Selection of biologics in severe asthma: a multifaceted algorithm

1. Omalizumab

Omalizumab, the first biological approved for severe asthma is a IgG1 humanized monoclonal antibody directed against the Cε3 domain of IgE, thus avoiding the union of IgE to its specific receptors. In patients 12 years of age and older, omalizumab is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and who have reduced lung function (FEV1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high- dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist. In children between 6 and 12 years of age the requisites are the same, except that FEV1 can be normal[1].

There are two published meta-analyses about the treatment of omalizumab in asthma[2,3], and a systematic review that was part of a health technology assessment[4]. In a recent review of all three of them, the conclusion was that the treatment with omalizumab induced a reduction of clinically significant asthma exacerbations and hospitalizations respect to placebo or standard of care in adults and adolescents[5]. Omalizumab was also associated with a reduction in inhaled corticosteroid use and improved asthma symptoms compared to placebo in adults and adolescents. Concerning pulmonary lung function, in the meta-analysis of Normansell et al[2], a very modest improvement for the change from baseline FEV1 predicted and morning PEF was observed with omalizumab compared with placebo.

In addition, after the approval of omalizumab, a great number of real life studies have been published. In a recent meta-analysis of 25 of them, Alhossan et al[6] concluded that the treatment with omalizumab associated with a large proportions of patients having a good to excellent response (Global Evaluation of Treatment Effectiveness scale); improvements in FEV1, AQLQ, and ACT; reductions in the use of oral and inhaled corticosteroid; and a reduction in the exacerbation and hospitalization rates.

As biological are expensive treatments, the identification of patients that could better respond to omalizumab is crucial. In a pooled analysis of two multicenter, double-blind, randomized, placebo-controlled phase III studies with omalizumab, the authors found that patients who benefit the most of omalizumab treatment were those receiving high doses of BDP, those with a history of frequent emergency asthma treatment, and those with poor lung function[7]. In addition, in a post hoc analysis of the INNOVATE study[8], Bousquet et al. found that patients with total serum IgE levels under 76 UI/L had a lower response that those patients with total serum IgE over this threshold, although no baseline characteristics were found to predict the response to omalizumab[9]. In another post hoc analysis of the EXTRA study, Hanania et al[10,11] explored whether there were differences in exacerbations in patients with different expressions on FE_{NO}, peripheral blood eosinophils and periostin. They found that after 48 weeks of omalizumab, reductions in exacerbations were greater in high versus low subgroups for all

doi: 10.18176/jiaci.0398

three biomarkers: FE_{NO} (>19 ppb), eosinophils (>260 μL), and periostin (> 50 ng/mL). In addition, a very recent study evaluated the response to omalizumab using patient enrichment criteria from clinical trials of novel biologics in asthma[12]. The authors selected the following criteria: peripheral eosinophil count (<300/μL vs ≥300/μL), FEV1 at baseline (FEV1 <65% vs FEV1 ≥65% predicted), use of inhaled beclomethasone dipropionate (<600 mcg/day vs ≥600 mcg/day), and LABA use (yes vs no). They found that the percentage of reduction of the exacerbation rate of omalizumab vs placebo was higher in patients with the higher cut-off levels of all the previous criteria as well as in patients with history of previous emergency asthma treatment or hospitalization. In the case of eosinophil counts and based on a negative binomial regression model, the authors stated that the efficacy benefit of omalizumab increased with increasing baseline eosinophil counts, suggesting that response to omalizumab is observed across a wide range of eosinophil levels, although it was better with higher eosinophil levels.

Another perspective is that based on real life studies. In the multicenter, prospective, PROSPERO study (Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab)[13], the authors concluded that Omalizumab treatment during 48 weeks in patients with asthma resulted in improved exacerbation rates, reduced hospitalizations, and improved ACT scores compared with pretreatment values, regardless of high (peripheral blood eosinophils ≥300 cells or FENO ≥25 ppb) or lower biomarker status (peripheral blood eosinophils ≤300 cells or FENO ≤25 ppb). They found greater improvement in lung function in adolescents. They also found that there were responder patients with IgE levels that felt outside the recommended limits. In a recent retrospective observational study of 340 severe asthmatics who had already been recruited for two of our previous studies, Sposato et al.[14] analyzed possible factors that may influence Omalizumab effectiveness in a real-life setting and found that older age, obesity, comorbidities, smoking habits, nasal polyposis and allergic poly-sensitization may reduce the effectiveness of Omalizumab treatment, whereas asthmatics with an asthma family history, the presence of rhinitis/sinusitis and a high level of total IgE may have a better response to Omalizumab.

