Query Details

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1. Please define CHOC if appropriate.

(the Clinical and Histological impact of treatment with Omalizumab in oral Corticosteroid-dependent patients with severe allergic asthma).

If this is too long , since the name of the study is defined in the body text, you can substitute in the section methos !CHOC! by "This".

This study is a randomized

2. Please confirm edits to this sentence "Omalizumab provided a slowing of forced expiratory...".

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3. Please confirm edits to this sentence "Monthly spirometry, FeNO measure...".

No, may be better

Monthly, a spirometry, FeNO measurement, daily OC dose, accumulated OC dose, recording of exacerbations and side-effects were assessed.

4. Please confirm the section headings are correctly identified.

No, 2.6.2.1 should be removed. These are measurements perforemed at the beginning and end of ths study as it is stated in the second line of this paragraph.

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Morphological study of bronchial biopsies (Transmission electron microscopy-TEM): The processing of biopsies for electron microscopy is described .....

5. Please confirm edits to this sentence "After removing extreme values from the control group...".

correct

6. Please confirm edits to this sentence "Twelve (75%) patients in the...".

correct

Original Research Article

Omalizumab in Severe Asthma: Effect on Oral Corticosteroid Exposure and Remodeling. A Randomized Open-Label Parallel Study

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Abstract

Introduction

Data on the clinical efficacy and remodeling of omalizumab therapy in patients on oral corticosteroids (OC) are limited.

Objective

The purpose of the study is to show that in patients with corticosteroid-dependent asthma, omalizumab is a corticosteroid-sparing therapy able to inhibit airway remodeling and to reduce disease burden (lung function impairment, exacerbations).

Methods

CHOC **AQ1** is a randomised open-label study evaluating the addition of omalizumab to the standard of care in patients with severe asthma receiving oral corticosteroids. The primary endpoint was represented by the change in OC monthly dose by the end of treatment and secondary endpoints included spirometry changes, airway inflammation (FeNO), number of exacerbations and airways remodelling assessed by bronchial biopsies studied by transmission electron microscopy. As a safety variable, adverse effects were recorded.

Results

Efficacy was assessed for 16 patients in the omalizumab group and 13 in the control group. The final cumulative mean monthly OC doses were 34.7 mg and 217 mg for the omalizumab and control group, respectively; the mean difference between groups adjusted for baseline was −148.1 [95% confidence interval (CI) −243.6, −52.5; $p = 0.004$]. OC withdrawal of 75% versus 7.7% ($p = 0.001$) was observed in the omalizumab and control group, respectively **AQ2** . Omalizumab provided a slowing of forced expiratory volume in one second (FEV_1) loss (70 mL versus 260 mL), a significant decrease in FeNO values and a reduction in the annual relative risk of clinically significant exacerbations of 54%. The treatment was well tolerated. The morphological study showed a significant decrease in basement membrane thickness in the omalizumab group (6.7 µm versus 4.6 µm) compared with controls (6.9 µm versus 7 µm) [mean difference between groups adjusted for baseline was −2.4 (95% CI −3.7, −1.2; $p < 0.001$], as well as a decrease in intercellular spaces (1.18 µm versus 0.62 µm and 1.21 µm versus 1.20 µm, $p = 0.011$, respectively). A qualitative improvement was also observed in the treated group.

Conclusions

Omalizumab showed a marked OC-sparing capacity and was associated with an improvement in clinical management that correlated with bronchial epithelial repair. In OC-dependent asthma, reversibility of remodelling is possible; the concepts that basement membrane enlargement is detrimental and that chronic airway obstruction is systematically irreversible are outdated (EudraCT: 2009-010914-31).

Christian Domingo and Rosa M. Mirapeix contributed equally to this work.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s40265-023-01905-5.

Key Points

The study shows the OC-sparing effect and restorative capacity on bronchial epithelium of a biological treatment.
Contrary to previously held beliefs, it shows that bronchial remodelling in patients with severe asthma is reversible with biologic therapy, despite a reduction in the dose of oral corticosteroids.
It allows reinterpretation of the histological changes found, so that the thickening of the basement membrane appears to be a protective reaction of the epithelium to exert the barrier function lost with the damage of the disease.
It reinforces the current idea of the importance of the bronchial epithelium in the pathophysiology of asthma (asthma as an "epithelial driven disease").

1. Introduction

Over the last 15 years, a new drug family has emerged for the treatment of severe asthma: the monoclonal antibodies (mAb). Initially recommended as the last step for treatment of severe uncontrolled asthma, recent guidelines now place mAb administration in front of that of oral corticosteroids.

The first mAb to be marketed was omalizumab, a humanised murine anti-IgE for allergic asthma [1, 2]. The pivotal studies were published at the beginning of this century [3, 4, 5, 6]. Since then, several other mAbs have been marketed [7]. The requirements for registration have evolved and become more strict: regulatory agencies now expect companies to demonstrate clinical benefits (decrease in

exacerbations and hospital admissions, improvement of pulmonary function testing, inhaled corticosteroid-sparing effect), not only in moderate/severe asthma, but in oral corticosteroid (OC)-dependent patients as well [8, 9, 10].

To date, a vast amount of papers have been published on omalizumab and have shown it to be well tolerated and clinically useful in the management of moderate/severe allergic asthma [3, 4, 5, 6]. In spite of this, the clinical information regarding certain aspects of the drug's activity is limited and the information on its performance in some specific situations, which have in fact been assessed in studies describing the development of more recent mAbs, is absent. Moreover, the information about the potential effects of mAbs on remodelling is scarce or absent.

To fill this gap, we designed a study to evaluate the Clinical and Histological impact of treatment with Omalizumab in oral Corticosteroid-dependent patients with severe allergic asthma (the CHOC study).

2. Material and Methods

The hypothesis to be tested was the following: omalizumab, an anti-IgE recombinant humanized monoclonal antibody, is a well-tolerated drug that aids the management of allergic corticosteroid-dependent patients with allergic asthma. Its strong points are: (a) it allows a reduction in OC intake, (b) it improves clinical management of patients by decreasing exacerbations and stabilizing pulmonary function and (c) it reverses histopathological changes in the bronchial wall, and also chronic inflammation.

2.1. Population

Patients were recruited from the asthma outpatient clinics of the pulmonary services at two hospitals (Hospital Parc Taulí and Hospital Clínico Universitario de Santiago de Compostela, Spain). Briefly, the study included adult corticosteroid-dependent patients with allergic asthma. The inclusion/exclusion criteria are described in the online resource 1. Briefly, the population studied comprised adult OC-dependent patients with allergic asthma eligible for omalizumab treatment who were not receiving specific immunotherapy.

