Chronic Spontaneous Urticaria

2nd Annual OSDPA "A Day in Derm" Conference
October 18, 2025

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Objectives

- Define Chronic Spontaneous Urticaria (CSU) and review its clinical features
- Review the impact of CSU on affected patients' physical and psychological quality of life and diagnostic work-up
- Explain the current understanding of CSU's pathophysiology
- Describe current and emerging treatment strategies for CSU

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Urticaria

- Raised, pink/erythematous, circumscribed wheals that are markedly pruritic
  - Range from a few mm to several cm in size and may coalesce
- Evanescent; Individual wheals typically arise and resolve within 30 min - 24 hrs
- Generally worsened by scratching
- Any area of the body may be involved; most commonly the trunk, arms, legs





Urticaria





Angioedema

- Localized and self-limiting swelling of the lower dermis or subcutaneous/submucosal tissue, due to temporary increase in vascular permeability
  - Most commonly occurs on the face
    - - perioral and periorbital regions, tongue
  - Typically associated with tingling, burning, tightness, and sometimes pain
  - Resolution is slower than wheals (up to 72 hrs)

Kolkhir P, et al. Nat Rev Dis Primers. 2022 Sep 15;8(1):61

Angioedema





Classification of Urticaria

- 10-20% will experience an episode during lifetime

- Classification is based on:
  - **Duration**
    - **Acute: < 6 weeks in duration**
      - Cause identified in 10-15%
      - > 90% chance of remission
    - **Chronic: > 6 weeks in duration**
      - Cause identified in < 5%
      - ≤ 50% chance of remission

  - **Identification of triggers**
    - Inducible triggers: cold, heat, pressure, UV/visible light, vibration, water, sweating, contact allergens, others
    - No inducible triggers: spontaneous

Cleveland Clinic

Kolkhir P, et al. Nat Rev Dis Primers. 2022 Sep 15;8(1):61

Chronic Spontaneous Urticaria

- Defined as episodic development of urticaria +/- angioedema without specific triggers that persists for > 6 weeks

- 57% present with only wheals
- ~37% present with both wheals and angioedema
- ~6% present only with angioedema

Cleveland Clinic

Zuberbier T, et al. Allergy 2022; 77: 734-66
Kolkhir P, et al. Nat Rev Dis Primers. 2022 Sep 15;8(1):61

Epidemiology of CSU

- Point prevalence in U.S. is 0.08 – 0.1%
  - No significant changes in global prevalence, incidence, and yrs life lived with disability for urticaria between 1990 - 2017
- Can occur at any age, but most common between 30–50 years
  - < 15% at 19 yrs or younger
- In adult patients, female:male ratio is ~2:1
  - Gender differences less pronounced in children with CSU

Cleveland Clinic

Kolkhir P, et al. Nat Rev Dis Primers. 2022 Sep 15;8(1):61
Kolkhir P. JAMA 2024; 332: 1464-1477

Characteristics of CSU

- Signs / symptoms of CSU can occur spontaneously any time of day but commonly during evening and night
- In most pts with moderate/severe CSU, wheals and/or angioedema occur daily or nearly daily basis or show an intermittent–recurrent course
- In some pts, stress, drugs (mostly NSAIDs), infections, or foods (rarely) can lead to CSU exacerbations.
  - NSAID hypersensitivity observed in up to 30% of CSU pts
- Mean or Median disease duration of ~1-4 yrs
  - Estimates for remission:1 yr (17%); 5 yrs (45%); 20 yrs (73%)
  - Relapses occur in 6-31% of pts

Cleveland Clinic

Kolkhir P, et al. Nat Rev Dis Primers. 2022 Sep 15;8(1):61
Balp, MM et al. Derm. Ther. 2022; 12: 15–27

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CSU Comorbidities

- Chronic Inducible Urticaria (CIU) is a comorbidity in > 10% of pts with CSU
  - Of 245 CSU pts, 36% had CIU confirmed by a positive challenge test, mostly symptomatic dermographism (25%) and cold urticaria (13%)
  - Multiple types of CIU may coexist in same CSU pt

- Autoimmune diseases present in ~30% of CSU pts
  - most frequently autoimmune thyroid diseases (~25%, mostly Hashimoto's thyroiditis), vitiligo, rheumatoid arthritis, lupus erythematosus, celiac disease, and diabetes mellitus (1–2%)

- Allergic diseases may be overrepresented (17% have atopy)

Kolkhir P, et al. Nat Rev Dis Primers. 2022 Sep 15;8(1):61
Sánchez, J. et al.. J. Allergy Clin. Immunol. Pract. 2017; 5, 464–470
Skander, et al. Eur. Ann. Allergy Clin. Immunol. 2021; 53, 91–93
Gonçalo M, et al Br J Dermatol. 2021 Feb;184(2):226-236

Disease Burden of CSU is Significant

- Physical Burden
  - Debilitating pruritus (most impactful symptom)
  - Concurrent CIU or angioedema
  - Physical appearance
  - Significant sleep impairment
  - Fatigue

- Other Contributing Factors
  - Delay in diagnosis and/or adequate treatment
  - Chronic nature of disease (≥ 5 years in up to ~ 60% of pts)
  - Unpredictable course (2nd most impactful symptom)
  - Presence of associated comorbid diseases

Cleveland Clinic

Maurer M, et al. Allergy. 2017 Dec;72(12):2005-2016
Kolkhir P, et al. *Nat Rev Dis Primers*. 2022;8(1):61. 16
Gonçalo M, et al. Br J Dermatol. 2021 Feb;184(2):226-236

CSU Impairs Quality of Life

- **Physical QOL**
  - Impaired ability to perform ADLs, participate in recreational activities, perform work tasks
- **Socioeconomic QOL**
  - Adverse affects on relationships, school/work performance (difficulty concentrating)
- **Psychological QOL**
  - Sense of lack of control over their lives
  - Embarrassment, frustration, self-consciousness, shame
  - Up to 33% of CSU pts have a psychiatric disorder
    - Risk of depression is 1.5x and risk of anxiety is 2x higher in CSU pts compared to those without CSU
    - Depression may have pathophysiological link in CSU pts to increases in the neuropeptide substance P
- Overall QOL impairment of CSU similar to pts with moderate to severe psoriasis and atopic dermatitis

Vietri J, et al. Ann Allergy Asthma Immunol. 2015;115(4):306-311; Huang Y, et al. Front Psychiatry. 2021;12:655802; Memet B, et al. Front Psychiatry. 2021;12:667978; Grob JJ, et al. Br. J. Dermatol. 2005; 152, 289–295

CSU Differential Diagnosis

- Chronic Inducible Urticaria (i.e., dermatographism, pressure, solar, cold…)
- Hereditary angioedema and ACE-inhibitor-associated angioedema
- Urticarial Vasculitis
- Paraneoplastic (Underlying Neoplasms)
- Infections
- Other autoimmune diseases (urticarial bullous pemphigoid, etc.)
- Endocrinopathies (thyroid dysfunction)
- Urticarial Drug Reactions
- Autoinflammatory disorders (Schnitzler's syndrome)
- Hypereosinophilic syndrome
- Cutaneous Mastocytosis

Kolkhir P, et al. Nat Rev Dis Primers. 2022 Sep 15;8(1):61
Kolkhir P. JAMA 2024; 332: 1464-1477

Diagnostic Evaluation

History and Physical Examination

- Onset (e.g. timing of symptoms with medication changes or other exposures)
- Frequency, duration, severity, localization of wheals and itching
- Pattern of symptoms (time of day, days per week, season, etc.)
- Precipitating factors (e.g. physical stimuli, exertion, stress, food, etc.)
- Relation to occupation and/or leisure activities
- Associated angioedema, systemic symptoms (HA, arthralgias, GI sxs, etc.)
- Known allergies, infections, systemic illnesses or other possible causes
- Family hx of urticaria and atopy
- Degree of QOL impairment
- Response to prior treatment
- General physical examination

Lesional Skin biopsy

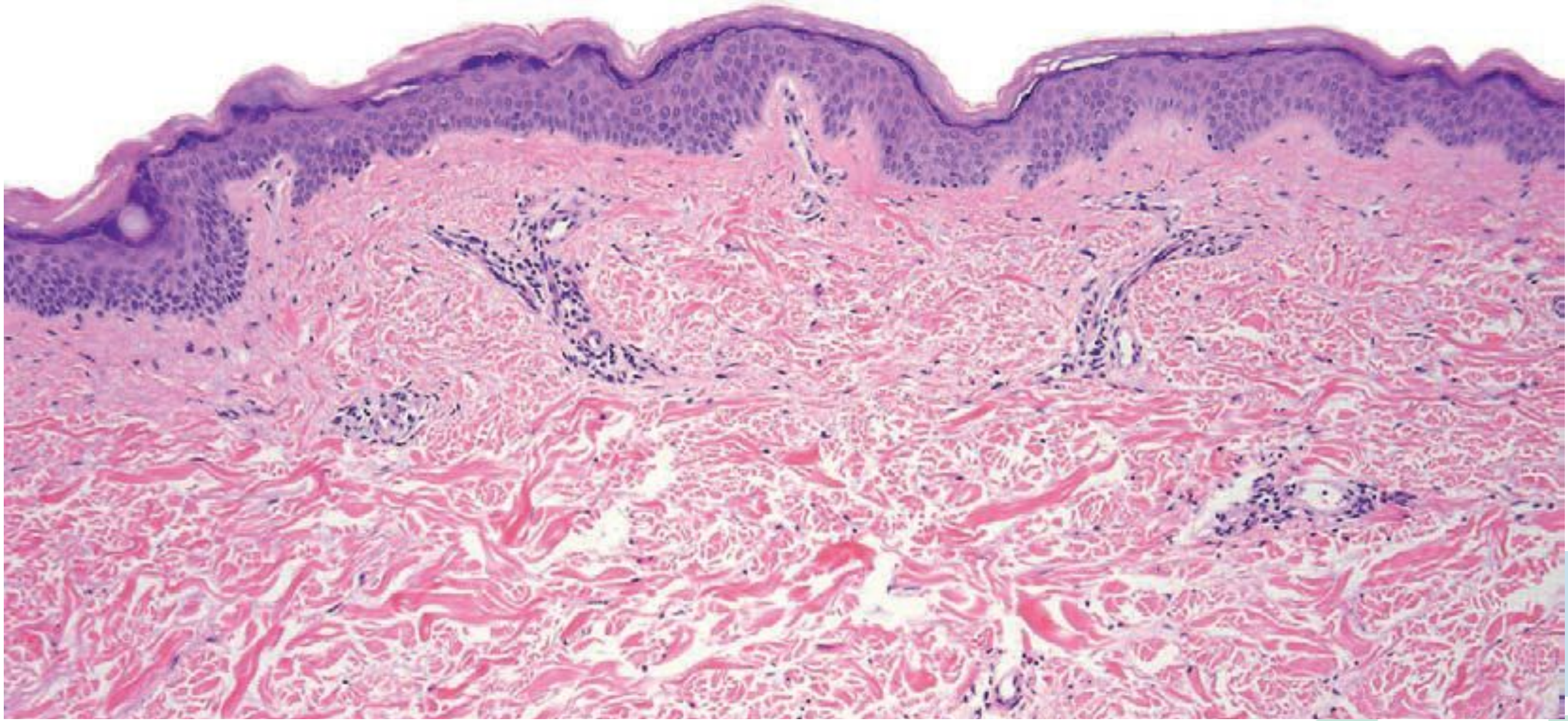
- Urticarial vasculitis
  - 4 “P’s”
    - Persistent (>24 hrs), painful, purpuric, pigmented (post-inflammatory)

- Urticarial-phase bullous pemphigoid
  - Older pts (> 65 yrs) with persistent lesions
    - Consider additional biopsy for DIF