Asthma comorbidities should also be considered when selecting a biologic. In this sense, omalizumab has proven to be effective in chronic urticaria, as confirmed by meta-analysis[15]. It is worthy to note that there are no clinical trails showing a significant reduction on the dose of oral corticosteroids in asthmatic patients treated with omalizumab. Reduction on the dose of oral corticosteroids has notwithstanding been described in observational studies[16-19]. Concerning allergic bronchopulmonary aspergillosis (ABPA), Xi et al[20], in a recent synthesis review of the published literature found that omalizumab treatment provided a clinically important reduction in serum IgE, exacerbation rates and steroid requirement, and also showed attenuated asthma symptoms and improved pulmonary function parameters in patients with ABPA. Finally, there is limited evidence showing efficacy of omalizumab in non-allergic asthma [18,21-23]

doi: 10.18176/jiaci.0398

2. Anti IL-5

In most asthmatic patients, the characteristic inflammatory pattern includes an increase in the number of T helper type 2 (Th2) lymphocytes, type 2 innate lymphoid cells (ILC-2s), natural killer (NK) cells, as well as mast cells, basophils, and activated eosinophils through the IL-5 pathway. Mepolizumab and reslizumab are monoclonal antibodies against IL-5, and benralizumab is a monoclonal antibody targeting the alpha chain of IL-5 receptor (IL-5Rα), are licensed as additional treatment in adult patients (18 years and older) with severe uncontrolled persistent eosinophilic asthma

a) Mepolizumab

In the DREAM study[24], 621 patients, 12-74 years of age, were randomized to receive placebo or one of three doses of intravenous mepolizumab (75, 250 or 750 mg) in parallel groups for a year. There was a decrease of approximately 50% in clinical significant exacerbations in all mepolizumab groups compared to placebo without a dose-response effect reported. Mepolizumab also reduced blood and sputum eosinophil counts with a dose-response effect in the number of eosinophils in sputum. A post hoc analysis of the DREAM trial showed that, overall, the reduction in exacerbations with mepolizumab was observed irrespective of IgE levels or atopy and were more frequent in winter months but treatment response was unaffected by season or atopy[25]. The MENSA study assessed the rate of exacerbations in patients receiving either intravenous (i.v.) (75 mg) or subcutaneous (s.c.) (100 mg) mepolizumab[26]. The rate of exacerbations was reduced by approximately 50% in both active groups compared to placebo. Also, an increase in FEV1 as well as in the asthma control questionnaire (ACQ) was observed in patients receiving the drug. Ortega et al.[27] conducted a post hoc analysis to assess the relationship between baseline blood eosinophil counts and efficacy of mepolizumab from the two aforementioned studies (DREAM and MENSA studies), stratifying patients by different baseline blood eosinophil thresholds. This analysis showed a close relationship between baseline blood eosinophil count and clinical efficacy of mepolizumab in patients with severe eosinophilic asthma and a history of exacerbations. The exacerbation rate reduction with mepolizumab versus placebo increased progressively from 52% in patients with a baseline blood eosinophil count of at least 150 cells/uL to 70% in patients with a baseline count of at least 500 cells/uL. At a baseline, an eosinophil count lower than 150 cells/uL, predicted efficacy of mepolizumab was reduced.
The SIRIUS trial, involving 135 patients, was conducted to compare the degree of oral corticosteroid reduction after receiving 100 mg of s.c. mepolizumab over a 20 week period against placebo[28]. There was a significant glucocorticoid sparing effect, a significant reduction of exacerbations and an improvement in asthma control in the group receiving mepolizumab. A 52-week, open-label extension of MENSA and SIRIUS studies (COSMOS) showed a favorable safety profile of mepolizumab and indicated a durable and stable effect over time, supporting long-term treatment in patients with severe eosinophilic asthma[29]. Finally, in the 24-week MUSCA study, mepolizumab was associated with significant improvements

doi: 10.18176/jiaci.0398

in quality of life (Saint George's Respiratory Questionnaire) in patients with severe eosinophilic asthma, and had a safety profile similar to that of placebo[30].

