Efficacy of mepolizumab in patients with concomitant severe eosinophilic asthma and severe chronic urticaria: an example of personalized medicine?

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Comorbidities of severe asthma (SA) are commonly observed, affecting patients' quality of life and impacting treatment efficacy [1]. A classification of comorbidities in SA distinguishes between syndromic and non-syndromic comorbidities, based on sharing or not a common T2 inflammation pathway, respectively. Since the profile of syndromic comorbidities is a patient's peculiarity, treatment of SA and comorbidities by a single biologic drug (e.g. anti-IgE, anti-IL-5/IL-5R, anti-IL-4Rα/IL-13) could represent a transition from precision medicine of the disease to personalized medicine of the patient with comorbidity [2].

In this context, the biological therapy of SA and severe chronic urticaria (SCU) presents interesting similarities: omalizumab was the first biologic proven to be effective in both conditions, and benralizumab, used to treat eosinophilic SA (SEA), is currently under scrutiny in SCU [3]. However, the use of biologics as personalized medicine of patients with co-occurring SA/SCU was never studied as separate entity. The low prevalence of CU in SA, which is 0.9% and 5.6% in SEA patients treated with mepolizumab and in allergic SA patients treated with omalizumab, respectively, could be involved in this paradox. Moreover, these studies did not provide information neither on the severity nor on the response of CU to asthma treatment [4-5].

Recently, three case reports from Germany described the efficacy of monoclonal antibodies targeting eosinophils, used to treat SEA, on co-occurring SCU [6-8], shedding new lights on this possible comorbidity.

We confirm these observations describing complete remission of SCU in 3 patients treated with mepolizumab for SEA.

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All patients were atopic women, between 35 and 59 years; two had asthma from adolescence, the third had a late onset disease. Asthma became progressively severe over time, being uncontrolled despite high-dosage ICS-LABA, with frequent need of oral corticosteroids.

Rhinosinusitis with nasal polyps (relapsing despite surgery) and non-steroidal anti-inflammatory drugs (NSAIDs)-exacerbated respiratory disease (NERD) coexisted in two patients; the third also had rhinosinusitis, but without nasal polyps nor NERD.

CU coexisted in all patients: it developed many years after asthma onset, and duration ranged between 3 and 8 years, becoming progressively SCU. NSAIDs induced CU exacerbations in all patients, suggesting NSAID-exacerbated cutaneous disease (NECD); in the two NERD patients, exacerbations of skin and respiratory symptoms coincided. No patient had autoimmune diseases, nor positivity for autoantibodies (anti-thyroid, anti-nuclear antibodies, rheumatoid factor).

Due to the greater burden of respiratory than cutaneous symptoms on quality of life, it was decided to start SA therapy.

Considering the comorbidities of the upper airways, the very low clinical relevance of allergic sensitizations and the peripheral blood eosinophil levels >300/μL, SEA was diagnosed and mepolizumab was prescribed, according to guidelines [9].

Within the first month of therapy, a significant improvement in asthma symptoms was observed, with a magnitude similar to mepolizumab super-responders [10]. Surprisingly, in just few days from the first administration of mepolizumab, skin symptoms completely disappeared. Clinical improvement was stable throughout the follow-up and no patient to this date discontinued mepolizumab treatment (mean follow-up 6 months) (Table 1).

Although limited to few patients, our results pose the question of whether precision therapy of asthma identified an unknown T2 comorbidity: in particular three items are worthy of discussion.

First, we questioned whether SEA/SCU co-occurrence was a comorbidity or random coincidence.

In Italy, considering the prevalence estimates of SA and SCU, the cumulative probability of a casual association between the two conditions is rather small (around 1.16 in 10’000 subjects) [11-12]; if we add the very low prevalence of urticaria found in clinical trials of SEA treated with mepolizumab (0.9%) [4] and the absence of autoimmunity in our patients, the likelihood of a random association decreases.

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Second, we assessed whether eosinophilia, treated with mepolizumab with efficacy on both SEA and SCU, supported the hypothesis of a specific comorbidity.

The close similarity with patients described in Germany, both in clinical features and treatment response, suggests that eosinophil suppression is a determinant factor, influencing the clinical outcome in both diseases.

The role of eosinophils in SA and CU is well known; however differences in the patterns of blood eosinophils between the two conditions are noteworthy. In asthma, high eosinophil blood counts are a signature feature of SEA, predicting the efficacy of biologics targeting eosinophils, while in SCU blood eosinophils are usually within the normal range. In our and German patients, blood eosinophils counts were higher than normal, thereby hinting at a key phenotypic difference among SCU occurring as separate disease or as comorbidity of SEA.

On the other hand, the low prevalence of CU found in large SEA cohorts [5], suggests that the presence of blood eosinophilia alone does not provide a sufficient pathogenetic explanation for the comorbidity.

As third point, we assessed whether NSAIDs cutaneous hypersensitivity, shared by all our patients, was determinant for syndromic T2 comorbidity SEA-SCU.

The latest classification of NSAIDs hypersensitivity divides clinical manifestations between respiratory and cutaneous diseases [13], but a recent work questions this definition, showing that a subset of patients with blended asthma and urticaria phenotype is present in patients with NSAIDs hypersensitivity, although in NECD patients blended reactions are almost never found [14].

In another work, the prevalence of patients with NECD was 9.3% within the phenotypic cluster of NERD patients with co-existing various types of urticaria; in this cluster the prevalence of patient with peripheral eosinophilia > 400cell/ml was 18.6 %; unfortunately, neither the prevalence of patients with both NECD and eosinophilia > 400cell/ml nor asthma severity of NECD patients, were documented [15]. Our patients may belong to this cluster, despite one not having NERD.

The therapeutic effect of mepolizumab in our patients suggests the pivotal role of eosinophils in patients with coexisting SEA and SCU-NECD, with and without NERD. Unfortunately, NECD/NERD were not described in the three German cases.

In conclusion, we confirmed the first findings on the efficacy of biologics drugs targeting eosinophils in SEA and concomitant SCU, suggesting they could become the personalized treatment for this

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association. Underlining mechanisms of this prospective syndromic T2 comorbidity remain elusive and are worthy of further exploration.

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Conflicts of Interest

Leonardo Antonicelli declares: consulting fees for GSK and AstraZeneca; payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing or educational events for GSK, AstraZeneca and Sanofi Genzyme; support for attending meetings and/or travel for Mylan.
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Table 1. Clinical response parameters measured before and after mepolizumab therapy (mean follow-up 6 months)

	Patient #1		Patient #2		Patient #3	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
ACT	8	25	8	21	16	22
UCT	2	16	0	15	5	16
Eosinophil count cells/mmc(%)	510 (10%)	30 (0.60%)	470 (5%)	130 (1.7%)	1420 (16.4%)	190 (3.3%)
FEV1 liters (% of predicted)	0.96 (48)	1.83 (90)	2.21 (77)	3.44 (120)	1.80 (63)	2.52 (86)
FEV1/FVC (% of predicted)	43 (58)	62 (80)	64 (78)	82 (104)	62 (81)	70 (86)

Abbreviations: ACT, asthma control test; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; UCT, urticaria control test.

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