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Omalizumab: when the non-responder is a late-responder

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Key words

Omalizumab, steroid-resistant asthma, spirometry, quality of life

Summary

Omalizumab is an anti-IgE monoclonal antibody available since 2006 for the treatment of GINA step 4 asthma. We studied a 41-year old male who has been suffering from severe steroid-resistant asthma with severe co-morbidity and treated with Omalizumab. He was found to be non-responder to the treatment until the 48th week, starting from which we began to see a distinct improvement in the symptoms and all the correlated parameters, in addition to remission of the co-existent allergy to milk.

Conclusions: we wish to point out the late response to Omalizumab, which occurred way beyond the times envisaged in literature. It seems possible that some patients are late responders to the drug.

Introduction

Omalizumab is a chimeric monoclonal antibody binding the free IgE before they bind to the FcεRI-II receptors on the mast cells and basophils. The drug has made it possible to significantly improve the quality of life and asthma control in patients with GINA step 4 asthma (1). The patients selected must have certain features to be considered as suitable for the treatment (2), but about 20% of these do not respond to the drug (3).

In this study we describe the case of a man suffering from steroid-resistant asthma associated with important co-morbidity treated with Omalizumab and non-responder after the 16 weeks envisaged for assessing the efficacy. Administration of the drug was prolonged over time, with a dramatic improvement of the clinical condition and the spirometric parameters.

Case Report

In December 2007, a 41-year old patient was brought to our notice, with a history of severe persistent asthma and oculorhinitis since 1983. The case history revealed past secondary thoracic trauma following a serious road accident with consequent breakage of the aortic arch treated surgically by means of endovascular prosthesis, MTHFR genotype mutation with repeated thrombotic episodes, steroid-induced bilateral cataract and allergy to cow's milk proteins (casein and lacto albumin). The patient did not present history of tobacco smoking. He was a trader.

The treatment under way at the time of the first visit was the combination preparation Salmeterol-Fluticasone 50/500 μg/day inhalation powder, Salbutamol spray metered dose inhaler (MDI) daily 3-4 times/day, prednisone 25 mg/day tablets, Momethasone 200 mcg/day intranasal

spray, Tiotropium bromide 18 mcg/day inhalation powder, Montelukast 10 mg/day tablets. (Tab.1). Sodium Warfarin tablets to prevent clotting.
The patient had frequent flare-ups, mainly on an infective basis, treated by increasing systemic steroids and antibiotics; he was also admitted to the Pneumology ward in 2004 and 2006 for the same reasons. In 2007, he entered 4 times in Emergency Room and he was subjected to 3 outpatient examinations.
Positive to skin prick test for dust mites, gramineae, alternaria and cladosporium while the total IgE dosage was 256 IU/ml with body weight of 95 kg.
The haematochemical examinations were regular, as well as immuno-rheumatological tests (ANA test, rheumatoid factor, ANCA, aspergillus specific Ige and IgG antibodies). Spirometry showed an important obstructive ventilatory syndrome (FEV1 57% FVC 67% FEV1/FVC 70%) (Tab.2). A physical examination of the chest revealed rale and hissing sounds during expiration. Thorax High Resolution Computed Tomography (HRCT) did not revealed relevant anomalies.
We used the Asthma Quality of Life Questionnaire score (AQLQ) to assess the patient's quality of life (4), with an initial score of 2,69 points.
The Asthma Control Test (ACT) used for assessment of asthma control gave a score of 6 points during the first visit (5).
The patient was selected as suitable for additional treatment with Omalizumab, administered subcutaneously in a dosage of 300 mg (2,4 ml) every two weeks (calculated on the basis of the total IgE baseline value and body weight), starting from February 2008.
The response to the drug was assessed every 16 weeks (as envisaged by the directives of the Italian Drug Agency, Agenzia Italiana del Farmaco - AIFA) (6), by monitoring the respiratory functions and asthma control (2). During the first control, as the protocol rules, we did not find any clinical improvement and the patient had two serious infective flare-ups which were treated in both cases by increasing oral steroid (prednisone 50 mg/day, then tapered) and antibiotics. Lack of response was confirmed by the spirometric test and the ACT questionnaire score (9 points). We decided to continue administering the drug, then carried out a second control at the 32nd week (substantially overlapping the previous one) and a third control at the 48th week (January 2009). Starting from this moment, the patient began to report physical wellbeing, which was confirmed by significant improvement of the spirometry (FEV1 88%, FVC 83%, FEV1/FVC 87%). The result of the thoracic examination was distinctly better and so were the symptoms related to oculorhinitis.
The clinical response was confirmed by the marked increase of the AQLQ and ACT scores (respectively 6,51 and 23 points). Symptoms control was found to be stable during the subsequent visits, and this made it possible for us to gradually reduce and then stop systemic steroid, Montelukast and Tiotropium, maintaining only inhalatory treatment with Salmeterol/Fluticasone 50/500 twice/day. The patient was also once again able to take milk and its derivatives.
In March 2009 spirometry was repeated, and showed further improvement of the parameters (FEV1 95% FVC 89% FEV1/FVC 87%) (Tab. 2).
The patient is currently taking only the combination Salmeterol/Fluticasone 50/500 and has no longer had flare-ups, not even after inflammatory episodes of the upper and lower airways, unlike the situation before starting treatment with Omalizumab.