b) Reslizumab

In two multicenter phase 3 trials, patients with inadequately controlled asthma with medium-to-high doses of ICS, 400 eosinophils/uL or higher in peripheral blood and at least one exacerbation the previous year, were randomized to receive either 3 mg/kg of intravenous reslizumab or placebo, for 1 year[31]. In both trials, patients receiving reslizumab had a significant reduction in the frequency of exacerbations compared to those receiving placebo. Adverse events were similar in both groups, the most common being worsening asthma symptoms and nasopharyngitis. Another phase 3 study further characterized the efficacy and safety of reslizumab in patients with asthma inadequately controlled by at least a medium-dose ICS and with a blood eosinophil count ≥400 cells/uL[32]. Patients were randomized to receive reslizumab 0.3 or 3.0 mg/kg or placebo administered once every 4 weeks for 16 weeks. The primary end point was change from baseline in pre-bronchodilator FEV1 over 16 weeks, and secondary end points included FVC, forced expiratory flow at 25-75% of FVC, patient-reported control of asthma symptoms, SABA use, blood eosinophil levels, and safety. Reslizumab significantly improved lung function, asthma control and symptoms, and quality of life. It was well tolerated in patients with inadequately controlled asthma (despite standard therapy) and elevated blood eosinophil levels. Overall, the 3.0-mg/kg dose of reslizumab provided greater improvements in asthma outcomes vs. the 0.3-mg/kg dose, with comparable safety[32].

A recent systematic review and meta-analysis revealed no differences between mepolizumab and reslizumab in terms of efficacy or safety measures[33].

c) Benralizumab

Benralizumab is a humanized anti-interleukin-5 receptor alpha chain (IL-5Ra) monoclonal antibody that binds to an epitope on the alpha subunit of IL-5R that is near the IL-5 binding site, thus inhibiting IL-5 receptor signaling independent of the ligand, leading to depletion of eosinophils and basophils. Benralizumab possess a dual mechanism against eosinophils because it neutralizes the key survival signal for these cells provided by IL-5, and also directly activates FcγRIIIa-induced antibody dependent cytotoxicity, driven by NK cells[34]. Pivotal Phase III studies with more than 3,000 uncontrolled severe asthma patients included, prone to exacerbations, had clearly documented a significant reduction in the exacerbation rate, symptom burden, oral corticosteroid maintenance doses and a consistent improvement of lung function. In comparison to placebo, the annual rates of asthma exacerbations were found to be reduced by 28% in the CALIMA study[35], 51% in SIROCCO[36] and 70% in ZONDA[37]. The results of these studies and a recent meta-analysis of benralizumab phase II and III studies [38] clearly supported a maintenance dose interval of 8 weeks which confers to benralizumab a clear advantage in terms of adherence and economy, compared with the rest of biological drugs whose maintenance regimen are between 2 to 4

doi: 10.18176/jiaci.0398

weeks. Post hoc analysis support too, a more intense clinical effect of benralizumab in terms of exacerbation rates and lung function, for patients with need of maintenance oral corticosteroid use, 3 or more severe asthma exacerbations, nasal polyps and air trapping [39,40], especially in those patients with blood eosinophils levels equal or higher than 300 mm^3.

3. Dupilumab

Dupilumab is a fully human IgG4 monoclonal antibody directed to the α subunit of the interleukin-4 receptor (IL4Rα). As IL4Rα can constitute a heterodimer with the common γ chain (γC) (type I receptor), and a heterodimer with the IL13α chain (IL13Rα1) (type II receptor), dupilumab blocks both receptors, which bind IL4 and IL13, respectively. Therefore dupilumab inhibits the downstream signaling of IL4 and IL13, which are two essential Th2 cytokines[41 42].

The pivotal LIBERTY ASTHMA QUEST trial enrolled 1902 patients that were on treatment with medium or high dose of ICSs and up to 2 additional controller medicines[43]. Dupilumab 300 mg every two weeks (qw2) following a load dose of 600 mg reduced the adjusted annualized rate of severe asthma attacks by 46% in the overall population. A relation with baseline eosinophils was observed: Patients with a baseline blood eosinophil between 150 to 300 per cubic millimeter, had an exacerbation rate 47% lower rate with dupilumab than with placebo); patients with an eosinophil count of 300 or more per cubic millimeter had a 67.4% lower rate with dupilumab than with placebo; patients with less than 150 eosinophils per cubic millimeter did not significantly differ in the exacerbation rate compared to placebo. The change from baseline in the FEV_1 before bronchodilator with dupilumab 300 mg q2w was 130 mL (9%) over matched placebo for the general population. This difference was of 210 mL (11%) or 240 mL (18%) in patients with ≥150 or ≥300 eosinophils/μL respectively. No significant difference over placebo was observed in patients with a blood eosinophil count of less than 150 per cubic millimeter at baseline. In patients with a FeNO of 50 ppb or more, the difference as compared with matched placebo was 0.39 liters. In a post hoc analysis, the greatest treatment benefit as compared with placebo was observed in patients with elevated type 2 biomarkers (both baseline blood eosinophil count of ≥150 per cubic millimeter and baseline FeNO ≥25 ppb)[44].

