

coagulation cascade and of its intensity were not able to predict the clinical response to omalizumab.

Our data confirm that the activation of the coagulation cascade represents a marker of CSU severity,¹ as it does not occur in subjects with a mild disease. The lack of an association between baseline plasma D-dimer levels and response to omalizumab suggests that the activation of the coagulation cascade, starting with the hyper-expression of tissue factor by eosinophils and endothelial cells triggering the extrinsic pathway, does not depend on a specific pathogenic mechanisms underlying CSU (such as IgE-mediated autoimmunity, IgG-mediated autoimmunity, or other hitherto unknown mechanisms⁹) but rather represents a relevant nonspecific amplification mechanism in a subset of severely affected patients. The reasons why the coagulation cascade is not activated in all patients with severe CSU need to be elucidated.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Efficacy of mepolizumab in patients with previous omalizumab treatment failure: Real-life observation

To the Editor,

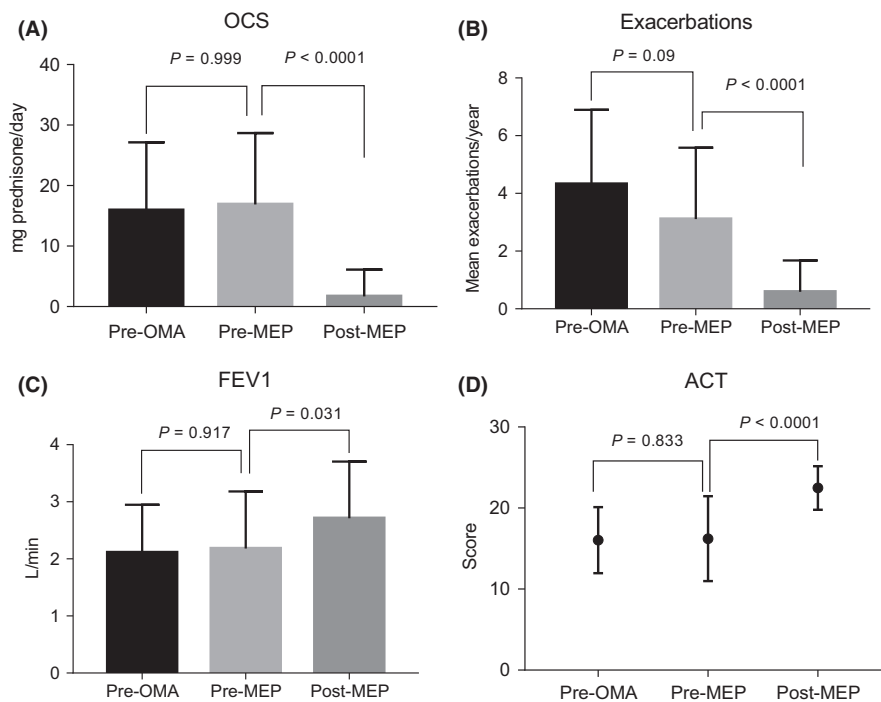
Asthma is a common chronic disease, usually characterized by reversible airflow obstruction and airway inflammation, with a worldwide prevalence of more than 315 million patients, with about 10% of them having a severe or uncontrolled form.¹ Usually, asthma symptoms can be controlled by inhaled corticosteroids, with or without long-acting β_2 -agonist. Other drugs can be added to improve the

control, such as long-acting antimuscarinic agents, antileukotrienes, or immunotherapy.²

Uncontrolled patients continue to exacerbate and often need oral corticosteroids (OCS), even in prolonged courses. Several biological drugs were introduced for severe asthma, with the aim of reducing exacerbations and the need for OCS.³ The first one, commercialized about 15 years ago, was the anti-IgE omalizumab (OMA),

TABLE 1 Main characteristics of the 27 patients, before omalizumab, before mepolizumab, and after 12 mo of mepolizumab. All data are expressed in mean and standard deviation (SD) or absolute number and percentage (%)

Parameter	Pre-OMA	Post-OMA (Pre-MEP)	P-Value	Post-MEP	% Diff Pre-MEP/Post-MEP (%)	P-Value
Exacerbations/12 mo	4.3 (2.6)	3.1 (2.4)	0.090	0.6 (1.1)	-81	<0.0001
Hospitalizations/12 mo	0.8 (1.3)	0.4 (0.8)	0.281	0.1 (0.4)	-82	0.044
OCS-dependent	25 (93%)	26 (96%)	0.999	5 (18%)	-70	<0.0001
OCS mg/d. mean	15.9 (11.2)	16.9 (11.6)	0.804	1.7 (4.4)	-90	<0.0001
Rhinitis	19 (70%)	19 (70%)	0.999	13 (48%)	-32	0.165
Nasal polyps	13 (48%)	13 (48%)	0.999	11 (41%)	-15	0.784
Dermatitis	2 (7%)	2 (7%)	0.999	1 (4%)	-50	0.999
FEV1 (L)	2.11 (0.83)	2.18 (0.98)	0.917	2.71 (0.97)	24	0.022
FEV1 (%)	67 (17)	74 (21)	0.245	86 (17)	16	0.031
FVC (L)	3.17 (1.14)	3.35 (1.25)	0.740	3.61 (1.16)	8	0.381
FVC (%)	82 (16)	92 (20)	0.091	98 (17)	6	0.365
FEV1/FVC	0.69 (0.1)	0.66 (0.08)	0.817	0.70 (0.08)	6	0.041
FeNO	63 (36)	76 (48)	0.338	38 (32)	-50	0.003
Eosinophils serum	1078 (672)	785 (397)	0.187	96 (43)	-88	<0.0001
IgE	645 (813)	835 (1134)	0.392	nd	Na	na
ACT	16 (4)	16 (5)	0.833	22 (3)	39	<0.0001

