Factors Affecting the Success of Step-up Therapy in Patients with Moderate-Severe Asthma: a Real-Life Study

Short Title: Step-up Therapy in Asthma

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Abstract

Introduction: Clinical practice guidelines recommend regularadjustment of treatment to achieve control of asthma. A step-up approach based on the degree of disease control should be followed.

Objective: To perform a real-lifeanalysis of the factors that affect the success or failure of this therapeutic strategy and of the criteria applied by clinicians when applying a step-up approach in a representative sample of patients diagnosed with moderate-severe asthma.

Material and Methods: We performed a multicenter retrospective cohort study involving 226 Spanish specialist physicians (98 allergologists, 127 pulmonologists, and 1 family physician).We included 1254 patients (787 women) diagnosed with moderate-severe asthma who underwent step-up therapy during 2016.

Results: Step-up was successful in 44% of cases. The factors associated with success were presence of < 2 comorbid conditions, lower grade of severity and therapy step before modification, absence of exacerbations during the previous year, fewer daytime/nighttime symptoms, and limitation in activities,as well as type of inhaled corticosteroid (ICS)/long-acting β_2-agonist(LABA) combination after modification, lower body mass index, and higher fractional exhaled nitric oxide. An early increase in the maintenance dose once a lack of control was detected (≤ 3 months, >3 to≤6months, > 6 to ≤ 12 months) was more likely to be successful.

Conclusion: The factors that determine whether or not this therapeutic strategy manages to control asthma are time since onset of clinical impairment, previous grade of severity, number of comorbid conditions, previous exacerbations, and frequency of symptoms.

Key words: Asthma. Treatment. Step up. Real-life.

Resumen

Introducción: Las guías de práctica clínica recomiendan el ajuste del tratamiento hasta alcanzar el control del asma, siguiendo un escalado progresivo basado en el grado de control de la enfermedad.

Objetivo: Realizar un análisis en vida real de los criterios que utilizan los clínicos para realizar el escalado terapéutico y de los factores que condicionan el éxito o el fracaso de esta estrategia terapéutica en una muestra representativa de pacientes diagnosticados de asma persistente moderada y grave.

Material y métodos: Estudio multicéntrico retrospectivo de cohorte en el que participaron 226 médicos especialistasespañoles (98 alergólogos, 127 neumólogos y un médico de atención primaria). Incluimos 1254 pacientes (787 mujeres) diagnosticados de asma persistente moderada o grave en los que se realizó un escalado de tratamiento durante 2016.

Resultados: El escalado terapéutico fue exitoso en el 44% de los casos. Los factores asociados con el éxito fueron la presencia de <2 comorbilidades, menor grado de gravedad y del escalón terapéutico de la terapia antes de la modificación, ausencia de exacerbaciones durante el año anterior, menos síntomas diurnos/nocturnos y limitación en las actividadesordinarias, así como el tipo de corticosteroide inhalado (ICS) / combinación de β_2-agonista de acción prolongada (LABA) después de la modificación, índice de masa corporal inferior y fracción del óxido nítrico exhalado superior. Un aumento temprano en la dosis de mantenimiento una vez que se detectó una falta de control (≤ 3 meses,> 3 a ≤ 6 meses,> 6 a ≤ 12 meses) también se asoció a un aumento de probabilidad de éxito.

Conclusión: Los factores que determinan si el escalado terapéutico logra controlar el asma son el tiempo transcurrido desde el inicio del deterioro clínico, el grado previo de gravedad, el número de afecciones comórbidas, las exacerbaciones previas y la frecuencia de síntomas.

Palabras clave: Asma. Tratamiento. Escalado. Vida real.

Introduction

The main objectives of asthma treatment are to achieve and maintain disease control,prevent exacerbations, prevent chronic airway obstruction, and reduce mortality to the lowest levels possible [1,2].

