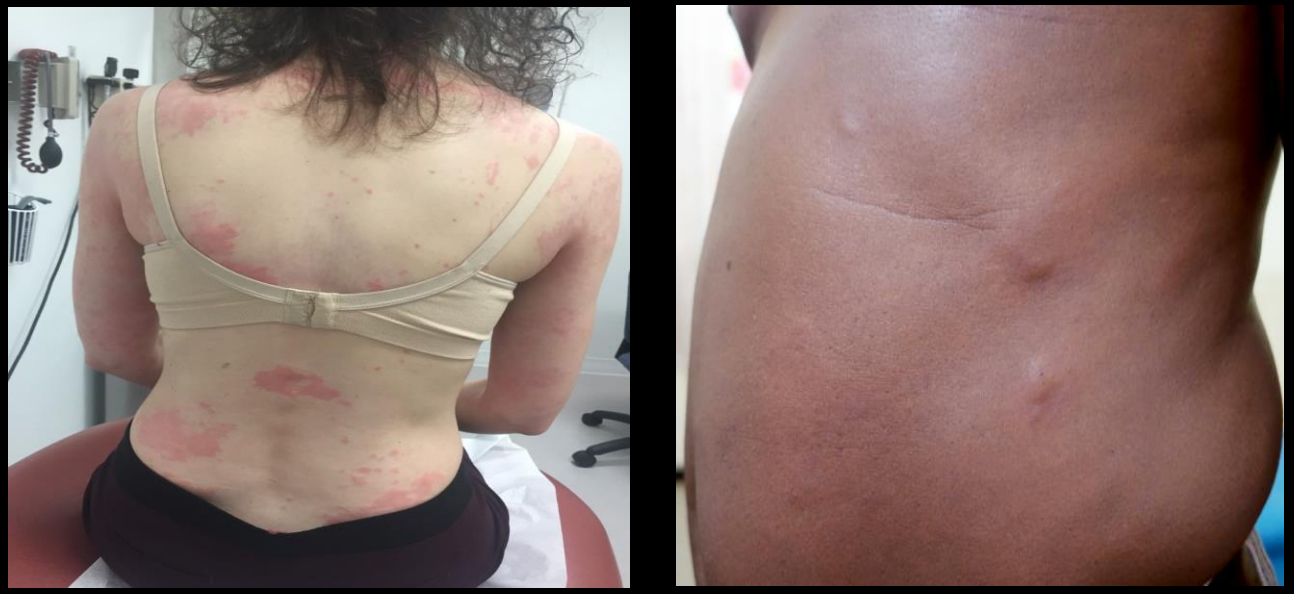
Chronic Spontaneous Urticaria: Treatment Options When Omalizumab Fails



Lang DM. Chronic Urticaria N Engl J Med 2022; 387: 824-31

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Learning Objectives

After participation, the learner will be able to:

- Relate appropriate management, based on best evidence, for patients with chronic spontaneous urticaria not improved on anti-IgE therapy.

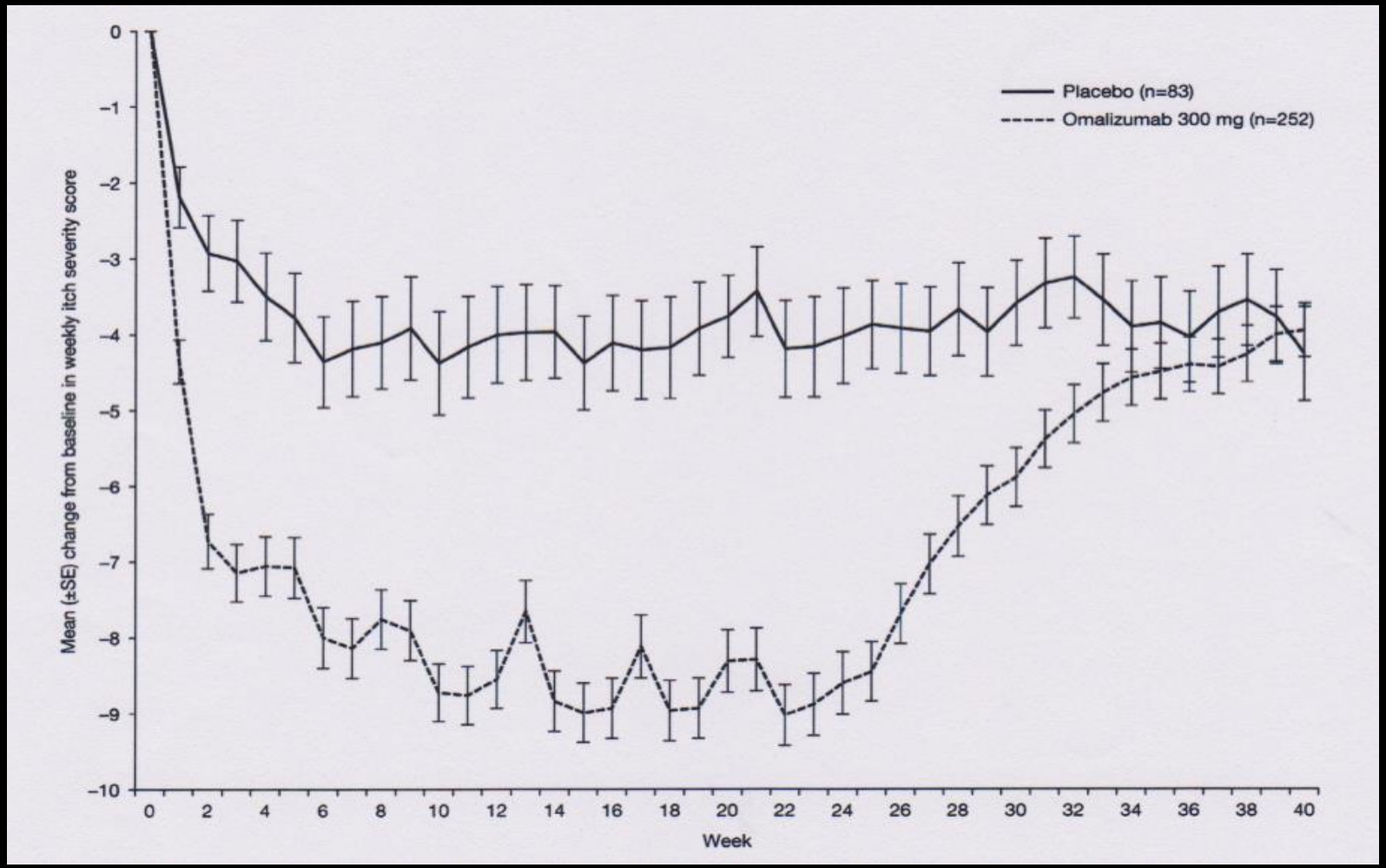
- Describe current therapeutic options for patients with chronic spontaneous urticaria not improved on anti-IgE therapy, and therapeutic options that will likely be available in the near future.

Therapeutic Role For Anti-IgE

- Phase III multicenter, double-blind RCT
- 24 week study in adults and adolescents with chronic urticaria who remained symptomatic despite regular use of antihistamines – including up to 4 times FDA approved doses, plus H2 antihistamines, anti-leukotrienes or both .
- Subjects maintained pre-randomization combination therapy, and were randomly assigned in a 3:1 ratio to receive injections every 4 weeks:
  - Omalizumab 300 mg
  - Placebo
- Primary objective: safety of omalizumab at dose of 300 mg compared with placebo, using modified ITT analysis.

Kaplan A., et al. J Allergy Clin Immunol 2013; 132:101-9.

Therapeutic Role For Anti-IgE



Kaplan A., et al. J Allergy Clin Immunol 2013; 132:101-9

Proportion of Subjects in 5 Randomized Controlled Trials Evaluating the Efficacy of Omalizumab Who Became Hive-Free and Who Experienced Clinically Meaningful Improvement

		Randomized Subjects		*UAS7 = 0	UAS7 = 0	UAS7 <6	UAS7 <6
Author, Year	**Study Duration#**	**Omalizumab 300 mg**	**Placebo**	**300 mg**	**Placebo**	**300 mg**	**Placebo**
Maurer, 2013	12 weeks	79	79	35	4	52	15
Kaplan, 2013	24 weeks	252	83	85	4	132	10
Saini, 2015	24 weeks	81	80	29	7	42	9
Hide, 2018	26 weeks	35	36	11	1	19	6
Yuan, 2021	20 weeks	167	83	62	4	81	9
Totals		**614**	**361**	**222 (36%)**	**20 (6%)**	**326 (53%)**	**49 (13%)**

Efficacy assessed at 12 weeks.
UAS 7 = Urticaria Activity Score over 7 days.

NNT = 3.3 ***NNT = 2.5***

Bernstein JS, Bernstein JA, Lang DM. Immunol Allergy Ciin North Am 2024 Nov;44(4):595-613.

