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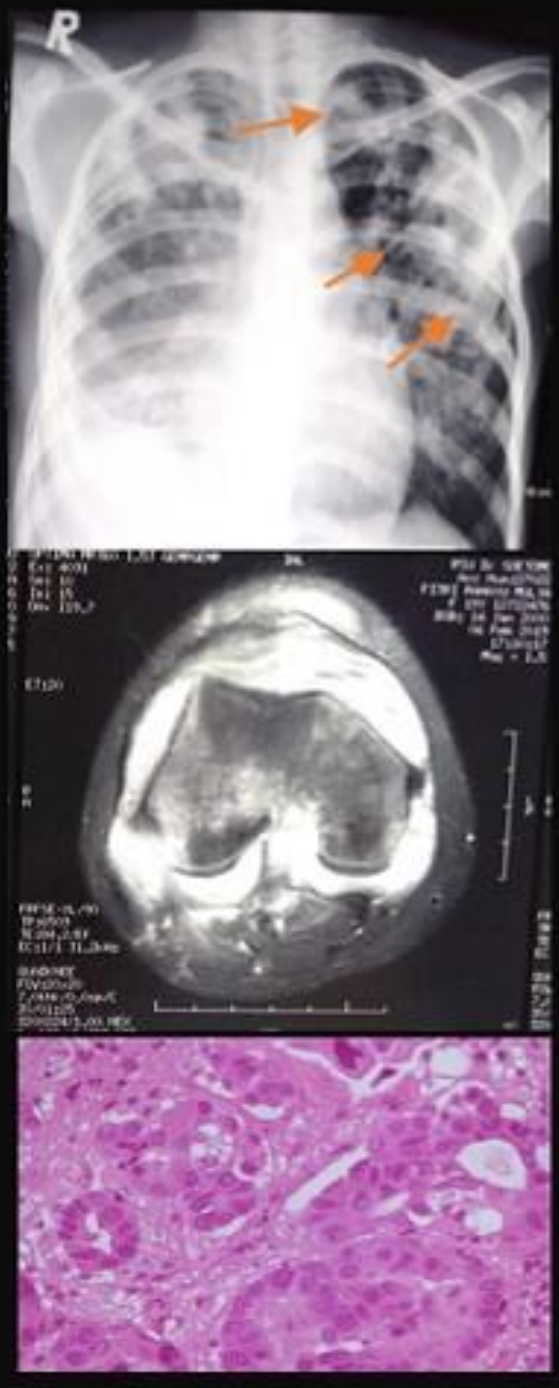

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INTRODUCTION

Jurnal Respirasi (JR) (p-ISSN: 2407-0831, e-ISSN: 2621-8372) was previously named Majalah Kedokteran Respirasi (MKR) which was established in 2010. The chief editor of MKR was Yusuf Wibisono, dr., Sp.P(K), FCCP. In 2015, MKR changed its name to **JR** with Winariani Koesoemoprodjo, dr., Sp.P(K), MARS, FCCP as its chief editor.

JR is a national journal published by Department of Pulmonology & Respiratory Medicine, Faculty of Medicine Universitas Airlangga/Dr. Soetomo General Hospital, Surabaya. **JR** is published three times a year, every January, May, & September, and contains 6 (six) complete texts in English. **JR** provides a forum for original article, case reports, and literature reviews.

ACCREDITATION

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- Lung Cancer
- Asthma
- Chronic Obstructive Pulmonary Disease (COPD)
- Asthma-COPD Overlap Syndrome (ACOS)
- Mediastinal Tumor
- Pleural Effusion
- Pneumothorax
- Fluidopneumothorax
- Chemotherapy
- Radiotherapy
- Superior Vena Cava Syndrome (SVCS)
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- Respiratory Distress
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- Pneumoconiosis
- Obstructive Sleep Apnea (OSA)
- Lung Mycosis
- Pneumocystis carinii
- Middle East Respiratory Syndrome Coronavirus (MERS CoV)
- Severe Acute Respiratory Syndrome (SARS)
- Immunology
- Endobronchial Ultrasound Bronchoscopy Procedure (EBUS)
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- Non-Invasive Ventilation (NIV)
- Pulmonary Disease and Other Actions

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REVIEW ARTICLE

REVIEW ARTICLE

Biological Therapy for Asthma

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ABSTRACT

Asthma is a heterogeneous chronic inflammatory disease in the respiratory tract that leads to recurrent episodic symptoms. Study about the mechanism of pathophysiology and immunology which stimulates chronic inflammation in asthma has been greatly developed. The understanding of inflammation mediator that is predominant on various asthma phenotypes could be useful for development of diagnosis and targeted therapy. Standard asthma therapy administered through the airway has limited effects only in the airway. The knowledge of molecular pathophysiology and immunology of this disease developed interest of the drugs that perform proximally from inflammation process in the airway, in this case is biological therapy. Several biological therapies have been investigated for its efficacy on human, including Anti IgE (Omalizumab), Anti Interleukin-5 (Mepolizumab, Reslizumab, Benralizumab), Anti Interleukin-4/Interleukin-13 (Dupilumab), and Anti Interleukin-17 (Secukinumab and Brodalumab).