In order to achieve control of asthma, clinical practice guidelines recommend regularadjustment of treatment comprising a step-up approach based on the degree of disease control after rechecking on diagnosis, adherence and technique [1,2].If asthma is not well controlled, treatment should be stepped up until control is achieved, with continuous evaluation of nonpharmacological measures, adherence, and modifiable aggravating and risk factors.Despite those recommendations, step-up is carried out in real-life practice without the necessary control of technique/adherence very often. The first recommendation for therapy is a short-acting β_2-agonist (as needed) in intermittent asthma, with the addition of a low-dose inhaled corticosteroid (ICS)in persistent asthma and increased dose of ICS combined with a long-acting β_2-agonist (LABA) in moderate and severe asthma. Controller medication (antileukotriene drugs, long-acting muscarinic antagonists, or biologics) can be added until the disease is controlled. GINA 2019 now recommends that all adults and adolescents with asthma receive symptom-controlled (mild asthma) or regular treatment that contains ICS to reduce the risk of serious exacerbations [1].

However, in daily clinical practice, disease remains uncontrolled in more than half of patients managed using this strategy [3]. Many factors are involved in the failure ofanti-asthmatreatment in a specific patient, despite the availability of potent and effective therapeutic tools. One factor that could contribute to failure is the absence of clearly specified, relevant clinical data in consensus guidelines to help clinicians with their decision to increase the dose of medication.

Several recommendations have been made to ensure that step-up therapy is effective [4-6],yet very few studies have examined the real-life criteria applied by physicians when deciding on a progressive dose increase in patients with uncontrolled asthma. Similarly, few data are available on the clinical factors that can affect the success of this approach. When and how to implement a sustained increase in the dose of maintenance medication and the aspects affecting its success or failure remain to be elucidated.

We designed a study to analyze the real-life factors that affect the success or failure of step-up therapy and the criteria applied by clinicians when adopting this approach in a representative sample of patients diagnosed with moderate-severe asthma.

Material and Methods

We performed a multicenter, retrospective, cohort studybased on data from 226 participating researchers in Spain. The researchers were all specialist physicians(98 allergologists, 127 pulmonologists, and 1 family physician). Each researcher included 5-10 consecutive patients who had attended their clinic during 2017 and had been diagnosed with persistent moderate-severe asthma under treatment with fixed combinations of ICS/LABA.

Therapy had been stepped up at least once during 2016.The face-to-face inclusion interview was held between January and March 2017. We retrospectively analyzed modifications to therapy during the previous year, the factors that led to the decision taken, and outcomes measured according to the degree of control of asthma(Figure 1). The complementary tests were performed according to the usual clinics practice. Prior to step-up, relevant factors associated with poor asthma control were valuated and acted on: therapeutic adherence, comorbidities, allergen and irritants exposure.

As this study was a retrospective real-life study, the asthma was managed following the investigator´s criteria and it reflects the clinical practice. However, the investigators were respiratory specialists and the Spanish Asthma management guidelines (GEMA), are extensively followed. Switching ICS/LABA combinations was allowed at the study. In severe asthma patients we have considered step up the change from step 5 to 6 of the GEMA.

The patients included signed the informed consent document before the interview and collection of their data for the study. A clinical history focusing on asthma was taken for all patients. This covered time since diagnosis, severity, control, associated comorbidities, and treatment administered.

Statistical analysis

Quantitative variables were expressed as measures of central tendency and dispersion (mean, standard deviation [SD], minimum, and maximum). Qualitative variables were reported as absolute and relative frequencies.

When inferential analysis proved necessary, parametric tests were used to evaluate continuous variables and nonparametric tests to evaluate ordinal, categorical, or nonparametric variables. All hypothesis tests were 2-sided, with significance set at 0.05. Nonnormally distributed variables were assessed using the Mann-Whitney test (unpaired data) or Wilcoxon test (paired data). The χ^2 test (or Fisher exact test where applicable) was used for the contingency table analysis and for the comparison of proportions and/or frequency distributions.

Logistic regression analysis was performed to determine predictors of success or failure of intensifying treatment based on patient outcome. Some variables were categorized for the statistical analysis, as follows: body mass index (< 25, 25-30, and>30), number of comorbid conditions (< 2 or≥ 2), time since diagnosis (≤or>10 years), duration of clinical impairment before therapy was modified(≤ 3 months, >3 to ≥ 6 months, >6 months), presence/absence of daytime symptoms (≤ 2 or> 2 times per week),forced expiratory volume in the first second (FEV_1, %)in baseline spirometry (< 60, 60-80, > 80), and eosinophil count (< 300 or≥ 300/mm^3).

