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CASE SERIES

Very long-term data on patients with severe eosinophilic asthma treated with mepolizumab: a case series

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Abstract

Background: Patients with severe asthma are often dependent on oral corticosteroids (OCS) and have frequent exacerbations. This article aims to report very long-term data of patients with severe eosinophilic asthma assessing asthma control, lung function, inhaled corticosteroid (ICS) dose reduction, and clinical and biological parameters of patients treated with mepolizumab.

Methods: Four cases of adult patients with severe eosinophilic asthma who were treated for 60 months or more with mepolizumab 100 mg/4 weeks, leading to the stable discontinuation of OCS, are presented. ICS dose, OCS dose and withdrawal date, lung function, eosinophil count, fractional exhaled nitric oxide, and asthma control test were recorded as well as exacerbations in the 12 months before commencing mepolizumab and in the 12 months before the last follow-up visit.

Results: Three of the patients were men, median age was 52.5 years (range 79–53), median length of asthma before mepolizumab start was 67.5 months (range 24–240), three had chronic rhinosinusitis without nasal polyposis and two were atopic. All had eosinophil counts >300 cells/μL at baseline. The median follow-up was 73.5 months (range 71–74), and OCS withdrawal from baseline occurred after a median of 13 months of mepolizumab treatment (range 12–39). A substantial reduction of ICS treatment was registered as well as improvement in asthma control test, fractional exhaled nitric oxide and functional parameters, and a significant reduction of exacerbations in the last 12 months before last visit was observed as compared to the 12 months before baseline (from a median of 4 (range 3–6) to 0; p=0.0286).

Conclusions: Mepolizumab could be a 'disease-modifying' agent, with high tolerability and a good efficacy profile in the long term.

Keywords: biological agents, eosinophilic asthma, eosinophilic severe asthma, inhaled corticosteroids, mepolizumab, severe asthma, sparing effect.

Citation

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Introduction

Bronchial asthma is one of the most common and well-known chronic respiratory diseases. A small percentage of patients with asthma have severe asthma (between 3% and 10%, depending on the case series), typically manifesting with poor symptom control, frequent flare-ups and recurrent use of oral corticosteroids (OCS). Most patients with refractory disease have severe eosinophilic asthma (SEA), characterized by type 2 inflammation, with a variable response to inhaled and systemic steroids.[1,2]

IL-5 is the most important cytokine related to eosinophilic inflammation. A vast body of literature, consisting of clinical trials, real-life evidence, systematic reviews and meta-analyses of double-blind, placebo-controlled studies, with the IL-5 antagonist mepolizumab, have shown great clinical efficacy in patients with evidence of eosinophilic inflammation.[3,4] In particular, the steroid reduction study with mepolizumab (SIRIUS) demonstrated that mepolizumab could not only decrease asthma exacerbations, improving patient quality of life, but also significantly diminish daily OCS intake (with reduction in

50% of patients and complete discontinuation in 14%).[5] In a recent Italian, multicentre, long-term, real-world efficacy study of 3 years of mepolizumab administration, we demonstrated, on behalf of the Severe Asthma Network Italy (SANI) group, that the percentage of patients dependent on oral steroids decreased from 54% to 21% and then to 11% in the second year and 6% in the third year of administration.[6] The steroid-sparing effect of biological agents, such as mepolizumab, is crucial especially in light of the risk of steroid-related dose-dependent morbidity (including adrenal suppression, hypertension, cataracts, fractures and diabetes).[7] Notably, the steroid-sparing effect has also recently been incorporated into the concept of 'clinical remission', that is, prolonged absence of significant asthmatic symptoms as measured by a validated instrument, optimization and stabilization of lung function, and finally absence of systemic corticosteroid use for exacerbations or disease control for ≥12 months amongst patients with severe asthma undergoing therapy with biological agents.[8] Similarly, a recent consensus conducted in the United States emphasized that, in the context of criteria for clinical remission of asthma under treatment, the "continued use of control therapies (inhaled corticosteroids (ICS), ICS/LABA [long-acting beta agonist], leukotriene receptor antagonist) should also be included only at low to medium doses of ICS as defined by the most recent GINA guidelines".[9] Asthma is a chronic disease, and both the continued use of OCS and asthma exacerbations over time are a major problem for patients. On behalf of the SANI group, Bagnasco et al. showed that, during treatment with the anti-IL-5 mepolizumab, relapses were reduced by 84.6% in the first year, 90% in the second year and 95% in the third year.[6] Overall, however, data on the safety and efficacy of anti-IL-5 agents in SEA beyond 36 months are still scarce.

