REVIEW ARTICLE

Use of dupilumab on the treatment of moderate-to-severe asthma: a systematic review

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SUMMARY

OBJECTIVE: *The objective of this article was to conduct a systematic review of the treatment of moderate-to-severe asthma by administrating Dupilumab.*

METHODS: *A search on the online databases EBSCO, Scielo, PubMed, Medline Bireme, Lilacs, and The New England Journal of Medicine was conducted, publications from 2010 to 2018 were selected. The inclusion criteria were articles which contained control groups, tested the validity of Dupilumab, and verified the response of patients through controlled tests. For the search of such articles, the following keywords were used: "Dupilumab", "asthma", "Bronchial Asthma" AND "Asthma, Bronchial" AND their correspondent in Portuguese "asma", "Asma brônquica" and "Asma brônquica". The exclusion criteria were literature reviews, news, articles without control groups, articles on different subjects, Dupilumab studies on other diseases, articles concerning asthma without the use of Dupilumab, and repeated articles on the databases were discarded.*

RESULTS: *The literature considers that the medication shows a good response for the treatment of moderate-to-severe asthma and assists in the improvement of lung function, aside from resulting in few side effects. It presents good efficacy, safety, and tolerance by patients.*

CONCLUSIONS: *Dupilumab is promising for the treatment of asthma, whereas conventional therapy is deemed to be insufficient. More additional studies are needed to confirm the long-term safety and effectiveness.*

KEYWORDS: *Dupilumab. Asthma. Bronchial diseases. Anti-Asthmatic Agents.*

INTRODUCTION

The objective of this review is to evaluate the results from efficacy tests for a new medication available in the market that promises to improve the life quality of patients with moderate-to-severe asthmatic disease, as an alternative to conventional treatment. The medication under discussion is Dupilumab, already in use in the United States and European Union and approved by ANVISA (National Health Surveillance Agency) in December of 2017 for use in the Brazilian territory. For this article, clinical tests on the use of Dupilumab in comparison with control groups (placebo) for the treatment of asthma were selected.

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METHODS

This article is a literature review based on the search for the keywords "Dupilumab" and "asthma", and their Portuguese equivalent "asma" on the online databases EBSCO, Scielo (Scientific Electronic Library Online), PubMed (US National Library of Medicine), Medline Bireme (Medical Literature Analysis and Retrieval System Online), Lilacs (Literatura Latino-Americana de Ciências da Saúde), and The New England Journal of Medicine.

The inclusion criteria were articles published from 2010 to 2018 written in English, Spanish or Portuguese, containing control groups and patients with moderate-to-severe asthma under treatment with Dupilumab. Given the diversity of studies found, some exclusion criteria were necessary to narrow down the results. The first exclusion criteria were studies on asthma without the use of Dupilumab, studies about Dupilumab usage on other diseases, literature reviews, news, case reports, and repeated articles. As a second exclusion criterion, articles without a control group of patients with moderate-to-severe asthma under Dupilumab treatment were discarded.

A total of 165 articles were found in the online databases. After reading the titles and abstracts, we excluded articles that were repeated on the search databases, articles that did not concern the study topic, news, literature reviews, articles about Dupilumab usage on other diseases, and articles with asthmatic patients who did not use Dupilumab (first exclusion criteria). We found that 159 articles did not correspond to the current study purpose; thus, only six articles remained to be fully read. The second exclusion criterion was the lack of control groups on the treatment of moderate-to-severe asthma with Dupilumab; this excluded one more article, with only five articles remaining that included all the criteria mentioned above. These five articles were used for the final text (Table 1).

