ABOUT THE AUTHOR

Marcus Maurer, MD

Professor of Dermatology and Allergy
Director of Research
Department of Dermatology and Allergy
Charité - Universitätsmedizin Berlin

Prof Maurer is a Dermatologist and Allergologist, and he also trained in experimental pathology at the Beth Israel Deaconess Hospital and Harvard Medical School in Boston (1995-1998); Board certification for Dermatology (2000) and Allergology (2003). Assistant Professor at the Allergie-Centrum-Charité at Charité – Universitätsmedizin Berlin (2004-2005). Since 2005, full professor at Charité. Prof. Maurer a coordinator of the Global Allergy and Asthma European Networks of urticaria and angioedema centers of reference and excellence, UCARE and ACARE. His areas of clinical interest include angioedema, urticaria, mastocytosis, pruritus, skin infections, and allergic diseases. His research is focused on the biology of mast cells, neuroimmunology, inflammation, innate immunity and tolerance. He has supervised more than 60 clinical trials, phase 1 through 4. Prof. Maurer has contributed to more than 600 publications in peer-reviewed journals and 40 books and book chapters.

MANAGEMENT OF CHRONIC URTICARIA AND ITCH: BEYOND HISTAMINE BLOCKADE

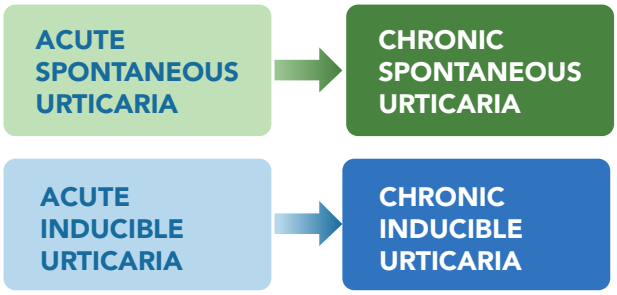
The importance of platelet activating factor in urticaria and its treatment

KEY CLINICAL TAKEAWAYS

- Urticaria, while not generally dangerous, significantly impacts quality of life and warrants medical attention. Chronic spontaneous urticaria (CSU) can last several years.
- The pathophysiology of CSU involves skin mast cell degranulation and release of histamine and other proinflammatory mediators including platelet-activating factor (PAF).
- The treatment algorithm for CSU begins with second-generation antihistamines, which can be confidently increased up to four fold the standard dose if needed.
- Rupatadine is the only second-generation antihistamine that inhibits both histamine and PAF, making it a suitable first-line choice for urticaria.
- Rupatadine has an excellent efficacy and safety profile in the treatment of both adult and pediatric CSU.

Urticaria is a skin condition characterized by the presence of wheals (also known as hives), angioedema, or both. Wheals are swollen areas of variable size that are often surrounded by reflex erythema (called a flare).[1] They typically cause itching or burning and disappear within 24 hours or less.[1] Angioedema involves an area of pronounced swelling, sometimes accompanied by pain, and takes longer to resolve (up to 72 hours) than the wheals.[1]

Urticaria falls into two distinct categories: inducible urticaria, which arises under specific environmental conditions such as heat, cold, or sun, and spontaneous urticaria, which has no known definite trigger.[1] Both inducible and spontaneous urticaria can be acute or chronic (lasting more than 6 weeks, **Figure 1**).



PREVALENCE AND IMPACT

At least 25% of people experience some form of urticaria throughout their lifespan, while chronic spontaneous urticaria (CSU) occurs in up to 1% of the population.[2] It can arise in both adults and children and affects women twice as often as men.[2] Because CSU lasts 3 to 5 years,[2] on average, it is not realistic to "let it run its course." Patients' quality of life depends on good treatment.

Although self-limited and usually not dangerous, chronic urticaria can cause substantial physical discomfort and psychological distress. The intense pruritus, for example, can significantly impair daily function and disrupt sleep.[3] Close to half of patients experience psychosocial impairments associated with chronic urticaria such as anxiety, depression, or insomnia.[4] Patients also worry their symptoms could signal

something of greater clinical concern and that angioedemia, when present in or near the upper airway, could obstruct their breathing. Reassurance is thus paramount and helps set the stage for successful treatment.

CSU DRIVERS AND DIAGNOSIS

We know that the signs and symptoms of CSU arise from pathological activation of mast cells. But what triggers the process in the first place? The strong association between CSU and major auto-immune diseases such as Hashimoto's thyroiditis and rheumatoid arthritis points to an auto-immune etiology in at least a proportion of cases.

