Hot topics from the Assemblies

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Mepolizumab for eosinophilic chronic obstructive pulmonary disease

Authors: Pavord ID, Chanez P, Criner GJ, *et al.* *N Engl J Med* 2017; 377: 1613–1629.

Summary: Eosinophilic chronic obstructive pulmonary disease (COPD) is characterised by a peripheral blood differential eosinophil count of 2% or more. This phenotype is found in roughly 40% of patients with COPD. These patients have an increased frequency of exacerbations, but benefit from inhaled glucocorticoids as part of a triple therapy regime. However, 30–40% of these patients continue to have significant exacerbations, meaning targeted therapy to reduce eosinophil counts could play a role in future therapy. Mepolizumab blocks interleukin-5 and has been associated with a decreased rate of exacerbation in eosinophilic asthma.

Pavord *et al.* conducted two, phase 3, randomised, placebo-controlled, double-blind, parallel group trials in 16 and 15 countries, respectively: mepolizumab *versus* placebo as add-on treatment for frequently exacerbating COPD patients (METREX); and mepolizumab *versus* placebo as add-on treatment for frequently exacerbating COPD patients characterized by eosinophil level (METREO). Mepolizumab was given as a subcutaneous injection every 4 weeks over 1 year alongside regular inhaled triple therapy. The main end-point measured was annual rate of moderate or severe exacerbations. METREX studied the use of 100 mg and METREO the use of 100 mg and 300 mg, *versus* placebo.

In the METREX study, there was a statistically significant reduction in the modified intention-to-treat population with an eosinophilic phenotype. METREO also showed significance, but only in the 100 mg group. A higher eosinophil count at screening was associated with improved outcomes. Mepolizumab was also shown to have a similar safety profile as the placebo.

These studies concluded that among patients with an eosinophilic COPD phenotype who still have exacerbations despite maximal triple therapy the 100 mg regimen of mepolizumab reduced the rate of exacerbation over placebo. This study rigorously analyses the use of mepolizumab and suggests it offers significant benefit to patients. If this is the case, then we are closer to tailoring treatment for patients with eosinophilic COPD and reducing morbidity and mortality in this group.

Reviewed by: Caitlin Morgan (UK, Assembly 5)

Impact of rhinitis on work productivity: a systematic review

Authors: Vandenplas O, Vinnikov D, Blanc PD, *et al.* *J Allergy Clin Immunol Pract* 2017; in press [https://doi.org/10.1016/j.jaip.2017.09.002].

Summary: It is now a widely accepted fact that exposure to various materials in the workplace may contribute to the development of allergic rhinitis. Apart from the livelihood of the workers, the recurrent episodes may also significantly impair work productivity. However, the association between disease prevalence and work productivity has remained unclear.

To further address this question, Vandenplas *et al.* undertook a rigorous statistical approach to make a quantitative estimate of the impact of allergic rhinitis on work productivity. In this systematic review, they analysed the results of studies published between 2005 and 2015 which addressed the impact of allergic rhinitis on work productivity. 30 studies were included, all of which used the Work Productivity and Activity Impairment–Allergy Specific instrument for estimating the magnitude of the work productivity impairment related to allergic rhinitis.

From the pooled data analyses, the authors found an estimated 3.6% of patients (95% confidence interval: 2.4–4.8%) missed work time due to allergic rhinitis whereas 35.9% (95% CI: 29.7–42.1%) had impaired at-work performance. The pooled analysis also underscored an estimated 39.4% (95% CI: 34.8–44.0%) loss of work-productivity as a result of allergic rhinitis. The severity of allergic rhinitis symptoms was found to be the most consistent disease-related risk factor which could substantially alter work productivity. The authors identified that pharmacological treatment of allergic rhinitis could reverse the impact on work productivity. One of the reports included in this systematic review found a mean reduced work impairment among workers with allergic rhinitis who received levocetrizine (mean work impairment, days per month: 0.7; 95% CI: 0.5–0.9) than among those who received placebo (1.0; 95% CI: 0.8–1.3) (Bousquet *et al. Int Arch Allergy Immunol* 2009; 150: 75–82).