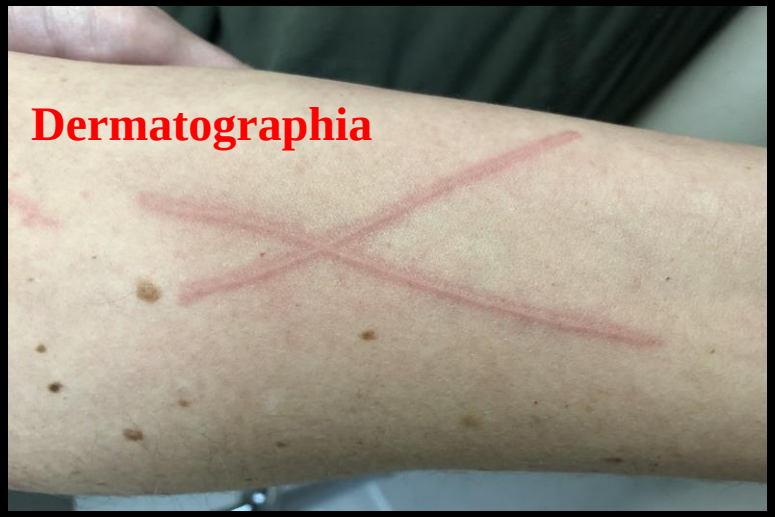
Chronic Inducible Urticaria

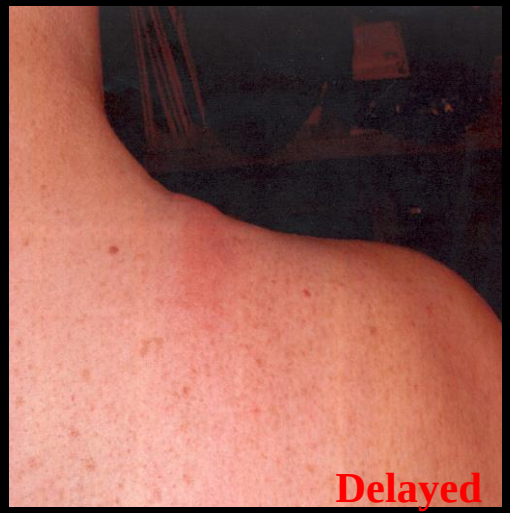
Let's Get Physical…

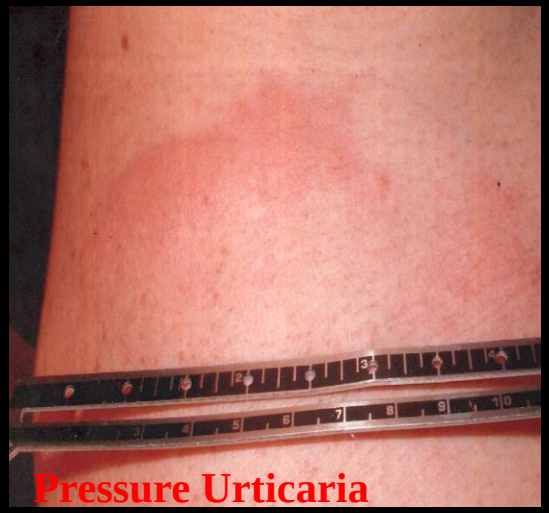
Syndrome	Challenge Procedure	Positive Result
Cholinergic	• Methacholine intradermal challenge • Partial immersion using hot water (42 C).	• Appearance of "satellite wheal" • Urticaria (1-3 mm wheals) at challenge site
Cold	Cold provocation testing (ice cube) on skin of forearm for 5 minutes	Development of urticaria at challenge site during rewarming of skin
Dermatographia	Stroking of skin with tongue blade	Erythema at site of stroking within 1-3 minutes
Delayed Pressure	Weights (15 lbs) suspended over shoulder for 10 or 15 minutes	Area of angioedema develops 2-12 hours later (peak = 4-6.5 hours) at site of pressure challenge.
Vibratory	Vortex mixer applied to forearm for 4 minutes	Development of angioedema sharply demarcated from normal skin

Lang DM, et al. Ann Allergy Asthma Immunol 2013; 111: 235-41

Chronic Inducible Urticaria

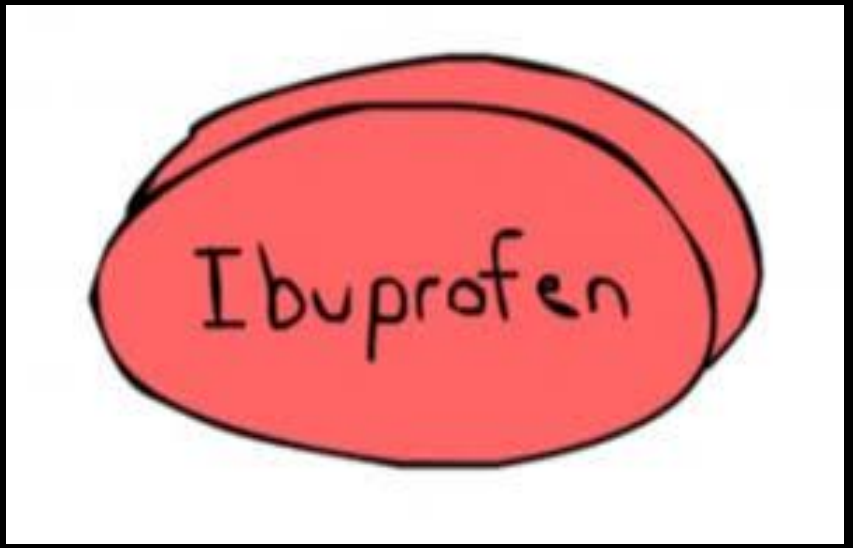


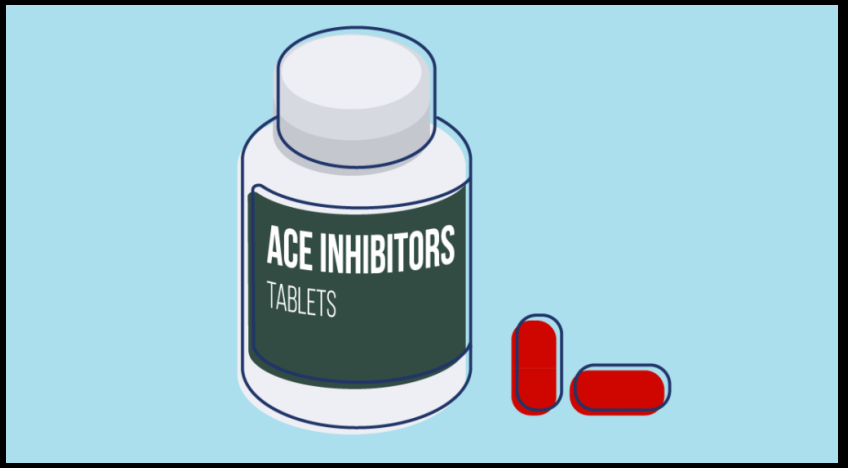




Lang DM. N Engl J Med 2022; 387: 824-31

Drugs





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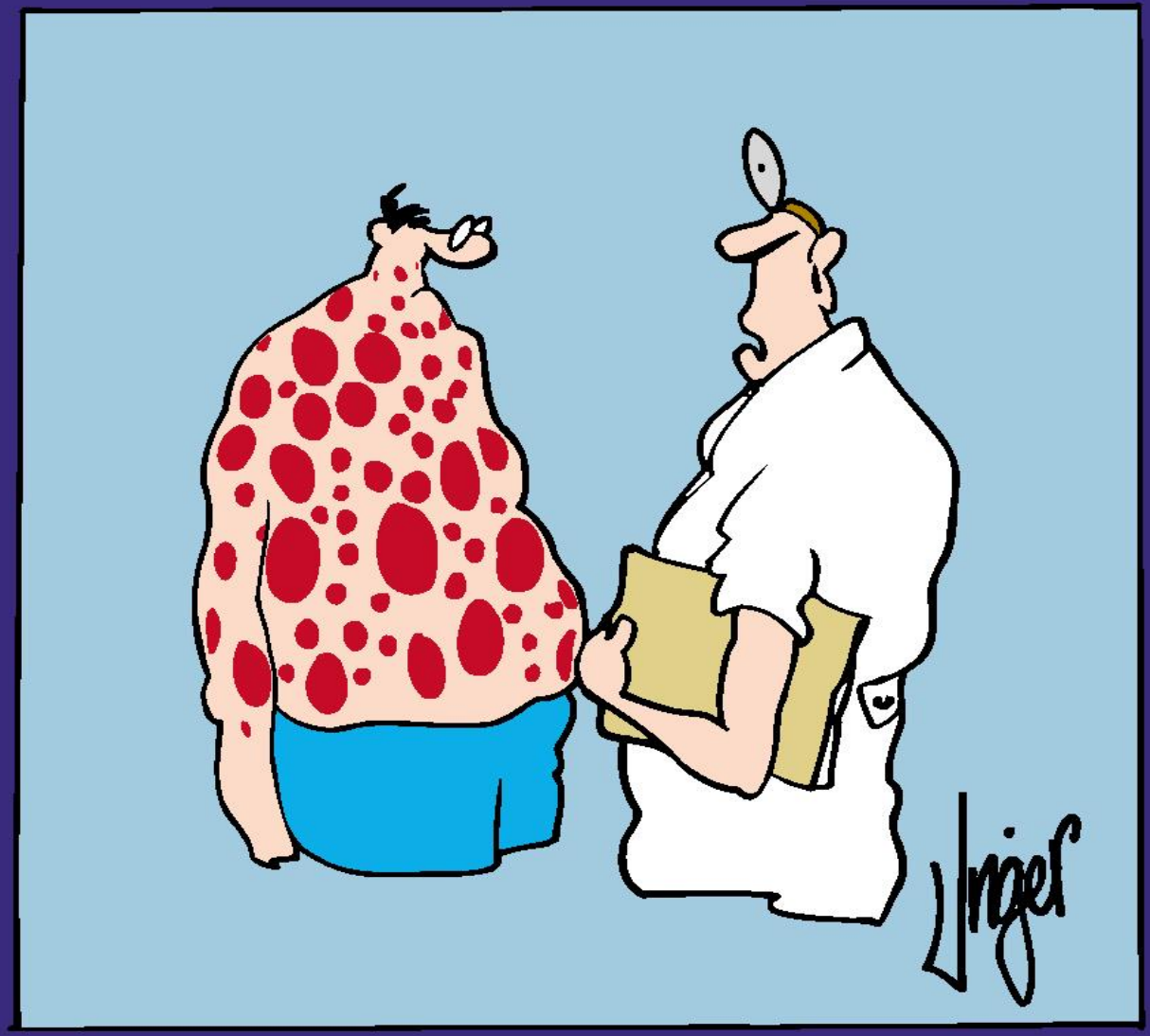