INTRODUCTION

Asthma is a heterogeneous chronic inflammation disorder in respiratory tract that impacts on about 300 million people around the world.[1] This chronic inflammation will trigger hyperresponsiveness in respiratory tract that could lead to recurrent episodic symptoms including wheezing, shortness of breath, chest tightness, and cough which mainly occur at night or dawn.[2] Majority of asthmatics can achieve controlled disease with standard controller therapy (high dose of inhaled corticosteroid (ICS) plus long-acting bronchodilator), however, about 5% of patients had severe uncontrolled asthma with standard therapy. Patients with severe uncontrolled asthma compared to patients with well controlled asthma experienced increased of hospitalization period, poor quality of life (QOL), impaired life style, and adverse effects from oral corticosteroid (OCS).[3]

Over the past decades, new understandings in complex asthma pathophysiology have led us to new therapeutic options for asthma. Clinicians and researchers have developed the knowledge that asthma is not a uniform disease, but a spectrum disease with various phenotypes that is defined by different clinical profiles (genetic, environtmental risk factor, age when onset, clinical manifestation, prognosis, response towards therapy, specific IgE, and eosinophil in body fluids) and molecular (chemokynes, cytokines, and protein products), called as endotype.[3]

Research on mediators and inflammatory cells that are predominant in various asthma phenotypes is continuing to develop diagnosis and targeted therapy such as biological therapy. Biological therapy is now indicated for uncontrolled severe asthma patients after particular stage of treatment.[1] This therapy is mostly targeting inflammation molecules from type 2 (T2) inflammation pathway and is effective in reducing exacerbation, maintaining the control of asthma symptoms, and reducing the use of systemic steroids and its side effects.[3] In this literature review, we discussed biological therapy for asthma.

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Asthma Immunopathogenesis

In the last decade, understanding the mechanisms of pathophysiology and immunology that stimulates chronic inflammation in asthma has been greatly developed. Complex interraction between cytokines, recruited cells, resident tissue, and extrinsic factor, such as allergen and respiratory virus, triggers airway injury and inflammation that sustains chronic asthma symptoms and contributes to the last stage of asthma, is called airway remodeling. Airway remodeling is an alteration of structure seen in small and large respiratory tract in some asthma patients, including subepithelial fibrosis, goblet cell hyperplasia, smooth muscle hypertrophy, reticular basement membrane thickening, and neovascularization.[4]

There are some cells and inflammatory mediators of asthma that have a bigger role than others. Those cells and mediators are Th2 lymphocytes, eosinophils, some growth factors, and cytokines. Th2 produces IL-5 and innate lymphoid cells (ILC)-2 to stimulate the recruitment and growth of eosinophil to the airway. IL-13 and IL-4 perform on B cells to induce class switching of immunoglobulin E (Ig E). Granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-3, and IL-5 are cytokines that are recognized in promoting eosinophil recruitment, growth, and differentiation. Additional cytokines that also have some roles are thymic stromal lymphopoietin (TSLP) and IL-33, which are synthesized by epithelium cell and fibroblast that promote maturation and activation of dendritic cell and naive type 2 limphoid cell (Th0). The activation of dendritic cell, with support of IL-23, IL-6 and transforming growth factor (TGF)-β, will produce Th17 and regulatory T cell (Treg) that secrete IL-17 as an addition. The activation of Th0 cell then enhances the production of IL-6, IL-5, and IL-4 which lead to the skew of inflammatory phenotypes to Th2 pattern.[4]

Th2 cell was found increasing in the majority patients of asthma, along with the elevation of cytokines produced by Th2, there are IL-13, IL-5, and IL-4. In the lung tissue, IL-13 and IL-4 have impactful effects on most airway structure, causing hallmark of asthma pathology: eosinophilic inflammation, increased maturation of goblet cells and secretion of mucus, development of fibroblasts, synthesis of collagen enhanced, and changes in responsiveness of bronchial smooth muscle to beta-adrenergic agonistic. The second most important effect of both interleukin is switching the production of IgM to IgE in B cell. IL-4 also induces naïve T cell development into Th2.[5] This complex framework shows potential target for development of intervention and new medicine.[4]

