Gender bias in clinical trials of biological agents for severe asthma: A systematic review

Pablo Ciudad-Gutiérrez*, Beatriz Fernández-Rubio☯*, Ana Belén Guisado-Gil
Servicio de Farmacia, Hospital Universitario Virgen del Rocío, Sevilla, Spain

* These authors contributed equally to this work.
* beatrizfernandezrub@gmail.com

Abstract

Asthma is one of the most common chronic diseases characterized by sex disparities. Gender bias is a well-documented issue detected in the design of published clinical trials (CTs). International guidelines encourage researchers to analyze clinical data by sex, gender, or both where appropriate. The objective of this work was to evaluate gender bias in the published CTs of biological agents for the treatment of severe asthma. A systematic review of randomized controlled CTs of the biological agents (omalizumab, benralizumab, reslizumab, mepolizumab or dupilumab) for the treatment of severe asthma was conducted. The literature search was performed using PubMed and EMBASE without language restrictions. This study followed the corresponding international recommendations. We identified a total of 426 articles, of which 37 were finally included. Women represented 60.4% of patients included. The mean percentage of women in these trials was 59.9%, ranged from 40.8% to 76.7%. The separate analysis by sex of the main variable was only performed in 5 of the 37 publications included, and none of the trials analyzed secondary variables by sex. Only 1 of the articles discussed the results separately by sex. No study included the concept of gender in the text or analyzed the results separately by gender. The proportion of women included in CTs was higher compared to publications of other disciplines, where women were under-represented. The analysis of the main and secondary variables by sex or gender, even the discussion separately by sex, was insufficient. This gives rise to potential gender bias in these CTs.

1. Introduction

The term “gender” in research could be defined as a systematic mistake associated with social construct, which incorrectly regards women and men as similar/different [1], whereas the term “sex” is related to biological characteristics based upon chromosomal assignment [2]. In 1993, The Food and Drug Administration (FDA) [3] published a guideline regarding the participation of women in clinical trials (CTs) and evaluating all clinical data by sex, but it was not reproduced in Europe [4]. A short time ago, The Sex and Gender Equity in Research (SAGER) guideline proposed analyzing clinical data by sex, gender, or both where appropriate [5].
Gender bias is a well-established term used in biomedical research to show the low sensitivity to gender among low women representation and absence of analysis separately by sex in CTs [6–9]. In Psychiatry, three studies about gender bias remarked that results were poorly stratified by sex [10–12]. In Neurology, one study conducted in 2015 highlighted that women were only represented in 19% of CTs included [13] and a systematic review in multiple sclerosis pointed out that only 15 of 55 studies included an analysis by sex of the primary endpoint [14]. Additionally, one article about gender bias in pulmonary diseases found out an under-diagnosis of chronic pulmonary obstructive disease in women (42%) with respect to men (58%) because higher smoking rates are usually attributed to the male population [15].

Asthma is one of the most common chronic and non-communicable diseases that affects around 334 million people worldwide, and its prevalence has been increasing by 50% every decade [16]. Many epidemiologic studies mention the presence of sex disparities in asthma prevalence and severity [17, 18]. As children, boys have an increased prevalence of asthma compared to girls (11.9% vs. 7.5%, respectively), and boys are also twice as likely as girls to be hospitalized for an asthma exacerbation [19]. However, during adolescence, there is a decline in asthma prevalence and morbidity in males concurrent with an increase in females. By adulthood, women have increased asthma prevalence compared to men (9.6% versus 6.3%, respectively), and women are three times more likely than men to be hospitalized for an asthma-related event [20].

Approximately 5–10% of asthmatic patients experience “severe asthma” because they require treatment with high-dose inhaled corticosteroids plus a long-acting beta-adrenoceptor agonist (LABA), leukotriene modifier or theophylline and/or systemic corticosteroids as background therapy to prevent a poor asthma control [21]. Over the past decade, an improved understanding of the complex pathophysiology of asthma has led to the development of new classification for phenotypes of asthma. This classification is based on clinical, physiological and inflammatory parameters in order to assign asthmatic patients to “phenotypic clusters”. Biological agents have demonstrated a beneficial role in certain clusters targeted at immunoglobulin E (IgE) or eosinophils [22]. Omalizumab was the first monoclonal antibody (mAb) developed for a specific subgroup of patients with uncontrolled IgE-mediated allergic asthma. Recently, anti-interleukin-5 (IL-5) (benralizumab, reslizumab and mepolizumab) and also anti-IL-4/IL-13 drugs (dupilumab) are been approved for patients with uncontrolled eosinophilic asthma [23].

