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Early View

Review

SEVERE ASTHMA – ADDING NEW EVIDENCES. Latin American Thoracic Society-ALAT

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SEVERE ASTHMA – ADDING NEW EVIDENCES.

Latin American Thoracic Society-ALAT

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ABSTRACT

This document constitutes a summary of the Clinical Practice Guidelines (CPGs) prepared at the initiative of the Latin American Thoracic Society (ALAT). Due to new evidence in the treatment of severe asthma, it was agreed to select 6 clinical questions, and the corresponding recommendations are provided herein. After considering the quality of the evidence, the balance between desirable and undesirable impacts and the feasibility and acceptance of procedures, the following recommendations were established: 1) We do not recommend the use of an ICS plus formoterol as rescue medication in the treatment of severe asthma. 2) We suggest performing many more high-quality randomized studies to evaluate the efficacy and safety of tiotropium in patients with severe asthma. 3) Omalizumab is recommended in patients with severe uncontrolled allergic asthma with serum IgE levels above 30 IU. 4) Anti-IL-5 drugs are recommended in patients with severe uncontrolled eosinophilic asthma (cut-off values above 150 cells/µL for mepolizumab and above 400 cells/µL for reslizumab). 5) Benralizumab is recommended in adult patients with severe uncontrolled eosinophilic asthma (cut-off values above 300 cells/µL). 6) Dupilumab is recommended in adult patients with severe uncontrolled allergic and eosinophilic asthma and in adult patients with severe corticosteroid-dependent asthma.

INTRODUCTION

Asthma is a global health problem, with approximately 300 million people affected. It is estimated that approximately 5% of the population suffers from asthma, although some reports indicate that this proportion may be higher in certain age groups. This represents a medical challenge and at the same time a significant health burden for both patients and health institutions. The morbidity and mortality from asthma is increasing [1- 2-3]. The prevalence of asthma in Latin America has been reported with averages of 17.3% (6-7 years old) and 15.8% (13-14 years old) [4]. However, epidemiological studies in adults are limited (Mexico 5%, Colombia 6.3%) [5]. Previous studies have revealed that most asthma patients in Latin America are not being treated, many suffer frequent exacerbations, and there is almost no awareness of the severity of the disease, not even among patients treated in specialized centres where other individuals also suffer from severe asthma [6-7]. On the other hand, Latin American physicians have not shown much adherence to the recommendations of the clinical practice guidelines (CPGs) [8]. This regional situation and the recognition of the importance of serious types of asthma motivated the ALAT Asthma Department to bring together a group of experts from all over the region to develop a clinical practice guideline on the diagnosis and management of severe asthma. Given recent evidence and new analysis methods, such as indirect comparisons for

biological drugs in the treatment of severe asthma, our group has selected 6 questions, which are presented herein.

METHOD

Guideline Development Group (GDG)

The GDG is composed of pulmonologists specialized in asthma, members of the ALAT Asthma Department and methodological experts with expertise in the development of systematic literature reviews (SRs) and CPGs (Figure 1). A core group met on multiple occasions through a network platform and had two face-to-face meetings. Scope of the document and clinical questions were agreed upon, and in the second meeting, the content and wording of the recommendations endorsed in the modified Delphi panel (DP) were reviewed in detail. Panel members disclosed all possible conflicts of interest. Those with relevant conflicts of interest participated in the discussions about evidence but did not participate in the formulation of recommendations.

Structured Clinical Questions

The GDG designed the complete clinical questionnaire. It was sought to be clear, precise, and specific to facilitate the search and review of scientific evidence and thus avoid recommendations that are not well adjusted to the clinical problems posed by the CPG. The PICO model was considered in most of the questions.

Comprehensive search for scientific evidence

The evidence was identified following internationally validated algorithms and strategies. MeSH terms were identified and used to build a sensitive and specific search strategy [9]. A preliminary search of relevant CPGs was carried out, followed by the identification, evaluation, and synthesis of all the relevant evidence.

In the comprehensive search for SRs, different search strategies were developed, and several databases were used. The Cochrane Library, the Campbell Collaboration Library of Systematic Reviews, the Centre for Reviews and Dissemination databases (includes DARE), the National Institute for Health Research (UK), the Database of Promoting Health Effectiveness Reviews (DoPHER), The ripDatabase, Medline, PubMed (the National Library of Medicine in the United States) and Embase, the NICE and the NIHR (National Institute for Health Research of UK) were consulted to identify high-quality HTAs. The databases that were consulted to identify published clinical studies were the following: the Cochrane Library up to 2017, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE) (Issue 1 2017), Medline 1950-2019 (OVID), Embase 1980-2019 (OVID),

CINAHL 1982-2019 (NLH Search 2.0), LILACS (1998 to 2019), ARTEMISA (1999 to 2019), and SciELO (1999 to 2019).

Quality assessment and the ranking of evidence

To establish the quality of the scientific evidence, the AGREE II tool [10] was used in the case of CPGs, while the AMSTAR II tool was used for SRs [11-12]. To assess the quality of the evidence, we chose to use the scale developed by SIGN [13-14], which uses two attributes to assess the quality of the scientific evidence (level of evidence): the study design and the risk of bias (Table 1).

Expert Formal Consensus (EFC)

A DP was carried out as a process to collect the opinion of experts representing the respiratory societies associated with ALAT [15,16]. EFC members received an invitation via email to review each of the clinical recommendations placed on a digital platform designed for this purpose and assigned a rating using a "Likert scale". A mean level of 7.0 was established as the minimum level of consensus, and 70% of responses were in the range of 7 - 9 on the Likert scale. GN members interacted among the participants, processing the information and filtering the relevant content. They modified the recommendations according to the clinical arguments of all panellists to send the new text to a new round of DP.

Drafting of the recommendations

GN members met on several occasions to review all the evidence related to the structured clinical questions and, according to the level of evidence, to be able to determine the grade of recommendation and the wording. The recommendations also considered the risk versus benefit ratio to guide decision-making. In accordance with SIGN, a careful analysis of evidence was carried out, as well as an analysis of the experience of the GDG members and the accessibility to diagnostic tests and therapeutic interventions, to qualify clinical recommendations and to express the level of confidence the GDG had in the recommendations (Table 2).