Elaborate pathogenic mechanisms are not always presenting the same clinical manifestations, this distinction of clinical manifestation is what defined as phenotype. Decades ago, the approach of asthma as a phenotype began with the concept of intrinsic asthma (nonallergic) and extrinsic asthma (allergic). Patients with extrinsic asthma developed the disease in the early age of their life, had atopic history, and had a clear allergic trigger as well as other allergic history, such as eczema or rhinitis, or family history. Intrinsic asthma is developed in the age of more than 40 years old, and is associated with the use of aspirin but not with allergic sensitization. When a clinical trial revealed that Th2 cytokine levels were not different both in extrinsic and intrinsic ashma, and ICS therapy was as effective as in mild to moderate asthma cases (that covered majority of asthma cases), the distinction of extrinsic and intrinsic asthma phenotype was left out.[6]

A study by Wenzel, *et al*. in 1999 became a new phase of the distinction of phenotype.[7] This study included 34 severe asthma patients with refractory corticosteroid-dependent; their lung function, endobronchial biopsy, clinical history, and allergy testing were evaluated. Fourteen severe asthmatics had nearly absent eosinophils in immunohistochemical examination, then called as eosinophil (-) group. The other 20 patients were categorized as eosinophil (+). The group of eosinophil (+) patients had experienced an increase in lymphocytes, macrophages, and mast cells, the subbasement membrane (SBM) was thickened and associated with the number of neutrophils. There was no difference in the number of neutrophil and bronchodilator response.[7] Other trials showed that individuals of eosinophil (+) group had higher TGF-β expression, more frequent of symptoms and more severe, and greater morbidity rate.[6]

Further study revealed several other endotypes, but for clinical manifestation, prior study by Wenzel, *et al*. is still relevant, which defined patients in two groups, eosinophilic asthma (Th2-high) and no-eosinophilic or

neutrophilic or paucigranulocytic (Th2-low).[8] Currently, non-eosinophilic asthma is the most challenging and controversial asthma manifestation. The result of the research showed that these phenotype asthmatics had severe symptoms and usually consumed a high dose of ICS, if did not receive OCS treatment yet. In contrast to its effect on eosinophils, the problem is corticosteroid inhibits neutrophil apoptosis, thus triggers the accumulation in the airway. Therefore, to distinguish the finding of primary pathology of this asthma phenotypes from secondary finding due to corticosteroid effect is difficult.[9]

On non-eosinophilic asthma, effector T cells that secrets IL-17 (Th17) was suspected to play some roles. Th17 cells development from T-cell precursors has not completely understood yet, however, it seems to rely on TGF-β, IL-6, and IL-23. IL-17 through various mechanisms, including induction from CXCL family, granulocyte macrophage CSF (GM-CSF), and granulocyte colony-stimulating factor (G-CSF), induces a great neutrophilic response.[5] A mechanism that triggers the expression of Th17 also has not been understood yet, but from the results of the studies, it showed a strong correlation between neutrophil cell expression in the airway of asthmatics by the presence of IL-17 levels and strong relation between IL-17 expression with asthma severity. Another study found that patients with enhanced Th17 cells number concurrent with elevation of airway eosinophils, and between Th17 markers and neutrophils in blood, sputum, and airway tissue were not correlated, hence the activity of airway neutrophils is suggested to be more relevant with the severity of asthma than the number of neutrophils.[9]

Table 1. Mediator cells are essential in asthma.[10]

Mediator	Role
Chemokine	Essential in inflammation cells recruitment to the airway, ultimately expressed in epithelial cells of airway. CCL11 (eotaxin) is relatively selective for eosinophil, while CCL17 and CCL22 recruit Th2 cell.
Cysteinyl leukotriene	A potent bronchocontrictor and pro-inflammatory mediator that mainly derived from mast cell and eosinophil. This compound is the only mediator that, if inhibited, is correlated with lung function development and asthma symptoms.
Cytokine	Stimulating inflammation response and determine the severity. The important cytokines include: • IL-1β and TNF-α, enhance inflammation response • GM-CSF, extends eosinophil life span
	• in the airway • Cytokine from Th2, including: o IL-5, required for eosinophil differentiation and life span o IL-4, essentials for Th2 cell differentiation and IgE expression o IL-13, required for IgE expression
Histamine	Secreted by mast cell, histamine contributes in bronchoconstriction and inflammation response. Antihistamine, unfortunately, has a minimal role in asthma therapy due to limited effication, side effects, and tolerance appearance.
Nitric oxide	A potent vasodilator which is mainly produced by nitric oxide synthase enzyme in epithel cells of airway.
Prostaglandin D2	A bronchoconstrictor compound that is mainly derived by mast cells. This compound is involved in Th2 cell recruitment into the airway.