Currently, the biological treatment with monoclonal antibodies has been shown to reduce asthma exacerbations and oral corticosteroid use, and improve lung function and quality of life in appropriately selected patients [24]. Because of differences in gender, analysis of gender bias should be taken into consideration when evaluating the efficacy and safety of asthma novel therapies [25]. Thus, this systematic review aims to evaluate gender bias in published CTs of omalizumab, benralizumab, reslizumab, mepolizumab and dupilumab in severe asthma.

2. Materials and methods

2.1 Eligibility criteria

This review protocol was registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY, DOI number: 10.37766/inplasy2021.1.0020) and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Equity 2012 Extension declaration [26]. We selected the studies that met the following inclusion criteria:
The study drug was omalizumab, benralizumab, reslizumab, mepolizumab or dupilumab.

CTs with a control group and random assignment.

Patients treated could be pediatrics or adults.

The aim of the CTs was the evaluation of the efficacy and safety of the study drug. CTs that additionally assessed other variables such as quality of life or pharmacokinetic/pharmacodynamics were not excluded.

Patients were diagnosed with severe asthma, with an eosinophilic or allergic phenotype.

We excluded:

- CTs in phase I.
- Post-hoc analysis of one or several previously published CTs, extension CTs of previously published trials as well as systematic reviews and meta-analysis. These works included the same patients that were evaluated in their original articles.
- Pilot studies with a small sample of patients (n < 50), short reports and letters to the editor, due to the absence of complete data from larger CTs.
- CTs that involved the evaluation of the treatment regimens based on mAb plus other therapies. Those studies that allowed concomitant medications, that is, drugs that are not being studied but which a patient is taking through all or part of a study, were included.

### 2.2 Information sources

An electronic literature search was performed using PubMed and EMBASE on May 1 2020, with no publication date or language restrictions. Search terms included a mixture of MeSH terms and free text (keywords and synonyms) combined with Boolean operators. The search strategy is detailed in Table 1. Besides, the reference lists of selected studies were hand-searched to identify any other relevant studies.

### 2.3 Study selection

Two independent reviewers (BFR and PCG) screened the titles and abstracts of all eligible publications for possible inclusion. To ensure inter-rater reliability, 100% of the articles were assessed independently by both authors. The articles included were full-length read before a final decision on inclusion. Any disagreement was settled by consensus with a third reviewer (ABGG).

### 2.4 Data collection and analysis

Reviewers independently extracted data and ABGG examined all extraction sheets to ensure their accuracy. We explicitly stated if there were any missing data from CTs. For each publication, the following variables were registered:

- Drug in research: omalizumab, benralizumab, reslizumab, mepolizumab or dupilumab.
- Year of publication.
- Age: 6 to 11 years (pediatrics patients) and/or ≥ 12 years old (adult patients).
- Financing of the trial: pharmaceutical industry or independent (the CTs were considered to be promoted by pharmaceutical companies if one of the authors was employed by a pharmaceutical company or if direct funding was specified).
Table 1. Complete search strategy for different databases.

