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# Long-term "real-life" safety of omalizumab in patients with severe uncontrolled asthma: A nine-year study

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ABSTRACT

*Background:* Randomized Controlled Trials showed that omalizumab exhibited a good safety and tolerability profile in patients with moderate-to-severe asthma. However, safety data of long-term treatment with omalizumab are scarce. Our aim was to assess the safety of omalizumab in patients under long-term treatment in a real-life setting.

*Methods:* Difficult-to-control asthmatic patients treated with omalizumab up to 9 years were retrospectively evaluated. Mild to severe adverse events any and reasons for discontinuation were recorded.

*Results:* Ninety-one patients (26.4% males, mean age 49.9 ± 14.9 years) were included: mean treatment length, 3.8 ± 2.6 years; mean individual monthly dose, 514.5 ± 345.7 mg (range, 150–1200 mg). A total of 10,472 single injections were given cumulatively to the 91 patients (115 single injections per patients, on average, over a treatment period up to 9 years). Fifty-nine patients (64.8%) were treated for a period of time from 3 to 9 years, 14 of whom from 6 to 9 years. A high proportion of patients who discontinued treatment dropped out within the first year (18, 39.1%), mainly for reasons unrelated to treatment. Six patients (6.6%) discontinued omalizumab for treatment-related adverse events: arthralgia/myalgia (3 patients); urticaria, angioedema (1 patients); metrorrhagia (1 patient); relapsing *herpes labialis* (1 patient). Four other patients complained of mild adverse events (rhinitis/conjunctivitis, injection site reaction, fatigue, thrombosis) but continued the treatment. Anaphylaxis was not reported.

*Conclusions:* Long-term treatment with omalizumab appears remarkably safe and well tolerated in real-life setting. Prolonged omalizumab treatment for many consecutive years did not increase the risk of side effects, particularly anaphylaxis.



## 1. Introduction

Omalizumab is a monoclonal antibody indicated as add-on therapy for the treatment of adolescent and adults with severe asthma inadequately controlled, despite optimal treatment with high-dose inhaled corticosteroids (ICS) plus long-acting $\beta_2$-agonists (LABA) [1].

In Randomized Controlled Trials (RCTs) the efficacy of omalizumab was shown over a relatively short treatment period of time, ranging from 16 to 60 weeks [2–6]. With regard to safety profile, omalizumab was found to be generally well tolerated with a frequency and severity of adverse events (AEs) similar to that seen in patients receiving placebo or best available therapy [7].

Data on efficacy and safety from real-life observational studies are consistent with the results of RCTs [8]. However, the majority of real-life studies reported data collected over a period ranging from 1 to 2 years [9–18]. Only a few reports with a longer observation period are available: the Tzortaki 2012 study analyzed a cohort of 60 patients with a 4-year treatment period [19]; the Tiro 2013 study reported data of 47 patients who completed a 3-year treatment course [20]. Particularly, the long-term safety of omalizumab was

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assessed in the Epidemiological Study of Xolair Evaluating Clinical Effectiveness and Long-Term Safety in Patients with Moderate-to-Severe Asthma (EXCELS). The first results of this long-term (≤5 years) cohort study, pertaining the cardiovascular and cerebrovascular adverse events [21] and the risk of cancer [22], were recently published.

Here we report on safety data from 91 consecutive patients with poorly controlled severe asthma treated with omalizumab up to 9 years. With this observational study we assessed the frequency and severity of treatment-related AE over a considerably long treatment period of time and analyzed the reasons for discontinuation.

## 2. Material and methods

### 2.1. Patients

This real-life retrospective analysis was conducted in two tertiary referral Asthma Centers in Southern Italy (at the University Hospital of Bari and the University Hospital of Foggia, respectively).