CCL: ligand chemokine; GM-CSF: granulocyte macrophage colony-stimulating factor; IL: interleukin; Th2: lymphocyte T helper 2; TNF: tumor necrosis factor (Adapted from Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019)

Eosinophilic asthma patients had increased number of eosinophil in the sputum and the airway. Patients with phenotypes including eosinophil comprises individuals with allergen-exacerbated asthma, aspirin-exacerbated asthma, and idiopathic eosinophilic asthma. Approximately 50% of severe asthmatics has proven the presence of eosinophilia in the airway. These cells were attracted into systemic circulation by IL-5, then enter the lung vasculature and make their way into airway tissue under eotaxin influence. Once eosinophils entered the tissue, proteins from their granules were released, including eosinophil peroxidase, major basic protein (MBP), eosinophil cationic protein, and eosinophil-derived neurotoxin, that directly became toxic to the epithelial and airway structures. Pro-inflammatory cytokines, for example IL-25, IL-13, IL-8, IL-4, GM-CSF, and chemokines, including RANTES and eotaxin, also can be synthesized and released by eosinophils in large number. These products will lead to severe eosinophilic inflammation in the airway and may also trigger the recruitment of neutrophils.[5]

The pathophysiology of both different groups have the same outcomes, hyperresponsiveness and constriction of airway. If those conditions are going chronically, both of them will promote airway remodeling. Basically, the target of asthma therapy is to prevent further airway remodeling.

Asthma Therapy

GINA recommends that all adults and adolescents with asthma are better to receive inhaled corticosteroid (ICS) therapy, either as needed (in mild asthma) or daily, to reduce the risk of serious exacerbations and control the symptoms of asthma. SABA-only treatment of asthma on adults and adolescents is no longer recommended. In mild asthma patients, the treatment that can be used is low dose of ICS everyday or combination of low dose ICS-formoterol if needed.[10]

For uncontrolled asthmatics (persistent symptoms and/or exacerbations), although they have taken low dose of ICS, first, clinicians should re-check the problems such as technique of inhaler use, adherent, comorbidities, and persistent allergen exposure. If all the problems have been resolved, consider step-up therapy, combination of low dose ICS-LABA is preferred. In patients who received therapy but remain exacerbation, the risk of exacerbations can be reduced by the combination of a low dose of ICS-formoterol (with budesonide or beclomethasone) as reliever and maintenance. In patients with poor symptoms and/or exacerbations despite therapy of step 4-5, they should be referred to the center of asthma specialist for phenotypes assessment and consideration of additional treatment including biological therapy.[10]

For patients with controlled asthma and maintained for about 3 months, consider to step-sown therapy, until the lowest treatment for patients that controls both exacerbations and symptomsis found. During step-down therapy, ICS should not be withdrawn unless to confirm the diagnosis of asthma.[10]

