Clinical Communications

Secondary loss of response to mepolizumab in severe eosinophilic asthma

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Clinical Implications

- Loss of response to mepolizumab can occur after several months or years of effective treatment. This loss of response is associated with recurrence of airway eosinophilia. Understanding its underlying mechanism will be key to improve the management of those patients.

TO THE EDITOR:

We herein present 2 cases of severe uncontrolled eosinophilic asthmatics whose asthma remained controlled for 1 year or more after treatment with mepolizumab (anti-IL-5 monoclonal antibody [mAb]), but eventually developed a loss of response to mepolizumab. Sputum cell count analysis showed an initial decrease in airway eosinophilia followed by recurrence of airway inflammation, in spite of low blood eosinophils and continued treatment with mepolizumab.

A 51-year-old man, ex-smoker of 8 pack-years, started developing asthma symptoms at age 34 along with nasal polyposis. Reversible airflow obstruction was documented by spirometry. He had severe recurrent asthma exacerbations and had been steroid dependent since 2007. Skin allergy testing was negative for common respiratory allergens. He experienced 6 asthma exacerbations in 2016 requiring an increase in his dose of oral corticosteroids (OCS). His treatment is detailed in Table I. Blood eosinophil counts showed 1400 cells/μL and sputum differential eosinophil counts were 58.5%.

He was started on 100 mg of monthly subcutaneous (SC) mepolizumab in September 2016. His respiratory symptoms improved markedly, and his forced expiratory volume in 1 second (FEV_1) increased from 1.70 to 2.28 L (65% of predicted). Eosinophilic suppression was apparent both in blood (200 cells/μL) and sputum (3.3%). He was weaned off prednisone and remained well controlled for more than 2 years without taking any course of OCS.

In January 2019, his respiratory symptoms worsened and his FEV_1 declined (1.62 L). There was no change in his treatment nor environment; he was adherent to monthly mepolizumab injections. His blood eosinophil counts remained at 200 cells/μL, whereas his sputum eosinophil counts showed some increase in airway eosinophils (6.3%). Mepolizumab was stopped and benralizumab (anti-IL-5 receptor mAb) was initiated with marked improvement of his symptoms and spirometry as well as depletion of blood and sputum eosinophil counts (Table I).

A 57-year-old woman, never smoker, started experiencing asthma symptoms at age 42. Skin allergy testing was positive for *Dermatophagoides pteronyssinus* and ragweed. Variable expiratory airflow obstruction was diagnosed through variability of her FEV_1 during exacerbations compared with baseline (1.96 L vs 2.56 L). She had been steroid dependent since 2009. In spite of this treatment, she was experiencing an average of 6 asthma exacerbations per year requiring an increase in her OCS dose. Airway eosinophilia had been documented on many occasions with sputum eosinophil counts ranging from 4% to 40%. She had been previously treated with omalizumab from October 2014 to March 2015 without improvement in her asthma control. She experienced 6 asthma exacerbations in 2015-2016 requiring an increase in her OCS dose. Her treatment is presented in Table I. Her blood eosinophil counts showed 300 cells/μL, and sputum differential eosinophil counts were 40.5%.

Mepolizumab was initiated in 2016. Although her symptoms markedly improved, there was no significant change in her FEV_1. She was weaned from OCS. Serum eosinophil counts (200 cells/μL) and sputum differential eosinophil counts decreased (1.3%). Her asthma remained well controlled for almost 2 years without any asthma exacerbations requiring OCS.

In March 2018, her respiratory symptoms worsened; she had 3 asthma exacerbations requiring prednisone. There was no change in her environment or treatment. She was adherent to mepolizumab injections. Although her blood eosinophil counts remained low (100 cells/μL), her sputum differential eosinophil count was high (48%) despite treatment with mepolizumab. In March 2018, mepolizumab was stopped and benralizumab was initiated. Since then, she had one exacerbation after an upper respiratory tract infection requiring prednisone, her FEV_1 improved, and her blood and sputum differential eosinophil counts were undetectable.

Mepolizumab was approved by the Food and Drug Administration in 2015 for the treatment of severe uncontrolled eosinophilic asthma. Asthmatics with at least 0.15×10^9 blood eosinophils/L at treatment initiation, or 0.3×10^9 blood eosinophils/L in the previous year, showed a 47% reduction in asthma exacerbations after treatment with 100 mg of monthly SC mepolizumab.[1] Follow-up studies demonstrated a sustained efficacy up to 4 years after treatment initiation.[2]

These cases illustrate the concept of *secondary inefficacy*, also known as *secondary loss of response* or *secondary nonresponse*, defined as a loss of response to a treatment over time although patients had initially achieved primary response.[3] This is different from *primary inefficacy* where patients do not show a response after treatment initiation.[3]

To our knowledge, this is the first description of secondary loss of response to mepolizumab in the treatment of severe uncontrolled eosinophilic asthma. Most of the data on secondary inefficacy of mAbs come from the use of anti-TNF mAb in the treatment of rheumatologic and inflammatory bowel diseases, where 25% to 40% of patients will stop therapy because of secondary inefficacy.[3]

Several hypotheses can be advanced to explain a secondary loss of response. The development of neutralizing antidrug antibodies (ADAs) may explain a loss of treatment efficacy. In an open-label extension study of mepolizumab (COLUMBA), which followed 347 subjects treated with mepolizumab for an average of 3.5 years,[2] 27 (8%) of them developed ADAs. However, the ADAs were not neutralizing, and no loss of clinical response was