**FIGURE 1** Graphic representation of the changes postomalizumab and after 12 mo of mepolizumab vs pre-omalizumab in: (A) mean yearly exacerbations; (B) mean dose of OCS (daily mg of prednisone); (C) mean FEV1 prebronchodilation; and (D) mean ACT score

to be prescribed in severe allergic asthmatic patients⁴. The efficacy and safety of OMA are now supported by controlled and real-life evidence. Nonetheless, a small proportion of patients treated with OMA remain poorly controlled. The introduction of new biological agents (ie, IL-5 antagonists) provided, more recently, viable alternatives especially for patients with eosinophilic asthma. Thus, in patients not responder to OMA and with eosinophilic asthma, a switch from OMA to IL-5 antagonists can be empirically attempted.

We performed a retrospective observational study involving six severe asthma clinics (Genoa, Arenzano, Reggio Emilia, Verona, Rome, Cuneo) in Italy. The evaluation parameters (exacerbations/hospitalizations in the previous year, blood eosinophil count, asthma control test [ACT], OCS intake, pulmonary function, total IgE, and exhaled nitric oxide [FeNO]) were recorded at three time points: pre-OMA, end-OMA (that is pre-MEP), and after 1 year of MEP. Other clinical aspects were also considered: rhinitis, nasal polyposis,

and atopic dermatitis. The MEP treatment period, after OMA discontinuation, was between May 2017 and November 2018, so that all patients received the drug for at least 1 year. All the patients had initially received OMA for severe uncontrolled allergic asthma, according to the prescription rules of Italian Drug Authority. We considered as nonresponder to OMA, patients who could not discontinue or escalate daily dose of OCS, who persisted with 2 or more exacerbations/year or needed at least 1 hospitalization. Before the switch to MEP (100 mg SQ/28 days), a period of 1-month washout was observed. All patients had >150 eosinophils/mm³ and an historical of at least 300/mm³ in the previous 12 months. No Ethical Committee approval was needed, since the drugs were prescribed according to current indications as part of the standard of care.

At November 30, 2018, 27/240 severe asthmatic patients, (14 female, mean age 57 ± 11.7 years; age range 21–81) previously treated with OMA, were switched to MEP. The average onset of the disease was 33 ± 17 years, and its mean duration before treatment with OMA was 23 ± 18 years. All patients were sensitized to perennial allergens, and six (22%) were ex-smoker. Before OMA treatment, 25/27 patients were OCS-dependent (mean daily prednisone dose 15.9 ± 11.2 mg), with a mean exacerbation rate of 4.3 ± 2.6 year. The mean IgE level pre-OMA was 645 ± 813 UI/mL, and the eosinophil count was 1078 ± 672 cells/ μ L (Table 1). The mean duration of OMA treatment was 20 months (range 6–60). There was no apparent difference between OMA responders and nonresponders in the baseline parameters (Table S1).

At OMA discontinuation (pre-MEP), blood eosinophil count was 785 ± 397 μ L, decreasing to 96 ± 43 μ L after 1 year of MEP ($P < 0.0001$). Before switching to MEP, 26/27 patients (96%) were still on chronic OCS, with a mean daily prednisone dose of 16.9 ± 11.6 mg, that decreased to 1.7 ± 4.4 mg after MEP ($P < 0.0001$) (Figure 1A). Main comorbidities were as follows: rhinitis (70%) and nasal polyposis (48%), whereas atopic dermatitis was seen in 7% and bronchiectasis 15% of patients (Table 1). After 1 year of MEP, the mean exacerbations decreased by 81%, from 3.1 ± 2.4 year to 0.6 ± 1.1 year ($P < 0.0001$) (Figure 1B). The switch to MEP reduced hospitalizations from 0.4 ± 0.8 year to 0.1 ± 0.4 year ($P = 0.044$). After MEP, there was an increase in FEV₁ from 2.18 ± 0.98 L to 2.71 ± 0.97 L, with an absolute mean increase of 530 mL ($P = 0.022$) (Figure 1C). There was no change in forced vital capacity after MEP ($P = 0.381$), whereas the Asthma Control Test score increased from 16 ± 5 to 22 ± 3 ($P < 0.0001$) (Figure 1D). No apparent difference among the MEP responder patients could be seen.