Discussion

The patient examined had poorly controlled severe asthma (GINA step 4), with considerable impairment of the

Table 1 - Treatment at first and last visit

First visit- 01/2008	Last visit- 3/2009
Salmeterol/fluticasone 50/500 μg twice daily (inhalation powder)	Salmeterol/fluticasone 50/500 μg twice daily
Salbutamol 300-400 μg/day (MDI)	Salbutamol (MDI) unfrequently
Prednisone 25 mg/day (tablets)	
Mometasone 200 μg/day (intranasal spray)	
Tiotropium bromide 18 μg/day (inhalation powder)	
Montelukast 10 mg/day (tablets)	

Table 2 - Spirometry at first and last visit

First visit- 01/2008	Last visit- 3/2009
FEV1 57%	FEV1 95% (+38%)
FVC 67%	FVC 89% (+22%)
FEV1/FVC 70%	FEV1/FVC 87% (+17%)

spirometric values and serious co-morbidity. From the various studies reported in literature, it is seen that positive response to treatment with anti-IgE antibody is mainly assessed on the basis of the response and symptoms control even in the absence of significant improvements of the respiratory function (2).

Health-related quality of life (HRQoL) was assessed by means of the AQLQ score (4). The AQLQ is composed of 32 questions which cover four domains: activity limitation, symptoms, environmental stimuli and emotional function. Subjects recall their experiences during the previous 2 weeks and score a number of asthma-related problems on a 7-point scale from 1 (maximum impairment) to 7 (no impairment). We used an overall summary index, which is the mean of the responses to the 32 items (total AQLQ score). The AQLQ was found to be valid, reproducible and responsive to change over time and a change in questionnaire score of 0.5 or more points has been determined to be the minimal clinically important difference (7). AQLQ score at first visit revealed a quality of life compromised in any evalued aspects (2,69 points).

The symptoms control was monitored by means of the ACT, which is a brief validated questionnaire consisting of 5 questions for adults and 7 for children, and has shown good correlation with the changes in pulmonary function and the HRQoL (5, 8). The score of the abovementioned questionnaire is expressed in a range between 5 and 25 points, with the lowest score indicating the lack of asthma control and consequently a poorer quality of life.

In the case in question, the ACT carried out during the first visit showed very poor control of the disease which was already impaired by the severe thoracic trauma suffered during the car accident and the repeated thrombotic events.

From the data present in literature and the Omalizumab data sheet it is clear how assessment of the treatment efficacy must be done after 16 weeks starting from the first administration of the drug; this is because it takes 70 to 90 days to obtain the down-regulation of the FcεRI receptors on the mast cells and basophils (9, 10). Moreover, the time schedule is regulated by the AIFA by monitoring the treatment efficacy on a site specially instituted for the purpose starting from the end of 2008 (6).

The element of novelty in this clinical case is the extremely delayed symptomatological and instrumental response to the drug (48 weeks).