2.2. Outcomes

Primary efficacy outcome includes (a) change in OC monthly dose by the end of treatment. Secondary efficacy outcomes include (a) spirometry changes, (b) airway inflammation [fraction exhaled of nitric oxide (FeNO)], (c) number of exacerbations and (d) reversibility of the histological changes in the bronchial mucosa. Safety outcomes include (a) adverse events related to drug treatment.

2.3. Type of Study

Phase IV, open-label randomised parallel study (EudraCT: 2009-010914-31) with two groups treated with best standard care receiving OC: the omalizumab group receiving omalizumab as add-on therapy and the control group not receiving omalizumab. Although the study had an open design, the pathologist and the clinicians were blinded to the clinical and pathological findings, respectively.

2.4. Stages of the Study

The study comprises three stages (online resource 2).

2.4.1. Stabilization Period

The stabilization period was planned to last at least 3 months. During this period patients received the best standard care for asthma according to the Global Initiative for Asthma (GINA) (Salmeterol/Fluticasone 50/500 Acuhaler® bid, montelukast 10 mg/once a day, OC and salbutamol on request). At the beginning of this period, patients receiving prednisolone were switched to 6-methyl-prednisolone (6-MP); 4 mg of 6-MP was considered equivalent to 5 mg of prednisolone. OC doses were progressively tapered (2 mg/day of 6-MP every 2 weeks) until a decrease of 10% or more in the forced expiratory volume in one second (FEV_1) was observed. The daily dose of 6-MP was then increased by 2 mg every 2 weeks until the FEV_1 returned to its previous levels and the process was repeated. At the third failed attempt to reduce the OC dose, we considered that the minimum dose required had been attained. A written informed consent was obtained.

2.4.2. Run-In Period

The run-in period was a 4-week period, before randomisation, after the patient had agreed to participate in the trial.

2.4.3. Follow-Up/Treatment Period

Patients were randomised to receive or not receive a subcutaneous dose of omalizumab. Omalizumab dose was based on body weight and initial serum immunoglobulin E (IgE) (approximately equal to 0.016mg/kg × body weight (in kg) × IgE (in International Units/mL) per 4 weeks for a 12-month period. During the treatment period, the oral corticosteroid decrease protocol followed was the same as during the stabilisation period; 6-MP was progressively tapered (2 mg/day every 2 weeks) until FEV_1 fell by 10% or more. The 6-MP dose was then increased to the previous dose until the FEV_1 returned to its previous levels. The procedure was repeated throughout the follow-up.

2.5. Randomisation

Patients were assigned to their group according to a randomisation list linked to a treatment arm. Patients were allocated to one arm or another according to a ratio of 1:1.

2.6. Study Protocol

2.6.1. Definition of Exacerbations

Exacerbations were classified into three groups. Mild exacerbations were those that required occasional (< 3 days) increase of OC and/or antibiotics. Moderate exacerbations included increase of OC intake (≥ twice the baseline dose) during ≥ 3 days and/or antibiotics plus unscheduled ambulatory visit. Severe exacerbations included increased OC intake (≥ twice the baseline dose) ≥ 3 days and/or antibiotics plus hospital admission.

2.6.2. Measurements

At the beginning and end of the study, the following tests were performed in each patient: skin prick test, spirometry, FeNO measurement, blood analysis (including IgE) and bronchoscopy with bronchial biopsies for morphological study via transmission electronic microscopy (TEM).

After 6 months, blood analysis was performed, including IgE levels **AQ3** .

Monthly spirometry, FeNO measurement, daily OC dose, monthly accumulated OC dose, recording of exacerbations and side-effects were assessed.

Technical details of every test can be found in the online resource 3 and 4.

2.6.2.1. Morphological Study of Bronchial Biopsies (Transmission Electron Microscopy—TEM)

The **AQ4** processing of biopsies for electron microscopy is described in the online resources 5–8. We studied the degree of the epithelial damage, focussing on the thickness of the basement membrane, the intercellular space of the epithelium and characteristics of the epithelium and cilia following standardised methods [11, 12]. The measurements were performed twice by the same EM expert, in two different time periods separated by a minimum of 3 months.

2.7. Sample Size Calculation

The sample size for this study was 28 randomised patients in each of two treatment groups. The sample size was calculated to achieve a power greater than 80% using a two-sided *z*-test at a significance level of 5% and based on the primary efficacy endpoint percentual change from baseline in monthly oral corticosteroids at the end of follow-up, expecting to find decreases of 50% [standard deviation (SD), 50] in the omalizumab group and 10% (SD, 50%) in the control group.

An interim efficacy analysis was planned after 50% of recruitment, that was oversaw by an independent data monitoring committee. Test boundaries were determined using the Pocock spending function (see Table S1 in online resource 9).

2.8. Statistical Analysis

Between-group differences in changes (end minus baseline) of continuous outcomes (both clinical and morphological) were analysed by means of linear regression models adjusting for basal measures. End-study measures from the morphological study were analysed by means of logistic regression models for dichotomous outcomes and proportional odds ordinal logistic regression models for ordered outcomes, adjusting for basal measures. Longitudinal analysis of all clinical measurements collected throughout the months of follow-up was performed by means of generalised linear mixed effects models, including interaction term between study group and follow-up time in all models allowing the groups' changes to differ over time. Annual exacerbation rate ratios (total and by severity) were estimated using negative binomial generalised linear models.

R version 4.2.0 was used for all analyses [13]. The mixed model function of the GLMMadaptive package [14] was used to fit the mixed-effects models, the vglm function of the VGAM package [15] was used to fit ordinal logistic models, the glm.nb function of the MASS package [16] was used to fit negative binomial models and results were visualized using the ggplot2 package [17].