| Healthcare Database | Search strategy |
|---------------------|-----------------|
| PubMed              | (omalizumab)AND ((severe asthma) OR (allergic asthma) OR (eosinophilic asthma) OR (refractory asthma)) AND (randomizedcontrolledtrial[Filter]) |
|                     | (reslizumab)AND ((severe asthma) OR (allergic asthma) OR (eosinophilic asthma) OR (refractory asthma)) AND (randomizedcontrolledtrial[Filter]) |
|                     | (mepolizumab)AND ((severe asthma) OR (allergic asthma) OR (eosinophilic asthma) OR (refractory asthma)) AND (randomizedcontrolledtrial[Filter]) |
|                     | (dupilumab)AND ((severe asthma) OR (allergic asthma) OR (eosinophilic asthma) OR (refractory asthma)) AND (randomizedcontrolledtrial[Filter]) |
|                     | (benralizumab)AND ((severe asthma) OR (allergic asthma) OR (eosinophilic asthma) OR (refractory asthma)) AND (randomizedcontrolledtrial[Filter]) |
| EMBASE              | omalizumab:ab,ti AND ('severe asthma':ab,ti OR 'allergic asthma':ab,ti OR 'eosinophilic asthma':ab,ti OR 'refractory asthma':ab,ti) AND [randomized controlled trial]/lim |
|                     | reslizumab:ab,ti AND ('severe asthma':ab,ti OR 'allergic asthma':ab,ti OR 'eosinophilic asthma':ab,ti OR 'refractory asthma':ab,ti) AND [randomized controlled trial]/lim |
|                     | mepolizumab:ab,ti AND ('severe asthma':ab,ti OR 'allergic asthma':ab,ti OR 'eosinophilic asthma':ab,ti OR 'refractory asthma':ab,ti) AND [randomized controlled trial]/lim |
|                     | dupilumab:ab,ti AND ('severe asthma':ab,ti OR 'allergic asthma':ab,ti OR 'eosinophilic asthma':ab,ti) AND [randomized controlled trial]/lim |
|                     | 'refractory asthma':ab,ti] AND [randomized controlled trial]/lim |
|                     | benralizumab:ab,ti AND ('severe asthma':ab,ti OR 'allergic asthma':ab,ti OR 'eosinophilic asthma':ab,ti) AND [randomized controlled trial]/lim |

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- Location: United States, Europe, Japan, Asia, Australia or the rest of the world (ROW).
- Trial phase: I, Ia, IIB, IIa, IIIa, IIIb or IV.
- Comparator: placebo or active drug (best standard of care or optimized asthma therapy).
- Objectives of the trial: efficacy and safety, and if a pharmacodynamic/pharmacokinetic evaluation was performed.
- Diagnosis: severe allergic, referring to the one that requires treatment with high dose inhaled corticosteroids plus a long-acting beta-adrenoceptor agonist (LABA), leukotriene modifier or theophylline and/or systemic corticosteroids, or uncontrolled eosinophilic asthma, caused by high levels of eosinophils.
- Asthma controllers at entry: medication that patients were taking for asthma control before starting the clinical trial (inhaled corticosteroids, long-acting beta-agonists, leukotriene receptor antagonists, oral corticosteroids, or short-acting beta-agonists).

For the analysis of gender and sex differences and in order to characterize the gender sensitivity of the trials, we followed the Spanish recommendations for the study and evaluation of gender differences in CTs of drugs [27], the FDA guide [3] and the European Commission [28]. In the same way, the methodology was based on the SAGER guidelines [5] similar recommendations published in Canada [29] and previous publications [11]. The variables analyzed were:

- Percentage of female authors among all authors.
- The number of patients recruited.
- The number of women included and the percentage of women among patients recruited.
• If there were (or not) sex or gender-stratified results of the main and secondary outcomes.

• If the discussion of the results was analyzed by sex and gender.

• If pregnancy was cited as an exclusion criteria, the studies analyzed the interaction between hormone replacement therapy and study drug, included women using hormonal contraceptives, analyzed the interaction between hormonal contraceptives and the study drug, analyzed the influence of the drug on the pharmacokinetics of hormonal contraceptives, investigated the effects of the phase of the menstrual cycle on the response to the drug, and studied the influence of the phase of the menstrual cycle on the pharmacokinetics of the drug.

We also applied a subgroup analysis for the variables: date of publication, location, comparator, drug, age of patients, objectives and sample size.

3. Results

426 records were identified through database searching. After the elimination of duplicates, 353 records were screened by title and abstract. We assessed 91 articles for eligibility; 55 were excluded because they did not meet the eligibility criteria. One clinical trial [30] was identified from a post-hoc study, so 37 studies were finally included Fig 1.

Table 2 indicates the characteristics of the trials included in the study [30–66]. In most publications, the study drug was omalizumab (16), followed by benralizumab (9), mepolizumab (5), dupilumab (4) and reslizumab (3). The age of patients was ≥12 in 34 studies, <12 in two studies and only one included a population ranging from 6 to 20 years. Most trials were funded by pharmaceutical companies. The majority of the studies were carried out worldwide (25), followed by those accomplished in the United States (7), Europe (2), Asia (1), Japan (1) and the United States + Canada (1). Twenty-one trials were in phase III, 8 in phase II, 4 in phase IV and the rest were not specified (4). The comparator was placebo in 35 trials and other asthma therapies (“best standard care or optimized asthma therapy”) in the remaining studies. The trials measured the variables of efficacy and safety (35), efficacy, safety and quality of life (1) and efficacy, safety and pharmacokinetic (1). Sixteen studies included patients with severe allergic asthma and 21 with uncontrolled eosinophilic asthma. Most patients were treated with inhaled corticosteroids + LABA as asthma controllers before starting biological treatment.