Urticaria



Urticaria

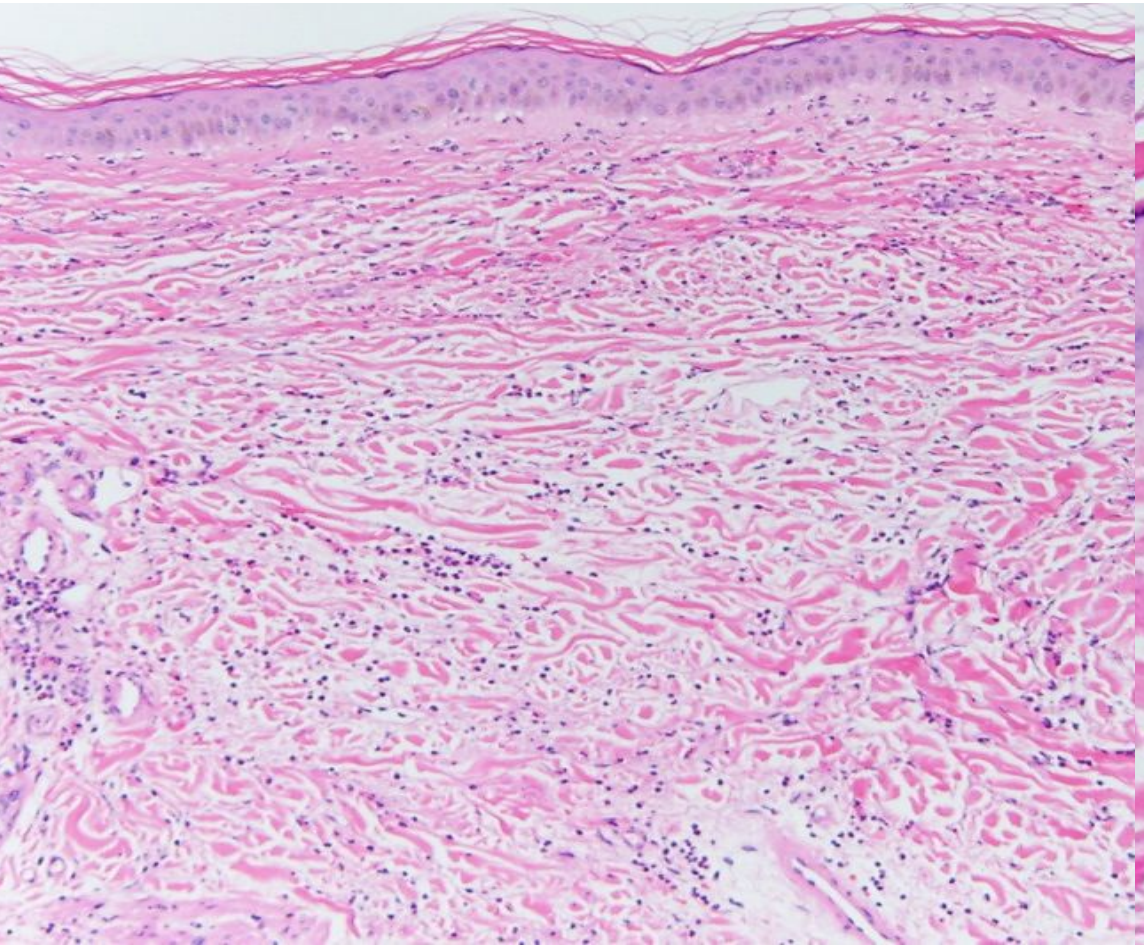


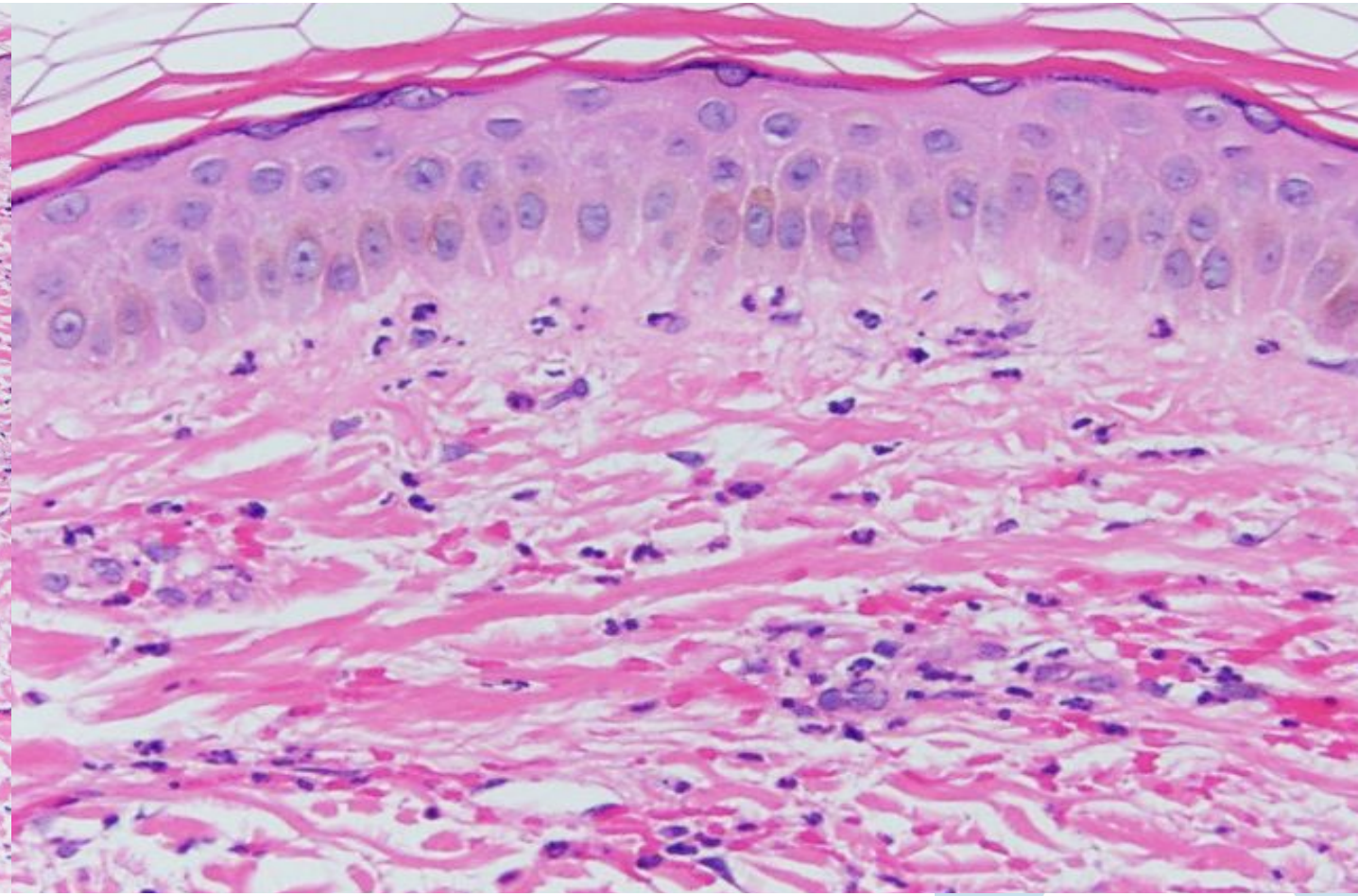
- Mild superficial perivascular inflammatory infiltrate with eosinophils and neutrophils
- Dermal edema present but can be subtle; deep dermal inflammation usually absent

Urticarial Vasculitis



Urticarial Vasculitis





- Fixed urticarial lesions that are often painful and heal with pigment alteration or purpura
- Histologic evidence of vasculitis, which may be subtle but includes erythrocyte extravastion and endothelial damage

Urticarial-Phase Bullous Pemphigoid





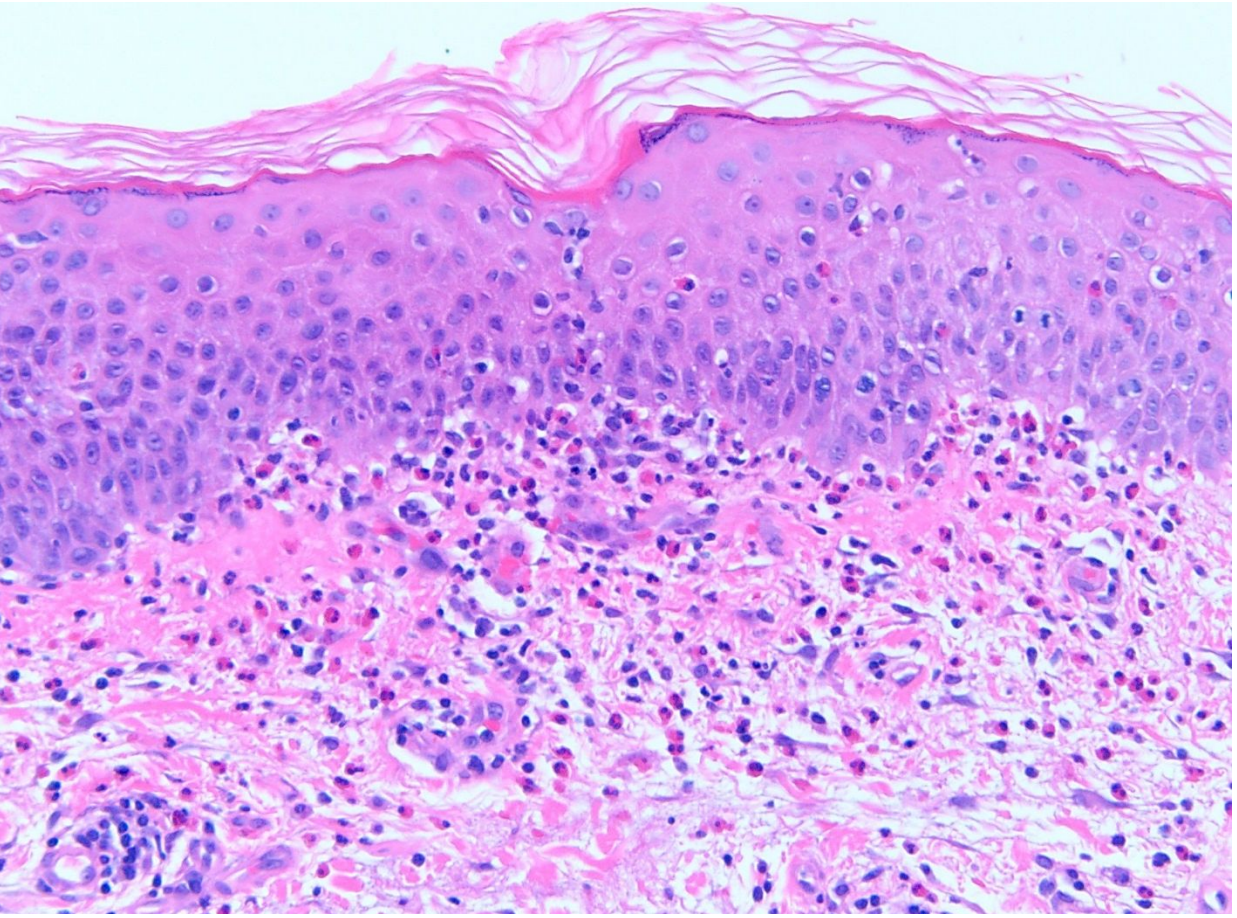
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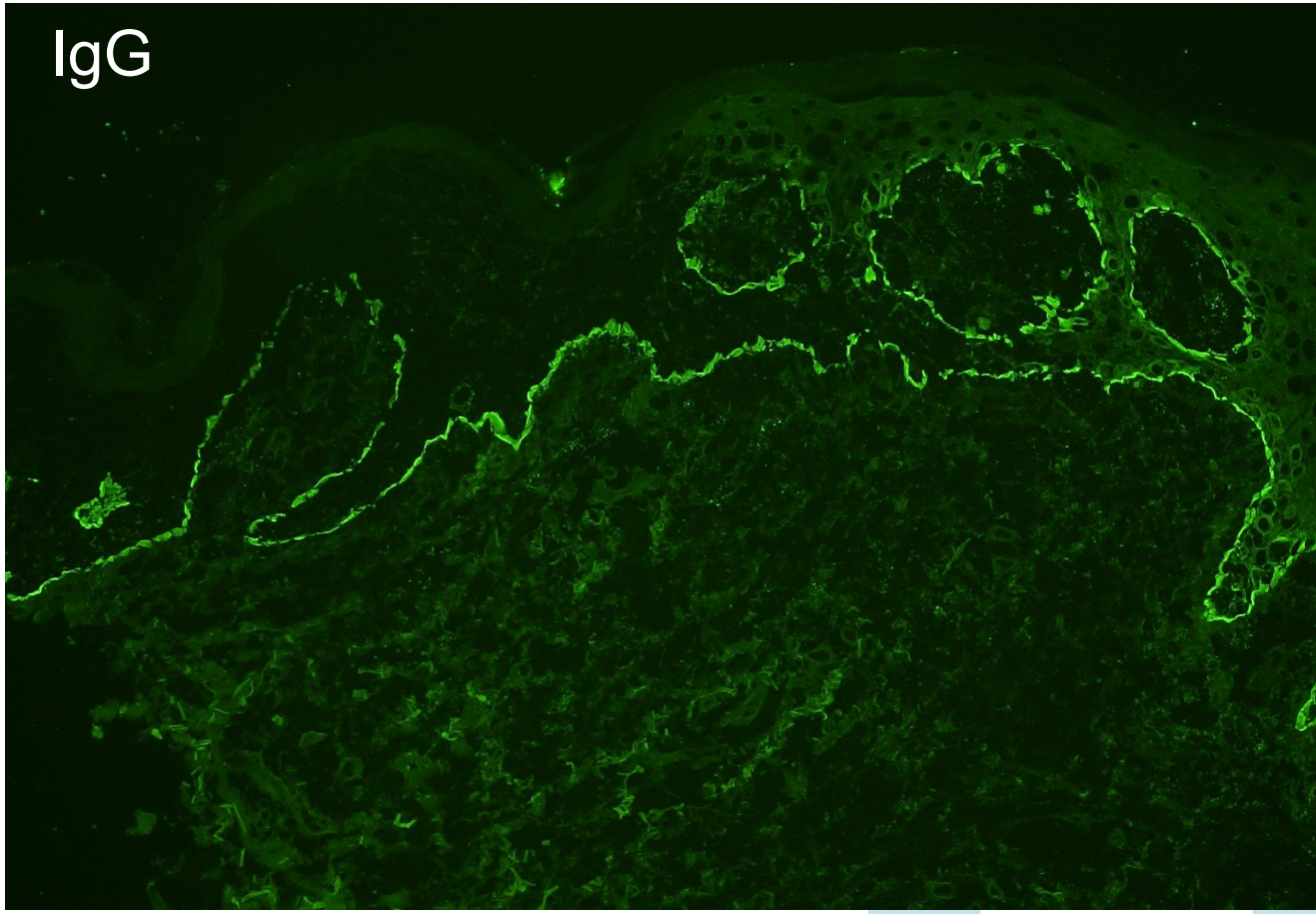


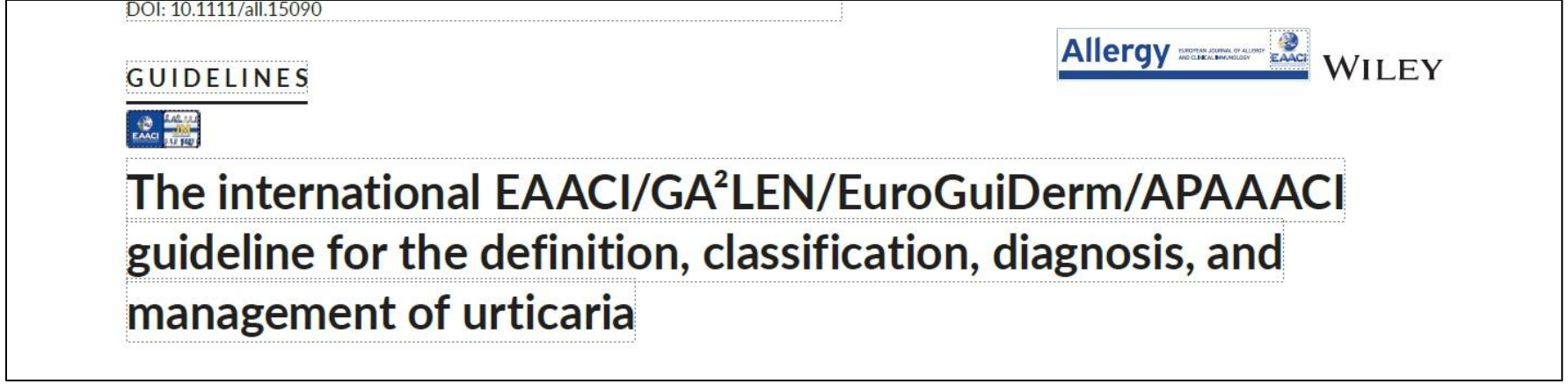


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Urticarial-Phase Bullous Pemphigoid







- Basic tests recommended include CBC with diff, CRP and/or ESR, and in specialized care total IgE and anti-thyroid peroxidase (TPO) IgG levels
  - Strong expert consensus (>75% agreement)

- Aim is to help exclude other diagnoses and possibly identify comorbidities and underlying causes such as autoimmunity, infection, and cancer

- Latter 2 added based on evidence that CSU can be due to autoallergic or autoimmune-mediated skin mast cell activation
  - Pts with autoimmune CSU more likely to have low total IgE and elevated anti-TPO IgG
  - High ratio of anti-TPO IgG : total IgE is currently best surrogate marker for autoimmune CSU

Zuberbier T, et al. Allergy. 2022 Mar;77(3):734-766; Kolkhir P. JAMA 2024; 332: 1464-1477; Zuberbier T, et al. J Allergy Clin Immunol. 2022 Dec;150(6):1249-1255

Additional Diagnostic Testing

Should we be routinely ordering laboratory tests on patients with CSU?