We can distinguish between two types of autoantibody-mediated responses in urticaria: an auto-allergic response, in which IgE bound to receptors on mast cells reacts to auto-antigens such as thyroid peroxidase or interleukin 24, and (less commonly) a type IIb autoimmune response, which tends to be more severe. Both these processes lead the mast cells to degranulate and release histamine, interleukins, platelet activating factor (PAF), vascular endothelial growth factor, and various other vasoactive substances.[2]

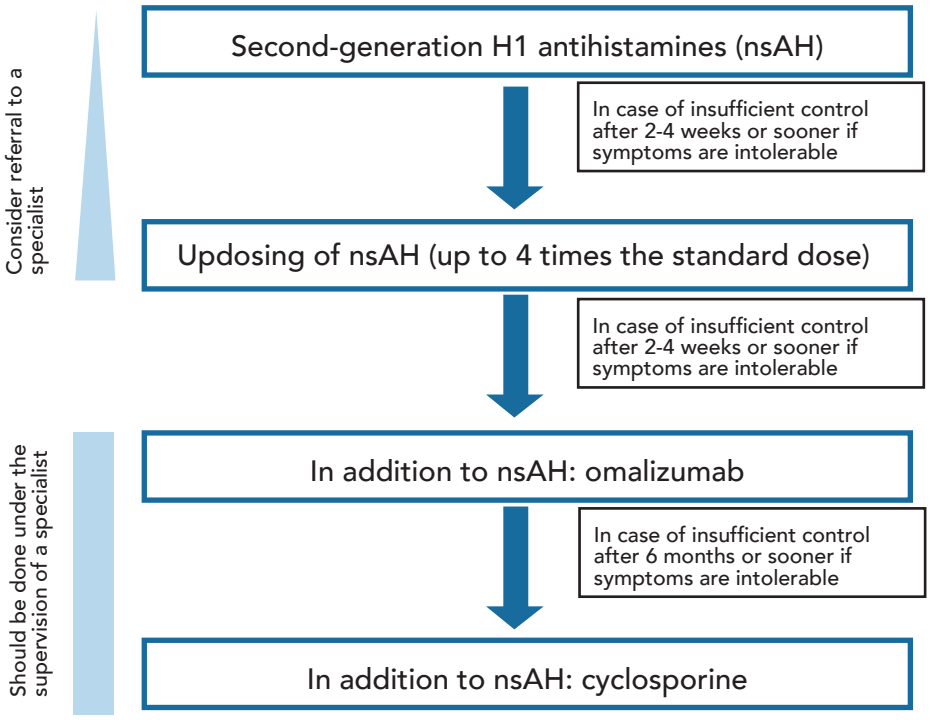
The diagnosis of CSU begins with a history (which could lead to further investigations) and a physical examination to characterize the lesions. A limited non-specific workup can help to rule out differential diagnoses.[3] Current auto-antibody screening tests for type IIb CSU include the autologous serum skin test (ASST) and the basophil testing. These tests can help to predict the course of CSU and the response to specific treatments.[2]

RAISING THE TREATMENT BAR

The goal of CSU treatment is simple, but ambitious: treat the disease until it is gone. Recent treatment advances have made this goal achievable. The team that developed the 2018 international EAACI/GA²LEN/EDF/WAO urticaria guidelines described the objective of treating patients with urticaria as "aiming at complete symptom control, considering as much as possible the safety and the quality of life of each individual patient."[1] To this end, treatment should follow the principle of "treating as much as needed and as little as possible."[1]

The treatment algorithm in the guidelines involves a stepwise approach that begins with second-generation antihistamines.[1] Compared to their first-generation predecessors, these newer antihistamines have the advantage of a superior safety profile including a reduced propensity for sedation. If standard doses do not achieve full control, the dose can be increased up to four times. If this strategy fails to control the disease, the biologic drug omalizumab is added to the antihistamine regimen (it should be noted that patients with type IIb autoimmune CSU tend to have a poorer response to omalizumab). The last step in the algorithm sequence is cyclosporine. A short course of

ALGORITHM FOR THE MANAGEMENT OF CSU[1]



Short-term treatment of flare-ups with corticosteroids can be considered at any time

glucocorticosteroids may also be considered in case of severe exacerbation.