We therefore wanted to focus on the very long-term data of patients with SEA to assess asthma control, lung function, ICS reduction, and clinical and biological parameters of patients treated for 60 months or more with mepolizumab 100 mg/4 weeks, leading to the stable discontinuation of OCS while on biologics.

Methods

We collected the data of an exemplary selection of patients with SEA treated for a long time (at least 60 months) with mepolizumab subcutaneously 100 mg/4 weeks, leading to the stable discontinuation of OCS while on biologics.

Only adult patients were included; the diagnosis of asthma was clinical and confirmed by the finding of reversibility of the obstruction or by the methacholine test. All enrolled patients had type 2 asthma, confirmed by an elevated blood eosinophil count.

All patients were eligible for treatment with mepolizumab according to the Italian Regulatory Agency's prescriptive criteria (severe uncontrolled asthma, eosinophil count >150 cells/μL at the time of first administration and >300 cells/μL in the previous 12 months, presence of at least two exacerbations in the previous 12 months, systemic steroid therapy lasting more than 6 months). The first administration took place between June 2017 and January 2019, and only patients with at least 60 months of observation were selected.

For all the patients, data on asthma control, exacerbations, lung function, ICS and OCS use (converted into prednisone equivalent), and clinical and biological parameters were collected at baseline and yearly until month 60. Eosinophil counts, fractional exhaled nitric oxide (FeNO) and asthma control test (ACT) values were also collected.

Results were assessed using percentages, means and standard deviations, or median and interquartile range 25–75%. Changes in quantitative characteristics over time were assessed using Student's *t*-test or Wilcoxon's non-parametric test for paired data. Statistical significance was set at $p<0.05$. The Wilcoxon signed-rank test was used to analyse paired data before and after the observation period.

Results

The clinical history of four individuals was collected. Three were men, median age was 52.5 years (range 79–53), and all were white. The median length of asthma history before commencing mepolizumab was 67.5 months (range 24–240), only one was a smoker, three had chronic rhinosinusitis without nasal polyposis (CRSsNP), and two were atopic. All had eosinophil counts >300 cells/μL at baseline. Baseline data are reported in Table 1. The median follow-up was 73.5 months (range 71–74), and OCS withdrawal occurred after a median of 13 months (range 12–39) (Figure 1A). Data at the end of follow-up are reported in Table 2 and Figure 1.

Consent for publication

Consent for publication was obtained from the patients.

Case 1

Here, we present the case of a 53-year-old white man, a former modest smoker, who worked as a construction restorer, with a diagnosis of type 2 asthma made in 2009. In his medical history, he also had vertebral scoliosis, mild sleep apnoea syndrome, allergic rhinitis and congenital solitary kidney. This patient was allergic to house dust mites, *Cladosporium herbarum*, grasses, *Parietaria* and

Table 1. Baseline patient characteristics.

Case	All	1	2	3	4
Asthma phenotype	4/4	Type 2	Type 2	Type 2	Type 2
BEC, cells/mm^3	705 (540–1870)	670	540	740	1870
FeNO, ppb	53.5 (35–80)	80	53	35	54
Serum IgE, IU/mL	953 (134–1258)	134	953 IU/mL	NA	1258 IU/mL
FEV_1 %	74 (65–105)	75%	73%	105%	65%
ACT score	13.5 (12–15)	13	15	14	12
CRSsNP	3/4	Yes	Yes	Yes	Yes
Atopy (positive prick test)	2/4	Yes	Yes	No	No
Exacerbations in the 12 months before starting mepolizumab	4 (3–6)	4	6	4	3
Hospitalizations	1 (0–1)	1	0	1	1
Asthma medications					
Inhaled corticosteroid dose	–	Fluticasone propionate 1000 µg per day	Fluticasone furoate 368 µg per day	Budesonide 640 µg per day	Fluticasone propionate 1000 µg per day
Tiotropium bromide	–	Yes	Yes	Yes	Yes
Salbutamol (as needed)	–	Yes	Yes	Yes	Yes
Montelukast	–	Yes	Yes	Yes	No
Prednisone daily dose, mg	18.75 (5–25)	25	12.5	25	5

All the results are reported as median (range). ACT, asthma control test; BEC, blood eosinophil count; CRSsNP, chronic rhinosinusitis without nasal polyps; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second.

