TITLE: Monoclonal antibody treatment for severe uncontrolled asthma in Spain: Analytical map.

SHORT TITLE: Map of monoclonal antibodies for asthma in Spain

FUNDING: FORO AUTONOMICO DE ASMA-SEPAR (Spanish Respiratory Society)

ABSTRACT

BACKGROUND:

Monoclonal antibodies (mABs) have become available to treat more efficiently patients with severe uncontrolled asthma (SUA). However, the use of mABs is lower than expected given the prevalence of SUA, with significant disparities in the use of these treatments.

OBJECTIVE:

To evaluate the proportion of patients with SUA treated with mABs in Spain, and to analyse some of the factors that could determine these prescription patterns.

METHODS:

An analysis was performed on the data provided from the Hospitals National Health System (NHS) 2018 catalogue where Chest Diseases Department and a Hospital Pharmacy were available.

Random sampling was performed to determine the sample size, stratifying proportionally by geographic area and hospital level.

Characteristics of the participating sites, as well as the prescribing of mABs were collected, which included geographic area, hospital levels, prescribing medical specialities, types of clinics, and mABs prescribed.

RESULTS:

Data from 90 hospitals were analysed (Response rate 64.3%). Level 4 hospitals, the Canary Islands geographical area, and the presence of a high complexity Asthma Healthcare Unit (ACU) were associated with a higher probability that the SUA was treated with mABs.

CONCLUSION:

The map of the prescribing of mABs for SUA in Spain shows a significant variation by geographic area, hospital level, type of clinic, and the accreditation level of the ACUs. At the current time, there appears to be significant under-prescribing of these treatments.

KEY WORDS: Severe asthma; monoclonal antibodies; Mepolizumab; Dupilumab: Omalizumab; Reslizumab; Benralizumab.

BACKGROUND:

Asthma affects around 5% of the world population (1). The mortality rate is around 0.88% of all causes of mortality (2,3). Patients with severe asthma have elevated health costs and incidence of work disability (4-7). The prevalence of severe uncontrolled asthma (SUA) in Spain is 3.9%, similar to that described in other populations (8,9). Systemic corticosteroids are often needed in the treatment of these patients, which can lead to significant side effects (10,11). Monoclonal antibodies (mABs) have have led to a more efficient treatment of these patients and with fewer side effects (12,13).

As these are high cost drugs, choosing the most suitable for each patient needs to be optimised by looking for maximum efficiency (14,15). Different characteristics of the patient are assessed to achieve the most accurate therapeutic indication (15,16). However, in many cases, the treatment chosen initially does not achieve adequate control of the disease which is then achieved on changing to another drug (17).

It is well known that the health care organisation has a significant impact on the results obtained. In this sense, the Spanish Society of Respiratory Diseases (SEPAR) promoted the accreditation of Asthma Healthcare Units (ACU) (18).

Recent studies mention that the use of mABs is lower than expected given the prevalence of SUA, and they also identified disparities in the use of these treatments that could be due to socio-economic factors or the health organisation (19,20).

OBJECTIVES:

The aim of the current study is to evaluate the proportion of patients with SUA treated with mABs in Spain, and to analyse some of the factors that could determine these prescription patterns.

METHODS:

The present study is based on an aggregated data survey collected from the Hospital Pharmacy lists of patients with SUA that are, or have been, treated with mABs in the last 5 years.

An analysis was performed on the data provided from the Hospitals National Health System (NHS) 2018 catalogue (21). The candidate hospitals had to belong to the NHS of any Autonomous Community, have a Chest Diseases Department and a Hospital Pharmacy, as well as details of the prescription of mABs in patients with SUA that are, or have been, on treatment in the last 5 years. All private hospitals and those public ones that did not have a Chest Diseases Department and a Hospital Pharmacy were excluded.

A questionnaire was completed by Chest Disease specialists by means of a computerised form (open from 1st July to 4 November 2019).

Sample size

Random sampling was performed to determine the sample size, stratifying proportionally by geographic area (North, East, Central, South, Canary Islands) and hospital level, established by number of beds (level 1: ≤250; level 2: 251-500; level 3: 500-800; and

level 4: >800), based on a finite population of 189 hospitals that fulfilled the inclusion criteria, which was adopted as a sampling framework. Using this sample and taking into account the finite population sampling correction factor, in order to estimate an unknown proportion (assuming a case weighting of 50%) with a 95% confidence and with an estimation error of ±5%, data were needed from 112 hospitals. Anticipating 20% with insufficient data or would decline to participate, it was necessary to recruit 140 hospitals.

