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Mepolizumab for the Treatment of Chronic Asthma. A Meta-Analysis of Randomized Placebo-Controlled Trials

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INTRODUCTION

- Asthma is a progressive inflammatory disease which is a major cause of disability, health resource utilization and poor quality of life for those who are affected.[1]
- Asthma is the most common chronic disease among children and young adults, particularly because of its early onset.[1]
- It is estimated that more than 50% of asthma has an allergic background.[2]
- About 50% of patients with severe asthma have allergic-atopic asthma.[3]
- Current treatment for asthma suggested by Global Initiative for Asthma (GINA) guidelines includes several reliever and controller drugs, specially inhaled corticosteroids which reduce airway inflammation. Other drugs include β2 agonists and anti-leukotrienes.[4]
- Interleukin-5 (IL-5) plays a key role in the pathogenesisof eosinophilic disorders including asthma.[5]
- Mepolizumab is a fully humanized monoclonal antibody that binds to IL-5, and it may represent a useful therapeutic option to control exacerbations and improve quality of life in asthma patients with persistent airway eosinophilia and moderate to severe asthma.[5]

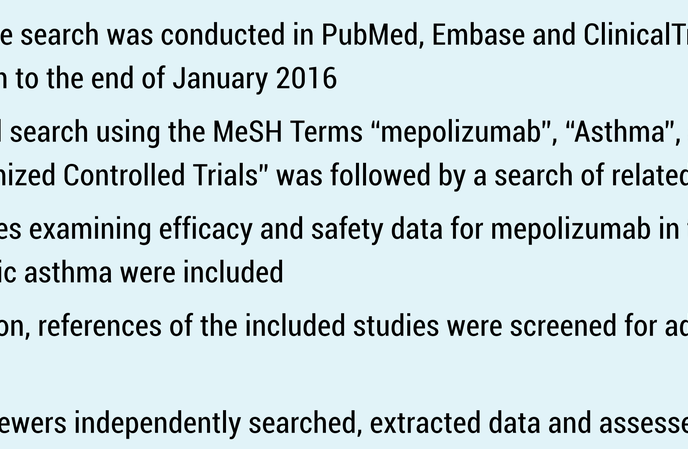
OBJECTIVE

- To evaluate the efficacy and safety of mepolizumab as compared to placebo in patients with chronic asthma.

MATERIALS AND METHODS

- Literature search was conducted in PubMed, Embase and ClinicalTrials.gov from inception to the end of January 2016
- An initial search using the MeSH Terms "mepolizumab", "Asthma", and "Randomized Controlled Trials" was followed by a search of related citations
- All studies examining efficacy and safety data for mepolizumab in the treatment of chronic asthma were included
- In addition, references of the included studies were screened for additional studies
- Two reviewers independently searched, extracted data and assessed risk of bias using the Jadad scale and differences adjudicated via consensus discussion.
- The primary outcomes included were eosinophil counts in blood and sputum, exacerbations, and forced expiratory volumes.
- Secondary outcome was adverse events due to mepolizumab.

RESULTS

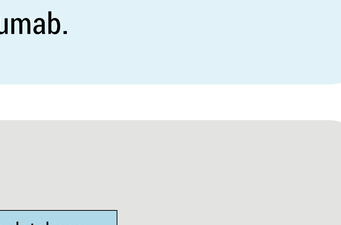


1 FEV1% Predictive values

1.1 Blood Eosinophils

Study or Subgroup	Mepolizumab Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Floodpage 2007	-0.309	0.25	112	-0.035	0.33	119	76.8%	-0.27[-0.35, -0.20]
Halder 2012	-0.28	2.08	29	-0.03	1.74	32	3.1%	-0.25 [-1.22, 0.72]
nair 2009	-0.61	0.47	9	-0.05	0.23	10	20.2%	-0.56[-0.90, -0.22]
Total (95% CI)			**150**			**161**	**100.0%**	-0.33[-0.50, -0.16]

Heterogeneity: Tau²= 0.01; Chi²= 2.62, df = 2(P = 0.27); I²= 24%
Test for overall effect: Z = 3.76 (P = 0.0002)

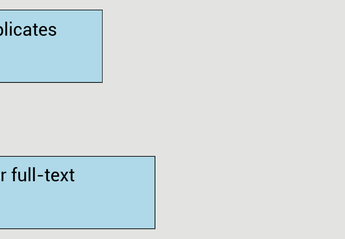


Mepolizumab significantly reduced eosinophils in blood samples compared to placebo (MD -0.33X10⁹/L, 95% CI -0.50 to -0.16; 3 studies, 311 participants)

1.2 Sputum Eosipnophils

Study or Subgroup	Mepolizumab Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Halder 2012	-16.6	25.3	9	0.6	15.3	10	3.2%	-17.20[-36.26, 1.86]
nair 2009	-6.07	6.6	29	-0.21	7.2	32	96.8%	-5.86[-9.32, -2.40]
Total (95% CI)			**38**			**42**	**100.0%**	-6.22[-9.63, -2.82]

Heterogeneity: Chi²= 1.32, df = 1(P = 0.25); I²= 24%
Test for overall effect: Z = 3.58 (P = 0.0003)