- Extensive general screening or work-up for rare causes not recommended
  - No improvement in pt outcomes, cost/benefit not favorable

Utility of routine laboratory testing in management of chronic urticaria/angioedema

James A. Tarbox, MD; Ravi C. Gutta, MD; Cristine Radojicic, MD; and David M. Lang, MD*

- 356 CSU pts who had diagnostic testing (BMP, CBC, ANA, ESR, CRP, TSH, TPO, etc.) as part of their urticaria evaluation
  - 166 with urticaria and angioedema (AE), 187 with only urticaria, and 3 with only AE
- Among 1,872 tests ordered, 319 (17%) had abnormal results
  - 30 abnormal test results led to changes in management (1.60% of all tests)
- Of 356 pts, only 1 pt (0.28%) improved/benefited from a subsequent change in management
- Conclusion: Laboratory testing in CSU pts referred for Allergy/Immunology evaluation rarely leads to management changes resulting in improved outcomes of care

Lang DM, et al. Ann Allergy Asthma Immunol May 2011

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CSU is a Mast Cell Driven Disease

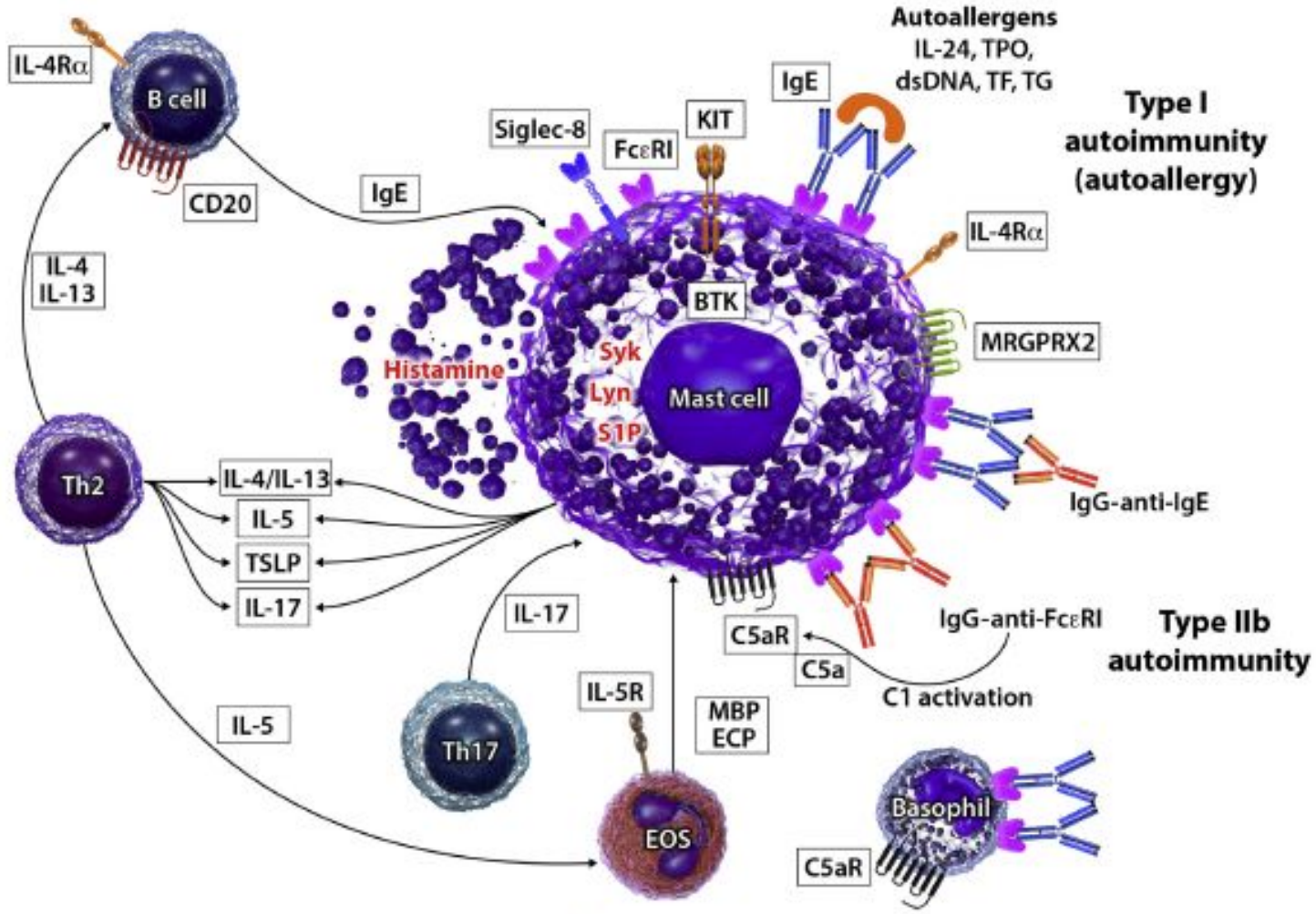


FIG 1. Type I and type IIb CSU endotypes.[8] *dsDNA*, Double-stranded DNA; *C5aR*, complement 5a receptor; *C1*, complement 1; *CD20*, cluster of differentiation 20; *MBP*, major basic protein; *ECP*, eosinophilic cationic protein; *TSLP*, thymic stromal lymphopoietin.

Review article

Chronic spontaneous urticaria and chronic inducible urticaria

Rina Lee, MD, and Jonathan A. Bernstein, MD *Cincinnati, Ohio*

Chronic spontaneous urticaria guidelines: What is new?

Check for updates

Torsten Zuberbier, MD,[a,b] Jonathan A. Bernstein, MD,[c] and Marcus Maurer, MD[a,b] *Berlin, Germany, and Cincinnati, Ohio*

International Urticaria Guidelines*

*2-4 wks

sgAH

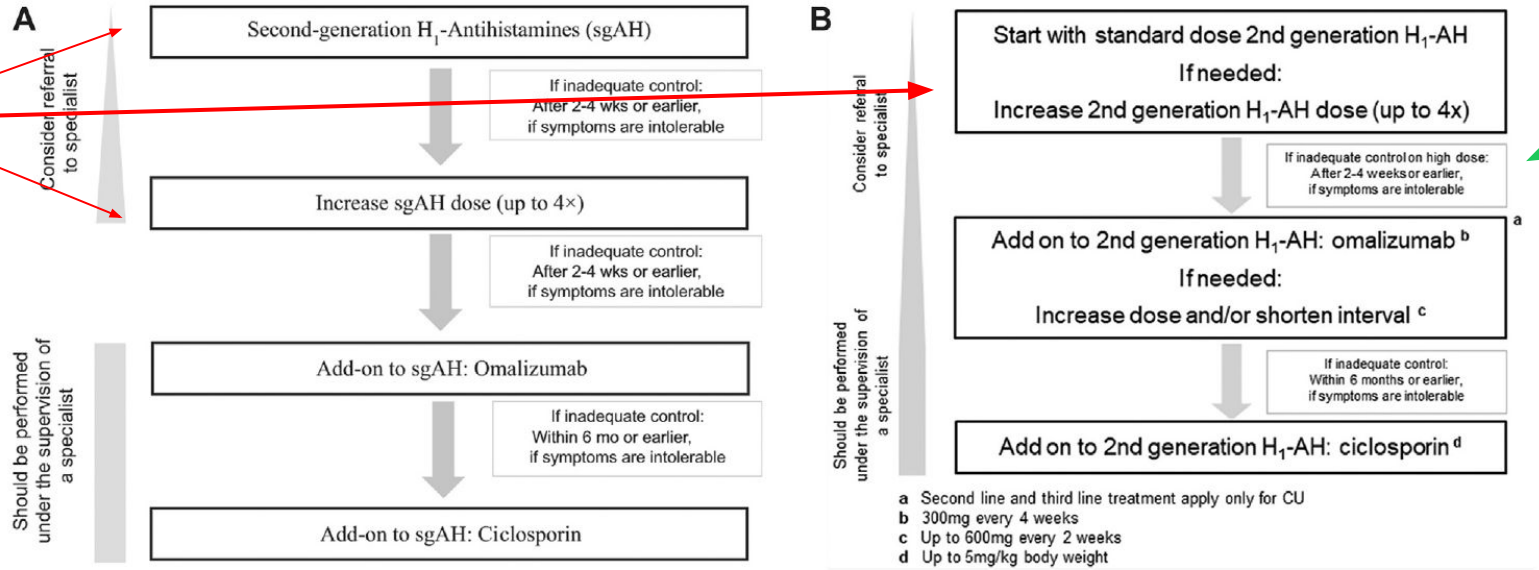


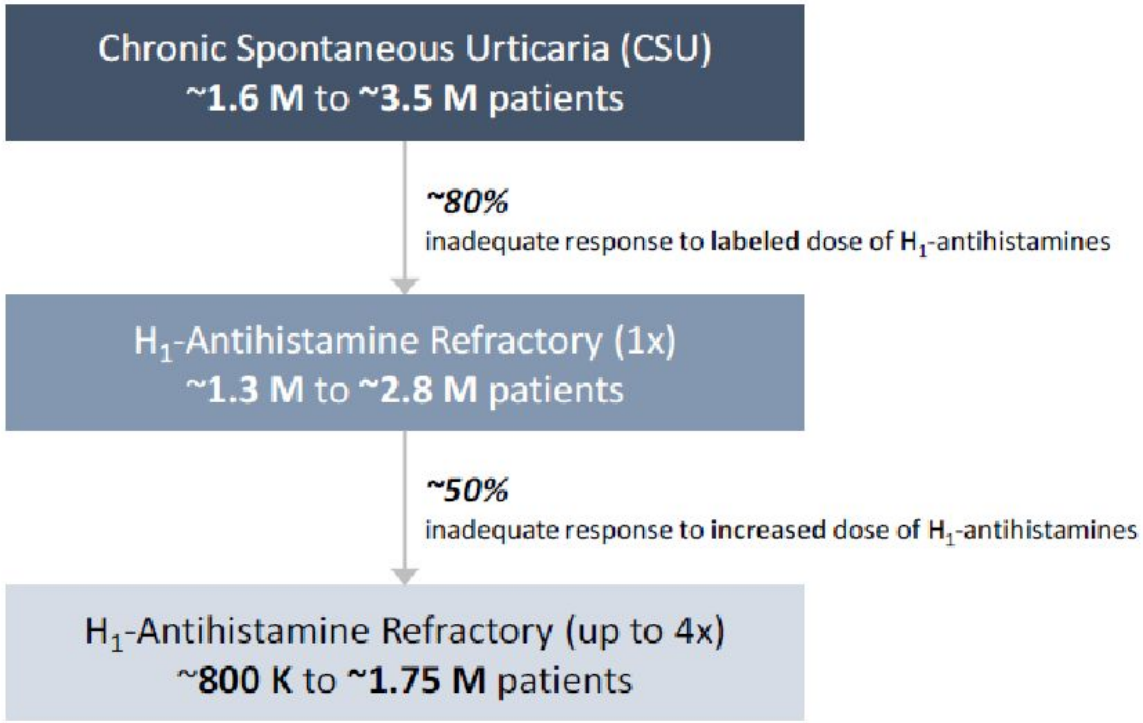
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*Participants included 50 societies: including American Academy of Allergy, Asthma and Immunology and American Academy of Dermatology (2021)

Plan to update q4 yrs

Refractory Urticaria Epidemiology

CSU Epidemiology : ~800K to 1.7M US Patients Refractory to High Dose H1



OURCES: Maurer et al. *Allergy*. 2011 Mar;66(3):317-30; Staevska et al. *J Allergy Clin Immunol*. 2010 Mar;125(3):676-82; Van den Elzen et al. *Clin Transl Allergy* (2017) 7:4

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Next Step

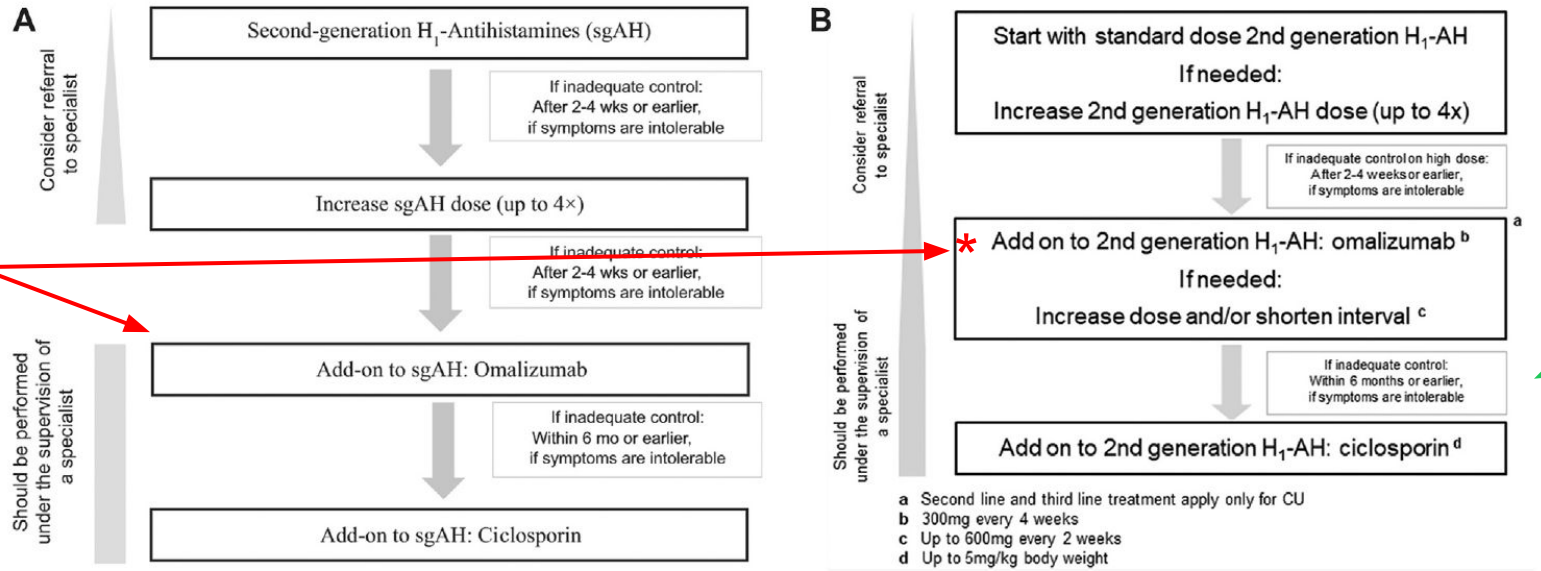


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*6 months

*Participants included 50 societies: including American Academy of Allergy, Asthma and Immunology and American Academy of Dermatology

Omalizumab Response

Omalizumab for severe chronic spontaneous urticaria: Real-life experiences of 280 patients

Zahava Vadasz, MD, PhD[a], Yuval Tal, MD[b], Menachem Rotem, MD[c], Vered Shichter-Confino, MD[d], Keren Mahlab-Guri, MD[e], Yael Graif, MD[f], Aharon Kessel, MD[a], Nancy Agmon-Levin, MD[g], Ramit Maoz-Segal, MD[g], Shmuel Kivity, MD[h], Shira Benor, MD[h], Idit Lachover-Roth, MD[i], Yuri Zeldin, MD[j], Migel Stein, MD[k], Ori Toker, MD[b], Gamal Hassoun, MD[l], Shira Bezalel-Rosenberg, MD[e], Elias Toubi, MD[e], Ilan Asher, MD[e,*], and Zev Sthoeger, MD[e,*]; for The Israeli Forum for investigating and treating Chronic Spontaneous Urticaria (CSU)

Clinical Implications

- In severe chronic spontaneous urticaria, attempts at increasing omalizumab dosing intervals or stopping therapy typically failed, suggesting that continuous treatment is needed to maintain remission.

