medical education activities for ELEA, GSK, TEVA, AstraZeneca.

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.

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