Evolution of occupational asthma: Does cessation of exposure really improve prognosis?

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Summary
Aim: To assess the evolution of occupational asthma (OA) depending on whether the patient avoids or continues with exposure to the offending agent.

Methods: Study in patients diagnosed with OA using a specific inhalation challenge. Patients underwent the following examinations on the same day: clinical interview, physical examination, forced spirometry, methacholine test and determination of total IgE. Clinical improvement, deterioration or no change were defined according to the changes seen on the GINA severity scale at the time of diagnosis.

Results: Of the 73 patients finally included, 55 had totally ended exposure and 18 continued to be exposed at work. Clinical improvement was observed in 47% of those who had terminated exposure and in 22% of those who remained exposed; clinical deterioration was observed in 14% and 17% respectively (p = 0.805). Logistical regression analysis, including the type of agent and the persistence or avoidance of exposure among the variables, did not show any predictive factors of clinical evolution. Similarly, the changes in FEV1 and in bronchial hyperresponsiveness were not associated with the avoidance or continuation of exposure to the causative agent.
Introduction

Occupational asthma (OA) is the most frequent work-related respiratory disease in developed countries [1,2] and it is estimated that roughly 10% cases of bronchial asthma and between 15 and 25% of adult onset asthma may be of occupational origin [3,4].

For workers with OA caused by a respiratory sensitizer, complete and definitive removal from exposure to the sensitizing agent has usually been recommended as the most efficient therapeutic approach [5–9]. However, bearing in mind that cessation of exposure is often not feasible [10], in recent years a number of meta-analyses have been carried out to compare the effects of these two management options [11–14]. The results of these systematic reviews indicate that the available data on the prognosis of OA are insufficient to enable physicians to provide confident, informed advice to patients with the disease.

Probably this conclusion is reached because the majority of the more than 100 papers published so far are heterogeneous single-center studies, with small patient samples and based on a single causative agent; all apply an observational approach and, for ethical reasons, none have randomized patients to avoid or continue exposure to the causative agent [15,16].

The aim of the present study is to assess the evolution of all patients diagnosed with OA in the last ten years at two centers in our country according to the persistence or cessation of exposure to the causative agent and, on the basis of the GINA classification, of asthma severity [17]. The study design also allows an assessment of the influence on the prognosis of OA of variables that have not been widely studied to date, such as the medical treatment received and the type of causative agent.

Material and methods

Patients and design

This cross-sectional study was approved by the Ethics Committee of the two participating centers. Using the databases from each center, all patients who had been diagnosed with immunological OA by specific inhalation challenge (SIC) were selected. All patients included had at least one year of follow-up since diagnosis. Between September 2010 and June 2011, patients were scheduled for a visit at the pulmonary function laboratory after having discontinued treatment with inhaled corticosteroids and long-acting beta2 agonists 24 h previously and the use of short-acting beta2 agonists at least six hours previously. All patients provided written informed consent prior to participation.

First, a careful review of clinical histories at the time of diagnosis was carried out. The GINA classification that patients had at the time of diagnosis was made retrospectively with data from the clinical history and was based primarily on the treatment that patients were receiving at this time. Later, patients were interviewed again, placing special emphasis on whether they had avoided exposure with the causative agent, time between diagnosis and avoidance of exposure and, in the case of persistence of exposure, whether they worked with protection or not. They were also asked about any medication they used. With this information, the classification of asthma severity was established in accordance with the new GINA guidelines [17]. Patients also completed the asthma control questionnaire (ACQ) [18]. Spirometry and a methacholine challenge were then performed. Finally, blood analysis was performed, and eosinophil count and total IgE were recorded.

Patients were considered to present clinical improvement or deterioration when a change in the GINA asthma severity classification in either direction was observed. Improvement or deterioration in bronchial hyperresponsiveness and/or the degree of bronchial obstruction was recorded when changes in the PC20 > 2 folds were observed or in FEV1 > 10% with respect to the value at the time of diagnosis.

Atopy and smoking status

Patients were considered atopic if they had at least one positive prick test to any common environmental allergen [19]. Non-smokers were patients who had never smoked and ex-smokers were those who had not smoked for at least six months. The number of pack-years was calculated.

Spirometry and methacholine challenge

Spirometry was performed with a Datospir 200 (Sibel, Barcelona) instrument, following the European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines [20]. The reference values used were those proposed for the Mediterranean population [21]. Bronchial challenge with methacholine was performed with the method described by Chai et al. [22] (Online repository). The methacholine challenge was considered negative if the PC20 FEV1 was higher than 16 mg/ml, in accordance with ATS guidelines [23].