On the EBSCO platform, 20 articles were found; none of these were selected for the study after the exclusion criteria mentioned above were applied. Among these studies, 14 were news, three literature reviews, one focused on patients with sinusitis and atopic nasal polyps under treatment with Dupilumab, one was about Dupilumab as treatment for atopic dermatitis and, finally, one was on another subject. On the Lilacs database, only 1 article was found and not excluded based on the first criterion; however, it did not include a control group and was excluded. On The New England Journal of Medicine, 13 studies were found; of these, three were selected based on the inclusion criteria; one article was a duplicate, two were literature reviews, three were news, two were studies regarding atopic dermatitis, and two were articles without the use of Dupilumab; these were, therefore, excluded. On Medline, 64 articles were found; of these, 21 were news, 20 literature reviews, seven studies did not focus on Dupilumab use, six were about nasal polyps, rhinitis and sinusitis, six were about atopic dermatitis, two articles were duplicates; only one was selected based on the inclusion criteria of the research. On the Pubmed platform 67 studies were found, and only one met the inclusion criteria; 22 were literature reviews, 16 were news, 12 were articles about the use of Dupilumab in atopic dermatitis, six were about other diseases, four were duplicates, three did not include the use of Dupilumab, one was a case report and, finally, two were about unrelated subjects to this research. On the Scielo database, no article was found with the keywords (Figure 1).

The study included five articles containing control groups and patients with moderate-to-severe asthma in treatment with Dupilumab (Table 2).

