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REVIEW



The spectrum of therapeutic activity of mepolizumab

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ABSTRACT

Introduction: The basis of the development of the anti-interleukin-5 monoclonal antibody mepolizumab was the acknowledgment of the crucial importance of this cytokine in promoting eosinophils production, activation, and survival, which is associated with the eosinophilic asthma phenotype, as well as with other disorders characterized by high levels of eosinophils.

Areas covered: All the available literature on the outcomes treatment with mepolizumab in eosinophilic disorders are reviewed, including asthma, chronic rhinosinusitis, esophagitis, granulomatosis with polyangiitis, eosinophilic chronic obstructive pulmonary disease, hypereosinophilic syndrome, and allergic bronchopulmonary aspergillosis.

Expert opinion: The efficacy of mepolizumab in eosinophilic asthma is clearly demonstrated by a number of controlled trials and by meta-analyses. Among other eosinophilic disorders, controlled trials are available for chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis, hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis, and eosinophilic chronic obstructive pulmonary disease. Allergic bronchopulmonary aspergillosis, as well as other minor eosinophilic disorders, are backed only by case reports and are waiting controlled trials to verify the therapeutic role of mepolizumab.

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1. Introduction

The availability of biologic treatments, and particularly of monoclonal antibodies, was a significant advance in the management of several diseases. In fact, identifying a precise mechanism of crucial importance in the pathophysiology of a given disease and developing a monoclonal antibody that block such mechanism fulfills the requirement for the modern concept of precision medicine, which is defined as 'a medical model that proposes the customization of healthcare, with medical decisions, treatments, practices, or products being tailored to the individual patient' [1]. Respiratory allergy, including allergic rhinitis, rhinosinusitis and asthma is a feasible application for precision medicine. If the paradigm of 'united airways disease' (UAD) is used, heterogeneous conditions and multiple phenotypes and endotypes may be observed, including sinonasal disorders with or without nasal polyps and lower airway diseases. The currently known UAD pheno-endotypes were recently revised and an approach based on 'treatable traits' to classify and manage UAD was proposed, in which the identified pathophysiological mechanisms drive the choice of a targeted treatment [2]. Treatable traits in asthma may be defined according to the role of the IgE-mediated mechanism or of the cell type inducing airway inflammation, particularly eosinophils. In the first instance, the anti-IgE monoclonal antibody omalizumab has shown ample evidence of efficacy in severe asthma not controlled by standard-of-care therapy, and a clinical success also in a number of other allergic and non-allergic disorders was

reported [3]. The acknowledgment of the crucial importance of interleukin-5 (IL-5) in promoting eosinophils production, activation and survival was the premise for the development of the anti-IL-5 monoclonal antibody mepolizumab, a humanized N-glycosylated IgG 1/k antibody targeting the α -chain of IL-5 and preventing its interaction with the α subunit of the IL-5 receptor [4–6].

2. Mepolizumab as a treatment for eosinophilic asthma

It is well known that eosinophils play a major role in the pathogenesis of asthma and that a persistent eosinophilic inflammation is often present in severe, difficult to treat, asthma [7–10]. For many years, the only effective treatment for such asthma was based on corticosteroids, which are burdened, especially when systemic administration is needed, by important adverse effects [11,12]. The possibility to block the mechanisms underlying eosinophilic asthma was soon investigated following the availability of mepolizumab, but the results of the first studies were disappointing, because inconsistent variations in clinical parameters, including pulmonary function and airway hyper-responsiveness (AHR), as well as in the depletion of eosinophils, were observed [13–15]. When studies were restricted to patients with high eosinophils counts in blood and clinically severe asthma, the efficacy of mepolizumab became apparent. In the first of such studies,

Article Highlights

- Among biologic agents, the role of monoclonal antibodies is gaining increasing importance in many allergic and immunological disorders.
- The anti-Interleukin-5 monoclonal antibody mepolizumab is acknowledged as an effective treatment for the eosinophilic asthma phenotype, as well as for other disorders characterized by high levels of eosinophils.
- The efficacy of mepolizumab in eosinophilic asthma is clearly demonstrated by a number of controlled trials and by meta-analyses and is approved by regulatory agencies
- Among other eosinophilic disorders, controlled trials are available for chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis, hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis, and eosinophilic chronic obstructive pulmonary disease.
- Further approval by regulatory agencies concerns eosinophilic granulomatosis with polyangiitis (already acquired in USA), and chronic rhinosinusitis with or without nasal polyps (under evaluation).