There are many second-generation antihistamines available but one of the newest second-generation antihistamines, rupatadine, offers the unique benefit of inhibiting both histamine and platelet-activating factor (PAF). This makes it a good choice for urticaria, especially in cases where PAF is suspected to contribute significantly to the disease process.

WHY PAF MATTERS IN URTICARIA

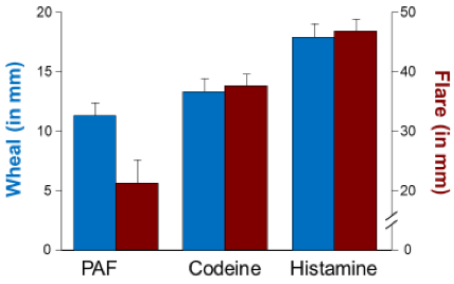
PAF is one of the pro-inflammatory substances released by mast cells. But PAF is also produced by other immune cells, such as basophils, lymphocytes, and macrophages, as well as platelets and endothelial cells.[6]

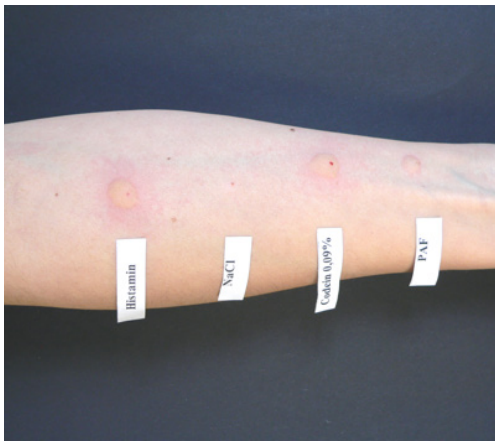
A potent signalling phospholipid, PAF contributes to the development of pruritus and plays a major role in recruiting blood cells to the skin, leading to the lesions characteristic of urticaria.[5] These effects of PAF occur independently of mast cell histamine synthesis and release.[5] Histamine is pre-formed in the mast cell granules and gets released by degranulation, while PAF is synthesized upon mast cell activation and degranulation and binds to its own receptor. PAF and histamine act separately on endothelial cells.

When injected into the skin, PAF produces a wheal, just as histamine does. PAF wheals appear and disappear in the same pattern seen with histamine wheals, although they produce smaller flare reactions.[5] A presentation of prominent wheals with small flares suggests that PAF is a key driver of the disease process.

In fact, indirect evidence suggests that CSU can come with its own "PAF signature." When compared to controls, patients with CSU make more PAF. This holds especially true for CSU patients who do not respond to standard antihistamines: in a study of 283 CSU patients and 111 controls, antihistamine nonresponders had significantly higher levels of serum PAF than antihistamine responders and controls.[6] In the study, both a higher urticaria activity score and a high PAF level significantly predicted poor response to antihistamine treatment.[6] This led the investigators to conclude that therapies that modulate PAF effects could be effective in CSU patients refractory to antihistamines.[6]

PAF INDUCES WHEAL AND FLARE REACTIONS



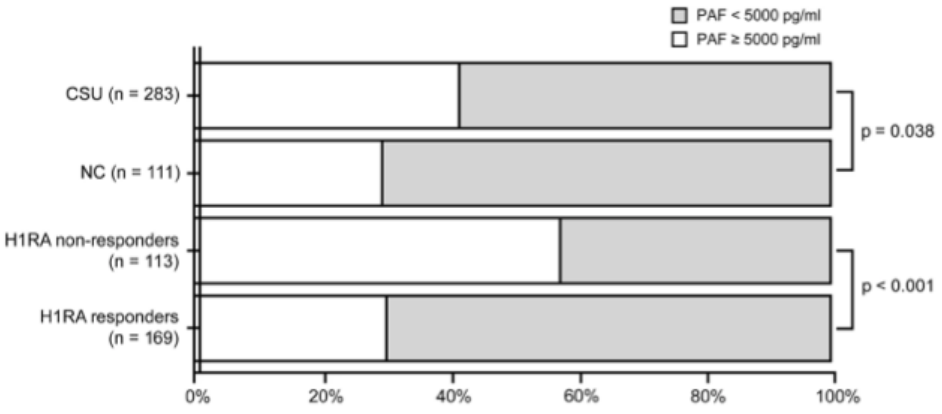


Krause, K., et al., 2013

RUPATADINE AND PAF INHIBITION

Rupatadine's dual action—against histamine and against PAF—sets it apart from other second-generation antihistamines. As demonstrated in an *in vivo* study, the second-generation antihistamines cetirizine and loratadine inhibit a histamine-