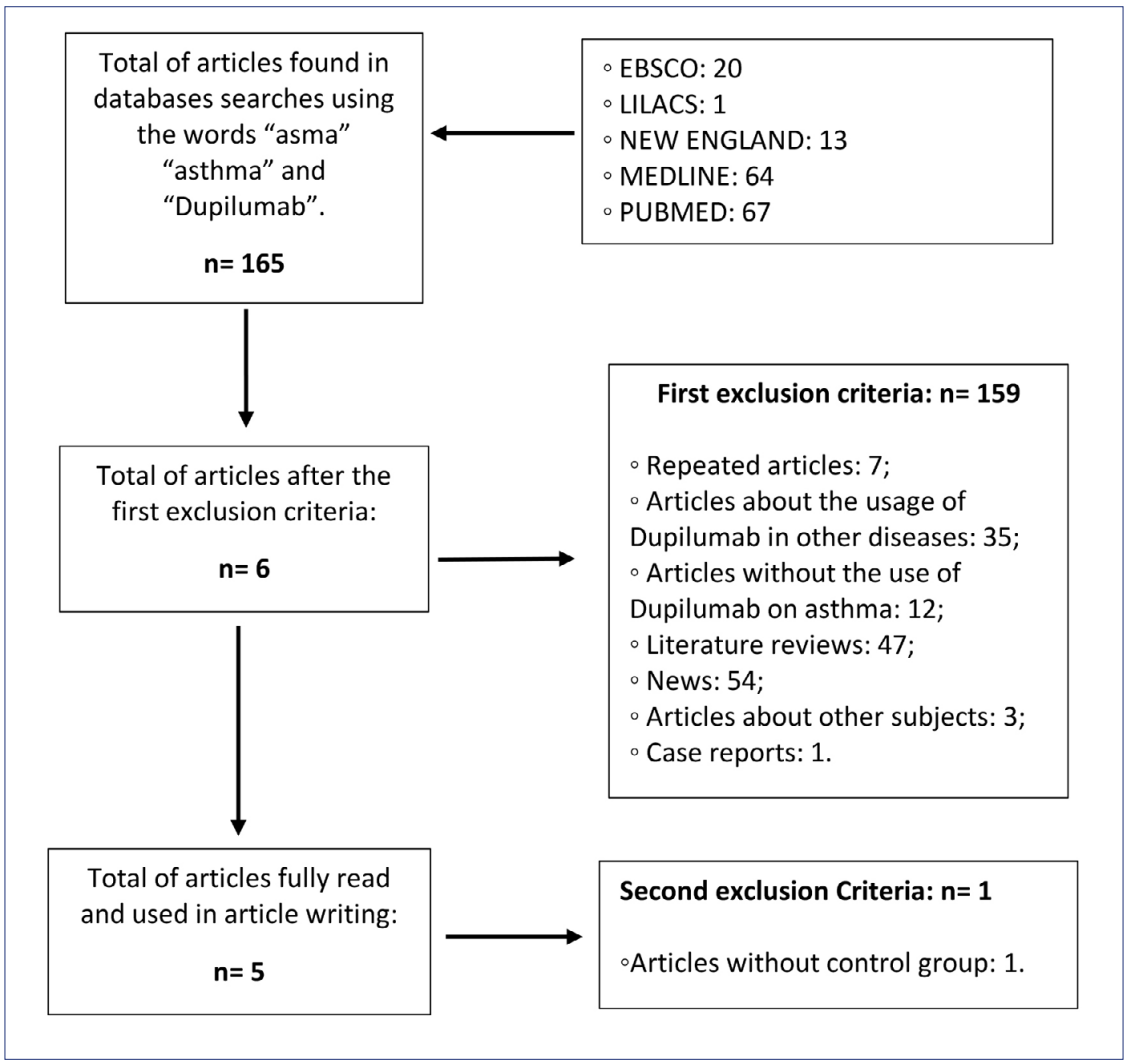
DISCUSSION

According to the World Health Organization (WHO)[6], asthma is a chronic inflammatory disease of the airways, which is characterized by a recurrent crisis of shortness of breath and wheezing. During an asthma attack, the bronchi are swollen and narrow the airways, making the intake and outlet of air from the lungs difficult. The usual symptomatology entails insomnia problems, daytime fatigue, a negative impact on academic and professional performance, and

TABLE 1. SEARCH RESULTS OF THE DATABASES AND SELECTION OF THE ARTICLES.

Database	First Criterion		Second Criterion	
	Total	Included	Total	Included
EBSCO	20	0	0	0
SCIELO	0	0	0	0
MEDLINE	64	1	1	1
LILACS	1	1	1	0
PUBMED	67	1	1	1
NEW ENGLAND J	13	3	3	3
Total	165	6	6	5

FIGURE 1. FLOWCHART OF ARTICLE SELECTION.



a decrease of physical activity standards; problems that reflect directly on the personal quality of life.

Per WHO estimates, all around the world, 235 millions of people have asthma. It is the most common chronic disease among children. However, it has low mortality rates compared to other respiratory diseases, such as chronic obstructive pulmonary disease (COPD)[6].

The causes of asthma are not completely understood, but it is evident that there is an association between genetic predisposition, environmental exposure to inhaled substances and allergenic substances, such as dust mites, animal hair, pollen, chemical irritants, and air pollution, which may result in the irritation of the respiratory tract mucous membranes or cause allergic reactions. Other triggers to the disease are meteorological changes, extreme emotional reactions, and physical exercises, as well as certain drugs like aspirin, other non-steroid anti-inflammatory drugs, and beta-blockers[6].

Most asthma patients have the disease at a low to medium degree and use inhaled corticosteroids with or without the association of bronchodilators or beta-agonists drugs, through inhalation or intravenous administration. However, for severe asthma cases, conventional therapy is often insufficient, leading to several hospitalizations and low life quality, besides being related to secondary inflammatory diseases with an unbalance of interleukins and immune cells. In those cases, frequently, magnesium sulfate or ipratropium bromide are used, along with gas mixtures of oxygen and helium, methylxanthines and non-invasive ventilatory support[7].

Recently, new drugs are being introduced in the industry for the treatment of moderate-to-severe asthma, the so-called monoclonal antibodies, biological drugs synthesized from living organisms that act specifically at the therapeutic targets of the disease's physiopathology. The first biological drug for the treatment of moderate-to-severe asthma was

TABLE 2. SUMMARY OF CHARACTERISTICS OF SELECTED ARTICLES.