which included patients with uncontrolled eosinophilic asthma and frequent exacerbations, some positive outcome were detected. In fact, a reduction in the number of exacerbations and an improved quality of life were observed in actively treated compared with placebo-treated patients, though there was no significant difference in pulmonary function, symptoms, and AHR [16]. In a randomized, double-blind trial on patients with persistent sputum eosinophilia and asthma symptoms despite prednisone treatment, mepolizumab treated patients had a significant reduction in prednisone use, accompanied by significantly fewer exacerbations and a decrease in eosinophil number [17]. In the multicentric, double-blind, placebo-controlled trial named Dose Ranging Efficacy And safety with Mepolizumab in severe asthma (DREAM) were enrolled 621 patients with a history of recurrent severe asthma exacerbations and eosinophilic inflammation. In this trial patients were randomly assigned to receive one of three doses of intravenous (IV) mepolizumab or placebo at 4-week intervals [18]; 154 patients were assigned to 75 mg mepolizumab, 152 to 250 mg mepolizumab, 156 to 750 mg mepolizumab, and 159 to placebo. The rate of exacerbations was 1.24 in the 75 mg group, 1.46 in the 250 mg group and 1.15 in the 750 mg, with no differences among actively treated groups, but with a highly significant difference between the rate in active each group and the exacerbation rate of 2.40 in the placebo group. A significant lowering of blood and sputum eosinophil counts was found. The authors concluded that the reported effects were clinically important and imply that blocking IL-5 meets a major medical need in patients with severe eosinophilic asthma. A cluster analysis was aimed at identifying distinctive patient characteristics within subgroups of patients included in the DREAM trial. Exacerbation rate ratios were estimated for each cluster comparing mepolizumab to placebo. Such analysis identified four primary clusters, consisting of blood eosinophils, airway reversibility and body mass index. The decrease in exacerbations was significantly higher in patients treated with mepolizumab (clusters 2, 3, and 4) with raised eosinophils (this defining the responder population). The low airway reversibility (cluster 2) was associated with a 53% reduction in exacerbations, while in the group with

higher airway reversibility the outcome was associated with the body mass index, being observed less exacerbation in the nonobese than in obese patients [19]. A further factor influencing the response to mepolizumab was suggested to be the route of administration, based on the longer effect on the serum levels of antibodies achieved by subcutaneous (SC) administration compared with IV administration [20]. The first trial on SC administration was the Steroid Reduction with Mepolizumab Study (SIRIUS), involving 135 patients with severe eosinophilic asthma. The primary objective was the corticosteroid-sparing effect of 100 mg SC of mepolizumab every 4 weeks for 20 weeks, other outcomes including the rate of asthma exacerbations, asthma control, and safety profile. The median percentage reduction from baseline in the corticosteroid dose was 50% in the mepolizumab group, as compared with no reduction in the placebo group, the difference being highly significant. In patients treated with mepolizumab, in spite of receiving a lower corticosteroid dose than in placebo-treated patients, a relative decrease of 32% in the annualized exacerbations rate ($P = 0.04$) and a reduction of 0.52 points concerning asthma symptoms, as assessed by the Asthma Control Questionnaire was measured ($P = 0.004$). As to safety, mepolizumab and placebo had similar profiles [21]. The Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) trial was performed in a double-blind, double-dummy fashion on 576 patients with recurrent asthma exacerbations and persistence of eosinophilic inflammation even with high doses of inhaled corticosteroids. Mepolizumab was administered as 75 mg IV dose, 100 mg SC dose or placebo every 4 weeks for 32 weeks. The study outcomes included the rate of exacerbations and the changes in pulmonary function, as measured by forced expiratory volume in 1 second (FEV1), and in quality of life, as assessed by the St. George's Respiratory Questionnaire (SGRQ) and the 5-item Asthma Control Questionnaire (ACQ-5). In addition, safety was evaluated. A reduction by 47% of the exacerbations rate in patients receiving IV mepolizumab and by 53% in patients receiving SC mepolizumab was observed, both significantly higher ($P < 0.001$). The rate of exacerbations requiring emergency department (ED) visit or hospitalization was 32% in patients receiving IV mepolizumab and 61% in patients receiving SC mepolizumab. At study ending, compared with placebo-treated patients, a mean increase from baseline in pre-bronchodilator FEV1 100 ml greater in treated with IV mepolizumab and 98 ml greater in those SC mepolizumab (both significant) were detected. A larger improvement was observed for post-bronchodilator FEV1, which corresponded to 146 ml with IV mepolizumab and 138 ml with SC mepolizumab. This suggests that mepolizumab is modifying a process independent of airway smooth muscle contraction. In addition, the improvement from baseline in SGRQ and the ACQ-5 questionnaires was significantly higher in both active treatments than in placebo treatment.