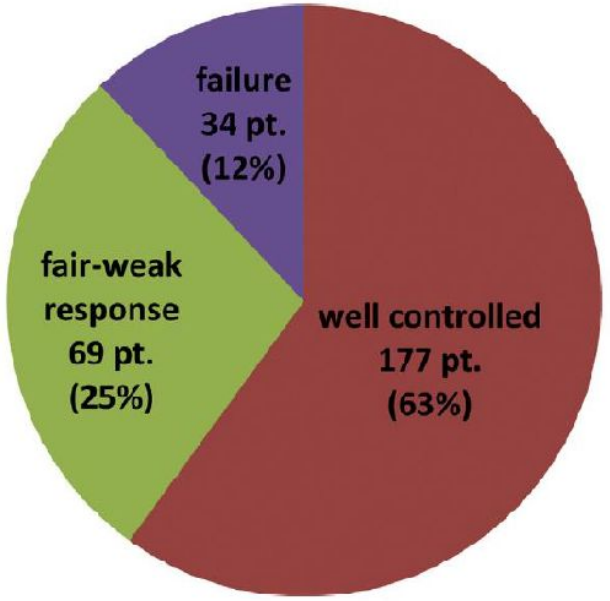
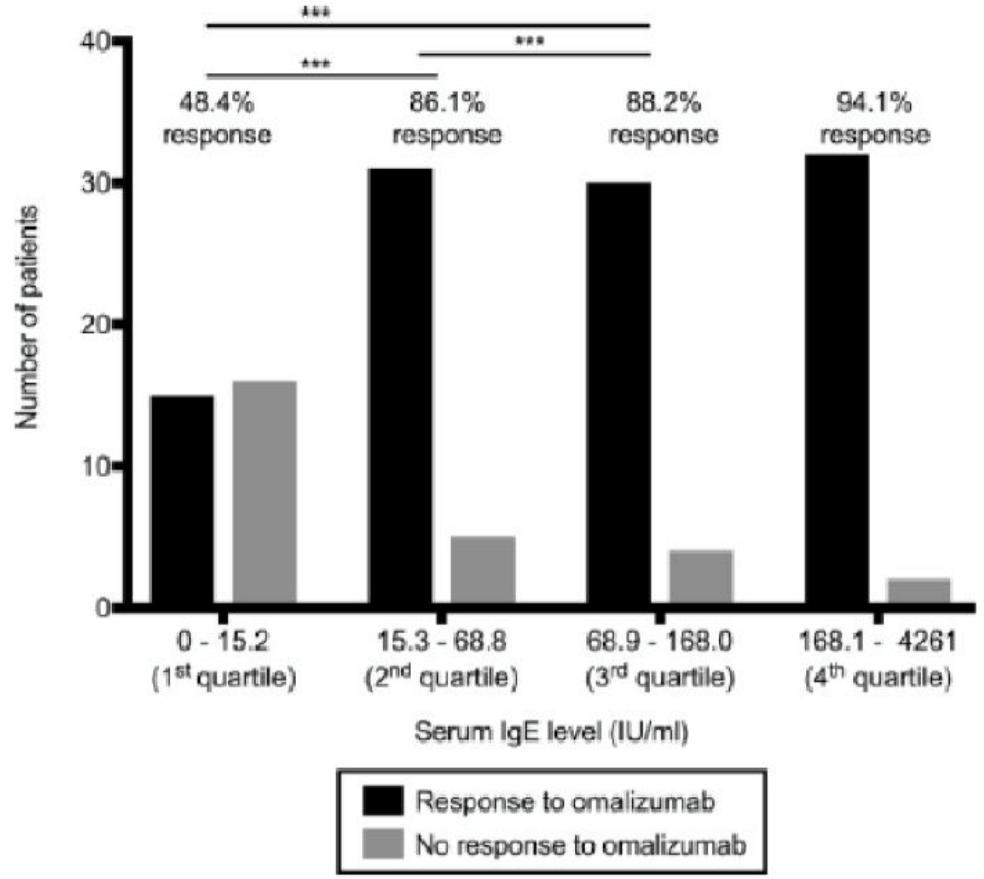


FIGURE 1. The percentage of well-controlled patients, fair-weak, and failures in all omalizumab-treated patients with CSU. *pt.*, Patient.

J Allergy Clin Immunol Pract. 2017;5(6):1743-5.

Serum IgE and Omalizumab Response

Need for biomarkers and phenotyping- IgE to start?



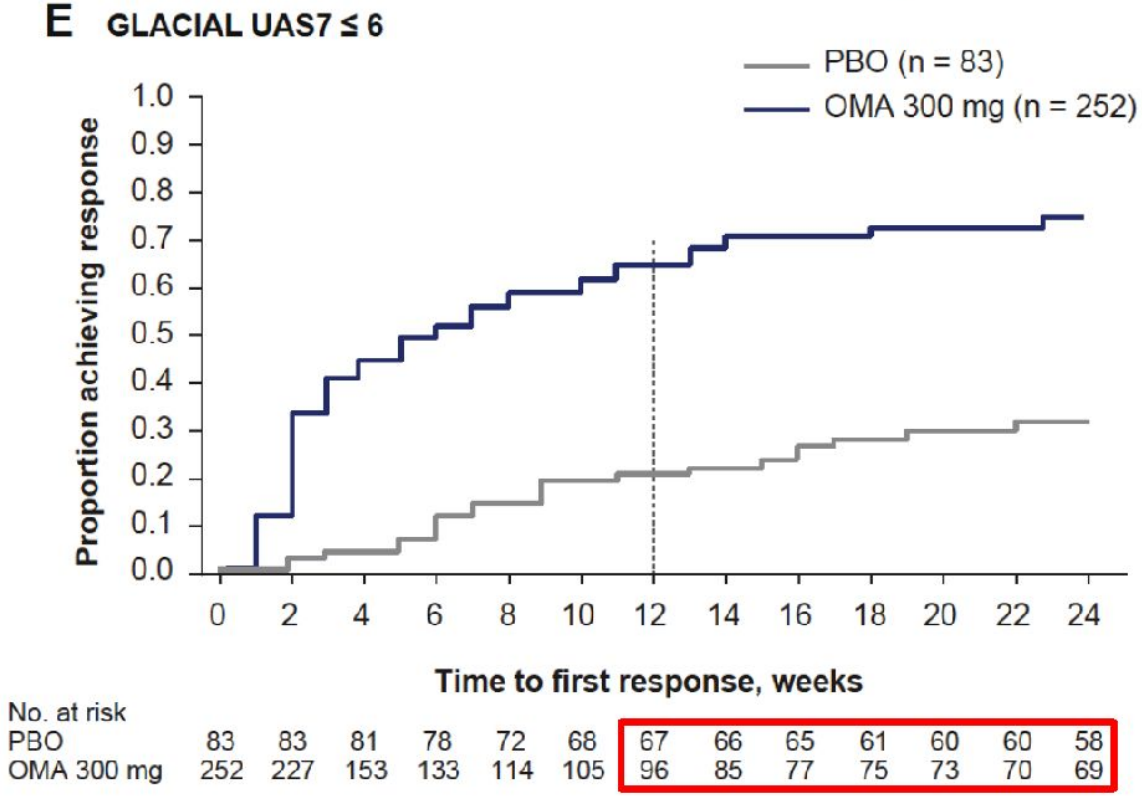
Straesser, et al. J Allergy Clin Pract 2017

Demographics n=137

73% Female
average Age 45
50% with thyroid antibodies

Omalizumab time until response

12-16 weeks of omalizumab 300 mg appears sufficient to determine response



Omalizumab Normal Dosing Failure—next steps?

New Guidelines
UPDATE

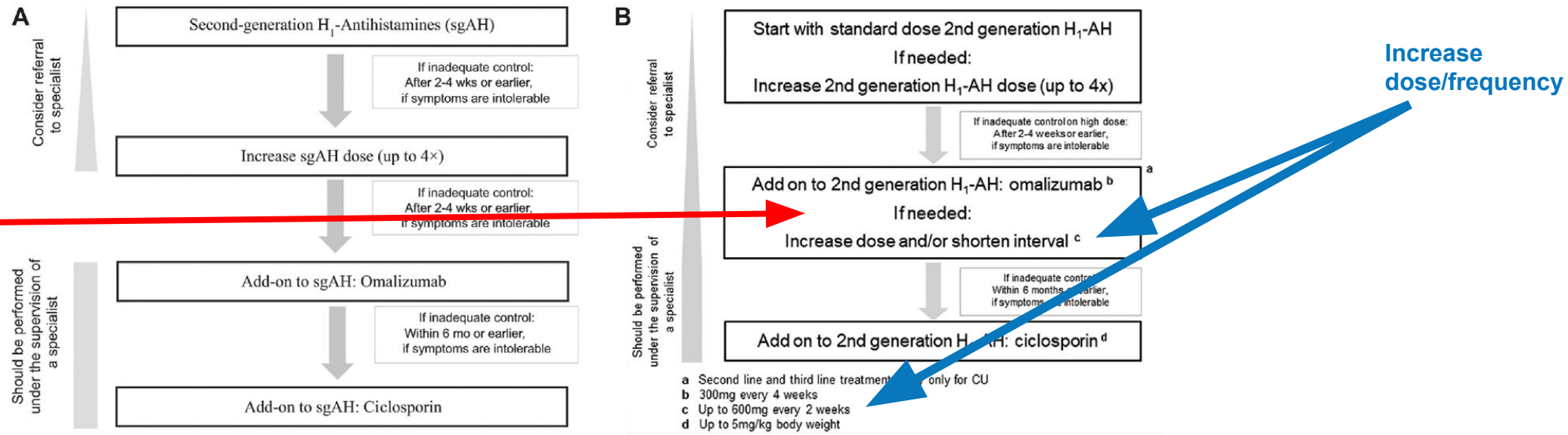


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Post Omalizumab

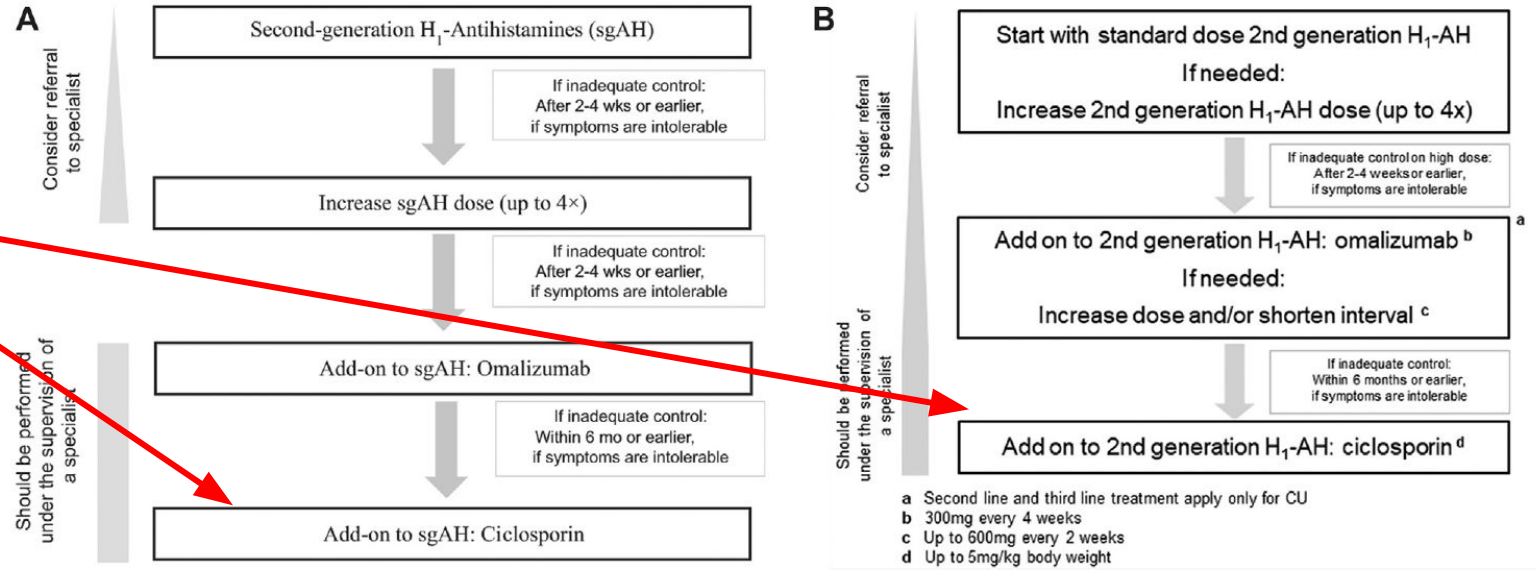


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Cyclosporine

Dose: 2.5–5 mg/kg daily

Efficacy:

- Very good efficacy even in severe cases (60-70% response)
- Rapid onset (sometimes within days)
- Possibility of long-lasting remission

Adverse effects:

- Hypertension, renal dysfunction, GI, headache, tremor, hirsutism, hyperlipoproteinemia, gingival hyperplasia, leukopenia, neuropathy, infections & neoplasia

Suggested monitoring:

- Baseline: BP, renal function, electrolytes, lipoproteins, LFT
- Follow-up: BP, renal function, electrolytes monthly x 3 then periodically
- Drug levels about every 3 weeks in some patients

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NEXT???

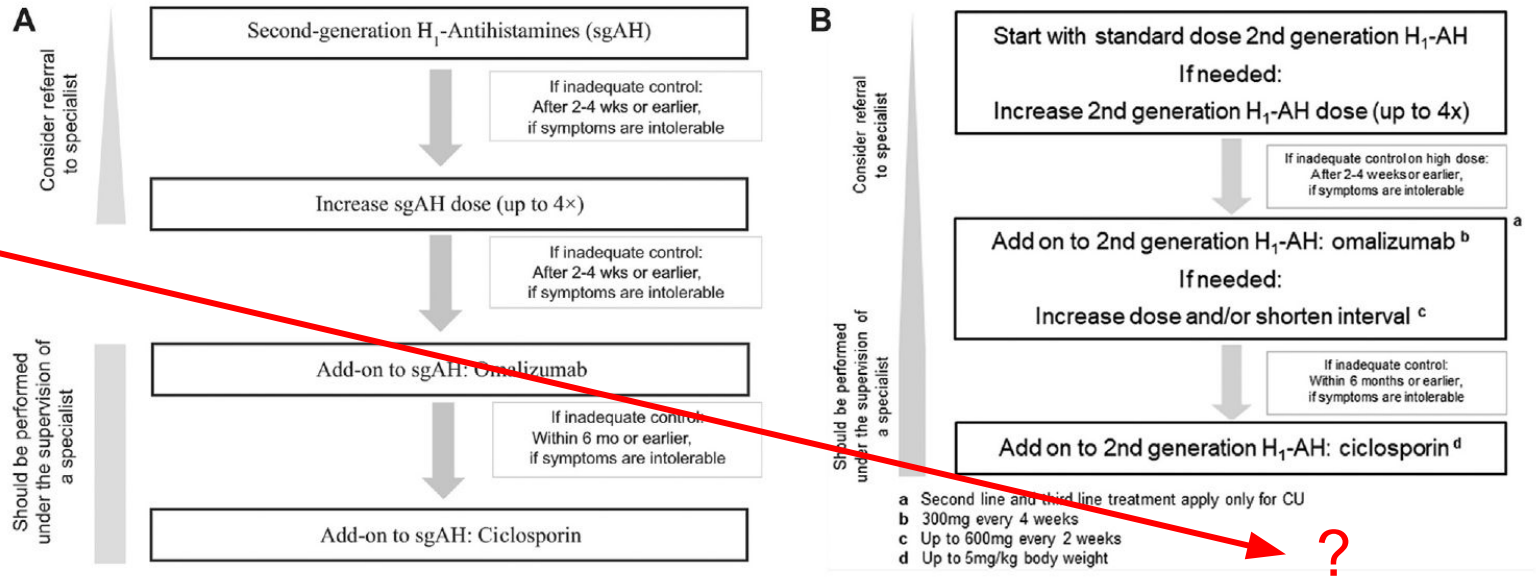
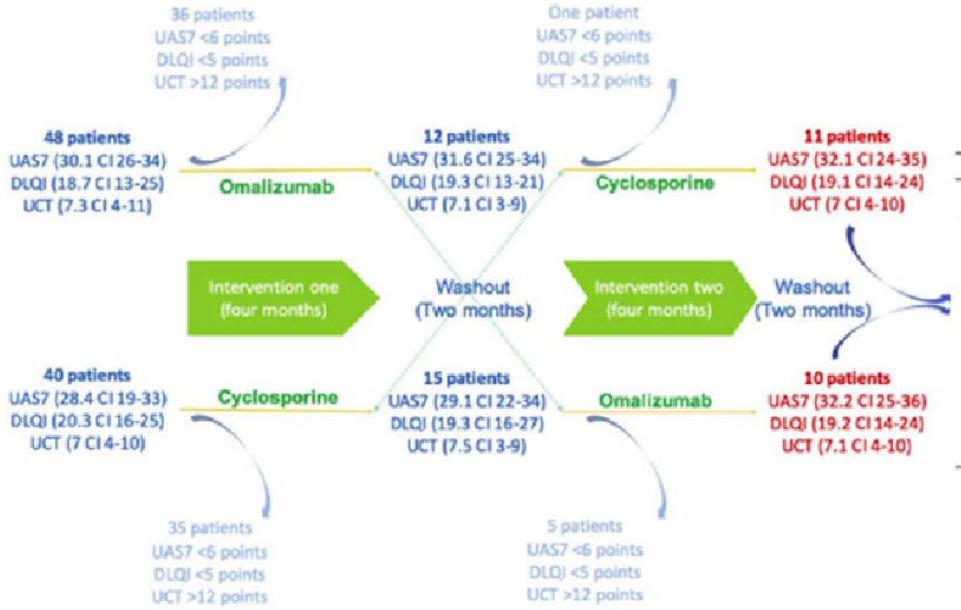