MORE PAF, LESS ANTIHISTAMINE RESPONSE

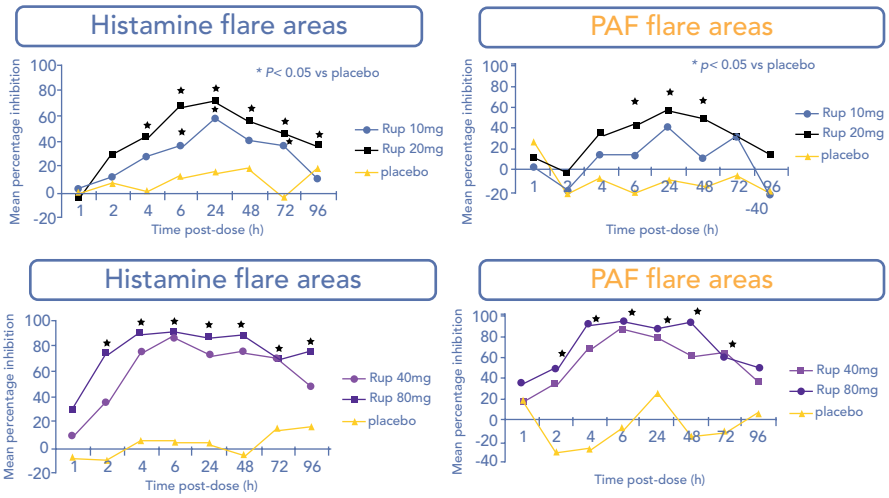


Ulambayar et al. Clin Transl Allergy 2019; 9:33.

induced wheal as effectively as rupatadine, but do not inhibit a PAF-induced wheal.[7] Given what we know about the role of PAF in chronic urticaria, it makes sense to target both histamine and PAF in CSU treatment.

Rupatadine shows a clear dose response in its inhibitory effect on both histamine- and PAF-induced flare areas. Doses of 40 mg and 80 mg are more effective with almost 100% inhibition of histamine and PAF flares than the 10 mg and 20 mg dose. In clinical terms, "more is better."

INHIBITION OF FLARE AREAS BY RUPATADINE



Izquierdo I. Drugs Today 2003; 39:451.
Picado C. Expert Opin Phamacother 2006; 7:1989.

RUPATADINE IN CLINICAL TRIALS AND PRACTICE

Numerous clinical trials have documented rupatadine's effectiveness against CSU and other forms of urticaria. In one study, designed to assess superiority, 70 CSU patients were randomized to receive either cetirizine or rupatadine. After 3 weeks, evaluations of total symptom score, number of wheals, and pruritus revealed greater reductions in these parameters with rupatadine than with cetirizine.[8] At 6 weeks, the number and size of wheals and the intensity of erythema showed a significantly greater reduction in the rupatadine arm than in the cetirizine arm ($p < 0.05$).[8] In a double-blind, randomized, parallel-group, multicentre, placebo-controlled study of pediatric CSU, patients aged 2 to 11 received either rupatadine, desloratadine or placebo oral solutions, adjusted by age over 6 weeks. Both therapies yielded a highly significant improvement in urticaria symptoms compared to placebo ($p < 0.001$), without any concerning side effects.[9] Of note, rupatadine but not desloratadine was statistically superior to placebo ($p < 0.005$) in reducing pruritus (-57%). Active treatment was also associated with a statistically significant improvement in quality of life.[9]

Rupatadine also performs well in inducible urticaria. A study of patients with cold urticaria randomized subjects to receive placebo, rupatadine 20 mg, or rupatadine 40 mg. Both doses were highly effective in reducing critical temperature thresholds ($p < 0.001$) and critical stimulation time thresholds ($p < 0.001$) without an increase in side effects.[10] Some patients with cold urticaria have such a high sensitivity that any water temperature below 27°C, which can hardly be described as cold, will trigger their symptoms. Rupatadine has been shown to work effectively on such patients, bringing their symptom-triggering threshold down to as little as 4 °C.[11]