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

2.9. Institutional Review Board Approval

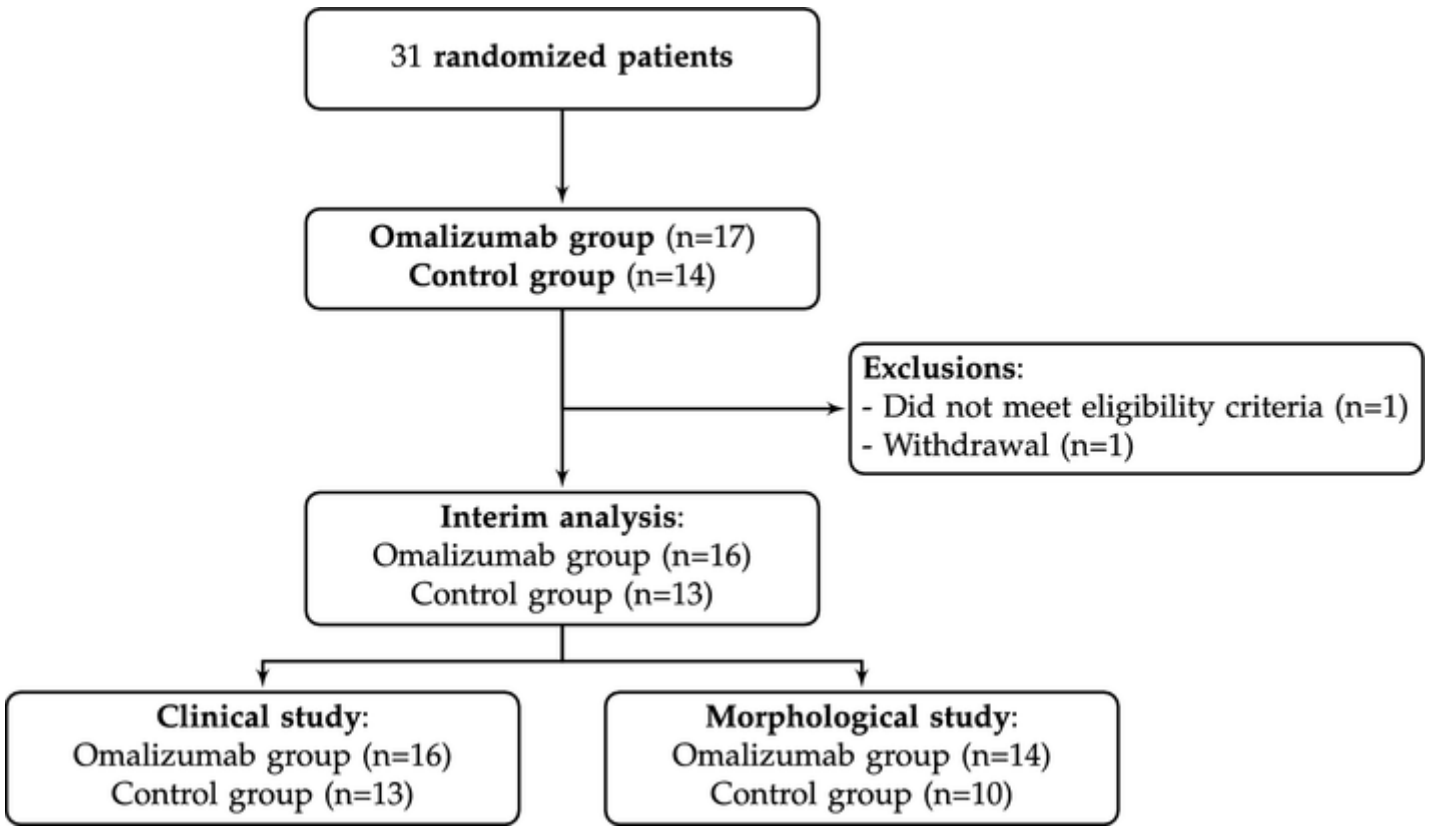
The study was approved by the Institutional Review Board of both hospitals. Written informed consent was obtained from every patient. The study was registered with EudraCT number 2009-010914-31. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

3. Results

Initially, 31 patients were randomised, of which two were excluded. The study was stopped for efficacy, with 16 patients in the omalizumab group and 13 patients in the control group, and proceeded to the analysis of the rest of the data (Fig. 1).

Fig. 1

Study flowchart



3.1. Clinical Results

At entry, both groups exhibited similar demographic and clinical characteristics (Table 1).

Table 1

Baseline data for omalizumab group and control group

	Omalizumab group	Control group
	N = 16	*N* = 13
Age, mean (SD)	47.2 (14.0)	46.5 (13.9)
Women, *n* (%)	11 (68.8%)	8 (61.5%)
FEV_1 (%), mean (SD)	78.4 (20.2)	79.8 (12.3)
FeNO (ppb), median (P25, P75)	18.0 (14.0, 38.0)	18.5 (14.5, 36.5)
IgE (IU/mL), median (P25, P75)	96.5 (71.2, 169)	145 (80.0, 332)
Monthly OC dose (mg), median (P25, P75)	150 (120, 248)	240 (90.0, 300)
Daily OC dose (mg), median (P25, P75)	4.5 (4.0, 6.5)	6.0 (4.0, 8.0)

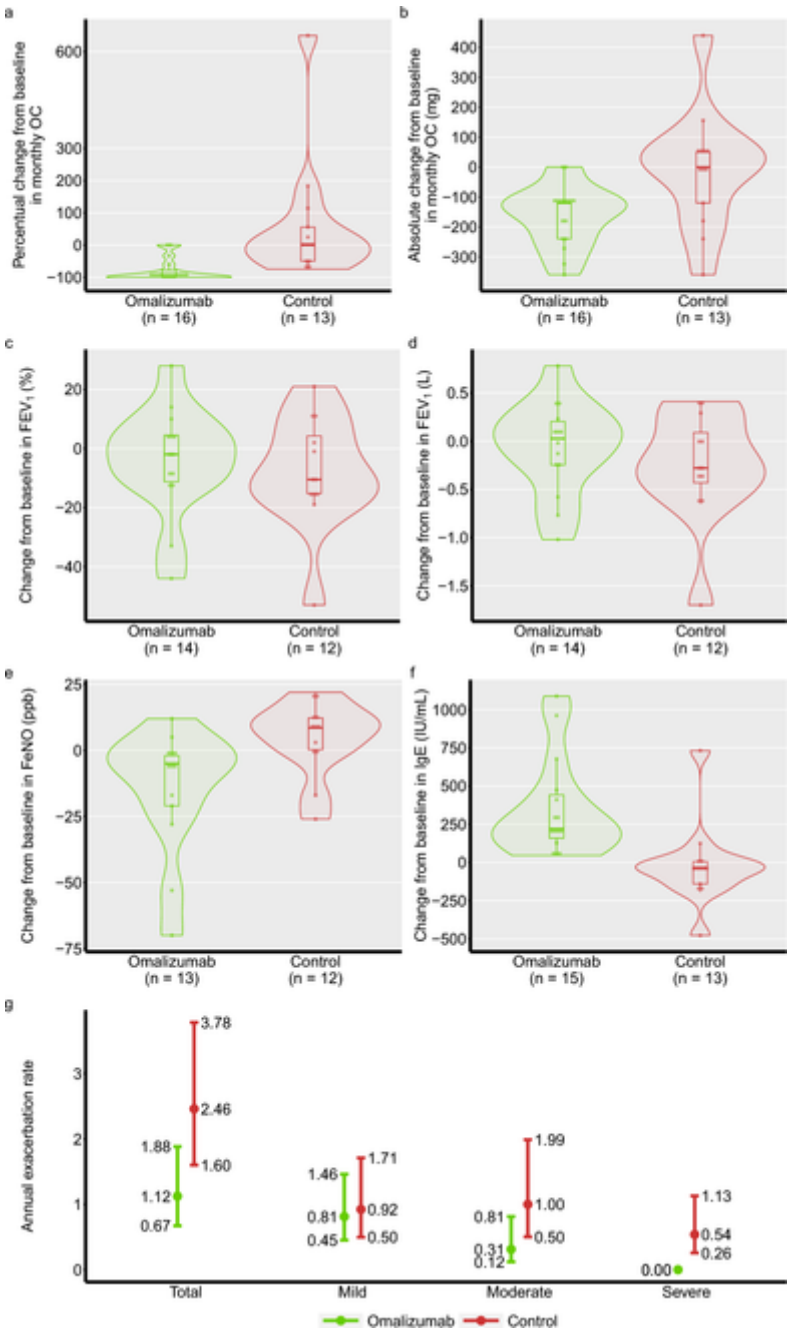
FeNO fraction of exhaled nitric oxide, FEV_1 forced expiratory volume in 1 s, *IgE* Immunoglobulin E, *OC* oral corticosteroid, *P25* 25th percentile, *P75* 75th percentile, *ppb* parts per billion, *SD* standard deviation.