The data were analyzed using SPSS v18.0 (SPSS IBC, USA) or a subsequent version.

Step-up was considered successful if the patient fulfilled all of the following conditions at the face-to-face (inclusion) visit: no need for an additional dose increase after the first change, no asthma exacerbations, no treatment-induced adverse effects, and controlled disease, defined as an ACT score≥ 20.Step-up therapy was consideredto have failed if the

patient did not fulfill all of the conditions for therapy to be considered successful. Exacerbations were identified retrospectively from systemic corticosteroid use or an increase from a stable maintenance dose, for at least 3 days and/or hospitalizations or unscheduled doctor visits requiring systemic corticosteroids [7].

Results

The study population included 1254 patients, of whom 787 (63%) were women. The mean (SD) age was 49.6 (16.6) years, with a mean (SD) age at diagnosis of asthma of 37 (18.6)years. Most patients were nonsmokers(89%). As for asthma diagnosis, 62% had allergic asthma, 75% had moderate-persistent asthma, and 25% had severe-persistent asthma.At the inclusion visit, disease was controlled (ACT ≥ 20) in 57% of patients, in 61% of moderate and in 44% of severe ones. Disease was uncontrolled (ACT < 20) in 43% of patients, in 39% of moderate and in 56% of severe ones.The mean (±SD) time patients were followed was 7.5 ±3.8 months. Step-up was successful in 44% of cases.

The allergologist/pulmonologist's reasons for stepping up therapy were essentially clinical: daytime symptomsmore than twice per week (35% of cases), limitations in activities (19%), exacerbations (12%), and nighttime symptoms/awakening (10.5%). More complex parameters such as the ACT were evaluated in all patients but only used in 4.6% of cases for step-up. Lung function were evaluated in 2165 patients (99,9 %) and its changes led to step-up only in 9% of cases. Fractional exhaled nitric oxide (FeNO) levels were evaluated in 549 patients (25,3 %) and was the main reason for changing therapy in 0.5% of cases. (Table 1).

The most frequent change was to increase the dose of ICS in the ICS+LABA combination, until reaching a high dose. In patients in whom a new drug was added to maintenance treatment, LAMA was the most frequently added drug (Table 2).

Comorbid conditions associated with asthma were recorded in 49% of patients, and 32% of patients had at least 2 conditions associated with the disease. The most frequent concomitant diseases were rhinoconjunctivitis (64.5%), nasal polyposis (18%), gastroesophageal reflux disease (16%), depression-anxiety (13.6%), and sleep apnea-hypopnea syndrome (8%).

The factors associated with the success of step-up therapy were as follows: presence of < 2 comorbid conditions, lower grade of severity and lower therapeutic step before modification, absence of exacerbations during the previous year, fewer daytime/nighttime symptoms, and limitation of activities, as well as the type of ICS/LABA combination after modification, younger age, lower body mass index, and higher FeNO value. Male sex was also associated with the success of step-up therapy. Similarly, duration of uncontrolled disease also proved to be decisive with respect to the success or failure of step-up therapy: the sooner therapy was stepped up, the more likely it was to be successful(Table 3).

The factors that were not shown to be associated with the success or failure of step-up were blood eosinophil counts, result of the bronchodilation test, FEV_1 values in baseline spirometry, smoking, and type of asthma (allergic or nonallergic)(Table3).

A logistic regression analysis was performed with success/failure of step-up as the dependent variable and variables with a p value< 0.20 in the bivariate analysis in table3 as independent variables.

Figure 2 shows the odds ratio and its corresponding 95% confidence intervals. The factors favoring failure of step-up were female sex, ≥ 2 comorbid conditions associated with asthma, severe vs moderate asthma, previous exacerbations, and daytime/nighttime symptoms. Furthermore, the type of ICS/LABA used after the change was a predictive factor, since one of the factors of success was using the combination fluticasone propionate/formoterol compared with fluticasone propionate/salmeterol. There were no statistically significant differences between the remaining combinations and fluticasone propionate/salmeterol.