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Cyclosporine +Omalizumab

Cyclosporine and omalizumab together: A new option for chronic refractory urticaria

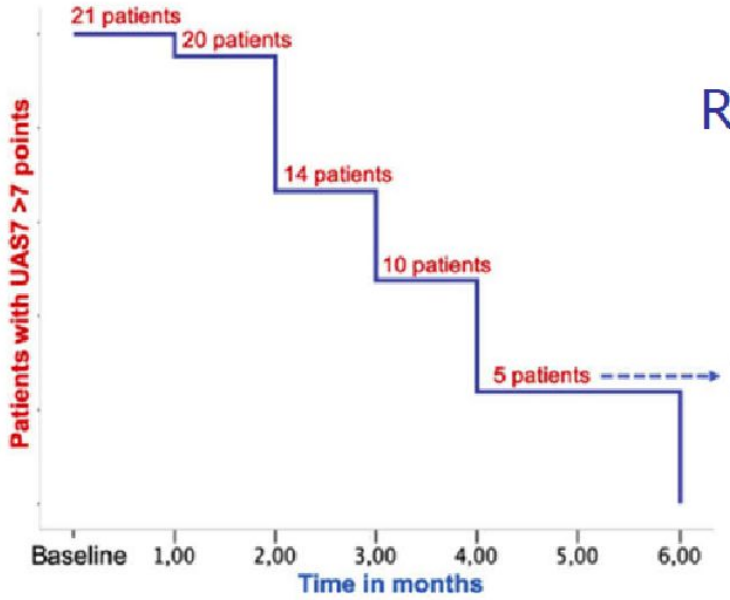


Patients without response (n 21)	
Age (years)	29 years (19 to 48)
Duration of urticaria (years)	3 years (2 to 7)
Gender (female)	13 patients
Inducible Urticaria	10 patients
Angioedema	6 patients
UAS7	30.7 points (CI 24-36)
HSS7	15.5 points (CI 10-18)
ISS7	15.1 points (CI 10-17)
AAS*	58 points (CI 34-70)
DLQI	19.3 points (CI 14-24)
UCT	7.05 points (CI 4-10)

Sanchez J et al. J Allergy Clin Immunol Pract. 2020;8(6):2101-3.

Cyclosporine +Omalizumab

Combination of OMA + CSA

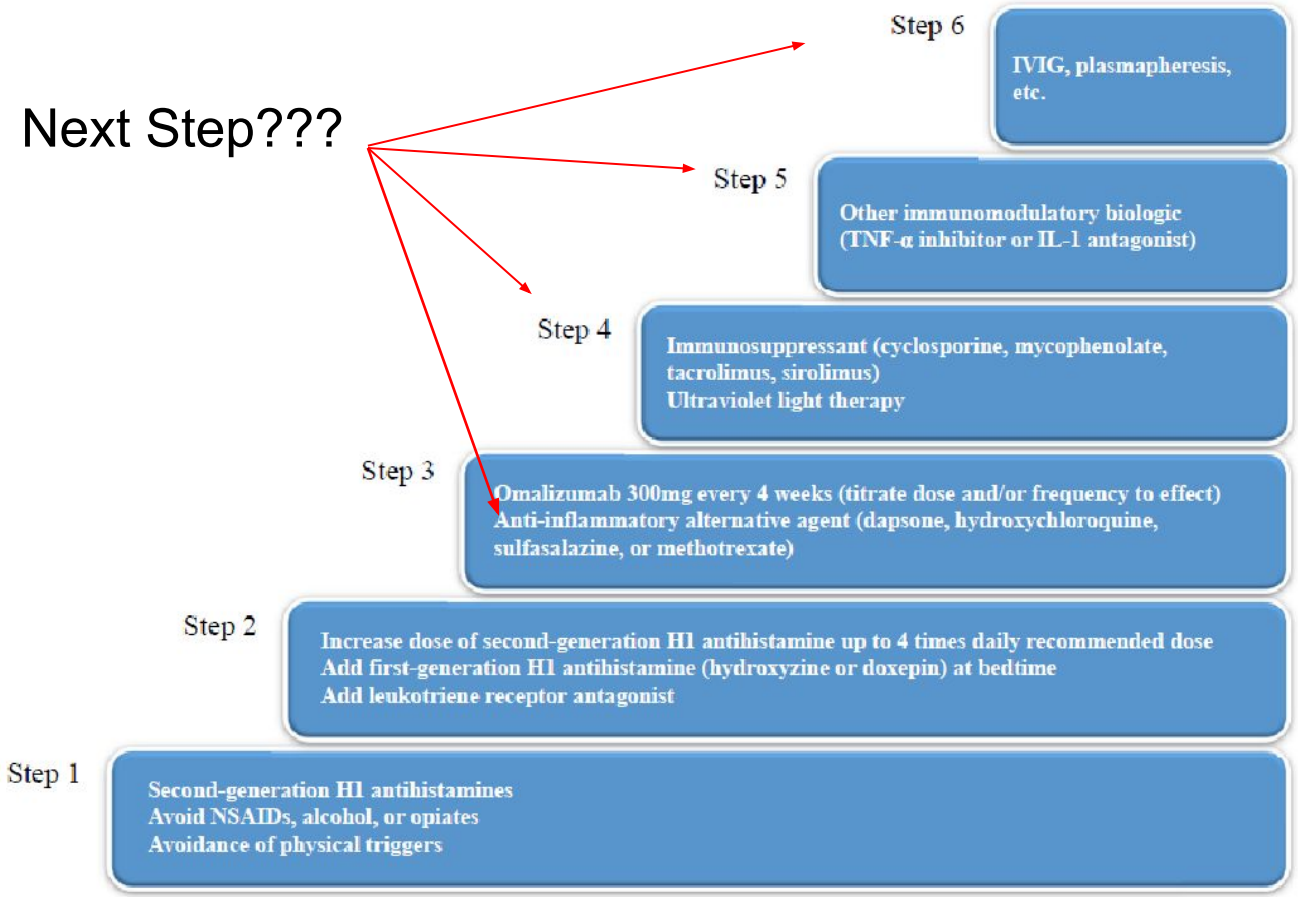


Response in 2-4 months

Patients without clinical response (n 5)	
Age (years)	29 years (24 to 32)
Duration of urticaria (years)	3 years (4 to 7)
Gender (female)	4 patients
Inducible Urticaria	3 patients
Angioedema	2 patients
UAS7	28 points (CI 19-34)
HSS7	14 points (CI 10-17)
ISS7	14 points (CI 11-18)
AAS*	56 points (CI 38-66)
DLQI	17.3 points (CI 15-23)
UCT	8 points (CI 5-9)

Sanchez J et al. J Allergy Clin Immunol Pract. 2020;8(6):2101-3.

Stepwise Approach-Anti-Inflammatory Agents, Immunosuppression, Biologics, Infusions, etc



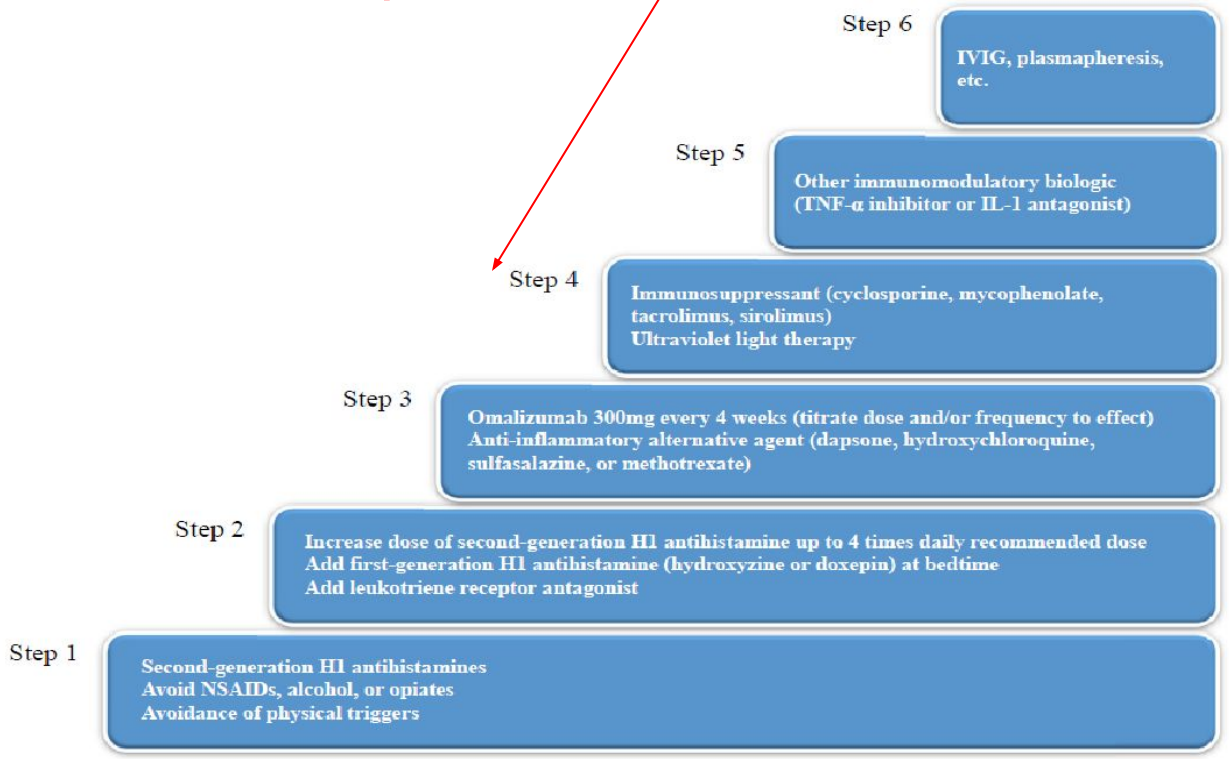
Mixed Results:
+ case studies

*No universal consensus

Stepwise Approach

Novel therapeutics

STEP 4-7???



New Options Emerge In 2025!

Including a Familiar Friend

Potential Targets

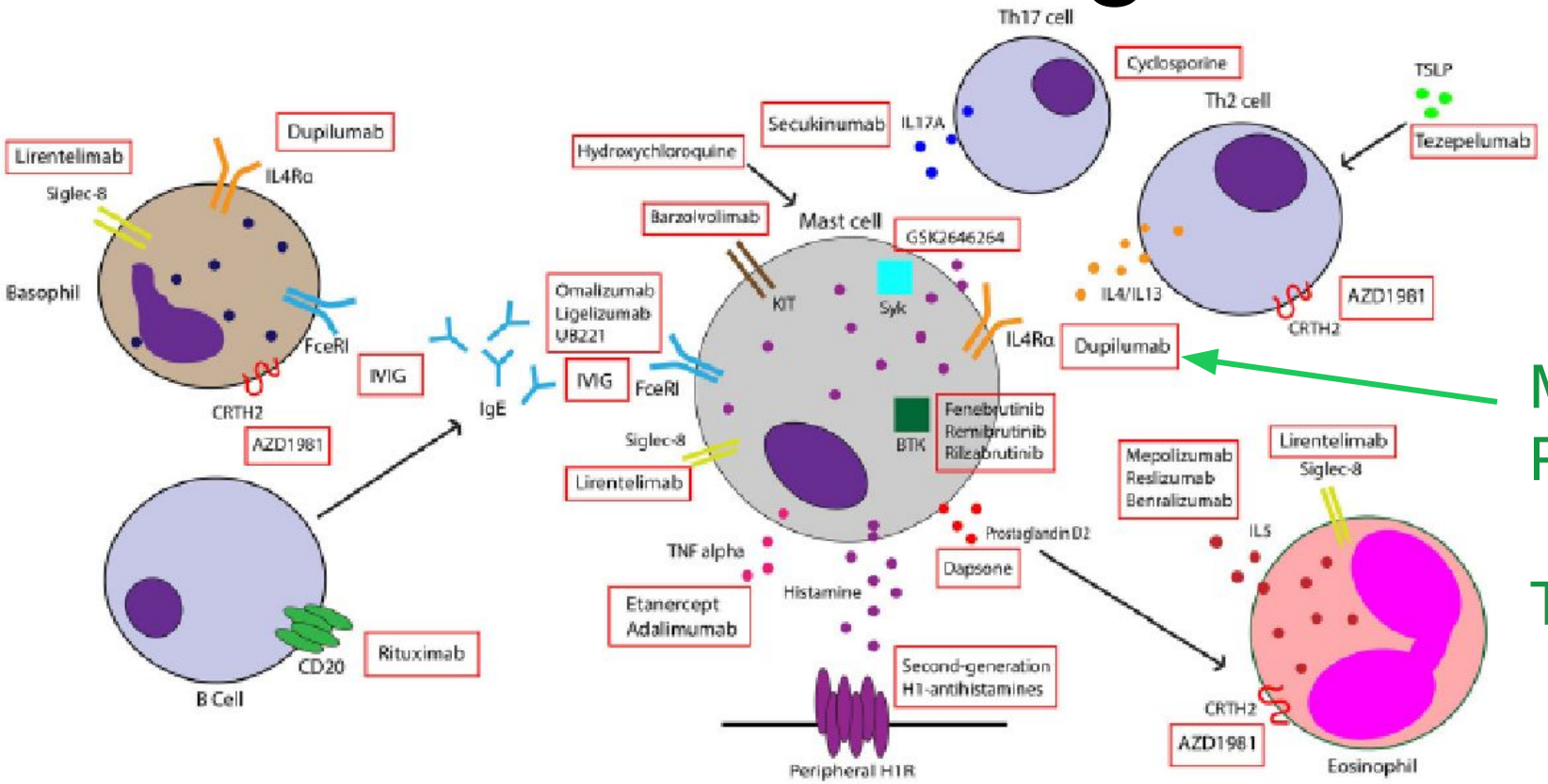


Fig. 1 Mechanism of action of some existing and novel therapies for chronic spontaneous urticaria