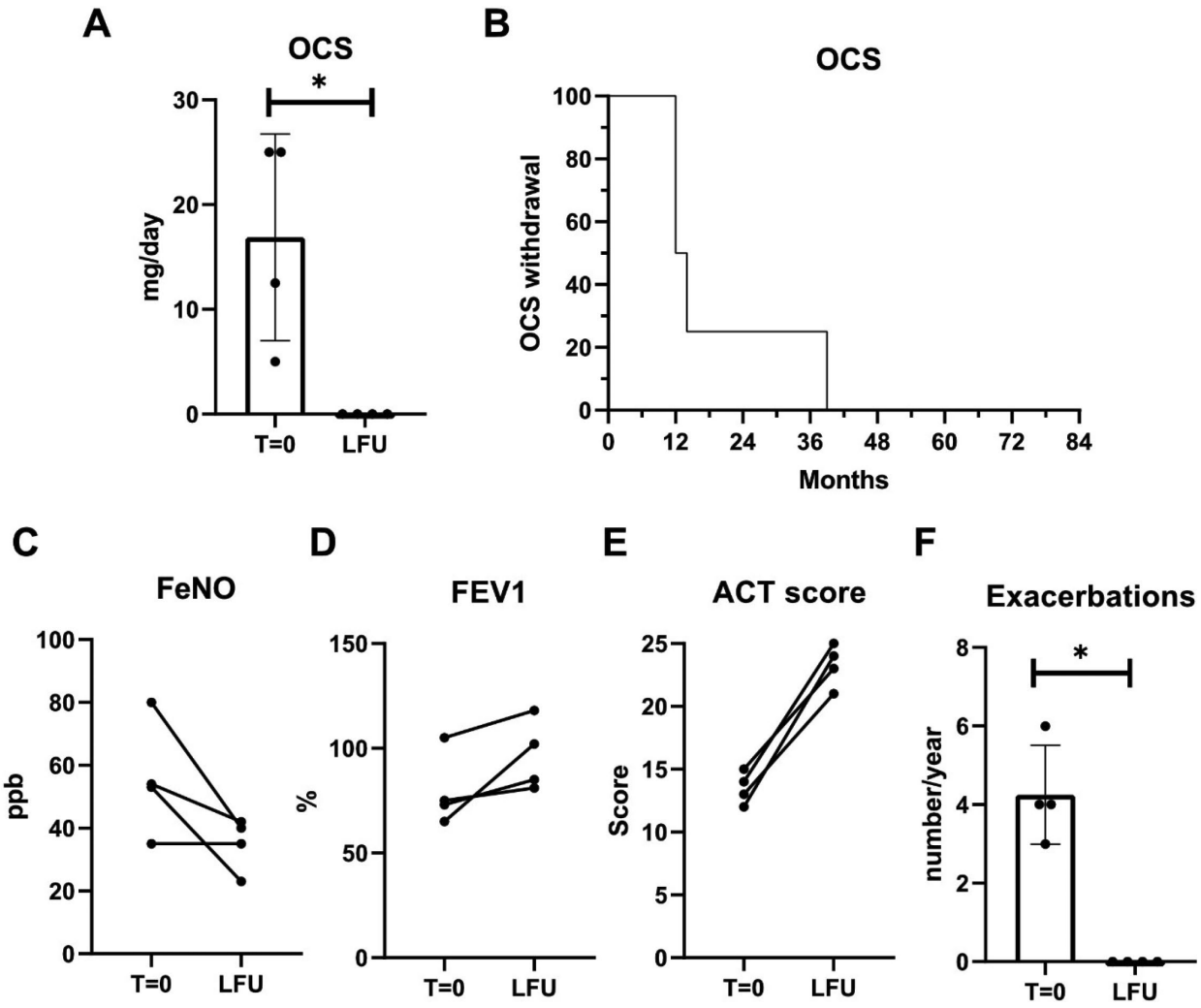
cypress. In December 2017, he had a total serum IgE level of 134 IU/mL, a FeNO level of 80 ppb and a blood eosinophil count (BEC) of 670 cells/mm^3. At baseline, spirometry showed a forced expiratory volume in 1 second (FEV_1) of 75% of predicted and a FEV_1-to-forced vital capacity (FVC) ratio of 65%. The patient was on treatment with salmeterol/fluticasone 50/500 µg, two inhalations daily; tiotropium bromide 2.5 µg, two inhalations daily; montelukast 10 mg, one tablet daily; and salbutamol 100 µg as needed. Asthma control was not optimal (ACT score of 13), four courses every 12 months of prednisone 25 mg daily and frequent use of salbutamol as needed for asthma flare-ups and persistence of dyspnoea from moderate exertion.

