ORIGINAL ARTICLES

Management According to the Global Initiative for Asthma Guidelines of Patients With Near-Fatal Asthma Reduces Morbidity and Mortality

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OBJECTIVE: To assess the effect of adequate outpatient care as defined by guidelines of the Global Initiative for Asthma (GINA) on the long-term outcome of near-fatal asthma.

PATIENTS AND METHODS: Fifty-three patients who had experienced a near-fatal attack of asthma were treated according to the GINA guidelines and followed for a mean of 49 months (intervention group). Clinical and spirometric measurements corresponding to the periods before the attack (obtained retrospectively) and after the attack (obtained prospectively) were compared to measurements from 40 near-fatal asthma patients who had not been managed according to the GINA guidelines and who were followed for a mean of 51 months (historic control group).

RESULTS: There were no deaths in the intervention group and 6 deaths (15%) in the control group (P=.005). The mean (SD) number of new near-fatal asthma attacks was significantly lower in the intervention group (0.17 [0.61]) than in the control group (1.6 [1]) (P<.001). Emergency visits following a near-fatal asthma attack decreased from 0.9 (1.8) to 0.3 (0.6) in the intervention group and hospital admissions decreased from 3.4 (5.1) to 0.5 (1.4) (P<.001). Eosinophil count decreased from 390 (411) × l0^9 cells/L to 159 (121) × l0^9 cells/L (P=.01) and forced expiratory volume in 1 second increased from 68% (23%) of predicted to 76% (20%) (P=.006).

CONCLUSIONS: Management according to the GINA guidelines of patients who had experienced a near-fatal asthma attack was associated with a decrease in asthma morbidity and mortality

Key words: Near-fatal asthma. Education and asthma. Asthma guidelines. Global Initiative for Asthma.

El tratamiento según la guía de la Global Initiative for Asthma (GINA) reduce la morbimortalidad de los pacientes con asma de riesgo vital

OBJETIVO: Valorar el efecto de un adecuado tratamiento ambulatorio, de acuerdo con las recomendaciones de la guía de la Global Initiative for Asthma (GINA), en la evolución a largo plazo del asma de riesgo vital (ARV).

PACIENTES Y MÉTODOS: Durante una media de 49 meses se realizó el seguimiento de 53 pacientes que habían sobrevivido a una crisis de ARV y que se trataron de acuerdo con las recomendaciones de la GINA (grupo de intervención). Se obtuvieron datos clínicos y espirométricos retrospectivos y prospectivos (antes y después del ataque de ARV, respectivamente) y se compararon con los de 40 pacientes con ARV que no fueron tratados según las recomendaciones de la GINA (grupo control histórico) y cuyo seguimiento medio fue de 51 meses.

RESULTADOS: No se registraron fallecimientos en el grupo de intervención, mientras que en el grupo control murieron 6 pacientes (15%) (p = 0,005). Los nuevos ataques de ARV fueron significativamente menores (p < 0,001) en el grupo de intervención, con una media ± desviación estándar de 0,17 ± 0,61, frente a 1,6 ± 1 en el grupo control. En el grupo de intervención las visitas a urgencias descendieron de 0,9 ± 1,8 a 0,3 ± 0,6 después de la crisis de ARV (p = 0,03), y los ingresos hospitalarios pasaron de 3,4 ± 5,1 a 0,5 ± 1,4 (p < 0,001); el recuento de eosinófilos en sangre periférica descendió de 390 ± 411 a 159 ± 121 células × 10^9/l (p = 0,01) y el volumen espiratorio forzado en el primer segundo aumentó del 68 ± 23% al 76 ± 20% (p = 0,006).

CONCLUSIONES: En los pacientes que han presentado una crisis de ARV el tratamiento siguiendo las recomendaciones de la GINA se asocia a un descenso de la morbilidad y la mortalidad del asma.

Palabras clave: Asma de riesgo vital. Educación y asma. Guías del asma. Global Initiative for Asthma.

