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Mepolizumab in the management of severe eosinophilic asthma in adults: current evidence and practical experience

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***Abstract*:** Eosinophils represent approximately 1% of peripheral blood leukocytes in normal donors and their maturation and differentiation in the bone marrow are mainly regulated by interleukin (IL)-5 [Broughton *et al.* 2015]. IL-5, a cytokine that belongs to the β common-chain family, together with IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF), stimulates also the activation and survival of eosinophils and, to some extent, of basophils. IL-5 binds to a heterodimer receptor composed of the specific subunit IL-5Rα and a common subunit βc shared with IL-3 and GM-CSF. Human eosinophils express approximately a three-fold higher level of IL-5Rα compared with basophils. Major sources of IL-5 are T-helper 2 (Th2) cells, mast cells, CD34+ progenitor cells, invariant natural killer (NK) T-cells, group 2 innate lymphoid cells (ILC2s), and eosinophils themselves. ILC2s control not only eosinophil number but also their circadian cycling through the production of IL-5.

Keywords: asthma, eosinophilia, exacerbations, IL-5, mepolizumab, personalized medicine, severe asthma, targeted therapy

Introduction

Paul Ehrlich announced the discovery of the eosinophil in a presentation to the Physiological Society of Berlin on 17 January 1879 [Ehrlich, 1879a]. His next paper contained an extensive description of these cells [Ehrlich, 1879b]. Ehrlich identified peripheral blood eosinophils thanks to their capacity to be stained by eosin. He suggested that eosin interacted, like a 'magic bullet', with a specific eosinophil receptor. Ehrlich's hypothesis of 'chemical affinities' in biological processes is epitomized in his maxim *corpora non agunt nisi fixata*, namely, a substance is not biologically active unless it is bound by a receptor. This led him to the use of a magic bullet to treat a given disease. Thus, Ehrlich was not only the founder of modern immunology, but he was also a pioneer in pharmacological sciences.

Eosinophils represent approximately 1% of peripheral blood leukocytes in normal donors and their maturation and differentiation in the bone marrow are mainly regulated by interleukin (IL)-5 [Broughton *et al.* 2015]. IL-5, a cytokine that belongs to the β common-chain family, together with IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF), stimulates also the activation and survival of eosinophils [Yamaguchi *et al.* 1991] and, to some extent, of basophils [Bischoff *et al.* 1990; Hirai *et al.* 1990]. IL-5 binds to a heterodimer receptor composed by the specific subunit IL-5Rα and a common subunit βc shared with IL-3 and GM-CSF [Rosas *et al.* 2006; Takatsu, 2013]. Human eosinophils express approximately a three-fold higher level of IL-5Rα compared with basophils [Kolbeck *et al.* 2010]. Major sources of IL- 5 are T-helper 2 (Th2) cells, mast cells, $CD34^+$ progenitor cells, invariant natural killer (NK) T-cells, group 2 innate lymphoid cells (ILC2s), and eosinophils themselves [Fallon *et al.* 2006; Nussbaum *et al.* 2013; Phillips *et al.* 2003]. ILC2s control not only eosinophil number but also their circadian cycling through the production of IL-5 [Nussbaum *et al.* 2013].

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Table 1. Clinical trials of mepolizumab in asthma.

Study	Disease severity	Dosage/delivery	Outcome summary
[Menzies-Gow *et al.* 2003]	Mild asthmatics	750 mg iv every 4 weeks for 3 months	↓ Eosinophils within bronchial mucosa
[Flood-Page *et al.* 2003]	Mild asthmatics	750 mg iv every 4 weeks for 3 months	↓ Blood eosinophils ↓ Airway eosinophils by 50% No effect on PEF, FEV_1 and bronchial hyperresponsiveness
[Flood-Page *et al.* 2007]	Moderate asthmatics	250 or 750 mg iv every 4 weeks for 3 months	↓ Blood and sputum eosinophils No effect on PEF, FEV_1 and AQLQ
[Haldar *et al.* 2009]	Severe eosinophilic asthmatics	750 mg iv every 4 weeks for 1 year	↓ Blood eosinophils ↓ Exacerbations ↑ AQLQ No effect on FEV_1
[Nair *et al.* 2009]	Prednisone-dependent eosinophilic asthmatics	750 mg iv every 4 weeks for 5 months	↓ Blood and sputum eosinophils ↓ Exacerbations Prednisone-sparing effect
[Pavord *et al.* 2012]	Severe eosinophilic asthmatics	1 of 3 doses (750, 250 or 75 mg) iv every 4 weeks for 13 months	↓ Blood and sputum Eosinophils ↓ Exacerbations No effect on FEV_1 and AQLQ
[Ortega *et al.* 2014b]	Severe eosinophilic asthmatics MENSA STUDY	100 mg sc every 4 weeks for 8 months	↓ Blood eosinophilia ↓ Exacerbations ↑ FEV_1 ↑ ACQ-5 score
[Bel *et al.* 2014]	Severe eosinophilic asthmatics SIRIUS STUDY	100 mg sc every 4 weeks for 6 months	↓ Blood eosinophils ↓ Exacerbations Glucocorticoid sparing-effect ↑ ACQ-5 score
[Haldar *et al.* 2014]	Severe eosinophilic asthmatics	750 mg iv every 4 weeks Outcome after cessation	Rapid increase in blood and sputum eosinophils followed by increased of asthma symptoms and exacerbations