"Try to remember all the things you've eaten in the past three days."

Choosing Wisely®

An initiative of the ABIM Foundation

American Academy of Allergy, Asthma & Immunology

American Academy of Allergy Asthma & Immunology
www.aaaai.org

Five Things Physicians and Patients Should Question

1 Don't perform immunoglobulin G (IgG) tests or an indiscriminate battery of immunoglobulin E (IgE) tests in the evaluation of allergy.

Specific IgG testing does not indicate an allergic illness and thus should not be obtained in evaluation of patients for allergic disease. Skin testing and specific IgE testing to both inhalant and food allergens has a high false positive rate, in some cases greater than 50 percent. Thus, history should be the guide to testing.

2 Don't order sinus computed tomography (CT) or indiscriminately prescribe antibiotics for uncomplicated acute rhinosinusitis.

Viral infections cause the majority of acute rhinosinusitis and only 0.5 percent to 2 percent progress to bacterial infections. Most acute rhinosinusitis resolves without treatment in two weeks. Uncomplicated acute rhinosinusitis is generally diagnosed clinically and does not require a sinus CT scan or other imaging. Antibiotics are not recommended for patients with uncomplicated acute rhinosinusitis who have mild illness and assurance of follow-up. If a decision is made to treat, amoxicillin should be first-line antibiotic treatment for most acute rhinosinsutis.

3 Don't routinely do diagnostic testing in patients with chronic urticaria.

In the overwhelming majority of patients with chronic urticaria, a definite etiology is not identified. Limited laboratory testing may be warranted to exclude underlying causes. Targeted laboratory testing based on clinical suspicion is appropriate. Routine extensive testing is neither cost effective nor associated with improved clinical outcomes. Skin or serum-specific IgE testing for inhalants or foods is not indicated, unless there is a clear history implicating an allergen as a provoking or perpetuating factor for urticaria.

4 Don't recommend replacement immunoglobulin therapy for recurrent infections unless impaired antibody responses to vaccines are demonstrated.

Immunoglobulin (gammaglobulin) replacement is expensive and does not improve outcomes unless there is impairment of antigen-specific IgG antibody responses to vaccine immunizations or natural infections. Low levels of immunoglobulins (isotypes or subclasses), without impaired antigen-specific IgG antibody responses, do not indicate a need for immunoglobulin replacement therapy. Exceptions include IgG levels <150mg/dl and genetically defined/suspected disorders. Measurement of IgG subclasses is not routinely useful in determining the need for immunoglobulin therapy. Selective IgA deficiency is a contraindication for administration of immunoglobulin.

5 Don't diagnose or manage asthma without spirometry.

Clinicians often rely solely upon symptoms when diagnosing and managing asthma, but these symptoms may be misleading and be from alternate causes. Therefore spirometry is essential to confirm the diagnosis in those patients who can perform this procedure. Recent guidelines highlight spirometry's value in stratifying disease severity and monitoring control. History and physical exam alone may over- or under-estimate asthma control. Beyond the increased costs of care, repercussions of misdiagnosing asthma include delaying a correct diagnosis and treatment.

3

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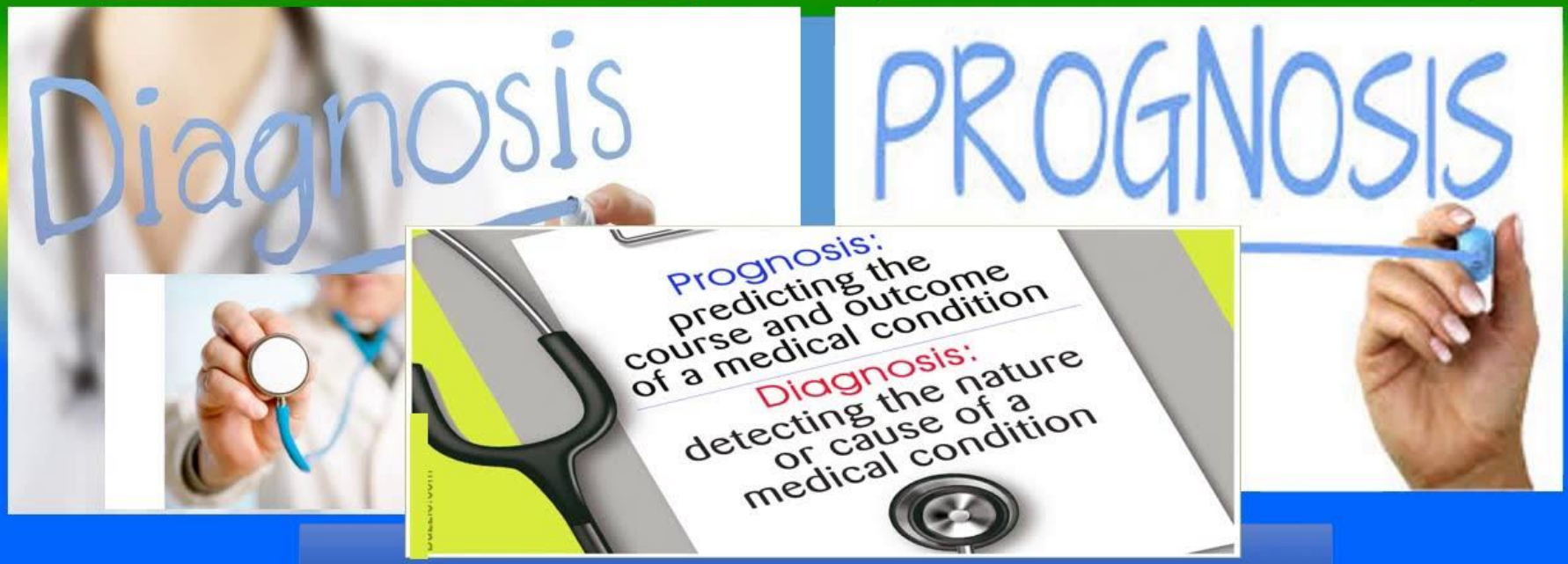
Difference Between

