Should a prescription database be used to search uncontrolled severe asthmatics?

Abstract

Introduction: Many uncontrolled severe asthmatics are not on biologic therapy. We hypothesized that using a prescription database could help us identify them.

Material and methods: 3,309 patients, who received at least one Montelukast prescription in 2019, were extracted from our prescription database. Number of packages/year, types and dosages of ICS, LABA, ICS/LABA, LAMA and monoclonal antibodies were considered for each patient. In our analysis, for subjects that took > 7 packages of ICS/LABA + LTRA +/– LAMA (high adherent) the number of oral corticosteroids (OC) packets prescribed for each of them was also looked upon.

Results: Patients that took ICS/LABA or ICS/LABA + LAMA continuously with high ICS doses were 188 (25.6%) and 117 (39.3%) respectively (total: 305 — 29.5%). Among them, 58 (30.9%) and 53 (45.3%) (total: 111 — 36.4%) were prescribed more than 2 OC packages. Whereas, 21 (11.2%) and 24 (20.5%) patients (total: 45 — 14.75%) received at least 4 OC package prescriptions.

Conclusions: Approximately 36% of patients in continuous step-4/5 of GINA guidelines treatment may have severe uncontrolled asthma (overusing OC) which needed biologic treatment. In our opinion, a prescription archiving database may be a tool that can help us identify patients with severe asthma phenotype that would deserve a biologic treatment.

Key words: asthma, severe, prescription, electronic database, biologic, treatment

Introduction

According to the GINA guidelines, therapy should be modulated in line with asthma severity. In case of poor control of the disease we can progressively increase the dose of inhaled corticosteroids (ICS), add a leukotriene receptor antagonist (LTRA) and/or a long-acting muscarinic antagonist (LAMA) or, in more severe cases, add a low dose of oral corticosteroids (OC) or consider a biologic treatment [1].

The task force of the European Respiratory Society (ERS) and the American Thoracic Society (ATS) has recently defined severe asthma as asthma requiring treatment with a high-dosage of inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids to prevent it from becoming “uncontrolled”, or remaining “uncontrolled” despite this therapy [2, 3]. This task force has recently reported that the severe asthma population accounts for 5–10% of the global asthma patients that may take advantage
of a biologic treatment. However, there are very few reports that focus on the real prevalence of severe asthematics in Italy. In particular, we do not know how many asthematics are affected by uncontrolled severe asthma, despite a regular high level treatment, that may benefit of a biologic therapy (Omalizumab, Mepolizumab, Benralizumab or Dupilumab). We have found only one study that analyzed such issue in Japan where it was found that 2.3% of the asthmatic population had severe uncontrolled asthma of which only 3% was on biologic therapy [4]. As a result, many severe asthematics remain under-treated, significantly affecting both direct and indirect health costs due to the continuous and numerous exacerbations that characterize their disease [5, 6]. Seeking and better treating these patients could also have implications not only in asthma clinical improvement but also in terms of reducing severe asthma management costs. Therefore, we thought that using a local prescription database, could help us find how many severe asthematics, despite optimal adherence to treatment, showed poor disease control and that therefore needed monoclonal antibody therapy.

**Material and methods**

We consequently extracted all patients who had received at least one prescription of Montelukast in 2019 from the prescription database of the Tuscan USLSUDEST (southern Tuscany: Siena, Arezzo and Grosseto districts). This criterion was chosen because Montelukast has an exclusive asthma indication which allowed us to identify only asthmatics (excluding those with COPD). At this point, asthma therapy was also evaluated for each subject. Number of packages/year, types and dosages of ICS, LABA, SABA (salbutamol) ICS/LABA, LAMA and monoclonal antibodies were considered. The population was then divided into the following groups: Group 1, including patients with low adherence to ICS/LABAs + LTRA; Group 2, with individuals showing low adherence to ICS and/or LTRA; Group 3, with subjects treated with ICS/LABA + LTRA +/- LAMA + Biologic; Group 4, with patients showing high adherence to ICS/LABAs + LTRA and Group 5, with individuals presenting high adherence to ICS/LABAs + LTRA + LAMA. The number of OC packets prescribed during the year under review was also considered for each patient with the purpose of evaluating the number of exacerbations for each group. Having had more than 7 ICS/LABAs prescriptions/year was considered to be highly adherent to treatment. On the basis of the maximum dosage that can be delivered by each ICS device, the population of subjects with “high adherence” was divided into those in treatment with low, medium and high doses of ICS. For the purpose of this study, only patients belonging to the last two groups (with high adherence to therapy) were analyzed, because they could be patients with severity levels 4–5 of the GINA guidelines. In accordance with such guidelines [2], uncontrolled asthmatics were those that showed frequent exacerbations (≥ 2/year) and therefore who were prescribed more than 2 OC packages. The use of data from the prescribing database has been approved by the local ethics committee.

