Case Report

Skipping a single dose of mepolizumab resulted in significant clinical and functional deterioration

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ABSTRACT

Therapy with biologics is now the first choice of add on therapy in the management of severe asthma. However, little is known about the consequences of poor adherence to therapy on asthma control and lung function. Here, we report a case of an asthmatic patient with severe eosinophilic asthma whose asthma was ameliorated by mepolizumab use and whose symptoms had worsened, and asthma control was lost after skipping one single dose of the drug.
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Key words:
- Severe asthma
- Mepolizumab
- Adherence to therapy
- Eosinophils

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INTRODUCTION

Severe asthma affects approximately 3.7% of asthma patients and is an important factor of morbidity, mortality and poor Health Related Quality of Life[1,2]. During the last decades new treatments targeting disease mechanisms -referred as biologics, have been introduced in the therapy of asthma, resulting in a revolution in disease control, improvements of lung function and reduction of exacerbations. These treatments include monoclonal antibodies, recombinant cytokines and fusion proteins with the former to be at the moment the only approved biological therapy for severe asthma also included in the disease recommendations[3,4].

Mepolizumab is one of the currently approved biologics used for the treatment of severe eosinophilic asthma and is administered subcutaneously every 4 weeks. Mepolizumab, is a fully humanized IgG1 kappa monoclonal antibody, which binds IL-5 and prevents binding to the α-chain of the IL-5 receptor[5] and reduces the number of eosinophils by causing maturational arrest in the bone marrow and apoptosis through cytokine deprivation in the blood eosinophils[6]. Mepolizumab use, also results to a reduction of asthma exacerbations, improvements of lung function and asthma control[7,8] and also acts as a steroid sparing agent[9]. Studies have shown that drug discontinuation is related with a progressive increase of blood eosinophils and symptom relapse[10]. However, little is known about the

exact results of skipping a single drug dose in patients in long-term treatment who are adequately controlled for a long period of time.

Here, we report a case of an asthmatic patient with severe eosinophilic asthma whose asthma was ameliorated by mepolizumab use and whose symptoms had worsen and asthma control was lost after skipping one single dose of the drug. For the publication of this case report, the patient provided a written informed consent.

CASE REPORT

A 37 years old never smoker female patient was followed up in our asthma clinic for approximately 7 years due to severe asthma. Her asthma first appeared around the age of 16. The patient also had allergic rhinitis, nasal polyposis and osteoporosis the latest causing a fracture of the right femur 2 years ago. On physical examination the patient had wheezing on lung auscultation but no other findings. There was no evidence of occupation exposure to irritating factors.

Her asthma medication included a fixed dose combination of formoterol fumarate/budesonide 9/320μg 2 inhalations twice daily, a maintenance dose of oral corticosteroids (prednisolone tablets 5mg-7.5mg per day), salbutamol pMDI as rescue medication while she was also taking tablets of risedronate sodium, calcium and vitamin D3 for the treatment of osteoporosis. Despite therapy, the patient reported limitation on every day activities, nocturnal symptoms (awakenings due to cough and breathlessness), she reported use of 2-3 puffs of rescue medication per day, and in the latest year she had experienced 8 asthma exacerbations (treated with oral corticosteroids at a dose of 30 mg prednisolone per day for 5-7 days each). The results of the Asthma Control Questionnaire (ACQ-5) was 2.4 (in this questionnaire a score of <0.75 is indicative of controlled asthma while a score of >1.50 is indicative of uncontrolled asthma) and the score in the Saint George Respiratory Questionnaire (SGRQ) was 36.4 (Symptoms: 39.1, Activity: 41.7, Impact: 32.5). Blood eosinophils were 720/μL, total IgE was 52.5IU and skin prick tests were positive for common aeroallergens.