A comparable safety profile of mepolizumab and placebo was detected [22]. The better outcome achieved with SC administration compared with IV administration in reducing exacerbations requiring ED offered confirmation to the suitability of using such route for mepolizumab treatment. A post-hoc

analysis of the figures from DREAM and MENSA studies had as the primary outcome the annualized rate of exacerbations in patients stratified according to baseline eosinophil counts and baseline blood eosinophil ranges. A global number of 1192 patients, 846 receiving mepolizumab and 346 receiving placebo was analyzed. A significantly lower overall rate of exacerbations per patient per year was found in mepolizumab treated than in placebo gradually treated patients ($P < 0.0001$) with a reduction rate with mepolizumab vs. placebo increased from 52% in patients with a baseline blood eosinophil count of at least 150 cells per μL to 70% in patients with a baseline count of at least 500 cells per μL . Less than 150 cells per μL at baseline was associated with reduced efficacy of mepolizumab. These data lead the authors to conclude that the use of baseline eosinophils count could be used as a predictor biomarker to select patients who are likely to respond importantly to mepolizumab [23]. The Mepolizumab adJunctive therapy in subjects with Severe eosinophilic Asthma (MUSCA) placebo-controlled, parallel-group, multicentric trial included 274 patients treated with mepolizumab and 277 patients treated with placebo. The primary endpoint was the mean change from baseline in the quality of life assessed by the SGRQ total score at week. Safety was also evaluated in all patients receiving at least one dose of trial medication. Mepolizumab showed significant improvement vs. placebo ($P < 0.0001$) at week 24 from baseline in SGRQ total score. In both MENSA and MUSCA trials the change in SGRQ was well over the minimally clinically important difference. As to safety, 70% of mepolizumab patients and 74% of placebo patients reported at least one on-treatment adverse event, the most common being headache, and nasopharyngitis; 5% and 8% patients had a serious adverse event in the mepolizumab and placebo groups, respectively; the most common being asthma [24]. The global results from controlled trials were analyzed in Cochrane systematic reviews, the first in 2015 including eight studies [25] and the update in 2017 including 13 studies on monoclonal antibodies, also comprising reslizumab and benralizumab, targeting IL-5 or its receptor (IL-5R). An overall number of 6,000 patients were included in these studies, four using mepolizumab, four reslizumab and five benralizumab (one contributing no data because of early termination). The studies were mostly on patients with severe eosinophilic asthma, and eight studies recruited patients in pediatric age (but higher than 12 years), though the results were not reported distinctly. In all trials on anti-IL-5 treatments reduced rates of clinically significant asthma exacerbation were assessed in around half in participants with severe eosinophilic asthma on at least medium-dose ICS. Also in patients treated with reslizumab and benralizumab a significant reduction in exacerbation rates was observed. Quality of life, as measured by SGRQ and Asthma Quality of Life Questionnaire (AQLQ) was improved with all anti-IL-5 agents, but did not exceed the minimum clinically important difference. All anti-IL-5 yielded a small but significant improvement in mean pre-bronchodilator FEV1. No serious adverse events with any anti-IL-5 treatment were reported, with a reduction in favor of mepolizumab likely to be due to a beneficial effect on asthma-related serious adverse events. All three agents strikingly reduced blood eosinophils, benralizumab resulting in almost complete depletion. The

authors concluded that the available trials support the use of anti-IL-5 treatments as an addition to standard of care in patients with severe eosinophilic asthma, approximately halving the rate of asthma exacerbations in treated patients. Further research on biomarkers for evaluating treatment response, optimal duration, risk of relapse on withdrawal and long-term effects of treatment was claimed [26]. Very recently, two additional systematic reviews were performed. The first analyzed the efficacy of mepolizumab, benralizumab, and reslizumab, performing a matching-adjusted indirect comparison (MAIC), which is thought to be a robust method to indirectly compare treatment efficacies from trials with heterogeneous patient populations. After matching adjustment, benralizumab and mepolizumab reduced the exacerbation rate by 52% and 49% respectively, compared with placebo, and reduced the rate of exacerbations requiring ED visits or hospitalization by 52% for both treatment. Benralizumab and mepolizumab had a comparable effect in improving pre-bronchodilator FEV1 at 32 weeks. The analysis showed that benralizumab and reslizumab patient populations were too different to produce a sufficient sample size for a reliable estimate for MAIC. The authors conclusion was that when baseline patient characteristics across asthma trials were matched, mepolizumab and benralizumab had comparable efficacy [27]. The other systematic review compared the efficacy and safety of mepolizumab and reslizumab from five studies providing data for exacerbation rate, lung function, quality of life and safety. Compared with placebo, both monoclonal antibodies reduced the exacerbation rates by a value above the minimal clinical important difference (MCID). In addition, improvements in lung function, asthma control and asthma-related quality of life were observed, but below the MCIDs. There was no difference observed for serious adverse events and number of patients dropping out [28].