RESULTS

To correctly prepare the body of the guideline, 17 clinical questions were selected (Table 3). A total of 157 SRs were found in PubMed and 21 SRs were found in Embase with the search strategies used. Specific search strategies were carried out for some of the therapeutic interventions to complement the information, and 167 additional SRs were found. In some cases, such as antileukotrienes and theophylline, search strategies were conducted to identify RCTs, and 301 abstracts were located. Three rounds of the modified Delphi panel were performed. Of the 17 clinical questions analysed, only one, question 3, referring to the definition of difficult-to-treat asthma, did not

reach a minimum level of consensus, a mean of 7.0 and a percentage of 70% in the DP; therefore, it was rejected, as agreed upon by the members of the GDG (Table 4). Thus, sixteen questions formed part of the clinical recommendations of the guideline. The final recommendations are outlined in Table 5 and are detailed below. An analysis of 6 questions and their recommendations are presented in this document by consensus.

CLINICAL RECOMMENDATIONS

Question 7: What is the indication for the on-demand use of the combined therapy of an ICS and formoterol associated with maintenance treatment with an ICS and an LABA in patients with severe asthma?

Justification: The use of a combination of an inhaled corticosteroid (ICS) plus a long-acting bronchodilator (LABA) through a single inhaler or single maintenance and relief therapy (SMART) has been suggested to treat mild to moderate asthma. The question that arises is whether such a strategy can be indicated in patients with severe asthma.

Research: Exhaustive research was carried out (157 documents in PubMed, 21 in Embase, 497 in the TRIP database and 4 in different databases), and 4 documents were selected (1 clinical practice guide, 3 systematic literature reviews).

Evidence Summary

An SR published by Cates et al. [15] included 3 clinical trials, one of which was performed with symptomatic patients with asthma exacerbation in the year prior to the study but no diagnosis of severe asthma. A significant reduction in the number of hospitalizations (odds ratio (OR) 0.68, 95% CI: 0.40; 1.16) and severe exacerbations was reported when the combination of an ICS and formoterol vs. terbutaline was used (OR 0.54, 95% CI: 0.44, 0.65). Another SR published by the same authors [16] reported that patients with mild to moderate asthma, non-severe according to the 2014 ATS/ERS criteria, treated with a combination of budesonide and formoterol as rescue and maintenance therapy instead of the use of an ICS registered a lower use of rescue medicine (OR -0.16, 95% CI: -0.27; -0.05). Regarding the safety of using formoterol vs. terbutaline, the first had less of an effect on serum potassium, heart rate, blood pressure and the QT interval. The 2014 ATS/ERS guidelines suggested that reducing the LABA dose improves the control of asthma in children with asthma of any degree of severity; therefore, there is no specific recommendation for the use of β_2-agonist bronchodilators [3].

Recently, Sobieraj et al. [17] published an SR meta-analysis that included 16 controlled clinical trials (22,748 patients). The authors found that patients with persistent asthma treated with the SMART strategy had a decreased risk of asthma exacerbations. In this meta-analysis, the authors

included three clinical trials conducted in patients who received high doses of an ICS. Unfortunately, none of the three studies met the 2014 ATS/ERS criteria for treating severe asthma. The evidence found for patients aged 4 to 11 years was limited.

Conclusions and recommendations

We have not found high-quality evidence that shows efficacy and safety for the addition of a combination of an ICS plus formoterol as rescue treatment to standard therapy in patients with severe asthma. Considering extrapolated data from different populations, the use of a combination of an ICS plus formoterol as rescue treatment in patients who have the same maintenance combination is suggested to improve symptoms quickly (level of evidence 1+, grade of recommendation B). Further high-quality randomized studies are needed to evaluate the efficacy and safety of using a combination of an ICS plus formoterol as a rescue treatment in patients with severe asthma (conditional recommendation).

Question 10: Is there any additional benefit when adding a long-acting anticholinergic drug (tiotropium) to ICS and LABA treatment in patients with severe asthma?

Justification: Long-acting anticholinergics (LAMAs) are indicated as a third option for the treatment of patients with moderate asthma; however, their benefit in patients with severe asthma is unknown, which is why the following question arises.

Research: Exhaustive research was carried out (157 documents in PubMed, 21 in Embase, 497 in the TRIP database and 4 in different databases), and 4 documents were selected (3 systematic literature reviews and 1 controlled clinical study).

Evidence Summary

Tiotropium

An SR published by Rodrigo et al. [18] included 13 clinical trials, 4,966 patients, but only one trial was performed in patients classified as severe and with 48 weeks of treatment. Notably, in this study, the number of exacerbations suffered by patients in the previous year was unclear.

However, the SR results showed a decrease in the frequency of exacerbations (18.2% vs. 24.0%), with an NNT of 17 and improvement in the results of forced expiratory flow (FEF) and forced expiratory volume in 1 second (FEV1), supporting the use of triple therapy. The quality of life (QoL) and symptoms also showed statistically significant improvement.

Kew et al [19] published an SR that included 4 clinical trials, 1,197 asthma patients treated with a combination of an ICS and an LABA, where the diagnosis of severe asthma was at the investigator's

discretion. The authors did not show data regarding previous exacerbations suffered by patients to establish if they had severe uncontrolled asthma. The results showed that those patients who received tiotropium as an adjuvant drug had fewer exacerbations requiring oral corticosteroids than those patients who received placebo. However, the difference was not statistically significant (OR 0.76, 95% CI: 0.57; 1.02). The authors reported a moderate level of evidence. The QoL evaluated by the Asthma Quality of Life Questionnaire (AQLQ) did not show significant differences (mean difference (MD) 0.09, 95% CI: 0.03, 0.20) and failed to decrease the incidence of adverse events (OR 0.60, 95% CI: -0.24; 1.47; I^2 = 76%).

Another SR published by Rodrigo et al. [20] was carried out to evaluate the efficacy and safety of tiotropium in adolescents with moderate to severe asthma. The authors included 3 controlled clinical studies; however, two were conducted in patients with moderate asthma, and only one was carried out in patients with severe asthma for 12 weeks. The meta-analysis included the 3 studies, but no severity stratification was carried out to determine whether there were differences in patient groups. Taking into account the results of the only study that considered patients with severe asthma, the improvements in the pulmonary function tests, FEV1 (DM -0.10, 95% CI: -0.21; 0.01), symptoms (ACQ-7) (relative risk (RR) 0.53, 95% CI: -0.15; 1.78) and incidence of exacerbations (RR 0.69, 95% CI: -0.43; 1.12) did not show statistically significant differences.