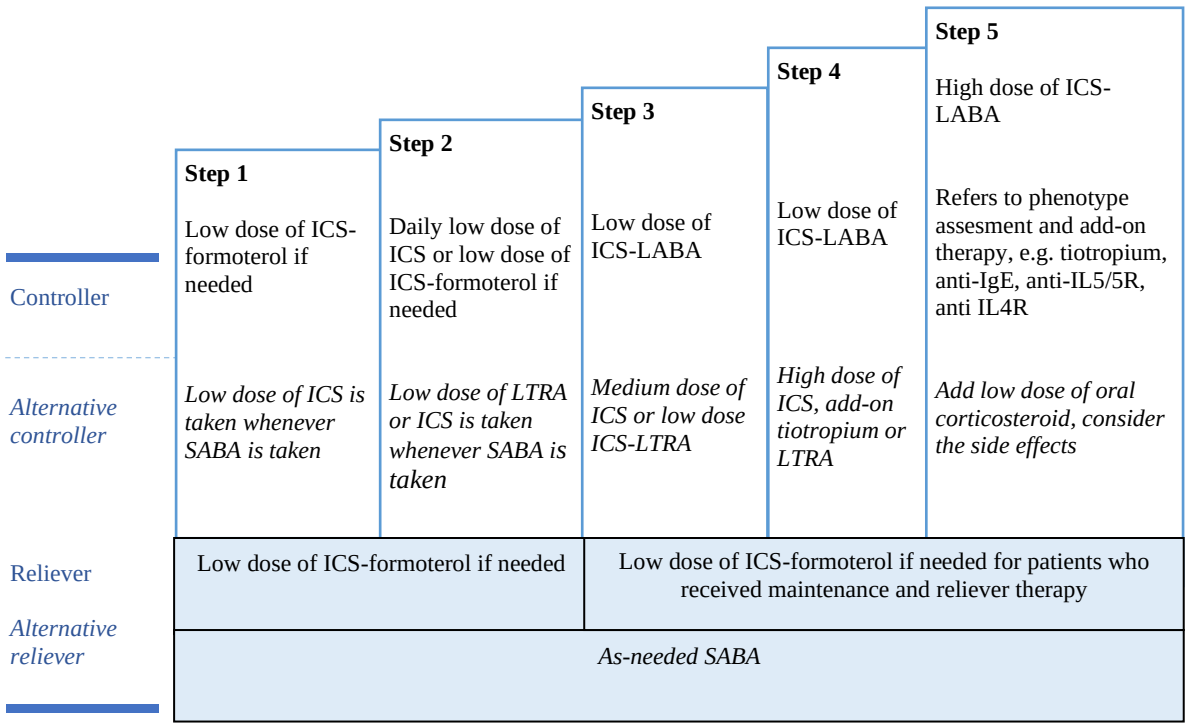

Figure 1. Step ladder therapy options for asthma by GINA. ICS : inhaled corticosteroid, LABA : long acting beta agonist, LTRA: Leukotriene receptor antagonist, SABA : Short acting beta agonist (Adapted from Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019)

Biological Therapy for Asthma

Standard therapy for asthma is given through the airway, hence it has limited effects only in airway area. After the molecular pathophysiology of this disease was understood, the interest of medicine that proximally works from inflammation in the airway was developed. This article reviews several biological therapies on human that have already been investigated for its efficacy.

Anti-Immunoglobulin E: Omalizumab

IgE is the first molecule targeted by the monoclonal antibody for asthma treatment.[11] B cell synthesizes IgE as a response towards the activation of the allergen from cell-mediated immune response.[3] Approximately 70% of asthmatics have the same allergic asthma phenotypes that are characterized by specific IgE for aeroallergens (in-vitro test or skin prick), and in many cases, the increase of total IgE serum occured.[12]

Omalizumab acts as anti-IgE antibody on human that specifically binds Fc site from unbound-IgE and forms IgE-omalizumab complexes. It reduces free IgE levels and prevents IgE from binding to FCεRI. Without the binding of IgE to FCεRI, mast cells degranulation will be absent and inflammatory mediator release will be inhibited.[8] This medicine, on moderate to severe allergic asthma, has been showing a moderate efficacy.

Based on the recommendations by Global Initiative for Asthma (GINA), European Medicines Agency (EMA), and Food and Drug Administration (FDA), omalizumab is indicated for adults and children more than 6 years old with moderate to severe persistent allergic asthma that is mediated by IgE and remains uncontrolled despite has been given of GINA treatment step 4, patients with higher blood IgE phenotype levels, and have sensitivity to perennial allergen. Omalizumab is administered subcutaneously every 2-4 weeks according to body weight and total baseline of IgE. Although Europian drug label approves that this medicine is suitable for long-term use, after 16 weeks of treatment, patients shoud be re-evaluated to assess the efficacy of this medicine before deciding to continue the therapy.[1]

For more than 15 years, omalizumab has been clinically used for allergic asthma treatment and has shown beneficial outcomes in several trials. In 2014, Cochrane review evaluated 25 trials of moderate to severe allergic asthmatics, and omalizumab was compared with placebo. Omalizumab was found to reduce asthma exacerbations by approximately 25%, it was also reduced hospitalizations and ICS dose.[3] Several studies have shown clinical benefit of anti-inflammatory with omalizumab and an alteration of airway pathology. Djukanovic, *et al*. presented asthma patients with mild steroid naive treated with omalizumab had their eosinophils decreased, along with the decreased of IL-4 and FcεRI+ secreting cells, IgE+ cells, and CD3+ T lymphocytes in submucosa and epithelial compared to placebo patients.[13] This findings are supported by a study that showed omalizumab reduced the level of circulating T lymphocytes and eosinophils. Hoshino, *et al*. presented omalizumab was significantly reduced airway wall thickness compared to placebo.[14]

Both in adults and children, the most common adverse events were nasophayngitis, headache, sinusitis, and upper respiratory infection. Anaphylaxis was developed only in 0.07% patients of placebo group and 0.14% patients in treated group, and this can occur anytime in the treatment course.[15] Omalizumab was not widely used due to its high-cost, requires dosing 1-2 times per month, requires more than one subcutaneous injection, and perhaps the most important thing is its incapability to predict the response towards therapy.[6]

Anti Interleukin-5

IL-5 is a primary cytokine that plays a role to recruit, activate, and maintain survival of eosinophils, and by blocking this pathway, anti–IL-5 biological therapy of anti IL-5 will reduce eosinophilic inflammation in the airway.[3]

Mepolizumab

Mepolizumab is a monoclonal antibody in human against IL-5 and inhibits eosinophilic inflammation selectively, also reduces the counts of eosinophils in both blood and sputum.[13] In multiple randomized control

trials, mepolizumab has proven its ability to reduce asthma exacerbations and OCS use, also improves asthma control and lung function.[3]