Between March 2007 and March 2016, 91 patients with uncontrolled severe persistent asthma were treated with omalizumab. Patients with a history of variable respiratory symptoms and variable airflow limitation, as shown by Forced Expiratory Volume in 1 s ($FEV_1$)/FVC reduction <80% and positive broncodilator reversibility test (increase of >12% and 200 mL from baseline after 400 mcg salbutamol), were diagnosed as having asthma. Severe asthma was defined as "asthma that requires Step 4 or 5 treatment, e.g. high-dose ICS/LABA, to prevent it from becoming 'uncontrolled', or asthma that remains 'uncontrolled' despite this treatment, when the patients have been on regular controlled treatment for several months, as indicated by GINA 2017 report [1]. No patients with Asthma COPD Overlap Syndrome was treated with omalizumab.

The 91 patients were retrospectively assessed for side effects and any reasons for discontinuation. Data were collected from patients' medical records that were prospectively filled during the follow-up visits. Patients were selected for add-on treatment with omalizumab based on: age (≥12 years); positive skin prick tests or *in vitro* tests for at least one perennial allergen; total serum IgE levels between 30 and 1500 kU/L; body weight between 20 and 150 Kg; reduced lung function ($FEV_1$ <80% predicted); frequent daily and nocturnal symptoms and severe exacerbations (defined as an acute or sub-acute worsening in symptoms and lung function from the patient's usual status), including hospitalizations and access to emergency room, despite high dose of ICS and LABA.

Omalizumab was administered subcutaneously at the dose calculated taking into account the patient's pre-treatment total IgE serum level and body weight [23]. Depending on the dose, omalizumab was administered either every 2 or every 4 weeks. The ICS/LABA dosage during the treatment period was the maximum tolerated (GINA step 4 or 5).

All patients treated with omalizumab at least once (one single administration session) were considered for tolerability and safety evaluation.

AEs were considered treatment-related if: 1) occurred within 1–5 days from the exposition to the drug (for AEs already described in the literature); 2) disappeared after drug discontinuation and occurred again after resuming drug administration following a washout period (for AEs not described in the literature previously).

All patients included in the study signed an informed consent form. The study was conducted according to Good Clinical Practice and in observance of the Declaration of Helsinki with successive modifications. The study was approved by the Ethical Committee of one of the institutions involved (University Hospital of Foggia).

### 2.2. Statistical analysis

Data description was primary based on means and standard deviations (SD), range, or frequencies for categorical endpoints. Comparisons between means were made using the Student's t-test. Crude comparisons of frequencies were made using 2 × 2 contingency tables, analyzed by the $\chi 2$ test. The whole analysis was performed by R 3.3.2 (R Core Team, 2016) [24].

## 3. Results

The clinical characteristics of the study population and the type of pharmacological treatment before starting omalizumab are reported in Table 1. Ninety-one patients (mean age 49.9 ± 14.9 years; 26.4% males; mean duration of asthma from initial diagnosis: 22.3 ± 15.6 years) with severe persistent asthma (mean $FEV_1$, 1.8 ± 0.7 L, 61.8% ± 22.9% predicted), poorly controlled with conventional treatment, were consecutively enrolled from March 2007 to March 2016. In particular, these patients lamented 2.1 ± 2.7 yearly exacerbations requiring oral corticosteroids, on average (prior to starting omalizumab). Three out of 91 had used oral corticosteroids as controller therapy in the 12 months prior to omalizumab. Moreover, 71 (78%) of these patients had used rescue medication (salbutamol) more than twice a week in the 12 months prior to omalizumab. The mean total IgE level prior to treatment with omalizumab was 380.1 ± 424.2 kU/L, whereas the mean body weight was 74.8 ± 20.4 Kg. Seventeen out of 91 patients (18.7%) had a smoking history, 3 of whom were current smokers (Table 1).

From March 2007 to March 2016, a total of 10,472 omalizumab single administrations were given cumulatively to the 91 patients (115 single injections per patients, on average, over a treatment period up to 9 years).

The 91 patients analyzed were treated for an average of 3.8 ± 2.6 years (range 0.2–9 years), with 32 (35.2%) of them for less than 3 years, 45 (49.4%) for 3–6 years and 14 (15.4%) for more than 6 years. The mean individual omalizumab monthly dose was 514.5 ± 345.7 mg (range, 150–1200 mg). Finally, 43 of patients (47.3%) received administrations every two weeks.