Reference	Date of publication	Number of individuals and age group	Medication dosage	Outcome
Busse et al.[1]	May, 2018	1902 patients aged ≥12 years were randomized in a 2: 2: 2: 1 ratio. three groups. Duration of 52 weeks	Group 1: 634 patients. 300 mg of Dupilumab every two weeks. Group 2: 364 patients, 200 mg of Dupilumab every two weeks. Group 3: 317 patients, placebo.	Dupilumab had an excellent response to moderate to severe uncontrolled asthma, provides improvement in respiratory function and control of asthma. Severe exercise reduction and improved quality of life
Castro et al.[2]	June, 2018	1902 patients aged ≥12 years with uncontrolled asthma divided in 2: 2: 1 ratio. Three groups. Duration of 52 weeks.	Group 1: 300 mg of Dupimulab every two weeks. Group 2: 200 mg of Dupimulab every two weeks. Group 3: Placebo.	Patients who received Dupimulab had a significant improvement in lung function, asthma control, and minor exacerbations of severe asthma compared to the placebo group.
Rabe et al.[3]	June, 2018	210 patients aged ≥ 12 years. Two groups. Duration of 24 weeks.	Group 1: 200 mg of Dupimulab every two weeks. Group 2: Placebo.	The use of Dupimulab decreases the exacerbation of severe asthma and improved FEV1.
Wenzel et al.[4]	April, 2016	769 patients aged≥ 18 years, of whom 611 were in the Dupimulab and 158 in the placebo group. Five groups with a ratio of 1: 1: 1: 1: 1. Duration of 24 + 16 weeks.	Group 1: 200 mg of Dupimulab every 4 weeks. Group 2: Dupimulab 300 mg every 4 weeks. Group 3: 200 mg of Dupimulab every 2 weeks. Group 4: 300 mg of Dupimulab every 2 weeks. Group 5: Placebo.	Groups using Dupilumab, except for 200 mg every 4 weeks, showed a significant improvement in FEV1, reduced asthma exacerbation and eosenophilia. The best results were found in the 300 mg Dupilumab group every 2 weeks.
Wenzel et al.[5]	June, 2013	104 patients, divided into two, each with 52 patients. One group received Dupilumab and the other placebo. Duration of 12 weeks.	Group 1: 300 mg Dupilumab weekly. Group 2: Placebo.	The use of Dupilumab reduced asthma exacerbations and levels of inflammatory markers associated with Th2, in addition to showing improvement in lung function.

Subtitle: "≥" = Bigger or equal. Th2= T-helper-2-cell. FEV1= forced expiratory volume in 1 s.

the monoclonal antibody known as Omalizumab approved in 2003 by the United States' *Food and Drug Administration* (FDA), whose use was released to patients aged 12 years old or older. This medication targets the Fc fraction of free IgE antibodies and lymphocytes membranes. Such treatment was approved in 2005 by the *European Medicines Agency* (EMA) to individuals with uncontrolled severe allergic asthma, aged between 6 and 12 years and older than 12 years. Since then, several other monoclonal antibodies that target the IL-5 were produced in order to treat asthma. On the current scenario, researchers study monoclonal antibodies targeting the interleukins IL-13 and IL-4, in addition to Th2 cells[8].

This was the scenario when Dupilumab was released, a fully human monoclonal antibody that acts against the alpha-receptor of the interleukin 4 (IL-4) by inhibiting the IL-4/IL-13 signaling, used as a subcutaneous injection. On the treatment of patients with asthma, it is used instead of glucocorticoids or corticosteroids to obtain the most beneficial results at the disease control and treatment[9].

In a study performed with previously treated asthmatic patients, the concomitant use of Dupilumab reduced the glucocorticoids use on 70,1%, compared with the placebo group (retrenchment of 41,9%); the results were very promising. At the same case, 80% of the patients had a reduction of glucocorticoids dose of at least 50%, 69% had a dose adjustment to less than 5 mg a day, and 48% had the use of glucocorticoids completely discontinued. The rates of severe asthma exacerbation were 59% lower than in the placebo group, apart from an increase in forced expiratory volume in the first second (FEV1), which indicates improvement of lung function[3].

On uncontrolled asthma, the complementary use of Dupilumab every two weeks reduced twice as many episodes of exacerbated asthma attacks compared to placebo. FEV1 demonstrated a significant increase over time with the use of Dupilumab, but

4,1% of the patients exhibited eosinophilia after the treatment initiation[2].