Table 3 shows the sex-related characteristics of the studies. The mean percentage of female authors among all the authors was 17.5% (range 0–37.5). The total number of patients included in these studies was 16742. The average number of patients per study was 452 (range 61–1902). There were 10108 participants women, with an average number of women per study of 273 (range 29–1197). Women represented 60.4% of patients included. The mean percentage of women in these trials was 59.9%, ranged from 40.8% to 76.7%. The separate analysis by sex of the main variable was carried out in only 5 of the 37 studies included. Moreover, none of the studies analyzed secondary variables between the subpopulation of men and women. Only 1 of the 37 trials discussed results separated by sex. No study included the concept of gender in the text or analyzed the results separately by gender. Pregnancy was an exclusion criterion in 11 trials. None of the included studies analyzed any of the other gender or sex-related variables.

Table 4 shows the proportion of women and sex-related characteristics in the different subgroups of the CTs. The five trials that considered the analysis by sex in the main outcome were carried out with patients ≥12 years using placebo as comparator. Moreover, they were published between 2011 and 2020 and aimed at efficacy and safety evaluation.
Fig 1. Study selection flowchart.

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Table 2. Characteristics of CTs included.

| Study               | Drug      | Age of patients (years) | Funding | Location | Phase | Comparator | Objectives | Diagnosis | Asthma controllers at entry |
|---------------------|-----------|-------------------------|---------|----------|-------|------------|------------|-----------|----------------------------|
| Busse et al., 2001  | Omalizumab| ≥12                     | Ph. companies | Worldwide | III   | Placebo    | Efficacy and safety | SAA       | ICs + SABA                 |
| Milgrom et al., 2001| Omalizumab| <12                     | Ph. companies | USA       | III   | Placebo    | Efficacy and safety | SAA       | ICs + SABA                 |
| Soler et al., 2001  | Omalizumab| ≥12                     | Ph. companies | Worldwide | II    | Placebo    | Efficacy and safety | SAA       | ICs + SABA                 |
| Ayres et al., 2004  | Omalizumab| ≥12                     | Ph. companies | Europa    | -     | Best standard of care | Efficacy and safety | SAA       | ICs + SABA                 |
| Holgate et al., 2004| Omalizumab| ≥12                     | Ph. companies | Worldwide | III   | Placebo    | Efficacy and safety | SAA       | ICs + SABA + LABA           |
| Vignola et al., 2004| Omalizumab| ≥12                     | Ph. companies | Worldwide | -     | Placebo    | Efficacy and safety | SAA       | ICs + SABA                 |
| Humbert et al., 2005| Omalizumab| ≥12                     | None       | Worldwide | III   | Placebo    | Efficacy and safety | SAA       | ICs + LABA                 |
| Lanier et al., 2009 | Omalizumab| <12                     | Ph. companies | USA       | III   | Placebo    | Efficacy and safety | SAA       | ICs+ SABA                  |
| Ohta et al., 2009   | Omalizumab| ≥12                     | Ph. companies | Japón     | III   | Placebo    | Efficacy and safety | SAA       | ICs + LABA, LTRAs, OCs and theophylline |
| Bousquet et al., 2011| Omalizumab| ≥12                     | Ph. companies | Worldwide | IV    | OAT        | Efficacy and safety | SAA       | ICs + LABA                 |
| Busse et al., 2011  | Omalizumab| 6–20                    | Ph. companies | USA       | IV    | Placebo    | Efficacy and safety | SAA       | ICs + LABA                 |
| Hanania et al., 2011| Omalizumab| ≥12                     | Ph. companies | Worldwide | IIIb  | Placebo    | Efficacy and safety | SAA       | ICs + LABA                 |
| Bardelas et al., 2012| Omalizumab| ≥12                     | Ph. companies | USA       | IV    | Placebo    | Efficacy and safety | SAA       | ICs + LABA, LTRAs, theophylline and zileuton |
| Rubin et al., 2012  | Omalizumab| ≥12                     | Ph. companies | Worldwide | III   | Placebo    | Efficacy, safety and QL | SAA       | ICs + LABA                 |
| Li et al., 2016     | Omalizumab| ≥12                     | Ph. companies | Worldwide | III   | Placebo    | Efficacy and safety | SAA       | ICs + LABA                 |
| Ledford et al., 2017| Omalizumab| ≥12                     | Ph. companies | USA       | IV    | Placebo    | Efficacy and safety | SAA       | ICs + LABA                 |
| Castro et al., 2014 | Benralizumab| ≥12                    | Ph. companies | Worldwide | IIIb  | Placebo    | Efficacy and safety | SEA       | ICs + LABA                 |
| Nowak et al., 2015  | Benralizumab| ≥12                    | Ph. companies | USA + Canada | II   | Placebo    | Efficacy and safety | SEA       | ICs + LABA                 |
| Bleeker et al., 2016| Benralizumab| ≥12                    | Ph. companies | Worldwide | III   | Placebo    | Efficacy and safety | SEA       | ICs + LABA                 |
| Fitzgerald et al., 2016| Benralizumab| ≥12                    | Ph. companies | Worldwide | III   | Placebo    | Efficacy and safety | SEA       | ICs + LABA                 |
| Park et al., 2016   | Benralizumab| ≥12                    | Ph. companies | Asia      | Ia    | Placebo    | Efficacy and safety | SEA       | ICs + LABA                 |
| Ferguson et al., 2017| Benralizumab| ≥12                    | Ph. companies | Worldwide | III   | Placebo    | Efficacy and safety | SEA       | ICs + LABA                 |
| Nair et al., 2017   | Benralizumab| ≥12                    | Ph. companies | Worldwide | III   | Placebo    | Efficacy and safety | SEA       | ICs + LABA                 |
| Zeitlin et al., 2018| Benralizumab| ≥12                    | Ph. companies | USA       | IIIb  | Placebo    | Efficacy, safety and PK | SEA       | ICs + LABA                 |
| Panettieri et al., 2020| Benralizumab| ≥12                    | Ph. companies | Worldwide | III   | Placebo    | Efficacy and safety | SEA       | ICs + LABA                 |
| Flood-Page et al., 2007| Mepolizumab| ≥12                    | Ph. companies | Worldwide | II    | Placebo    | Efficacy and safety | SEA       | ICs+ SABA                  |