Statistical analysis

Data are tabulated providing median and range of each variable for quantitative variables and absolute frequencies.
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Results

Between 2000 and 2009, 178 patients at the two centers were diagnosed with OA with a positive SIC. One hundred and five patients were excluded from the study because contact was lost or they refused to participate (Fig. 1). Table 1 compares the baseline characteristics of the patients finally included and those excluded and Table 2 compares the baseline characteristics and the results obtained in the follow-up between exposed and non-exposed patients.

Analysing patients according to exposure to high or low molecular weight agents, changes were only observed in the variables related to atopy. Patients who avoided contact with high molecular weight agents improved their symptoms of rhinitis, conjunctivitis and the percentage of eosinophils in blood (p = 0.002, 0.004, 0.018, respectively), while in those who remained exposed the symptoms of rhinitis and conjunctivitis deteriorated (p = 0.039 and 0.012, respectively) although the percentage of eosinophils in blood also fell (p = 0.003). These changes, with the exception of an improvement in rhinitis in the patients who avoided contact (p = 0.020), were not observed in patients exposed to low molecular weight agents (Table 1 online repository).

Comparing the characteristics at the time of diagnosis of individuals who presented clinical improvement (n = 30) with those who remained unchanged (n = 32) or those who deteriorated (n = 11) patients who improved showed a higher degree of severity on the GINA classification,
although they had higher FEV₁ and better FVC than those who deteriorated (Table 3). No significant differences were observed in the univariate analysis in the rest of the variables analysed.

Performing a logistical regression analysis considering the changes in the GINA classification as independent variable and comparing subjects who improved with those who remained stable or deteriorated, no predictors of these changes in the GINA classification were found (Table 2 online supplement). Only one model which included avoidance of the agent, better FEV₁, and better FEV₁/FVC quotient/ratio presented a sensitivity of 77% and a specificity of 65%, although the differences were not significant (Fig. 2, Table 3 online supplement). In the same analysis, considering the changes in FEV₁ or in PC20 as independent variables, no predictors of the effect were found (Table 2 online repository).

Performing a new logistic regression analysis, also considering the changes in the GINA classification as independent variable but comparing the individuals who improved or remained stable with those who deteriorated, again no variables predicting the effect were found (Table 4 online repository). Only one model, which in this case included time elapsed between symptom onset and diagnosis, a poorer FEV₁, FVC and FEV₁/FVC%, presented a sensitivity of 84% and a specificity of 36%, although again the differences were not significant (Fig. 3, Table 5 online repository). Interestingly, neither avoidance of the causative agent nor the type of agent was associated with worse prognosis.

Multiple Factor Analysis showed that with three components the percentage of variability explained was 36.8%. However, when four variables were removed a rate of 50% was obtained with the three first components, the results being very similar. Representing the subjects in the three main axes in three dimensions, no groupings were formed (Table 2 online repository). Only one model which included avoidance of the agent, better FEV₁, and better FEV₁/FVC quotient/ratio presented a sensitivity of 77% and a specificity of 65%, although the differences were not significant (Fig. 2, Table 3 online supplement). In the same analysis, considering the changes in FEV₁ or in PC20 as independent variables, no predictors of the effect were found (Table 2 online repository).

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The most significant result of the present study is probably the fact that avoiding exposure to the causative agent of OA did not statistically significantly improve the prognosis of these patients. The analyses performed show that avoiding exposure does not lead to clinical improvement and that the percentage of patients who deteriorate is independent both of the type of agent and of whether or not the agent is avoided. Nor was termination or persistence of exposure associated with any changes in the degree of obstruction or bronchial hyperresponsiveness.

The majority of studies included in four recent meta-analyses [11–14] focus on clinical aspects, and few studies have centered on evaluating the degree of obstruction in terms of the FEV₁ or the degree of bronchial hyperresponsiveness as determined by PC20 methacholine. To our knowledge, few studies to date have analyzed the degree of bronchial inflammation assessed by the eosinophil count in induced sputum in patients who either continued or terminated exposure. In these studies, the cessation of exposure showed a trend of improvement in sputum eosinophilia [26,27].

In relation to the clinical aspects of OA, the systematic review conducted by Rachiotis et al. [12], found that complete symptomatic recovery varied from 0% to 100% with a pooled prevalence of 32%. Similar results were reported by Vandenplas et al. [28]. The present study is the first to establish improvement or deterioration by determining the severity of the asthma according to the GINA guidelines [17]. Although 44% of patients who avoided exposure improved compared with only 22% of those who remained exposed, the differences were not significant. In fact, the patients who improved were the ones who presented poorer classifications on the GINA at the time of diagnosis, regardless of whether or not they avoided exposure.