TABLE I. Patients' characteristics before, during, and after treatment with mepolizumab

Characteristics	Case 1	Case 2
At treatment initiation with mepolizumab		
Age (y)	51	57
Sex	M	F
Age at onset of asthma (y)	34	42
Atopy	No	Yes
Nasal polyposis	Yes	No
Total IgE (KUI/L)	52	136
Previous treatment with omalizumab	No	Yes
Smoking history	Ex-smoker (8 pack-years)	Never smoker
Asthma treatment	Prednisone 5 mg die, fluticasone/salmeterol 500 bid, ciclesonide 400 bid, theophylline 400 die	Prednisone 7.5 mg/5 mg, mometasone 800 bid (LABA and LTRA were tried previously)
FEV_1 (L) pre-/post-BDT (%pred)	1.70 (48%)/1.98 (56%)	2.58 (95%)/2.66 (97%)
Sputum eosinophil count (%)	58.5	40.5
Blood eosinophil count (10^9 cells/L)	1.4	0.3
Asthma exacerbations in year preceding mepolizumab initiation	6	6
Date of initiation of mepolizumab	September 2016	April 2016
Year 1		
Sputum eosinophil count (%)	3.3	1.3
Blood eosinophil count (10^9 cells/L)	0.2	0.2
FEV_1 (L) pre-/post-BDT (%pred)	2.28 (65%)/2.44 (70%)	2.56 (96%)/2.75 (103%)
Exacerbations, n	0	0
Prednisone dose (mg)	0	5/0
Year 2		
Sputum eosinophil count (%)	6.3	48.0
Blood eosinophil count (10^9 cells/L)	0.2	0.1
FEV_1 (L) pre-/post-BDT (% pred)	1.62 (47%)/1.89 (55%)	1.95 (72%)/1.97 (73%)
Exacerbations, n	0	3
Prednisone dose (mg)	0	0
Date of cessation mepolizumab	January 2019	March 2018
After initiation of benralizumab		
Sputum eosinophil count (%)	0.5	0.0
Blood eosinophil count (10^9 cells/L)	0.0	0.0
FEV_1 (L) pre-/post-BDT (%)	2.29 (67%)/2.40 (70%)	2.45 (95%)/2.50 (97%)
Exacerbations, n	0	1
Prednisone dose (mg)	0	0

%pred, Percent predicted; *BDT*, bronchodilator; *bid*, twice daily; *FEV_1*, forced expiratory volume in 1 s; *LABA*, long-acting beta2 agonist; *LTRA*, leukotriene receptor antagonist.

reported in this study.[2] Mukherjee et al[4] described 10 patients with primary inefficacy of mepolizumab, none of whom had neutralizing ADAs.

Secondary loss of response to mepolizumab may also be due to poor medication adherence. However, we received reports from the injection programs confirming adherence to mepolizumab, and interrogation of pharmacy records confirmed adequate medication prescription refill for all patients.

Although we observed a significant decrease in blood eosinophils from baseline in our patients, their blood eosinophil counts were still 0.2 and 0.1 $\times$ 10^9 cells/L, respectively, while on mepolizumab. By comparison, the geometric mean of blood eosinophil counts in the COLUMBA study was 0.5 $\times$ 10^9 cells/L.[2] Therefore, it is likely that mepolizumab was never able to suppress eosinophils completely in these patients, which translated into deterioration in their asthma 2 years after treatment initiation.

Insufficient drug levels (either systemically or at the site of action) may also be responsible for a lack of efficacy of mepolizumab. There have been some concerns that the monthly dose of mepolizumab 100 mg SC may be too low to reach effective airway drug levels in a subset of severe asthmatics. At this dose, blood eosinophils are effectively suppressed, but blood eosinophil progenitors (EoPs), airway eosinophils, and airway EoPs are only marginally decreased.[4,5] It is also known that IL-5 is not only produced by CD4+ (Th2) lymphocytes, but also by type 2 innate lymphoid cells (ILC2s) that reside in the airways.[6] The locally derived airway IL-5 by ILC2s may not be effectively suppressed by low-dose mepolizumab, which may allow for *in situ* airway eosinophilopoiesis, leading to persistent airway eosinophilia and poor asthma control despite treatment with mepolizumab.[4] To palliate these limitations, weight-adjusted reslizumab (another anti-IL-5 mAb) was shown to lead to significant airway eosinophil and EoP reduction in 10 patients with poor response to monthly 100 mg mepolizumab SC.[4] Benralizumab is an mAb that targets the IL-5 receptor α expressed on eosinophils and basophils inducing an antibody-dependent cell-mediated cytotoxicity and, hence, apoptosis of target cells. It

was shown to effectively suppress blood eosinophils and EoPs, airway eosinophils, EoPs as well as bone marrow eosinophils in asthmatics,[7,8] which could theoretically lead to improved asthma control in this subset of patients. Supporting this hypothesis, the blood eosinophil counts of our patients dropped to zero after benralizumab initiation, which was never achieved with mepolizumab. This major eosinophilic suppression is likely to explain the positive clinical response to benralizumab of these patients.

In conclusion, a loss of efficacy of mepolizumab can occur several years after an initial good clinical response. More research is needed to understand the mechanisms of secondary loss of response to anti-IL-5 mAb therapy.

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