(Continued)
4. Discussion

The results of the current study show that, in general, the proportion of women included in the CTs of omalizumab, benralizumab, reslizumab, mepolizumab and dupilumab in severe asthma was higher (60.4%) than the percentage of men. This percentage of females included in the studies is similar to the percentage of women with severe asthma reflecting a low gender bias regarding the inclusion of women in these CTs [67]. However, the separate analysis by sex of the main variable was carried out in only 5 of the 37 studies included, only 1 of the 37 trials discussed results separated by sex and no study included the concept of gender in the text. Additionally, the mean percentage of female authors among all the authors was low, just 17.5%.

Previous systematic reviews of gender bias that characterized women’s participation in HIV (human immunodeficiency virus) [68] or depression [10] clinical studies, concluded that this population was under-represented, so our work proves that the main CTs of the mAb used in severe asthma achieved, at least, a larger inclusion of women. Possible explanations for this fact could be that mAb are the most recent therapy for asthma, and consequently international recommendations [27–29] would have had an impact on the design of the CTs. However, the CTs included showed far-from-negligible gender bias in other variables such as sex-stratification of the main and secondary outcomes, the discussion of the results analyzed by sex and the absence of the concept of “gender” in the text. A potential reason why sex and gender considerations were not included is that sex and other demographic information such as age or race...
Table 3. Proportion of women and other characteristics of sex assessment.

