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Long-term responsiveness to mepolizumab after failure of omalizumab and bronchial thermoplasty: Two triple-switch case reports

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ABSTRACT

Severe asthma affects between 5 and 10% of patients with asthma worldwide and requires best standard therapies at maximal doses. A subgroup of patients remains refractory to all treatments. We describe two case reports with severe allergic asthma who progressively worsened over the years despite the best therapy. The patients were first treated with omalizumab, which was completely ineffective, and then with bronchial thermoplasty (BT), again without clinical benefit. Since our patients met the AIFA criteria for inclusion in mepolizumab treatment, a therapy with this anti-IL5 biological agent was initiated. In the first case (a 53-year-old female), after the second mepolizumab administration, symptoms improved progressively, with a reduction in the number and severity of exacerbations, so the patient could finally be discharged from hospital. At follow-up, it was possible to reduce oral corticosteroids and continuing with inhaled corticosteroids/long-acting beta-agonists and montelukast. The patient had only one exacerbation/year. Symptom control and quality of life improved significantly. In the second case report (a 55-year-old male), after the sixth mepolizumab administration, symptoms improved progressively, with a reduction in the number and severity of exacerbations. At follow-up, it was possible to reduce and stop oral corticosteroids, continuing with inhaled therapy and montelukast. Symptom control and quality of life improved significantly.These are the first cases of patients unresponsive to sequential omalizumab and BT but with good and prolonged clinical response to mepolizumab. Both cases suggest that also after the failure of two consecutive third-line treatments, a third treatment (mepolizumab) should be attempted.

1. Introduction

Severe asthma affects between 5% and 10% of patients with asthma and requires best standard therapies at maximal doses. Over 50% of the costs are absorbed by this disease in the Western countries [1]. Frequent use of oral corticosteroids (OCS) involves systemic side effects that are often irreversible and serious. There is a subgroup of patients refractory to all treatments, including OCS, who have a poor control of asthma symptoms with recurrent exacerbations. This leads to a serious deterioration in the quality of life (QoL), loss of working or school days, and increased individual and social costs with consistent consumption of health care resources including hospitalization in the intensive care unit (ICU) [1,2]. The advent of omalizumab and subsequently of bronchial thermoplasty (BT) have made it possible to meet the needs of a significant number of patients with severe refractory asthma. However, many subjects are poor candidates for these new therapeutic options because they are unsuitable or do not respond satisfactorily, since there are no predictive biomarkers yet in the real-life setting to guide treatment. The choice is made even more difficult since asthma is a heterogeneous syndrome that can be better described as a constellation of phenotypes or endotypes, each with distinct cellular and molecular mechanisms, rather than as a single disease [3]. One of these phenotypes is eosinophilic asthma, and the recent availability of a new biological agents, like mepolizumab, an anti-IL5 monoclonal antibody (mAb), can help clinicians to treat this subgroup of patients effectively [4]. A certain percentage of subjects may have characteristics that can indicate treatment with both omalizumab or anti-IL5 agents, but there are currently no head-to-head studies which make it possible to give definite recommendations for the preferential use of one agent versus the others. Here we describe two patients with a severe asthma resistant to all treatments,

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including omalizumab and BT, but who showed a dramatic response to mepolizumab. Written informed consent was obtained from the patients for publication.

