Clinical Communications

Mepolizumab for allergic bronchopulmonary aspergillosis: Report of 20 cases from the Belgian Severe Asthma Registry and review of the literature

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Clinical Implications

- Our data provide further evidence supporting the effectiveness of mepolizumab in allergic bronchopulmonary aspergillosis because it decreases the dose of oral corticosteroids and the rate of exacerbations, and improves asthma control and quality of life.

Allergic bronchopulmonary aspergillosis (ABPA) has been documented in 5% to 10% of patients with oral corticosteroid (OCS)-dependent asthma.[1] Oral itraconazole,[2] aerosolized amphotericin B,[3,4] and omalizumab[5] have been proposed as steroid-sparing options. However, these treatments have limited documented efficacy, and adverse effects may limit therapy. Itraconazole is efficient in less than 50% of patients while it has a number of side effects including nausea, vomiting, elevation of liver enzymes, QT/QTc prolongation, adrenal insufficiency, and drug interactions. Its prolonged use has been associated with the emergence of azole-resistant *Aspergillus fumigatus* isolates.[6] Treatment with aerosolized amphotericin B is limited by adverse events such as bronchospasm. Although reports of 102 patients with ABPA treated with omalizumab describe improvement in asthma symptoms and decreased exacerbations,[5] no large randomized trials have been conducted, and dosing of omalizumab can be complicated by high total serum IgE levels in ABPA. There is thus still an unmet need in the management of ABPA. Because inflammation in ABPA is characterized by eosinophils, it is worthwhile exploring the usefulness of anti−IL-5 in this condition. Mepolizumab, an anti−IL-5 mAb, decreases severe exacerbations and the OCS maintenance dose in severe eosinophilic asthma,[7] but the effectiveness of this biotherapy in ABPA has been described only in selected case reports that are summarized in Table E1 in this article's Online Repository at www.jaci-inpractice.org.

The aim of this study was to evaluate the effectiveness of mepolizumab 100 mg every 4 weeks in patients with ABPA reported to the Belgian Severe Asthma Registry.[8]

This prospective observational study included 20 patients who fulfilled the diagnostic criteria for ABPA issued by the International Society for Human and Animal Mycology Working Group in 2016.[9] This definition requires, besides a predisposing condition such as asthma or cystic fibrosis, the presence of 2 major criteria (total IgE > 1000 kU/L and positive skin prick test results or specific IgE for *A fumigatus*) and at least 2 minor criteria (eosinophilia > 500/μL in steroid-naive patients; new or recent chest computed tomography abnormalities such as nodules, mucoid impactions, or pulmonary opacities; positive serum IgG for *A fumigatus* > 27 mgA/mL). When all other criteria are met, a value of total IgE less than 1000 kU/L is also considered acceptable for diagnosis. Data are entered into the registry on a voluntary basis by local investigators. The registry has been approved by the Ethics Committee of Ghent University and patients signed informed consent.

All patients underwent measurements of blood eosinophils, spirometry, and asthma control using either the Asthma Control Test or the Asthma Control Questionnaire at baseline and after treatment for 6 months with mepolizumab (1 month after the fifth injection). In some patients, asthma quality of life (asthma quality of life questionnaire, n = 5), fractional exhaled nitric oxide (FENO, n = 8), and sputum cell counts (n = 3) were also available. Clinically significant exacerbations were defined as a deterioration in asthma requiring systemic corticosteroids for at least 3 days, or hospitalization and/or emergency visits. For patients receiving maintenance OCS, at least double the dose for 3 days was required. Exacerbations were recorded during the year before baseline and after treatment for 6 months with mepolizumab (annualized rate).

We evaluated the outcome of available clinical parameters at baseline and after treatment for 6 months with mepolizumab. The data were expressed as the median value and interquartile range (IQR). Comparison between variables at baseline and after 6 months of treatment were made using Wilcoxon signed rank test.

The 20 patients demonstrated positive specific IgE for *A fumigatus* (median, 19.3 kU/L; IQR, 0.48-100 kU/L) and 18 of them had a total serum IgE level greater than 1000 kU/L (median, 3657 kU/L; IQR, 875-27,368 kU/L). Two patients with total IgE levels less than 1000 kU/L met all other criteria and were thus considered as having ABPA. All patients showed blood eosinophil counts higher than 500/mm^3. Seventeen patients exhibited positive IgG for *A fumigatus* (83.6 mgA/mL; IQR, 18-200 mgA/mL). All patients completed a chest computed tomography scan before treatment and 16 of them had pulmonary opacities. Sixteen were found with bronchiectasis, of whom 10 patients had multilobar central bronchiectasis with plugs, 2 patients had unilobular peripheral bronchiectasis with plugs, and 4 patients had multilobular peripheral bronchiectasis without plugs. In 7 patients, we found concomitant chronic rhinosinusitis.

The cohort included 58% females, and subjects had a mean body mass index of 33 kg/m^2 and a mean age of 63 years. The mean age at onset of asthma was 35 years (3 patients reporting onset of asthma before 12 years). All the patients were treated with high-dose inhaled corticosteroids and long-acting β2-agonists. One-third of the patients were ex-smokers (median pack-years, 25), and 1 patient had been treated with omalizumab without improvement in the past, while 1 had stopped itraconazole because of significant side effects.

