Through the MIRRA and what we found there

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Shareable abstract (@ERSpublications)
A series of *post hoc* MIRRA studies have illuminated eosinophilic granulomatosis with polyangiitis as an eosinophil-driven disease from various perspectives https://bit.ly/468pj86

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Eosinophil clustering in local tissues often characterises undesirable physiological responses. By the 1990s, the pathogenic nature of specific granule proteins derived from eosinophils had become apparent, solidifying their recognition as the primary producers of inflammatory mediators, including abundant reactive oxygen species and cysteinyl leukotrienes. Since then, it became a common consensus that they are a therapeutic target in allergic diseases.

The term "eosinophilic" is, in clinical practice, quite ambiguous, as it is used even in cases where eosinophilia and inflammation coexist. Whether eosinophils are causing the issue or whether they are harmless or even beneficial can vary significantly depending on the disease and individual cases. Actual eosinophilic inflammation is thought to be characterised not only by the cell increase or accumulation but also by their activation, which involves the release of physiological active substances within the cells, such as granule proteins [1]. It should be noted that eosinophils, due to the frequent occurrence of their cytolysis/ETosis, may render conventional tissue examinations inadequate [2]. Currently, there is a perceived need to distinguish between "eosinophil-driven disease" and "eosinophil-associated disease".

Mepolizumab is a neutralising antibody against interleukin (IL)-5, known as a master regulator that enhances eosinophil maturation and functions. Its efficacy on asthma was anticipated from development; however, in an early clinical study focused on airway hyperresponsiveness as an outcome in mild asthma, the effectiveness of mepolizumab could not be demonstrated [3]. Nevertheless, the efficacy was subsequently confirmed when targeting refractory eosinophilic asthma, with a decrease in exacerbations as the outcome. Consequently, mepolizumab is now widely used for eosinophilic asthma, with accumulating real-world data [4]. It can be stated that mepolizumab has revealed the diversity of asthma pathology. Given the negligible side-effects of anti-IL-5 or anti-IL-5-receptor antibodies, discussions have deepened regarding the physiological role of eosinophils and IL-5 as a whole.

Eosinophilic granulomatosis with polyangiitis (EGPA), previously referred to as Churg–Strauss syndrome, is a condition characterised by eosinophilia and refractory systemic vasculitis that typically occurs in adults. EGPA is a relatively rare disease, but it imposes a significant disease burden on affected patients. The phase 3 Mepolizumab in Relapsing or Refractory EGPA (MIRRA) study is a multicentre, double-blind clinical trial that randomly assigned 136 participants with relapsing or refractory EGPA to receive either mepolizumab or placebo, in addition to standard care [5]. The primary end-points of the study were the accrued weeks of remission over a 52-week period and the proportion of participants in remission at both week 36 and week 48. Secondary end-points included the time to first relapse and the average daily glucocorticoid dose. The results showed that 28% of patients treated with mepolizumab and 3% of those who received a placebo achieved accumulated remission lasting 24 weeks or more. Similarly, 32% and 3% of mepolizumab and placebo groups, respectively, experienced remission at both weeks 36 and 48. Reduced glucocorticoid use compared to placebo was also observed.

It is evident that oral corticosteroids (OCS), which are the first-line treatment for achieving remission and long-term management in EGPA, have various well-documented side-effects. At present, the realistic goal of our EGPA treatment is considered to be the reduction of OCS to the lowest possible dose while achieving clinical remission. *Post hoc* analysis focusing on this aspect demonstrated that 78–87% of patients benefited from mepolizumab [6]. Furthermore, another *post hoc* analysis was conducted focusing on the vasculitic phenotype that often occurs in antineutrophil cytoplasmic antibody (ANCA)-positive patients [7]. Overall, irrespective of Birmingham Vasculitis Activity Score, Vasculitis Damage Index score and historical ANCA positivity, patients treated with mepolizumab were generally associated with clinical benefit.

In the current issue of *ERJ Open Research*, JAYNE *et al*. [8] present the results of additional *post hoc* analyses conducted to further elucidate whether various aspects of the disease and treatment history can predict the response to mepolizumab. The study also aimed to provide additional insights into the OCS-sparing effects of mepolizumab in EGPA patients. The analysis revealed that patients treated with mepolizumab exhibited a longer duration of remission and a higher proportion of patients in remission at weeks 36 and 48 when compared to those receiving a placebo. These findings held true across various subgroups, including baseline refractory disease status, immunosuppressant use, EGPA duration, relapse frequency and OCS use of $\leqslant$20 mg·day^{-1}. Furthermore, irrespective of immunosuppressant use and disease duration, patients treated with mepolizumab were more likely to experience clinical benefits such as achieving remission, reduced exposure to OCS and lower relapse rates. On average, patients treated with mepolizumab received 1423.1 mg less corticosteroid treatment over the 52-week study period compared to those on placebo, which is equivalent to a daily reduction of 4.3 mg.