Notably, out of 10,472 single injections, no immediate systemic reactions (anaphylaxis or generalized urticaria) were observed. Immediate local reactions were noted only in one patient, who received 398 injections in total. Thus, approximately 6 months from the start of the treatment, reactions consisting in injection site swelling (wheals at the injection site; 2–3 cm in diameter), when the patient had received already 44 injections, were noted only once. Successively, moderate pain at the injection site was reported at each injection session (354 out of 10,472 injections; 3.4%).

A certain number of delayed treatment related AEs was registered, leading to 6 drop-outs (6 out of 91 patients, 6.6%) (Table 2). These treatment-related AE leading to discontinuation were: arthralgia/myalgia (3 patients: one discontinued the treatment during the first year; another during the second year and the last during the eighth year); delayed urticaria and angioedema (1 patient, who discontinued the treatment during the third month); metrorrhagia (one patient, who discontinued the treatment after four years); relapsing *herpes labialis* (one patient, who discontinued the treatment after two years) (Table 2). Another patient discontinued the treatment only temporarily (18 months), due to persistent arthralgia. During the discontinuation period, the rheumatic symptoms subsided, but the respiratory conditions and the functional parameters deteriorated markedly, inducing the patient to ask for the treatment to be resumed. Side effects reappeared, but were mild enough to be tolerated for the following 63 months.

Besides the injection site pain described above as an immediate local reaction, other 3 patients complained of mild to moderate

**Table 1**
Clinical characteristics of the patients prior to omalizumab.

| | Patients N = 91 |
|---|---|
| Mean age ± SD, yr | 49.9 ± 14.9 |
| Median (range) | 48 (12–70) |
| Age distribution, n (%) | |
| < 60 | 72 (79.1) |
| ≥ 60 | 19 (20.9) |
| Men, n (%) | 24 (26.4) |
| Mean body weight ± SD, Kg | 74.8 ± 20.4 |
| Median (range) | 74 (24–152) |
| Mean body mass index ± SD, Kg/m$^2$ | 28.4 ± 8.6 |
| Median (range) | 27,15 (18–39.5) |
| Mean total serum IgE level ± SD, kU/L | 380.1 ± 424.2 |
| Median (range) | 251 (32–2237) |
| Mean $FEV_1$ ± SD, L | 1.8 ± 0.7 |
| Median (range) | 1.8 (0.8–3.3) |
| Mean $FEV_1$ ± SD, % predicted | 61.8 ± 22.9 |
| Mean duration of asthma ± SD, yr | 22.3 ± 15.6 |
| Median (range) | 15 (1–45) |
| Mean asthma exacerbations requiring systemic corticosteroid treatment in the 12 months before omalizumab (SD), n | 2.1 ± 2.7 |
| Median (range) | 2 (0–12) |
| Patients using concomitant oral corticosteroids in the 12 months before omalizumab, n (%) | 3 (3.2) |
| Patients using rescue medication (salbutamol) in the 12 months before omalizumab, n (%) | 71 (78) |
| Smoking history: current smokers/former smokers, n (%) | 3(3.3)/14(15.4) |
| Allergic rhino-conjunctivitis, n (%) | 73 (80.3) |
| Other allergies (food allergy, drug allergy), n (%) | 8 (8.8) |

Yr, year; SD, standard deviation; $FEV_1$, forced expiratory volume in 1 s.