TABLE 1. Baseline functional characteristics before initiation of treatment with mepolizumab

	Pre		Post		Response (%)
	Actual	**%pred**	**Actual**	**%pred**	
FEV_1	1.80	53.6	1.96	58.3	8.9 (160ml)
FVC	3.68	89.8	3.75	91.5	
FEV_1/FVC	48.9		52.3		
FEF_{25-75}	0.83	25	0.96	28	

Abbreviations: Pre: pre bronchodilation, post: post bronchodilation, pred: predicted, FEV1: Forced Expiratory Volume in one second, FVC: Forced Exhaled Vital Capacity, FEF25-75: Forced Expiratory Flow in the middle 50% of FVC

The patient was put on treatment with mepolizumab (100mg SC every 4 weeks). The baseline pulmonary test results before initiation of mepolizumab are shown on Table 1. From the first dose the patient showed a significant symptom improvement ACQ-5 was zero (totally controlled asthma) and FEV1 increased from 53.6 to 84.8 For 6 months the patient continued with subjective and clinical benefit, with no exacerbations and no need for systemic steroids. However, after 6 months of therapy the patient missed one dose of mepolizumab and was reassessed one month after the programmed administration which caused a 2 months interval between the doses. In this appointment the patient reported symptom relapse (cough and dyspnea during everyday activities and nocturnal awakenings due to symptoms of asthma) and need for rescue medication daily., lung function deteriorated (FEV1 dropped to 63% predicted), ACQ-5 was 2 (indicating uncontrolled asthma) and SGRQ deteriorated (Total score 21.4, Symptoms: 35.2, Activity: 29.2, Impact: 12.5). During clinical and laboratory examination there were no signs of infection. Mepolizumab therapy was re-administered and the patient's symptoms and lung function improved within one month gaining total asthma control. The patient was advised not to miss any more doses. Her asthma remained well controlled and after 12 months of treatment the patient discontinued OCS. Today, after approximately 30 months of treatment the patient is well controlled, without any exacerbations and without need for OCS. Alterations in lung function, ACQ-% and SGRQ are shown on Figure 1 (a-c).

DISCUSSION

Studies have shown that mepolizumab withdrawal results to a significant increase in blood eosinophils at 0-3- and 3-6-months post cessation and in sputum eosinophils at 0-3 months but no further. Also, a deterioration in asthma symptoms has been observed all over the next 12 months of follow up as well as a rise on asthma exacerbations between 3-6 months, and after 6 months the rate of