Diagnosis

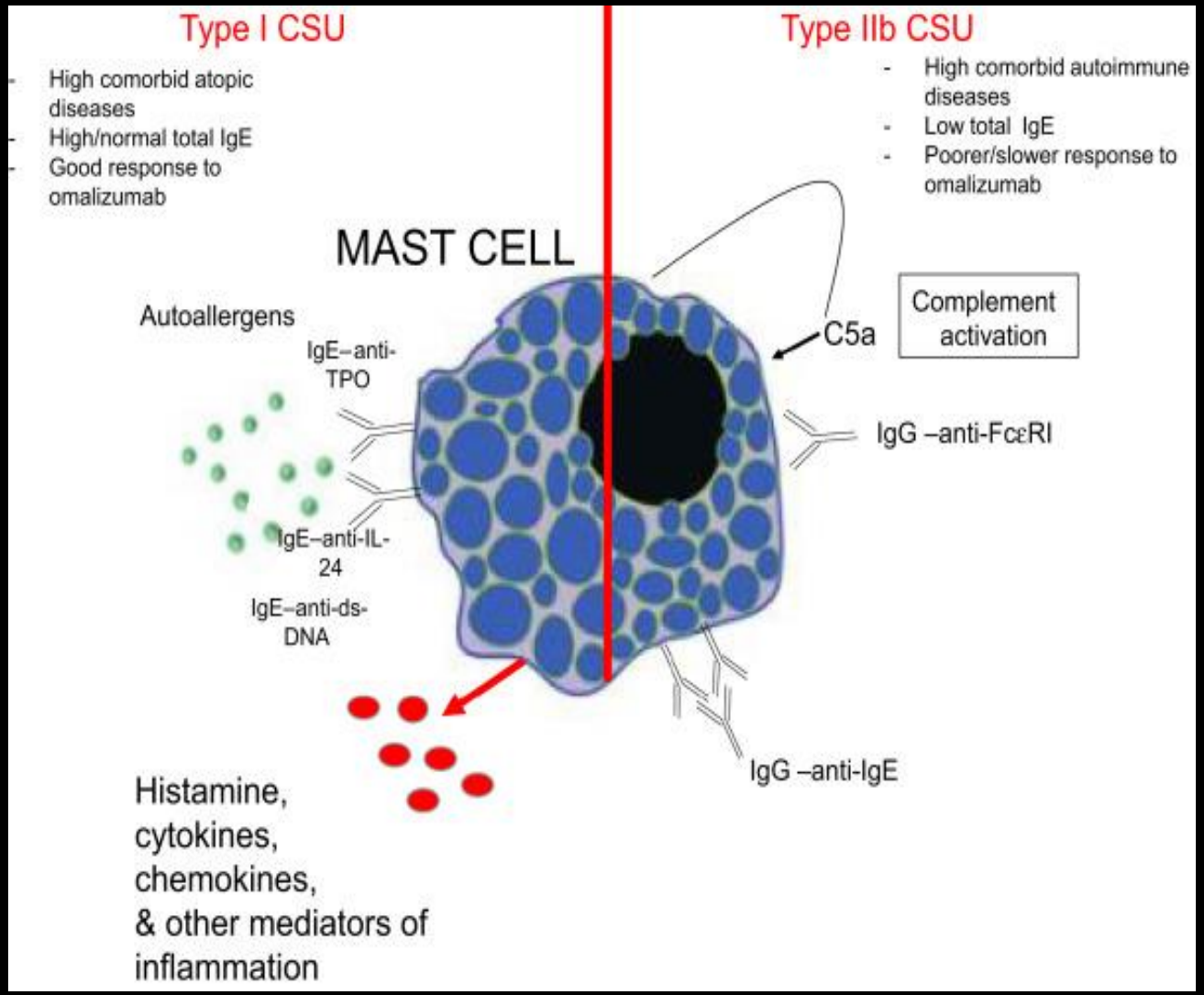
Prognosis



https://www.youtube.com/watch?v=tS0azXPH0vI

Diagnostic Evaluation

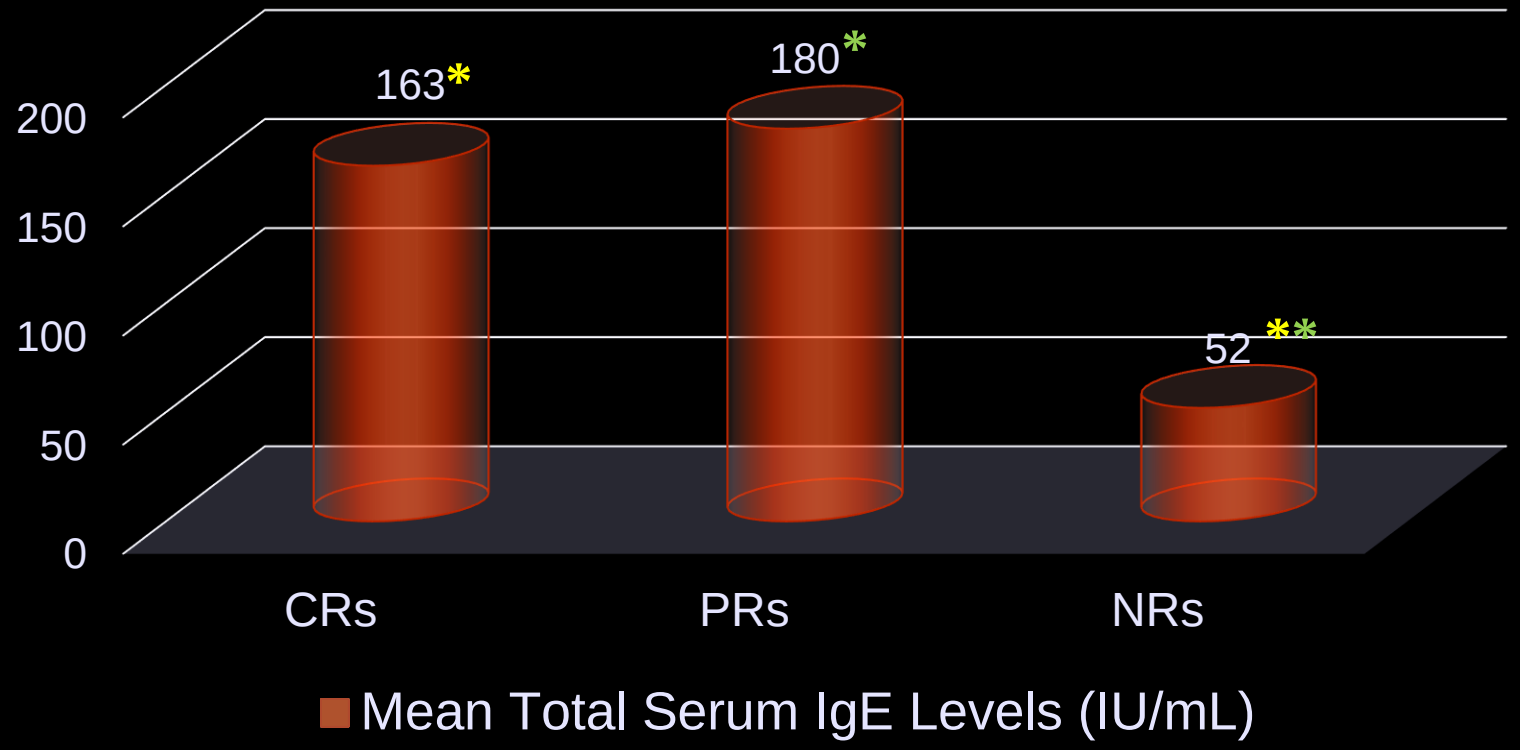
- CBC with differential
- Anti-TPO
- TSH
- ESR (or CRP)



Asero R, et al. J Allergy Clin Immunol Pract 2023; 11: 2302-8

Omalizumab: IgE Predicts Clinical Response

- Meta-analysis of 10 interventional studies, 866 patients
  - Higher Serum Total IgE levels in CRs vs NRs and PRs vs NRs.
  - No significant difference: CRs vs PRs