In January 2018, the patient was admitted to the Pulmonology Department for acute respiratory failure from severe asthma exacerbation. For these reasons, after discharge, mepolizumab 100 mg, one vial subcutaneously, was introduced starting in March 2018. In the following months, progressive clinical improvement with the absence of flare-ups was observed. Tapering of OCS was started by discontinuing it in April 2021. OCS was not withdrawn earlier due to arthralgia/myalgia requiring slower tapering. Only mild dyspnoea persisted from moderate exertion. In October 2023, the ACT score improved (score was 21) as did biological and functional parameters. In light of the good asthma control, it was also possible to discontinue tiotropium and reduce the dosage of ICS by discontinuing salmeterol/fluticasone 50/500 µg and starting budesonide/formoterol 160/4.5 µg, two inhalations twice a day. No asthma flare-ups, even in the absence of OCS and with a lower dose of ICS, were observed since OCS withdrawal. The patient continued the biological therapy at home as self-administration.

Case 2

Here, we present the case of a 52-year-old white man, a non-smoker, working as an administrative clerk. He had a clinical history of CRSsNP and allergic rhinitis with turbinate hypertrophy and underwent turbinectomy in 2002 and 2015. A diagnosis of severe asthma was made in 2016 with frequent exacerbations (on average six flare-ups every 12 months) despite therapy with vilanterol/fluticasone 184/22 µg once daily; tiotropium bromide 2.5 µg, two inhalations daily; montelukast 10 mg, 1 tablet daily; and salbutamol 100 µg as needed. In 2017, a skin prick test was

Figure 1. Long-term data of patients on mepolizumab treatment: reduction of OCS (baseline to LFU (A); time to withdrawal (B)); FeNO (reduction (C)); FEV_1 (baseline to LFU (D)); ACT score (baseline to LFU (E)); exacerbations (baseline to LFU (F)).



ACT, asthma control test; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; LFU, last follow-up; OCS, oral corticosteroids.

positive for grasses, dust mites, olive tree and cat epithelium. BEC was 540 cells/mm^3, total serum IgE 953 IU/mL, FeNO 53 ppb, FEV_1 73% and FEV_1-to-FVC ratio 63%. The patient required continuous use of OCS (on average prednisone 12.5 mg per day) with persistence of poor symptom control (ACT 15).

After a few months with omalizumab (started in February 2017 at a dosage of 300 mg SC every 15 days), discontinued due to six asthma exacerbations over the course of the year resulting in OCS bursts, mepolizumab 100 mg/4 weeks was started in January 2018. The clinical picture gradually improved, and after about 1 year it was possible to discontinue OCS after a slow tapering. In March 2023, the FEV_1 was 85% (+15%) compared with 2017, FeNO 23 ppb, BEC 0.8 cells/mm^3 and ACT 24. No moderate-to-severe asthma exacerbations after starting mepolizumab were observed; therefore, montelukast and tiotropium were also discontinued, and the dosage of vilanterol/fluticasone was reduced to 92/22 µg once daily. In light of the clinical stability and absence of side-effects of mepolizumab, the patient continued mepolizumab.

