



Martin Metz

Professor of Dermatology,
Institute of Allergology at the
Charité – Universitätsmedizin
Berlin, Germany

“**Every patient with CSU
should receive effective
and safe treatment**”

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Q1 Your research highlights the increased mortality risk in patients with chronic spontaneous urticaria (CSU), particularly from comorbidities like suicide and malignant neoplasms. What are the key takeaways from your recent study on this topic, and how do you believe these findings should change clinical practice?

For me, there are two main takeaways from the study. The first is that we still don't take CSU seriously enough. It is a debilitating disease that places a significant burden on patients, sometimes even leading to suicidal thoughts, as we can see in this study. The second takeaway is directly connected to the first: every patient with CSU should receive effective and safe treatment. Too many patients continue to receive no treatment or ineffective/inadequate treatment, including those that can be harmful over time, such as high doses of oral corticosteroids.

Q2 Your work sits at the intersection of mast cell biology, neuroimmunology, and pruritus. Can you explain the complex interplay between the nervous system and mast cells in causing chronic itch, and how your research aims to disrupt this cycle?

Mast cells are long-lived cells typically located near blood vessels and sensory nerves in the skin. When activated, they can rapidly release numerous mediators. Interestingly, some of the receptors on mast cells that cause activation and

degranulation are receptors that can bind neuropeptides released from sensory nerves. Vice versa, some of the mast cell-released mediators bind to receptors on sensory nerves and cause itch. The best-known mediator in this context is histamine, but there are other itch-inducing mast cell mediators, including cytokines and proteases. Therefore, mast cells are not only the most important effector cells in allergies, but the close communication between mast cells and sensory nerves is also an important component of chronic pruritus in various skin diseases. We aim to better understand this communication and identify targets to disrupt this cycle.

Q3 Your recent publication on the treatment of CSU points to a need for more effective disease-modifying therapies beyond antihistamines and omalizumab. What emerging treatments, such as Bruton's tyrosine kinase inhibitors or anti-KIT monoclonal antibodies, show the most promise for inducing long-term remission?

As of today, we cannot say much about long-term remission through disease-modifying therapies in CSU. While these potential aspects of novel drugs are certainly interesting, none of the studies were designed to investigate them. Current standard treatment options in CSU, antihistamines and omalizumab, are symptomatic treatments that are unlikely to show any relevant disease modification. In contrast, emerging CSU treatments that target Bruton's tyrosine kinase, KIT, and

IL-4 receptor show potential for inducing long-term remission. The mechanisms leading to disease modification may include effects on autoantibody production or changes in the inflammatory microenvironment in the skin. These are exciting new areas of investigation that we need to explore in the future.

Q4 As the head of speciality outpatient clinics for pruritus, you work with patients who have debilitating itch. What is the most misunderstood aspect of chronic pruritus from a clinical perspective, and how does your research into its neuroimmunological basis seek to correct that?

From a clinical perspective, the biggest problem with chronic pruritus is that we do not see it. In some diseases, such as atopic dermatitis, lichen planus, or urticaria, we can see the itchy skin lesions. In patients with very

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severe chronic pruritus, the skin can appear perfectly normal (chronic pruritus of undetermined origin) or, as is the case in chronic prurigo, we see secondary scratch lesions without any primary skin alterations. It is important to understand how much these patients suffer and how effective (or non-effective) our treatment efforts are. To support this, we have developed patient-reported outcome measures that can aid in the daily management of these patients. Additionally, understanding and explaining

the neuroimmunological basis of chronic pruritus can help physicians understand that there is a real reason for the condition and that a targeted treatment can indeed help these patients.

Q5 Beyond the skin, chronic urticaria and pruritus have significant systemic impacts. What is the next frontier of research in understanding the systemic comorbidities of these mast cell-mediated diseases, and what role do you see for biomarkers in predicting and managing these risks?

There are different aspects that need to be considered when looking for systemic comorbidities in chronic urticaria and chronic pruritus. On one hand, these comorbidities are derived from the consequences of signs and symptoms on our patients' quality of life. For example, we see much higher rates of anxiety and depression in these patients, and



we still have to characterise this better to raise awareness for the need for highly effective and safe treatment options. Instead of classical biomarkers, patient-reported outcome tools, such as quality-of-life assessment and screening for psychological comorbidities, are of importance. On the other hand, there are certain systemic comorbidities that are associated with chronic urticaria and chronic pruritus. For chronic urticaria, there is, for example, a higher rate of patients with other autoimmune diseases. In chronic pruritus, there may be systemic comorbidities that are the underlying cause of the condition. It will be important to further characterise biomarkers that identify these underlying causes. An important future area of research is to identify biomarkers that can predict treatment response and thus allow for patient-tailored treatment.

Q6 Given the significant unmet needs in treating patients with CSU, where do you believe future research should be focused? Should the priority be on refining existing treatments, identifying new molecular targets, or on a more personalised, stratified approach to therapy?

The goal of any treatment in CSU is complete control of the disease, meaning no more signs and symptoms. To achieve this, we will have to identify new molecular targets, but the refinement of existing treatments will also be necessary. For available therapies, the focus will be on identifying specific biomarkers that predict the response to treatment, therefore leading to a more personalised, stratified approach. Most importantly, with both existing and future treatment options, we need to be able to decide on the treatment options



best suited for each individual patient based on shared decision-making processes.

Q7 In the field of mast cell-mediated diseases, which aspects of the innate immune system do you believe are most critical for future investigations, and how might that research lead to preventative strategies rather than more reactive treatments?

In the past, only a few diseases have been considered to be truly mast cell-mediated. This includes Type I allergies, urticaria, and mastocytosis. In these diseases, the main focus will be on understanding how the activation of mast cells can be best controlled and how we can prevent any signs and symptoms. While the focus here is clearly on the biology of mast cells themselves, understanding the contribution of other immune cells, including those of the adaptive system, will be crucial

for both preventative strategies and possibilities for disease modification. We anticipate, however, that there are more or less important roles for mast cells in other diseases. Here, the contribution of mast cells needs to be characterised in detail, and the interaction between cells of the innate and adaptive immune system, as well as resident cells of the respective tissues (i.e., sensory nerves, fibroblasts, etc.), needs to be explored.

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