Chuang K-W et al. J Allergy Clin Immunol Pract 2023; 11:2382-9


What
Do I Do
Now

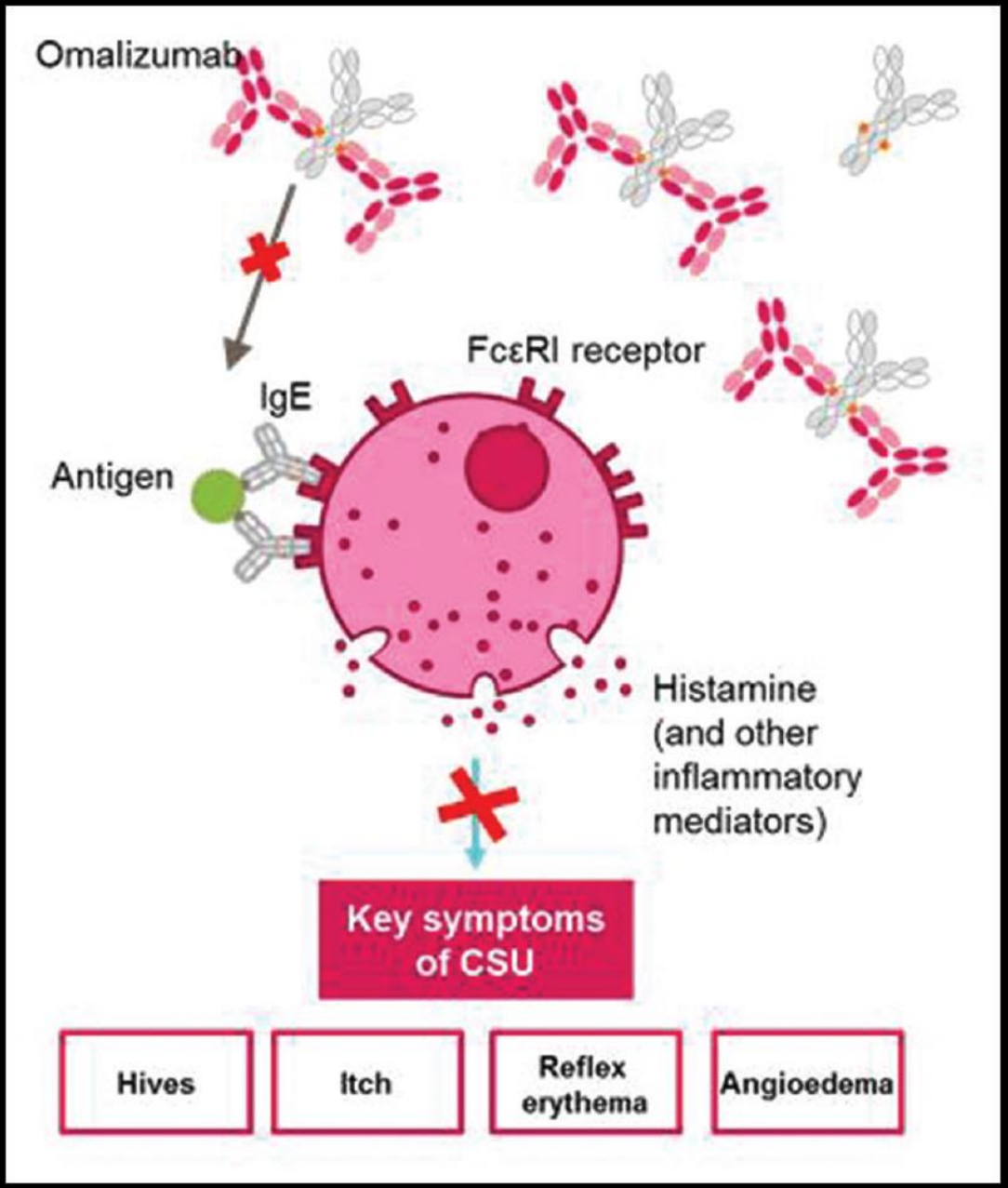
Step Care for Chronic Urticaria

Step 1	Step 2	Step 3
• Start monotherapy with second-generation H_1-antihistamine • Perform comprehensive history taking and physical examination • Recommend avoidance measures and lifestyle changes as appropriate • Consider limited laboratory testing or targeted testing as appropriate; routine extensive laboratory testing is not warranted • Record patient-reported outcome measures serially at initial and follow-up visits	• Dose escalation of second-generation H_1-antihistamine • Adjunctive therapies: H_2-antihistamine Antileukotriene agent • Short-term use of oral glucocorticoids to restore control (if needed)	• Biologic agent (omalizumab) or Cyclosporine • Alternative agents: Dapsone, Stanozolol, Hydroxychloroquine, Sulfasalazine, Colchicine, Mycophenolate, Others • Short-term use of oral glucocorticoids to restore control (if needed)

Lang DM. N Engl J Med 2022; 387: 824-31

Options

- Anti-IgE
- Cyclosporine
- Alternative Agents
- Anti-IL4/IL-13
- Coming Soon
  - BTK Inhibitor
  - Anti-Kit
  - Others…

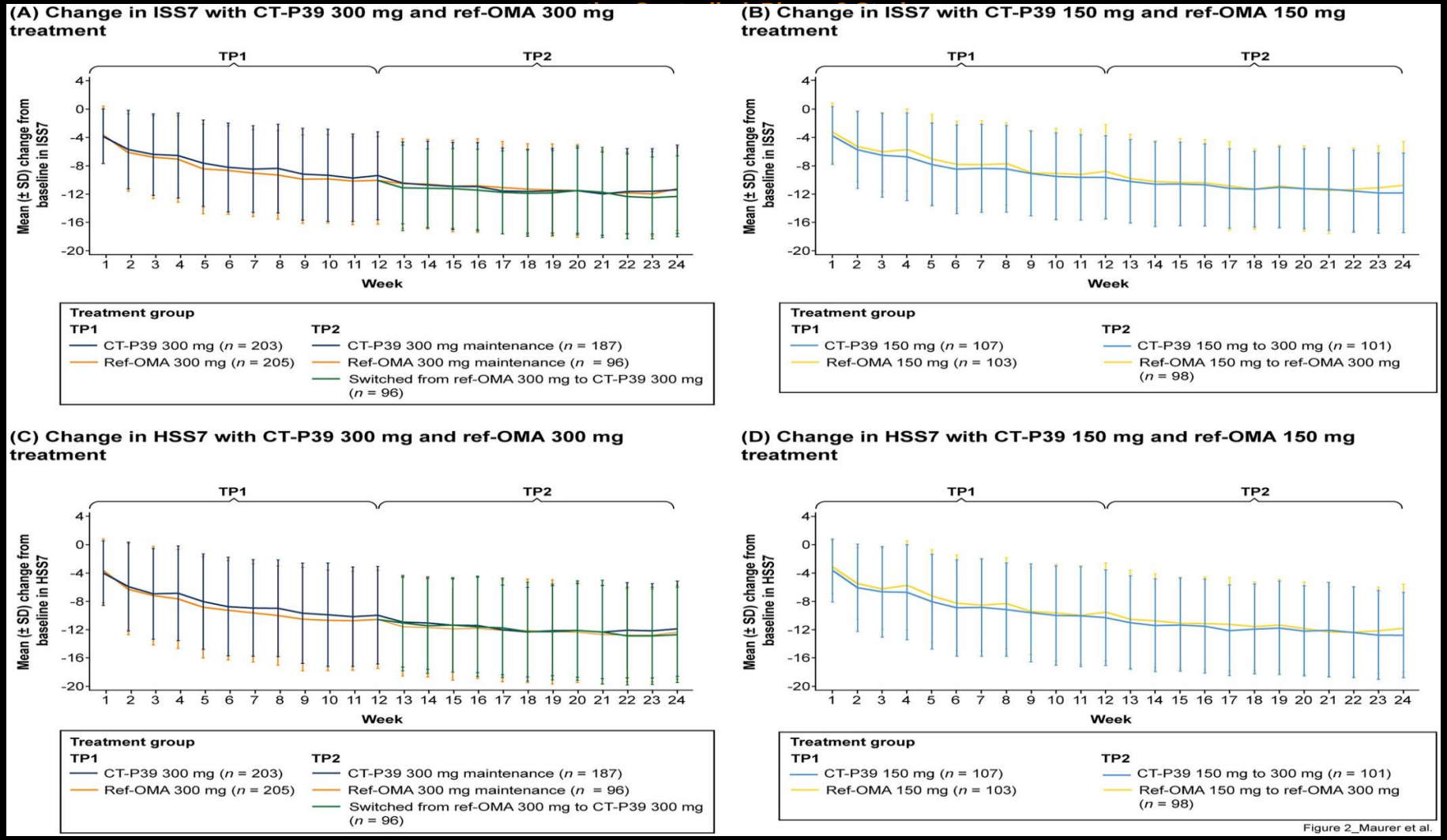


Godse K, et al. Indian Dermatol Online J 2016;7:6-11

Omalizumab - Igec

- A biosimilar drug is a highly similar version of an already licensed biological; to gain approval, a biosimilar must demonstrate no clinically meaningful differences in efficacy & safety compared with the reference product.
- Chemical and biological analyses have confirmed Omalizumab - Igec is highly similar to omalizumab with respect to primary and higher order structure, modifications and post-translational forms, purity/impurity, and biological activity.
- Approved by FDA, March 9, 2025:
  - Severe persistent asthma
  - CRSwNP
  - IgE mediated food allergy
  - CSU
- “Interchangeability supported by positive Phase III data…”

RDBPG active-controlled Phase 3 multi-center study with two 12-week treatment periods



Saini SS, et al. Allergy. 2025;. Epub ahead of print

Efficacy of Omalizumab

- Anti-IgE treatment can improve CSU
  - IgE Elevated or WNL: Autoallergic CSU
  - IgE Low: Autoimmune CSU
- Omalizumab binds to circulating IgE.
- In type I autoallergic CSU, this can lead to rapid improvement.
- In type IIb autoimmune CSU, omalizumab-induced reduction of free IgE can also lead to downregulation of FcεRI on skin mast cells, the target of mast cell-activating IgG autoantibodies, but improvement is more gradual.

Maurer et al. J Allergy Clin Immunol Pract 2023; In Press

Refractory Urticaria/Angioedema

Alternative Agents

"… any therapeutic agent other than antihistamines or corticosteroids used to treat patients with refractory chronic urticaria"