Case 3

A 49-year-old white woman, housewife, non-smoker, with a previous history of surgery for umbilical hernia and volvulus, headache, insomnia, and CRSsNP and had undergone functional endoscopic sinus surgery in 2006 and 2017. A diagnosis of eosinophilic bronchial asthma was made in 1998 without history of atopy. Since then, symptoms were under control until 2016, and between 2016 and 2017, five courses per year of OCS for asthma flare-ups (prednisone average daily dose 25 mg), with

Table 2. Long-term outcomes of mepolizumab treatment.

Case	All	1	2	3	4
Follow-up, months	73.5 (71–74)	74	74	73	71
Oral corticosteroid withdrawal, months	32.75 (12–39)	39	12	12	14
BEC, cells/mm^3	NA	40	0.08	NA	NA
FeNO, ppb	37.5 (23–42)	40	23	35	42
Serum IgE, IU/mL	673 (195–1074)	195	1074	NA	673
FEV_1, %	93.5 (81–118)	81%	85%	118%	102%
ACT score	23.5 (21–25)	21	23	25	24
Exacerbations in the 12 months before last follow-up	0	0	0	0	0
Hospitalizations	0	0	0	0	0
Asthma medications					
Inhaled corticosteroid dose	–	Fluticasone propionate 500 µg per day	Fluticasone furoate 184 µg per day	Budesonide 320 µg per day	Fluticasone propionate 500 µg per day
Tiotropium bromide	–	No	No	No	No
Salbutamol (as needed)	–	Yes	Yes	Yes	Yes
Montelukast	–	Yes	Yes	Yes	No
Prednisone daily dose, mg	0	0	0	0	0

All the results are reported as median (range). ACT, asthma control test; BEC, blood eosinophil count; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second.

admissions to the emergency department and hospitalization for severe asthmatic flare-ups, requiring high doses of intravenous steroids. The current therapy at the beginning of 2018 was budesonide/formoterol 320/9 µg, two inhalations twice daily; tiotropium bromide 2.5 µg, two inhalations daily; salbutamol 100 µg as needed; and beclomethasone nasal spray 100 µg, two inhalations daily. Montelukast was used with no advantage, then discontinued.

At baseline, BEC was 740 cells/mm^3, FeNO 35 ppb, FEV_1 105% and FEV_1-to-FVC ratio 85%. The ACT score was 14. In light of poor asthma control, it was decided to start mepolizumab 100 mg/4 weeks in February 2018. In the following months, the clinical condition and asthma control improved and after 12 months the patient no longer required OCS due to the absence of exacerbations. In September 2023, inhalation therapy was reduced by switching to budesonide/formoterol 160/4.5 µg, two inhalations twice daily, as needed, and continuing beclomethasone nasal spray 100 µg, two inhalations daily. Spirometry showed FEV_1 of 118% and the ACT score was 25/25, BEC was 36 cells/mm^3 and FeNO value was 21 ppb. No adverse events had appeared during the 6 years of therapy with mepolizumab, and the patient continued the treatment.

Case 4

Here, we discuss the case of a 53-year-old man, a construction painter and non-smoker. He had a clinical history of spontaneous urticaria, type 2 asthma, and CRSsNP complicating SEA diagnosed in 2016. In 2017, he experienced a hospitalization for severe asthmatic exacerbation with acute respiratory failure. Current therapy was salmeterol/fluticasone 50/500 µg, two inhalations daily; tiotropium bromide 2.5 µg, two inhalations daily; salbutamol 100 µg, as needed; ebastine 10 mg, 1 tablet daily; prednisone 5 mg, 1 tablet daily; and pantoprazole 40 mg, 1 tablet daily. In 2016, a BEC of 1870 cells/mm^3 was detected before the diagnosis of eosinophilic granulomatosis with polyangiitis. This patient was sensitized to house dust mites and grasses with a total serum IgE level of 1258 IU/mL. In December 2017, had had an ACT score of 12, FeNO of 54 ppb, FEV_1 of 65% and FEV_1-to-FVC ratio of 58%.

Given the poor asthma control also by the presence of persistent dyspnoea and three exacerbations during the previous 12 months, bronchial obstruction and CRSsNP, in April 2018, mepolizumab 100 mg/4 weeks was added to conventional therapy. In the following months, the patient's overall health status and asthma control improved, OCS and methotrexate were discontinued as of June 2019. By March 2023, BEC was 10 cells/mm^3, FeNO 42 ppb, FEV_1 102% (+57% respect to baseline), FEV_1-to-FVC 84 and ACT score 24/25, confirming marked improvement in symptoms and asthma control. After starting mepolizumab, the patient no longer had asthma exacerbations, and the biologic agent was well tolerated so that, since August 2021, he has continued home therapy with periodic follow-up visits.