Introduction

Numerous studies conducted in recent years have evaluated the clinical features of near-fatal asthma and the risk factors associated with this condition.[1-6] Surprisingly,

however, little attention has been paid to the clinical outcome of patients following a near-fatal asthma attack. In one study that followed 145 patients treated with mechanical ventilation for 6 years after a near-fatal attack, Marquette et al[7] found that 60% of the patients were readmitted to hospital at least once and that 22% died due to a new attack. This seemingly unfavorable prognosis could be explained by 2 factors: *a)* the nature of the disease (ie, the patients might have had a particularly severe form of asthma, with very poor prognosis and a predisposition to new near-fatal episodes), and *b)* the possible influence of several factors related to inadequate management and/or poor adherence to treatment. Several features that have been described in patients with near-fatal asthma would corroborate the first hypothesis; these include highly variable lung function,[8,9] an excessive use of bronchodilators between attacks, a worsening of symptoms in the 12 months prior to an attack,[6,10] frequent hospital admissions, and a history of asthma episodes requiring intensive care and mechanical ventilation.[11,12] Supporting the second hypothesis, several studies have reported that both inadequate treatment and poor adherence to treatment are associated with deteriorated lung function and are serious risk factors for severe asthma exacerbations.[13-17] One recent study suggested that the reduced incidence of near-fatal asthma attacks in Spain was probably related to an improvement in the overall management of the disease.[18] In one small group of patients with near-fatal asthma, for example, Molfino et al[19] found that appropriate treatment with inhaled corticosteroids and adherence to previous treatment prevented new near-fatal crises.

Generally speaking, good clinical practice guidelines regarding the management of asthma, such as those issued by the Global Initiative for Asthma (GINA),[20] are mostly based on expert opinions or on findings of studies which were not specifically designed to evaluate the effectiveness of such guidelines. The effectiveness of the GINA guidelines in preventing near-fatal asthma attacks, for example, has yet to be proven.

Given the little information available, it could be hypothesized that the poor prognosis associated with near-fatal asthma might be related to poor management strategies, and if this were true, new life-threatening episodes could be prevented by implementing adequate treatment plans. The aim of this study was therefore to determine whether the management according to the GINA guidelines of patients who had experienced a near-fatal asthma attack was associated with an improved clinical outcome.

Patients and Methods

Study Design

In this intervention study, we evaluated the clinical features of patients who had survived a near-fatal asthma attack before and after participating in an asthma treatment program based on the GINA guidelines published in 1995.[20] The results for this intervention group were compared to those of a historic control group involving 40 patients with near-fatal asthma who did not participate in a specific treatment program.

Methods

We included patients referred to the specialized asthma clinic in 2 tertiary care hospitals in Barcelona, Spain, after experiencing a near-fatal asthma attack. Asthma was defined as a clinical history consistent with the disease and one or both of the following: *a)* an increase of over 12% in forced expiratory volume in 1 second (FEV_1) measured by spirometry following inhalation of salbutamol, and *b)* a 20% decrease in baseline FEV_1 triggered by 8 mg/mL or less of methacholine.[21-23] A near-fatal asthma attack was defined as a serious asthma exacerbation in association with respiratory failure in which the patient required mechanical ventilation or in which $PaCO_2$ was greater than 50 mm Hg and/or pH was less than 7.30. Patients for whom there were doubts regarding the diagnosis of a near-fatal asthma attack were excluded from the study, as were patients unable to read or write. The study protocol was approved by the ethics committee at each of the participating hospitals and written informed consent was obtained from all patients.

The patients in the intervention group were treated and followed in accordance with the GINA guidelines[20] and monitored exclusively by 2 respiratory medicine specialists (1 in each participating center). All the patients were provided with general information about asthma and its treatment, shown how to use inhalers and peak flow meters correctly, and asked to log their peak flow measurements. They were also taught how to vary their treatment in accordance with changing symptoms and peak flow measurements. To help them in this task, a set of cards containing a description of different therapeutic strategies were used. Inhalation treatment was prescribed in accordance with clinical severity, as recommended in the GINA guidelines.[20] Inhalation agents consisted mainly of inhaled corticosteroids (budesonide, beclomethasone, and fluticasone) and long-acting inhaled selective β_2 adrenergic agonists (salmeterol and fluticasone). Follow-up visits were held every 3 months or when necessary in the case of asthma exacerbations or deterioration. The mean follow-up time after a near-fatal asthma attack was 49 months (range, 4-84 months).

