Unlocking the pathogenesis of chronic spontaneous urticaria to inform the future treatment landscape

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Agenda

- Diagnosing CSU: Reducing the impact on patients
- What lies beneath: The pathogenesis of CSU
- CSU treatment landscape: Current recommendations and future therapies

CSU, chronic spontaneous urticaria.

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Expert panel

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Recognizing the emotional and physical burden of CSU

CSU can be challenging to manage and substantially affects QoL beyond skin manifestations[1–3]

Physical

- Skin manifestations (e.g. angioedema)
- Pain and itching
- Disease- and symptom-control status

Emotional and psychological

- Anxiety, depression and fear
- Dissatisfaction/frustration with treatment
- Fatigue and sleep disturbances

Socioeconomic

- Work functionality and productivity loss
- Increased healthcare costs and resource use
- Socializes less frequently

Role function and relationships

- Interference in daily activities (avoid triggers)
- Negative effect on personal and family relationships

Meaningful patient–physician engagement is needed to support individualized treatment that addresses unmet emotional and holistic care needs, in addition to effective disease and symptom control

CSU, chronic spontaneous urticaria; QoL, quality of life.

1. Goldstein S, et al. *Acta Derm Venereol.* 2019;99:1091–8; 2. Maurer M, et al. *Allergy.* 2017;72:2005–16; 3. Wagner N, et al. *Dermatol Ther (Heidelb).* 2021;11:1027–39.

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Remaining unmet needs and burden for patients living with CSU

Real-world evidence highlights ongoing unmet needs in CSU, with patients often remaining undertreated, highlighting a need for greater awareness of guidelines and management[1–5]

- Diagnostic and treatment delays while enduring symptoms
- Angioedema under-reported yet significantly impacts HR-QoL, sleep and daily functionality
- Adequate disease and symptom control remain challenging
- Gap between physician-perceived disease severity vs patient perception and experience
- Suboptimal patient satisfaction with treatment and effectiveness of medication

CSU, chronic spontaneous urticaria; HR-QoL, health-related quality of life.

1. Wagner N, et al. *Dermatol Ther (Heidelb).* 2021;11:1027–39; 2. Maurer M, et al. *Clin Exp Allergy.* 2020;50:1166–75; 3. Maurer M, et al. *Allergy.* 2017;72:2005–16; 4. Sussman G, et al. *Allergy.* 2018;73:1724–34; 5. Hoskin B, et al. *Curr Med Res Opin.* 2019;35:1387–95.

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PRO tools in CSU

Activity

Control

QoL

Wheals ± angioedema

UAS7

- Once- or twice-daily diary-based PRO
- Once- and twice-daily reporting yield similar results (ASSURE-CSU data)[1]

UCT

- Strong correlation with UAS[2]

CU-Q2oL

- Good sensitivity for assessing change, with an MCID of 3–15 in cohorts in Europe and Asia[2]

Angioedema ± wheals

AAS

- Valid and reliable test–retest assessments
- Sensitive to change in activity (MCID 8)[2]

AECT

- First valid and reliable PRO to measure recurrent angioedema[3]

AE-QoL

- High sensitivity to change (MCID 6)[2]

AAS, Angioedema Activity Score; AECT, Angioedema Control Test; AE-QoL; Angioedema QoL Questionnaire; CSU, chronic spontaneous urticaria; CU-Q2oL, Chronic Urticaria QoL Questionnaire; MCID, minimally clinically important difference; PRO, patient-reported outcomes; QoL, quality of life; UAS, Urticaria Activity Score; UAS7, UAS over 7 days; UCT, Urticaria Control Test.

1. Hollis K, et al. *Am J Clin Dermatol.* 2018;19:267–74; 2. Maurer M, et al. *Int Arch Allergy Immunol.* 2020;181:321–33;
3. Weller K, et al. *J Allergy Clin Immunol Pract.* 2020;8:2050–7.e4.