The recent studies have shown a benefit in patients with severe eosinophilic asthma phenotype. Nair, *et al*. evaluated the effect of mepolizumab to spare steroid in patients with eosinophil in sputum and symptoms in the airway although they have been treated with prednison and high dose of ICS before. In this small study, they found that when mepolizumab was compared to placebo, it helped to reduce eosinophil numbers in sputum and blood as well as prednisone sparing without improving asthma exacerbations. Despite the high doses of corticosteroids, mepolizumab therapy was also shown to reduce the number of exacerbations and improve AQLQ scores in patients with history of recurrent severe exacerbations and a refractory eosinophilic asthma.[16]

Recently, studies by SIRIUS (Steroid Reduction with Mepolizumab Study) and MENSA (Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma) have noted the benefit of mepolizumab in patients with eosinophilic asthma. When compared to placebo, the rate of exacerbations in patient who received IV mepolizumab was reduced by 47% and 53% in SC mepolizumab patients. Furthermore, the exacerbations requiring emergency room visits or hospitalization decreased by 32% for IV and 61% for SC mepolizumab. In addition, after being assessed by SGRQ (St. George's Respiratory Questionnaire) and ACQ-5 (5-item Asthma Control Questionnaire), patients in both the IV and SC mepolizumab groups showed significant improvement in quality of life and asthma control. The study of SIRIUS also evaluated mepolizumab's sparing effects against steroid compared to placebo in patients with severe asthma and peripheral blood eosinophilia during maintenance systemic glucocorticoids and found that the possibility of a reduction in glucocorticoid-dose was 2.39 times greater in the mepolizumab group.[16] Mepolizumab treatment in eosinophilic asthma patients on chronic OCS promotes a reduction in OCS dosage by 50%.[3]

Mepolizumab is now has been approved to be administered to patients ≥12 years old with severe eosinophilic asthma phenotype. According to the guideline by National Institute for Health and Clinical Excellence (NICE) in the UK, mepolizumab is indicated on patients with the count of blood eosinophil ≥300 cells/µl within previous 12 months and asthma exacerbations ≥4 times which requires systemic steroid or continous OCS and is given at least 5 mg/day of prednisolone within previous 6 months.[1] This drug is administered subcutaneously at 100 mg per dose every 4 weeks. The clinical response should be observed in 4 months, and the treatment with mepolizumab shoud be continued in limitless period if clinical response has been achieved.[3] Mepolizumab has positive long-term security profile. There is no report of anaphylaxis occured that is associated with mepolizumab.[1]

Reslizumab

Reslizumab is human monoclonal antibody anti IL-5 that neutralizes the circulation of IL-5 by preventing it from binding with eosinophil.[13] Reslizumab has been investigated in several RCT of uncontrolled eosinophilic asthma patients and has proven consistently to reduce asthma exacerbations and absolute eosinophil count (AEC) and also improved lung function.[3] Reslizumab, recently received FDA approval under the trade name CINQAIR, is an additional maintenance treatment for severe asthma patients ≥18 years old with eosinophilic phenotype (AEC ≥400 cells/µl).[15] Reslizumab is the only biological drug that is administered intravelously (IV) using doses according to patient's body weight with 3 mg doses per kg every 4 weeks. Reslizumab was well tolerated and the side effects were similar to placebo group. However, during RCT, there were three cases of anaphylaxis occured, thus FDA gave warning label.[3]

Benralizumab

Benralizumab is a monoclonal antibody on human that targets human IL5Rα (alpha subunit of IL-5 receptor) found in eosinophil and basophil. In prior study evaluating patients with mild atopic asthma, single IV dose of benralizumab showed reducing the number of peripheral blood eosinophil.[15] In 2017 Cochrane review, it presented a significant decrease of asthma exacerbations in benralizumab-treated patients regardless their AEC. However, benralizumab had greater impact on patients with AEC ≥300 cells/µl. The improvement of quality of life and ung function were

only significant in the group with higher number of eosinophils. In the trial by ZONDA, benralizumab has significantly proven to reduce the use of OCS by 75% in patient with long-term OCS and AEC ≥150 cells/µl, as well as reducing annual asthma exacerbations by 70%.[3]

Benralizumab is approved for uncontrolled eosinophilic asthma patients ≥12 years old with AEC ≥300 cells/µL. In order to reduce tissue eosinophilia (called as induction phase), benralizumab is administered every 4 weeks, subcutaneously, and at doses of 30 mg as three initial doses, then for maintenance every 8 weeks thereafter. A trial shoud be performed for 4 months to assess clinical response towards therapy. Benralizumab is well tolerated in general, but may trigger hypersensitivity reaction including urticaria, anaphylaxis, and angioedema.[3]