The following data were recorded for all patients before and after the near-fatal asthma attack that led to their inclusion in the study: *a)* clinical variables, including asthma severity and treatment, and adherence to treatment according to the patient's physician; *b)* laboratory results, including eosinophil count (calculated using an automatic cell counter); lung function parameters (forced spirometry measurements before and after inhalation of salbutamol[22] [Datos-pir-500; Sibelmed, Barcelona, Spain]) and allergy test results (standard respiratory skin allergen tests[24]); *c)* asthma morbidity, including number of near-fatal attacks, hospital admissions, and visits to emergency departments due to asthma; and *d)* outcome of new near-fatal attacks.

Because ethical restraints prevented us from using a prospective control group, we collected data for 40 patients who had experienced a near-fatal asthma attack and were admitted to another tertiary care hospital (Complejo Hospitalario Universitario Juan Canalejo, A Coruña, Spain). The patients fulfilled the same inclusion criteria as those in the intervention group, and the mean follow-up time was 51 months (range, 12-90 months). The patients were monitored by different physicians in accordance with standard clinical practice and did not follow any specific control programs.

Statistical Analysis

Results are expressed as means (SD) and percentages. The *t* test for unpaired data was used to compare qualitative data between groups and the χ^2 test to compare quantitative data. Kaplan-Meier curves were also used to analyze dichotomized

TABLE
**Comparison of Demographic, Clinical, and Lung function Variables and Eosinophil Count in Intervention
and Control Groups[a]**

	Intervention Group (n=53)			Control Group (n=40)	
	Before Near-Fatal Attack	After Near-Fatal Attack	P[b]	After Near-Fatal Attack	P[c]
Demographic Characteristics					
Mean age, y		41 (15)		55 (19)	<.001
Men, %		51		35	.1
Asthma characteristics					
Disease duration, y		15 (9)		27 (15)	<.001
Presumed NSAID intolerance, %		28		29	.9
Positive skin test results, %		55		66	.3
Variables analyzed					
Morality, %	–	0	–	15	.003
Moderate to severe asthma[d], %	74	85	.07	85	.1
Regular use of inhaled corticosteroids, %	41	100	<.001	92	.04
Inhaled steroid dose, µg/day	–	1380 (907)	–	1315 (623)	.7
Regular use of oral corticosteroids, %	24	3	.04	17	.02
Near-fatal attack episodes per patient, No.	0.4 (0.8)	0.17 (0.61)	.17	1.6 (1)	<.001
Emergency visits per patient, No.	0.9 (1.8)	0.3 (0.6)	.03	0.7 (0.9)	.038
Hospital admissions per patient, No.	3.4 (5.1)	0.5 (1.4)	<.001	1.46 (2.15)	.01
Eosinophil count (cells $\times 10^9 \times L^{-1}$)	390 (411)	170 (139)	.01	291 (586)	.2
FEV_1, % of predicted	68 (23)	78 (23)	.006	74 (24)	.5
Increase in FEV_1 after salbutamol, %	15.8 (12.2)	12.1 (10.7)	.89	18 (16)	.03
Reported nonadherence to treatment	–	23	–	51	.007
Smokers	–	9	–	14	.01

Abbreviations: FEV_1, forced expiratory volume in 1 second; NSAID, nonsteroidal antiinflammatory drugs.
[a]Data are shown as means (SD) or percentages.
[b]Comparison of variables before and after near-fatal attack in intervention group.
[c]Comparison of variables after near-fatal attack between intervention and control groups.
[d]According to Global Initiative for Asthma classification system.[20]

variables. Statistical significance was set at a value of P less than .05, and data were analyzed using version 6.1.2 of the statistical software package SPSS (SPSS, Inc, Chicago, Illinois, USA).

Results

The Table shows the demographic and clinical characteristics of the patients in the intervention and control groups. Both patient age and disease duration were higher in the control group than in the intervention group.