Discussion

Delay in diagnosis, the degree of intensity of the symptoms prior to diagnosis and patients’ age have been suggested as prognostic factors [7,29–33] that determine the persistence of asthma. In the present study, avoidance of exposure to the causative agent and a lower degree of bronchial obstruction may explain the improvement in symptoms, although the associations were not significant. When comparing the subjects who deteriorated with those who remained stable or improved, longer delay in diagnosis and above all the greater alteration in the spirometry parameters seemed to be associated with poor prognosis, but no association was found between poor prognosis and the type of agent or avoidance or continuation of exposure.
These results suggest that OA probably does not differ greatly from non-occupational allergic asthma, since the rate of patients who deteriorate is around 15% and is independent of the treatment administered and of the avoidance or continuation of exposure. The percentage of patients with difficult-to-control severe asthma in the general population is around 10% [34].

Probably the overall improvement of OA should be assessed not only in terms of the improvement of symptoms but also of the degree of obstruction and the degree of bronchial hyperresponsiveness. In the present study we did not find a relation between any of the variables (once again including the type of agent or the avoidance or continuation of exposure) and a deterioration or improvement in FEV₁. Chang Yeung et al. [32], studying 185 workers exposed to plicatic acid, found higher values for those who terminated exposure. Paradoxically, Moscato et al. [4] studying 25 patients exposed indistinctly to HMW or LMW agents found better values for subjects who remained exposed. In fact, there is little information available on how rapidly lung function declines in those who continue to be exposed, or how removal from exposure affects lung function. Piirila et al. [35] reported a mean rate of decline of 40 ml/year in 91 selected subjects with isocyanate-induced OA, although 12 of these remained exposed to the causative agent during the follow-up period. A recent report focused only on patients who terminated exposure observed that FEV₁ declined rapidly in exposed workers and continued to decline, but at a slower rate, following removal of exposure [16].

The situation is similar in the case of bronchial hyperresponsiveness. The systematic review by Rachiotis et al. [12] found a pooled estimate of persistent hyperresponsiveness of 73%. Patients whose disease had been attributed to a LMW agent, and those from European workplaces were less likely to have persistent hyperresponsiveness. De Groene et al.’s meta-analysis [14] found differences depending on the criterion used to assess bronchial hyperresponsiveness. Indeed, only two studies out of the eight which analysed the standard mean difference in the follow-up showed an improvement in the degree of bronchial hyperresponsiveness in patients who avoided exposure [6,32]. However, the situation is more confusing in the studies that analysed the changes obtained by subtracting the PC20 values during follow-up from the baseline values. In four studies [30,33,36,37] in which the causative agent was LMW, an improvement was observed in two [32,37]. In the present study, taking as significant a two-fold change in the PC20 methacholine, no differences were found in relation to the exposure or to the type of causative agent; nor did we identify any factors that might predict these changes.

In view of these results we performed a multiple factor analysis, a descriptive multivariate statistical technique useful to analyse several groups of variables defined in the same samples [24,25]. In our study, the multiple factor
analysis confirms that avoiding exposure is not related to improvement or deterioration of the disease.

This study has a number of limitations. First, the fact that the severity of asthma was significantly lower in the patients who were not included may have introduced a bias in the results. The study does not account for the healthy worker effect. The unavailability of the degree of asthma control at the moment of diagnosis may be a source of error; however, this factor would not have introduced bias, because both the exposed and the non-exposed groups received similar initial treatment. Information was available on the degree of asthma control in the follow-up assessment. Very few patients were not controlled with the ACQ [18], and there were no differences regarding avoidance or persistence of exposure to the causative agent. Other limitation of the present study is the relatively low number of study subjects. However, we consider that the results obtained are important enough to be highlighted in a descriptive manner. Finally, another possible limitation was the fact that the degree of improvement of the patients was not analysed: patients whose asthma symptoms decreased from severe to intermittent or from severe to moderate and vice versa were analysed in the same way. Breaking down these multiple changes would have created different groups and would have complicated the analysis.

In conclusion, our results do not seem to support the recommendation that patients diagnosed with OA should change their work place. Despite these findings, however, there is insufficient evidence to recommend a change in current management guidelines recommending adequate avoidance of work place sensitizers, and especially chemicals, in workers with confirmed OA. Future well-designed prospective studies to further address the efficacy of environmental interventions in treating occupational asthma are required to confirm these findings. In the meantime, the best option seems to be to individualize the treatment strategy according to the patient.

Authors contributions

Dr Munoz had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2014.08.001.

References