Anti Interleukin-4/ Interleukin-13

In pathogenesis of atopic asthma, IL-13 and IL-4 are key cytokines that are expressed by mast cells and Th2 cells. Redundancy in the pathway of IL-4/IL-13 is produced from complex receptor system that shares receptor IL-4 (IL-4Rα). The binding of this receptors mediate the signaling of downstream through activator of transcription factor 6 (STAT-6) and signal transducer that induces airway inflammation by activation of macrophages, dendritic cells and eosinophils, airway remodeling through proliferation and activation of fibroblast, the activation of B cell that causes IgE switching class, stimulation of goblet cells and airway epithelium cells that triggers activation of airway smooth muscle cells, and mucus secretion that promotes hyperresponsiveness in the airway.[15]

Dupilumab

Dupilumab is a monoclonal antibody that performs in subunit IL-4Rα to inhibit IL-13 and IL-4. In a IIA phase study, dupilumab that was given once in a week at doses of 300 mg subcutaneously versus placebo was significantly reduced asthma exacerbations in moderate to severe asthmatics and increased eosinophil levels. Dupilumab caused a significant improvement on FEV1 and ACQ scores, decreased of symptoms, nocturnal awakening, and the use of short acting beta agonist. In addition, dupilumab also reduced biomarkers Th2 inflammation-related including TARC (thymus and activation-regulated chemokine), eotaxin-3, IgE serum, and FENO.[16] In patients who use OCS as prior treatment, dupilumab has been known to reduce consumption of OCS significantly up to 70% as well as exacerbations rate by 60%, also improved lung function, and almost half of patients was enable to quit OCS use.[3]

FDA is approving dupilumab as an additional maintenance therapy in moderate to severe asthma patients by age ≥12 years old with eosinophilic phenotype or OCS-dependant asthma, also approved by EMA as an additional therapy for severe asthma with type 2 inflammation which is marked by elevation of blood eosinophils and/or FeNO on ≥12 years old adolescent who is inadequate to receive maintenance of high dose ICS plus another medicine. Dupilumab is administered subcutaneously at 400 mg as an initial dose (two injections of 200 mg) then 200 mg every 2 weeks thereafter, or initial dose of 600 mg (two injections of 300 mg) then 300 mg every 2 weeks thereafter. Initial dose of 600 mg, according to EMA, is recommended only for asthmatics with OCS-dependant or moderate-severe atopic dermatitis (that also an indication of dupilumab).[1]

Another Anti Il-4/Il-13 Therapy

Lebrikizumab is a humanoglobulin G4 monoclonal antibody (IgG4) which inhibits IL-3. In a RCT of lebrikizumab therapy, it presented a better improvement of lung function in patients with high level of pre-treatment serum periostin. Periostin is a matricellular protein secreted by bronchial epithel cell as a response towards IL-13. Serum periostin may be a biomarker for identify asthma patients who are associated with IL-13 and responsive to therapy anti IL-13. Antoher trial of SC lebrikizumab with the doses of 125, 250, or 500 mg compared to placebo in asthma patients who did not receive ICS, found that although FEV1 was increased in all groups, the increase of lebrikizumab compared to placebo was not significant statistically or clinically, moreover there was no significant difference in FEV1 on patients with high periostin serum compared to patients with low serum periostin. Further studies are needed to evaluate these findings.[15]

Tralokinumab is an IgG4 monoclonal antibody against IL-13 that has been recognized to inhibit

bronchial hyperresponsiveness and airway eosinophilia in clinical trial. In the recent phase II study in moderate to severe asthma, tralokinumab was associated with the improvement of lung function assessed by FEV1 as well as the reduction of short-acting beta agonist use. Interestingly, the increase of FEV1 was higher in tralokinumab group that presented an elevation of IL-13 sputum compared to patients without IL-13 sputum. Moreover, the increase of FEV1 was contionously increased within 12 weeks after tralokinumab discontinued. However, this study did not show any improvement on ACQ-6 (6-item Asthma Control Questionnaire) scores in tralokinumab group compared to placebo. Generally, tralokinumab is well tolerated with acceptable safety profile.[15] Pitrakinra is a recombinant variant of human IL-4 that competitively blocks IL-4Rα complex, thus interfering the signaling of IL-4 and IL-13 downstream. In patients with atopic asthma, pitrakinra has proven to reduce the effect of late asthmatic response after allergen test characterized by weaker decrease of FEV1 in pitrakinra treated group compared to placebo.[15]

Anti Interleukin-17

Th17 cell is a part from CD4+ T cells that is related to severe phenotype of asthma which is quite unresponsive to corticosteroids and is responsible to secrete cytokines IL-21, IL-22, IL-17F, and IL-17A. Studies have reported that there was an increase of IL-22, IL-17A, and IL-17F levels in the bronchial biopsies and brochoalveolar lavage (BAL) fluids of patients with moderate to severe asthma. IL-22, IL-17A, and IL-17F were involved in stimulating the improvement of neutrophilic inflammation in the airway, mucous cells metaplasia, and proliferation of smooth muscle.[15]

