Efficacy of Mepolizumab in Patients With Severe Eosinophilic Asthma and Concomitant Severe Chronic Urticaria: An Example of Personalized Medicine?

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Comorbidities of severe asthma (SA) are common and affect both patients' quality of life and the efficacy of treatment [1]. A classification of comorbidities in SA differentiates between syndromic and nonsyndromic comorbidities, based on whether or not, respectively, a common T2 inflammation pathway is shared. Since the profile of syndromic comorbidities is patient-specific, treatment of SA and comorbidities with a single biologic drug (eg, anti-IgE, anti–IL-5/IL-5R, anti-IL-4Rα/IL-13 agents) could represent a transition from precision medicine to personalized medicine [2].

In this context, interesting similarities can be observed between biological therapy for SA and severe chronic urticaria (SCU). Omalizumab was the first biologic proven to be effective in both conditions, and benralizumab, which is used to treat severe eosinophilic asthma (SEA), is currently under scrutiny in SCU [3]. However, the use of biologics specifically as personalized medicine in patients with co-occurring SA and SCU has never been studied. The low prevalence of CU in SA, which is 0.9% in SEA patients treated with mepolizumab [4] and 5.6% in allergic SEA patients treated with omalizumab [5], could partly account for this paradox. Moreover, these studies did not provide information on the severity of CU or on the response of CU to asthma treatment [4,5].

Three recent case reports from Germany described the efficacy of monoclonal antibodies targeting eosinophils used to treat SEA and concomitant SCU [6-8], thus shedding new light on this potential comorbidity.

We confirm these observations by reporting 3 cases of complete remission of SCU in patients receiving mepolizumab for SEA.

All 3 patients were atopic women aged between 35 and 59 years. Two had had asthma from adolescence, the third had late-onset disease. Asthma became progressively severe over time and remained uncontrolled despite high-dose inhaled corticosteroids and long-acting ß-agonists, which were frequently supplemented with oral corticosteroids.

Two patients had co-occurring rhinosinusitis with nasal polyps (relapsing despite surgery) and nonsteroidal anti-inflammatory drug (NSAID)–exacerbated respiratory disease (NERD); the third also had rhinosinusitis, but without nasal polyps or NERD.

All 3 patients also had CU, which developed many years after onset of asthma. This lasted between 3 and 8 years and gradually progressed to SCU. NSAIDs induced CU exacerbations in all 3 patients, suggesting NSAID-exacerbated cutaneous disease (NECD); in the 2 NERD patients, exacerbations of skin and respiratory symptoms coincided. No patient had autoimmune diseases or positive autoantibody results (antithyroid, antinuclear, rheumatoid factor).

The greater burden of respiratory symptoms than cutaneous symptoms on quality of life led us to start SA therapy.

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

Asthma symptoms improved significantly during the first month of therapy, with a magnitude similar to that observed for mepolizumab super-responders [10]. Surprisingly, the skin symptoms had disappeared completely only a few days after the first dose of mepolizumab. The improvement in symptoms remained stable throughout the follow-up, and none of the 3 patients has discontinued mepolizumab to date (mean follow-up of 6 months) (Table).

Table. Clinical Response Parameters Measured Before and After Mepolizumab Therapy (Mean Follow-Up, 6 Mo)

	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/μL (%)	510 (10%)	30 (0.60%)	470 (5%)	130 (1.7%)	1420 (16.4%)	190 (3.3%)
FEV_1, L (% predicted)	0.96 (48)	1.83 (90)	2.21 (77)	3.44 (120)	1.80 (63)	2.52 (86)
FEV_1/FVC (% predicted)	43(58)	62 (80)	64 (78)	82 (104)	62 (81)	70 (86)

Abbreviations: ACT, asthma control test; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; UCT, urticaria control test.

Although limited to few patients, our results raise the question of whether precision therapy of asthma identified an unknown T2 comorbidity. Three specific items are worthy of discussion.

First, we questioned whether SCU was a comorbidity of SEA or a random coincidence. Considering the prevalence estimates for SA and SCU in Italy, the cumulative probability of a causal association between the 2 conditions is rather small (around 1.16 in 10 000 persons) [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 the cases we report, the likelihood of a random association decreases.

Second, we assessed whether eosinophilia treated with mepolizumab, which proved effective in both SEA and SCU, supported the hypothesis of a specific comorbidity. The close similarity to the patients described in Germany [6-8], both in terms of clinical features and response to treatment, suggests that suppression of eosinophils is a key factor, affecting the clinical outcome in both diseases.

The role of eosinophils in SA and CU is well known, although differences in the patterns of blood eosinophils between the 2 conditions are noteworthy. High eosinophil blood counts are a signature feature of SEA and, as such, predict the efficacy of biologics targeting eosinophils, while in SCU, blood eosinophils are usually within the normal range. In the cases we describe and the German patients [6-8], blood eosinophil counts were higher than normal, thereby hinting at a key phenotypic difference between SCU occurring as a separate disease or as a comorbidity of SEA.

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

Third, we assessed whether cutaneous hypersensitivity to NSAIDs, which was common to all 3 patients, was determinant for syndromic T2 comorbidity in SEA-SCU. The latest classification of hypersensitivity to NSAIDs divides clinical manifestations between respiratory and cutaneous conditions [13]. However, this definition has been questioned, indicating that a subset of patients with a blended asthma and urticaria phenotype can be identified among patients with hypersensitivity to NSAIDs, even though blended reactions are almost never found in NECD patients [14].

In another study, the prevalence of patients with NECD was 9.3% within the phenotypic cluster of NERD patients with various concomitant types of urticaria. In this cluster, the prevalence of patients with peripheral eosinophilia >400/μL was 18.6%; however, neither the prevalence of patients with both NECD and eosinophilia >400/μL nor the severity of asthma among NECD patients was documented [15]. The patients we report may belong to this cluster, despite one not having NERD.

The therapeutic effect of mepolizumab in the 3 cases discussed here suggests the pivotal role of eosinophils in patients with concomitant SEA and SCU-NECD, with and without NERD. Neither NECD nor NERD was described in the 3 German cases [6-8].

In conclusion, we confirmed initial findings on the efficacy of biologics targeting eosinophils in SEA and concomitant SCU, suggesting that these agents could become the personalized treatment for this association. The underlying mechanisms of this prospective syndromic T2 comorbidity remain elusive and warrant further exploration.

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Conflicts of Interest

Leonardo Antonicelli: consulting fees for GSK and AstraZeneca; payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from GSK, AstraZeneca, and Sanofi Genzyme; support for attending meetings and/or travel from Mylan.

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The remaining authors declare that they have no conflicts of interest.

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