Khan DA. J Allergy Clin Immunol Pract 2013

Refractory Urticaria/Angioedema: Alternative Agents

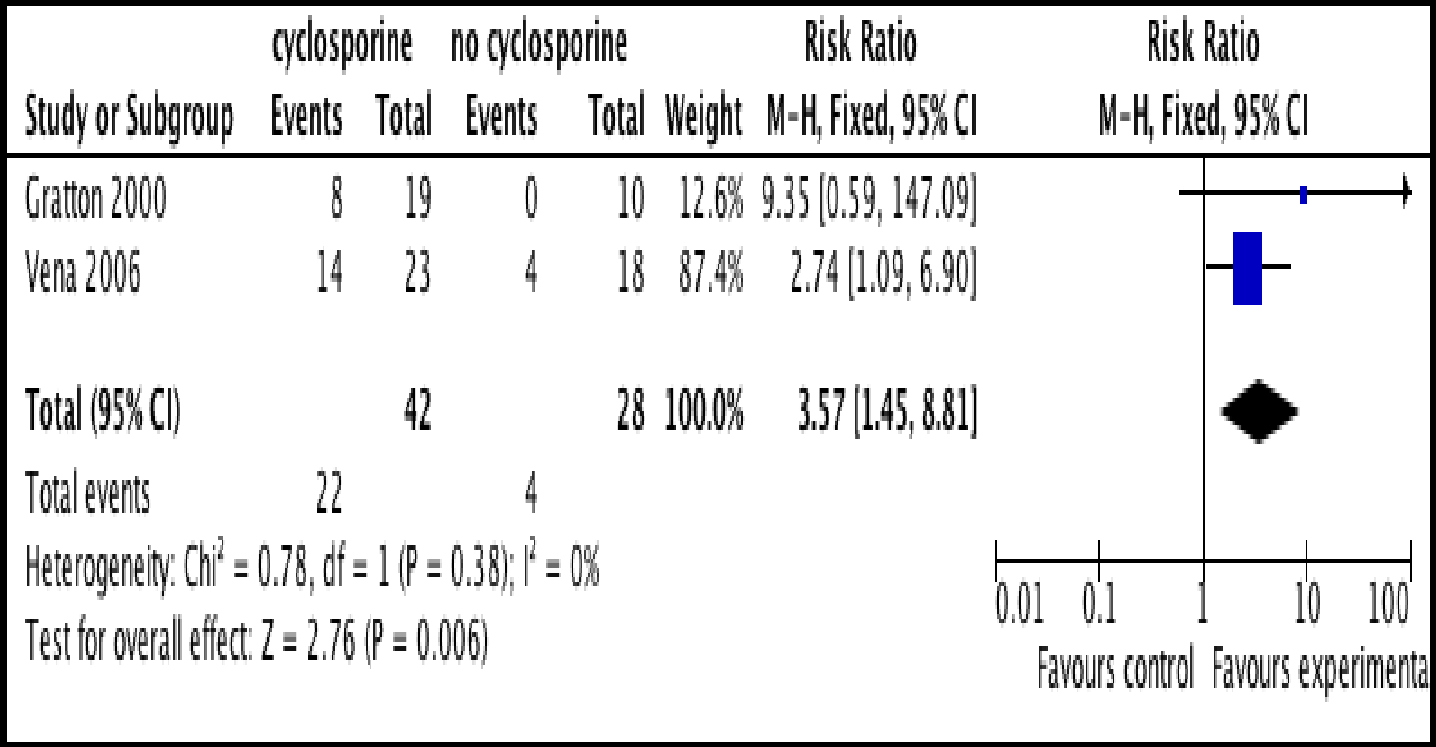
- Colchicine
- Sulfasalazine
- Mycophenolate
- Methotrexate
- Dapsone
- Sirolimus
- Anti-TNF
- Warfarin
- IVIG
- Stanozolol
- Hydroxychloroquine
- Omalizumab
- Cyclosporine
- Others…

Khan DA. J Allergy Clin Immunol Pract 2013

Evaluating Therapeutic Utility of Alternative Agents for Refractory Chronic Urticaria/Angioedema

- Case Series and Case Reports are subject to bias, and do not provide high quality evidence.
- Only 5 agents have been studied in randomized controlled trials:
  - Dapsone
  - Hydroxychloroquine
  - Stanozolol
  - Cyclosporine – 3 RCTs
  - Omalizumab

Cyclosporine



Study or Subgroup	cyclosporine Events	Total	no cyclosporine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gratton 2000	8	19	0	10	12.6%	9.35 [0.59, 147.09]
Vena 2006	14	23	4	18	87.4%	2.74 [1.09, 6.90]
Total (95% CI)		**42**		**28**	**100.0%**	**3.57 [1.45, 8.81]**
Total events	22		4			

Heterogeneity: $Chi^2 = 0.78$, $df = 1$ ($P = 0.38$); $I^2 = 0\%$

Test for overall effect: $Z = 2.76$ ($P = 0.006$)

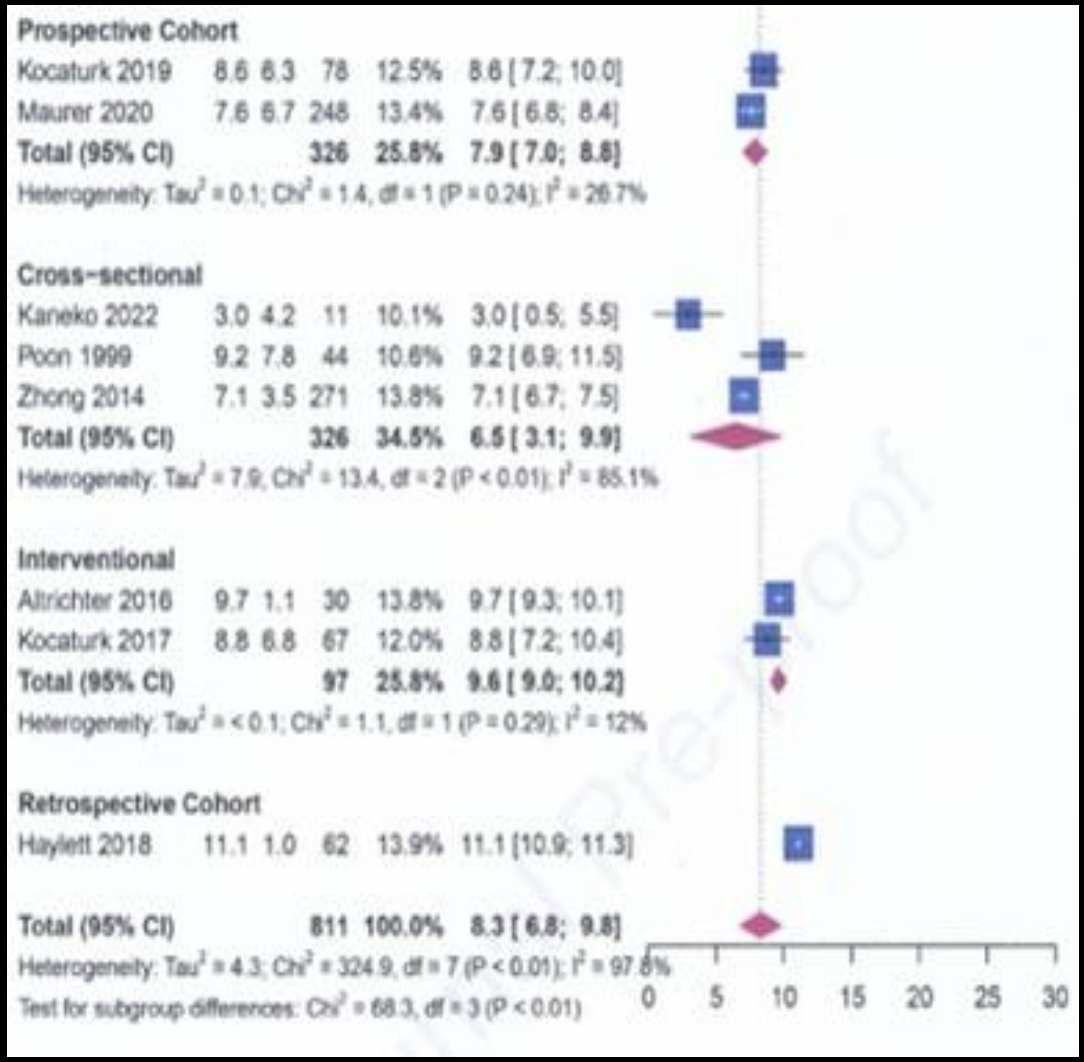
3.57 times more likely to experience benefit in symptom scores *

* UAS + USS

• *Bernstein JA, Lang DM, Khan D, eds.J Allergy Clin Immunol 2014;133:1270-7.*

Meta-Analysis: Cyclosporine for CSU

- 18 studies (N=909), including 2 RCTs
- Assessed efficacy and safety.
- Adverse events dose-dependent; occur in >50% treated with moderate dose.
- Efficacious at low-moderate dose; suggest dose of 1-5 mg/kg/day; 3 mg/kg/day “reasonable starting dose for most patients”.



Kulthanan, et al. J Allergy Clin Immunol Pract 2018; 6:586-599.