Secukinumab and brodalumab

Biologic agents that target IL-17RA or IL-17A are recently in clinical study for asthma. Secukinumab is a monoclonal antibody that targets at IL-17A and has been showing its ability to reduce clinical symptoms in other Th-17-mediated disease, such as psoriasis and rheumatoid arthritis. A phase II clinical study involving uncontrolled asthmatics has been completed, but the results are not available yet. Brodalumab, a monoclonal antibody targeted to IL-17RA, recently was investigated in a phase II clinical study for patients with moderate to severe asthma using Asthma Quality Control (AQC) scores as the main outcome. The results showed no differences in AQC scores among patients treated by brodalumab and patients who received placebo, but in bronchodilator reversibility, a meaningful response was seen.[15]

SUMMARY

Gonitis TB is a hematogenous spread of M.Tb from Asthma is a heterogenous chronic inflammation disease in the airway. Chronical inflammation will trigger hyperresponsiveness in the respiratory tract that could lead to recurrent episodic symptoms including wheezing, shortness of breath, chest tightness, and cough especially at night or dawn. Over the years, inflammation associated with ‘asthma’ is assumed mainly stimulated by Th2 cell that releases pro-inflammatory cytokines such as IL-13, IL-5, and IL-4, which contributes in IgE production and eosinophil-related inflammation. Therefore, elements from this pathway become natural target for biological therapy that targeted molecularly. Biological therapy for asthma are anti IL-5, anti IL-4/IL-13, and anti IgE. Biological therapy is given to uncontrolled severe asthma. Overall, biological therapy which is now approved for severe asthma is possible to reduce the rate of exacerbations by approximately 50% and lessen the use of high dose ICS.

REFERENCES

1. Rogliani P, Calzetta L, Matera MG, et al. Severe Asthma and Biological Therapy: When, Which, and for Whom. *Pulm Ther* 2020; 6: 47–66.
2. Mangunrejo H, Widjaja A, Kusumo D, et al. *Asma: Pedoman Diagnosis dan Penatalaksanaan di Indonesia*. Jakarta: Perhimpunan Dokter Paru Indonesia, 2004.
3. McGregor MC, Krings JG, Nair P, et al. Role of Biologics in Asthma. *Am J Respir Crit Care Med* 2019; 199: 433–445.
4. Viswanathan RK, Busse WW. Biologic Therapy and Asthma. *Semin Respir Crit Care Med* 2018; 39: 100–114.
5. Corren J. Inflammatory Disorders Associated with Allergy: Overview of Immunopathogenesis and Implications for Treatment. *Immunol Allergy Clin* 2017; 37: 233–246.
6. Wenzel SE. Asthma Phenotypes: The Evolution from Clinical to Molecular Approaches. *Nat Med*

2012; 18: 716–725.
7. Wenzel SE, Schwartz LB, Langmack EL, et al. Evidence that Severe Asthma can be Divided Pathologically into Two Inflammatory Subtypes with Distinct Physiologic and Clinical Characteristics. *Am J Respir Crit Care Med* 1999; 160: 1001–1008.
8. Busse W, Corren J, Lanier BQ, et al. Omalizumab, Anti-IgE Recombinant Humanized Monoclonal Antibody, for the Treatment of Severe Allergic Asthma. *J Allergy Clin Immunol* 2001; 108: 184–190.
9. Borish L. The Immunology of Asthma: Asthma Phenotypes and Their Implications for Personalized Treatment. *Ann Allergy, Asthma Immunol Off Publ Am Coll Allergy, Asthma, Immunol* 2016; 117: 108–114.
10. Asthma GI for. *Global Strategy for Asthma Management and Prevention*. Wisconsin, http://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf (2019).
11. Fajt ML, Wenzel SE. Biologic Therapy in Asthma: Entering the New Age of Personalized Medicine. *J Asthma* 2014; 51: 669–676.
12. Pepper AN, Renz H, Casale TB, et al. Biologic Therapy and Novel Molecular Targets of Severe Asthma. *J Allergy Clin Immunol Pract* 2017; 5: 909–916.
13. Djukanović R, Wilson SJ, Kraft M, et al. Effects of Treatment with Anti-Immunoglobulin E Antibody Omalizumab on Airway Inflammation in Allergic Asthma. *Am J Respir Crit Care Med* 2004; 170: 583–593.
14. Hoshino M, Ohtawa J. Effects of Adding Omalizumab, An Anti-Immunoglobulin E Antibody, on Airway Wall Thickening in Asthma. *Respiration* 2012; 83: 520–528.
15. McCracken JL, Tripple JW, Calhoun WJ. Biologic Therapy in the Management of Asthma. *Curr Opin Allergy Clin Immunol* 2016; 16: 375–382.
16. Nair P, Pizzichini MMM, Kjarsgaard M, et al. Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia. *N Engl J Med* 2009; 360: 985–993.