3.1.1. Oral Corticosteroid Use

At the end of follow-up, mean monthly accumulated OC doses were 34.7 mg (SD, 81.6 mg) and 217 mg (SD, 186 mg) for the omalizumab and the control group, respectively. These figures corresponded to mean percentual changes from baseline of 79% less (SD, 36%) in the omalizumab group and 61% more (SD, 191%) in the control group (Fig. 2a) and the mean difference between groups adjusted for basal measures was −148.1 (95% CI −243.6, −52.5; $p = 0.004$). Mean absolute differences were −163.8 mg (SD, 102 mg) and −8.8 mg (SD, 196 mg) for the omalizumab and the control group, respectively (Fig. 2b); when adjusted for basal measures, mean difference between groups was −170.5 (95% CI −264.5, −76.5; $p < 0.001$). After removing extreme values from the control group as sensitivity analysis, the adjusted mean differences were −96.1 (95% CI **AQ5** −139.4, −52.9; $p < 0.001$) in percentual changes and −132.7 (−195.9, −69.5; $p < 0.001$) in absolute changes. Twelve (75%) patients in the omalizumab group and only 1 (7.7%) patient in the control group withdrew from OC treatment **AQ6** ($p = 0.001$).

Fig. 2

Changes from baseline in clinical outcomes at the end of follow-up and annual exacerbation rate by study group and severity. *FeNO* fraction of exhaled nitric oxide, FEV_1 forced expiratory volume in 1 s, *IgE* Immunoglobulin E, *OC* oral corticosteroid



3.1.2. Pulmonary Function Tests

Regarding pulmonary function, at the end of follow-up the control group lost 260 mL (SD, 580 mL) while the omalizumab group only lost 70 mL (SD, 480 mL) from baseline [mean difference between groups adjusted for basal measures: 226.2 (95% CI −185.7, 638.1), $p = 0.268$]. In percent scale, FEV_1 decreased 7.9% (SD, 19.1%) and 4.3% (SD, 18.3%) in the control and the omalizumab group, respectively [mean difference between groups adjusted for basal measures: 2.79 (95% CI −10.3, 15.9), $p = 0.662$] (Fig. 2 c, d).

3.1.3. Airway Inflammation

Significant difference between groups was found in change from baseline in airway inflammation measured by FeNO values [mean difference between groups adjusted for basal measures: −17.3 (95% CI −25.6, −8.94), $p < 0.001$], with a reduction of 14.8 parts per billion (ppb) (SD, 23.5 ppb) in the omalizumab group while the control group experienced an increment of 4.3 ppb (SD, 14 ppb) (Fig. 2 e). Note that mean final FeNO value in the omalizumab group was 17.7 ppb (normal value).

3.1.4. Immunoglobulin E Changes

Significant difference between groups was also found in change from baseline in IgE values [mean difference between groups adjusted for basal measures 425.8 (95% CI 199.5, 652.0), $p < 0.001$], observing a mean decrement of 20.8 IU/mL (SD, 268 IU/mL) in the control group and a mean increment of 355 IU/mL (SD, 320 IU/mL) in the omalizumab group (Fig. 2 F), equivalent to a mean ratio of 3.8 compared with baseline. Additional data are given in the online resource 10 (Figs. S1, S2, S3).