Step Care for Chronic Urticaria

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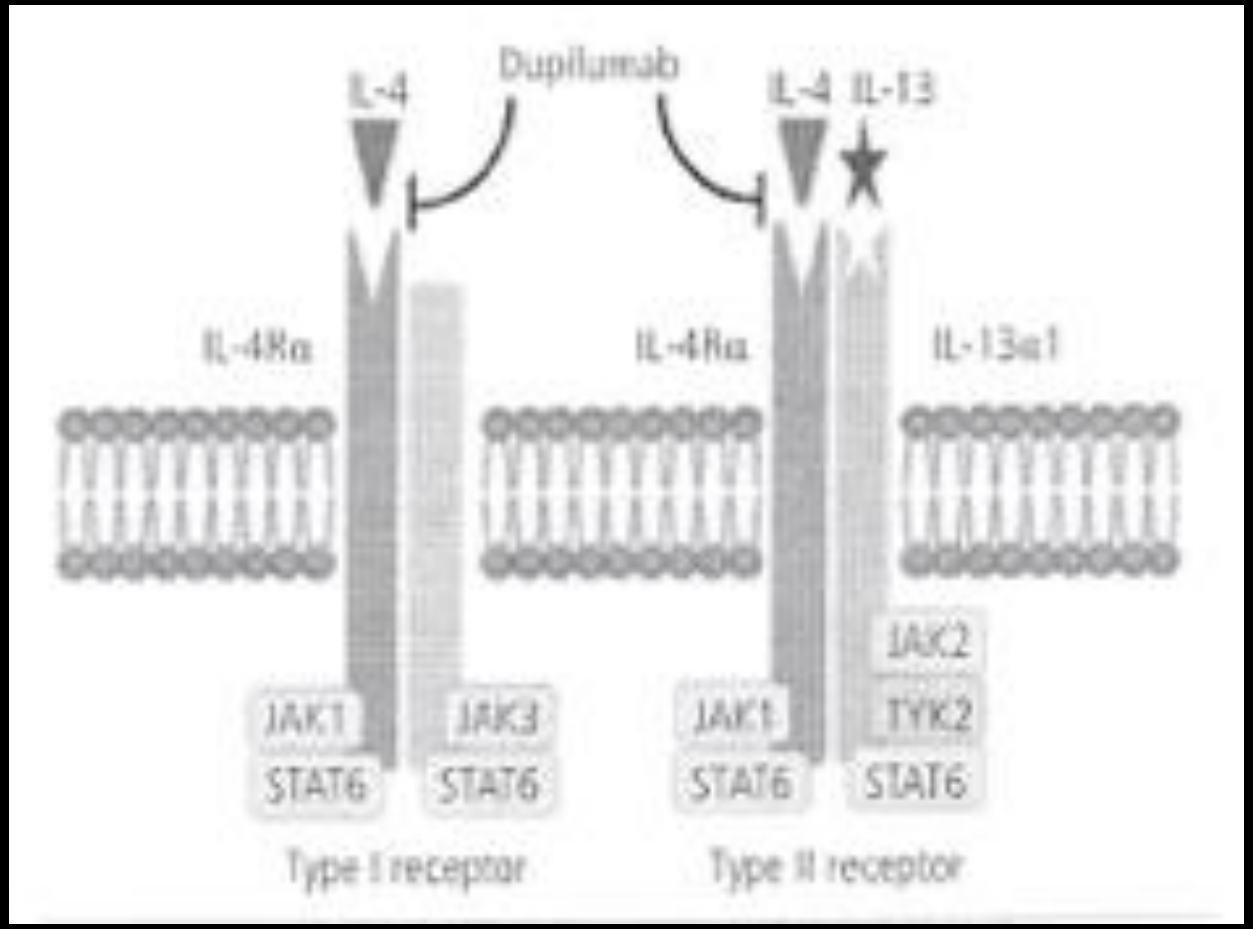
Lang DM. N Engl J Med 2022; 387: 824-31

Emerging Therapies Under Investigation

Agent	Mechanism of Action	ClinTrials Identifiers	Phase	CSU	CIndU	Comparator - Omalizumab
Remibrutinib	BTK inhibitor	NCT05030311, NCT05032157, NCT06042478, NCT05513001, NCT05795153, NCT05976243	3	Yes	Yes	Yes
Rilzabrutinib	BTK inhibitor	NCT05107115	2	Yes		
Dupilumab	IL4Rα inhibitor	NCT04180488, NCT05526521	3	Yes		Yes
Tezepelumab	anti-TSLP	NCT04833855	2	Yes		Yes
AK006	anti-Siglec-6	NCT06072157	1	Yes		
EP262	MRGPRX2 antagonist	NCT06077773	2	Yes		
Barzolvolimab (CDX-0159)	anti-KIT	NCT05405660, NCT05368285	3	Yes	Yes	
Briquilimab	anti-KIT	NCT06162728	1,2	Yes		

Bernstein JS, et al., Immunol Allergy Ciin North Am 2024 Nov;44(4):595-613.

Therapeutic Role For Anti-IL4/IL13



J Investig Allergol Clin Immunol 2022; 32: 99.

Liberty CSU-Cupid

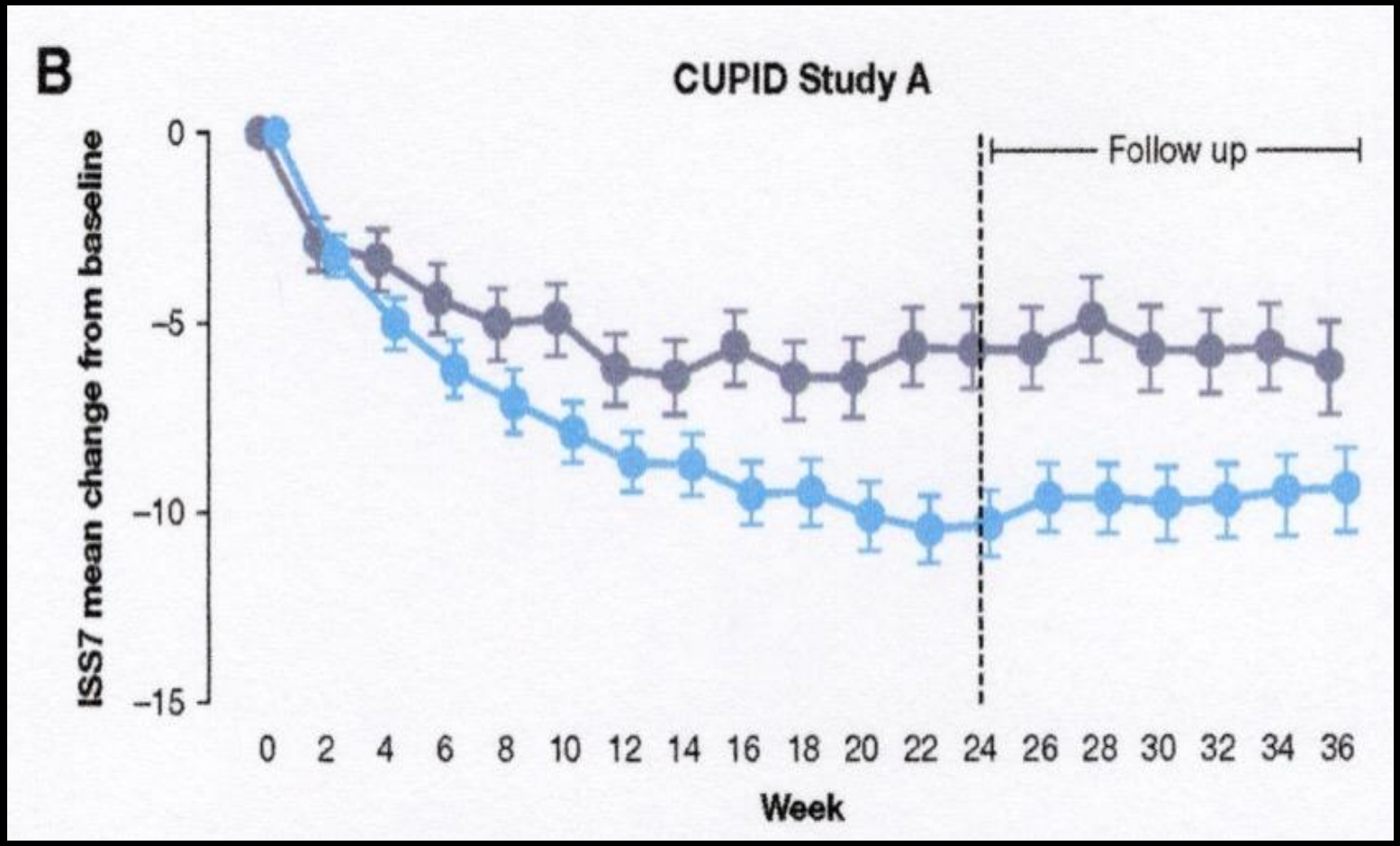
- Two Phase 3 RDBPC trials
  - Cupid A: Omalizumab-naïve
  - Cupid B: Omalizumab Failure

	UAS7	ISS7
Cupid A	Difference -8.5 [95%CI = -13.2 to -3.9] p = 0.0003	Difference -4.2 [95%CI = -6.6 to -1.8] p = 0.0005
Cupid B	Difference -5.8 [95%CI = -11.4 to -0.3] p = 0.0390	Difference -2.9 [95%CI = -5.7 to -0.07] p = 0.0449*