ACQ-5, Asthma Control Questionnaire-5; AQLQ, Asthma Quality of Life Questionnaire; FEV_1, forced expiratory volume in one second; iv, intravenously; PEF, peak expiratory flow; sc, subcutaneously.

Mepolizumab in adults with eosinophilic asthma

Given the critical role of IL-5 in influencing several activities of eosinophils, this cytokine and its receptor attracted the attention of pharmaceutical industries as a possible target in the treatment of hypereosinophilic diseases including eosinophilic asthma [Varricchi *et al.* 2016]. Mepolizumab (Nucala; GlaxoSmithKline, London, UK) was the first anti-IL-5 humanized monoclonal antibody described over 15 years ago [Zia-Amirhosseini *et al.* 1999]. Mepolizumab binds to IL-5 with high specificity (maximal inhibitory concentration <1 nm) and affinity (approximately 4.2 pM), thus preventing its binding to the α chain of the IL-5R complex on eosinophils and basophils. A preclinical study on the pharmacology and safety of mepolizumab in naïve and *Ascaris suum*-sensitive *Cynomolgus* monkeys demonstrated that a single intravenous (iv) dose reduced blood eosinophilia for 6 weeks without affecting acute bronchoconstriction [Hart *et al.* 2001]. Two initial studies evaluated, in a randomized, double-blind, parallel group, the effects of iv anti-IL-5 in a small group of mild asthmatic patients (Table 1). Although anti-IL-5 produced a decrease in blood eosinophils and partial reduction of airway and bone marrow eosinophils, there were no effects on airway hyperresponsiveness (AHR) and late response to inhaled allergens [Flood-Page *et al.* 2003; Leckie *et al.* 2000]. Similarly, in a multicenter study to evaluate safety and efficacy of iv mepolizumab in patients with moderate persistent asthma, the treatment produced a rapid and marked reduction in blood eosinophils, without improving lung functions and symptoms [Flood-Page *et al.* 2007]. These initial studies produced frustrating results, and several investigators questioned the efficacy of this targeted therapy on asthma treatment [Flood-Page *et al.* 2003; Wenzel,

2009]. In fact, no significant effects were found in terms of AHR, peak expiratory flow (PEF), and forced expiratory volume in one second (FEV_1) despite a remarkable reduction in blood eosinophilia [Flood-Page *et al.* 2003; Leckie *et al.* 2000].

Retrospectively, two major factors could explain these preliminary results. First, an incorrect selection of patients with mild or moderate asthma without significant eosinophilia and airway eosinophilic inflammation; second, perhaps, the iv administration of mepolizumab. The latter observation is relevant because there is evidence that subcutaneous (sc) administration of human polyclonal immunoglobulins provides more prolonged serum levels of immunoglobulins compared with iv infusion [Spadaro *et al.* 2016]. The two subsequent studies in patients with refractory eosinophilic asthma demonstrated some efficacy of mepolizumab in the control of severe asthma. The first one was a study on patients who had refractory eosinophilic asthma and a history of recurrent severe exacerbations [Haldar *et al.* 2009]. Patients received iv infusion of mepolizumab at monthly intervals for one year. This treatment caused fewer severe exacerbations than placebo with a significant improvement in the Asthma Quality of Life Questionnaire (AQLQ) score and a decrease in blood and sputum eosinophils. However, also in this study there were no significant differences with respect to symptoms, FEV_1 and AHR. The second study involved patients with sputum eosinophilia and symptoms despite prednisone treatment [Nair *et al.* 2009]. Although this was a study on a small group of patients receiving mepolizumab in 5 monthly iv infusion of 700 mg, the use of anti-IL-5 was associated with a reduction in prednisone dose, reduction in eosinophil numbers and asthma control.