The Table also shows morbidity, lung function measurements, and eosinophil count before and after the near-fatal attack for the patients in the intervention group and after the attack for those in the control group. No deaths due to asthma occurred in the intervention group and only 5 patients (9%) experienced a new near-fatal asthma attack. (In 3 of the patients the attack was caused by accidental ingestion of nonsteroidal antiinflammatory drugs.) Eleven patients (20%) in this group required readmission to hospital due to asthma. In the control group, in contrast, 6 patients (15%) died as a result of a new asthma attack, 11 (27%) had a new near-fatal attack, and 19 (47%) developed exacerbations that required hospitalization. The number of deaths, new near-fatal attacks, emergency department visits, and hospitalizations due to asthma was significantly lower in the intervention group than in the control group. Because follow-up times varied from patient to patient, we used the Kaplan-Meier method to analyze morbidity and new near-fatal attacks

(Figures 1 and 2, respectively) and found that the differences between the groups remained significant. We also found a significantly higher number of patients on inhaled corticosteroids in the intervention group than in the control group, as well as a smaller increase in FEV_1 following inhalation of salbutamol. Most of the patients in the 2 groups were receiving high doses of inhaled corticosteroids, but there was a smaller percentage of smokers in the intervention group and adherence to treatment was also reported as being better. On comparing data from before and after the treatment program in the intervention group, we found a statistically significant decrease in eosinophil count and the number of emergency visits and hospitalizations due to asthma, and a significant increase in FEV_1 following the near-fatal asthma attack.

After matching the control group to the intervention group by age and lung function (the former being reduced to 29 patients), the differences we had observed remained significant. Specifically, in the control group, 4 patients (14%) died, 9 (31%) had new near-fatal attacks, 10 (34%) visited an emergency department, and 14 (48%) required hospitalization due to asthma. These figures were all significantly lower in the intervention group.

Discussion

The main finding of this study was that the implementation of the GINA guidelines[20] to manage patients who had survived a near-fatal asthma attack was clearly associated with a favorable outcome as it prevented
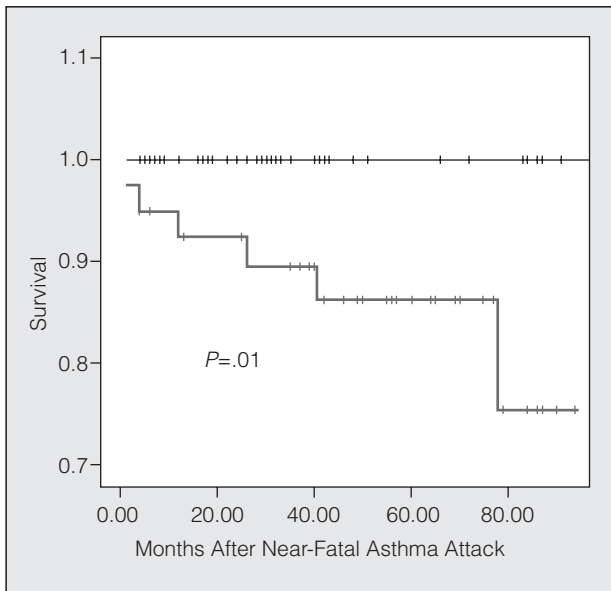
Figure 1. Comparison of mortality in intervention group (blue) and control group (green) using the Kaplan-Meier method.
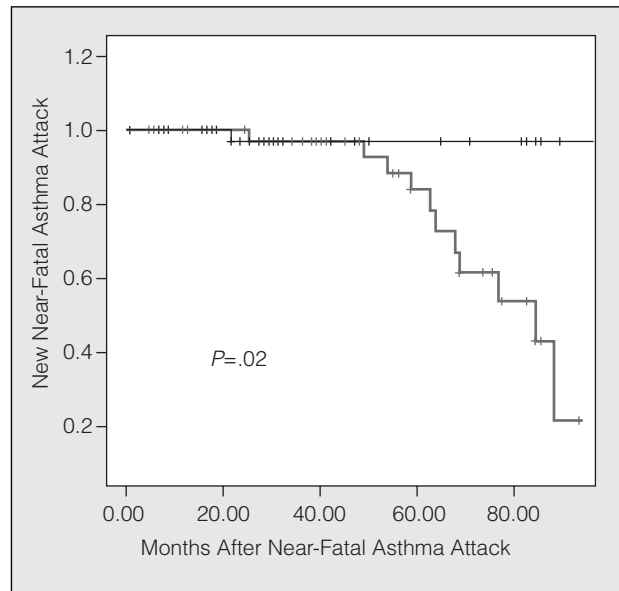

Figure 2. Comparison of new near-fatal asthma attacks in intervention group (blue) and control group (green) using the Kaplan-Meier method.

new life-threatening attacks and reduced asthma-related morbidity and mortality. In recent years, there has been a sharp increase in the number of national[25] and international[20] guidelines and expert consensus documents dealing with the management of asthma. Although some studies report high asthma-related morbidity because physicians do not adhere sufficiently closely to the guidelines,[26-28] few studies have actually evaluated the effectiveness of these guidelines. In particular, the effectiveness of the GINA guidelines in reducing long-term morbidity and mortality in patients who have had a near-fatal asthma attack has never been analyzed.