3.1.5. Exacerbations

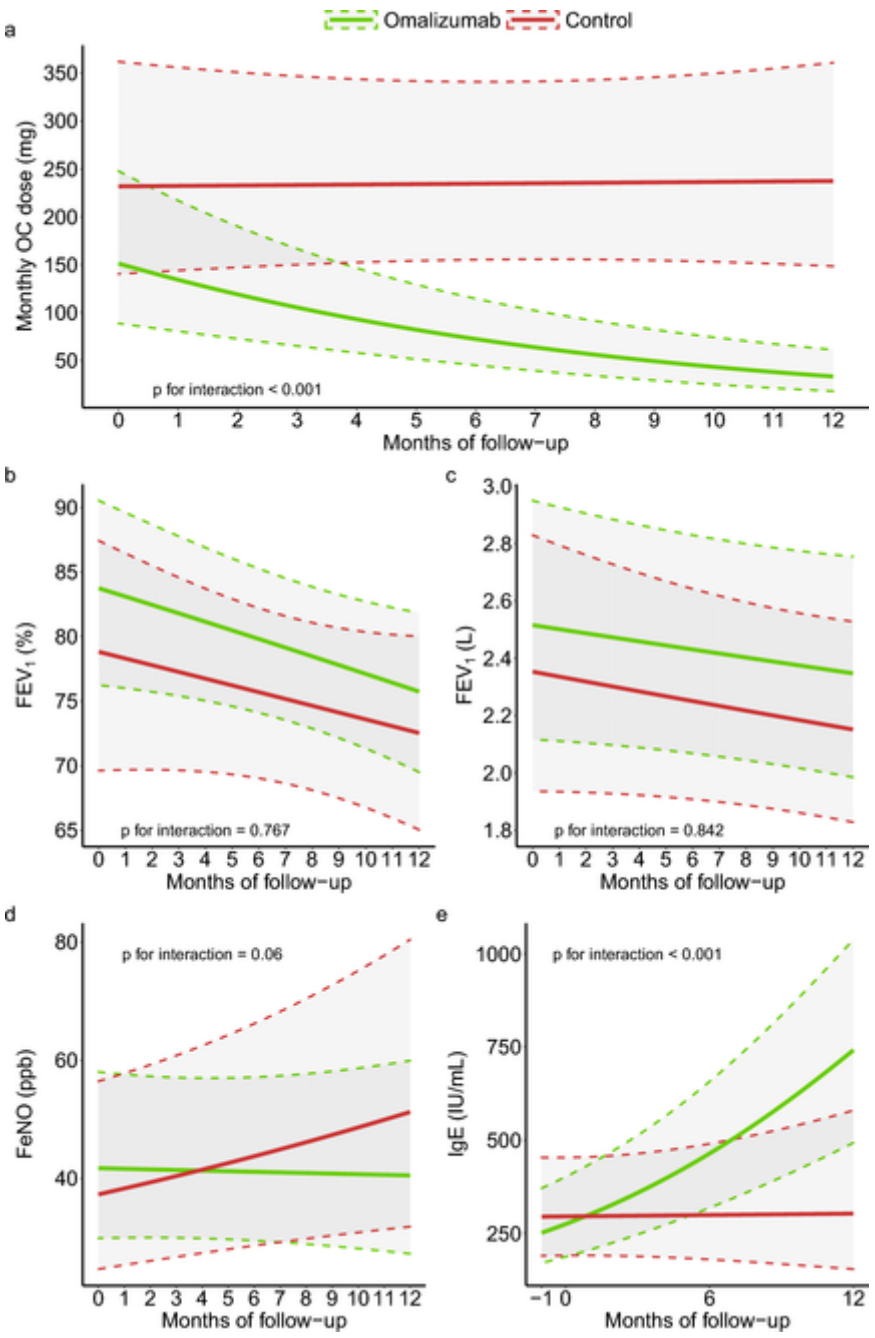
The estimated annual rates of clinically significant exacerbations were 1.12 (95% CI 0.67, 1.88) in the omalizumab group and 2.46 (95% CI 1.6, 3.78) in the control group Fig. 2 g). Thus, compared with the control group, the annual exacerbation rate ratio was 0.46 (95% CI 0.23, 0.89). The annual relative risk reduction was 54%. By severity, the annual rate ratio for mild exacerbations was 0.88 (95% CI 0.37, 2.1), and for moderate exacerbations, it was 0.31 (95% CI 0.09, 0.97). No severe exacerbations were observed in the omalizumab group during follow-up. Mean duration of the exacerbations was 13 days (SD, 14.8 days) in the omalizumab group and 31 days (SD, 33.6 days) in the control group ($p = 0.093$). Additional data are given in the online resource 10 (Figs. S4, S5).

3.1.6. Longitudinal Trends of the Clinical Outcomes by Study Groups

The longitudinal analysis showed that lung function, airways inflammation and OC cumulative monthly dose had constantly more favourable trends in omalizumab group (Fig. 3) (interaction term $p < 0.001$). As expected, IgE levels increased over time for the omalizumab group, but not for the control group (see also Fig. S6 in the online resource 10).

Fig. 3

Longitudinal trends of clinical outcomes by study group. *FeNO* fraction of exhaled nitric oxide, FEV_1 forced expiratory volume in 1 s, *IgE* Immunoglobulin E, *OC* oral corticosteroid



3.2. Morphological Study

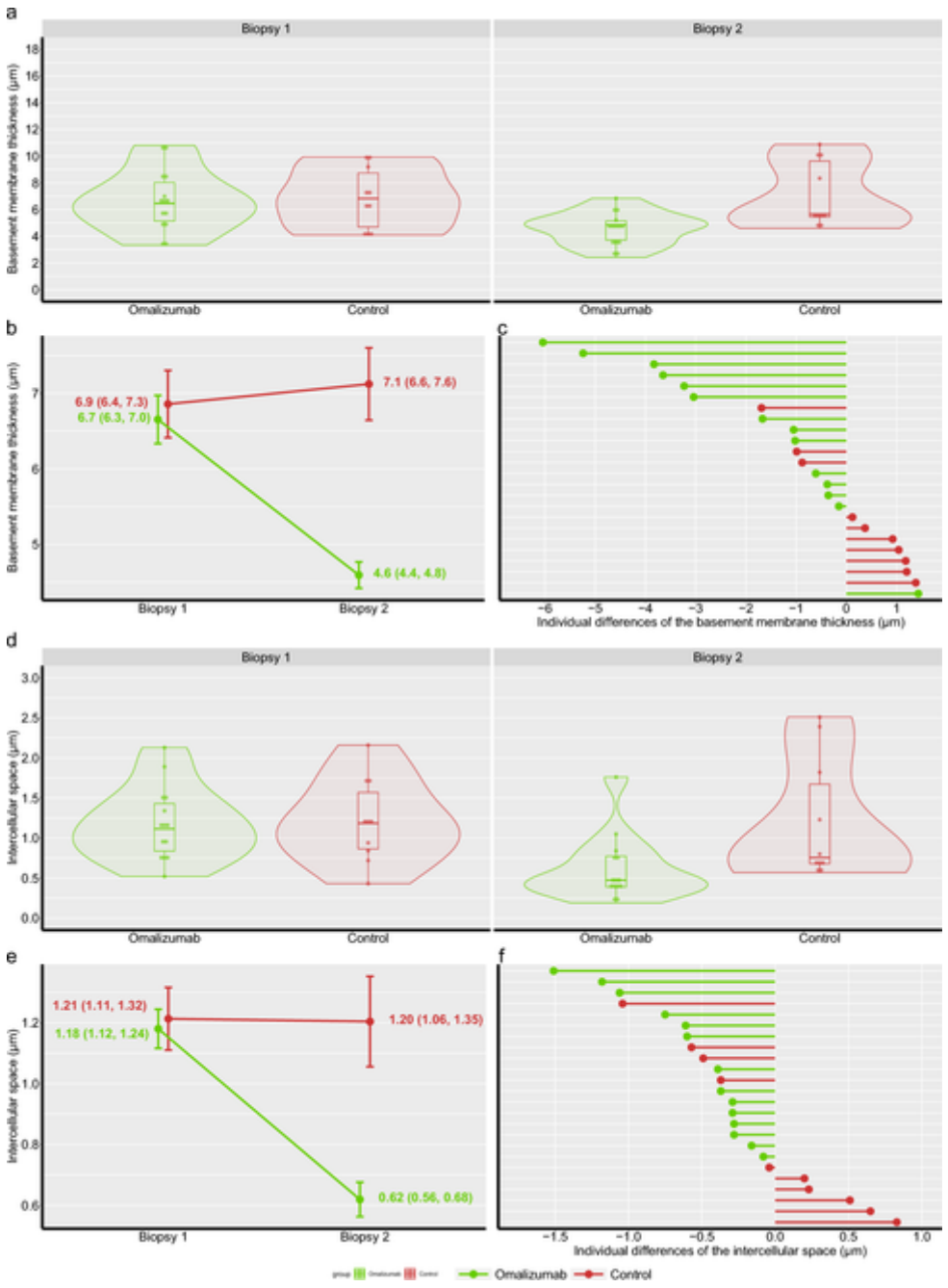
No statistically significant differences were observed between the two groups at entry in any of the parameters studied.