Contact was made with investigators of Chest Diseases Departments of 140 hospitals and 100 Principal Investigators signed the participation commitment document. Sites were considered valid if they provided the information necessary to evaluate the total number of patients currently treated with mABs and the size of the reference population of the site.

Variables collected

Details of characteristics of the participating sites, as well as the prescribing of mABs were collected, which included, geographic area, hospital levels, prescribing medical specialities (chest diseases, allergy, and paediatrics), types of clinics, and mABs prescribed. The clinics were classified based on the type of health care activity and accreditation level into 3 categories: 1) general clinic, if its activity contemplated the treatment of any accepted respiratory disease; 2) ACU, if the activity was specifically dedicated to asthma, but not accredited by SEPAR; 3) accredited ACU, if any level of SEPAR accreditation available (18). The main difference between ACU and accredited ACU is that the last one has been evaluated and accredited by SEPAR.

The SUA prevalence was calculated by multiplying the reference population of each site by the percentage of adults in the Spanish population (84.2%) (22), the estimated prevalence of asthma in an adult population (5%) (1), and the proportion of asthma

patients with SUA (3.9%) (8). The prevalence of treatment with mABs in patients with SUA was calculated by dividing the number of patients currently treated with any mABs by the estimated number of patients with SUA.

Statistical analysis

A random selection was made of the hospital sites in each geographical area, so that the resulting sample size in each area was proportional to the number of hospitals and at their level.

The data are presented as mean and standard deviation (SD), mean and interquartile range, or absolute and relative frequencies, where appropriate.

The comparisons of the prevalence of the current treatment with mABs between geographical areas, hospital levels, and types of asthma clinic, were made using the Mann-Whitney or Kruskal-Wallis test, where applicable. Furthermore, the number of patients treated with mABs was analysed using a linear regression model that included the geographical area, hospital level, and type of clinic as predictors.

All the analyses were performed using Programming language R (version 3.5.1, 2018). A significance level of $p \leq 0.05$ was used.

Ethics

This work was carried out according to the 1983 revision of the 1975 Helsinki Declaration. All the participating PIs were informed about the study, and a signed informed consent was obtained from all of them.

RESULTS

A total of 91 hospitals participated in the study, one of them being rejected due to not providing the necessary data, therefore 90 sites were analysed (64.3% of the hospitals initially selected) (Figure 1).

Table 1 shows the characteristics of the 90 sites included according to geographical area. The East area made up 30% of the hospitals, followed by the South with 26.7%. The reference populations varied between 45,000 and 833,297 inhabitants, the higher mean population corresponding to the central area with 340,000 inhabitants per hospital. Around one-third (33.4%) of the hospitals are Level 2 (Table 1).

All the Chest Diseases Departments of the hospitals analysed prescribed mABs, compared to 66.7% of Allergy Departments and 62.2% of Paediatric Departments (Table 1). In 53.3% of hospitals, there are mABs prescription evaluation committees, varying between 20% in the Canary Islands and 66.7% in the East area (Table 1).

There was an ACU in 67.6% of the hospitals, although unevenly distributed, with 91.7% in the Centre area and 37.5% in the South area. Just under two-thirds (63.3%) of the hospitals had an ACU accredited by SEPAR, although there was a wide variability, between 81.8% in the Centre area and 25% in the Canary Islands. As regards accreditation levels, high complexity ACU predominated in the North area, where 62.5% had this level and, specialized ACU in the South area (Table 1).

In some health areas there are agreements that prioritise the choice of anti-IL5 mABs, as such that the prescribing doctors must be limited to use the drugs including in these agreements, with a significant variation between areas. Thus, mepolizumab can be prescribed in almost all the sites analysed, whilst reslizumab can only be prescribed in 58.3% of the hospitals in the South area, and omalizumab is available in all the hospitals.

As regards the geographical area, no significant differences were observed in the number of patients treated in each hospital in the last 5 years, although those of the Canary Islands and the Centre area tended to treat more cases (Figure 2.a). However, when the analysis is performed according to hospital level, significant differences were observed between hospital level 3 and 4, which treated more patients than those of level 1 and 2 (Figure 2.b).

The prevalence of patients with SUA treated with mABs showed significant differences, between 20.3% in the Canary Islands and 11.5% in the North area (Figure 3.a).

By market share, although omalizumab is more often prescribed in all the geographical areas, the majority of its prescribing is seen in the East area, mepolizumab in the Canary Islands, reslizumab in the North area, and benralizumab in the East area (Figure 3.b). The percentage of patients with SUA that received treatment with mABs was significantly higher in level 3 hospitals (Figure 4).

