

Prospective follow up after omalizumab discontinuation in a cohort of children with severe asthma

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To the Editor,

The efficacy of omalizumab in controlling asthma symptoms, reducing exacerbations, and healthcare utilization in children and adolescents with severe asthma is well documented.¹ However, data on the persistence of response after omalizumab discontinuation are still very limited in the pediatric population^{2–6}; furthermore, no prospectively collected data are available.

This study aims at describing asthma course 1 year after discontinuation of omalizumab in a prospective cohort of children and adolescents with severe allergic asthma.

The patients were consecutively enrolled in a multicenter web-based database promoted by the Italian Pediatric Respiratory Society in six pediatric pulmonary centers (Ancona, Bergamo, Firenze, Milano, Padova, Pavia) that agreed to participate in the study. The study was approved by the Pediatric Ethics committee of the Tuscany Region, no. 165/2015. Written informed consent was obtained by all the parents and assent was obtained by children >11 years old.

In the patients recruited, omalizumab has been discontinued after at least 2 years, based on clinicians' judgment, because a good clinical response had been reached. Although suspension criteria

have not been equally defined across centers, patients were assessed at enrollment (T0, when omalizumab was discontinued), and asthma outcome measures (number of asthma exacerbations defined as worsening of asthma symptoms treated with systemic steroids >3 days), asthma control according to Global Initiative for Asthma (GINA), the Composite Asthma Severity Index (CASI), and spirometry were available (see Table 1). Patients were reassessed after 3, 6, and 12 months (T1, T2, and T3, respectively). Moreover, the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) was administered at T0 and T3. Full criteria for inclusion and additional follow-up details are reported in the Supporting Information.

Four children (6–11 years old) and 16 adolescents (12–17 years), treated with omalizumab for 2.0–8.2 years, were recruited. Table 1 summarizes their characteristics at recruitment and during the follow-up.

At T3, 19 children were free of a biologic therapy while one, a 15-year-old adolescent, restarted omalizumab 9 months after stopping it, as asthma worsened (four acute exacerbations treated with systemic steroids, including two requiring hospitalization; worsening of asthma control according to GINA and CASI scores).

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TABLE 1 Characteristics of 20 children at recruitment and their clinical and laboratory variables at recruitment and during the follow-up.

Children's characteristics at recruitment					
Age (years), median (min-max)	15 (9–17)				
Male, n (%)	14 (70)				
Duration of omalizumab therapy (years), median (min-max)	3.0 (2.0–8.2)				
Allergic comorbidities ^a , n (%)	9 (45)				
Allergic sensitization to perennial allergens, n (%)	20 (100)				
Clinical and laboratory variables at enrollment and during follow up	T0 (stop omalizumab)	T1 (after 3 months)	T2 (after 6 months)	T3 (after 12 months ^b)	T3 vs. T0/T1 p
GINA Step 4, n (%)	13 (65)	12 (60)	11 (55)	9 (45)	—
GINA Step 5, n (%)	3 (15)	3 (15)	3 (15)	5 (25)	—
Patients with at least one steroid course, n (%) ^c	3 (15)	1 (5)	2 (10)	3 (15)	—
GINA score					
Controlled, n (%)	17 (85)	17 (85)	13 (65)	19 (95)	—
Partly controlled, n (%)	2 (10)	3 (15)	5 (25)	0 (0)	—
Not controlled, n (%)	1 (5)	0 (0)	2 (10)	1 (5)	—
CASI score, median (IQR)	4 (4–5)	4 (3.5–5)	4 (3–5.5)	4 (3–6) ^d	.892 ^e
FEV ₁ (% pred), mean (SD)	93.5 (10.3)	91.9 (11.6)	91.0 (13.2)	90.2 (11.0) ^d	—
FEV ₁ (z-score), mean (SD)	−0.54 (0.87)	−0.69 (0.99)	−0.73 (1.04)	−0.84 (0.91) ^d	.154 ^f
FEV ₁ /FVC (ratio), mean (SD)	0.85 (0.07)	0.86 (0.07)	0.86 (0.10)	0.86 (0.07) ^d	—
FEV ₁ /FVC (z-score), mean (SD)	−0.11 (1.14)	0.09 (1.23)	0.05 (1.75)	−0.08 (1.14) ^d	.783 ^f
FEF _{25–75} (% pred), mean (SD)	90.9 (21.0)	93.1 (25.4)	85.6 (22.7)	87.4 (18.6) ^d	—
FEF _{25–75} (z-score), mean (SD)	−0.45 (0.95)	−0.35 (1.14)	−0.71 (1.07)	−0.61 (0.85) ^d	.428 ^f
PAQLQ total score, median (IQR)	6.9 (6.5–7.0)	n.d.	n.d.	6.9 (6.6–7.0) ^d	.413 ^e
PAQLQ symptoms, median (IQR)	6.9 (6.3–7.0)	n.d.	n.d.	7.0 (6.6–7.0) ^d	.096 ^e
PAQLQ activities, median (IQR)	6.8 (6.6–7.0)	n.d.	n.d.	6.8 (6.5–7.0) ^d	.898 ^e
PAQLQ emotions, median (IQR)	7.0 (6.9–7.0)	n.d.	n.d.	7.0 (6.6–7.0) ^d	.254 ^e
Blood eosinophils (cells/mm ³), median (IQR)	n.d.	370 (285–440) ^g	n.d.	565 (330–700) ^g	.020 ^e
Total IgE (kU/L), median (IQR)	n.d.	816 (609–1152) ^g	n.d.	374 (276–710) ^g	.015 ^e