Further studies investigated particular aspects. Kelly et al. induced airway inflammation in subjects with mild allergic asthma by segmental allergen challenge before and 1 month after a single IV 750 mg dose of mepolizumab and studied eosinophils in the blood, bronchoalveolar lavage, and endobronchial biopsies. The challenge induced in patients not treated with mepolizumab an increase in blood eosinophils, in bronchoalveolar lavage eosinophilia and in the production of eosinophil peroxidase in bronchial mucosa. In mepolizumab treated subjects the allergen-induced increase in blood eosinophils was abolished, while airway eosinophilia and eosinophil peroxidase were reduced but not eliminated, allowing to suggest that mepolizumab reduced eosinophil numbers but had a partial effect on airway eosinophil activation markers, which showed a maintained cell functionality [29]. Shrimanker et al. studied by a post hoc comparison the asthma exacerbations occurring during treatment with mepolizumab or placebo in the available trials. Testing the hypothesis that exacerbations differ with respect to change in symptom scores, FEV1 values, and inflammatory profile, they found that the association between exacerbations and a lower sputum eosinophil number result in less severe symptoms compared with placebo [30]. In addition, cost-effectiveness evaluations were performed. Based on the data from MENSA

trial a within-trial economic analysis was done, with the objectives to quantify the incremental costs of asthma-related exacerbation, of asthma-related exacerbation requiring ED visits or hospitalization, and of asthma-related total healthcare resource utilization. The mean medical costs of asthma-related exacerbations at 8 months corresponded to \$969, \$852, and \$1692 for mepolizumab 75 mg IV, 100 mg SC, and placebo, respectively. The costs for ED or hospitalizations due to asthma-related exacerbations were \$901, \$795, and \$1557 for mepolizumab 75 mg IV, 100 mg SC, and placebo. As well, asthma-related healthcare resource utilization was lower for the mepolizumab groups versus placebo. The difference was significant ($P = 0.02$) for the costs for ED or hospitalizations [31]. A study resulted from the invitation by the National Institute for Health and Care Excellence to the manufacturer of mepolizumab to submit evidence on the clinical and cost effectiveness of mepolizumab for the treatment of severe eosinophilic asthma, predominantly based on DREAM, MENSA and SIRIUS trials. The economic outcome was calculated by the usual cost-effectiveness tools, i.e. quality-adjusted life-year (QALY) and incremental cost-effectiveness ratio (ICER). Add-on mepolizumab compared with standard-of-care (SoC) was £27,418 per QALY gained if patients stopped mepolizumab after 1 year unless the number of exacerbations decreased at least 50% or a decrease in corticosteroids dose was achieved. The ICER for add-on mepolizumab was £29,163 per QALY gained compared with SoC. This ICER was not solid for patients continuing treatment in presence of corticosteroid dose reduction where exacerbations had decreased by less than 50%. The conclusion was that add-on mepolizumab could be recommended as an option for treating severe eosinophilic asthma when the suspension rule suggested by the company was applied [32].

As far as the optimal duration of treatment is concerned, a 52-week, multicenter, open-label extension, phase IIIb study on patients who received mepolizumab or placebo in MENSA and SIRIUS trials had the primary objective to evaluate the long-term safety of mepolizumab and the efficacy assessed by the annualized exacerbation rate and durability of response. A global number of 558 patients treated with mepolizumab and 358 treated with placebo were studied, 36 and 58 patients experiencing an adverse reaction, respectively, of which 13 and 29 were systemic or local reactions. No mepolizumab-related anaphylaxis was reported. The mepolizumab treatment was found to exert a long-lasting response, as shown by maintaining reductions in exacerbation rate and oral corticosteroids doses [33]. Very recently, this outcome was confirmed in an open-label extension study in patients enrolled in the DREAM, using as efficacy endpoints the annualized exacerbation rates, changes from baseline in Asthma Control Questionnaire scores, and blood eosinophil counts; 347 patients were enrolled for a mean duration of 3.5 years. The most commonly reported adverse reactions were headache, respiratory infection, bronchitis, and asthma worsening, 23% of patients experiencing one or more reactions; six fatal events were reported, none of them being related to mepolizumab. In patients treated for 156 weeks or more, the exacerbation rate was 0.74, with a 56% reduction from the off-treatment period between DREAM and the extension study. Also, the mean Asthma Control Questionnaire score was decreased by

0.47 points, and blood eosinophil counts declined by 78% [34]. The overall results from the two prolonged study support the long-term safety and efficacy of mepolizumab in patients with severe eosinophilic asthma.