3.2.1. Thickness of the Basement Membrane (BM)

Figure 5 shows the thickening of BM. The omalizumab group showed a marked decrease in BM thickness, while controls presented a slight increase [mean difference between groups adjusted for basal measures −2.4 (95% CI −3.7, −1.2), $p < 0.001$]. The decrease in BM thickness occurred in 13 out of 14 patients (92.9%) of the omalizumab group and in only 3 out of 10 (30%) of the control group (Fig. 4).

Fig. 4

Transmission electron microscopy outcomes

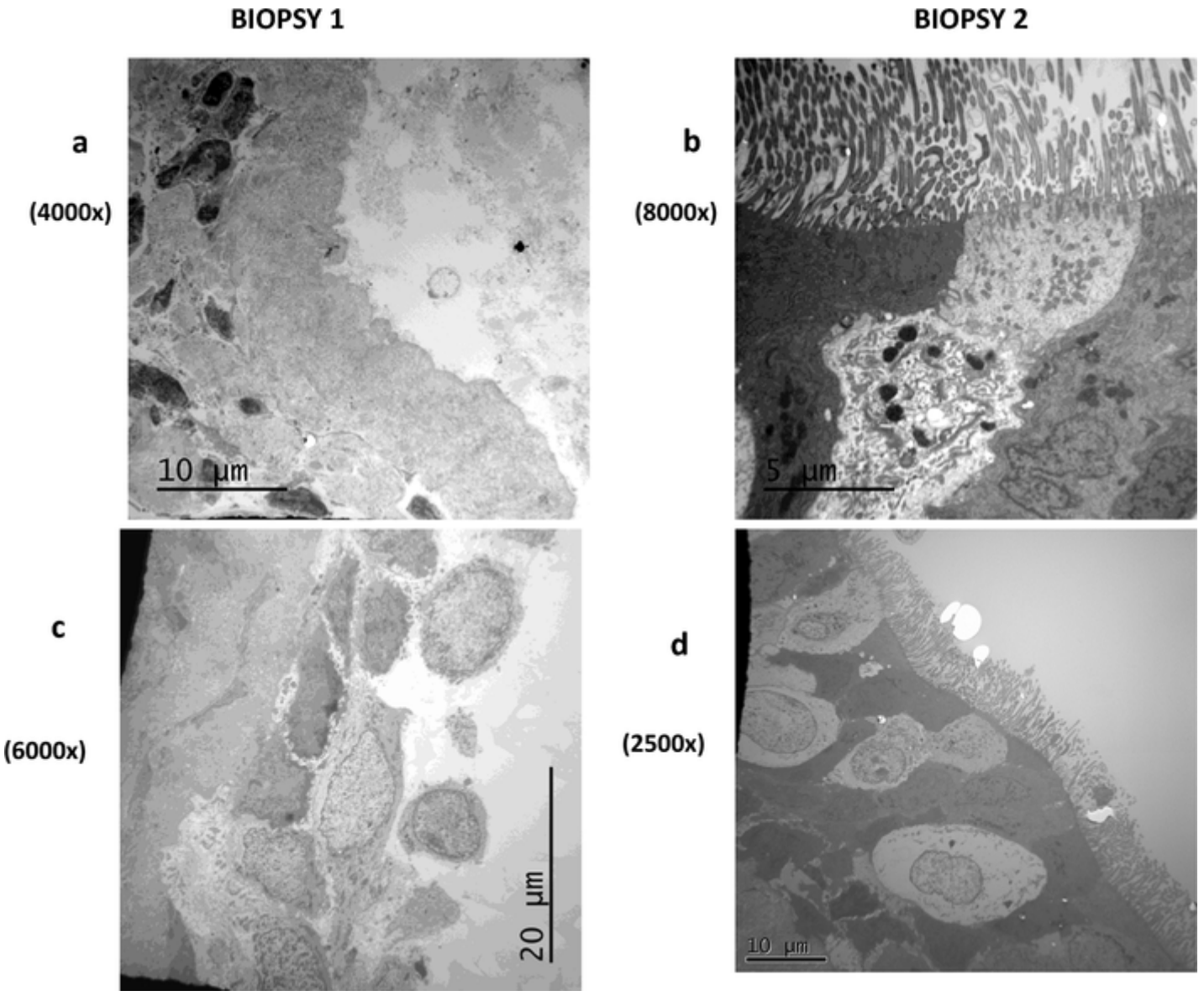


3.2.2. Intercellular Space

Similar to thickness of the BM, the omalizumab group showed a marked decrease in intercellular spaces, and controls remained stable [mean difference between groups adjusted for basal measures −0.56 (95% CI −0.98, −0.14), $p = 0.011$]. In the omalizumab group all patients presented reductions in the intercellular space compared with only 5 out of 10 controls (Figs. 4, 5).

Fig. 5

Improvement in epithelial damage in the omalizumab group. Note the changes in the bronchial biopsy before and after 1 year of omalizumab treatment. **a** The thickening of the BM and the absence of bronchial epithelial cells. **b** The return to normal, disappearance of intercellular spaces and reappearance of cilia. **c** The initial biopsy from another patient, showing the disappearance of cilia, the appearance of intercellular spaces and denudation of cells. **d** Twelve months after omalizumab treatment, a picture of normal ciliated epithelium with palisade cells and reappearance of cilia



3.2.3. Damage to the Epithelium and Cilia Description

We observed considerable detachment of the bronchial epithelium (Fig. 5). In the first biopsy (at entry), patients in the omalizumab group showed more severe damage in the epithelium (two patients showed a total loss of the columnar epithelium) than patients in the control group, although there were no statistically significant differences between groups (online resource 10, Fig. S7). Statistically significant differences were found between groups at the end of the study adjusting for basal damage ($p = 0.0499$). Additionally, a higher percentage of improvers during the follow-up in the omalizumab group (64.3%) than the control group (20.0%) was observed (online resource 10, Fig. S8). The two patients of the omalizumab group who showed a total loss of the columnar epithelium at entry showed reappearance of the columnar cells, although some detachment was still present.

