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Longterm clinical outcomes of omalizumab therapy in severe allergic asthma: Study of efficacy and safety

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ABSTRACT

Omalizumab has been shown to be an effective add-on therapy for patients with uncontrolled severe persistent allergic asthma. There has been a steady accumulation of evidence on the long-term effectiveness of omalizumab; however, data on real-life outcomes beyond one year of treatment is limited. In this study, we report on long-term outcomes of omalizumab treatment. We collected data from our severe asthma registry on hospitalisations, exacerbations, corticosteroid sparing, asthma control, lung function, biomarkers and side effects, to determine if the benefit was sustained and treatment was safe on the long term. Forty-five patients [mean age 44.9 years (range 19–69), females 37/45 (82%), mean duration of omalizumab treatment = 60.7 ± 30.9 months (range 23–121) were included in the analysis. We observed a reduction in the annual acute asthma related hospital admissions for the total population from 207 at baseline to 40 on treatment (80.7% reduction), whilst the per patient annual hospitalisations were reduced from a mean of 4.8 to 0.89 post-omalizumab treatment ($p < 0.00001$). There was a 76.7% reduction in daily mean maintenance OCS dose (prednisolone equivalent) from 25.8 mg ($n = 43$) to 6.0 mg ($p < 0.0001$), associated with clinically significant improvement in asthma control questionnaire (ACQ) from mean score of 4.1 (range 3.7–4.7) to 2.27 (range 0.5–4.1) $p < 0.0001$. The mean % predicted FEV_1 has improved from 59.2% at baseline to 75.7% on treatment ($p = 0.001$). There was a statistically non-significant reduction in median peripheral blood eosinophils (PBE) from 300 cells/μl (range 40 −1050) at baseline to 175 cells/μl (range 0–1500) post-treatment ($p = 0.068$), and statistically significant reduction of median fraction exhaled nitric oxide (FeNO) level from 37 parts per billion (range 12–178) to 24 ppb (range 7–50) ($p = 0.0067$). The work/school missed days were reduced in 17/19 patients who were at employment or school. The overall safety profile of the treatment seemed acceptable and was consistent with published experience. In conclusion, results from this real-life study demonstrate that improved outcomes in patients with severe allergic asthma are sustained with longer-term omalizumab therapy.

1. Introduction

Asthma is characterised by bronchial inflammation, airway hyper-responsiveness and reversible bronchial obstruction [1]. Inadequately controlled severe asthma is associated with increased risk of exacerbations, leading to increased emergency room (ER) visits and hospital admissions [2].

Over 70% of severe asthma patients have allergic immunoglobulin E (IgE)-mediated disease. Many require maintenance oral corticosteroids (OCS) therapy which is associated with significant adverse effects [3–5], which prompted the need for the development of more effective and safe treatment through specific targeting of IgE.

Omalizumab is a recombinant humanised IgG1 monoclonal anti-IgE antibody that binds IgE at the same epitope that binds to the IgE receptor [6]. Clinical trials have demonstrated efficacy of omalizumab as an adjunctive treatment in severe allergic asthma (SAA) (reducing the rate of exacerbations and asthma-related ER visits/hospitalisations, as well as improving asthma-related quality-of-life and enabling a significant reduction in the dose of inhaled or oral corticosteroids) [7–12]. It is approved in the European Union (EU) as adjunctive therapy in patients with persistent

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SAA that remains uncontrolled despite treatment with high-dose inhaled corticosteroids (ICS) and a long-acting β2-agonist [13]. In the UK, it has been approved for use by the National Institute of Care Excellence (NICE) for patients fulfilling certain criteria [14], which include a total serum IgE range between 30 and 1500 international units/mL (IU/mL). Using omalizumab outside this range may also be effective [15,16]. Omalizumab is the only available anti-IgE therapy in clinical use, with potential predictors of a good response to it include pretreatment high fractional exhaled nitric oxide (FeNO), peripheral blood eosinophil (PBE) counts, serum periostin, and impaired baseline lung function [17,18].

The optimal duration of treatment with omalizumab is uncertain with current practice advocates lifelong treatment [19,20]. Majority of post license real life studies have described efficacy up to 52 weeks [21–27], with few further studies reported on omalizumab efficacy and safety beyond 52 weeks in both adults and children [31]. . The "eXpeRience" international registry open label study from 14 countries reported on 943 patients with up to 2 years of follow up, demonstrating sustained benefit in asthma outcomes including exacerbations reduction [28]. Similar sustained benefit of up to 2 years was also observed in a paediatric French population [29]. Up to 3 years benefit was reported in 26 patients demonstrating significant improvement in symptoms and lung function [30], and up to 7 years benefit was reported in 7 patients from Italy showing incremental year on year improvement in asthma outcomes [32]. In the UK to date, there were no reports on omalizumab efficacy/safety beyond the 52 weeks. Apex I study was of 136 patients from 10 centres in UK with 52 weeks follow up data, reported 64% reduction in OCS use and 53% reduction in exacerbations [26]. Apex II enrolled 252 patients from 22 centres in the UK with 52 weeks follow up data showing an improvement in symptoms, lung function, and a reduction in exacerbations [33]. The Birmingham regional severe asthma service (BRSAS) has considerable experience in the clinical use of omalizumab that extends over 10 years. In this study, we report on the effectiveness and safety of omalizumab in a responder population with mean treatment duration of 5 years (range 2–11 years).