| Study                  | Total of patients | Total of women | Percentage of women | Analysis by sex of the main outcome | Analysis by sex of secondary outcomes | Discussed results analyzed by sex |
|------------------------|-------------------|----------------|---------------------|-------------------------------------|--------------------------------------|----------------------------------|
| Busse et al., 2001     | 525               | 310            | 59.0%               | No                                  | No                                   | No                               |
| Milgrom et al., 2001   | 334               | 231            | 69.2%               | No                                  | No                                   | No                               |
| Soler et al., 2001     | 546               | 278            | 50.9%               | No                                  | No                                   | No                               |
| Ayres et al., 2004     | 312               | 220            | 70.5%               | No                                  | No                                   | No                               |
| Holgate et al., 2004   | 246               | 150            | 61.0%               | No                                  | No                                   | No                               |
| Vignola et al., 2004   | 405               | 223            | 55.1%               | No                                  | No                                   | No                               |
| Humbert et al., 2005   | 419               | 279            | 66.6%               | No                                  | No                                   | No                               |
| Lanier et al., 2009    | 628               | 203            | 32.3%               | No                                  | No                                   | No                               |
| Ohta et al., 2009      | 315               | 171            | 54.3%               | No                                  | No                                   | No                               |
| Bousquet et al., 2011  | 400               | 259            | 64.8%               | No                                  | No                                   | No                               |
| Busse et al., 2011     | 419               | 177            | 42.2%               | No                                  | No                                   | No                               |
| Hanania et al., 2011   | 850               | 557            | 65.5%               | No                                  | No                                   | No                               |
| Bardelas et al., 2012  | 271               | 180            | 66.4%               | No                                  | No                                   | No                               |
| Rubin et al., 2012     | 116               | 89             | 76.7%               | No                                  | No                                   | No                               |
| Li et al., 2016        | 609               | 328            | 53.9%               | Yes                                 | No                                   | No                               |
| Ledford et al., 2017   | 176               | 123            | 69.9%               | Yes                                 | No                                   | No                               |
| Castro et al., 2014    | 606               | 417            | 68.8%               | No                                  | No                                   | No                               |
| Nowak et al., 2015     | 110               | 77             | 70.0%               | No                                  | Yes                                  | No                               |
| Bleecker et al., 2016  | 1205              | 796            | 66.1%               | No                                  | No                                   | No                               |
| Fitzgerald et al., 2016 | 1306             | 807            | 61.8%               | No                                  | No                                   | No                               |
| Park et al., 2016      | 106               | 65             | 61.3%               | No                                  | No                                   | No                               |
| Ferguson et al., 2017  | 211               | 129            | 61.1%               | Yes                                 | No                                   | No                               |
| Nair et al., 2017      | 220               | 135            | 61.4%               | No                                  | No                                   | No                               |
| Zeitlin et al., 2018   | 103               | 42             | 40.8%               | No                                  | No                                   | No                               |
| Panettieri et al., 2020| 233               | 157            | 67.4%               | Yes                                 | No                                   | No                               |
| Flood-Page et al., 2007| 362               | 202            | 55.8%               | No                                  | No                                   | No                               |
| Haldar et al., 2009    | 61                | 29             | 47.5%               | No                                  | No                                   | No                               |
| Pavord et al., 2012    | 621               | 387            | 62.3%               | No                                  | No                                   | No                               |
| Bel et al., 2014       | 135               | 74             | 54.8%               | No                                  | No                                   | No                               |
| Ortega et al., 2014    | 576               | 329            | 57.1%               | No                                  | No                                   | No                               |
| Wenzel et al., 2013    | 104               | 52             | 50.0%               | No                                  | No                                   | No                               |
| Wenzel et al., 2016    | 776               | 490            | 63.1%               | No                                  | No                                   | No                               |
| Castro et al., 2018    | 1902              | 1197           | 62.9%               | No                                  | No                                   | No                               |
| Rabe et al., 2018      | 210               | 127            | 60.5%               | No                                  | No                                   | No                               |
| Castro et al., 2011    | 106               | 63             | 59.4%               | No                                  | No                                   | No                               |
| Castro et al., 2015    | 953               | 581            | 61.0%               | No                                  | No                                   | No                               |

(Continued)
would have been analyzed as a covariate in some of these trials. However, guidelines recommend the inclusion of this valuable information in published studies [3–5]. Additionally, none of the trials followed a hormonal interaction approach to analyze the potential interaction with drugs such as hormonal contraceptives.