Multiple Potential Pathways

Th2 pathway target

Dupilumab

Approved for other indications

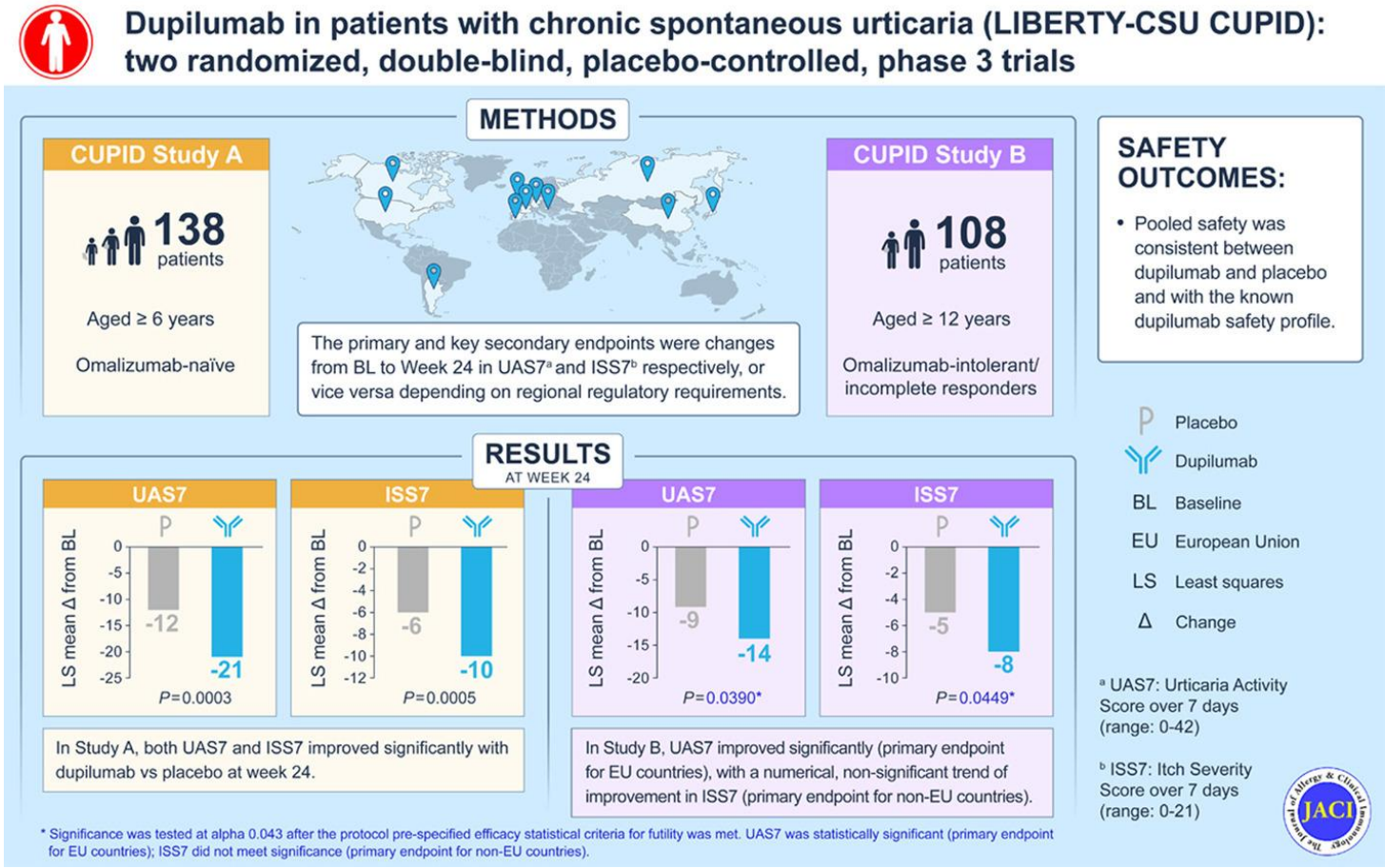
- IL-4 and IL-13 contribute to Th2-type immune response through their effects on T-cell differentiation and IgE class switching.
- Levels of IL-4 and/or IL-13 are elevated in the serum of patients with CSU
- Skin biopsy specimen of patients with CSU exhibit an increase in the number of cells expressing IL-4 at the mRNA level

OPTIONS:

Dupilumab - inhibits IL-4 and IL-13 signaling through blockade of their shared IL-4α receptor subunit

- LIBERTY-CUPID study

Dupilumab



Study B: Possibly not powered for significance due to COVID enrollment period

Thus request for Study C

Journal of Allergy and Clinical Immunology DOI: (10.1016/j.jaci.2024.01.028)

Dupilumab- Response vs IgE level

Figure 3. Dupilumab treatment led to a reduction in total serum IgE over 24 weeks

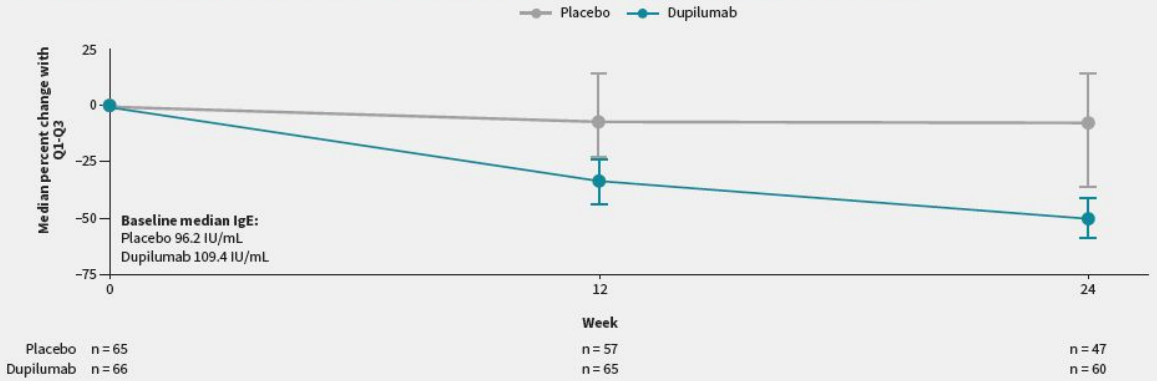
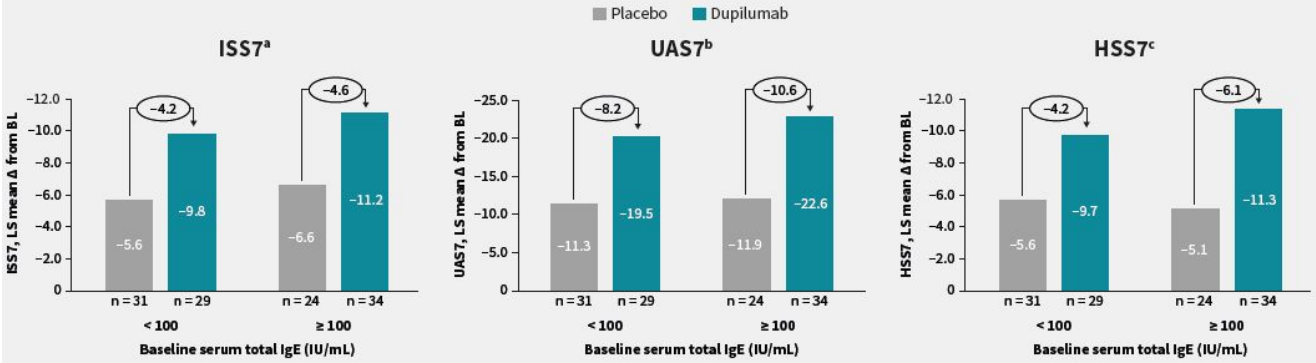


Figure 4. Dupilumab treatment led to significant improvements in ISS7, UAS7, and HSS7 regardless of whether baseline serum total IgE was < 100 IU/mL or ≥ 100 IU/mL



BL data are presented as mean (SD). [a]ISS7, range 0–21; primary endpoint. [b]UAS7 is a composite of ISS7 and HSS7, range 0–42; secondary endpoint. [c]HSS7, range 0–21; secondary endpoint.

Dupilumab-safety

Table 2. Overall TEAEs reported in ≥ 5% of patients in any treatment group were comparable for placebo and dupilumab

n %	Placebo (n = 68)	Dupilumab (n = 70)
Any TEAE	40 (58.8)	35 (50.0)
TEAEs reported in ≥ 5% of patients in any treatment group (by primary SOC and PT)		
Skin and subcutaneous tissue disorders	18 (26.5)	10 (14.3)
CSU	6 (8.8)	3 (4.3)
Angioedema	5 (7.4)	1 (1.4)
General disorders and administration site conditions	10 (14.7)	9 (12.9)
Injection-site reactions[a]	2 (2.9)	4 (5.7)
Selected AE		
Conjunctivitis[b]	1 (1.5)	0
Treatment-emergent SAE[c]	5 (7.4)	2 (2.9)

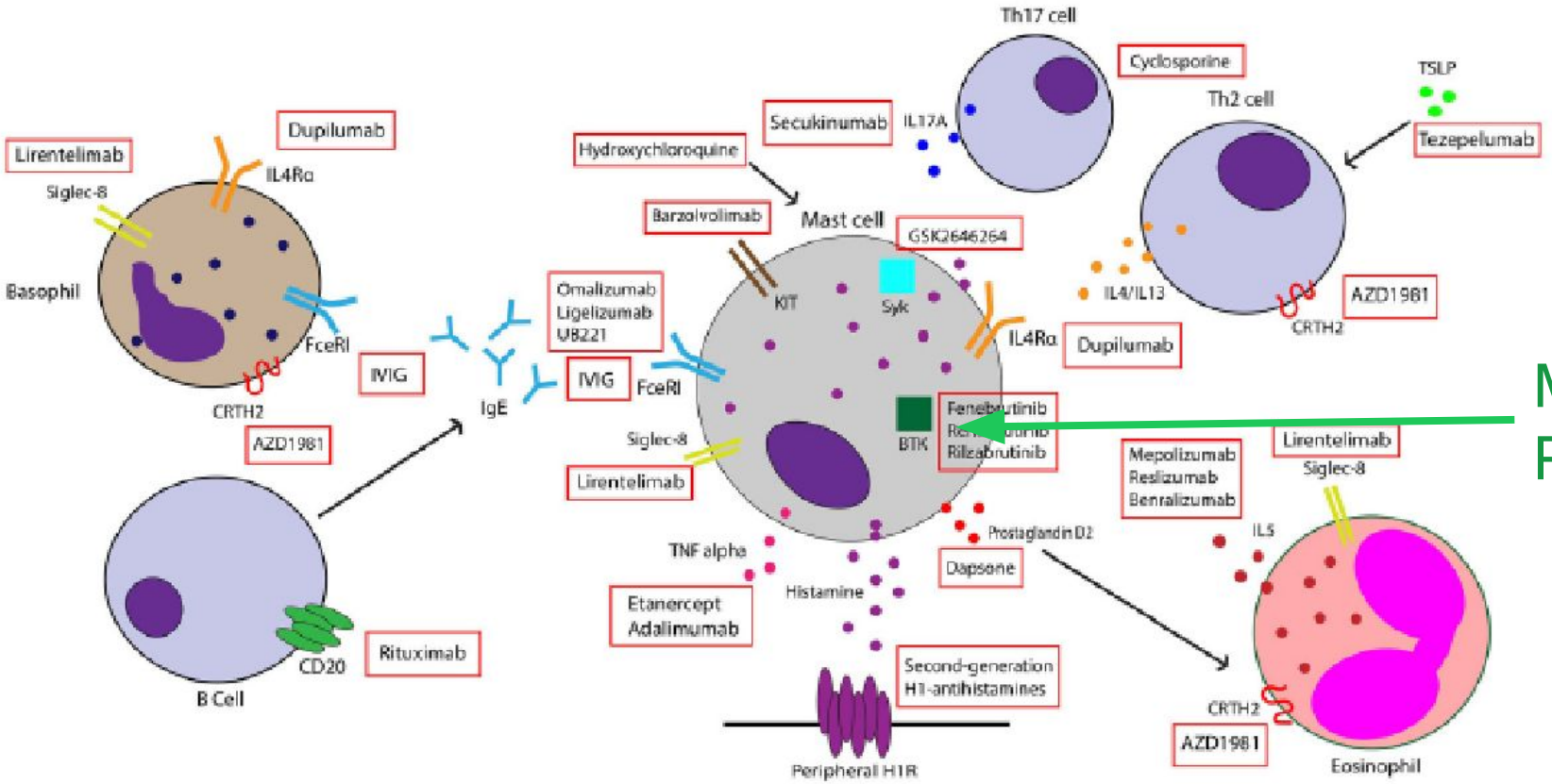
[a]Injection-site reactions by MeDRA High Level Term, n (%): placebo 9 (13.2); dupilumab 8 (11.4). Includes injection-site erythema, injection-site induration, injection-site pain, injection-site pruritus, and injection-site reactions. [b]Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation. [c]SAE terms (PT) include: COVID-19 pneumonia, depression, suicide, dyspnea, hemorrhoids, upper abdominal pain, nausea, angioedema, and atopic dermatitis.
AE, adverse event; COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class.

Safety summary

- TEAEs involving skin and subcutaneous tissue disorders, including CSU and angioedema, were more common in the placebo-treated group than in the dupilumab-treated group

*** Dupilumab– post CUPID- Study C– FDA approved 2025**

Potential Targets



Multiple Potential Pathways – BTKi

Fig. 1 Mechanism of action of some existing and novel therapies for chronic spontaneous urticaria

BTK Inhibition

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REVIEW ARTICLE

Bruton's tyrosine kinase inhibition—An emerging therapeutic strategy in immune-mediated dermatological conditions

Pedro Mendes-Bastos[1] | Ana Brasileiro[2,3] | Pavel Kolkhir[4,5,6] | Stefan Frischbutter[4,6] | Jörg Scheffel[4,6] | Sherezade Moñino-Romero[4,6] | Marcus Maurer[4,6]

BTK Inhibitors and Dermatologic Disease

TABLE 1 BTK inhibitors in development (phase II+) for treatment of immune-mediated dermatological diseases

Drug	Other names	Manufacturer/developer	Indication	Phase	Trial identifier (status)
Branebrutinib	BMS-986195	Bristol–Myers Squibb	Atopic dermatitis	II	NCT05014438 (recruiting)
			SLE[a]	II	NCT04186871 (recruiting)
Fenebrutinib	GDC-0853	Genentech	CSU	II	NCT03137069 (completed)
				II	NCT03693625 (terminated)
			SLE	II	NCT02908100 (completed)
Remibrutinib	LOU064	Novartis	CSU	II	NCT03926611 (completed)
				II	NCT04109313 (active, not recruiting)
				III	NCT05030311/ NCT05032157 (not yet recruiting)
				III	NCT05048342 (not yet recruiting)
Rilzabrutinib	PRN1008	Principia Biopharma/Sanofi	Pemphigus vulgaris	II	NCT02704429 (completed)
				III	NCT03762265 (active, not recruiting)
			IgG4-related disease	II	NCT04520451 (recruiting)
			Atopic dermatitis	II	NCT05018806 (recruiting)
Tirabrutinib	GS-4059	Gilead	CSU	II	NCT04827589 (withdrawn)
			Pemphigus	II	JapicCTI-184231

Note: Trial identifier and status information taken from clinicaltrials.gov, with the exception of JapicCTI-184231 (NIPH Clinical Trials Search at https://rctportal.niph.go.jp/en)

Abbreviations: CSU, chronic spontaneous urticaria; SLE, systemic lupus erythematosus.

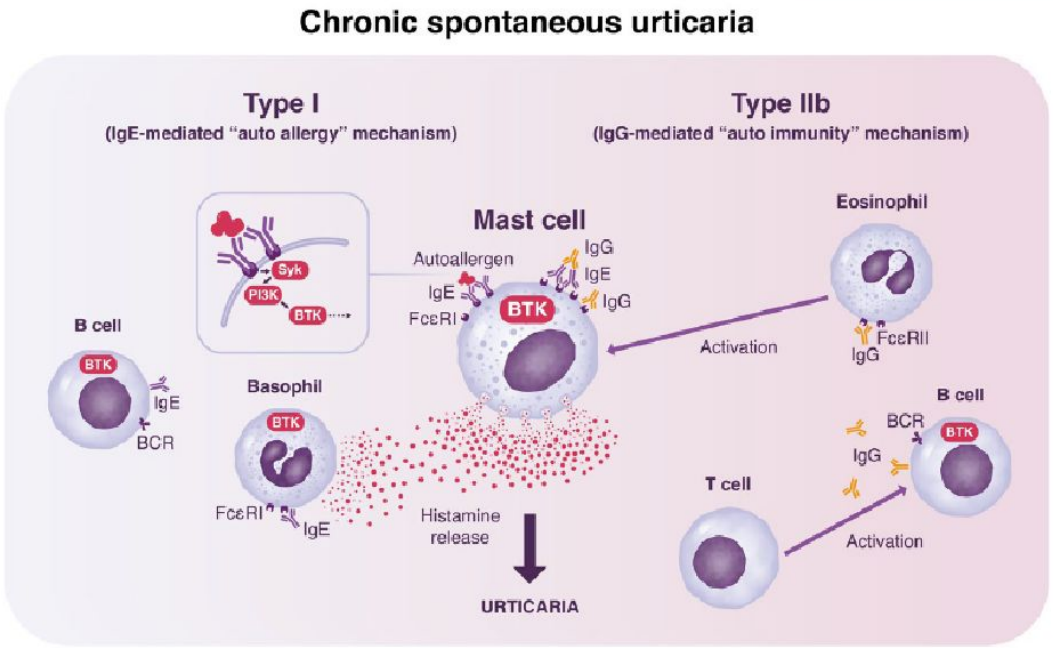
[a]In addition to autoimmune disorder, rheumatoid arthritis and primary Sjögren's syndrome.