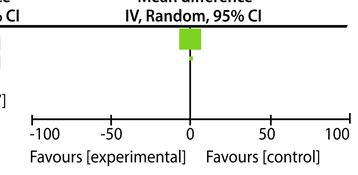


Mepolizumab significantly reduced sputum eosinophils compared to placebo (MD -6.22X10⁹/L, 95% CI -9.63 to -2.82; 2 studies, 80 participants)

1.3 FEV1

Study or Subgroup	Mepolizumab Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Floodpage 2007	0.14	0.68	112	0.13	0.62	119	96.1%	0.01[-0.16, 0.18]
nair 2009	0.1	0.95	9	0.1	0.9	10	3.9%	0.00[-0.83, 0.83]
Total (95% CI)			**121**			**129**	**100.0%**	-0.01[-0.16, -0.17]

Heterogeneity: Chi²= 0.00, df = 1 (P = 0.98); I²= 0%
Test for overall effect: Z = 0.11 (P = 0.91)

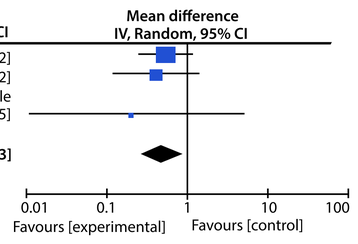


No significant difference was found between Mepolizumab and placebo for FEV1 (MD, 0.01, 95% CI -0.16 to 0.17; 2 studies, 250 participants)

1.4 Exacebaration

Study or Subgroup	Mepolizumab Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Floodpage 2007	11	116	20	126	63.2%	0.56 [0.25, 1.22]
Halder 2012	20	29	27	32	29.0%	0.41 [0.12, 1.42]
Halder 2014	0	0	0	0		Not estimable
nair 2009	0	9	2	11	7.9%	0.20 [0.01, 4.75]
Total (95% CI)		**154**		**169**	**100.0%**	**0.48 [0.25, 0.93]**
Total events	31		49			

Heterogeneity: Chi²= 0.48,df = 2(P = 0.79); I²= 0%
Test for overall effect: Z = 2.19 (P = 0.03)

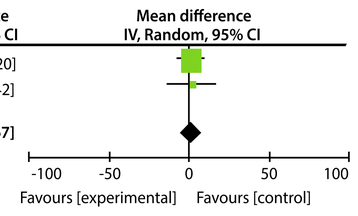


Mepolizumab significantly reduced the risk of exacerbation compared to placebo (OR, 0.49, 95% CI 0.25 to 0.93; 3 studies, 323 participants)

1.5 FEV1% of Predictive value

Study or Subgroup	Mepolizumab Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Halder 2012	6.9	20.6	29	6.2	1.3	265	81.3%	0.70 [-6.80, 8.20]
nair 2009	3.1	18	9	1.3	17.4	11	18.7%	1.80 [-13.82, 17.42]
Total (95% CI)			**38**			**276**	**100.0%**	**0.91 [-5.82, 7.67]**

Heterogeneity: Chi²= 0.02, df = (P =0.90); I²= 0%
Test for overall effect: Z = 0.26 (P = 0.79)



No significant difference was found between Mepolizumab and placebo for FEV1% of predicted value(MD 0.91, 95% CI -5.85 to 7.67; 2 studies, 314 participants)

- A total of seven RCTs (including one recently completed, unpublished trial) involving 1910 participants were included.
- The common adverse events reported with mepolizumab were: headache, chest pain, nasopharyngitis, erectile dysfunction, fatigue, rash, upper respiratory tract infection and sinusitis.

DISCUSSIONS

- Despite receiving high doses of inhaled or oral corticosteroids, upto 5% of asthmatics return with severe symptoms, frequent exacerbations, enhanced airway remodeling, and a greater mortality risk due to asthma.
- Around 20% to 40% of these patients with severe resistant asthma have persistent airway and tissue eosinophilia
- The level of tissue eosinophilia has been correlated with asthma severity[6]
- IL-5 has been reported to be the most important interleukin responsible for eosinophilic airway inflammation in asthmatics[7]
- Mepolizumab is a humanized monoclonal antibody against IL-5
- Mepolizumab selectively inhibits eosinophilic airway inflammation and induces a significant reduction in severe asthma exacerbations, regardless of IgE levels in blood and atopy.
- However, early studies have demonstrated that mepolizumab does not modify pulmonary function[8]
- In clinical trials, mepolizumab was associated with a significant decrease in exacerbation rate, improvement in quality of life, and good safety profile
- Thus, mepolizumab represents a useful and innovative therapeutic option in asthmatic patients with persistent airway eosinophilia
- However, appropriate patient selection is essential to avoid treatment failure, because several studies confirm that in a specific subgroup of patients, eosinophils play an important role in exacerbations and mepolizumab therapy may have clinical benefit.
- Available literature demonstrate that anti-IL-5 treatment is safe for clinical use. It was very well tolerated in all clinical trials. The adverse event profile of Mepolizumab was comparable to placebo in large trials[9]

CONCLUSION

- Our findings indicates that mepolizumab significantly lowers blood and sputum eosinophil counts, and also effectively reduced asthma exacerbation frequency, but showed no significant improvement on functional airway outcome
- Further larger randomized controlled trials are needed to confirm these findings.

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Poster Presented at ISPOR 7th Asia-Pacific Conference, September 3-6, 2016, Suntec Singapore Convention & Exhibition Center, Singapore