1.1. Case report 1

A 53-year-old female Caucasian nonsmoker had a history of severe allergic asthma since 1999, which started after a pregnancy and progressively worsened over the years despite best standard therapy and optimal compliance. This patient had a body weight of 52 kg; was allergic to dust mites, Cladosporium herbarum, dog and cat dander, grass, pellitory, and cypress; and had a total serum IgE level of 115 IU/mL. Forced expiratory volume in 1 second (FEV1) was 75% of predicted, FEV1/forced vital capacity (FVC) ratio was 65%, with a significant reversibility (12%) at the bronchodilator test with 400 μg inhaled salbutamol. She was employed as a supermarket cashier and her clinical history included several comorbidities such as gastro-esophageal reflux, with regular treatment with proton-pump inhibitors, hypothyroidism, steroid-induced osteoporosis, and bilateral cataracts. Between 1999 and 2016, she had been hospitalized 35 times, with further 11 emergency room visits due to increasingly frequent severe asthma exacerbations, despite regular courses with OCS, taken for more than 6 months a year, in addition to maximal dosage of long-acting beta-agonists (LABA) and inhaled corticosteroids (ICS). Over the last 5 years, the patient had to be admitted to the respiratory intensive care unit (RICU) nine times, for noninvasive mechanical ventilation with face mask due to severe asthma exacerbation with acute hypoxemic respiratory failure. Given the bad control of asthma, the patient was enrolled in the INNOVATE trial in 2005 and then treated with omalizumab as add-on therapy to formoterol/budesonide (160/4.5 μg) with two inhalations twice daily and as needed (twice a day on an average). Unfortunately, at the third dose, the experimental therapy was suspended due to a skin rash. In the following years, the therapy was modified by replacing budesonide/formoterol with beclomethasone/formoterol extrafine (100/6 μg) two inhalations twice daily plus as needed, montelukast 10 mg daily, tiotropium bromide 18 μg per day, theophylline 300 mg twice daily, and methylprednisolone 4 mg daily (to be increased in case of an exacerbation). Differential diagnosis investigations were performed, in particular antineutrophil cytoplasmic antibodies (ANCA) and high-resolution chest computed tomography (CT) negative for vasculitis ruled out eosinophilic granulomatosis with polyangiitis (EGPA). In 2012, the patient was enrolled in a single-center clinical protocol on BT (Alair™; Boston Scientific, Marlborough, MA, USA); since FEV1 was above 60% of predicted and considering the poor control of asthma, she underwent three scheduled sessions as per the standard protocol. Baseline scores of asthma control test, asthma control questionnaire, and Asthma Quality of Life Questionnaire are reported in Table 1, which shows a very poor control of the disease with really bad QoL. After the third session of BT, an asthmatic crisis occurred which required hospitalization in RICU. Endobronchial biopsies and bronchoalveolar lavage were taken from lobes treated during the session. These procedures showed the presence of intraepithelial eosinophils and lymphocytes and prominent smooth muscle and goblet cell hyperplasia. After an initial improvement in asthmatic symptoms, however, the asthma severity returned to the baseline level within 12 months. Considering the ineffectiveness of BT and the recurrent asthma exacerbations, in 2013 we decided to try again with omalizumab (Xolair®; Novartis Pharma, Basel, Switzerland), discontinued earlier in 2002 because of an adverse skin reaction during the INNOVATE trial. Before starting regular treatment, a drug provocation test was carried out with the commercial drug in the prefilled syringe. The patient did not show any allergic reactions and we started therapy with omalizumab 300 mg administered by subcutaneous (SC) injection every 4 weeks. We hypothesize that the adverse reaction to the trial drug but not to the commercial drug was probably due to different excipients of the two formulations. Again, a lack of improvement in asthma control led to interruption of the therapy after 12 months. The patient was again admitted to our RICU in December 2016 due to a very severe asthma exacerbation with acute respiratory failure. Treatment required mechanical ventilation, intravenous (IV) methylprednisolone, oxycodone, beta-2 agonists and anticholinergic bronchodilators, and ICS, but due to recurrent severe bronchospasm, SC adrenaline, IV magnesium sulfate, morphine sulfate, and high dosage steroid boluses had to be administered as needed almost daily. After 4 weeks, the patient was discharged following a satisfactory clinical improvement, but after 7 days she was readmitted to RICU for a new severe asthma exacerbation. To rule out other causes of clinical deterioration, a number of tests were carried out: CT scan of chest and neck, fiberoptic laryngoscopy, 24-h urine collection for catecholamines and metanephrines (to rule out pheochromocytoma), serum tryptase, and ANCA. Despite systemic steroids, the complete blood cell count revealed a peripheral eosinophilia of 300 cells/μL. The clinical picture remained critical until February 2017, when AIFA approved mepolizumab (Nucala®; GlaxoSmithKline, Brentford, UK) for the treatment of severe refractory eosinophilic asthma. Based on blood eosinophil levels, on

Table 1
"First case report: clinical outcomes 24 months before and after mepolizumab".