In addition, data from real-life studies are available. Such studies expand the knowledge on the efficacy of a given treatment because patients are recruited from current clinical practice and thus the limitations from the strict rules to be admitted to a trial are removed. In a small study, 14 patients with refractory eosinophilic asthma, whose mepolizumab treatment started between June 2017 and January 2018, the evaluation at baseline and after 24 weeks of treatment of the asthma control test score showed a significant increase in the score ($P < 0.0001$). This important improvement in symptom control was accompanied by a strong reduction in blood eosinophil numbers, a significant increase in FEV1 ($P < 0.01$), and a significant decrease in exacerbation numbers ($P < 0.001$). Thus, real-life experience confirm the positive outcome of controlled trials [35]. Another recent real-life study addressed the eligibility of mepolizumab, compared with other monoclonal antibodies in patients with severe uncontrolled asthma. In a cohort of 670 patients, 20% were eligible for mepolizumab, 31–41% were eligible for omalizumab (the different rate depending on eligibility criteria used) and 5% were eligible for reslizumab. Overlapping in eligibility to treatment was variable: in the 101 patients eligible to mepolizumab not currently receiving omalizumab 27 to 37% were omalizumab-eligible and 18% were reslizumab-eligible. The eligibility for mepolizumab and omalizumab was superior to that for reslizumab. Despite some overlap, the patient groups eligible for treatment with anti-IL-5 or anti-IgE therapies were frequently different, highlighting the diverse severe asthma phenotypes and endotypes [36]. An emerging phenotype is characterized by the occurrence of bronchiectasis, which are present in up to 50% of patients with severe uncontrolled asthma, a good control being achieved in a pilot study on patients treated with mepolizumab [37]. The most recent achievement concerns the ability of mepolizumab to improve the small airway function, that is usually hardly modified by asthma treatments, in severe eosinophilic asthma, such improvement being associated with clinical control of the disease [38].

3. Mepolizumab in other eosinophilic disorders

Because of the crucial importance of IL-5 in eosinophils biology, the efficacy of blocking IL-5 by mepolizumab makes it a candidate to treat various eosinophil-associated disorders. As recently reviewed by Roufosse, if some of them are in the preliminary stage of case reports, others are supported by an increasing number of studies [39]. The most investigated eosinophilic disorders are chronic rhinosinusitis with nasal polyposis, eosinophilic esophagitis, hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis, allergic bronchopulmonary aspergillosis, and eosinophilic chronic obstructive pulmonary disease.

3.1. Mepolizumab in chronic rhinosinusitis with nasal polyposis

Chronic rhinosinusitis with nasal polyps (CRSwNP) is defined by the persistence of symptoms, which consist of nasal

stuffiness, nasal discharge, facial pain or pressure, cough from post-nasal drip, and loss of smell, for more than 12 weeks [40]. In particular, loss of smell is significantly associated with impaired quality of life [41]. The currently available treatments may improve only temporarily the olfactory function in patients with CRSwNP. More effective treatments must target the persistent abolition of inflammation and the induction of a normal turnover of the olfactory epithelium. The occurrence of sinonasal eosinophilia in CRSwNP, define the endotype of eosinophilic CRSwNP [42]. Due to the critical importance of IL-5 in stimulating the production and survival of, eosinophils, mepolizumab is currently evaluated, as well as other biologic agents, as a treatment for this endotype of CRSwNP. Mepolizumab was found to be valuable in the treatment of refractory nasal polyposis in selected populations. In a double-blind, placebo-controlled trial on subjects aged 18 to 70 years suffering with recurrent nasal polyposis necessitating surgery, patients were treated with 750 mg of mepolizumab by intravenous injection or placebo each 4 weeks, up to six doses, added to treatment with nasal topical corticosteroids. The primary endpoint consisted of the number of patients no more needing surgery at week 25. A composite endpoint of endoscopic nasal polyp score and nasal polyposis severity assessed by a visual analog scale (VAS) score was used. Fifty-four patients received mepolizumab and 51 received placebo. A significantly greater proportion ($P = 0.006$) of mepolizumab treated patients compared with placebo-treated patients no longer required surgery at week 25, with concomitant improvement in nasal polyposis severity VAS score and endoscopic nasal polyp score. No difference in the safety profile of mepolizumab and placebo was found [43]. A systematic review and meta-analysis included seven studies (four randomized control trials, one case-control, and two case series, using anti-IL-5 therapy (mepolizumab/reslizumab) and anti-IgE therapy (omalizumab). The measure of efficacy were nasal polyp score, computed tomography score, and symptom scores. Both anti-IL5 therapy and anti-IgE therapy resulted in a standard mean difference of nasal polyp score improvement of -0.66 and -0.75 , respectively, between biologic therapy and placebo. The authors concluded that biologic therapies may be effective in the treatment of recalcitrant nasal polyposis in selected population, though additional high-level evidence is needed to establish clinical efficacy [44]. As far as the smell loss causing impairment in quality of life is concerned [41], a recent report described that in a patients with severe asthma from dust mites allergy and concomitant CRSwNP, no previous treatment, including oral and injective corticosteroids, was unsuccessful in the loss of smell, while mepolizumab treatment resulted in good clinical control of both asthma and CRSwNP, and particularly in complete recovery of the smell loss after 4 months of treatment [45]