A study carried out in children from 6 to 11 years of age published by Szefler et al. [21] included symptomatic patients with severe asthma treated with a high-dose ICS plus an LABA or antileukotrienes or with a medium-dose ICS plus two additional controllers for 4 months prior to admission. For 12 weeks, patients received a dose of either 5 mg or 2.5 mg of tiotropium or placebo. When compared with placebo treatment, the results showed an improvement in FEV1 with the 5 mg dose (adjusted mean difference (AMD) 139 mL, 95% CI: 75; 203; P <0.001), but the improvement was not significant with the 2.5 mg dose (AMD 139 mL, 95% CI: 28; 99; P <0.27). There were no statistically significant differences in the symptom score (tiotropium 5 mg 80.8%, tiotropium 2.5 mg 79.4% and placebo 76.9%). The incidence of adverse events was lower in patients treated with tiotropium 5 mg (n=56; 43.1%) and tiotropium 2.5 mg (n=59; 43.4%) than in patients treated with placebo (n=66; 49.3%). Most of the adverse events were mild to moderate.

Conclusions and recommendation

We suggest the use of tiotropium as a third controller due to its risk-benefit profile in patients with severe asthma. The use of tiotropium as an add-on to ICS/LABA treatment in children 6 years of age and adults with asthma shows a slight improvement in symptoms, pulmonary function, and exacerbations. However, this is a weak recommendation due to the limited information available in clinical studies carried out in patients with severe asthma

(level of evidence 1-, grade of recommendation B). Further high-quality randomized studies are needed to evaluate the efficacy and safety of using tiotropium in patients with severe asthma. (Conditional recommendation).

Question 11: What is the efficacy and safety of anti-IgE monoclonal antibodies in the treatment of severe asthma in children and adults?

Justification: Omalizumab is a humanized monoclonal antibody with high affinity for serum IgE, and it has been approved for the treatment of allergic asthma. There is new information regarding this drug; therefore, we have decided to reformulate this question.

Research: Exhaustive research was carried out (224 documents in PubMed, 21 in Embase, 497 in the TRIP database and 4 in different databases), and 6 documents were selected (3 clinical practice guidelines and 3 systematic literature reviews).

Evidence Summary

Omalizumab

A SR carried out by Normansell et al, included 25 controlled clinical studies, 7 of which were conducted in patients considered to have severe asthma [22]. The meta-analyses of patients with severe asthma showed an improvement in the number of exacerbations in both patients treated with high doses of an ICS (OR 1.00, 95% CI: 0.5; 1.99, 277 patients) and those treated with an ICS plus oral corticosteroids (OR 1.65, 95% CI: 0.66; 4.13; 95 patients). When compared to placebo, there was a significant improvement in asthma control (OR 1.69, 95% CI: 1.26; 2.26) and the quality of life (57.5% vs 38.6%; P <0.01) and a reduction in the use of rescue medications (mean difference (MD) -0.30, 95% CI: 0.49; 0.10). As the results showed heterogeneity in the subgroup of patients with severe asthma, it was not possible to conduct a meta-analysis when analysing pulmonary function. Regarding the safety variables, there were no significant differences between the group that received omalizumab and the control group.

A health technology assessment (HTA) published by Norman et al. [23] selected 11 controlled clinical trials, one of which included paediatric patients. When compared to placebo, omalizumab reduced exacerbations in both adult patients (rate ratio (RT) 0.74; 95% CI: 0.55; 1.00) and paediatric patients (RT 0.66; 95% CI: 0.44; 1.00). There is no solid evidence in children.

The ERS/ATS 2014 CPG [3] reported that, when comparing placebo with omalizumab, the latter improved the quality of life (65% vs. 57%; RR: 1.19, 95% CI: 1.08; 1.30; 4 studies) and asthma control (mean difference in ACQ score: 0.87, 95% CI: 0.6; 1.14; 1 study) and showed a reduction in the need for systemic corticosteroids (RR: 0.73, 95% CI: 0.56; 0.94). In paediatric patients treated

with omalizumab, the therapy reduced the need for corticosteroid dosage (MD: 14%, 95% CI: 5; 21%) and hospitalization (MD: 5%, 95% CI: 1; 6%). However, omalizumab had no significant effect on the quality of life or asthma control.

The ATS CPG 2018 [24], which based its recommendation mainly on a Cochrane SR published in 2014 [25], suggests the use of omalizumab treatment in patients older than 6 years with asthma inadequately controlled with high-dose inhaled corticosteroids and the use of at least one additional controller and who are sensitized to at least one aero allergen and present high IgE levels (30-1300 IU ml in patients aged 6 to 11 years and 30-700 IU/ml in patients older than 12 years).

The GINA CPG 2019 recommendations [26] suggest the use of omalizumab in patients older than 6 years with moderate to severe asthma inadequately controlled in Step 4 of treatment and high levels of IgE.

Indirect comparisons

A “network meta-analysis” published by Nachef et al. [27] compared omalizumab versus mepolizumab in patients 12 years of age and older. The authors included 18 studies with omalizumab (4854 patients) and 4 studies with mepolizumab (1620 patients). The results showed that there was no difference in the improvement in FEV1 with either drug; however, both were superior to placebo (omalizumab 138.05, 95% CI: 83.08; 193.01 vs mepolizumab 147.32, 95% CI: 116.36; 178.28). When comparing both cases in relation to asthma control, no clinically significant difference was obtained in ACQ scores (mepolizumab 0.78, 95% CI: 0.93; 0.62 vs omalizumab 0.76, 95% CI: 1.15; 0.37) or in AQLQ scores (mepolizumab 0.82, 95% CI: 0.71; 0.92 vs omalizumab 1.2, 95% CI: 1.11; 1.28).

Conclusions and recommendations

We recommend the use of omalizumab in patients with severe uncontrolled allergic asthma and with serum IgE levels above 30 IU. We suggest the use of subcutaneous omalizumab in patients older than 6 years with severe asthma that is inadequately controlled. The benefit seems to outweigh the risks of presenting adverse events (level of evidence 1+, grade of recommendation A - adults) (level of evidence 1-, grade of recommendation A - paediatric patients) (strong recommendation).

Question 12. What is the efficacy and safety of anti-IL-5 monoclonal antibodies in the treatment of severe asthma in children and adults?

Justification: IL-5 is a pro-eosinophilic type 2 cytokine that binds to its receptor, IL-5R, on eosinophils and basophils; it promotes the recruitment of eosinophils and their activation and

contributes to eosinophilic inflammation of the airway. We currently have two humanized monoclonal antibodies against interleukin 5 (anti-IL5): mepolizumab and reslizumab. The answer to this question should be focused on reducing exacerbations and improving the quality of life, pulmonary function, and asthma control.

Research: Exhaustive research was carried out (218 documents in PubMed, 21 in Embase, 497 in the TRIP database and 4 in different databases), and 9 documents were selected (9 systematic reviews).