The number of patients treated in each hospital by the Chest Diseases department in which they were analysed according to geographical area and type of clinic. No differences were observed between the numbers of patients with SUA treated with mABs according to geographical area, but there were differences as regards the hospital levels. Chest Diseases departments of level 3 and 4 hospitals treated significantly more patients than those of level 1 and 2 (Figure 5). Likewise, the Chest Diseases departments of hospitals with an ACU with any level of accreditation treated more patients than the hospitals without an ACU (47.5 and 28.6, respectively) (Figure 6.a). The number of patients treated increased significantly in accredited ACUs compared to non-accredited ones (55.1 and 34.4, respectively) (Figure 6.b), as well as to a higher accreditation level, with a mean of 31.1 patients for basic ACUs, 60.5 for specialised ones, and 68.9 for those of high complexity (Figure 6.c).

In the multivariate analysis it was observed that level 4 hospitals, the Canary Islands geographical area, and the presence of a high complexity ACU was associated with a higher probability that the SUA was treated with mABs (Table 2).

DISCUSSION

The results of this study appear to confirm significant differences in the prescribing of mABs depending on the geographic area, the hospital level or the type of care unit, similar to that reported by other authors (19,20,23). Likewise, it seems obvious that there is under-prescribing of these treatments (24,25). This disparity in the treatment of patients with asthma with no relationship to the baseline severity of the illness has been seen in other treatments (26).

The rate of under-treatment seems high, since only between 11.5% and 20% of patients with SUA receive treatment with mABs, similar to that reported by other authors (23). Even taking into account that 30% of patients with SUA are not eligible for mABs treatment due to their endo-phenotype (27), this indicates that more than 50% of these patients are not being treated with mABs, when it is probably indicated.

This under-treatment may be due to different causes. On the one hand, mABs are high cost drugs, which may have cost-related barriers (14,19,28,29). On the other hand, psychosocial factors of the patient can determine the perception of symptoms, the level of adherence to treatment, and the prescribing by the doctor (30,31). It is also known that in asthmatic patients of lower socio-economic levels it is less likely that they receive a prescription of inhaled corticosteroids, which could be extrapolated to the prescribing of mABs (26). Another aspect to consider is that less than 10% of patients with uncontrolled asthma, frequent exacerbation, and hospital admissions are referred to specialist clinics (32,33).

The differences in the rates of SUA patients treated with mABs, as well as in the market share of each drug, can also be due to different factors. Firstly, it should be taken into account that the management of the health system is different in each of the areas studied (34). These different approaches in management are the main reason that there are agreements for the preferential prescribing of a mAB in 41% of the sites and committees for the evaluation of treatment in 53% of hospitals. Given that there are currently no clear scientific criteria to establish the prioritisation of an mAB, the preferential prescription agreements do not seem to be efficient for the management of these patients, given that the more complex is a patient the more necessary it seems to individualise their diagnostic and therapeutic approach (35-37).

Another factor that could justify the variation in prescribing between geographic areas may be the prevalence of the asthma, which is different between relatively nearby areas (38,39). The difference between relatively close populations has also been observed in other studies, and it is mainly attributed to environmental factors. Especially relevant, in this sense, are the findings in the German population, where significant differences are observed in the prevalence of asthma symptoms in the East German population compared to that of West Germany, ethnically very similar, but with relevant environmental differences, especially before the reunification of the country (40). This environmental influence seems reinforced by the results of some recent studies, such as that of Karelia, where the same genetic variant is associated with opposite effects on the risk of allergic diseases, probably related to environmental changes (41).

Promotions carried out by the pharmaceutical companies can also have an influence on prescribing, in their relationship with the health systems, as well as with potential medical prescribers in the circulating of the scientific evidence or in the promotion of research (42,43).

As regards the prescribing medical specialties, a 100% of all Chest Disease clinics are prescribers, compared to 66.7% of those of Allergy clinics, and 62.2% of Paediatric clinics. This might be related, at least in part, with the wider target population of patients of Chest diseases clinics compared to both Allergists and Pediatricians. Indeed, some mAB are only licensed for adult non-allergic patients (25,35-37).