3.2. Mepolizumab in eosinophilic esophagitis

Eosinophilic esophagitis (EoE) is defined by eosinophilic inflammation of the esophagus causing abdominal pain, vomiting, reflux, dysphagia, and food impactions. If untreated, remodeling and fibrosis of the esophagus resulting in stricture formation may occur. The standard treatment, that includes

food-restriction diets or drugs such as proton pump inhibitors or swallowed topical corticosteroids, is often ineffective [46]. The first trial on mepolizumab treatment was performed in 2010 on 11 adults with active EoE (as assessed by >20 peak eosinophil number/high power field and dysphagia). The patients were randomized to receive 750 mg of mepolizumab or placebo in two IV infusions with a 1-week interval. If complete remission (<5 peak eosinophil number) was not achieved after 8 weeks, two further doses 4 weeks apart of 1500 mg of mepolizumab or placebo were administered. The treatment outcome was evaluated by clinical, endoscopical, histological indexes, and blood and tissue biomarkers. A significant reduction ($P = 0.03$) of esophageal eosinophilia was observed in mepolizumab treated patients (-54%) compared with placebo-treated patients (-5%) after 4 weeks of treatment. The eosinophils in the number remained stable after the two additional administration in both groups. The expression in the esophageal epithelium of transforming growth factor beta1 (TGF- β 1) and tenascin C (TN-C) was significantly reduced ($P = 0.05$ and $P = 0.033$, respectively) after 13 weeks of treatment. Clinically, limited improvement of symptoms was seen, although a trend was seen between 4 and 13 weeks after initiation of mepolizumab treatment. The safety of mepolizumab was satisfactory in front of the high dose of 1500 mg [47]. In an international, multicenter, double-blind, randomized study, 59 children with EoE were enrolled based on a peak count of esophageal intraepithelial eosinophils of ≥ 20 at baseline. Mepolizumab was administered by three infusions with 4-weeks interval of 55, 2.5, or 10 mg/kg with no placebo control group. The peak and mean esophageal eosinophil counts were 122.5 ± 8.78 and 39.1 ± 3.63 , respectively. One month after the last infusion, peak eosinophil counts were <5 in 8.8% of children, with no differences among groups receiving different doses of mepolizumab. Reduced peak and mean eosinophil counts to <20 were found in 31.6% and 89.5% of children, respectively. A higher mean baseline esophageal intraepithelial eosinophil count was associated with a greater reduction in the mean count ($P < 0.0001$) [48]. However, in a systematic review and network meta-analysis including 11 studies with a global number of 456 patients assessing the efficacy of six pharmacologic treatments (budesonide suspension and viscous, fluticasone, esomeprazole, prednisone and mepolizumab, and placebo as well, viscous budesonide was found to be the most effective therapy for EoE [49].