	Baseline (6 months before mepolizumab)	6 months after starting mepolizumab	12 months after starting mepolizumab	24 months after starting mepolizumab
AQLQ score	1.78	5.39	5.0	5.7
ACQ score	4.6	1.4	1.7	1.0
ACT score	5	20	22	23
Exacerbations	2	0	0	0
ER visits (n°)	2	0	1	0
Hospitalizations (n°)	2	0	1	1
Hospitalizations duration (days mean)	41	0	7	7
Days miss from work (days)	98	0	7	7
OCS daily dose (methylprednisolone mg)	32	0	16	4
Prebronchodilator FEV1 (% (L) predicted	75(1.7)	90(1.80)	111(2.20)	114 (2.22)
Prebronchodilator FVC (% (L) predicted	66(2.50)	68(2.40)	85(2.67)	86(2.67)
Prebronchodilator FEV1/FVC (% predicted	68	75	83	83

References values: AQLQ score: 7-point scale (7 = no impairment; −1 = maximum impairment); ACQ score: 7-point scale (0 = no impairment; 6 = maximum impairment); ACT score: 5-question survey (5 = severely uncontrolled; 25 = totally controlled).
Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; ACQ, asthma control questionnaire; ACT, asthma control test; ER = Emergency Room; OCS = Oral Cortico-Steroids; FEV1 = Forced Expiratory Volume in 1 second); FVC = Forced Vital Capacity.

February 26, we immediately started treatment with mepolizumab 100 mg, to be administered SC once every 4 weeks. After the second administration, asthma symptoms improved progressively, and the patient was finally discharged on April 11. In the following period and after the twenty-fourth dose, it was possible to reduce OCS at low doses (4 mg of methylprednisolone/day), interrupt theophylline, and continuing regular treatment only with ICS/LABA and montelukast. The patient had only one exacerbation/year; and it was demonstrated a stabilization of functional parameters, and a significant control of symptoms. Finally, the QoL progressively improved allowing the patient to resume her job (Table 1).

1.2. Case report 2

A 55-year-old male Caucasian ex-smoker had a history of severe allergic asthma since 1988, which started after early onset of oculorhinitis and occasional assumption of aspirin. The asthmatic symptoms progressively worsened over the years despite best standard therapy (LABA plus ICS and montelukast) and optimal compliance. No history of gastroesophageal reflux. At our first evaluation the patient had quitted smoke since one year, the FEV1 was 59% of predicted with significant improvement after short-acting bronchodilator. Exhaled nitric oxid was 80 ppb and total IgE was 800 KU/L. Allergy tests showed sensitization to mite and ragweed. Autoantibodies and precipitins were negative. The CT scan showed some bronciectasis and thickening of bronchial walls. In the last months the patient was admitted to the ER for severe exacerbation with respiratory failure. The inhaled treatment was potentiated at maximum and prednisone 5mg/day was added without besefit and persistence of symptoms and exacerbation, so that the patient became unable to work. Thus an anti-IgE (omalizumab) treatment was started at 450 mg SQ every 2 weeks. After 18 doses (9 months) the patient remained symptomatic and with frequent exacerbations, thus he underwent BT, in 3 sessions: The treatment was completed in february 2015. Also in this case, there was no appreciable response in term of symptom, exacerbations and steroid dependance, plus two episodes of pneumonia. Progressively, a respiratory failure needing long term oxygen developed. On march 2017, since blood eosinophils were 700/mmc, we started the treatment with the anti-IL5 mepolizumab at 100 mg SQ every 4 weeks. After the 6th administration symptoms progressively subsided, QoL improved and respiratory function paramentes normalized. At july 2019 the patient had receives 26 doses of mepolizumab, there were no exacerbations in the last year, and no ER admissions or hospitalizations. Eosinophils had fell to 130/mmc. Baseline scores of asthma control test, asthma control questionnaire, and Asthma Quality of Life Questionnaire are reported in Table 2, which shows a very poor control of the disease with really bad QoL. It was also possible to progressively reduce OCS and interrupt the OCS use, continuing regular treatment only with ICS/LABA and montelukast. The patient had only one exacerbation in 2018 and no exacerbation in 2019. Finally, it were demonstrated a stabilization of flussimetric parameters, a significant control of symptoms, and progressive improved of QoL parameters (Table 2).