Evidence Summary

Mepolizumab

An SR and meta-analysis published by Liu et al. [28], which included 3 clinical studies of severe eosinophilic asthma, showed that mepolizumab therapy reduced the risk of exacerbations (OR 0.30, 95% CI 0.13, 0.67, p=0.004) and significantly improved AQLQ scores (MD 0.26, 95% CI 0.03, 0.49, p = 0.03) compared with placebo. It was observed that mepolizumab significantly lowered eosinophil counts in sputum (MD 26.05%, 95% CI 29.34, 22.77%, p=0.0003) and blood (MD 0.05 L, 95% CI 20.04, 0.13 L, p=0.29).

Yancey et al. [29] compared mepolizumab versus placebo and included 4 clinical trials (n=1388) of patients with severe eosinophilic asthma. Mepolizumab produced a 51% reduction in the rate of exacerbations requiring hospitalization (RR 0.49; 95% CI, 0.30-0.80; p=0.004) and in emergency room visits (RR, 0.49; 95% CI, 0.33-0.73; p <0.001) compared with placebo.

An SR published by Powell et al. [30] compared intravenous mepolizumab (IV) to placebo and reported a significant reduction in the exacerbation rate with the use of IV mepolizumab (RR 0.52, 95% CI 0.43, 0.64).

A post hoc meta-analysis of the SR published by Farne et al. [31], performed on data from phase III, MENSA, and MUSCA studies, showed a reduction in the mean exacerbation rate of 49-70% and an improvement in SGRQ and ACQ-5 scores in patients treated with mepolizumab compared with patients treated with placebo.

Reslizumab

A meta-analysis comparing the effect of reslizumab versus placebo published by Li et al. [32] showed fewer exacerbations (OR=0.46, 95% CI: 0.35, 0.59, p＜0.00001) and lowered blood eosinophil counts (standardized mean difference (SMD) -475.62, IC 95%: -528.41, -422.83, p＜ 0.00001), as well as improvements in FEV1 (SMD 0.16, 95% CI: 0.10 to 0.23, p＜0.00001) and

symptom control as determined by ACQ score (SMD -0.26, IC 95%: -0.36, -0.16, p＜0.00001), in patients treated with reslizumab.

Indirect comparisons:

To assess the efficacy of mepolizumab and reslizumab, an SR and meta-analysis published by Henriksen et al. [33] showed a 53% reduction in exacerbations (95% CI: 46; 59) in favour of both anti-IL-5 drugs compared to placebo. When compared with placebo, mepolizumab and reslizumab showed significant improvements in lung function (112.93 ml; 95% CI: 82.44; 143.31), asthma control (−0.29 points; 95% CI: −036, −0.23) and asthma-related QoL (0.32; 95% CI: 0.22; 0.43).

An SR published by Farne et al. [31] compared the effect of anti-IL5 and anti-IL-5R biological agents versus placebo. This review showed a reduction of exacerbations by using SC mepolizumab (RR 0.45, 95% CI: 0.36, 0.55), IV mepolizumab (RR 0.53, 95% CI: 0.44, 0.64), reslizumab (RR 0.43, 95% CI: 0.33, 0.55) and benralizumab (RR 0.62, 95% CI: 0.55, 0.70). Although an improvement in the quality of life was observed, it did not exceed the minimal clinical difference for the ACQ or the SGRQ. An improvement in lung function was determined with all biological agents versus placebo. However, the improvement was statistically significant with SC mepolizumab (MD 0.11 L, 95% CI: 0.06, 0.17), IV mepolizumab (MD 0.08, 95% CI: 0.02-0.15), reslizumab (MD 0.11 L, 95% CI: 0.07, 0.15) and benralizumab (MD 0.10, 95% CI: 0.05, 0.14). No serious adverse events were shown with any anti-IL5 compared with placebo**.**

Nachef et al. [27] performed an efficacy comparison between mepolizumab and omalizumab. The authors found that there were no significant differences in the asthma control questionnaire score, FEV1 or peak expiratory flow rate (PEFR). Both drugs reduced the calculated exacerbation rate per year by 50%.

An SR published by Casale et al. [34] indirectly compared reslizumab with benralizumab using a Bayesian network meta-analysis. Eleven studies were carried out in patients with severe eosinophilic asthma. Reslizumab significantly improved the ACQ score (-0.37; CrI, -0.63 to -0.10; Pr = 100%) and the AQLQ score (-0.32; CrI, 0.03 to 0.60; Pr = 99%) compared with benralizumab. This indirect comparison suggested that reslizumab might be more effective than benralizumab in patients with eosinophilic asthma (benralizumab, ≥300/μL; reslizumab, ≥400/μL) and with 2 or more exacerbations in the previous year.

A network meta-analysis carried out by He et al. [35], which evaluated the effect of anti-IL-5 and anti-IL-5R antibodies, showed significant improvements in FEV1 (SMD 0.18; 95% CI: 0.12-0.23; p <0.001) and in AQLQ scores (SMD 0.20; 95% CI: 0.13–0.26; p <0.001) in patients treated with monoclonal antibodies compared with those treated with placebo. There were no significant

differences in exacerbation risks between individuals treated with monoclonal antibodies and those treated with placebo (RR 0.68, 95% CI 0.11, 4.14, p = 0.097).

Conclusions and recommendations

Anti-IL-5 as an add-on treatment for patients with severe uncontrolled eosinophilic asthma is recommended. We suggest cut-off values of blood eosinophils above 150 cells/µl for the use of mepolizumab and above 400 cells/µl for the use of reslizumab. There is not enough evidence confirming the use of these drugs in children under 12 years of age (level of evidence 1+, grade of recommendation A - adults) (strong recommendation) (level of evidence 1-, grade of recommendation B - paediatric patients). (It is recommended to carry out research, and the use of these drugs is dependent on the results of clinical studies.)

Question 13. What is the efficacy and safety of anti-IL-5 receptor monoclonal antibodies in the treatment of severe asthma in children and adults?

Justification: IL-5 is a pro-eosinophilic type 2 cytokine that binds to its IL-5R receptor expressed on eosinophils and basophils, promoting eosinophil recruitment and activation and contributing to eosinophilic inflammation of the airway. It is possible that patients with severe asthma have high blood and/or sputum eosinophil counts. Benralizumab is a monoclonal antibody that blocks the α-chain of the IL-5 receptor. Thus, there is a need to answer this question in terms of reducing exacerbations and improving the quality of life, lung function, and asthma control.

Research: Exhaustive research was carried out (218 documents in PubMed, 21 in Embase, 497 in the TRIP database and 4 in different databases), and 10 documents were selected (10 systematic literature reviews).