The well-defined dose-response action of rupatadine adds to the medication's flexibility, as patients who do not improve with the standard (10 mg) dose may well respond to a higher dose. It is not necessary to titrate the dose incrementally in a step-wise fashion: in line with the international guidelines, the dose can be increased directly from 10 to 40 mg.[1] If the urticaria symptoms resolve, the dose can be titrated back down to 20 mg—and titrated back to 40 mg if symptoms return. If even 40 mg proves insufficient, the dose can be safely increased to 60 or 80 mg as an alternative to adding omalizumab to the regimen. The clinical approach is to establish control as soon as possible and then determine the lowest effective dose, following the principle of

"treating as much as needed and as little as possible." The improvement in itch seen with rupatadine is often quite rapid. In a subgroup analysis of 206 Japanese patients with itch, either as an isolated symptom or associated with urticaria or dermatitis, responders to rupatadine 10 mg experienced a 1-point improvement in total pruritus score within 3-7 days of treatment.[12] Given this rapid onset, it is reasonable to consider a dose increase (20 mg) if a patient has not responded appreciably to the 10 mg dose within two weeks.[12]

ASSESSING TREATMENT RESPONSE

Several validated instruments and scales are available to evaluate response to treatment. Some measure disease activity, others evaluate disease control, and still others focus on quality of life. The scores help clinicians make treatment decisions while giving patients a tangible indicator of their progress.

The urticaria control test (UCT), a validated instrument, is especially efficient and easy to use in clinical practice[13,14]. Consisting of just 4 questions, it encompasses physical symptoms, quality of life, and degree of disease control. Patients respond to the questions with a number from 0 to 4, with 4 representing the best result. A total score of 12 or more (out of 16) indicates well-controlled disease. With the current treatments available, there is no reason to aim for anything less than complete or near-complete control.

URTICARIA CONTROL TEST

1. How much have you suffered from the physical symptoms of the urticaria (itch, hives (welts) and/or swelling) in the last 4 weeks?				
[0] Very much	[1] Much	[2] Somewhat	[3] A little	[4] Not at all
2. How much was your quality of life affected by the urticaria in the last 4 weeks?				
[0] Very much	[1] Much	[2] Somewhat	[3] A little	[4] Not at all
3. How often was the treatment for your urticaria in the last 4 weeks not enough to control your urticaria symptoms?				
[0] Very Often	[1] Often	[2] Sometimes	[3] Seldom	[4] Not at all
4. Overall, how well have you had your urticaria under control over the last 4 weeks?				
[0] Very much	[1] A little	[2] Somewhat	[3] Well	[4] Very Well

Weller et al. J Allergy Clin Immunol 2014: 133;1365.

LOOKING AHEAD

Researchers have used rupatadine for other skin disorders involving itch, often with excellent results. This should not come as a surprise, given that mast cells drive inflammation in many skin diseases. If the standard dose doesn't work, updosing is an option.

The future promises still more options for people with urticaria and other itch-inducing skin disorders. The advent of omalizumab has spurred the investigation of other biologics that target specific cells or soluble targets in the disease process. The list includes, but is not limited to sekukinumab, benralizumab, lirentelimab, avdoralimab and ligezulimab.

Fortunately, clinicians need not wait for these agents to provide effective treatment to our patients with urticaria. The current tools at our disposal allow us to send these patients a confident message: "You have come to the right place, and we can help you."

TREATING CSU IN THE REAL WORLD: Q&A WITH DR. MAURER

Q: What is the role of pseudoallergens and elimination diets in CSU?

A: While pseudoallergens in food may play a role in a minority of cases, we no longer advocate a pseudoallergen-free diet as a routine strategy, because it requires too much effort for too little reward. It may be worthwhile if the patient history provides compelling clues. We know that CSU is an autoimmune disease and know how to treat it on that basis.

Q: Can CSU arise in pregnancy, and is rupatadine safe for pregnant women?

A: Research has shown that CSU may get worse, better, or not change at all during pregnancy. While all newer antihistamines appear to be safe during pregnancy, we should be prudent and opt for those with the most long-term

safety data, such as loratadine and cetirizine.

Q: Does sedation increase at higher doses of rupatadine?

A: I have never observed sedation at 40 mg and only rarely at 80 mg. As with all medications, the right balance between efficacy and side effects varies between patients.

Q: How significant is stress as a urticaria trigger and what mechanism is involved?

A: About half of patients report stress as a trigger. Stress induces the peripheral release of neuropeptides, including substance P, which is a prototype ligand of the MRGPRX2 receptor. This translates to a peripheral inflammatory response that can result in mast cell degranulation.