3.3. Mepolizumab in hypereosinophilic syndrome

Hypereosinophilic syndrome (HES) is a myeloproliferative disorder characterized by persistent eosinophilia, defined as more than 1500 cells per microliter associated with multiple organ damage [50]. An international, randomized, double-blind, placebo-controlled trial evaluated the safety and efficacy of mepolizumab in patients with HES. To be admitted, patients must be negative for the Factor interacting with PAPOLA and CPSF1-Platelet-Derived Growth Factor Receptor Alpha (FIP1L1-PDGFR α) fusion gene and must require prednisone monotherapy, 20 to 60 mg per day, to keep a stable clinical status and a blood eosinophil count of less than

1000 per microliter. The reduction of the prednisone dose to 10 mg or less per day for eight or more consecutive weeks was the primary endpoint, which was reached in 84% of mepolizumab treated patients and in 43% of placebo-treated patients ($P < 0.001$) with no raise in clinical activity of HES. In 95% of mepolizumab treated patients a blood eosinophil count of less than 600 per microliter for eight or more consecutive weeks was achieved, compared with 45% of placebo-treated patients ($P < 0.001$). Severe adverse events (one of them fatal) concerned seven mepolizumab treated patients and five placebo-treated patients [51]. Another trial investigated the response to mepolizumab in patients with lymphocytic variant HES (L-HES), characterized by marked overproduction of IL-5 by dysregulated T cells. Patients recruited in the trial were evaluated by T-cell phenotyping and T-cell receptor gene rearrangement patterns, also measuring their serum thymus-and-activation-regulated chemokine (TARC) levels. L-HES was diagnosed in 13 of 63 patients with HES. The ability of mepolizumab to attenuate corticosteroids in patients with L-HES was comparable to those with a normal T-cell profile, but less patients with L-HES maintained eosinophil levels below 600/ μ L. Increased serum TARC levels (>1000 pg/mL) had no significant impact on the ability to reduce corticosteroid doses. This trial showed that mepolizumab is an effective corticosteroid-sparing agent for patients with L-HES, though in some patients eosinophil levels remain above 600/ μ L, indicating partial neutralization of overproduced IL-5 or participation of other eosinophilopoietic factors [49]. Roufosse et al. investigated the long-term safety and efficacy of mepolizumab (750 mg) in HES, with the frequency of adverse events as primary endpoint and optimal dosing frequency, corticosteroid-sparing effect and development of anti-mepolizumab antibodies as secondary endpoints for a mean treatment duration of 251 weeks. The incidence of adverse events was 932 per 100 subject-years in the first year, decreasing to 461 events per 100 subject-years after 48 months. Three serious adverse events possibly related to mepolizumab, including one fatal event, were reported. The median daily prednisone dose progressively decreased from the initial 20 mg, the median daily dose over the course of the study being was 1.8 mg and 62% of patients being prednisone free without other HES medications for ≥ 12 consecutive weeks. No neutralizing antibodies were detected. The conclusive remark was that mepolizumab is effective and well tolerated as a long-term corticosteroid-sparing agent in patients with HES [52,53].

3.4. Mepolizumab in eosinophilic granulomatosis with polyangiitis

Eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss syndrome, is a small vessel vasculitis associated with asthma and eosinophilia. Its understanding is steadily increasing but there is room to expand the knowledge on pathophysiologic and diagnostic uncertainties [54]. In a multicenter, double-blind, parallel-group, phase 3 trial, participants with relapsing or refractory EGPA and taking a stable prednisolone or prednisone dose were randomly assigned to treatment with mepolizumab 300 mg or placebo,

administered SC every 4 weeks. The primary endpoints were the weeks of remission over a 1-year period and the proportion of participants in remission at week 36 and 48. In addition, the annualized relapse rate and safety were assessed. Out of 136 participants, 68 participants received mepolizumab and 68 received placebo. Active treatment resulted in significantly more weeks of remission than placebo ($P < 0.001$) and a higher rate of patients in remission at both week 36 and week 48 ($P < 0.001$). Remission did not occur in 47% of mepolizumab treated patients compared with 81% of placebo-treated. Also, the outcome of annualized relapse rate was significantly better in mepolizumab patients than in placebo patients (1.14 vs. 2.27, $P < 0.001$). The safety profile of mepolizumab did not differ from that observed in previous studies on mepolizumab. Thus, in patients with EGPA, mepolizumab gave significantly more weeks in remission and a higher proportion of patients in remission compared with placebo, although only half patients treated with mepolizumab had protocol-defined remission [55]. No other controlled trial is available thus far.

3.5. Mepolizumab in allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is a complex pulmonary disorder characterized by recurrent episodes of wheezing, fleeting pulmonary opacities, and bronchiectasis. ABPA is not rare, being estimated five million cases worldwide, but despite 60 years of research, its pathogenesis, diagnosis, and treatment remain controversial [56]. The effect of mepolizumab on ABPA was evaluated until now only by case reports. As reviewed by Hirota et al. the outcome is apparently beneficial, being possible to observe the case of a patient with ABPA resistant to omalizumab but responsive to mepolizumab as assessed by both asthmatic symptoms and improvement of chest radiological findings [57]. However, no reliable estimation of efficacy is feasible in absence of data from controlled trials.