Regarding the extent (focal or extensive) of the damage to the epithelium, the percentage of patients in the omalizumab group with focal involvement increased from 35.7% to 50% at the end of the study, while in the control group the percentage of patients showing extensive involvement notably increased from 70% to 90% (online resource 10, Fig. S9). Nevertheless, adjusting for basal measures, no statistically significant difference between groups at the end of the study was observed ($p = 0.064$). Finally, regarding the qualitative evaluation of the changes observed in the cilia, the percentage of patients in the omalizumab group with no absence or focal absence increased from 35.7% to 71.4% at the end of the study, while in the control group these figures decreased from 50% to 40%. Adjusting for basal measures, a statistically significant difference between groups at the end of the study was observed ($p = 0.038$).

In the initial and final biopsies, we observed some ultrastructural abnormalities, such as axoneme bubble, presence of only one singlet and supernumerary singlets, presence of compound cilia and ciliary oedema and ciliary disorientation. Abnormalities present in the first biopsy persisted in the second biopsy, independently of the group. When ciliogenesis occurred in the second biopsy (mainly in the omalizumab group), ultrastructural abnormalities were rare, except for the presence of some ciliary disorientation (Fig. S10).

3.3. Side Effects

Regarding side effects, the treatment was well tolerated and there were some side effects reported in the online resource 11. Only arthromyalgia, which persisted at the end of the treatment, could be considered a drug-related side effect. None of the patients abandoned the treatment.

4. Discussion

The purpose of our study was to elucidate the clinical and histological benefits of a 1-year treatment with omalizumab in the most severe population of patients with asthma, namely those who were OC-dependent. Omalizumab has demonstrated its inhaled corticosteroid (ICS)-sparing capacity, but there were no randomised clinical trials designed to show its OC-sparing capacity. The Cochrane Review [18] concluded that omalizumab treatment was associated with a significant probability of reducing inhaled corticosteroid doses or of withdrawing them completely. The mean dose reduction was −118 µg equivalent of beclomethasone dipropionate. In the subgroup of patients who received oral steroids, it was not clear whether this benefit occurred. In a subgroup analysis of an open-label parallel group study, Siergiejko et al. [19] found that at week 32, 62.7% of patients in the treated group were able to stop or reduce OCs compared with 30.4% of controls. The real-life study eXpeRience [20] found a relative reduction of 50% at month 24, and APEX (a UK retrospective study) found a 34% reduction in the mean total quantity of OCs prescribed per year and complete cessation of OC use after 12 months in 48% of patients [21]. In a 2-year observational prospective study [22], we found that omalizumab allowed OC withdrawal in 74.2% of

patients. It is normally considered that real-life studies obtain better results than randomised clinical trials, but CHOC presented results of the same order as the best real-life studies.

One of the key parameters used by regulatory agencies for registering a mAb is its capacity to decrease the rate and the severity of exacerbations. The INNOVATE study [23] showed that the clinically significant exacerbation rate (the primary efficacy variable), adjusted for an observed imbalance in exacerbation history, was 0.68 with omalizumab and 0.91 with placebo (26% reduction) during the 28-week treatment phase. Without adjustment, a similar magnitude of effect was seen (a reduction of 19%), although it did not reach statistical significance. In our study, the annual exacerbation rate ratio showed a 54% reduction of total exacerbations. Regarding severe exacerbations, the INNOVATE [23] study showed a 50% annualised reduction. In our study none of the omalizumab patients presented severe exacerbations during follow-up. In addition, in our study the duration of the exacerbation was halved. To summarise, our data show that omalizumab helped to reduce exacerbations, especially the most severe ones.

Two real-life studies involving OC-dependent patients (eXpeRience registry [20] with 28.1% of patients receiving OC and in the Xpertise trial [24] with 46%) showed a decrease in exacerbations of above 80%.

In addition to exacerbations, some studies have measured the emergency room visits or hospitalisations. The INNOVATE [23] study, in which OC-dependent patients accounted for 22% of the sample, and 78% were on inhaled corticosteroids, reported an annualized 44% reduction in emergency room visits. In a real-life study, Molimard et al. [25] found a 65% reduction in annual emergency visits, following omalizumab therapy. In Germany, in a population of 280 patients of whom 46% were OC-dependent, Korn et al. [24] reported an 82% reduction in exacerbations and a 78% reduction in hospitalisations. In our study, emergency visits were addressed indirectly. Exacerbations were defined as severe if they required hospital admission. The absence of severe exacerbations in the omalizumab group indirectly reflects the absence of hospitalizations, despite the decrease or withdrawal of OCs.

Another purpose of a biological treatment is to improve or minimize the loss of lung function. In OC-dependent patients, the main point is to demonstrate this at the same time as the reduction in OC use. The Normansell Cochrane Review [18] included two studies with 732 participants and showed a significant difference in the mean improvement of FEV_1 compared with baseline in moderate/severe asthma (67.29 mL). The eXpeRience trial [20] showed an improvement in FEV_1 of 8.7% after 2 years. No information is available on pulmonary function testing changes in OC-dependent patients. We observed FEV_1 losses of 70 mL in the treated group and 260 mL in the control group. We regard these differences as being clinically relevant. After 1 year of treatment, omalizumab was able to slow down the loss of lung function in the most severe group of patients, although the loss continued to be higher than expected in a healthy population. There are two possible explanations for this finding: the limited follow-up (maybe a longer treatment period might bring down the loss of FEV_1 to within normal limits) or the limited effect on the thickness of the smooth muscular layer.

The changes in airway inflammation are represented by FeNO values. FeNO reflects the activity of IL13 which is released by Th2 lymphocytes, as well as innate lymphoid cells. Significant changes were observed at the end of the follow-up. Moreover, in the omalizumab group, the final mean FeNO value was within normal limits (below 25 ppb, the value specified by GINA for diagnosis of a type 2 asthma). Thus, omalizumab treatment clearly contributed to down-regulating the bronchial inflammation, despite the decrease in OC intake. In the control group, the increased FeNO values reflect the activity of the Th2 cascade and/or the persistence of the stimulus of alarmins, whose release did not diminish because the integrity of the bronchial ciliated epithelium did not improve.