Several studies have proven that asthma affects men and women differently [17–19]. According to The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study [69], a unique study that recruited more than 4000 women and assessed more than 3300 of their children, exists a sex disparity in asthma: until puberty, asthma is more common and severe in boys, but after puberty, this disease becomes more common in women. Some recent articles have found an association between asthma and female sex hormones that could explain this fact [20]. Although the relationship remains unclear, the main hypothesis is that estrogen fluctuations directly modulate immune pathways crucial in asthma pathogenesis because of the anti-inflammatory action of these hormones [18]. In spite of all these reasons, none of the CTs analyzed the interaction between hormone replacement therapy and the study drug or investigate the effects of the phase of the menstrual cycle on the response to the drug. This fact goes against international recommendations and could respond to a possible attempt to avoid increases in the final cost of trials.

Furthermore, we found that more than half of the trials did not state whether pregnancy was a reason for exclusion. Even so, it is proved that there is a connection between pregnancy and asthma severity, but with a variable effect [70].

The CTs of the five mAb approved for the treatment of severe asthma were included in this study. Nevertheless, the percentage of women included in the CTs of the different drugs varied between them. Omalizumab’s trials were the ones that included a smaller proportion of women, probably related to the fact that it was the first drug launched and therefore its trials started earlier. However, in the two latest CTs ofomalizumab, conducted both in 2016, an analysis by sex of the main outcome was performed. In contrast, the most recent CTs of benralizumab included the highest percentage of women, two of them analyzed the main outcome by sex and one discussed the results based on sex. On the other hand, the design of dupilumab’s or reslizumab’s CTs, was similar so the percentage of women included was almost identical. It could be explained by the presence of common research authors in these studies.

We should also mention that we included CTs carried out just in children, adults, or both. It is remarkable that a clinical study that enrolled more than 400 inner-city children, adolescents and young adults (6–20 years old) [58] was the only one that brought up socio-economic aspects from the participants, although the percentage of women was below the average. Besides, another publication included males and premenarchal females aged 6 to 12 years [49]. In this case, despite the interest in the effects of the phase of the menstrual cycle on the response to the drug, sex-related variables were not included in the design.

The main strength of this work is that it is the first systematic review performed on the recently commercialized mAb used in severe asthma which tries to assess gender of bias in CTs. Besides, two of the largest health databases that incorporate articles from the highest-

| Study            | Total of patients | Total of women | Percentage of women | Analysis by sex of the main outcome | Analysis by sex of secondary outcomes | Discussed results analyzed by sex |
|------------------|-------------------|----------------|---------------------|-----------------------------------|--------------------------------------|----------------------------------|
| Björmer et al., 2016 | 265               | 174            | 65.7%               | Yes                               | No                                   | No                               |
| Total            | 16742             | 10108          | 60.4%               | 5/37                              | 0/37                                 | 1/37                             |

Table 3. (Continued)
impact medical journals, PubMed and EMBASE, were employed without date and language restrictions, and both CTs conducted in adults and children were included.

The main limitation was that the exclusion of post-hoc trials could prevent the inclusion of studies that subsequently evaluated variables based on sex. Moreover, pilot studies were excluded because our study assesses variables that are generally evaluated at the end of the clinical trial and preliminary results from pilot studies were commonly included in larger CTs.

Table 4. Proportion of women and other characteristics of sex assessment according to the different subgroups.