In severe allergic asthmatics, sensitized to perennial allergens, OMA remained for years the only therapeutic additional choice, but a small proportion of them did not respond satisfactorily to the treatment. In our population, we identified 27/240 (11.2%) patients who failed to respond to OMA in term of exacerbations, hospitalization, use of OCS, symptoms, or pulmonary function. Due to the absence of any biomarker able to predict response to biologicals, the only empirical approach in nonresponder patients was to try to switch to the other available biological treatment. In Italy, the only anti-IL-5 (MEP) became available since about 2 years. We attempted to switch to

MEP the 27 patients with a previous poor response to OMA and to evaluate their characteristics. After 1 year of MEP, those patients had a significant and measurable benefit, and the most apparent changes were seen in exacerbations, hospitalizations, and OCS intake.

The use of the anti-IL-5 reslizumab in patients inadequately controlled by OMA was, recently described, with a reduction in daily OCS dose, exacerbations, and an improvement in ACT.⁵ The effects of MEP in allergic patients were evaluated, showing that exacerbation rate and OCS dose reduction were comparable in patients previously treated with OMA and in naïve ones.⁶ OMA is generally considered more appropriate in allergic patients, where the pathogenic mechanism seems reasonably IgE mediated and a responsible allergen is identified, although positive results were obtained also in non-IgE-sensitized subjects.⁷ On the other hand, other studies^{8,9} demonstrated the efficacy of IL-5 antagonists in allergic patients. Therefore, in the concomitant presence of high IgE levels, high eosinophils, and a clinically relevant sensitization to a perennial allergen, in principle, both drugs could be used.

The present results suggest that, when the anti-IgE-strategy fails and severe asthma maintains a high-eosinophil profile, a switch to IL-5 antagonists is a reasonable choice, evidence the need for predictive biomarkers and the pivotal role of real-life studies.

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CONFLICT OF INTEREST

The authors have no conflict of interest in relation to this work.

DISCLAIMER

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SUPPORTING INFORMATION

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

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Minimal important difference of the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL)

To the Editor,

Chronic spontaneous urticaria (CSU) is a common skin disorder characterized by the sudden appearance of pruritic wheals, angioedema or both, for a period of at least 6 weeks.¹ CSU is typically associated with a high impact on patients' Health Related Quality of Life (HRQoL)² and needs to be treated effectively.¹ Despite the improvement of CSU pharmacotherapy over recent years, many patients have an unsatisfactory response to the currently available drugs. Moreover, CSU is a disease of long duration and its activity may vary considerably over time. For these reasons, the assessment of HRQoL is important to make decisions about treatment.^{1,3}

The Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) is the only validated tool to evaluate disease-specific HRQoL impairment in patients with CSU.⁴ It was originally developed in Italian⁴ and is now available in German, Spanish, Polish, Brazilian-Portuguese, Turkish, Greek, Persian, Thai,⁵ and Hebrew.⁶ CU-Q2oL has been shown to have the required psychometric properties in terms of construct validity, internal consistency, reliability, and responsiveness in all validated versions. The EAACI/GA²LEN/EDF/WAO guideline for urticaria¹ recommends

the use of CU-Q2oL for assessing disease impairment and monitoring response to treatment. Therefore, it is important to understand how changes CU-Q2oL scores are linked to changes in HRQoL impairment and how to interpret the clinical relevance of changes in CU-Q2oL scores associated with disease variability and treatment responses.^{7,8}

Health Related Quality of Life changes over time may be evaluated in two ways: by calculating the mean change difference of scores between treatment and control groups (distribution-based approach) and by determining whether a minimal important difference (MID) has been achieved (anchor-based approach).⁹ The MID is defined as the smallest change in an outcome measure perceived as beneficial by patients.⁹ This concept evolved as a way to overcome the shortcomings of the "statistically significant difference."

To date, the absence of a known MID for CU-Q2oL represents a limitation to the interpretation of score changes of this measure for patients, physicians, and researchers. To close this gap, we determined the MID of CU-Q2oL. We investigated 130 consecutive patients who were receiving treatment for CSU (66.7% antihistamine, 4.6% oral corticosteroids, 16.6% antihistamine plus oral corticosteroids,

Table S1. Comparison between OMA responders and OMA nonresponders according to the baseline parameters. All data are expressed in mean and standard deviation (SD) or absolute number and percentage (%).

PARAMETER	PRE-OMA RESPONDERS (N= 213)	PRE-OMA NONRESPONDERS (N= 27)	p-value
Exacerbations/12 m	4.1 (2.1)	4.3 (2.6)	NS
Hospitalizations/12 m	0.7 (1.1)	0.8 (1.3)	NS
OCS-dependent	191 (90%)	25 (93%)	NS
OCS mg/day. mean	16.2 (10.4)	15.9 (11.2)	NS
FEV1 (%)	70 (17)	67 (17)	NS
FVC (%)	85 (15)	82 (16)	NS
FeNO	69 (42)	63 (36)	NS
Eosinophils serum	984 (701)	1078 (672)	NS
IgE	680 (829)	645 (813)	NS
ACT	15 (4)	16 (4)	NS

NS: not significant