**Results**

The number of patients that took at least one package of Montelukast in 2019 in USL Sudest-Toscana was 3,309 (resident population: 831,480). The amount of subjects for each group was reported in Figure 1A. 1,125 (34%) asthmatics showed higher adherence to ICS/LABA. 92 of them were treated with a biologic (step 5). In Table 1, are reported the number of patients (adherent to ICS/LABA treatments) with low, medium and high ICS dosages and the mean number of packages of various asthma medications used in each group. Individuals that regularly took ICS/LABA + LTRA or ICS/LABA + LTRA + LAMA (more than 7 packages) with high doses of ICS were 188 (25.6%) and 117 (39.3%) respectively (total: 305–29.5%). Among them, 58 (30.9%) and 53 (45.3%) patients (total: 111–36.4%) had been prescribed more than 2 packages of OC (Figure 1 B, C). 21 (11.2%) and 24 (20.5%) subjects (total: 45–14.75%), in continuous treatment with ICS/LABA + LTRA or ICS/LABA + LTRA + LAMA, had been given at least 4 OC packages (Figure 1B, C).

**Discussion**

This analysis has shown that a remarkable number of asthmatics with high adherence to treatment and elevated ICS doses (111–36.4%) may have a poor disease control (≥ 2 OC prescriptions/year) and therefore they should be also considered for a biologic treatment. Only less than half of the severe asthmatics were already on such therapy (92 patients). The GINA guidelines suggest a treatment with a biologic treatment when patients being treated with high-
dose inhaled corticosteroids, combined with a LABA and a second controller, have at least two exacerbations per year requiring OCs. Our results clearly underestimate the number of patients who need a biologic treatment, as only a small number of subjects (with at least 1 Montelukast prescription) were included in this analysis. In fact, it should be considered that in 2019 asthmatics from the same area, aged between 18–40 years, who were given at least one prescription of Salbutamol and/or at least 2 packages of an ICS or ICS/LABA, were about 65,000. Therefore, patients deserving a biologic treatment can presumably be far more numerous. This study also highlights that a prescription archiving database could be a useful tool to identify subjects with uncontrolled severe asthma and who may be prescribed also a biologic therapy. These patients, otherwise, would escape a correct classification of disease severity and therefore an adequate treatment. As already mentioned, other authors have also used a prescribing database to identify the severity of asthma patients according to the therapy level prescribed. They found that 823 subjects included in the population studied (2.5%) had severe asthma, that 267 of them (32.4%) had poor disease control [4] and that consequently deserved a biologic treatment, similarly to what was observed in our analysis (111 patients — 36.4%). Consequently, a prescriptive database could be a tool for monitoring adherence to treatment and to establish a precise level of asthma severity that clinicians should use during an outpatient medical checkup or during hospitalization of an asthmatic patient. This system could allow us to identify severe asthmatics to be directed to a biologic treatment, otherwise unidentified, and who, as we have seen, could be more than 30% of the patients on regular ICS/LABA + LTRA +/- LAMA therapy. Seeking and then treating them adequately, especially those who show an excessive consumption of oral corticosteroids, could lead to economic savings in the management of disease exacerbations and hospitalizations. In fact, according to a recent study, the economic impact of severe asthma was estimated to be € 8,554/patient/year [7]. Generally, asthma biologic therapy is not considered cost-effective considering current high prices [8]. However, directing therapy only to responders, using also biomarkers before initiating it, monitoring for response to treatment and focusing on those patients receiving oral corticosteroids may improve biologic therapy cost-effectiveness [8]. On the other hand, another aspect that must be considered is that the excessive use of oral corticosteroids, particularly when they are > 4 packs/year, (a cut-off considered as an overuse of such medications) has potential adverse clinical outcomes [9]. We found that 45-14.75% of patients in continuous therapy with ICS/LABA + LTRA +/- LAMA took more than 4 packages of OCs, being, therefore, at high risk of complications induced by an excessive corticosteroid therapy (osteoporosis, diabetes, others). These
are the patients who must certainly be sought (even by using a prescription database) and who must be immediately put on biologic therapy. In fact, omalizumab, mepolizumab, benralizumab, and dupilumab can all reduce the need for OCS in severe asthma, besides decreasing the exacerbation rate and improving several patient-related outcomes [10].

A limitation of this tool (based on a prescription database) is that we do not know whether these patients are performing inhalation therapy correctly. If they don’t use inhalers properly, (make mistakes with the inhalers,) they obviously have to be trained to use them correctly (in the inhalation technique) and verified whether just this intervention can be enough to reduce the consumption of OCS before prescribing a biological therapy. Another question is not knowing exactly whether patients with 2 or more OCS prescriptions have actually taken this drug. Furthermore, the exact inhaled dose (puffs performed) by each patient is not known. All that should be verified for each patient.

### Conclusions

In conclusion, approximately 36% of asthmatics in continuous step-4/5 treatment, according to GINA guidelines, showed an overuse of OCS (severe uncontrolled asthma phenotype) for which biologic treatment should be required. A prescription archiving database may be a tool that can help us identify uncontrolled severe asthmatics for referral to biologic therapy.

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