Discussion

Asthma treatment guidelines recommend switching to high-dose ICS therapy for patients with severe asthma, who do not respond adequately to lower doses. Poor disease control and the need for frequent cycles or continuous use of OCS despite this step up are more frequently seen in the severe eosinophilic phenotype resistant to ICS. For these patients, the choice of monoclonal antibodies targeting eosinophilic inflammation, such as mepolizumab or benralizumab, has led to a significant improvement in clinical outcomes, allowing most of them to be free of OCS.[4–7] However, there are also concerns and evidence regarding the long-term use of high-dose ICS, with some data showing an increased risk of cumulative dose-related side events such as adrenal suppression, osteoporosis-related fractures, cataracts and diabetes.[10] Based on these observations, GINA recommends reducing ICS doses as soon as possible in patients who respond positively to biological agents; however, GINA acknowledges that there is still no robust clinical evidence to support the safety or best method for this approach.[2] Currently, only a few studies have addressed this issue. One of these is the SHAMAL study conducted with benralizumab.[11] This study showed that patients on therapy with the monoclonal antieosinophil can achieve significant reductions in ICS therapy while maintaining asthma control. In fact, 110 (92%) patients reduced their ICS-formoterol dose: 18 (15%) to medium doses, 20 (17%) to low doses and 72 (61%) only as needed. Furthermore, in 113 (96%) patients, the reductions were maintained until week 48 and 114 (91%) of the patients in the reduction group had zero exacerbations during tapering. To date, SHAMAL represents the most comprehensive study supporting ICS dose reduction in patients responding positively to biological agents. SHAMAL builds on the results of the preliminary, single-arm, open-label ANDHI–In Practice sub-study, in which more than half of patients with SEA controlled with benralizumab were able to reduce high-dose ICS while maintaining asthma control.[12] The demonstration of a favourable effect of monoclonal antibodies in patients with SEA on the gradual reduction of ICS doses, without loss of stability of symptoms and asthma exacerbations, would support the concept of clinical remission during treatment, pointing to a 'disease-modifying' effect of biologics in some respects.

In this case series, we aimed to analyse the effects of mepolizumab on the reduction of ICS intake in patients stably controlled by this biologic agent leading to OCS withdrawal and characterized by different types of the clinical picture (Case 1: severe type 2 asthma, steroid withdrawal syndrome; Case 2: steroid-resistant type 2 asthma, CRSsNP and switch omalizumab-mepolizumab; Case 3 and 4: severe eosinophilic asthma and CRSsNP). In this explanatory case series, all patients were on mepolizumab for almost 6 years, with a reduction of ICS treatment, improvement in ACT and functional parameters, and a significant reduction of exacerbation in the last 12 months before the last evaluation as compared to 12 months before the baseline. These findings point out the role of mepolizumab as a 'disease-modifying' agent, further highlighting its high tolerability and efficacy profile.

This study has some strengths and limitations. The most obvious strength is that these results are unique, as similar studies on very long-term data on mepolizumab are lacking. There still remain many unmet needs on the crucial aspect of ICS reduction following therapy with biologic agents; that is, how long after the start of therapy with biologic agents, are we allowed to perform ICS de-escalation? What diagnostic tools and/or predictive markers could help us in this choice? Another limitation is the number of patients enrolled; this study is a pilot project and therefore further confirmations on larger populations will be necessary in the future.

Conclusions

In conclusion, our study reported on the cases of four patients with SEA on mepolizumab 100 mg/4 weeks for almost 6 years, leading to completed withdrawal of OCS and with a reduction of ICS treatment, improvement in ACT and functional parameters, and a significant reduction of exacerbation in the last 12 months before the last evaluation as compared to 12 months before baseline.

Contributions: CL cared for the patient and drafted most of the manuscript. FM cared for the patient and was involved in the drafting of the manuscript. AB was involved in the drafting and was responsible for the revision of the manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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