Dupilumab has also shown efficacy in the reduction of oral corticosteroids. In the LIBERTY ASTHMA VENTURE trial 210 patients (103 in the dupilumab arm and 107 in the placebo arm) with severe asthma and regular use of maintenance oral corticosteroids in the 6 months prior to enrolment were included)[45]. Dupilumab (300 mg q2w) reduced the use of oral corticosteroids by 70.1% (median reduction of 100%) compared with 41.9% in the case of placebo (median reduction of 50%). Again, in patients with ≥300 eosinophils/μL, the decrease was greater (80% on average with dupilumab and 43% for placebo. In spite of the reduction in oral corticosteroids patients treated with dupilumab had 59% and 71% fewer exacerbations in the overall population and in patients with ≥300 eosinophils/μL. Also, dupilumab improved the FEV1 by 220 mL compared with placebo in the

overall population, and by 320 mL (25%) in patients with ≥300 eosinophils/μL. In patients with less than 150 eosinophils/μL, dupilumab treatment resulted in a rate of severe asthma exacerbations that was 60% lower than the rate with placebo and in an FEV1 that was higher by 0.24 liters. Transient eosinophilia was observed in approximately 1 in 7 dupilumab-treated patients.

Also, dupilumab has shown efficacy in patients with CRSwNP, with a positive effect of dupilumab on nasal polyp score, CT score, 22-item SinoNasal Outcome Test, and sense of smell in patients with CRSwNP refractory to topical corticosteroids[46]. A recent study of dupilumab 300 mg weekly versus placebo in patients with eosinophilic esophagitis, has shown significantly improvements in dysphagia, esophageal eosinophil counts, endoscopic features, histology, and esophageal distensibility compared with placebo[47]. In addition, dupilumab has been licensed for the treatment of atopic dermatitis[48,49].

doi: 10.18176/jiaci.0398

References

1. https://www.ema.europa.eu/documents/product-information/xolair-epar-product-information_en.pdf.
2. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. Cochrane Database Syst Rev 2014:CD003559.
3. Lai T, Wang S, Xu Z, et al. Long-term efficacy and safety of omalizumab in patients with persistent uncontrolled allergic asthma: a systematic review and meta-analysis. Scientific reports 2015;5:8191.
4. Norman G, Faria R, Paton F, et al. Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation. Health Technol Assess 2013;17:1-342.
5. Omalizumab Treatment for Adults and Children with Allergic Asthma: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2015 Mar 9. Available from: https://www.ncbi.nlm.nih.gov/books/NBK280029.
6. Alhossan A, Lee CS, MacDonald K, Abraham I. "Real-life" Effectiveness Studies of Omalizumab in Adult Patients with Severe Allergic Asthma: Meta-analysis. J Allergy Clin Immunol Pract 2017;5:1362-70 e2.
7. Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H. Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. Chest 2004;125:1378-86.
8. Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy 2005;60:309-16.
9. Bousquet J, Rabe K, Humbert M, et al. Predicting and evaluating response to omalizumab in patients with severe allergic asthma. Respir Med 2007;101:1483-92.
10. Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. Annals of internal medicine 2011;154:573-82.
11. Hanania NA, Wenzel S, Rosen K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med 2013;187:804-11.
12. Casale TB, Chipps BE, Rosen K, et al. Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma. Allergy 2018;73:490-7.
13. Casale TB, Luskin AT, Busse W, et al. Omalizumab Effectiveness by Biomarker Status in Patients with Asthma: Evidence From PROSPERO, A Prospective Real-World Study. J Allergy Clin Immunol Pract 2018.
14. Sposato B, Scalese M, Milanese M, et al. Factors reducing omalizumab response in severe asthma. European journal of internal medicine 2018.
15. Zhao ZT, Ji CM, Yu WJ, et al. Omalizumab for the treatment of chronic spontaneous urticaria: A meta-analysis of randomized clinical trials. J Allergy Clin Immunol 2016;137:1742-50 e4.