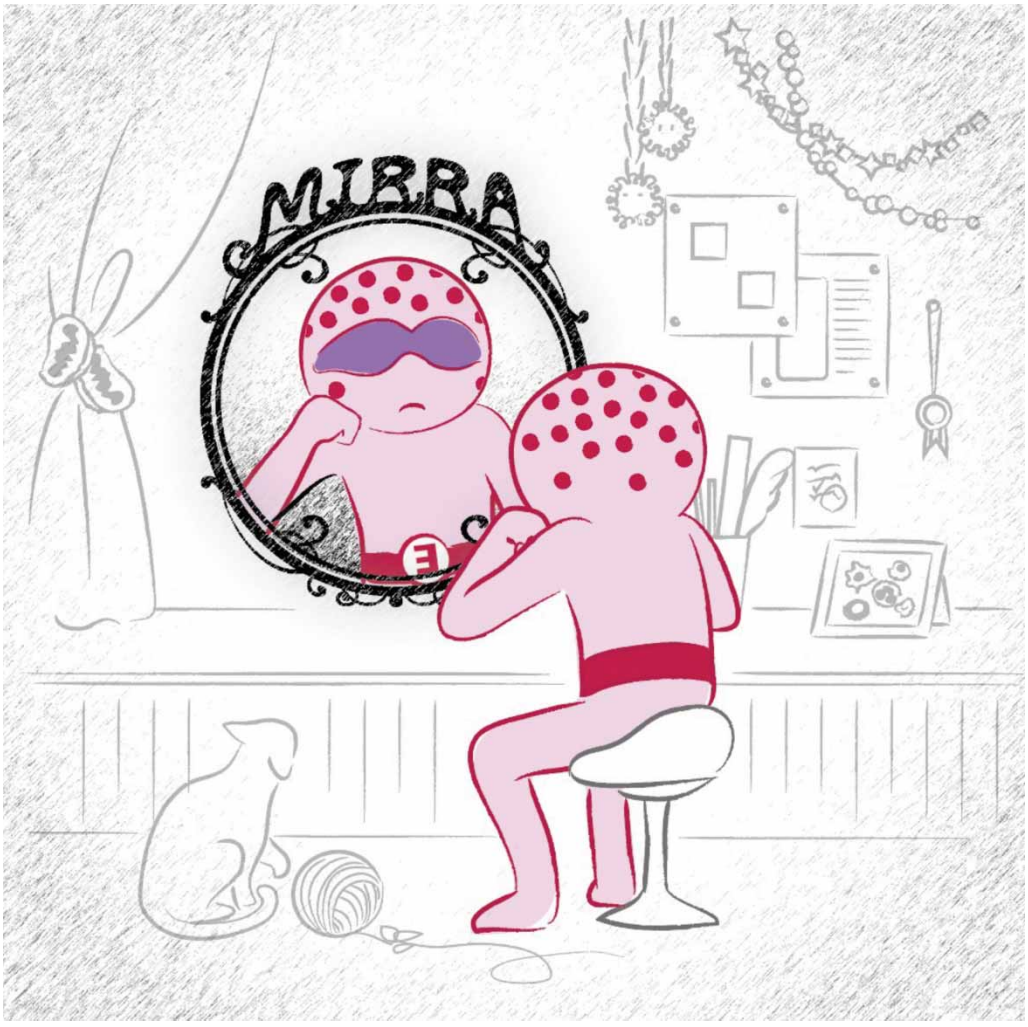

FIGURE 1 The MIRRA study mirrors the role of eosinophils in eosinophilic granulomatosis with polyangiitis.

A genome-wide association study has revealed genetic diversity within EGPA [9] and, given its clinical overlap with hypereosinophilic syndrome and the capacity to affect various organs, it is considered a substantially heterogeneous disorder in terms of pathophysiology [10]. Nevertheless, a series of *post hoc* MIRRA studies have illuminated EGPA as an eosinophil-driven disease from various perspectives (figure 1). Conditions threatening vital organs and life, such as renal dysfunction and heart failure, are excluded from the MIRRA study; thus, further evidence accumulation regarding the efficacy on severely affected patients and cost-effectiveness of biologics is anticipated. It would also be of interest to determine whether mepolizumab can contribute to reducing the dosage of immunosuppressants.

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