**Table 2**
Adverse events.

| | Patients N = 91 |
|---|---|
| Discontinuation for any reason, n (%) | 46 (50.6) |
| Treatment-related AEs | 6 (13.0) |
| Other than treatment-related AEs | 40 (87.0) |
| a) Personal | 24 (60.0) |
| b) Subjectively perceived lack of response | 12 (30.0) |
| c) Pregnancy | 3 (7.5) |
| d) Relapse of inflammatory bowel disease | 1 (2.5) |
| Immediate systemic reactions, n (%) | 0 (0) |
| Immediate local reactions, n (%) | 1 (1.1) |
| Type of AEs causing discontinuation (patient, n) | |
| Arthralgia/Myalgia | 3 |
| Urticaria, angioedema | 1 |
| Bleeding (methrorragia) | 1 |
| Relapsing herpes labialis | 1 |
| Patients with adverse events non-causing discontinuation, n (%) | 4 (4.4) |
| Type of AE not causing discontinuation | |
| Rhinitis and conjunctivitis | 1 |
| Injection site pain | 1 |
| Fatigue | 1 |
| Venous thrombosis | 1 |
| Drop-outs according to treatment year, n | |
| 1st yr, n (%) | 18 (39.1) |
| 2nd yr, n (%) | 4 (8.7) |
| 3rd yr, n (%) | 6 (13.1) |
| 4th yr, n (%) | 4 (8.7) |
| 5th yr, n (%) | 7 (15.3) |
| 6th yr, n (%) | 3 (6.5) |
| 7th yr, n (%) | 2 (4.3) |
| 8th yr, n (%) | 2 (4.3) |
| 9th yr, n (%) | 0 (0) |

AE, adverse events.

delayed side effects probably/possibly related to omalizumab, whose severity did not cause treatment discontinuation (Table 2). Thus, one patient reported rhino-conjunctivitis, another one lamented fatigue and, finally, one more patient left hand thrombosis.

Moreover, 40 out of the 91 patients (44%) discontinued omalizumab due to reasons other than AEs. See Table 2. Of these 40 patients, 24 (60%) discontinued the treatment for personal reasons (mainly due to lack of compliance to a treatment requiring regular administrations at outpatient clinic); 12 (30%) for subjectively perceived lack of efficacy; 3 (7.5%) due to patients' personal choice after they found to be pregnant, although no apparent increased birth prevalence of major anomalies has been observed in omalizumab treated pregnant women [25] (Table 2). One patient dropped-out because of relapse of inflammatory bowel disease after the second month of omalizumab treatment. Although this relapse was deemed not treatment related, the patient opted for discontinuation.

The majority of drop-outs occurred within the first year (18 out of 46 patients, 39.1%).

Fifty-six patients (61.5%) had co-morbidities of various kind when they started omalizumab treatment. However, their occurrence did not significantly differ ($p = 0.15$) between patients who continued treatment (31 patients, 68.9%) and drop-outs (25 patients, 54.3%) (Table 3).

Only one case of malignancy was reported in our population during omalizumab treatment. The patient was diagnosed with a gastro-intestinal stomal tumor (GIST) of the stomach one year after the beginning of omalizumab treatment. The tumor weight was about 8 Kg (mean diameter about 30 cm) and the proliferative index was low (Ki67 positive cells: 8%). Omalizumab was then discontinued and the patients underwent surgery. Two months after surgery the patient resumed omalizumab treatment (still ongoing).

Four patients had been affected by tumors prior to omalizumab treatment: one patient by spinal neurinoma, another one by ovarian cancer, another one by intestinal cancer and, finally, another one by breast cancer. Up to March 2016, these patients had been under treatment with omalizumab for 9, 2, 4 and 6 years, respectively, without any neoplastic recurrence (Table 3).

No cardiovascular or cerebrovascular event was reported in omalizumab-treated patients.

Population under treatment and drop-outs did not significantly differ in terms of gender, body weight, mean $FEV_1$ at baseline, frequency of administration (every 2 or 4 weeks), occurrence of