Urticaria Pathophysiology-BTK Inhibition

-BTK is involved in pathways that lead to the degranulation of skin MCs (TYPE I)

-BTK involved in production of circulating FcεRI-stimulating autoantibodies in a subset of chronic urticaria patients (TYPE IIb)

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Current Concepts of Patient Phenotypes (4)

TYPE I*
TYPE IIb*
TYPE I and TYPE IIb*
NEITHER*?

BTKi: Remibrutinib

Remibrutinib: Results of the Phase 3 REMIX-1 and REMIX-2 Studies

BTKi:Remibrutinib

REMIX-1 (NCT05030311)[1] and REMIX-2 (NCT05032157)[2] Are Two Identical Phase 3 Trials Conducted in Parallel

The global, multicenter, randomized, double-blind, phase 3 trials were designed to demonstrate the **efficacy, safety, and tolerability** of remibrutinib vs placebo in patients with CSU inadequately controlled by histamine 1-antihistamines (H_1-AHs)



Primary end point scenarios

- **Scenario 1**: change from baseline (BL) in weekly Urticaria Activity Score 7 (UAS7) at week 12[a]
- **Scenario 2**: co-primary end points, including change from BL in weekly Itch Severity Score (ISS7) and weekly Hives Severity Score (HSS7) at week 12 (FDA)[a]



Key secondary end points

- Well-controlled disease (UAS7 ≤6)[b] **at week 12**
- Complete disease control (UAS7 = 0)[b] **at week 12**
- Early onset of disease activity control, defined as achievement of **UAS7 ≤6 at week 2**
- Occurrence of treatment-emergent adverse events (AEs) and serious AEs during the study

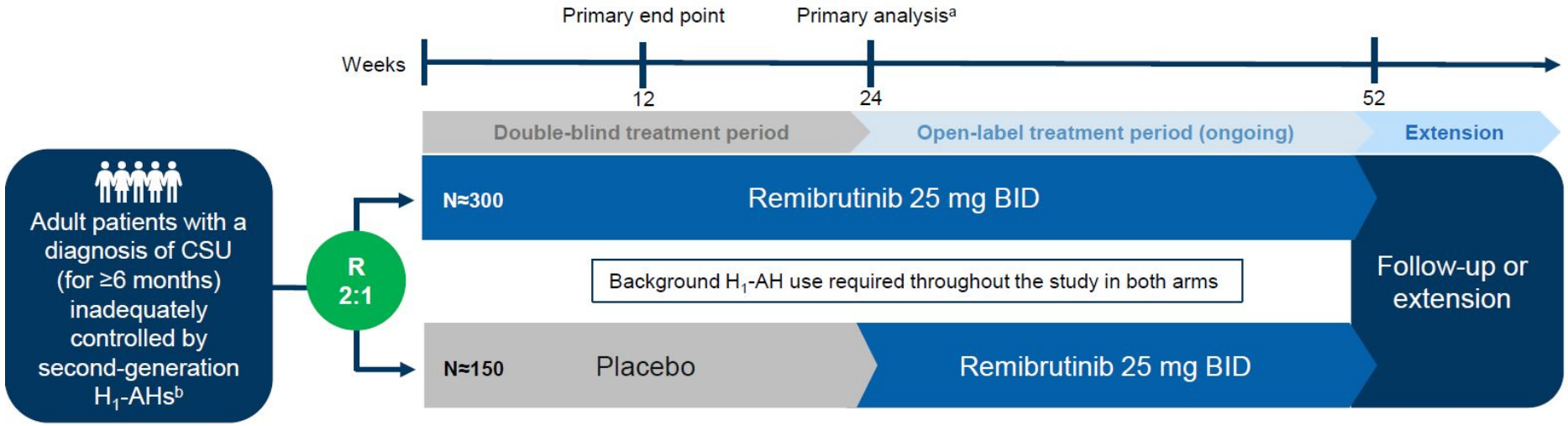
CSU, chronic spontaneous urticaria; FDA, Food and Drug Administration.
[a]Mean change from BL in UAS7, ISS7, and HSS7 at week 12 was evaluated using mixed model for repeated measures. [b]Proportion of patients achieving disease activity control and complete response was evaluated using logistic regression.

1. ClinicalTrials.gov. NCT05030311. Accessed November 10, 2023. https://clinicaltrials.gov/ct2/show/NCT05030311 **2.** ClinicalTrials.gov. NCT05032157. Accessed November 10, 2023. https://clinicaltrials.gov/ct2/show/NCT05032157

BTKi:Remibrutinib

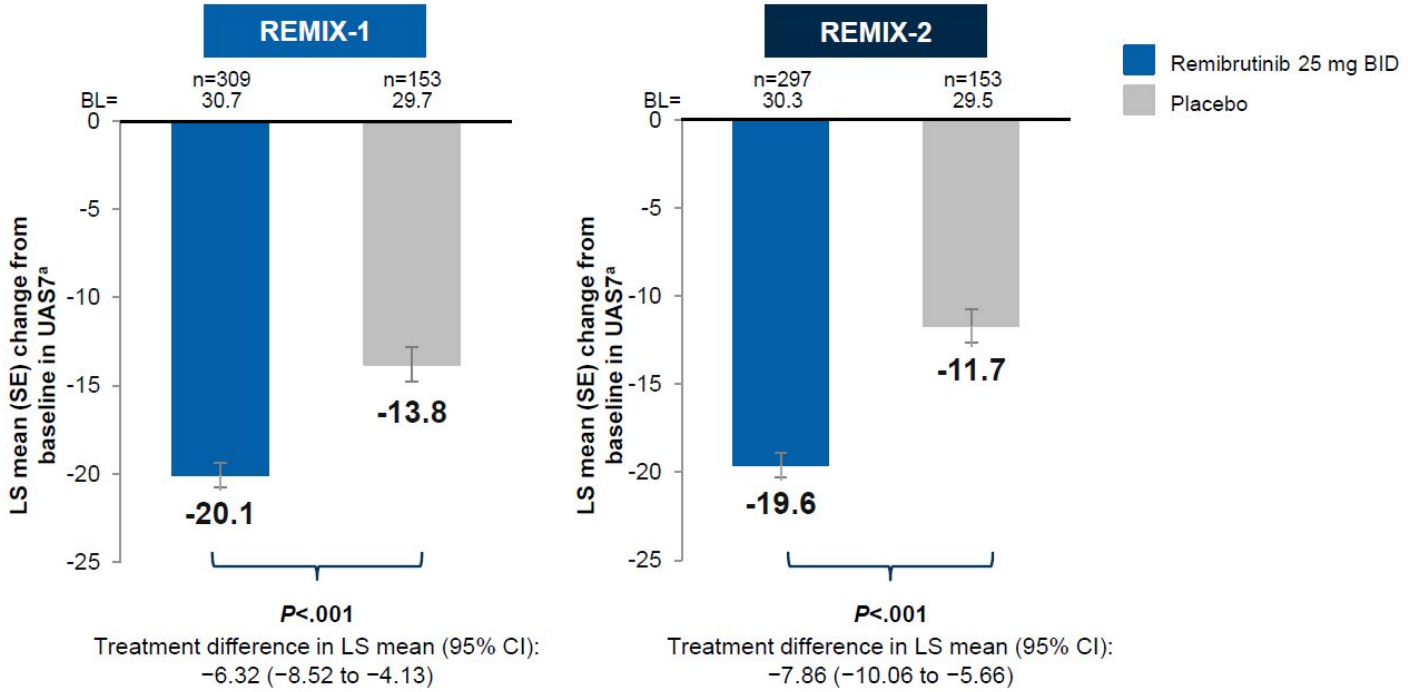
REMIX-1 and REMIX-2 Study Design[1-4]

Primary analysis was conducted when **all patients** had completed **week 24** of treatment or discontinued earlier and when **≥150 patients** across both trials completed the treatment period at **week 52**



BTKi:Remibrutinib

UAS7 Change from BL at Week 12



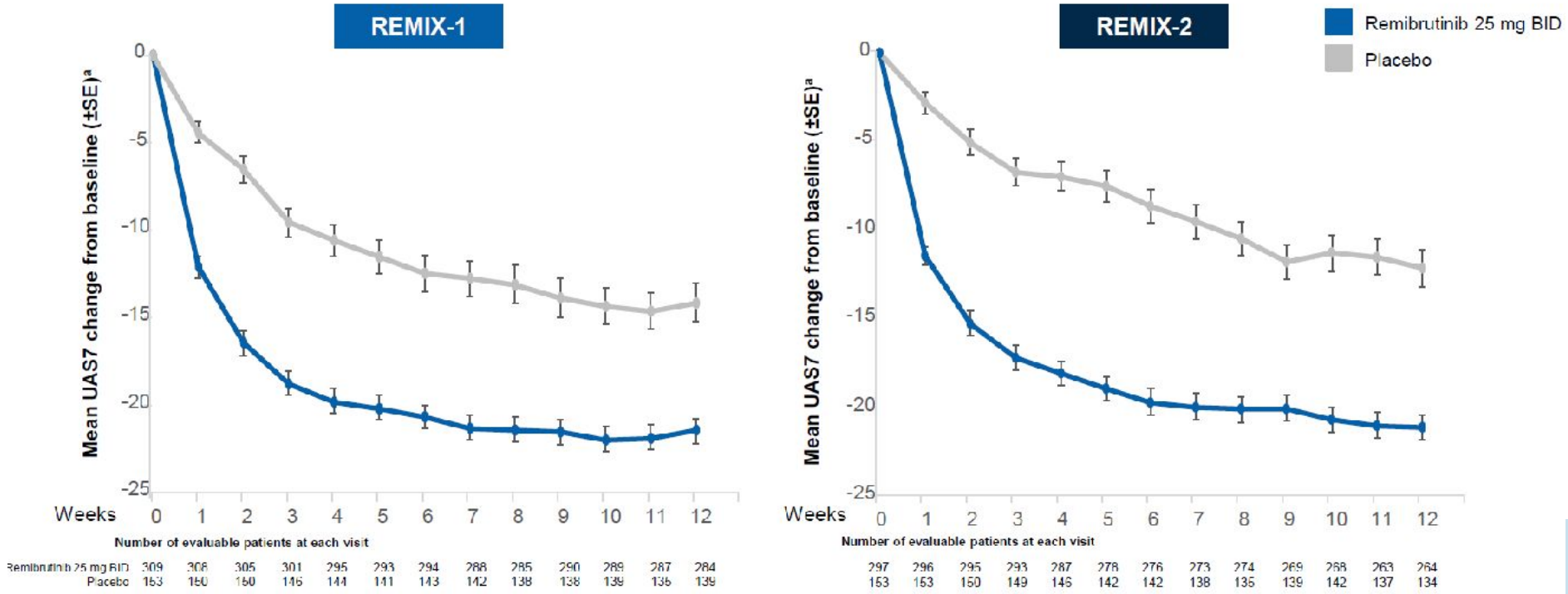
- Remibrutinib met the primary end point of change from BL in UAS7 at week 12

BID, twice daily; BL, baseline; LS, least squares; UAS7, weekly Urticaria Activity Score.
[a]Full analysis set; imputed data. Superiority defined as statistically significant difference in change from baseline with remibrutinib vs placebo at week 12 using a linear mixed model with repeated measures.
Saini S, et al. Abstract presented at: ACAAI 2023 Annual Meeting; November 9-13, 2023; Anaheim, CA. Abstract LB001.

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BTKi:Remibrutinib

UAS7 Change from BL Over Time



- UAS7 decreased from baseline from week 0 to week 12

BID, twice daily; BL, baseline; UAS7, weekly Urticaria Activity Score.
[a]Full analysis set; observed data
Saini S, et al. Abstract presented at: ACAAI 2023 Annual Meeting; November 9-13, 2023; Anaheim, CA. Abstract LB001.

BTKi:Remibrutinib

Overview of Safety Data

	Pooled REMIX-1 and REMIX-2	
	Remibrutinib 25 mg BID (n=606), n (%)[a,b]	Placebo (n=306), n (%)[a,b]
Overall AEs[c]	388 (64.0)	198 (64.7)
Infection AEs	199 (32.8)	104 (34.0)
Serious AEs	20 (3.3)	7 (2.3)
Serious infection AEs	4 (0.7)	2 (0.7)
AEs leading to treatment discontinuation	16 (2.6)	8 (2.6)
AEs leading to treatment interruption	48 (7.9)	26 (8.5)
Death	0	0

- The occurrences of AEs and serious AEs, key secondary end points, were balanced between treatment arms in both studies

AE, adverse event; BID, twice daily.
[a]Safety set. [b]Number of patients experiencing ≥1 event. [c]Overall AEs include infection AEs..
Saini S, et al. Abstract presented at: ACAAI 2023 Annual Meeting; November 9-13, 2023; Anaheim, CA. Abstract LB001.