Finally, as expected, there was a marked increase in blood IgE concentration, reflecting the treatment with the anti-IgE blocker [22]. Regarding safety, no relevant side effects related to treatment occurred that limited the treatment with omalizumab.

The histological study of the bronchial biopsies was performed by electronic microscopy [26, 27]. In the last two decades, the histopathological changes that occur in asthma have attracted attention. Initially, inflammation was identified as the main pathophysiological cause of chronicity of the disease. Later, attention has focussed on the disruption of bronchial epithelium [26] and the loss of cilia and thickening of the basement membrane of the epithelium [27] (especially the reticular layer).

The histological improvement observed in our study was dramatic. At entry, a marked denudation of the bronchial mucosa was observed, with loss of cilia, increased intercellular space and cell loss. The BM was also markedly thickened, but treatment with omalizumab reduced its thickness. BM thickening has traditionally been considered to be irreversible once it occurs. Riccio et al. [28] in a study without a control group already suggested that some degree of reversibility could occur as a result of omalizumab treatment. Our study is the first to establish that this benefit occurs after omalizumab in comparison with a control group. The BM enlargement probably develops as a protective mechanism, with the allergen or other impurities on one side and the antigen presenting cells on the other. The thicker the BM, the less likely the interaction between external noxae and subepithelial cells. Considering that the barrier function of the bronchial epithelium is markedly impaired, the thickening of the BM may contribute to regulating the deterioration of asthma. The bronchial cells are normally next to each other and there is no intercellular space, and desmosomes help to maintain the structure and the barrier function of the epithelium. One of the first disorders that occurs in cells is the loss of cilia, and subsequently, the loss of their function as cleaners of the mucosa, meaning that pollutants, allergens and viruses are able to remain in the airway. The appearance of intercellular space is a sign that precedes the absolute denudation of the mucosa. In some patients the cell loss is total; the BM comes into direct contact with the airway lumen and is exposed to pollutants, viruses and allergens. At this point, the functions of the bronchial epithelium break down. Although chronic treatment with OC has shown a certain reparative effect in some patients, the benefits observed in most of the patients receiving omalizumab were notably greater. These morphological changes should help to improve asthma control, decrease exacerbations and achieve other clinical benefits, in some cases allowing the withdrawal of the drug [29]. Thus, our results challenge the belief that chronic remodelling is irreversible, that the thickening of the BM is harmful and that chronic airway obstruction, when present, is irreversible [30].

There are several possible explanations for these morphological changes. In vitro studies have shown that several cells, especially smooth muscle cells, have receptors for IgE. This causes hyperplasia and hypertrophy of the smooth muscle layer [31]. The presence of IgE has

also been shown to favour the depositing of collagen fibres and extracellular matrix [32]. The blockade of the binding of IgE to its receptor prevents or postpones these deposits [32]. The remodelling caused by the presence of IgE can also be prevented by omalizumab [33]. This has a synergistic effect with the blockade of acetylcholine which also favours the deposition of extracellular matrix [34]. It should be noted that the influence of IgE in the remodelling process occurs in the absence of allergens. The blockade of IgE postpones these changes and the histological changes are manifested in a decrease in the thickness of the bronchial wall [35] or, in some cases, a complete reversibility of the airway obstruction [36]. Finally, the repair of the bronchial epithelium contributes to a decrease in the release of alarmins, thus limiting their harmful effect.

The most important limitation of the study is the lack of placebo in the control group. We could not obtain an oily solution similar to omalizumab, and thus we would have had to use a placebo that would have had a very different appearance. Since the nurses collaborating in the study in charge of treatment administration would have easily differentiated the placebo from omalizumab, and the treatment was administered at the hospital day unit (where patients on biologics are usually treated), the possibility that patients would have identified the treatment/placebo was very high. Therefore, we thought it was better to plan the study as a parallel randomised but open-label study. To minimise the influence of the lack of placebo in the interpretation of the results, the pathologist, as well as the clinicians, were blinded to the clinical and pathological findings, respectively.

5. Conclusions

In summary, CHOC fills in some of the gaps in the literature regarding the benefits omalizumab can offer in OC-dependent patients with allergic asthma. It is the first randomised study to show the clinical benefits of omalizumab, including the slowing down the loss of respiratory function, despite the OC decrease. Moreover, it is also the first study to show the histological abnormalities that occur in patients with severe allergic asthma with chronic OC treatment, and the capacity of omalizumab to facilitate the repair of the bronchial epithelium, given that some of the patients returned to normality. It thus prompts us to rethink the interpretation of remodelling changes and to abandon the widespread idea that chronic remodelling is irreversible. The histological recovery of the bronchial mucosa can help to explain the improvement in clinical management of the patients [35] and also the feasibility of withdrawing omalizumab in certain patients [29]. This would be in line with the current view on the importance of the bronchial epithelium in the pathophysiology of severe asthma [37].

The results of the CHOC study invalidate the current interpretations of the data. The idea that BM thickening is detrimental can be considered outdated and erroneous. This process occurs in order to replace the barrier or protective function of the bronchial epithelium, which is damaged in patients with asthma. Taken together, the results lead us to conclude that omalizumab is a disease-modifying drug. Finally, the concept of remission has recently been introduced. Future research may clarify whether the changes observed in CHOC can help explain the clinical remission achieved by some patients [38].

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Declarations

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Conflicts of Interest C.D. declares having received financial aid for travel support and speakers bureaus from Novartis, Sanofi, GSK, TEVA, MSD, Esteve, Almirall, Astra-Zeneca, Chiesi, Menarini, Pfizer, Ferrer, Stallergenes, ALK-Abelló, Allergy therapeutics, Hall Allergy, Inmunotek and Roxall. R.M.M., C.F. and F.G. declare that they have no conflicts of interest. No authors have any conflict of interest in relation to this study.

Availability of data and material The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval The study was approved by the Institutional Review Boards of both hospitals. Written informed consent was obtained from all patients. The study was registered with EudraCT number 2009-010914-31. The study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to participate Written informed consent was obtained from all patients.

Consent for publication Written informed consent was obtained from all patients.

Authors' contributions C.D.: conceptualization, funding acquisition, data curation, methodology, project administration, resources, supervision, verification, visualization and writing original draft. R.M.M: conceptualization, data curation, methodology, resources, supervision, verification, visualization and writing original draft. F.J.G.B.: data curation, resources, verification and writing—review and editing. C.F.: formal analysis, methodology, visualization and writing—review and editing. F.P.: data curation, resources, verification and writing—review and editing. All authors have read and approved the final version of the manuscript, and agree to be accountable for the work.

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Supplementary Information

Below is the link to the electronic supplementary material.

Supplementary file 1 (PDF 1949 KB)

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