| Subgroup        | Studies | Representation of women | Analysis by sex |
|-----------------|---------|-------------------------|-----------------|
|                 | N       | N patients | N women | Percentage | Analysis by sex of the main outcome | Analysis by sex of secondary outcomes | Discussion of results by sex |
|                 | N       |            |         |            | N/N Total Studies | N/N Total Studies | N/N Total Studies |
| Total           | 37      | 16742      | 10108   | 60.4%      | 5/37                  | 0/37                  | 1/37                 |
| Geography       |         |            |         |            |                      |                      |                      |
| USA             | 7       | 2035       | 1008    | 49.5%      | 1/37                  | 0/37                  | 0/37                 |
| USA+Canada      | 1       | 110        | 77      | 70.0%      | 0/37                  | 0/37                  | 0/37                 |
| EU              | 2       | 373        | 249     | 66.8%      | 0/37                  | 0/37                  | 0/37                 |
| Global          | 25      | 13803      | 8538    | 61.9%      | 4/37                  | 0/37                  | 0/37                 |
| Asia/Japan      | 2       | 421        | 236     | 56.1%      | 0/37                  | 0/37                  | 0/37                 |
| Drugs in study  |         |            |         |            |                      |                      |                      |
| Benralizumab    | 9       | 4100       | 2625    | 64.0%      | 2/37                  | 0/37                  | 1/37                 |
| Dupilumab       | 4       | 2992       | 1866    | 62.4%      | 0/37                  | 0/37                  | 0/37                 |
| Mepolizumab     | 5       | 1755       | 1021    | 58.2%      | 0/37                  | 0/37                  | 0/37                 |
| Omalizumab      | 16      | 6571       | 3778    | 57.5%      | 3/37                  | 0/37                  | 0/37                 |
| Reslizumab      | 3       | 1324       | 818     | 61.8%      | 0/37                  | 0/37                  | 0/37                 |
| Age of patients |         |            |         |            |                      |                      |                      |
| < 12 years      | 2       | 962        | 432     | 44.9%      | 0/37                  | 0/37                  | 0/37                 |
| ≥ 12 years      | 34      | 15361      | 9559    | 62.2%      | 5/37                  | 0/37                  | 1/37                 |
| 6–20 years      | 1       | 419        | 117     | 27.9%      | 0/37                  | 0/37                  | 0/37                 |
| Comparator      |         |            |         |            |                      |                      |                      |
| Placebo         | 35      | 16030      | 9629    | 60.1%      | 5/37                  | 0/37                  | 1/37                 |
| BSC             | 1       | 312        | 220     | 70.5%      | 0/37                  | 0/37                  | 0/37                 |
| OAT             | 1       | 400        | 259     | 64.8%      | 0/37                  | 0/37                  | 0/37                 |
| Date of publication |       |            |         |            |                      |                      |                      |
| 2001–2010       | 11      | 4153       | 2296    | 55.3%      | 0/37                  | 0/37                  | 0/37                 |
| 2011–2020       | 26      | 12589      | 7812    | 62.1%      | 5/37                  | 0/37                  | 1/37                 |
| Outcome         |         |            |         |            |                      |                      |                      |
| Efficacy+Safety | 35      | 16523      | 9977    | 60.4%      | 5/37                  | 0/37                  | 1/37                 |
| Efficacy+Safety +PK | 1      | 103        | 42      | 40.8%      | 0/37                  | 0/37                  | 0/37                 |
| Efficacy+Safety +QL | 1      | 116        | 89      | 76.7%      | 0/37                  | 0/37                  | 0/37                 |
| Sample size     |         |            |         |            |                      |                      |                      |
| N 0–100         | 1       | 61         | 29      | 47.5%      | 0/37                  | 0/37                  | 0/37                 |
| N 101–500       | 23      | 5578       | 3399    | 60.9%      | 4/37                  | 0/37                  | 1/37                 |
| N 501–1000      | 10      | 6690       | 3880    | 58.0%      | 1/37                  | 0/37                  | 0/37                 |
| N +1000         | 3       | 4413       | 2800    | 63.4%      | 0/37                  | 0/37                  | 0/37                 |

Abbreviations: EU = European Union, BSC = Best Standard Care, OAT = Optimized Asthma Therapy, PK = Pharmacokinetic, QL = Quality of Life, USA = United States of America.

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Similarly, short reports and letters to the editor were excluded due to the absence of complete data from CTs. The design of the study was limited to variables that were included in the CTs such as location or the phase of the study, but we did not analyze other relevant variables such as race or socioeconomic status. Therefore, we are awarded that evaluating the adequacy of women’s representation in CTs involves a more complex effort, so further studies should corroborate these results. Additionally, the cutoff for adult and pediatric age has been established at the age of 12, since most CTs distinguish between patients older or younger than 12 years. However, some adolescents may not reach puberty until they are not over the age of 12.

In conclusion, women represented more than half of the patients recruited in CTs of mAb for the treatment of severe asthma. The proportion of women in these CTs was higher than that reported by previous studies about other chronic diseases. However, the analysis of the main and secondary variables by sex or gender, as well as the discussion of the results separately by sex, are limited. Therefore, a potential gender bias in these CTs is found.

Supporting information
S1 Checklist. PRISMA 2009 checklist.

Author Contributions
Conceptualization: Beatriz Fernández-Rubio, Ana Belén Guisado-Gil.

Writing – original draft: Pablo Ciudad-Gutiérrez, Beatriz Fernández-Rubio.

Writing – review & editing: Pablo Ciudad-Gutiérrez, Beatriz Fernández-Rubio, Ana Belén Guisado-Gil.

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