**Table 3**
Comparison between patients who are under treatment and drop-outs.

| | Ongoing N = 45 | Drop-outs N = 46 | *P* |
|---|---|---|---|
| **Mean age, yr ± SD** | 50.6 ± 13.6 | 44 ± 15.5 | < 0.05 |
| **Gender** | | | |
| Female | 30 | 37 | 0.25 |
| Male | 14 | 10 | |
| **Body weight** | 74.4 ± 18.7 | 75.1 ± 22.2 | 0.87 |
| **Total serum IgE (kU/L), mean ± SD** | 460.4 ± 505.4 | 301.5 ± 312.3 | 0.08 |
| **Omalizumab dose** | 357.5 ± 162.7 | 298.4 ± 142 | 0.07 |
| **Mean $FEV_1$, L ± SD (%)** | 1.82 ± 0.74 | 1.74 ± 0.71 | 0.56 |
| **Frequency of administration** | | | |
| 2 weeks, n (%) | 23 | 20 | 0.4 |
| 4 weeks, n (%) | 22 | 26 | |
| **Duration of treatment, yr; mean ± SD** | 4.7 ± 2.6 | – | |
| **Duration of treatment, yr; mean ± SD** | | | |
| Any reason | – | 3.08 ± 2.7 | 0.86 |
| Treatment-related AE | – | 2.9 ± 2.3 | |
| **Comorbidities, n pts (%)** | 31 (68.9) | 25 (54.3) | 0.15 |
| Cancer (undiagnosed[a]) | 1 | 0 | |
| Previous cancer | 4 | 0 | |
| Chronic hepatitis C | 3 | 0 | |
| Depression/anxiety | 1 | 3 | |
| Alcohol addiction | 0 | 1 | |
| Nasal polyps | 6 | 7 | |
| Diabetes | 3 | 0 | |
| Thyroiditis | 6 | 4 | |
| Coagulopathy | 2 | 0 | |
| Hypertension | 13 | 8 | |
| Arrhythmia | 0 | 1 | |
| Rheumatoid arthritis | 1 | 1 | |
| Gastro-Esophageal Reflux Disease | 7 | 3 | |
| Glaucoma | 2 | 0 | |
| Parkinson disease | 0 | 1 | |
| Inflammatory bowel disease | 0 | 2 | |
| Sjögren Syndrome | 0 | 1 | |
| Urticaria | 1 | 2 | |
| Epilepsy | 0 | 1 | |

[a] Undiagnosed at start of treatment; yr, year; pts, patients; SD, standard deviation; $FEV_1$, forced expiratory volume in 1 s.

comorbidities (Table 3). In contrast, the mean age at entry of drop-outs was significantly lower than subjects who continued treatment; also the mean omalizumab dose received was lower in drop-outs, but at a marginal statistical significance (Table 3). Furthermore, no difference was reported in the duration of treatment between subjects who dropped out for treatment-related AE and those who discontinued the treatment for any other reasons (Table 3).

As for smoking status, 7 out of the 17 patients (41.2%), who were either current or former smokers, were still under treatment, while 10 (58.8%) dropped-out after a mean treatment period of 3.1 years. Only 1 out of these latter patients dropped-out due to an AE.

## 4. Discussion

This long-term observational study shows that, in patients with severe uncontrolled asthma, omalizumab is safe and well tolerated with only a 6.6% (6 out of 91) of patients discontinuing treatment because of treatment-related AEs, over a mean treatment period of 3.8 years. Thus 59 patients of our cohort (64.8%) received omalizumab for 3–9 years: of these only three discontinued treatment for treatment related AEs, while other 3 patients dropped-out during the first 3 years of treatment, suggesting that there was no trend toward an increase of incidence of treatment-related AEs with prolonged exposure to omalizumab.

Other observational studies reported a low discontinuation rate due to adverse events over a mean treatment period of 1–2 years [10–18]. The two long-term observational studies by Tsortaki [19] and Tiro [20], with a follow-up of 3 and 4 years, respectively, reported findings consistent with ours. This study, however, extends the length of follow-up to 9 years, representing the longest "real-life" observational study on omalizumab, to date.

Notably, no case of anaphylaxis was reported in our patients. In fact, data from RCTs and post-marketing surveillance showed that hypersensitivity reactions to omalizumab are infrequent (0.09–0.2% of cases) and anaphylaxis is rare, occurring in about 0.09% of patients [26]. However, as for all infrequent treatment related AEs, anaphylaxis may be underestimated in RCTs, due to the short study length. With regard to this, data from long-term observational studies with patients using omalizumab for several years, as our study, which reports on more than 10,000 administrations, provide additional information, suggesting that the rate of anaphylaxis do not increase over time, during treatment. These results confirm that omalizumab is exceptionally safe compared with other monoclonal humanized or chimeric antibodies administered subcutaneously or intravenously [27].