The changes in the clinical and biological outcomes are presented in Table I. There was a significant reduction in the maintenance OCS dose and in exacerbations. There was also a

TABLE I. Comparison of clinical outcomes at baseline and after 6 mo of treatment with mepolizumab

Outcome	Baseline	6 mo	*P* value
ACQ (n = 20)	3.14 (1.71-3.5)	2.00 (0.43-2.14)	.001
ACT (n = 20)	10 (8-13)	19 (10-21)	.033
AQLQ (n = 5)	3.6 (2.87-3.98)	4.84 (4.00-5.87)	.014
Post-BD FEV_1 (L)	1.50 (1.08-2.11)	1.84 (1.14-2.37)	.060
Blood eosinophils (cells/μL)	660 (438-980)	54 (25-115)	<.0001
Sputum eosinophils (%) (n = 3)	18 (1.4-44)	4.1 (0.4-38)	.130
FENO (ppb) (n = 8)	28 (15-57)	23 (12-74)	.64
OCS dose (mg/d) (n = 7)	8 (4-16)	4 (0-5)	.040
Exacerbations (/y)	3 (2-4.5)	0 (0-1)	<.0001

ACQ, Asthma Control Questionnaire; *ACT*, Asthma Control Test, *AQLQ*, asthma quality of life questionnaire; *Post-BD FEV1*, FEV_1 after bronchodilation with salbutamol; *ppb*, parts per billion.
OCS, methylprednisolone equivalent.
Exacerbations: Annualized rate. Data are expressed as median (IQR).

significant improvement in asthma control and asthma quality of life, a decrease in blood eosinophils, and a trend toward an improvement in FEV_1. Eighty percent of the patients significantly improved their asthma quality of life questionnaire score (increase of at least 0.5 points). Ninety percent of the patients had a significant improvement in their Asthma Control Questionnaire score (decrease of at least 0.5 points) and in their Asthma Control Test score (increase of at least 3 points). FENO failed to show any significant change. The decrease in sputum eosinophil counts did not reach significance likely due to the small number of patients.

Our data further confirm published case reports (see Table E1) that documented a significant decrease in blood eosinophil count, an increase in FEV_1, and an improvement in asthma control. Most importantly, we found a significant reduction in exacerbations and in the maintenance dose of OCS, findings that were not reported before. As documented previously in severe asthma, no significant reduction in FENO was observed with the use of mepolizumab in this cohort of patients with ABPA.[10] We did not expect FENO levels to decrease with anti−IL-5 therapy, because nitric oxide overproduction in asthma was shown to be driven by IL-13 mainly and no IL-5 involvement has been documented so far.

Novel biologics are now available in the management of severe asthma and offer new options to improve ABPA, a condition characterized by both marked eosinophilia and elevated IgE. These characteristics suggest a role for anti−IL-4/13 (dupilumab), a biologic with a broad anti−type 2 inflammatory action, in ABPA. Randomized controlled trials should be performed in this very specific and severe subpopulation of patients with asthma.

Our study has limitations, such as its observational design and some missing data due to nonmandatory fields in Belgian Severe Asthma Registry. However, this real-word study adds useful data on a particular type of eosinophilic asthma, named ABPA, that has been systematically excluded from randomized controlled trials with biotherapies.

To our knowledge, this is the largest series of patients with ABPA treated with mepolizumab. Despite the limitations inherent to the observational design, the data provide further evidence supporting the effectiveness of mepolizumab in ABPA as it decreases the dose of OCS and the rate of exacerbations and improves asthma control and quality of life.

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TABLE E1. Outcomes after initiation of mepolizumab treatment in patients described in the literature

Author (treatment tested)	Sex	Age (y)	Follow-up (mo)	Total IgE (IU/mL)		Blood eosinophil count (cells/μL)		ACT score		FEV_1 (L)		Radiology		OCS daily dose (mg)	
				T1	T2	T1	T2	T1	T2	T1	T2	T1	T2	T1	T2
Terashima et al[E1] (mepolizumab)	F	64	1	3400	No change (value NA)	3017	174	18	24	1.01	1.28	Lung infiltration Mucus plugs	No infiltrates No mucus plug	0	0
Oda et al[E2] (mepolizumab)	M	33	8	1505	NA	6370	64	5	25	2.36	3.16	Bronchiectasis Mucus plugs Lung infiltration	Attenuation of mucus plugs and infiltrates	20	2.5
Soeda et al[E3] (mepolizumab)	F	54	2	2145	No change (value NA)	1365	73	21	25	2.39	2.48	Bronchiectasis Mucus plugs	Attenuation of mucus plugs	0	0
	F	61	2	162	No change (value NA)	1856	32	24	24	NA	NA	Bronchial thickening Mucus plugs	Improvement	0	0
Hirota et al[E4] (mepolizumab)	F	56	14	1121	362	800	0	NA	NA	1.42	No change (value NA)	Bronchiectasis Mucus plugs Bronchial thickening	Improvement	NA	NA
Tsubouchi et al[E5] (mepolizumab)	F	60	5	4970	2025	283	20	NA	NA	1.43	1.49	Bronchiectasis Nodular shadows Mucus plugs	No mucus plugs Persistence of nodular shadows	10	5
Matsumoto et al[E6] (mepolizumab)	F	67	20	3163	2863	1163	121	NA	NA	0.77	1.76	Lung infiltration Bronchiectasis Centrilobular nodules Mucus plugs	Improvement of infiltrates	5	0
Altman et al[E7] (mepolizumab + omalizumab)	F	58	5	1730	298	1100	0	NA	NA	0.62	0.66	Bronchiectasis Upper fibrosis Nodules Mucus plugs	ND	20	0

ACT, Asthma Control Test; *F*, female; *M*, male; *NA*, not available; *ND*, not done; *Rx*, radiology findings; *T1*, before treatment with mepolizumab; *T2*, after treatment with mepolizumab.

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