3.6. Mepolizumab in eosinophilic chronic obstructive pulmonary disease

Up to 40% of patients with chronic obstructive pulmonary disease (COPD) show an eosinophilic phenotype, as defined by a peripheral-blood differential eosinophil count of 2% or more, corresponding to approximately 150 to 200 eosinophils per cubic millimeter (mm^3) [58]. In a 'proof of principle' randomized placebo-controlled trial on 18 patients with high eosinophil counts who were randomly assigned to mepolizumab or placebo, in actively treated patients the sputum eosinophil counts and the blood eosinophil counts decreased from 11% at baseline to 0.5% after 6 months and from 0.7% cells mm^3 to 0.03 cells mm^3 , respectively. In placebo-treated patients, the figures were from 7.4% to 22% in sputum and from 0.33 cells mm^3 to 0.26 cells mm^3 in blood. Actually, also the difference in placebo-treated were significant ($P < 0.05$), the authors suggesting the improved compliance to medication during the trial as a likely explanation of such result [59]. A phase 3, randomized, placebo-controlled, double-blind, parallel-group trials was performed comparing mepolizumab (100 mg or 300 mg) with placebo, administered by SC route

every 4 weeks for 52 weeks in patients with COPD with a history of moderate or severe exacerbations despite ICS-based triple maintenance therapy. The mean annual rate of moderate or severe exacerbations was 1.19 per year in patients receiving 100 mg of mepolizumab, 1.27 per year in patients receiving 300 mg of mepolizumab, and 1.49 per year in patients receiving placebo group. The rate of exacerbations in the 100 mg and 300 mg mepolizumab groups versus the placebo group was not significantly better than placebo for 100 mg ($P = 0.07$) as well as for 300 mg ($P = 0.14$). A superior effect of mepolizumab compared with placebo on the annual rate of moderate or severe exacerbations was found in patients with higher blood eosinophil counts at screening. The safety of mepolizumab was comparable to that of placebo [60]. The lack of significant reduction of the rate of exacerbations warrants further studies aimed at defining the eosinophilic phenotype in COPD patients and the specific effects of treatments targeting such phenotype [61]

4. Expert opinion

The introduction of biologic therapies for severe asthma was a milestone in the management of this challenging disease. Airway inflammation in severe asthma has been recently classified into T (type) 2 high and T2 low. The former is characterized by the generation of cytokines, particularly IL-4, IL-5 and IL-13, with regulatory activity on airway inflammation. The occurrence of T2-high inflammation is revealed by biomarkers that include eosinophils, FeNO and IgE. The available monoclonal antibodies include omalizumab (anti-IgE); mepolizumab, reslizumab and benralizumab (anti-IL-5 pathways), and dupilumab (anti-IL-4/IL-13). The treatment with such agents showed significant improvement in asthma symptoms, a reduced rate of exacerbations, and improved respiratory function [62]. Of interest, biologic agents were found to be successful also in disorders other than the initial target that drove their conception. This is true for the anti-IL-5 monoclonal antibody mepolizumab, which is approved to treat severe eosinophilic asthma phenotype but was shown to be effective also in other important eosinophilic disorders, including CRSwNP, EoE, HES, EGPA and eosinophilic COPD. Concerning other eosinophilic disorders, a good level of evidence, as supported by controlled trial, is still lacking.

The major field for clinical perspective of mepolizumab in the next years remains severe asthma, for which there is a clear evidence of efficacy when treatment with biologic agents is needed [63]. In particular, eosinophilic asthma, typified by increased expression of type 2 cytokines IL-4, IL-5, and IL-13 in the airway, concerns around 50% of patients with severe uncontrolled asthma [64]. A recent study assessed the eligibility of the different biologics in 128 patients with severe asthma. The rate of eligibility was 66% for omalizumab, 78% for mepolizumab, 41% for reslizumab, and 53% for benralizumab, respectively, with a variable overlap in treatment eligibility, 53% of patients being eligible for both omalizumab and mepolizumab, 37% for omalizumab and benralizumab, and 29% for all biologic agents [65]. Further studies are warranted to confirm these data as well as to define the role of biomarkers in identifying the most appropriate agent in single

patients and in characterizing the safety profiles of the different treatments [62]. As far as other eosinophilic disorders are concerned, it is likely the increasing evidence of mepolizumab effectiveness will result in further approval by regulatory agencies for eosinophilic granulomatosis with polyangiitis, which was already approved in USA, or chronic rhinosinusitis with or without nasal polyps.

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