The results of the present study indicate that a higher level of hospital and the accreditation of the ACUs are associated with a higher number of patients treated. This seems reasonable given that patients with severe asthma are those that have more life-threatening episodes and more complications arising from the baseline treatment, with which it is more likely they are referred to hospitals and a higher level ACU (11,44-46). The diagnosis of SUA requires a systematic and exhaustive assessment, which must preferably be made in an ACU, in an attempt to ensure adherence to the treatment, the follow-up of educational programs, and the correct management of the comorbidities (29,47-50). In accordance with these data, it has been demonstrated that the incorporation of specialists in the care of patients with severe asthma lead to significant modifications in care, with changes in the diagnosis in 23.6% of the patients, a decrease in rescue bronchodilators, a decrease in exacerbations in 67.6%, and a reduction of health spending of £231.6 per patient (51)

Omalizumab continues to have the highest share of the market, with mABs prescriptions exceeding 50% in all geographic areas. This is clearly different to that mentioned in other studies. In the USA, omalizumab in 2019 only represented 37% of the total market share (19). This may be due to the advantage of having been the first to be marketed, to the possible preference of the doctors for a drug with more post-marketing observation data, as well as its indication for allergic asthma where, currently, it has no rival among those currently authorised in Spain (19,52). Another factor to consider is the promotion and

communication strategy by the pharmaceutical companies, which might not be the same in all areas (42,43).

The present study has some limitations. It is a cross-sectional study, as such causality relationships cannot be established. An analysis has not been made on the results of the treatment with mABs as well as the reasons for starting these treatments.

In conclusion, the map of the prescribing of mABs for SUA in Spain shows a significant variation by geographic area, hospital level, type of clinic, and the accreditation level of the ACUs. At the current time, there appears to be significant under-prescribing of these treatments, which could be resolved, at least in part, with wider availability of accredited ACUs.

ABBREVIATIONS:

SUA: severe uncontrolled asthma
mABs: Monoclonal antibodies
SEPAR: Spanish Society of Respiratory Diseases
ACU: Asthma Healthcare Units
NHS: National Health System
SD: standard deviation
anti-IL5: anti interleukin 5

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Figure legends

Figure 1. Flow chart.

(1) https://www.msssi.gob.es/ciudadanos/prestaciones/centrosServiciosSNS/hospitales/docs/CNH2015.pdf.

(2) Hospitals that meet inclusion criteria, stratified by geographic area and number of beds.

(3) Number of hospitals required to be included (Randomly selected)

(4) Number of hospitals that was necessary to recruit anticipating 20% with insufficient data or that would decline to participate.

(5) Number of hospitals eventually included.

PI: Principal investigator.

Figure 2. Number of patients, expressed as mean (SD), with SUA treated with mABs in each hospital in the last 5 years by all the medical departments involved in the health care of these patients, according to geographical area (a) and hospital level (b).

SD: Standard deviation; SUA: severe uncontrolled asthma; mABs: monoclonal antibodies.

Hospital level (number of beds): Level 1: ≤250; Level 2:251-500; Level 3:501-850; Level 4:>850.

Figure 3. Percentage of patients with SUA treated with mABs according to geographical area. a) Mean prevalence of patients with SUA treated with any mABs (In percentage of estimated number of patients with SUA). b) Mean prevalence of patients with SUA treated with each mABs.

SUA: severe uncontrolled asthma; mABs: monoclonal antibodies.

Figure 4. Mean prevalence of patients with SUA treated with any mABs, in percentage of estimated number of patients with SUA (expressed as mean percentage (CI).

SUA: severe uncontrolled asthma; mABs: monoclonal antibodies; CI: Confidence interval 95%.

Hospital level (number of beds): Level 1: ≤250; Level 2:251-500; Level 3:501-850; Level 4:>850.

Figure 5. Number of patients, expressed as mean (SD), with SUA treated with mABs in each hospital currently treated by the Chest Diseases department, according to geographical area (a) and hospital level (b).

SD: Standard deviation; SUA: severe uncontrolled asthma; mABs: monoclonal antibodies.

Hospital level (number of beds): Level 1: ≤250; Level 2:251-500; Level 3:501-850; Level 4:>850.

Figure 6. Number of patients, expressed as mean (SD), with SUA treated with mABs in each hospital currently treated by the Chest Diseases department, according to the type of clinic and accreditation level. a) General clinic or Asthma Healthcare Unit (ACU); b) Asthma Healthcare Unit with any level of SEPAR accreditation available; c) Asthma Healthcare Unit with any level of SEPAR accreditation available, according to accreditation level.

SD: Standard deviation; SUA: severe uncontrolled asthma; mABs: monoclonal antibodies; SEPAR: Spanish Society of Respiratory Medicine.