Researchers performed a study with patients that had moderate-to-severe asthma and a high eosinophil count. A weekly dose of Dupilumab or placebo was administered. Patients were also instructed to discontinue conventional treatment during the study. The use of Dupilumab reduced asthmatic exacerbations by 87% compared to the placebo, in addition to improving most levels of pulmonary function. The research also revealed a reduction in biomarkers associated with inflammation by Th2 cells. In the same study, the safety and tolerability of the drug were evaluated. Concerning safety, Dupilumab was similar to the placebo and, in terms of effectiveness in the treatment of eosinophilic asthma, proved its effectiveness. Of the adverse reactions, the most common were nausea, headache, injection site reactions, and nasopharyngitis, all more frequent with the drug than with the placebo. Transient elevation of eosinophils in the peripheral blood of individuals also occurred, such as a rebound effect in response to IL-5 and blockade of IL-13 and IL-4. One patient developed hypereosinophilic syndrome; the treatment was discontinued, and corticotherapy was administered with immediate improvement[5].

In a second study with adults using corticosteroid therapy, the use of Dupilumab demonstrated significant increases in FEV1. The general population, as well as the group with eosinophil count below 300µL, presented similar results. As in the previous study, rates of asthmatic exacerbation were significantly reduced[4].

In a study that used dose variation to perform an analysis, the administration of 300 and 200 mg every two weeks presented better effectiveness when compared to the dose administered every four weeks. Both doses were well tolerated when compared to the placebo. In addition, the fact that Dupilumab was effective in patients who had an eosinophil count <300 and >300 cells/µL at the start of the study was of particular interest since other drugs are more effective in patients with high eosinophil counts[4].

CONCLUSIONS

It can be noticed that all the tests with control groups conducted up to now had similar results, showing that Dupilumab, a biological drug inhibitor of the interleukins IL-4 and IL-13 targeting Th2 cells, is promising for the treatment of asthma in moderate-to-severe cases when the conventional therapy proves to be insufficient because, aside from assisting with the symptoms control and reducing the exacerbation rate, it improves the patient pulmonary function. Its effects overcome the risks of collateral effects, such as peripheral eosinophilia and reactions at the injection site.

At the end of this review, we also concluded that additional more extensive trials are necessary to confirm the long-term effectiveness and safety of Dupilumab and evaluate the eosinophilic elevations that occurred in patients with asthma and serum elevated basal eosinophilia.

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Place of study: Hospital Servidor Público Estadual São Paulo (HSPE).

Author's contribuitions

Cíntia Bassani - Leonardo Saraiva - Article writing and methodology

Larissa Rossi; Kaian Siveris; Rafaella Lorenzon Sferelli; Luciana Kase Tanno - methodology.

RESUMO

OBJETIVO: *Este artigo teve como objetivo fazer uma revisão sistemática sobre o tratamento da asma moderada a grave, administrando Dupilumabe.*

MÉTODOS: *Foi realizada uma busca nas plataformas on-line Ebsco, SciELO, PubMed, Medline Bireme, Lilacs e New England Journal of Medicine. Foram selecionadas publicações de 2010 a 2018 referentes a artigos que continham grupos controle, que testaram a validade de Dupilumabe e verificaram a resposta dos pacientes por meio de testes controlados. Para a busca desses artigos, foram utilizadas as seguintes palavras-chave: "Dupilumab", "asthma", "Bronchial Asthma" and "Asthma, Bronchial". E o correspondente em português: "asma", "Asma brônquica" and "Asma brônquica". Os critérios de exclusão, revisões de literatura, notícias, artigos sem grupos de controle, artigos sobre diferentes assuntos, estudos de Dupilumabe sobre outras doenças, artigos sobre asma sem uso de Dupilumabe e artigos repetidos em plataformas de busca foram descartados.*

RESULTADOS: *A literatura aponta que a medicação apresenta boa resposta no tratamento da asma moderada a grave e auxilia na melhora da função pulmonar, além de resultar em poucos efeitos colaterais. Apresenta boa eficácia, segurança e tolerância pelos pacientes.*

CONCLUSÕES: *Dupilumabe é promissor para o tratamento da asma em que a terapia convencional se revela insuficiente. Maiores estudos adicionais são necessários para confirmar a segurança e a eficácia em longo prazo.*

PALAVRAS-CHAVE: *Dupilumabe. Asma. Broncopatias. Antiasmáticos.*

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