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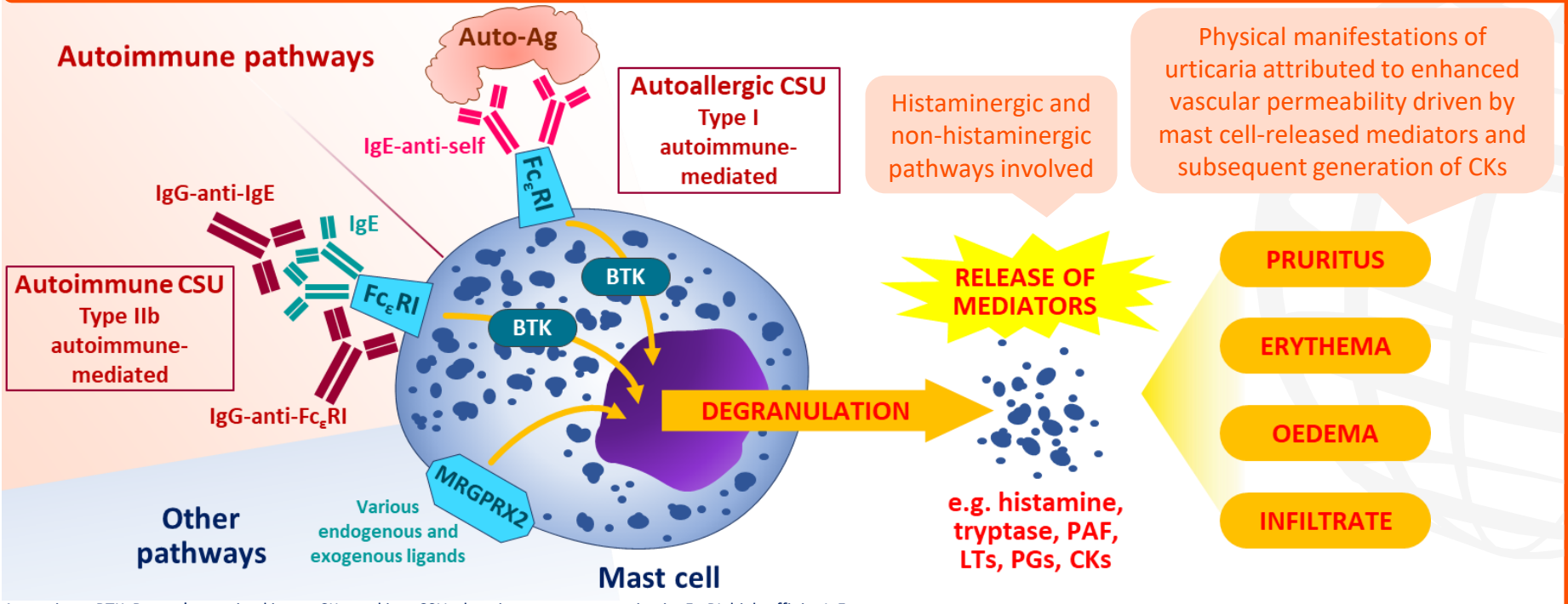
Understanding CSU as a mast-cell dependent disease

Aberrant mast cell activation and degranulation is central to the pathophysiology of CSU[1–4]



Ag, antigen; BTK, Bruton's tyrosine kinase; CK, cytokine; CSU, chronic spontaneous urticaria; $Fc_{\varepsilon}RI$, high-affinity IgE receptor; Ig, immunoglobulin; LT, leukotriene; MRGPRX2, Mas-related G protein-coupled receptor member X2; PAF, platelet activating factor; PG, prostaglandins.

1. Mendes-Bastos P, et al. *Allergy.* 2022;doi: 10.1111/all.15261; 2. Kolkhir P, et al. *J Allergy Clin Immunol.* 2017;139:1772; 3. Metz M, et al. *Clin Rev Allergy Immunol.* 2020;59:38–45; 4. Quan PL, et al. *Int J Mol Sci.* 2021 May;22:4421.

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Clinical management of CSU: Where are we now?

EAACI/GA²LEN/EuroGuiDerm/APAAACI: Recommended treatment algorithm for urticaria[1]

Consider specialist referral | **Perform under specialist supervision**

First line
sgAH at standard dose

If needed, increase sgAH dose (up to 4×)

If inadequate control after 2–4 weeks or earlier if symptoms intolerable

Second line*
Add on to sgAH: omalizumab 300 mg q4w

If needed, increase dose/shorten internal (up to 600 mg q2w)

If inadequate control within 6 months or earlier if symptoms intolerable

Third line*
Add on to sgAH: cyclosporine (up to 5 mg/kg body weight)

A short course of glucocorticosteroids may be considered in case of exacerbation

Treatment response rates:[2]

- First line: Effective in <50% patients. Increased dose improves response, but 25–33% of patients remain symptomatic
- Second line*: Complete response rates range from 26% to 83% (in clinical trials)
- Third line*: Some data to suggest benefit in omalizumab non-responders

*Second and third line only apply to chronic urticaria only. APAAACI, Asia Pacific Association of Allergy, Asthma and Clinical Immunology; CSU, chronic spontaneous urticaria; EAACI, European Academy of Allergy and Clinical Immunology; EuroGuiDerm, European Centre for Guidelines Development; GA²LEN, Global Allergy and Asthma European Network; q2w, every 2 weeks; q4w, every 4 weeks; sgAH, second-generation H_1-antihistamine.