This systematic review provides, for the first time, an effective estimate of the impact of allergic rhinitis on work productivity along with a clearer indication of the principal contributing factors which will help physicians and policy-makers to devise an effective strategy for a better work environment.

Reviewed by: Subhabrata Moitra (India, Assembly 6)

Hot topics are short (approx. 200 words) summaries of recent important articles in respiratory medicine written by early career ERS members. To become a hot topic author, please contact Aran Singanayagam: aransinga@gmail.com

Mycophenolate mofetil *versus* oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial

Authors: Tashkin DP, Roth MD, Clements PJ, *et al*.
Lancet Respir Med 2016; 4: 708–719.

Summary: Over the past few decades, published studies have shown that an important proportion of patients with systemic sclerosis (SSc) develop interstitial lung disease (ILD). In these patients, progressive ILD is the leading cause of mortality and available treatment options are limited. This study, SLS II, expands on findings from a previous study (SLS I) published in 2006 in the *New England Journal of Medicine* and is designed to compare the efficacy and safety of mycophenolate mofetil (MMF) administered for 2 years and oral cyclophosphamide (CYC) administered for 1 year, in symptomatic patients with SSc-related ILD.

198 patients from 14 US medical centres were screened over a period of more than 3 years and 142 were deemed eligible and randomised: 73 in the CYC arm and 69 in the MMF arm. Baseline characteristics for both groups were comparable, with no statistically significant differences between the two groups. Participants had an average age of 52 years and were predominantly women (73.9%); mean forced vital capacity (FVC) was 66.5% predicted and mean diffusing capacity of the lungs for carbon monoxide was 54% predicted among participants. No significant difference was found between the two treatment groups in the course of FVC % predicted over the entire 24 months of the study, and MMF treatment was therefore not found to be superior in efficacy compared with oral CYC. However, both treatments produced improvements in lung function, dyspnoea and modified Rodnan score, a score which evaluates patient's skin thickness, compared with baseline.

Overall, MMF appears to be better tolerated than CYC, with a good safety profile based on the number of treatment failures and patient withdrawal, and this is the first study showing efficacy of MMF in symptomatic patients with SSc-ILD. Evidently, physicians can now use both immunosuppressants for this group of patients and MMF appears to be less cytotoxic and at least as effective as CYC.

Reviewed by: Alexis Papadopoulos (UK, Assembly 12)

Monocyte-derived alveolar macrophages drive lung fibrosis and persist in the lung over the life span

Authors: Misharin AV, Morales-Nebreda L, Reyfman PA, *et al*.
J Exp Med 2017; 214: 2387–2404.

Summary: Tissue-resident alveolar macrophages (TR-AM) are depleted from the lung during early stages of bleomycin-induced lung injury and fibrosis. The recovery of the population of macrophages after bleomycin could be completely attributable to the recruitment and differentiation of monocyte-derived alveolar macrophages (Mo-AM). The authors used multiple lineage-trace mouse models where they selectively deplete TR- or Mo-AM and induced fibrosis with bleomycin. Deletion of TR-AM had no effect on the severity of the fibrotic phenotype. However, when depleting Mo-AM animals showed attenuated fibrosis as evidenced by normalised collagen levels and recovered lung compliance.

Moreover, the study of the gene expression of these cell populations using RNA sequencing indicated that genes are differently regulated through time, pointing to Mo-AM gradually changing their gene expression profile towards the expression of TR-AM genes. In addition, differences in expression of activation state genes showed no evidence of two different populations, but rather a complex and heterogeneous population. While in a healthy mouse the contribution of Mo-AM to the macrophage population is minimal (<5%) after 1 year of life, animals suffering and recovering from fibrosis showed a 50% contribution of Mo-AM to the population. With these results, the authors suggest consideration of the differentiation pathway from Mo-AM to TR-AM as a target for the therapy of fibrosis, rather than systemic depletion or recruitment inhibition of monocytes. Since many pathways are specific for the differentiation of alveolar macrophages (such as caspase 8 and RIPK3), targeting these pathways is predicted to slow down fibrosis development, without affecting circulating monocytes or resident macrophages.

Reviewed by: Elena Lopez Rodriguez (Germany, Assembly 3)