HELLENIC REPUBLIC
National and Kapodistrian University of Athens
EST. 1837

Systematic Review, Meta-Analysis and Network Meta-Analysis comparing anti-IL5 and anti-IL4/anti-IL-13 monoclonal antibodies for the treatment of severe, uncontrolled, eosinophilic asthma

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Introduction

- Eosinophilic asthma is a phenotype of severe asthma, characterized by elevated blood eosinophils (~2-3%). [1,2]
- Monoclonal antibody therapies targeting interleukin (IL)-4/IL-13 and IL-5 cytokine pathways, seem to reduce asthma exacerbations, improve lung function (as measured with FEV1) and asthma symptoms (as measured with asthma control questionnaires). [3,4]

OBJECTIVE

The scope of the present research was to explore the efficacy and safety of monoclonal antibodies that target IL-5 (mepolizumab and reslizumab) or its receptor (benralizumab) and the IL-4 and IL-13 receptor (dupilumab) compared to placebo, in adults with severe eosinophilic asthma.

METHODS

A systematic literature search was performed using the databases PubMed/Medline and CENTRAL. The studies selected were all randomized, double-blind, phase III, placebo-controlled trials, evaluating the safety and efficacy of the monoclonal antibodies in adults and children over 12 years with severe, uncontrolled, eosinophilic asthma. Information relating to predefined primary outcomes (clinically significant asthma exacerbations (CAEs)) and secondary outcomes for evaluation of asthma control (ACQ score), lung function (FEV1) and safety (serious adverse events (SAEs) and adverse events that led to discontinuation of treatment) was extracted from the articles to be used for data analysis.
A standard meta-analysis and an indirect comparison were performed.
The GRADE approach was used to define the quality of estimates.

RESULTS

The literature search identified 1511 studies. Only 9 studies involving a total of 6926 participants, fulfilled the inclusion criteria and were selected for quantitative and qualitative analysis. (Figure 1) The risk of bias assessment indicated that all the studies were rated as having a 'low' or 'unclear' risk of bias.

META ANALYSIS

Meta-analysis findings suggested that all treatments were more effective than placebo, based on reduced rates of clinically significant asthma exacerbations (Rate Ratios (RRs) 95% CI 0.46-0.52 - high to moderate certainty), a small improvement in FEV1 (Mean Difference (MD) 95% CI 0.11L-0.14L-moderate certainty), and were generally well tolerated, apart from benralizumab and dupilumab (moderate to low certainty) (Figure 2).

NETWORK META ANALYSIS

The indirect comparison did not show any statistically significant difference in exacerbation rates, FEV1 and serious adverse events (low to very low certainty). Based on ACQ-scores, mepolizumab was found to be more effective than reslizumab (MD 95% CI -0.17[-0.34,-0.04]) and benralizumab (MD 95% CI -0.17[-0.33,-0,01]), while based on adverse events that led to drug discontinuation, mepolizumab appeared to be safer than benralizumab (RR 95% CI 0.20[0.05,0.87]) and reslizumab (RR 95% CI 0.33[0.13,0.82]) (low to very low certainty) (Figure 3).

Figure 2: Meta-analysis results

Intervention	CAEs Rate Ratio (95% CI)	FEV1 Mean Difference, L (95%CI)	ACQ Mean Difference, (95%CI)	SAEs Risk Ratio (95%CI)	Dropouts due to AEs Risk Ratio (95%CI)
Mepolizumab 100mg SC	**0.46 [0.36, 0.58] (I^2 =0%)**	0.11 [0.06, 0.17] (I^2 =0%)	**-0.42 [-0.56, -0.28] (I^2 =0%)**	**0.63 [0.41, 0.97] (I^2 =0%)**	0.43 [0.11, 1.65] (I^2 =0%)
Reslizumab 3mg/kg IV	**0.46 [0.37, 0.59] (I^2 =0%)**	0.11 [0.06, 0.15] (I^2 =0%)	-0.25 [-0.34, -0.16] (I^2 =0%)	0.73 [0.50, 1.07] (I^2 =0%)	0.70 [0.34, 1.46] (I^2 =0%)
Benralizumab 30mg SC	**0.54 [0.45, 0.66] (I^2 =51%)**	0.12 [0.08, 0.16] (I^2 =0%)	-0.25 [-0.33, -0.16] (I^2 =5%)	0.78 [0.66, 0.93] (I^2 =0%)	2.13 [1.22, 3.69] (I^2 =0%)
Dupilumab 300mg SC	0.52 [0.46, 0.59] (I^2 =0%)	**0.14 [0.09, 0.19] (I^2 =38%)**	**-0.31 [-0.55, -0.08] (I^2 =57%)**	1.11 [0.74, 1.66] (I^2 =0%)	**0.99 [0.13, 7.67] (I^2 =71%)**
			Efficacy		Safety

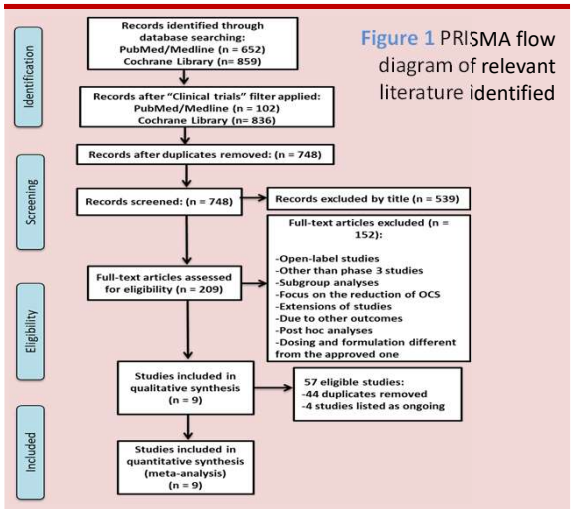

Figure 1 PRISMA flow diagram of relevant literature identified

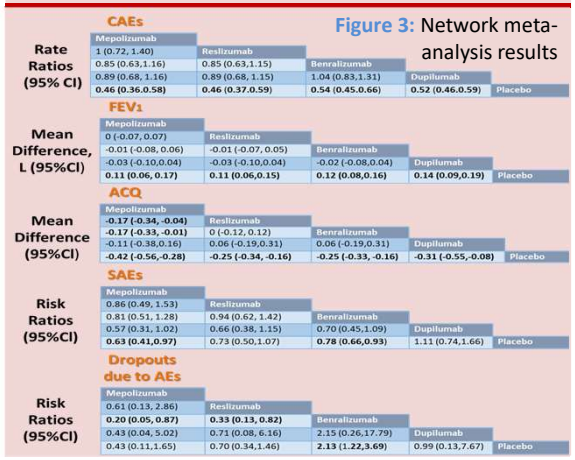

Figure 3: Network meta-analysis results

Conclusions

- Results suggest that the monoclonal antibodies are more effective than placebo.
- The indirect comparison did not show significant differences between the treatments, in terms of efficacy and safety.
- Head to head clinical trials should be conducted to confirm these findings.

References:

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