Our findings for the intervention group contrast with those reported by Marquette et al[7] for a comparable group of 145 patients with near-fatal asthma. In that study, 60% of the patients required readmission to hospital due to a severe exacerbation and 22% died following a new episode of asthma. In our study, only 20% of the patients in the intervention group (managed according to the GINA guidelines[20] and followed for 4 years) required readmission to hospital for asthma, and no deaths were recorded. Although a new near-fatal attack occurred in 5 patients, this was due to the accidental ingestion of nonsteroidal antiinflammatory drugs rather than poor control of symptoms in 3 cases. Our results for the control group, however, are very similar to those reported by Marquette et al,[7] as we recorded high rates of mortality (15%), hospital admissions (47%), and new near-fatal asthma attacks (27%). The differences detected between the patients in our intervention group and those studied by Marquette et al might be due to differences in treatment and follow-up strategies. This would support the hypothesis that the successful overall management of asthma has a favorable impact on the outcome of patients who have experienced near-fatal asthma attacks. The hypothesis is further supported by the findings of a study by Molfino et al,[19] in

which a small group of 12 patients were followed for 18 months after a near-fatal asthma attack. All of the 7 patients who agreed to participate in a close supervision program survived, while 2 of the 5 patients who did not died from an asthma crisis.

The findings of the present study also demonstrate the importance of patient adherence to treatment. Although both groups were receiving high doses of inhaled corticosteroids (approximately 1300 μg/d), low morbidity and mortality was only found in the intervention group, in which most patients appeared to adhere to treatment. Although the method used to report adherence to treatment was not objective, we believe that the higher adherence observed in the intervention group is the result of the educational component of the treatment program and the follow-up visits, which included information and training, written action plans, close supervision and frequent consultations, and self-treatment plans based on peak flow measurements and/or symptoms, in accordance with the GINA guidelines. Strategies of this kind have been seen to lead to a significant reduction in morbidity and mortality and an improvement in adherence to treatment.[29-31] In one case-control study in which 89 deaths due to asthma were identified, Abramson et al[32] found that the use of written action plans to control asthma symptoms was associated with a 70% reduction in the risk of death.

In line with other authors,[13-16,26-28] we detected serious deficiencies in the management of asthma before the near-fatal attack. Although all of our patients were prescribed inhaled corticosteroids after the attack, only 41% were on these drugs prior to the attack. Appropriate treatment with inhaled corticosteroids and adherence to treatment was associated not only with clinical improvement and reduced asthma-related morbidity, but also with improved lung function and a reduction in the number of patients who required continuous treatment with oral corticosteroids.

These findings are consistent with those reported by Suissa et al[33] and Campbell et al,[34] in that those authors found an association between reduced mortality and the use of inhaled corticosteroids in patients with asthma. The significant decrease in eosinophil count—an inflammatory marker in asthma—detected by our study is also of interest. It is well known that markers of airway inflammation found in sputum, bronchoalveolar lavage fluid, and peripheral blood are associated with clinical variables and lung function. Specifically, appropriate management of asthma with inhaled corticosteroids leads to a significant reduction in eosinophil count.[35]

In summary, we found that the management according to the GINA guidelines of a group of patients who had survived a near-fatal asthma attack had a positive impact as it considerably reduced asthma-related morbidity and mortality. Appropriate treatment of asthma, particularly that involving high doses of inhaled corticosteroids, close monitoring of patients, and patient education and self-treatment plans, contributes to improving adherence to treatment and controlling the disease. This is an efficient strategy, not only in patients with asthma in general, but also, and particularly, in patients who have experienced a near-fatal asthma attack.

Acknowledgments

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