Fatal asthma after omalizumab and controller therapy discontinuation

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To the Editor
Severe asthma (and near-fatal asthma) account for the majority of socio-economic and healthcare expenses. Severe asthma is characterized by the absence of control despite the maximal standard therapy (often requiring courses of systemic corticosteroids) (1), whereas near-fatal asthma implies respiratory failure with/without mechanical ventilation (2). During the last decade, the more detailed knowledge of the pathogenic mechanisms and the availability of biological agents (i.e. monoclonal antibodies) improved the therapeutic approaches (3). For historical and scientific reasons, the anti-IgE therapy (omalizumab) was the first available biological treatment used in severe allergic asthma. The clinical efficacy and safety of omalizumab is well documented in trials and real life (4), whereas it is not fully elucidated yet whether the treatment should be continued life-long or if it could be discontinued after some years (5).

We describe a clinical case of fatal asthma occurred after the discontinuation of omalizumab in a patient with severe asthma. The patient was a 28 year-old female, never smoker, referred to our services in 2007. She suffered from severe allergic asthma (> 2 exacerbations/year), with ascertained sensitization (Immuno-cap® Thermo Fisher Scientific, Uppsala, Sweden) to: mite (24.10 kU/L), cat dander (7.99 kU/L), olive (20.10 kU/L), Alternaria (88 kU/L) and grass (> 100 kU/L). The total IgE concentration was 323 kU/L (Phadia Diagnostics, Upssala, Sweden), exhaled nitric oxide was 132 ppb, and the asthma control test score was 12 at baseline. The clinical history documented some exacerbations during thunderstorms, emergency department admissions, and hospitalizations due to asthma attacks. After the baseline assessment, a treatment with omalizumab, in addition to standard treatment (6), was instituted (375 mcg subcutaneously every 4 weeks). A progressive improvement was observed from both the clinical and functional viewpoint. In particular, FEV1 increased from 72% to 94% of predicted value within few weeks, and then remained stable. The Asthma Control Test score never fell below 21 points. Noticeably, after starting omalizumab there

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were no more exacerbations, hospitalizations or emergency visits, and the controller therapy could be gradually reduced. The treatment was carried on from March 2007 to December 2012, for a total of 67 injections. According to the favorable and stable outcome, to the available literature (6) and to the willingness of the patient (also related to logistic aspects), the treatment was discontinued in December 2012. After omalizumab discontinuation, regular control visits were carried out until January 2015, then the patient was lost to follow-up. Until 2015 she reported only mild symptoms of asthma (< 2/month), well controlled with inhaled albuterol. On September 28 2015 the patient was admitted to emergency room for a severe asthma attack with respiratory failure, needing invasive mechanical ventilation. The patient died, despite the heavy medical therapy (high dose intravenous steroids, adrenaline, magnesium sulphate, theophylline) and the strenuous resuscitation manoeuvres. The autopsy confirmed the presence of severe bronchial obstruction, with eosinophil and neutrophil infiltration. Subsequently, we ascertained, on a historical basis, that the patient had recently increased the use of inhaled albuterol, and that she was not taking controller drugs for asthma. In addition, looking at the aerobiological data we noticed that the level of Alternaria spores was remarkably high, in the absence of thunderstorm-like conditions (figure 1), and that the patient was strongly sensitized to this allergen. The above described case evidences that: i) Asthma mortality still represents a critical issue in the management of the disease, particularly in youngsters) (7); ii) the role of “minor” but hazardous allergens as Alternaria can be underestimated in everyday clinical practice (8), thus the importance of the availability of aerallergen count has to be underlined; iii) it would be advisable not to discontinue omalizumab in patients with severe/near-fatal asthma who had previously achieved a satisfactory control. This latter fact remains controversial and matter of debate. There are studies showing that a relevant part of patients achieve a stable improvement after omalizumab discontinuation (9), and other studies would suggest that a prolonged (possibly life-long) therapy would produce more benefits (5). Indeed, this aspect is strictly dependent on the initial asthma diagnosis, on the type of allergic sensitization, and probably on the presence of previous near-fatal asthma, that is the most relevant risk factor for subsequent episodes (10). Our experience, as described above, would suggest caution in stopping omalizumab treatment in patients with severe asthma and near-fatal asthma sensitized to perennial allergens (i.e. Alternaria), which are recognized as particularly harmful. Finally, we have to consider that probably the patient reduced or stopped the use of controller drugs, and this is difficult to assess, whereas the administration of a subcutaneous drug (omalizumab) needing medical supervision is easier to certify.

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**References**