When patients are divided into moderate and severe asthma, the multivariate analysis indicates that the factors that significantly favour the failure were (odds ratio, 95% CI): ≥ 2 comorbidities (-0.605, 0.450-0.813); daytime symptoms (-0.394, 0.279-0.557) in moderate patients and daytime symptoms (-0.476, 0.260-0.870); BDP/FORM vs FP/SAL (0.292, 0.116-0.735) in severe patients.

Discussion

The recommended therapeutic strategy in asthma consensus guidelines [1,2]is to increase the dose of ICS in patients diagnosed with uncontrolled persistent asthma. This recommendation has become standard clinical office practice in patients with uncontrolled disease receiving low-to-medium doses of ICS/LABA (step-up). However, this basic structure is very general in nature and offers a uniform response to all patients with uncontrolled asthma, who generally vary considerably in terms of etiology, outcome, and prognosis. Nevertheless, few studies analyze the conditions that predict its success or failure in a specific patient [8].

Several studies have shown underestimation of the severity of asthma by clinicians, especially in patients with severe persistent asthma, so the use of objective measures for the assessment of these patients should be advised [9, 10]. However, according to the results, the decision is based on essentially clinical criteria, especially the presence of daytime asthma symptoms, as is the case in similar conditions such as chronic obstructive pulmonary disease [11]. However, although simple parameters could be used to identify asthmatic patient control [12], there is evidence that the use of more complex parameters such as the ACT scorecould increase the possibility of dose intensification being successful [10].

One of the factors that facilitates the success of step-up is ensuring that it is performed during the first months of clinical impairment: the chances of success increase, the earlier the intervention is applied. However, the time criterion is not mentioned in consensus guidelines [1,2], even though this may be a fundamental aspect of current treatment and of future risk in patients with uncontrolled asthma, especially those with moderate and severe disease: longer periods of poor control (and onset of exacerbations) increase the likelihood of a permanent, less reversible structural alteration that reduces the efficacy of intensifying any subsequent

maintenance treatment. Furthermore, systemic absorption of high doses of ICS is diminished in patients with intense inflammation of the airway [13], which could affect the response to therapy. Therefore, it is necessary to establish the window of opportunity that optimizes step-up therapy, which, according to the data obtained, should not be more than 3 months in a patient with clinical impairment, especially in cases of moderate and severe asthma.

Male sex was also associated with the success of step-up in our study, although this may be affected by the presence in the sample of a significantly greater percentage of severe asthma in women (29%) than in men (19.5%), given that lower severity of asthma increased the likelihood of successfulstep-up therapy.

High FeNO levels also favor the success of step-up therapy, probably because of the efficacy of increasing the ICS dose in asthma patients with an allergic or eosinophilic phenotype, in whom levels of this marker are generally elevated.

The type of combination recommended to the patient also enhances the success of step-up therapy: the combination of fluticasone/formoterol proved to be more effective for achieving a positive response to step-up. This finding could be associated with the fact that the marketed combination of fluticasone/formoterol at high doses makes it possible to double the dose both of the ICS and of the LABA, in contrast with other combinations, which only double the dose of the ICS, thus leading to an enhanced bronchodilation effect that would account for the improved outcome. In any case, patients receiving different combinations of therapy may not be homogeneous with respect to severity of asthma and other clinical characteristics, thus hampering comparison.

The main strengths of the present study are that it is a real-life investigation in a large number of patients managed according to the recommendations of clinical practice guidelines. It also evaluates efficacy and the conditions that facilitate efficacy.

Our study is subject to a series of limitations. It is a retrospective cohort study in which we analyzed a group of asthma patients without classifying them into endotypes, although it does try to evaluate the recommendations put forward in guidelines according to severity, irrespective of the patient's endotype. Also, the asthma was managed following the clinical practice and adherence was not registered in the case report form, although it was always valued before the step-up: asked by the specialists at their visits and/or using TAI questionnaire [14].