doi: 10.18176/jiaci.0398

16. Molimard M, de Blay F, Didier A, Le Gros V. Effectiveness of omalizumab (Xolair) in the first patients treated in real-life practice in France. Respir Med 2008;102:71-6.
17. Brusselle G, Michils A, Louis R, et al. "Real-life" effectiveness of omalizumab in patients with severe persistent allergic asthma: The PERSIST study. Respir Med 2009;103:1633-42.
18. de Llano LP, Vennera MdC, Álvarez FJ, et al. Effects of Omalizumab in Non-Atopic Asthma: Results from a Spanish Multicenter Registry. Journal of Asthma 2013;50:296-301.
19. Vennera Mdel C, Perez De Llano L, Bardagi S, et al. Omalizumab therapy in severe asthma: experience from the Spanish registry--some new approaches. The Journal of asthma : official journal of the Association for the Care of Asthma 2012;49:416-22.
20. Li JX, Fan LC, Li MH, Cao WJ, Xu JF. Beneficial effects of Omalizumab therapy in allergic bronchopulmonary aspergillosis: A synthesis review of published literature. Respir Med 2017;122:33-42.
21. Garcia G, Magnan A, Chiron R, et al. A proof-of-concept, randomized, controlled trial of omalizumab in patients with severe, difficult-to-control, nonatopic asthma. Chest 2013;144:411-9.
22. Pillai P, Chan YC, Wu SY, et al. Omalizumab reduces bronchial mucosal IgE and improves lung function in non-atopic asthma. Eur Respir J 2016;48:1593-601.
23. Bourgoin-Heck M, Amat F, Trouvé C, et al. Omalizumab could be effective in children with severe eosinophilic non-allergic asthma. Pediatric Allergy and Immunology 2018;29:90-3.
24. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 2012;380:651-9.
25. Ortega H, Chupp G, Bardin P, et al. The role of mepolizumab in atopic and nonatopic severe asthma with persistent eosinophilia. Eur Respir J 2014;44:239-41.
26. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med 2014;371:1198-207.
27. Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. The Lancet Respiratory Medicine 2016;4:549-56.
28. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 2014;371:1189-97.
29. Lugogo N, Domingo C, Chanez P, et al. Long-term Efficacy and Safety of Mepolizumab in Patients With Severe Eosinophilic Asthma: A Multi-center, Open-label, Phase IIIb Study. Clin Ther 2016;38:2058-70 e1.
30. Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. Lancet Respir Med 2017;5:390-400.
31. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two

multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 2015.
32. Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for Inadequately Controlled Asthma With Elevated Blood Eosinophil Levels: A Randomized Phase 3 Study. Chest 2016;150:789-98.
33. Henriksen DP, Bodtger U, Sidenius K, et al. Efficacy, adverse events, and inter-drug comparison of mepolizumab and reslizumab anti-IL-5 treatments of severe asthma–a systematic review and meta-analysis. European clinical respiratory journal 2018;5:1536097.
34. Pelaia C, Vatrella A, Bruni A, Terracciano R, Pelaia G. Benralizumab in the treatment of severe asthma: design, development and potential place in therapy. Drug Des Devel Ther 2018;12:619-28.
35. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. The Lancet 2016.
36. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. The Lancet 2016.
37. Nair P, Wenzel S, Rabe KF, et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. N Engl J Med 2017.
38. Liu T, Wang F, Wang G, Mao H. Efficacy and safety of benralizumab in patients with eosinophilic asthma: a meta-analysis of randomized placebo-controlled trials. Frontiers of medicine 2017:1-10.
39. FitzGerald JM, Bleecker ER, Menzies-Gow A, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. The Lancet Respiratory Medicine 2018;6:51-64.
40. Bleecker ER, Wechsler ME, FitzGerald JM, et al. Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma. European Respiratory Journal 2018;52:1800936.
41. Chung KF. Dupilumab: a potential new treatment for severe asthma. Lancet 2016;388:3-4.
42. Sastre J, Davila I. Dupilumab: A New Paradigm for the Treatment of Allergic Diseases. J Investig Allergol Clin Immunol 2018;28:139-50.
43. Castro M, Corren J, Pavord ID, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. New England Journal of Medicine 2018.
44. Corren J, Castro M, Chanez P, et al. Dupilumab improves symptoms, quality of life, and productivity in uncontrolled persistent asthma. Ann Allergy Asthma Immunol 2019;122:41-9 e2.
45. Rabe KF, Nair P, Brusselle G, et al. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. N Engl J Med 2018.
46. Bachert C, Mannent L, Naclerio RM, et al. Effect of Subcutaneous Dupilumab on Nasal Polyp Burden in Patients With Chronic Sinusitis and Nasal Polyposis: A Randomized Clinical Trial. JAMA 2016;315:469-79.
47. Wechsler JB, Hirano I. Biological therapies for eosinophilic gastrointestinal diseases. Journal of Allergy and Clinical Immunology 2018;142:24-31. e2.

doi: 10.18176/jiaci.0398

48. Beck LA, Thaci D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med 2014;371:130-9.
49. Thaci D, Simpson EL, Beck LA, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. Lancet 2016;387:40-52.

doi: 10.18176/jiaci.0398