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Novel treatment (new drug/intervention; established drug/procedure in new situation)

Omalizumab for exacerbations of allergic bronchopulmonary aspergillosis in patients with cystic fibrosis

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Abstract

Anti-IgE therapy was proposed to two teenagers with cystic fibrosis (CF) with allergic bronchopulmonary aspergillosis (ABPA) exacerbation, reluctant to a further course of oral steroids. Both patients experienced ABPA exacerbations within the past 3 years, requiring oral steroid bursts. Clinical, laboratory and radiographic features were consistent with ABPA exacerbations (representing at the time of evaluation the fourth and third episodes for patient 1 and 2, respectively). Total serum IgE was very high, >1000 kU/litre in both cases. Treatment consisting of subcutaneous injections of 375 mg anti-IgE (omalizumab) twice monthly was successful in rapidly improving respiratory symptoms and lung function. Based on clinical and functional improvement, interval between injections was progressively increased and treatment could be withdrawn after 11 injections, without recurrence at 20 weeks of follow-up after withdrawal.

BACKGROUND

With an annual incidence around 7.8%, allergic bronchopulmonary aspergillosis (ABPA) is an important, often recurring and devastating complication in cystic fibrosis (CF).¹ Its pathogenesis remains poorly understood. Moreover, diagnosis may reveal difficult as a complete picture is rarely seen,^{1,2} while absence of appropriate treatment will lead to irreversible lung damage and overtreatment can result in several serious side effects, including a specific risk of diabetes in pancreatic insufficient patients. Omalizumab, a humanised anti-IgE monoclonal antibody, is useful as add-on treatment in 60% to 70% of patients with severe allergic asthma remaining poorly controlled.³ Recent case reports of four CF patients with ABPA and severe side effects related to long-term continuous administration of steroids suggest that it could be useful in this context^{4,5} but its efficacy during acute exacerbations of the disease remained unknown.

CASE PRESENTATION

Both patients were 14 years old (patient 1 was male, patient 2 female), were homozygous for the F508del mutation and experienced previous episodes of ABPA within the past 3 years. Oral steroids and itraconazole for 3–4 months were effective for these exacerbations, with transient insulinotherapy needed for patient 2.

Patient 1 presented with his fourth ABPA exacerbation when anti-IgE treatment was considered. Forced expiratory volume in 1 s (FEV1) was 65% predicted. Skin prick test to *Aspergillus* was positive and blood testing revealed eosinophilia, precipitating IgG antibodies to *Aspergillus*, markedly increased total serum IgE (4261 kU/litre), and specific IgE to *Aspergillus fumigatus* (53.3 kAU/litre: class 5), recombinant *Aspergillus* f4 (17 kU/litre: class 3) and recombinant *Aspergillus* f6 (5.7 kU/litre: class 3) major allergens. Chest x ray did not show any infiltrate.

Patient 2 was at her third acute episode of ABPA, with FEV1 76% predicted and a recent lung infiltrate on chest x ray. Blood testing also revealed eosinophilia, precipitating IgG antibodies to *Aspergillus*, increased total serum IgE level (1526 kU/litre), and specific IgE to *Aspergillus* (18 kU/litre: class 4) and to recombinant *Aspergillus* f4 (class 3).

TREATMENT

A trial of omalizumab, 375 mg every 2 weeks for 4 months was proposed as an alternative to oral steroids.

OUTCOME AND FOLLOW-UP

Anti-IgE treatment resulted in rapid improvement of symptoms and normalisation of spirometry (FEV1 103% and 91% predicted after 3 and 2 weeks, respectively for patient 1 and 2). No side effects were observed.

After seven injections, based on previous experience in this condition (data not shown) and on clinical/functional improvement of our patients, the between-injection interval could be progressively increased, up to a total of 11 injections. Both patients remained stable up to 20 weeks following treatment withdrawal (FEV1 of 98 and 99% predicted, respectively).

DISCUSSION

These observations suggest for the first time that omalizumab may be effective not only during the chronic course of ABPA (as add-on treatment) but also to treat acute exacerbations of the disease, in the particular setting of CF.

Two case reports have been reported recently on the benefit of add-on treatment with omalizumab for steroid-dependent ABPA in CF patients. Van der Ent *et al*⁴ reported spectacular improvement of clinical signs and lung function within 4 h after a single dose of omalizumab and suggested that it might be used as a helpful diagnostic test for ABPA. We did not confirm this finding, which was not mentioned by Zirbes *et al*.⁵

Our patient 1 presented with a particularly high IgE level (presumably only partly scavenged by the currently maximal dose of omalizumab), which could potentially contribute to a more progressive improvement. However, a similar course was observed in two patients described by Zirbes *et al*,⁵ who had IgE levels below 900 kU/litre. Thus, while long-term response rate in asthma patients with IgE within the first quartile (below 76 kU/litre) is lower,³ the short-term response to omalizumab in acute exacerbation of ABPA cannot be predicted by serum IgE level.

LEARNING POINTS

These original case reports:

- Suggest that omalizumab could represent an effective treatment of acute exacerbations of allergic bronchopulmonary aspergillosis (ABPA) complicating cystic fibrosis (CF).
- Could be of major importance for cystic fibrosis patients and their doctors.
- Further support the relevance of targeting IgE in ABPA.
- Should prompt a randomised controlled trial to confirm efficacy of anti-IgE therapy of ABPA in both CF and non-CF settings, including during exacerbations of the disease.

Footnotes

Competing interests: None.

Patient consent: Patient/guardian consent was obtained for publication.

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