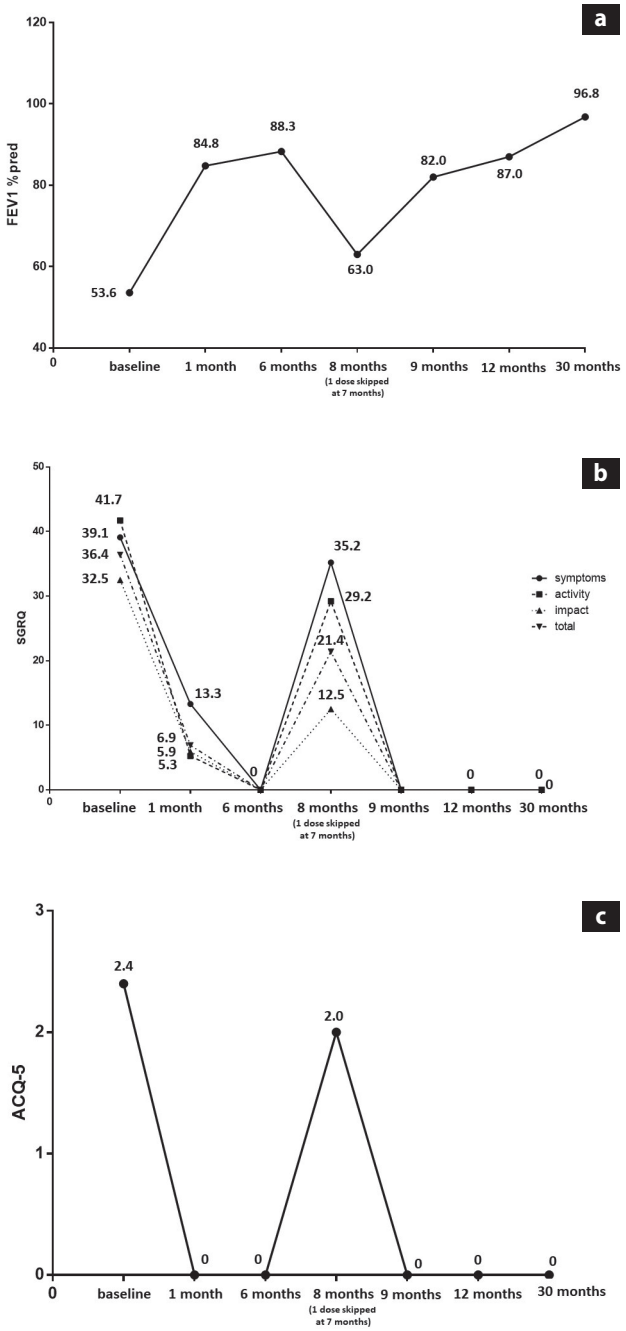

FIGURE 1.a-c. Alterations of a. FEV_1, b SGRQ and c. ACQ-5 at baseline and during the patients follow up

asthma exacerbations was the same as pretreatment[10]. According to the aforementioned observations, we can hypothesize that the drug lacks the potential to modify the disease. Furthermore, half-life for mepolizumab when administered subcutaneously varies between 16-26 days[6]. Interesting, in our case blood eosinophils increased and asthma symptoms deteriorated after skipping a single dose of mepolizumab showing that the drug was very effective in obtaining asthma control and deterioration occurred after approximately 2-3 drug half-lives. Importantly, all studies have shown that when the drug was resumed there was no negative impact on efficacy, which was also the case in our patient who improved rapidly after mepolizumab re-administration.

Our case report is not the first real life case of rapid clinical and functional deterioration after the drug discontinuation. A previously published case report has also shown that mepolizumab discontinuation after approximately 3 years of therapy also resulted in the loss of asthma control which has led to a severe exacerbation[11]. In this case also, mepolizumab re-administration resulted in clinical and functional improvement[9]. Since clinical experience from mepolizumab use is gained now, and no data of discontinuation are yet available, we believe that our manuscript provides important information regarding the results of discontinuing this biologic, even if the patient has previously gained total control of asthma.

Compliance to treatment is one of the most important problems in patients with asthma and is the main reason of treatment failure. Studies have shown that compliance to asthma treatment is approximately 20-30%[12] and fails to improve despite educational strategies such as asthma management plans and simplified inhaler devices[13]. Our patient skipped one dose and according to our clinical judgment since there were no signs of infection, this temporary discontinuation was the most probable cause of clinical and functional deterioration. Mepolizumab has been tested to be self-administered with a single-use prefilled syringe in an at home setting and it seems that most patients and caregivers are able to successfully administer the drug subcutaneously[14,15]. If this self-administration of therapy would have any positive effect to compliance has to be determined.

CONCLUSION

In conclusion, although treatment duration with biologics has not been determined, this case report shows that in everyday clinical practice patients should be informed that even a temporary discontinuation of mepolizumab could result in the loss of asthma control and in increase of the risk of an exacerbation.

CONFLICT OF INTEREST
None.

FUNDING
None.

ΠΕΡΙΛΗΨΗ

Παράλειψη μιας δόσης mepolizumab οδήγησε σε σημαντική κλινική και λειτουργική επιδείνωση

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Η θεραπεία με βιολογικούς παράγοντες αποτελεί πλέον την πρώτη επιλογή προσθήκης στη θεραπεία για τους ασθενείς με σοβαρό άσθμα. Παρόλα αυτά δεν είναι απολύτως γνωστές οι επιπτώσεις της πτωχής συμμόρφωσης στον έλεγχο του άσθματος και την αναπνευστική λειτουργία. Παραθέτουμε ένα περιστατικό μιας ασθενούς με σοβαρό ηωσινοφιλικό άσθμα που παρουσίασε σημαντική βελτίωση με τη χρήση mepolizumab και της οποίας τα συμπτώματα επιδεινώθηκαν και το άσθμα τέθηκε εκτός ελέγχου μετά από την παράλειψη μιας μόλις δόσης του φαρμάκου.

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Λέξεις - Κλειδιά: *Σοβαρό άσθμα, Mepolizumab, Συμμόρφωση στη θεραπεία, Ηωσινόφιλα*

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