1. Zuberbier T, et al. *Allergy*. 2022;77:734–66; 2. Fok JS, et al. *Allergy*. 2021;76:2965–81.

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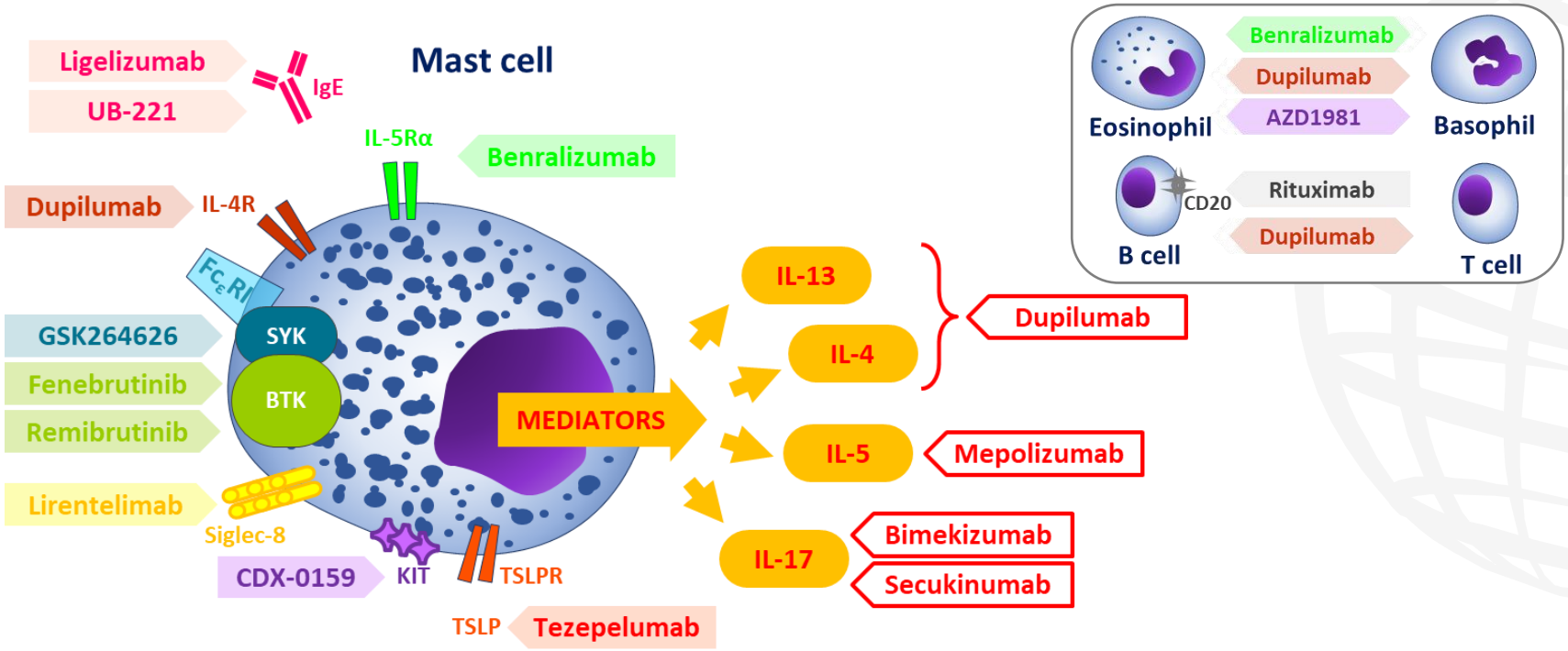
Emerging therapeutic targets for CSU

Targeting cellular and humoral pathogenic mediators in CSU[1–3]



BTK, Bruton's tyrosine kinase; CD, cluster of differentiation; CSU, chronic spontaneous urticaria; Ig, immunoglobulin; IL, interleukin; PGD2, prostaglandin D2; R, receptor; siglec-8, sialic acid-binding Ig-like lectin 8; SYK, spleen tyrosine kinase; TSLP(R), thymic stromal lymphopoietin (receptor).

1. Kolkhir P, et al. *Ann Allergy Asthma Immunol.* 2020;124:2–12; 2. Metz M, Maurer M. *Allergol Select.* 2021;5:89–95; 3. Toubi E, Vadasz Z. *Immunotargets Ther*. 2020;9:217–23.

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