2. Discussion and conclusions

The availability of new therapeutic strategies, both pharmacological and interventional such as anti-IgE (omalizumab) and BT, respectively, has proved to improve management of severe asthma in patients eligible for these treatments [7]. Unfortunately, many patients have been excluded because they are unsuitable or do not show a positive outcome, and also because there are no reliable biomarkers yet predictive of clinical response. At present, omalizumab is considered the gold standard treatment in severe allergic asthma, with positive clinical outcomes represented by a reduction of exacerbations, OCS sparing effect, and an improvement of QoL [8]. In clinical studies, such as the INNOVATE and other six studies on severe atopic asthmatics, baseline IgE was the only predictor of omalizumab efficacy since statistical significance was reached in the upper IgE quartile (p,0.001) [5,9]. In the first case report, the patient had an IgE level of 115 IU/mL, a low value likely predictive of a negligible response to the anti-IgE treatment. Also in the second case report, the patient met the criteria for inclusion in anti-IgE treatment but was non-responsive. Both patients then underwent BT treatment which it was the only other treatment available for patients with severe asthma without any clinical benefit. It is not easy to identify the cause(s) of such a poor outcome in these cases, although it is well known that BT has a clinical effectiveness varying between 50% and 75% among the treated patients [10].

One of the main unresolved issues of BT is the difficult selection of patients potentially responders to this therapeutic option. Some authors argue that as a result of this unnecessarily exposes some patients to a treatment that can potentially be ineffective or associated with an increase in exacerbations and hospitalizations following BT [10]. In the absence of predictive biomarkers, the best results are obtained thanks to a combination of factors that go in addition to the simple reduction of airway smooth muscle (ASMN), included appropriate patient selection, correct procedure technique and adequate number of thermal activations [10].

In our patients, an incorrect selection of the asthma phenotype really suitable for BT may have occurred, which led to a negative clinical outcome. In this regard, beyond the traditional clinical and inflammatory classification, phenotyping has recently been proposed also according to the type of ASM [12]. In vitro studies, mainly on animal

Table 2
"Second case report: clinical outcomes 24 months before and after mepolizumab".

	Baseline (6 months before mepolizumab)	6 months after starting mepolizumab	12 months after starting mepolizumab	24 months after starting mepolizumab
AQLQ score	1.67	4.25	5.2	5.6
ACQ score	5.4	2.0	1.6	1.0
ACT score	6	16	21	22
Exacerbations	3	1	1	0
ER visits (n°)	1	0	0	0
Hospitalizations (n°)	1	0	0	0
Hospitalizations duration (days mean)	8	0	0	0
Days miss from work (days)	0 (retired patient)	–	–	–
OCS daily dose (prednisone mg)	5	5 (every other day)	An 10-day cycle (5 mg/die)	0
Prebronchodilator FEV1 (% (L) predicted	59(2.23)	69(2.56)	84(3.16)	86(3.74)
Prebronchodilator FVC (% (L) predicted	94(4.53)	105(5.04)	120(5.80)	112(6.30)
Prebronchodilator FEV1/FVC (% predicted	49.3	50.8	54.6	59.3

References values and abbreviations: see table 1.