Q: Does rupatadine affect platelet counts?

A: No, it doesn't. You don't need to have any concern about this in either children or adults.

Q: How effective is rupatadine for the itch in atopic dermatitis (AD)?

A: We know from clinical experience that antihistamines don't work as well in AD as in urticaria or allergic rhinitis. While AD is partly driven by mast cells, we believe that other histamine-independent pathways contribute to the itch component. However, there is no harm in trying an antihistamine for AD, though you should not expect the same level of response. If it doesn't work, you can move on to other treatments.

Q: Might measuring PAF levels help us tailor therapy for CSU?

A: Measuring PAF has proven very challenging to date. For the time being we use indirect measures such as degrading enzyme levels, so we are not yet in a position to fine-tune therapy based on PAF levels.

Q: Can we predict which patients will have a poor response to omalizumab and tailor our treatment accordingly?

A: I generally recommend doing IgE and thyroid antibody (anti-TPO) tests. A low IgE and elevated anti-TPO are good markers of auto-immune CSU, which has a poorer response to omalizumab. In such a case, be ready to raise the dose of antihistamine more quickly.

Q: When starting a patient on omalizumab, do you continue or stop the antihistamine?

A: Patients who have no response to high-dose antihistamines can stop taking them before starting omalizumab. If they have a partial response, I keep them on the antihistamines until the omalizumab takes full effect. In some cases it makes sense to continue the combination indefinitely.

References

1. Zuberbier, Torsten, et al. "The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria." Allergy 73.7 (2018): 1393-1414.

2. Mandel, Victor Desmond, et al. "Chronic Spontaneous Urticaria: A Review of Pathological Mechanisms, Diagnosis, Clinical Management, and Treatment." EMJ 5.1 (2020): 29-39.

3. Schaefer, Paul. "Acute and chronic urticaria: evaluation and treatment." American family physician 95.11 (2017): 717-724.

4. Kolkhir, Pavel, et al. "New treatments for chronic urticaria." Annals of Allergy, Asthma & Immunology 124.1 (2020): 2-12.

5. Krause, K., et al. "Platelet-activating factor (PAF) induces wheal and flare skin reactions independent of mast cell degranulation." Allergy 68.2 (2013): 256-258.

6. Ulambayar, Bastsetseg, et al. "Increased platelet activating factor levels in chronic spontaneous urticaria predicts refractoriness to antihistamine treatment: an observational study." Clinical and translational allergy 9.1 (2019): 1-8.

7. Queralt, Mireia, et al. "Dual effect of a new compound, rupatadine, on edema induced by platelet-activating factor and histamine in dogs: Comparison with antihistamines and PAF antagonists." Drug development research 39.1 (1996): 12-18.

8. Dakhale, Ganesh N., et al. "Clinical effectiveness and safety of cetirizine versus rupatadine in chronic spontaneous urticaria: a randomized, double-blind, 6-week trial." International journal of dermatology 53.5 (2014): 643-649.

9. Potter, Paul, et al. "Rupatadine is effective in the treatment of chronic spontaneous urticaria in children aged 2–11 years." Pediatric Allergy and Immunology 27.1 (2016): 55-61.

10. Abajian, Marina, et al. "Rupatadine 20 mg and 40 mg are effective in reducing the symptoms of chronic cold urticaria." Acta dermato-venereologica 96.1 (2016): 56-59.

11. Metz, Martin, et al. "Rupatadine and its effects on symptom control, stimulation time, and temperature thresholds in patients with acquired cold urticaria." Annals of Allergy, Asthma & Immunology 104.1 (2010): 86-92.

12. Hide, Michihiro, et al. "Efficacy of increased dose of rupatadine up to 20 mg on itching in Japanese patients due to chronic spontaneous urticaria, dermatitis, or pruritus: A post hoc analysis of phase III clinical trial." Journal of Cutaneous Immunology and Allergy 2.5 (2019): 128-134.

13. Ohanyan, Tatevik, et al. "Responsiveness and minimal important difference of the urticaria control test." Journal of Allergy and Clinical Immunology 140.6 (2017): 1710-1713.

14. Kocatürk, Emek, et al. "Validation of the Turkish version of the Urticaria Control Test: correlation with other tools and comparison between spontaneous and inducible chronic urticaria." World Allergy Organization Journal 12.1 (2019): 100009.