Evidence Summary

Benralizumab

An SR, published by the NICE in 2019 [36], included 3 clinical studies, and benralizumab reduced the annual exacerbation frequency by 43% compared to placebo (RR 0.57, 95% CI: 0.47; 0.69, p <0.0001). The results demonstrated the greatest benefit in patients with high blood eosinophils (> 300 cells/µl) and in those patients who had more exacerbations over the 12-month period prior to the study (four or more exacerbations requiring corticosteroid therapy).

An SR published by Tian et al. [37], which included 9 controlled clinical studies on 2,321 patients, showed that exacerbation frequency increased (38.66%) in patients treated with placebo compared to those receiving benralizumab therapy (26.28%), who showed a significantly decreased risk of presenting exacerbations (RR 0.63, 95% CI 0.52; 0.76, p <0.00001). Regarding pulmonary function

tests, three studies did not find significant FEV1 differences in either group in comparison to the baseline values (SMD -0.10, 95% CI: -0.31; 0.10, p=0.33). The results of the meta-analysis regarding symptom control (ACQ score) showed a significant difference in favour of benralizumab versus placebo (SMD -0.10, 95% CI: -0.26; 0.06, p = 0.22) in patients with eosinophilic asthma, while regarding the quality of life (AQLQ score), there were no differences (SMD -0.11, 95% CI: -0.32; 0.10, p = 0.3). Regarding the incidence of adverse events, there were no differences between the benralizumab group (1,216 of 1,646) and the placebo group (622 of 847) (RR 1.00, 95% CI 0.95, 1.05, p = 0.96).

An SR carried out by Liu et al. in 2018 [38], which included the same studies (5 ECAs) as other systematic literature reviews, demonstrated that, compared with the placebo, benralizumab treatment helped in reducing exacerbations and improving lung function (FEV1), the quality of life, and the control of disease (ACQ score). The most effective dose was 30 mg.

Recently, Liu et al. [39] published another SR of eight clinical studies. A meta-analysis showed that the group treated with benralizumab had a lower risk of experiencing general adverse events (RR 0.94, 95% CI: 0.90, 0.98), serious adverse events (RR 0.82, 95% CI: 0.68, 0.98) or asthma exacerbation (RR 0.72, 95% CI: 0.61; 0.85) than the group treated with placebo. The authors concluded that benralizumab showed an adequate and safe profile in the treatment of eosinophilic asthma.

Indirect comparisons

A SR published by Cabon et al. [40] aimed to compare the clinical efficacy and safety of benralizumab with other anti-IL-5 monoclonal antibodies in patients with severe asthma. The authors included 10 clinical trials and 3,421 patients. The network meta-analysis outcomes regarding the reduction in the exacerbation rate were best with reslizumab 3 mg (51%), followed by mepolizumab 750 mg (22%) and mepolizumab 100 mg (13%). Regarding the Asthma Control Test, benralizumab was the most effective (MD -0.38, 95% CI: -0.97; -0.18, p <0.01). Reslizumab treatment was the most effective in improving the FEV1 values (MD 0.14L, 95% CI: 0.05; 0.24, p <0.01). Regarding safety outcomes, benralizumab showed the best safety profile of all (RR 0.94, 95% CI: 0.57; 1.54), but considering the incidence of serious adverse events, reslizumab had the best safety profile (RR 0.81, 95% CI: 0.22; 3.03).

Bourdin et al. [41] performed a comparison of benralizumab versus anti-IL-5 drugs (n = 1,524). After matching adjustment, benralizumab and mepolizumab reduced exacerbations compared with placebo by 52% and 49%, respectively (RR 0.94, 95% CI 0.78-1.13), and reduced the rate of exacerbations requiring hospitalization by 52% and 52%, respectively (RR 1.00, 95% CI 0.57-1.7524). An improvement in lung function was observed with the use of benralizumab (0.10 L in pre-

bronchodilator FEV1) versus mepolizumab (0.07 L in pre-bronchodilator FEV1) (MD 0.03L; 95% CI: −0.06; –0.12). It was difficult to generate a sufficiently effective sample size to produce a reliable estimate when comparing the benralizumab and reslizumab heterogeneous populations.

Another SR published by He et al. [35] included 21 clinical studies that evaluated treatment with benralizumab, mepolizumab, and reslizumab. In the “meta-analysis by pairs” extracted from 16 studies, an improvement in FEV1 was observed with the use of anti-IL-5 therapies versus placebo (SMD 0.18, 95% CI: 0.12; 0.23; p <0.001). Regarding lung function, the network meta-analysis showed the efficacy of mepolizumab, reslizumab and benralizumab (NMA: SMD 1.09; 95% CI: 1.04; 1.15; 1.11; 95% CI: 1.05; 1.18; 1.10; 95% CI 1.05; 1.15; respectively). The surface under the cumulative ranking curve showed the following results: reslizumab (SUCRA 77.7% probability), benralizumab (SUCRA 63.4% probability) and mepolizumab (SUCRA 58.9% probability). Regarding AQLQ score improvement, reslizumab was the most effective (85.6% probability), followed by benralizumab (62.3% probability) and mepolizumab (51.5% probability). There were no significant differences in the risk of exacerbation, but the SUCRA classification found that the risk of exacerbation was lowest with mepolizumab (23.1% probability), followed by benralizumab (38.5% probability) and finally reslizumab (57.6% probability). Regarding safety, reslizumab showed the lowest risk of presenting adverse events (NMA: RR, 1.44, 95% CI: 1.01; 2.05).

As previously mentioned, Casale et al. [34], when stating an indirect comparison, suggested that reslizumab might be more effective than benralizumab in patients with eosinophilic asthma (benralizumab, ≥300/μL; reslizumab, ≥400/μL) with 2 or more exacerbations in the previous year.

In another SR with network meta-analysis published by Edris et al. [42], the authors found no significant difference among those biological drugs. Anti-IL-5 drugs are the treatment alternatives with the largest number of clinical studies, and in regard to reducing exacerbations in eosinophilic asthma patients, they show superiority over placebo. However, the network meta-analysis outcomes did not show statistically significant differences among these drugs.

Conclusions and recommendations

The use of benralizumab is recommended in patients over 18 years of age with severe uncontrolled eosinophilic asthma (more than 300 cells/μl in blood) (level of evidence 1+, grade of recommendation A - adults) (strong recommendation). The use of benralizumab is not recommended in the paediatric population, as there are no published studies so far. More high-quality randomized studies are required to evaluate the efficacy and safety of benralizumab in patients with severe asthma, mainly in the paediatric population. (We recommend carrying out research, and the use of benralizumab should be based on the results of clinical studies.)

Question 15. What is the efficacy and safety of anti-IL-4 and IL-13 monoclonal antibodies in the treatment of severe asthma in children and adults?