Regarding immediate local reactions, we would like to emphasize that a local immediate moderate reaction, not leading to discontinuation, was observed only in one patient. Thus, this kind of reactions does not represent a concern for patients treated with omalizumab, even for many consecutive years.

With regard to the reasons leading to treatment discontinuation, the comparison between patients who continued omalizumab and drop-outs did not show a correlation between the frequency of drug administration (once or twice a month) and the rate of discontinuation, suggesting that compliance is not related to the treatment schedule. Therefore, the patient's decision to halt omalizumab treatment, which was the main reason of treatment

discontinuation in our cohort, seems unrelated to the inconvenience of frequent drug administrations at outpatient clinic. It has been suggested that adherence to omalizumab may be evaluated as function of previous patient non-adherence to asthma treatments of any kinds [8]. Thus, also non-adherence behavior by the patients may explain the observation that 37% of our patients withdrew in absence of AEs, also considering that most patients did so during the first year of treatment.

Smoking history seems not correlated to AE occurrence, since only one out of 17 patients with smoking history dropped out due to urticaria. Moreover, the treatment length of drop-outs with a smoking history (3.1 years, on average) was comparable to that of drop-outs without a smoking history (2.9 years on average).

Omalizumab discontinuation seems not related to the presence and severity of comorbidities, since no significant difference was reported in the prevalence of comorbidities between patients under treatment and drop-outs (Table 3). Some differences in the frequency of certain comorbidities between the groups were observed. Although these differences might suggest that specific comorbidities could influence the drop-out rate, it was not possible to perform any statistical inference.

Safety data on patients with some of the comorbidities observed in a "real life" setting are commonly not available from RCTs, owing to their exclusion criteria. Thus, three patients of our series with chronic hepatitis C are currently under treatment. Only two case reports on patients with chronic hepatitis C treated with omalizumab for asthma [28] or urticaria [29], with an observation period of 19 and 8 months, respectively, have been published to date. These reports showed that omalizumab is safe in terms of liver function. We confirm this conclusion in our patients (who have been in treatment for 1, 4 and 6 years, respectively), suggesting that there is no risk of HCV exacerbation during long-term omalizumab treatment.

As for the pathogen driven diseases, we did not report any case of parasitic infections, although IgE blockade may theoretically impair the immune control of parasites. Our long-term findings are in accordance with the overall low risk of parasitic infections reported in RCTs. This low risk was confirmed also by a specific study carried out in Brazil [30].

We reported, however, a case of relapsing *herpes labialis* possibly treatment-related, since discontinuation of omalizumab resulted in herpes remission and resuming omalizumab after a washout period caused relapse of herpetic lesions. To our knowledge, this adverse event was not reported neither in RCTs, nor in observational studies (although in some RCTs only treatment related/emergent AE with frequency higher than 5% are reported). This observation may suggest a possible effect of omalizumab on the immune control of specific viral infections.

Arthralgia and myalgia were the main cause of discontinuation in our patients (3 out of the 6 treatment related AEs leading to discontinuation). In one case, the treatment was resumed after a 6-month washout, but after a few months it was permanently halted due to the reappearance of severe arthralgia. This adverse event was mentioned in the Busse trial [6], which reported arthralgia in the omalizumab treated group at higher frequency compared to the placebo group, but not in other RCTs. According to the drug manufacturer, some risk of arthralgia/arthritis may exist with the use of omalizumab, with onset 1–5 days after the first or subsequent injections of omalizumab [31]. However, this risk is classified as rare [31]. This AE seems not related with the length of treatment, since two out of three patients discontinued by the second treatment year (after 6 months one patient and after 18 months the other one). Notably, 2 out of the 3 patients who discontinued omalizumab treatment because of unbearable arthralgia already lamented mild intermittent arthralgia before they started the treatment. Particularly, one of these 2 patients was successively diagnosed a seronegative arthritis and her rheumatic symptoms improved, but did not completely subside after stopping omalizumab treatment.