The DREAM trial was a large multicenter, double-blind, placebo-controlled study recruiting a large number of patients with severe asthma exacerbations and eosinophilic inflammation. Patients received one of three doses of iv mepolizumab (75 mg, 250 mg, or 750 mg) or placebo. A major aim of this study was to identify biomarkers less invasive than induced sputum and therefore more applicable in clinical practice. An important finding of the study was that blood eosinophil counts above 0.15×10^9/l were associated with drug effects. Another finding was that the lowest dose of mepolizumab had clinical and biological efficacy that was comparable with higher doses on exacerbation rates and blood eosinophil counts, respectively. Mepolizumab reduced the number of exacerbations and blood and sputum eosinophils despite a small effect on FEV_1, AQLQ and Asthma Control Questionnaire (ACQ) scores compared with placebo [Pavord *et al.* 2012].

The latter study represented an important progress in the selection of subgroups of patients affected by severe eosinophilic asthma with frequent exacerbations. A supervised cluster analysis with recursive partitioning approach was applied to the DREAM study to identify characteristics able to maximize the differences among subgroups [Ortega *et al.* 2014a]. The predictors identified were blood eosinophils, airway reversibility and body mass index.

Two studies evaluated the effects of sc mepolizumab in patients with severe asthma with more than two exacerbations in the previous year and a blood eosinophil count greater than 0.15×10^9/l at screening. In the SIRIUS trial, the primary outcome was the degree of the glucocorticoid-sparing effect of mepolizumab (100 mg sc every 4 weeks for 20 weeks) [Bel *et al.* 2014]. Anti-IL-5 reduced the glucocorticoid dose and exacerbations, while improving the control of asthma symptoms. Another conclusive research was the MENSA trial, a multicenter, double-blind, placebo-controlled study recruiting a large number of patients with severe eosinophilic asthma [Ortega *et al.* 2014b]. Mepolizumab (100 mg sc every 4 weeks for 8 months) reduced asthma exacerbations, eosinophilia and improved FEV_1 and QoL. Importantly, a pharmaco-economic evaluation of the latter study showed that mepolizumab is cost effective in that specific context [Basu *et al.* 2016]. A recent *post-hoc* analysis of data from the DREAM and MENSA trials has shown 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 authors noted a clinically-relevant reduction in exacerbation frequency, defined as at least a 30% decrease in this endpoint, in patients starting from a baseline count of 150 cells/μl and showing better outcomes in patients with over 300 eosinophils/μl [Ortega *et al.* 2016]. Even if the blood eosinophilic threshold is still under discussion, the use of this baseline biomarker could help to select patients who are likely to achieve more benefits in asthma control with mepolizumab. Based on the results of the SIRIUS and MENSA

trials, first the United States (US) Food and Drug Administration, and subsequently, the European Medicines Agency approved mepolizumab as an add-on maintenance treatment for severe eosinophilic asthma in adults. Nucala® (mepolizumab) is currently licensed in the US, Japan and more than 30 countries worldwide.

Conclusion

Several studies demonstrated that mepolizumab is well tolerated and efficacious in adults with severe eosinophilic asthma treated for up to 1 year. A recent study examined the outcome of patients with severe asthma after cessation of mepolizumab [Haldar *et al.* 2014]. In fact, there was some concern about a possible risk of 'rebound' of eosinophilic airway inflammation after stopping mepolizumab [Kim *et al.* 2004]. In addition, mepolizumab was associated with up-regulation of IL-5 synthesis by Th2 cells and overexpression of IL-5R by eosinophils [Stein *et al.* 2008]. Cessation of mepolizumab resulted in a rapid increase of blood eosinophils followed by a gradual increase in asthma symptoms and exacerbations [Haldar *et al.* 2014]. This observation emphasizes the importance of maintaining suppression of eosinophilic inflammation in these patients. Although eosinophil deficiency appears to have no effects on normal health [Gleich *et al.* 2013], these cells have been implicated in cancer rejection [Carretero *et al.* 2015] and several cancers are associated with eosinophilia [Simson *et al.* 2007]. It has been suggested that 'targeted anti-eosinophilic strategies may unmask or even accelerate progression' of certain tumors in patients with hypereosinophilic syndrome [Roufosse *et al.* 2010]. Consequently, long-term studies are required to evaluate the safety of targeted anti-eosinophilic treatments.

In conclusion, targeted therapy with mepolizumab appears to be effective in the treatment of severe eosinophilic asthma thereby echoing the concept of 'magic bullets' epitomized by Paul Ehrlich more than 130 years ago. In the current context, his maxim *corpora non agunt nisi fixata* can be translated as 'mepolizumab is pharmacologically active in severe eosinophilic asthma because it binds to IL-5'.

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