2. Methods

This was a retrospective severe asthma registry and case note review conducted at a single tertiary referral centre (The Birmingham Regional Severe Asthma Centre "BRSAS") in the UK. Patients with SAA who were treated with omalizumab 150–600 mg every 2 or 4 weeks for longer than 23 months, in accordance with the European Union label and NICE guidelines for the use of omalizumab [13,14] were included. These patients were classified as omalizumab responders, following a physician's Global Evaluation of Treatment Effectiveness (GETE) assessment after 16 weeks treatment trial. The selection criteria for this study meant that only patients who responded to omalizumab 16 weeks treatment trial and remained on long-term treatment up to March 2013 were included in the analysis. All data were entered onto a Microsoft Excel© spreadsheet. Statistical evaluation was conducted through paired pre and post treatment comparisons using a Wilcoxon signed ranks test and student t-test using MedCalc® version 12.7.0.0 statistical software (Ostend, Belgium). The cut-off level for statistical significance used in this study was $p < 0.05$ unless specified otherwise.

All included patients provided written consent. Patients were evaluated for the frequency of acute asthma related general practitioner (GP) visits, emergency department (ED) visits and hospitalisations. We also collected data on the use of oral corticosteroids (OCS), Asthma Control Questionnaire (7 questions [ACQ7]) scores lung function (forced expiratory volume in 1 s [FEV_1]), inflammatory biomarkers (FeNO and PBE), and work/school days missed (patient self-reported data, obtained by telephone interview). Data were compared between baseline (the 12 months preceding omalizumab therapy) and on-omalizumab treatment the most recent "latest" 12 months on treatment.

3. Results

3.1. Demographics

In March 2013, there were 625 patients on the BRSAS dendrite registry (Fig. 1) with severe/difficult to treat asthma, 169 (27%) met the NICE criteria for omalizumab use in severe asthma, 122 had 16 week omalizumab treatment trials, and 100/122 (82%) had good to excellent response and continued longterm on the treatment. Twenty-two patients discontinued due to lack of response (12 patients), pregnancy during the treatment (5 patients), or due to side effects (5 patients). Fifty-five patients were repatriated to their local hospital and not included in this analysis. The included 45 patients had a mean age of 44.9 years (range 19–69), predominantly females (81%), with a mean bodyweight of 85.9 kg (range 51.2–116) (Table 1). All of these patients had omalizumab therapy for ≥23 months (mean duration 60.7 ± 30.9 months, range 23–121).

3.2. Healthcare resource utilisation

Long-term treatment with omalizumab was associated with reductions in unscheduled hospitalisations, intensive care unit (ICU) admissions, and emergency attendances, when compared with baseline or pre-omalizumab treatment values (Fig. 2, Table 2). For the total group, there were 207 hospitalisations and 80 emergency attendances at baseline versus 40 and 42 respectively on long term treatment. This corresponds to 80.7% and 48.5% reduction in hospital admissions and emergency attendances, respectively. The mean annual per patient hospitalisations was reduced from 4.8 to 0.89 ($p < 0.00001$) (Fig. 2). The mean annual per patient emergency attendances were reduced from 4.4 to 3.0 (p-value 0.17). There was also statistically non-significant reduction in mean ICU admissions per patient per annum from 0.48 to 0.19 ($p = 0.13$) (Table 2).

3.3. Effect on OCS use

At baseline, 37/43 (82%) patients were receiving maintenance OCS, compared to 19/43 (44.2%) following long-term treatment with omalizumab [18/43 (41.9%) weaned off OCS treatment completely]. The mean daily maintenance OCS dose (prednisolone equivalent) was reduced from 25.8 mg to 6.0 mg ($p < 0.0001$) (76.7% reduction) (Fig. 3a). There was 49% reduction in the mean number of steroid courses per patient per annum 6.1–3.1 ($p < 0.001$) (Fig. 3b).

3.4. Changes in asthma control

Omalizumab treatment improved asthma control in all patients. The mean (SD) ACQ7 scores improved from 4.0 (±0.9) at baseline to 2.3 (±1.2) on treatment ($p < 0.0001$)(42.5% improvement) (Fig. 4). There was a clinically meaningful (≥0.5) reduction in ACQ score in 19 out of 20 patients. However, the post-treatment mean (SD) ACQ7 score, 2.2 (±1.2), remained higher than the recommended good control level of ≤1.5 [34]. At baseline all included patients with available ACQ data (20/20) had an ACQ >1.5 compared to 9/20 (45%) on treatment with 11/20 (55%) achieving the good control level of ACQ7<1.5.