One case of delayed urticaria and angioedema (occurring few hours after omaluzimab administration leading to discontinuation) was observed. This AE, included among the rare AEs by the manufacturer [31], was observed after the third administration sessions. Notably, this patient lamented the occurrence of some episodes of urticaria some months before starting omalizumab treatment.

Taken together, these four cases underline that certain AEs of omalizumab, such as arthralgia or urticaria, may occur at higher frequency in subjects who are already affected by these specific symptoms.

Moreover, we describe a case of metrorrhagia, which occurred after about 8 h after the administration session. This AE was reported for 3 times, at each single administration session, starting about 4 years from treatment inception, and ceased with drug discontinuation. Laboratory tests allowed exclusion of thrombocytopenia. Also in this case, we observed a reappearance of this AE when omalizumab was resumed after a washout period, supporting a possible causative effect of the drug. Bleeding was analyzed in RCTs as possible treatment related AE, but its frequency was not significantly higher in the active group compared to the placebo group [5].

One cases of venous thrombosis not leading to discontinuation (one patient with left hand thrombosis) was reported in our cohort. In the EXCELS post-marketing observational study, a higher rate of cardiovascular and cerebrovascular serious AEs (arterial and venous thrombosis) was noticed in omalizumab-treated patients compared to non-omalizumab treated patients. However, after adjusting for available confounders, the magnitude of risk was considerably reduced compared to the crude estimates [21]. Our data may lend support to the possibility of an increase in risk of thrombosis, justifying surveillance. On the other hand, our series include another patient with congenital thrombophilia (Factor V Leiden thrombophilia, under treatment with warfarin), who had been under treatment for 8 years and had not shown any thrombotic event.

Taken together, reports of bleeding and thrombosis in our series and in the literature may suggest that omalizumab interferes with haemostasis. Once more, surveillance is advisable owing to the apparently very low frequency of these AEs.

Only one patient in out cohort was diagnosed with a malignancy (GIST of the stomach) during his treatment period. Considering i) the tumor weight, ii) the tumor low proliferative index; iii) and that the tumor was diagnosed one year after the beginning of omalizumab treatment, we deemed the treatment unlikely to be related to the tumor, which was probably already present when the patient started it. For this reason, the treatment was resumed two months after the patient underwent surgery. As already mentioned, no relapse was seen after three additional years of treatment. Besides this case, other four patients, who had had tumors before starting omalizumab, had been under treatment for 9 (two patients), 6 and 2 years, respectively.

Collectively, these data are consistent with the results from the EXCELS study, showing that omalizumab was not associated with an increased risk of malignancies [22]. Our findings may further support the idea that long-term omalizumab treatment is safe also in patients with previous cancer, since it does not increase the risk of relapse.

The main strength of our work is its very long-term observational treatment period in a relatively large cohort of patients. Our results indicate that the drug can be administered for many years

without an increased risk of AEs. Moreover, we reported side effects, such as metrorrhagia and relapsing herpes *labialis*, not described before, which clinicians should be aware of. New observations would, then, confirm the possible causative role by omalizumab.

## 5. Conclusions

In summary, our safety data, collected in 91 patients with severe asthma treated with omalizumab up to 9 years, provide evidence that the treatment is safe and well tolerated in a "real life" clinical setting characterized by great patient heterogeneity. Prolonged exposure to omalizumab is not associated to an increase of incidence of AEs, particularly anaphylaxis.

## Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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## Author's contributions

I.F., M.L.T., F.F., E.M., C.P., G.K, A.S.R., A.N., M.A., L.G., L.D. and M.F.C. collected the data; L.M. D.DB. developed the concept of the study. D.DB. wrote the first draft of the manuscript, together with L.M., and performed statistical analyses; all authors reviewed and revised the manuscript, approved the final version and agreed to submit the manuscript for publication.

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