In summary, our study identified clinical tools that could be used to predict the outcome of step-up therapy. Previous studies only compared the enhanced performance of step-up therapy based on the ACT score in patients diagnosed with mild asthma [8]. Our approach facilitates the use of standard tools, which are generally easy to apply in clinical practice and improve the care of patients with uncontrolled severe/moderate asthma. In addition, aswe evaluate variables used in the daily clinical care of these patients, there are no increases in time or costs.

Conclusions

In daily practice, step-uptherapy is based essentially on clinical criteria.The factors that determine whether or not this therapeutic strategy manages to control asthma are time since onset of clinical impairment, previous grade of severity, number of comorbidities, previous exacerbations, and frequency of symptoms.

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Table 1. Main clinical reasons for performing step-up

Reason	No.	%
Daytime symptoms >2/week	437	34.9
Limitations in daily activities	243	19.4
Exacerbations	146	11.7
Nighttime symptoms/awakenings	131	10.5
Pulmonary function	111	8.9
Rescue therapy needed >2 times/week	92	7.3
Asthma control test	57	4.6
Other	15	1.2
Bronchodilator reversibility testing	14	1.1
FeNO	6	0.5
Total	1,252	100

Data were unavailable for 2 patients. FeNO, fractional exhaled nitric oxide.

Table 2: Summary of the main treatment changes after step-up

	Pre-changetreatment		Post-changetreatment	
	n	%*	n	%*
Higdose ICS+LABA	318	25.4	732	58.4
SABA	734	58.5	572	45.6
LTRA	125	10.0	192	15.3
LAMA	115	9.2	259	20.7
SAMA	39	3.1	36	2.9
OCS	18	1.4	34	2.7
Biologicaldrugs	15	1.2	36	2.9
LAMA/LABA	1	.1	2	.2
Theophylline	1	.1	1	.1

* Percentages calculated on the total number of patients analyzed (N=1254).

ICS: inhaled corticosteroids; LABA: long-acting beta2-agonist; SABA: short-acting beta2-agonist; LAMA: long-acting muscarinic antagonist; SAMA: short-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroids

Table 3. Factors associated with successful step-up

Factor	p Value
Male sex	<0.001
Lower age*	0.011
Lower BMI (<25, 25-30, >30)	0.007
<2 respiratory comorbidities	<0.001
Lower severity (moderate, severe)	<0.001
Less time since diagnosis (≤ or >10 y)	0.012
Lower prechange treatment step (step 3 to 6)	0.001
Lower post-change treatment step (step 3 to 6)	<0.001
Less time with clinical worsening before the change (≤3m, >3 to ≤6m, >6 to ≤12m)	0.039
Absence of exacerbations	<0.001
Absence of daytime symptoms (<2 times/week)	<0.001
Absence of nighttime symptoms	<0.001
Absence of limitations in daily activities	0.001
Well-controlled asthma according to ACT or ACQ	<0.001
Higher FeNO*	0.006
Post-change ICS/LABA combination	<0.001
Smoking	0.647
Allergic asthma	0.069
Age at diagnosis (≤ or >40 y)	0.387
FEV$_1$% predicted (<60, 60-<80, ≥80)	0.691
Rescue needed (≤ or >2 times/week)	0.508
Bronchodilator reversibility testing (+ or – result)	0.125
Eosinophilia (≤ or > 300 cells/µL)	0.659