Justification: IL-13 is a cytokine secreted by T helper type 2 (Th2) cells, CD4 cells, natural killer T cells, mast cells, basophil cells, and eosinophil cells, among others, and it is a central regulator in IgE secretion, mucus hypersecretion and bronchial muscle contractibility. It shares with IL-4 a multisubunit receptor expressed in several cells involved in the pathophysiology of allergy and asthma. As a result, there is a need to know which benefits are generated by anti-IL-13 drugs and which are generated by anti-IL-4 drugs in the treatment of patients with severe asthma.

Research: Exhaustive research was carried out (192 documents in PubMed, 21 in Embase, 497 in the TRIP database and 4 in different databases), and 7 documents were selected (6 systematic literature reviews and a post hoc analysis).

Evidence Summary

Lebrikizumab and Tralokinumab

Adult patients with uncontrolled asthma, despite the use of medium to high doses of an ICS plus the use of at least one second controller for at least 6 months prior to study entry, were included in the LAVOLTA 1 and LAVOLTA 2 studies. However, in those studies, lebrikizumab did not show a significant reduction in asthma exacerbations versus placebo [42].

Zhang et al [43] published a systematic review that compared the efficacy of tralokinumab versus placebo in patients with moderate to severe asthma. The authors included five studies involving 2,928 adults. The meta-analysis showed that tralokinumab did not reduce asthma exacerbations or improve asthma-related quality of life to a statistically meaningful degree versus placebo. However, tralokinumab did show improvement in FEV1 (MD 0.14 L, 95% CI: 0.08; 0.21, dosage of 300 mg every 2 weeks), (MD 0.20 L, 95% CI: 0.01; 0.39, dosage of 600 mg every 4 weeks) and FVC (MD 0.11, 95% CI: 0.01; 0.21). It did not increase the incidence of serious adverse events, but injection site adverse reactions were observed (OR 5.92, 95% CI: 1.61; 21.76). Three phase II controlled clinical trials of patients treated with tralokinumab therapy were taken into consideration. The subjects in those trials were patients with uncontrolled asthma, a history of exacerbations in the previous year, and treatment with medium to high doses of an ICS and an LABA for at least three months prior to the beginning of the study. The trials did not show improvement in asthma control, exacerbation rates, FEV1, FEF, or the QoL.

Another SR published by Li et al. [44] aimed to evaluate anti-IL-13 monoclonal antibodies. The authors included 5 studies (involving 3476 patients), two with lebrikizumab and 2 with tralokinumab. The results of this meta-analysis showed a lower risk of exacerbations in patients receiving anti-IL-13

therapies than in patients receiving placebo (MD 0.19, 95% CI: -0.27; -0.11). Subgroup analysis showed that patients with high periostin levels (>50 ng/ml) had a lower risk of asthma exacerbation (MD 0.30, 95% CI: -0.41; -0.19); however, no benefits of anti-IL-13 therapy were shown in patients with low periostin levels (MD 0.06, 95% CI: -0.18; 0.05). Outcomes of FEV1 showed an improvement in patients after receiving anti-IL-13 versus placebo (MD 0.09, 95% CI: 0.07; -0.12). There was also an improvement in QoL scores in patients treated with anti-IL-13 versus placebo (MD 0.16, 95% CI: 0.10; 0.21).

Dupilumab

Dupilumab is a monoclonal antibody directed against the alpha subunit of the IL-4 receptor and prevents the signalling of both IL-4 and IL-13, which are two key cytokines in type 2 asthma. Dupilumab is administered subcutaneously. A phase III trial (the Liberty Asthma Quest trial) showed a reduction in asthma exacerbations (46.9% - 200 mg and 70.5% - 300 mg) with the use of dupilumab compared with placebo. This response was higher in patients with high blood eosinophil levels [42].

In an SR published by Zayed et al. [45], a total of four clinical trials representing 2,992 patients were included. A reduction in asthma exacerbation rates was shown in the dupilumab group compared with the placebo group (RR 0.44; 95% CI: 0.35; 0.55). A subanalysis was performed based on blood eosinophil values; the outcome showed a reduction in asthma exacerbations in the patient groups with blood eosinophil counts of more than 150 cells/mm^3. Regarding FEV1 changes, a statistically significant difference was shown in patients receiving dupilumab (MD 0.14 L, 95% CI: 0.12; 0.17). There were no significant differences between the groups in the development of any adverse events (RR 0.99, 95% CI: 0.95; 1.02) or serious adverse events (RR 1.05, 95% CI: 0.8; 1.38). However, there was a higher incidence of discomfort due to injection site reactions in the group receiving dupilumab (RR 1.91, 95% CI: 1.41; 2.59).

In an SR and meta-analysis published by Xiong et al. [46], 5 clinical studies involving 3369 patients were included. The analysis showed significant improvements in lung function in the dupilumab group compared with the placebo group, mainly in FEV1 percentage (SMD=4.29, 95% CI: 2.78; 5.81) and QoL scores (SMD=4.39, 95% CI: 1.44; 7.34). There were also significant improvements in asthma symptom control as determined by ACQ-5 score (SMD=- 4.95, 95% CI: -7.30; -2.60) and a reduction in severe exacerbation risks (RR=0.73; 95% CI: 0.67; 0.79) in patients receiving dupilumab compared with placebo.

In a recent post hoc analysis of the Liberty Quest study [85], carried out in patients with allergic asthma (# 1083), it was shown that the administration of dupilumab 200/300 mg every 2 weeks versus placebo reduced the asthma exacerbation rate (36.9% vs 45.5%; both $p < 0.01$) and improved the FEV1 at week 12 (0.13 L vs 0.16 L; both $p < .001$).

Indirect comparisons:

Edris et al. [42] published a systematic review and network meta-analysis carried out on 30 clinical trials comparing all monoclonal antibodies in patients with severe asthma; however, no significant superiority was observed for one biologic over the others. All of them significantly reduced the risk of exacerbation compared with placebo. Dupilumab and tezepelumab improved lung function in patients with frequent exacerbations.