After a long period of apparent resistance to treatment, we obtained a good functional and clinical response registered by the net increase of the ACT score calculated during the last controls and associated with evident improvement of the spirometric obstruction indices. Mention must be made of the remission of the allergy to milk proteins, probably because of the blocking of the free IgE. The improvement of the clinical condition made it possible for us to stop not only systemic steroid but also the inhalatory drugs, except for the salmeterol/ fluticasone association.

Symptoms control in terms of reduction of the flare-ups was also evident, since exacerbations no longer occurred after stabilization of the respiratory condition, and these results are way beyond the data from earlier studies, which show a 50% reduction of the asthma exacerbations and 44% reduction in emergency care (9). These intercurrent infectious events were not qualified as adverse reactions to omalizumab, considering their frequency and characteristics during the previous clinical history. Besides, literature shows that, among adverse events, upper respiratory tract is mainly involved (11).

Consequently, the quality of life is improved and the AQLQ score in January is marked increased (6,51 points).

The decision to continue treatment with Omalizumab is usually made on the basis of the assessment of the response to the drug, characterized by better disease control, increased HRQoL and reduction of exacerbations. On the basis of these indications, our patient ought to have stopped the anti-IgE monoclonal antibody, and resumed conventional treatments at the maximum dosage, already shown to have poor efficacy. Moreover, the poor quality of life and frequent recourse to hospitals would have resulted in further costs in terms of reduction of working performance and medical expenses.

The decision to continue with treatment beyond the time schedules envisaged was mostly supported by one of our earlier reports (12) submitted during the international clinical trial on Omalizumab (CIGE025A2425), for which ours was the Coordinating Centre for Italy and for which the data are currently being published; the main end-point of the protocol was assessment of the persistence of the efficacy of the drug after 32 weeks of treatment. One of the patients enrolled was suffering from a serious and inveterate

form of asthma with a very large number of flare-ups and hospitalization and had responded to pharmacological treatment with Omalizumab at the 32nd week, well beyond the expected time schedules. This past experience led us to proceed with the treatment on this occasion as well.
The delayed response may be explained by the presence, on both occasions, of a severe form of asthma which probably led to significant remodelling of the bronchial walls (13).
It is a known fact that patients suffering from steroid-resistant asthma may be identified as a sub-phenotype characterized by marked inflammation of neutrophils, with less importance of the eosinophil component. There is greater evidence of tissue damage and bronchial remodelling in this group (14). The marked effect of Omalizumab on immuno-phlogosis (mainly on eosinophils and high affinity IgE receptors) (15) could have influenced these alterations, while, however, requiring longer times than those expected before clinically evident results could be observed.
In order to assess the economic impact of the new treatment strategy, a cost analysis was carried out. The cost related to the resources consumption (hospitalization, emergency room access, visit and pharmaceutical treatment) was estimated considering the public tariffs and the net price of the drugs (16, 17). In the period 2004-2007 the average annual healthcare cost was 5,446 euro. The total costs were 21,783 euro. This amount is underestimated because it does not consider some other further healthcare costs (e.g. the surgical intervention for the steroid-induced bilateral cataract), the indirect costs (cost supported by patient such us drug not reimbursed by National Healthcare Service and reduction of the working activity) and intangible costs (economic value associated to the poor quality of life) (18).
It is not feasible to carry out a complete cost analysis of the next 4 years (2008-2011) and to assess the cost effectiveness of Omalizumab as in previous analysis(19). It is possible to assume that due to the improvement of the morbidity level, there will be just the costs of the pharmaceutical treatment and not the costs of hospitalizations or Emergency room access. In addiction, considering the age of the patient, it could be interesting to give a monetary value to the difference with respect to the previous period in the working capability and in the quality of life. An analysis published in 2006 found that the indirect costs represent the 60% of the cost of illness (20).
In conclusion, Omalizumab is a therapeutic option which, in selected cases, is capable of substantially modifying the clinical history of serious asthma with relevant consequences on patient morbidity and quality of life. However, it is possible (and this fact must be given maximum consideration) that some patients are found to be apparently "non-responders" even after prolonged periods of treatment with the drug. It is to be hoped that studies on a larger scale will make it possible to identify with greater precision sub-phenotypes of asthma apparently resistant to Omalizumab and the predictive factors, if any, which can help prevent therapeutic failures or premature discontinuation of treatment.

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