Abbreviations: CASI, composite asthma severity index; FEF_{25–75}, forced mid-expiratory flow; FEV₁, forced expiratory volume in the first second; GINA, global initiative for asthma; GINA step 4–5, medium to high dose of ICS + LABA; n.d., not done; PAQLQ, pediatric asthma quality of life questionnaire.

^aAllergic rhinitis (eight patients) and/or food allergy (two patients).

^bOr end of follow up for one patient who resumed omalizumab.

^cT0: number of patients with steroid courses in the last 12 months; T1, T2, and T3: number of patients with steroid courses since the last assessment.

^dn = 19 subjects; one patient did not performed spirometry at T3 and therefore did not have CASI assessed; another patient did not have PAQLQ questionnaire.

^eWilcoxon signed rank test.

^fPaired T-test.

^gn = 18 subjects.

This child was the only patient uncontrolled according to GINA at time 0 when omalizumab was discontinued after 8.2 years based on good control of exacerbations. As for the other 19 patients, only four had one or two exacerbations requiring oral steroids during the

follow-up, and all 19 had good asthma control, according to GINA and CASI at the end of the follow-up period. PAQLQ (total score and individual domain scores) was superimposable to that of the beginning. No significant differences in spirometric values were

observed at T3 versus T0, not even for forced expiratory volume in the first second.

We observed increased serum eosinophil count as a surrogate of IgE-mediated inflammation rebound after 1-year omalizumab wash-out. In contrast, we found a decrease in total IgE levels, probably because total IgE levels are elevated during treatment due to the formation of omalizumab-IgE complexes having a slower elimination rate than free IgE.

Overall, our prospective cohort confirms previous retrospective data collection²⁻⁶ and shows a meaningful clinical and functional effect of omalizumab for at least 1 year after discontinuation. Of note, children who discontinued omalizumab therapy had good asthma control during the year of follow-up without an increase in the number of asthma exacerbations, asthma symptoms according to GINA, a composite asthma score as CASI, and PAQLQ score. Only one child resumed omalizumab therapy for worsening asthma, suggesting that a minority of children with severe allergic asthma may depend on biological therapy. As for the quality of life, even if PAQLQ has been previously found to be affected in children with asthma, particularly in those with severe disease,⁷ children enrolled in our study did not show an impairment after omalizumab discontinuation, probably because asthma was well-controlled.

In conclusion, although obtained in a limited number of cases, our prospectively collected findings strengthen the possibility that omalizumab discontinuation after good disease control may be a safe option in most children with severe asthma. However, after omalizumab discontinuation, children need to be closely monitored as data are still limited and prospective, larger, and longer data collections are needed to come to a more robust recommendation.

AUTHOR CONTRIBUTIONS

Valentina Agnese Ferraro: Conceptualization; writing—original draft; investigation; data curation; writing—review and editing. **Amelia Licari:** Conceptualization; investigation; writing—original draft; writing—review and editing. **Alessandro Volpini:** Conceptualization; investigation; writing—review and editing. **Grazia Fenu:** Investigation; writing—review and editing. **Maria Francesca Patria:** Investigation; writing—review and editing. **Manuela Seminara:** Investigation; writing—review and editing. **Elena Spada:** Methodology; formal analysis; writing—original draft; -writing—review and editing. **Franca Rusconi:** Conceptualization; investigation; writing—original draft; data curation; writing—review and editing; supervision.

CONFLICT OF INTEREST STATEMENT

V. A. F., A. L., M. F. P., M. S., E. S., and F. R. report no conflict of interest for this manuscript. A. V. reports financial and nonfinancial support in the past 3 years from Chiesi, LusoFarmaco, Momento Medico, and Fidia Sooft outside the submitted work. G. F. reports financial and nonfinancial support in the past 3 years from AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, and Sanofi outside the submitted work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author, A. L.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.