Another SR and network meta-analysis published by Iftikhar et al [48] included 7 trials with benralizumab, two with dupilumab, four with lebrikizumab, seven with mepolizumab, four with reslizumab and two with tralokinumab in subjects with eosinophilic asthma. All drugs were superior to placebo, except for tralokinumab. In terms of the magnitude of effect, dupilumab, followed by reslizumab and benralizumab showed the greatest increase in FEV1 (0.16 L, 95% CI: 0.08; 0.24, 0.13 L, 95% CI: 0.10; 0.17, 0.12 L, 95% CI: 0.08; 0.17). All drugs except tralokinumab showed reductions in ACQ scores. Mepolizumab was the most effective (-0.42, 95% CI: -0.55; -0.29), followed by dupilumab (-0.31, 95% CI: -0.50; -0.12), benralizumab (-0.28, 95% CI: -0.38 ; -0.18), and reslizumab (-0.26, 95% CI: -0.39; -0.13). In order of the magnitude of effect, dupilumab, followed by mepolizumab, benralizumab and reslizumab showed the greatest increase in QoL questionnaires scores (0.27, 95% CI: 0.09; 0.45), (0.26, 95% CI: 0.15, 0.37), (0.26, 95% CI: 0.10; 0.41), while tralokinumab showed no significant benefit. Dupilumab and reslizumab decreased asthma exacerbations (RR 0.37, 95% CI: 0.17, 0.80; and RR 0.64, 95% CI: 0.53, 0.78, respectively).

Conclusions and recommendations

We recommend the use of dupilumab in adult patients with severe allergic and eosinophilic asthma and in adult patients with severe corticosteroid-dependent asthma (level of evidence 1+, grade of recommendation A - adults) (strong recommendation).

A consistent efficacy of lebrikizumab and tralokinumab therapies in the treatment of patients with severe asthma has not been demonstrated; therefore, we do not suggest their use (level of evidence 1+, grade of recommendation A - adults) (conditional recommendation).

There are no studies in the paediatric population; therefore, we do not recommend the use of these drugs in paediatric patients (level of evidence 4, recommendation grade D - paediatric patients). (It is recommended to carry out research, and the use of these drugs is dependent on the results of these clinical studies.)

DISCUSSION

We did not find high-quality evidence to help us recommend the on-demand use of the combination of an ICS plus formoterol treatment in patients with severe asthma. New clinical trials need to be carried out to support this indication. We did not find robust and quality information to recommend the use of tiotropium in patients with severe asthma. Unfortunately, from the detailed analysis of the studies included in the published meta-analyses on tiotropium use in asthma treatment, regarding the inclusion of patients with severe asthma, we found discrepancies in the evaluation of less than 52 weeks and the number of patients included. Our group considered that more clinical studies are needed, complying with internationally accepted definitions, to demonstrate the efficacy and safety of tiotropium therapy in patients with severe asthma. A recommendation was made for the use of omalizumab in patients with severe uncontrolled allergic asthma. The use of anti-IL-5 drugs was recommended for patients with severe uncontrolled eosinophilic asthma. The use of dupilumab was recommended in patients with severe uncontrolled asthma of both allergic and eosinophilic phenotypes and in patients with severe corticosteroid-dependent asthma (Table 5). Severe asthma represents a serious health problem, and Latin America is not exempt. Most patients do not have access to an adequate evaluation and treatment of the disease. The profound diversity of the region, for example, in the genetic load, environmental pollution levels, tobacco smoke exposure, geographic and climate differences, and access to poor-quality health systems, has made severe asthma even more serious in Latin America. Throughout many surveys, our asthma department has found that patients as well as healthcare providers have a profound ignorance about severe asthma. A relevant fact is that the acceptance of clinical practice guideline recommendations among professionals treating patients with severe asthma is low.

Our group considered the inclusion of indirect comparisons among biological treatments, as there are no clinical trials with direct comparisons. After analysing all publications with indirect comparisons, we were unable to conclude if one biologic is better than the others. Therefore, new quality information is needed to respond to this concern.

We experienced a great challenge in developing an algorithm to help professionals classify phenotypes and treat patients with severe asthma in Latin America (Figure 2). Very few countries in the continent have centres that perform sputum induction procedures and exhaled nitric oxide measurements; therefore, we had to adapt the available information to our reality. Currently, for example, a patient with severe asthma living in Mexico will probably have to travel hundreds of kilometres to access such induced sputum procedures. Another example is Argentina, where, for instance, the measurement of exhaled nitric oxide has not yet been approved. All these disadvantages were considered when we developed the algorithm, with the understanding that there is a possible overlap in patients. Last, based on the problem already mentioned, we have considered not only the recommendations mentioned above but also drug access and availability in each country.

In summary, the questions analysed and presented in this document allowed our ALAT Asthma department group to make recommendations on the treatment of severe asthma adapted to real-life situations in Latin America. We expect that these recommendations will help professionals improve their knowledge and will assist in decision-making by helping the health system manage resources more accurately and conveniently. It will be important for our colleagues in the region to individualize the treatment approach for each patient, and for each variable that makes the management of this disease so complex, with even more complex clinical settings and resources.

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Table 1.- Evidence Grading System, SIGN 50

LEVELS OF EVIDENCE

1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+ Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 - Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++ High-quality systematic reviews of case-control or cohort studies
2 High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+ Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 - Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3 Non-analytical studies, e.g., case reports, case series
4 Expert opinion

GRADES OF RECOMMENDATION

A At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population; or
A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating the overall consistency of the results
B A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results; *or* extrapolated evidence from studies rated as 1++ or 1+
C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or*
Extrapolated evidence from studies rated as 2++
D Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2+

Modified from Scottish Intercollegiate Guidelines Network (SIGN). A guideline developer's handbook. Edinburgh: SIGN; 2019. (SIGN publication no. 50). [November 2019]. Available from URL: http://www.sign.ac.uk

Table 2.- Recommendation types

Recommendation wording and types

Evidence and judgement agreement	Recommendation
Undesirable consequences clearly outweigh desirable consequences	**Strong recommendation against**
Undesirable consequences probably outweigh desirable consequences	**Conditional recommendation against**
Balance between desirable and undesirable consequences is closely balanced or uncertain	**Recommendation for research and possibly conditional recommendation for use restricted to trials**
Desirable consequences probably outweigh undesirable consequences	**Conditional recommendation for**
Desirable consequences clearly outweigh undesirable consequences	**Strong recommendation for**

Wording of recommendations
"Strong" *recommendations should be made where there is confidence that, for the vast majority of people, the intervention/action will do more good than harm (or more harm than good). The recommendation should be clearly directive and include "****should/should not"*** *in the wording.*

"Conditional" *recommendations should be made where the intervention/action will do more good than harm for most patients. Conditional recommendations should include "**should be considered"** in the wording.*

Modified from Scottish Intercollegiate Guidelines Network (SIGN). A guideline developer's handbook. Edinburgh: SIGN; 2019. (SIGN publication no. 50). [November 2019]. Available from URL: http://www.sign.ac.uk