The p value is calculated based on the number of patients with available data for each factor.
*Factor studied as a continuous variable. BMI, body mass index; ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; FeNO, fractional exhaled nitric oxide; FEV$_1$, forced expiratory volume in the first second.
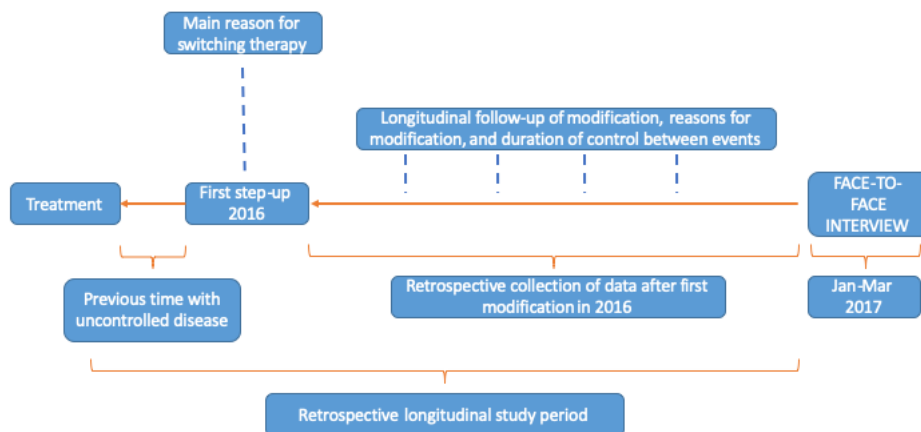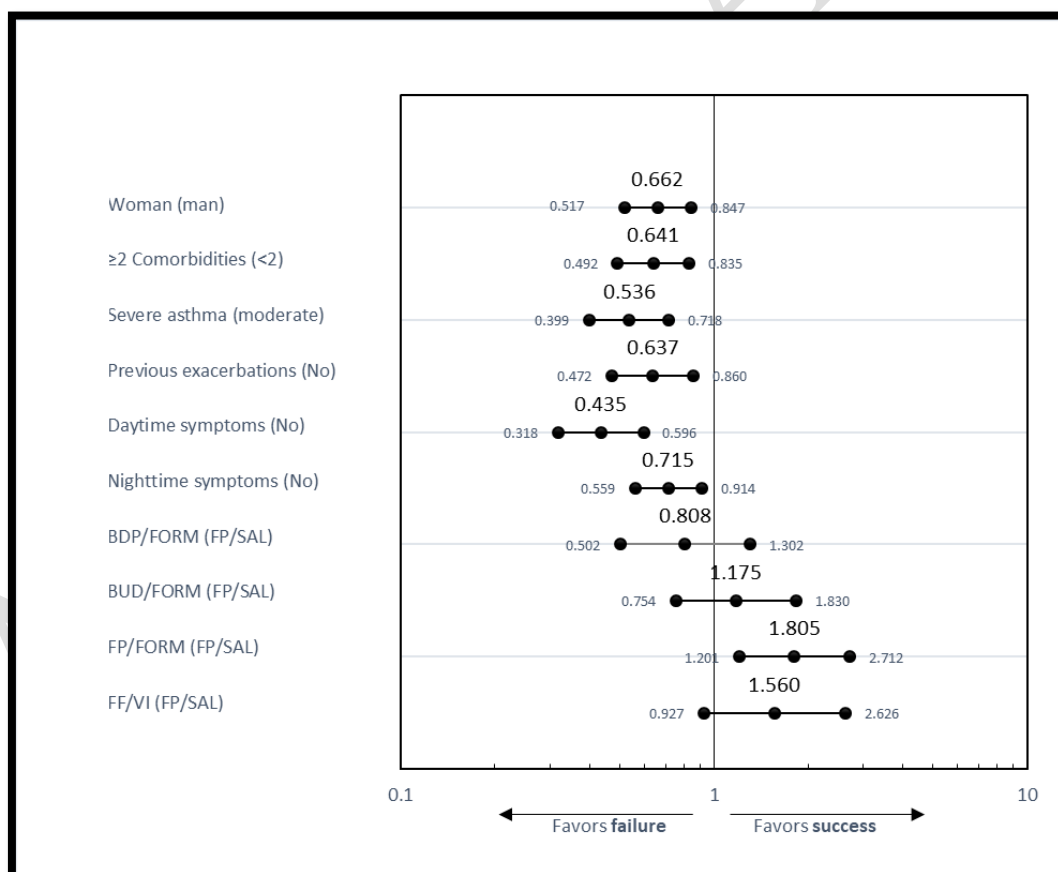
Figure 1. Studydesign

Figure 2. Odds ratio of statistically significant factors for step-up

Odds ratio with 95% confidence interval. The reference categories are shown in parenthesis. N = 1240 patients. The combinations of ICS/LABA are those prescribed after step-up. BDP, beclomethasone; FORM, formoterol; FP, fluticasone propionate; SAL, salmeterol; BUD, budesonide; FF, fluticasone furoate; VI, vilanterol