*** BTKi – potential option in refractory patients with TYPE I or TYPE IIb – FDA approved 2025**

Potential Targets

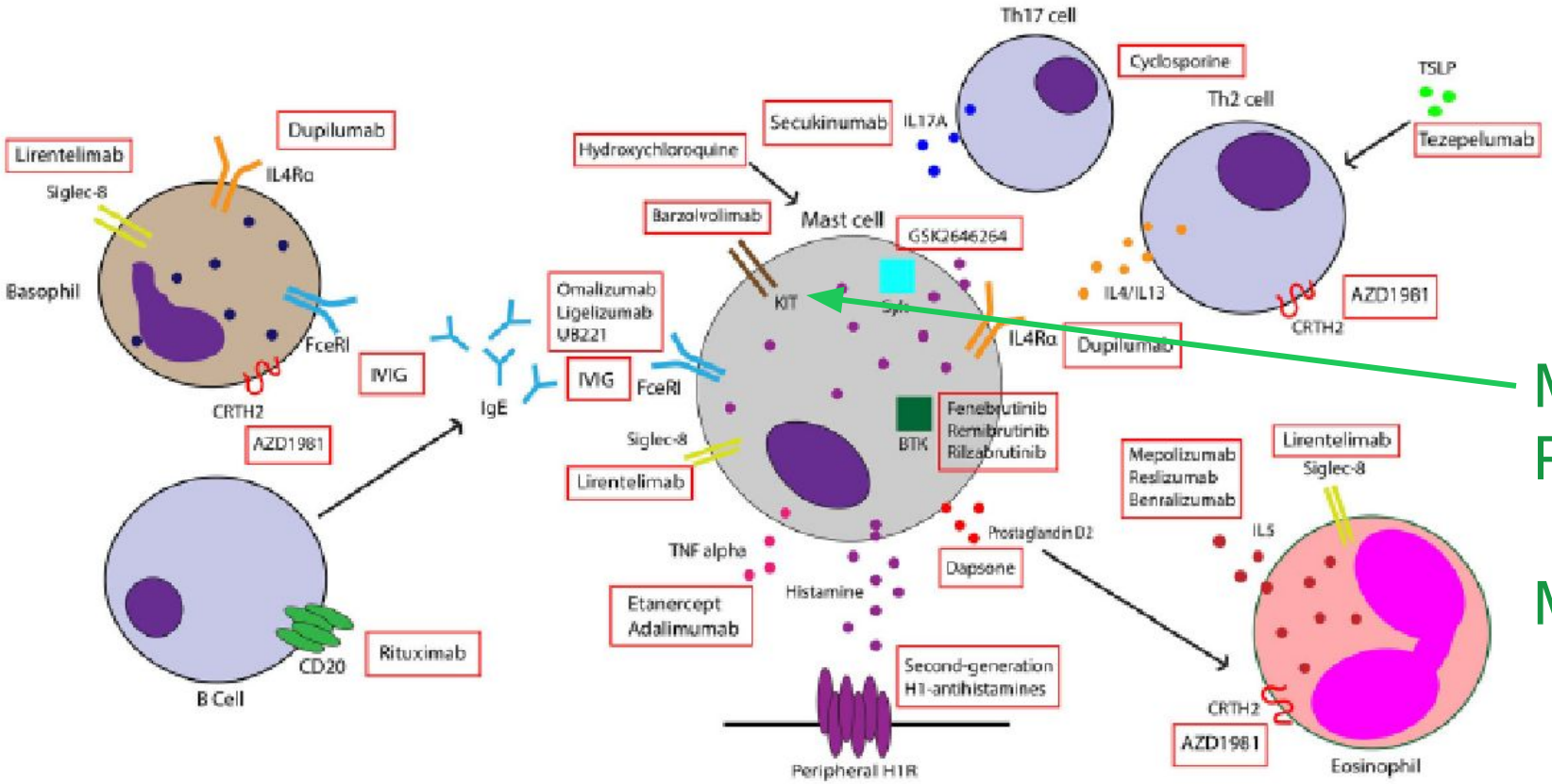


Fig. 1 Mechanism of action of some existing and novel therapies for chronic spontaneous urticaria

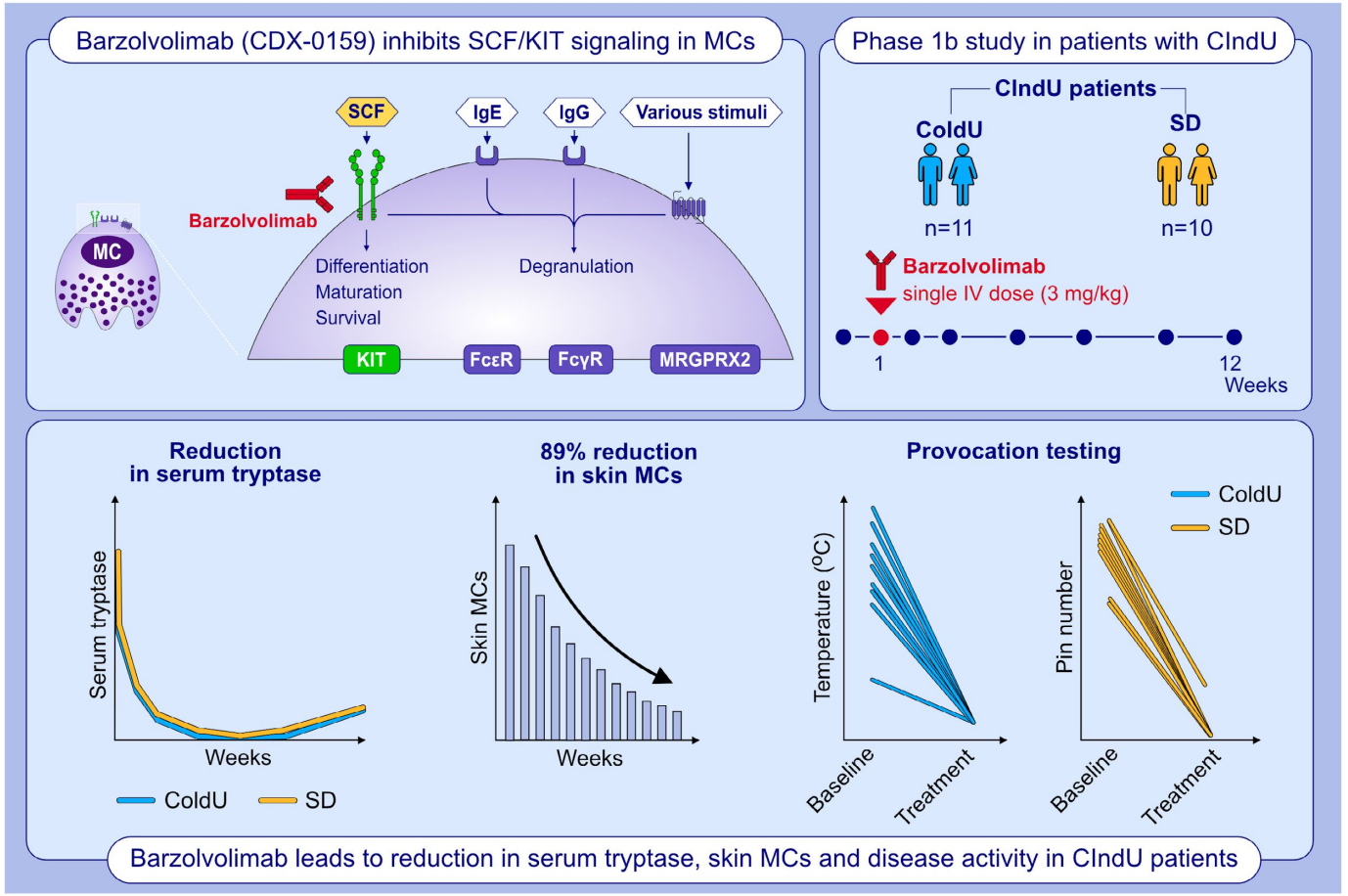
Multiple Potential Pathways

Mast Cell Target

Barzolvolimab

- Mast cells are involved in the pathophysiology of CSU in many patients
- KIT receptor activation by stem cell factor (SCF) is essential for mast cell function
- Barzolvolimab (CDX-0159) is a humanized antibody that inhibits KIT activation by SCF

Barzolvolimab



Mauer et al. Allergy . 2023 May;78(5):1269-1279.

Barzolvolimab-CSU

- randomized, double-blind, placebo-controlled, Phase 2 study
- 208 patients were randomly assigned on a 1:1:1:1 ratio to receive subcutaneous injections of barzolvolimab at 75 mg every 4 weeks, 150 mg every 4 weeks, 300 mg every 8 weeks or placebo during a 16-week placebo-controlled treatment period.
- After 16 weeks, patients then enter a 36-week active treatment period, in which patients not already randomized to barzolvolimab at 150 mg every 4 weeks or 300 mg every 8 weeks are randomized 1:1 to receive one of these two dose regimens; patients already randomized to these treatment arms remain on the same regimen as during the placebo-controlled treatment period.
- After 52 weeks, patients then enter a follow-up period for an additional 24 weeks. The primary endpoint of the study is mean change in baseline to Week 12 in UAS7.
- Secondary endpoints include other assessments of safety and clinical activity including ISS7, HSS7 and AAS7.

Mauer et al. Allergy . 2023 May;78(5):1269-1279.

Barzolvolimab-CSU

Summary of Clinical Activity Assessments at Week 12				
	300 mg q8w (n=51)	150 mg q4w (n=52)	75 mg q4w (n=53)	Placebo (n=51)
UAS7 Changes				
Baseline UAS7 (mean)	31.33	30.75	30.30	30.09
LS Mean change at Week 12	-23.87	-23.02	-17.06	-10.47
LS Mean difference from placebo (Confidence Interval, p value)	-13.41 (CI: -17.47, -9.34) **p<0.0001**	-12.55 (CI:-16.56, -8.55) **p<0.0001**	-6.60 (CI:-10.71, -2.49) p=0.0017	
Clinical Responses				
UAS7=0 (Complete Control)	37.5%	51.1%	22.9%	6.4%
UAS7≤6 (Well-controlled)	62.5%	59.6%	41.7%	12.8%

* Approximately 20% of enrolled patients received prior treatment with omalizumab. These patients experienced a similar clinical benefit as the overall treated population within their individual dosing groups.

Barzolvolimab was generally well tolerated with a favorable safety profile. Most adverse events were mild to moderate in severity; through 12 weeks, the most common treatment emergent adverse events in barzolvolimab treated patients were hair color changes (9%), urticaria (9%) and neutropenia (8%). The rate of infections was similar between barzolvolimab-treated patients and placebo with no apparent association between neutropenia and infections.

CSU: Future Targets

Table 2. Breakthrough treatments for chronic spontaneous urticaria (CSU): monoclonal antibodies.

Drug	Target	Mechanism of Action	Administration	Response	Clinical Trial Phase	References
Dupilumab	IL-4 R á (IL-4; IL-13)	The block of the alpha subunit of the IL-4 receptor, which is shared with the IL-13 receptor, thereby inhibiting both IL-4 and IL-13 signaling pathways	Subcutaneous	A significant reduction in UAS7; showed efficacy in biologic-naïve patients but limited efficacy in omalizumab-refractory patients	Phase III	NCT04180488, (LIBERTY-CUPID CSU) [16,17]
Barzolvolimab (CDX-0159)	Kit	The inhibition of Kit receptor, reducing mast cell survival and activation	Intravenous	Although the phase III study is still ongoing, in phase II a reduction in activity and quality of life scores has been reported	Phase III	NCT06445023; NCT06455202 [18]
Tezepelumab	TSLP	The inhibition of TSLP, a key initiator of type 2 inflammation	Subcutaneous	Preliminary results indicate a good response; however, the final data of phase II study are still not available	Phase II	NCT04833855 [19]
* Vixarelimab	IL-31 R	The block of the IL-31 and oncostatin M signaling pathways, reducing pruritus and inflammation	Subcutaneous	Although the phase II study in CSU is still ongoing, its promising results in the treatment of prurigo nodularis suggest potential benefits for CSU	Phase II	NCT03858634
Mepolizumab	IL-5	The inhibition of IL-5, reducing eosinophil migration and activation	Subcutaneous	Effective in reducing CSU symptoms, especially in patients with eosinophilic diseases	Phase I	NCT03494881 [20,21]
UB-221	IgE	Binding to IgE with high affinity, preventing interaction with mast cells and basophils	Intravenous	Although the phase II study in CSU is still ongoing, the drug appears to be promising due to its safety and its superior effectiveness in reducing IgE levels compared to omalizumab	Phase II	NCT05298215 [22]

IgE: immunoglobulin E; IL: interleukin; Kit: tyrosine kinase receptor Kit; R: receptor; TSLP: thymic stromal lymphopoietin; UAS7: Weekly Urticaria Activity Score.

Table 3. Breakthrough treatments for chronic spontaneous urticaria (CSU): small molecules.

Drug	Target	Mechanism of Action	Administration	Response	Clinical Trial Phase	References
Remibrutinib	BTK	The inhibition of BTK, a key component of FcεRI signaling in mast cells and basophils, thereby reducing the release of inflammatory mediators like histamine.	Oral	Rapid and sustained symptom control, good safety profile in antihistamine-refractory CSU	Phase III	NCT03926611, NCT05114057 [23–25]
Rilzabrutinib	BTK		Oral	Results of the phase II studies are still pending. However, given their mechanism of action, which closely mirrors that of remibrutinib, their potential effectiveness in CSU seems likely.	Phase II	NCT05107115
TAS 5315	BTK		Oral		Phase II	NCT05335499 [26]
TLL-018	JAK1	The selective inhibition of JAK1, reducing cytokine-driven inflammation.	Oral	Despite being in the early phase of study, its inhibitory effects on JAK 1 suggest it could be a promising therapeutic option for CSU.	Phase I	NCT06396026
Povorcitinib	JAK1, JAK2, TYK2	The inhibition of JAK1, JAK2, and TYK2, disrupting cytokine signaling.	Oral	Although the results of the phase I and II studies are still pending, their broad spectrum of action makes these molecules appear promising.	Phase II	NCT05373355 NCT05936567
* EP 262	MRGPRX2	The block of MRGPRX2 (the non-IgE mast cell receptor)	Oral	Given the emerging role of MRGPRX2 in CSU pathophysiology, blocking this receptor makes the drug a highly promising candidate, although the results from the phase II trial are still pending.	Phase II	NCT06077773

BTK: Bruton tyrosine kinase; FcεRI: high-affinity receptor for the fragment crystallizable region of immunoglobulin E; JAK: Janus kinase; MRGPRX2: Mas-related G protein-coupled receptor X2; TYK: tyrosine kinase.

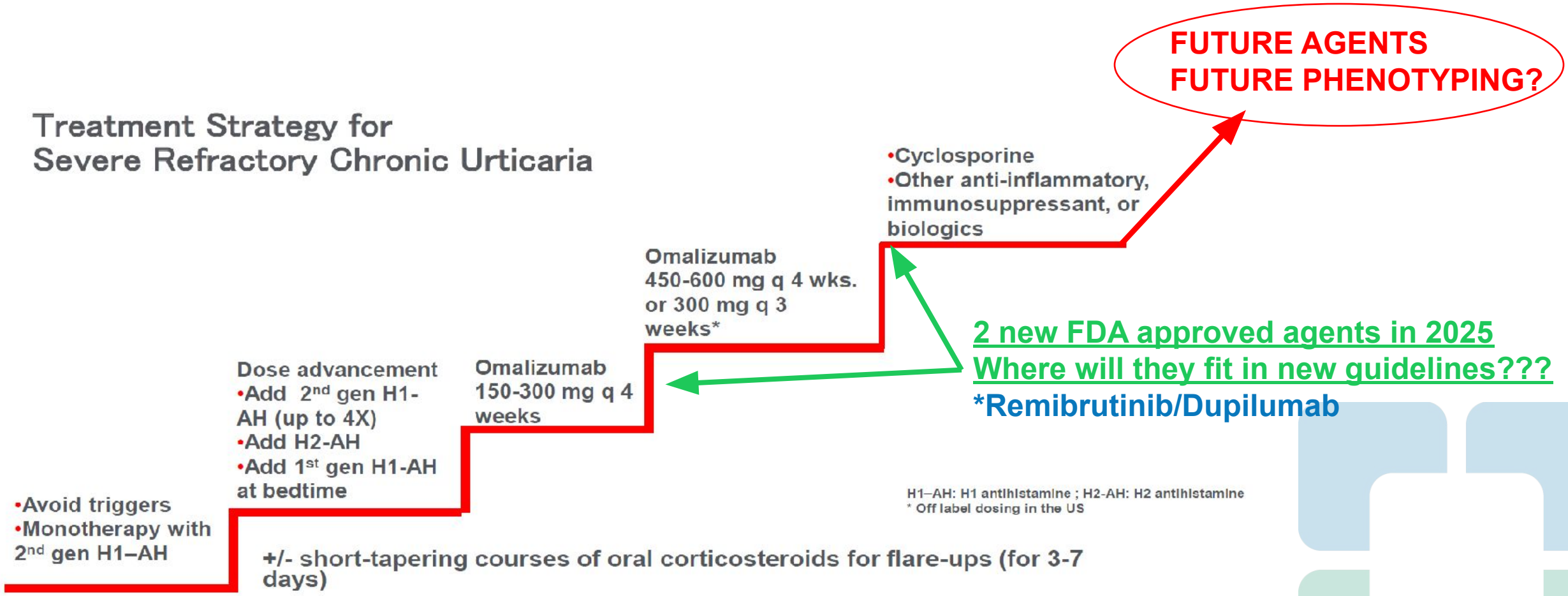
pharmaceuticals MDPI

Review

Therapies for Chronic Spontaneous Urticaria: Present and Future Developments

Riccardo Asero [1], Paolo Calzari [2], Silvia Vaienti [3] and Massimo Cugno [4,*]

Stepwise Approach



THANK YOU


"I must say, Mr. Jennings, you have the worst case of Hives I've ever seen."