Table 3.- ALAT Severe Asthma Guidelines. Questions

1. What is the definition of severe asthma?
2. What criteria are used to diagnose uncontrolled asthma?
3. What criteria are used to diagnose difficult-to-treat asthma?
4. What are the risk factors identified and associated with the development of severe asthma?
5. What are the phenotypes of severe asthma?
6. What are the predictive biomarkers for therapy response of patients with severe asthma?
7. What is the indication for the on-demand use of the combined therapy of an ICS and formoterol associated with maintenance treatment with an ICS and an LABA in patients with severe asthma?
8. Is there any additional benefit in adding theophylline in patients with severe asthma?
9. Is there any additional benefit in adding antileukotrienes in patients with severe asthma?
10. Is there any additional benefit when adding a long-acting anticholinergic drug (tiotropium) to ICS and LABA treatment in patients with severe asthma?
11. What is the efficacy and safety of anti-IgE monoclonal antibodies in the treatment of severe asthma in children and adults?
12. What is the efficacy and safety of anti-IL-5 monoclonal antibodies in the treatment of severe asthma in children and adults?
13. What is the efficacy and safety of anti-IL-5 receptor monoclonal antibodies in the treatment of severe asthma in children and adults?
14. What is the efficacy and safety of methotrexate in the treatment of severe asthma in children and adults?
15. What is the efficacy and safety of anti-IL-4 and IL-13 monoclonal antibodies in the treatment of severe asthma in children and adults?
16. What is the efficacy and safety of macrolides in the treatment of severe asthma in children and adults?

17. What is the efficacy and safety of bronchial thermoplasty in the treatment of severe asthma in children and adults?

Table 4.- Delphi panel results.

Statistics of the modified Delphi panel.

Question Number	Round 1		Round 2		Round 3	
	Mean	Agreement %	Mean	Agreement %	Mean	Agreement %
ON - 1 FN - 1	7.0	67	7.4	89	8.5	100
ON - 2 FN - 2	7.0	67	7.2	78		
ON - 3 FN - E	6.2	56	6.4	72	E	E
ON - 4 FN - 3	7.4	83				
ON - 5 FN - 4	6.6	78	7.6	83		
ON - 6 FN - 5	7.5	83				
ON - 7 FN - 6	7.5	78				
ON - 8 FN - 7	8.3	89				
ON - 9 FN - 8	7.4	83				

ON - 10 FN - 9	6.1	56	7.6	94	8.3	100
ON - 11 FN - 10	7.3	78				
ON - 12 FN - 11	7.9	89				
ON - 13 FN - 12	8.1	89				
ON - 14 FN - 13	8.7	100				
ON - 15 FN - 14	7.4	78				
ON - 16 FN - 15	7.0	67	7.6	89		
ON - 17 FN - 16	7.3	78				

ON: original number of the question, FN: final number of the question, E: eliminated question as agreed upon by the GDG. The mean and agreement percentage of the modified Delphi panel were calculated. Questions 1 and 10 underwent major changes after the 2nd round; therefore, the GDG decided to conduct a 3rd round on both questions.

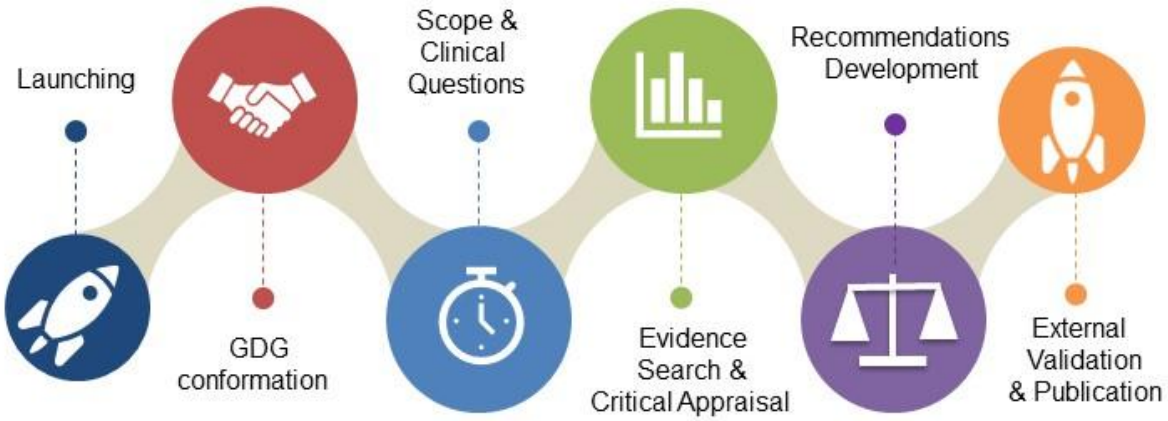
Table 5.- Recommendation summaries and the level of evidence.

#	Recommendations	Level of Evidence	Grade of Recommendation	Judgement
6	There is not enough good-quality evidence to support the on-demand use of an ICS plus formoterol in patients with severe asthma.	1+	B	Conditional
9	Tiotropium (LAMA) should be considered as a third controller added to ICS plus LABA treatment in children older than 6 years and adults.	1-	B	Conditional
10	We recommend the use of omalizumab in adult patients and children with severe uncontrolled allergic asthma (cut-off values greater than 30 IU).	1+ (Adults) 1- (Children)	A A	Strong Strong
11	We recommend the use of monoclonal anti-IL-5 antibodies in patients with severe uncontrolled eosinophilic asthma (cut-off values greater than 150 cells/µL for mepolizumab and greater than 400 cells/µL for reslizumab). There is no evidence to recommend the use of monoclonal anti-IL-5 antibodies in	1+ (Adults) 1- (Children)	A B	Strong Conditional recommendation for use restricted to trials

	children.			
12	We recommend the use of benralizumab in patients with severe uncontrolled eosinophilic asthma (cut-off values greater than 300 cells/µL). There is no evidence to recommend the use of monoclonal anti-IL-5 antibodies in children.	1+ (Adults) 1- (Children)	A	Strong Conditional recommendation for use restricted to trials
14	We recommend the use of dupilumab in adult patients with severe allergic and eosinophilic uncontrolled asthma and in adult patients with severe corticosteroid-dependent asthma. Lebrikizumab and tralokinumab have not been able to demonstrate consistent efficacy in the most important outcomes in patients with severe asthma; therefore, we do not suggest their use.	1+ (Adults) 1+ (Adults)	A A	Strong Strong recommendation against

Recommendations synthesis and judgement.

Figure 1.- Overall development process of the CPG



Modified from Mayorga J, Velasco L, Ochoa F. Guías de Práctica Clínica Basadas en Evidencia, cerrando la brecha entre el conocimiento científico y la toma de decisiones clínicas. Documento de la serie MBE, 3 de 3. Gac Mex Oncol. 2015;6(6):329–34.

Figure 2. Not Controlled Severe Asthma. Treatment algorithm