models, have shown two types of ASMs: the first one is called "hyper-reactive" (characterized by some markers such as sm-α-actin expressing exaggerated contractile response to external stimuli) and the second one is named "secretive" (characterized by the ability to produce cytokines). These asthma phenotypes are not separated and can often turn one into the other by identifying a "switching" phenotype. Regarding the switch between biologicals, a recent post hoc analysis on patients previously enrolled in two randomized clinical trials (RCTs) on mepolizumab showed that anti-IL-5 agents can be effective in patients non-responsive to omalizumab, [13]. (Since the populations eligible for mepolizumab or omalizumab partially overlap, a multicenter, open-label, single-arm, 32-week trial (OSMO study) was performed to evaluate the effect of mepolizumab in patients with severe eosinophilic asthma previously unsuccessfully treated with omalizumab [14]. This trial demonstrated that, after directly switching from omalizumab to mepolizumab, patients with uncontrolled severe eosinophilic asthma experienced clinically significant improvements in asthma control, health status, and exacerbation rate,. Also a recent Italian retrospective study showed that, when omalizumab fails in patients with severe allergic and eosinophilic asthma, a switch to IL-5 antagonists is an effective choice, although this highlights the need for predictive biomarkers and real-life studies [15].

In this paper, two patients unresponsive to omalizumab and BT finally had an excellent and long-term clinical response to mepolizumab. These patients had a Type-2 High asthma endotype, with potential indication to both omalizumab and mepolizumab. Only the latter, recently introduced in clinical practice, made it possible to gain control of an otherwise critical and potentially fatal situation. Very important outcomes were the possibility of stopping OCS treatment in the presence of steroid-induced comorbidities and gaining optimal control of a severe unstable asthma, refractory to any other innovative treatment including omalizumab and BT. Indeed, OCS are included in the current treatment recommendations, but there are concerns about their potential overuse in this setting for the high risk of side effects and the relevant economic impact of OCS-related adverse events in severe asthma patients [16,17]. The significant reduction of exacerbations after the onset of mepolizumab therapy allowed marked improvement in the QoL and the return to normal life. Our cases also suggest the importance of a sufficiently prolonged treatment with mepolizumab, because the onset of response can vary from a patient to another. These case reports are an interesting example of how effective a "personalized approach" to treatment conjugating research at a molecular level and clinical definition of target phenotypes can be. Cost-benefit considerations, however, imply that new, expensive treatments require a careful and thorough evaluation of patients by clinicians, while researchers still have much to investigate to identify outcome predictors. This new data suggest that also after the failure of two consecutive third-line treatments, a third treatment (mepolizumab) should be considered and attempted. In the future, however, it will be mandatory to have predictive biomarkers in clinical practice in order to be able to choose the right treatment option for the right patient.

Authors' contributions

LC cared for the patient and drafted most of the manuscript. MF cared for the patient and was involved in the drafting of the manuscript. PG was involved in the drafting and was responsible for the revision of the manuscript.

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Availability of data and materials

Data sharing is not applicable to this article as no datasets were generate or analyzed during the current study.

Ethics approval and consent to participate

Not applicable.

Consent to publication

Consent for publication was obtained from the patients.

Declaration of competing interest

Carlo Lombardi participated has received lecture fee and advisory board fees from GlaxoSmithKline (GSK), AstraZeneca, Novartis, Chiesi, Boehringer Ingelheim, Mylan, Mundipharma. Francesco Menzella participated in contracted research and clinical trials for Novartis and Sanofi, and has received lecture fees and advisory board fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Mundipharma, and Novartis. Passalacqua Giovanni participated in clinical trials, advisory boards and received lecture fees from GSK, AstraZeneca, Novartis, Chiesi, Boehringer Ingelheim, Mylan, Mundipharma, Stallergens, MSD, Thermofisher.

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None.

Abbreviations

BT	bronchial thermoplasty
AIFA	Italian Medicines Agency
ICU	Intensive Care Unit
MAB	monoclonal antibody
FEV1	Forced expiratory volume in 1 second
FVC	forced vital capacity
LABA	long-acting beta-agonists
ICS	inhaled corticosteroids
ANCA	antineutrophil cytoplasmic antibodies
CT	computed tomography
EGPA	eosinophilic granulomatosis with polyangiitis
SC	subcutaneous
IV	intravenous
QoL	Quality of Life
ASM	airway smooth muscle (ASM)
RCTs	randomized clinical trials

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2019.100967.

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