* alpha = 0.043

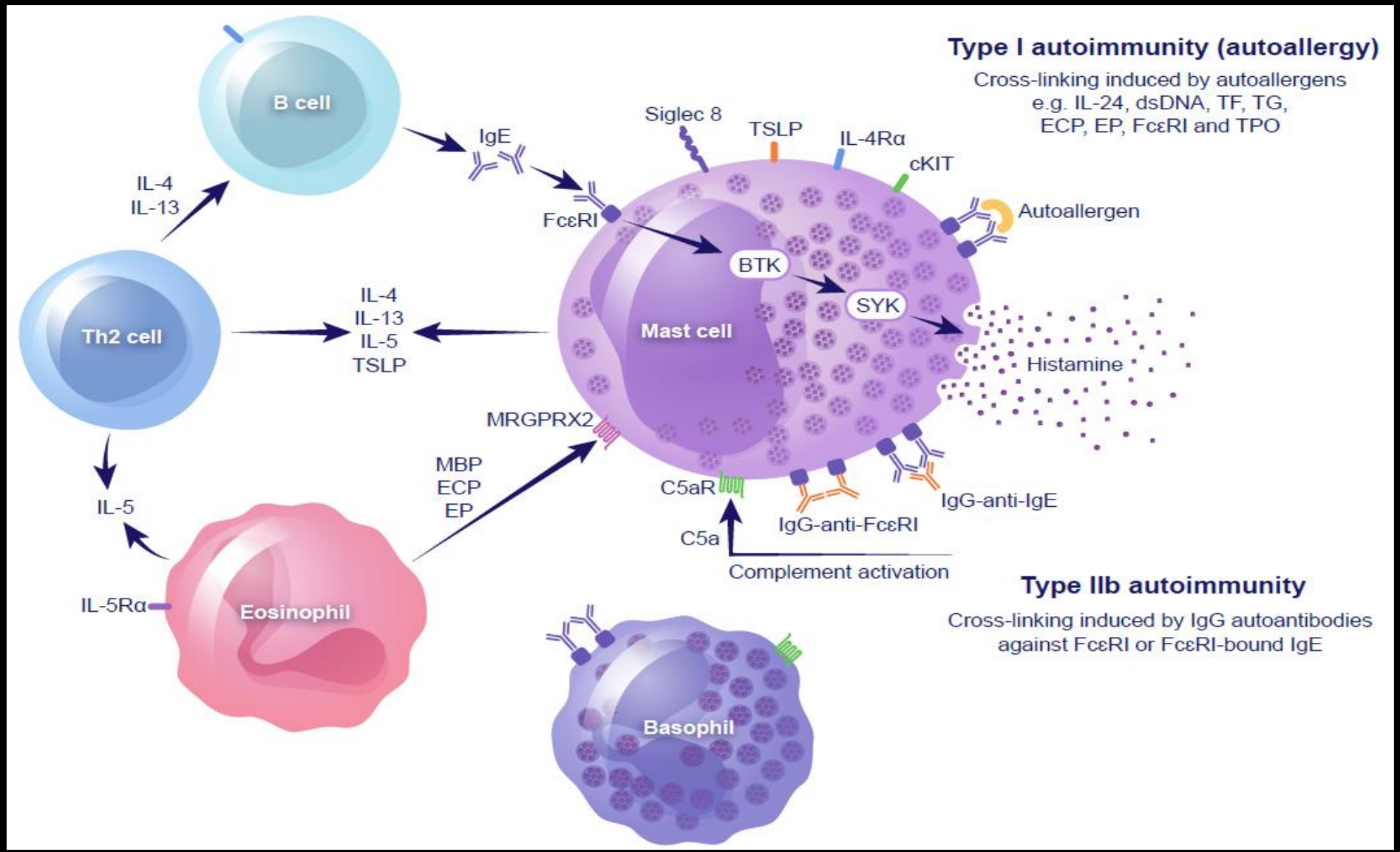
Maurer M., et al. J Allergy Clin Immunol 2024; 154: 184-194

Therapeutic Role For Anti-IL4/IL13
Liberty CSU-Cupid



Maurer M., et al. J Allergy Clin Immunol 2024; 154: 184-194

Type I and Type IIb Autoimmunity



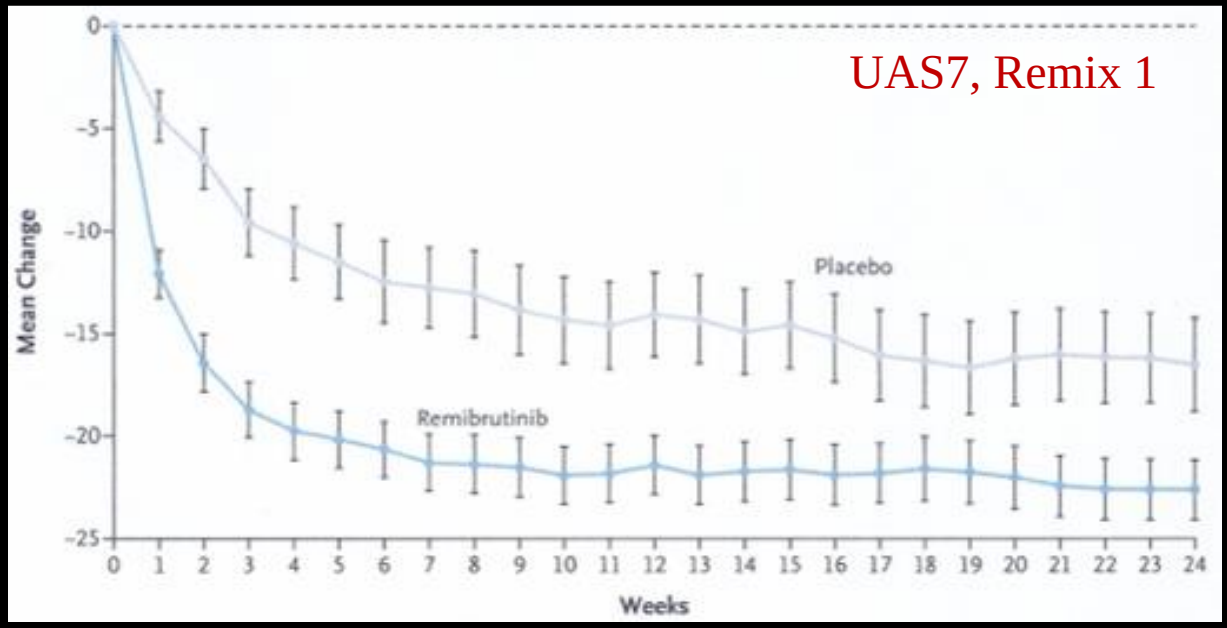
Lang DM, et al. Ann Allergy Asthma Immunol. 2025 Apr;134(4):408-417.

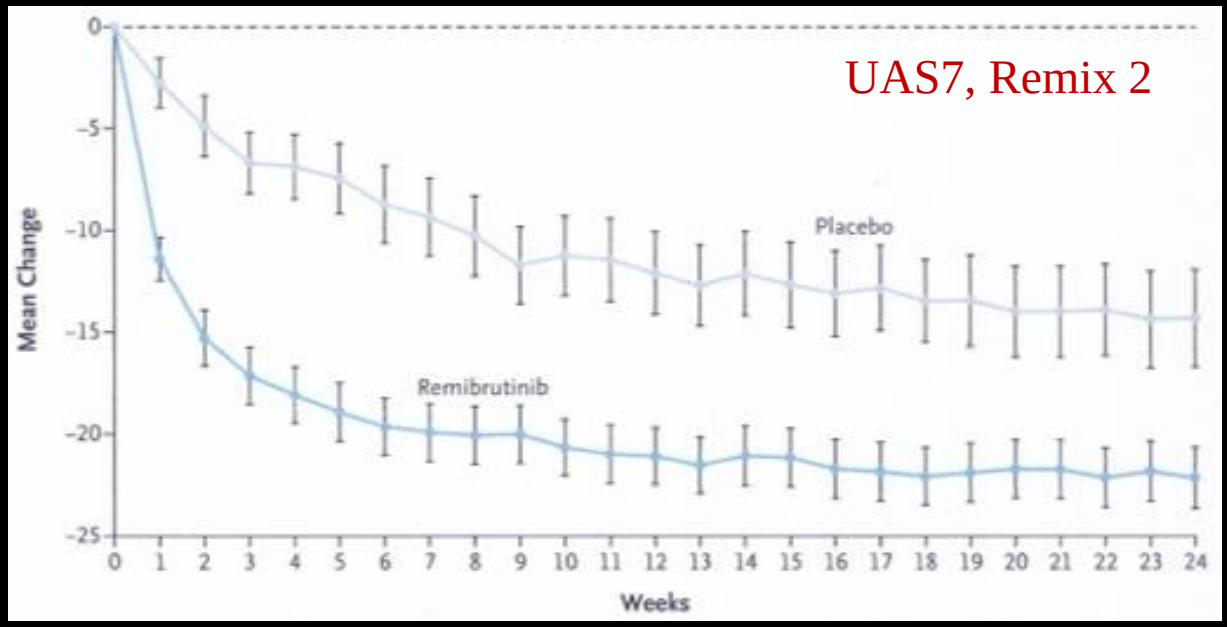
Therapeutic Role for BTK Inhibition

- Multicenter RDBPC trials
  - REMIX 1 (N = 470)
  - REMIX 2 (N = 455)
- Subjects randomly assigned 2:1
  - Remibrutinib 25 mg BID
  - Placebo BID
- Primary endpoint: Change in UAS7 at week 12
  - REMIX 1: -20.0+/-0.7 vs -13.8+/-1.0, p<0.001
  - REMIX 2: -19.4+/-0.7 vs -11.7+/-0.9, p<0.001

Metz M, et al. ***N Engl J Med 2025; 392: 984-994.***

Remibrutinib – Phase 3 Trial

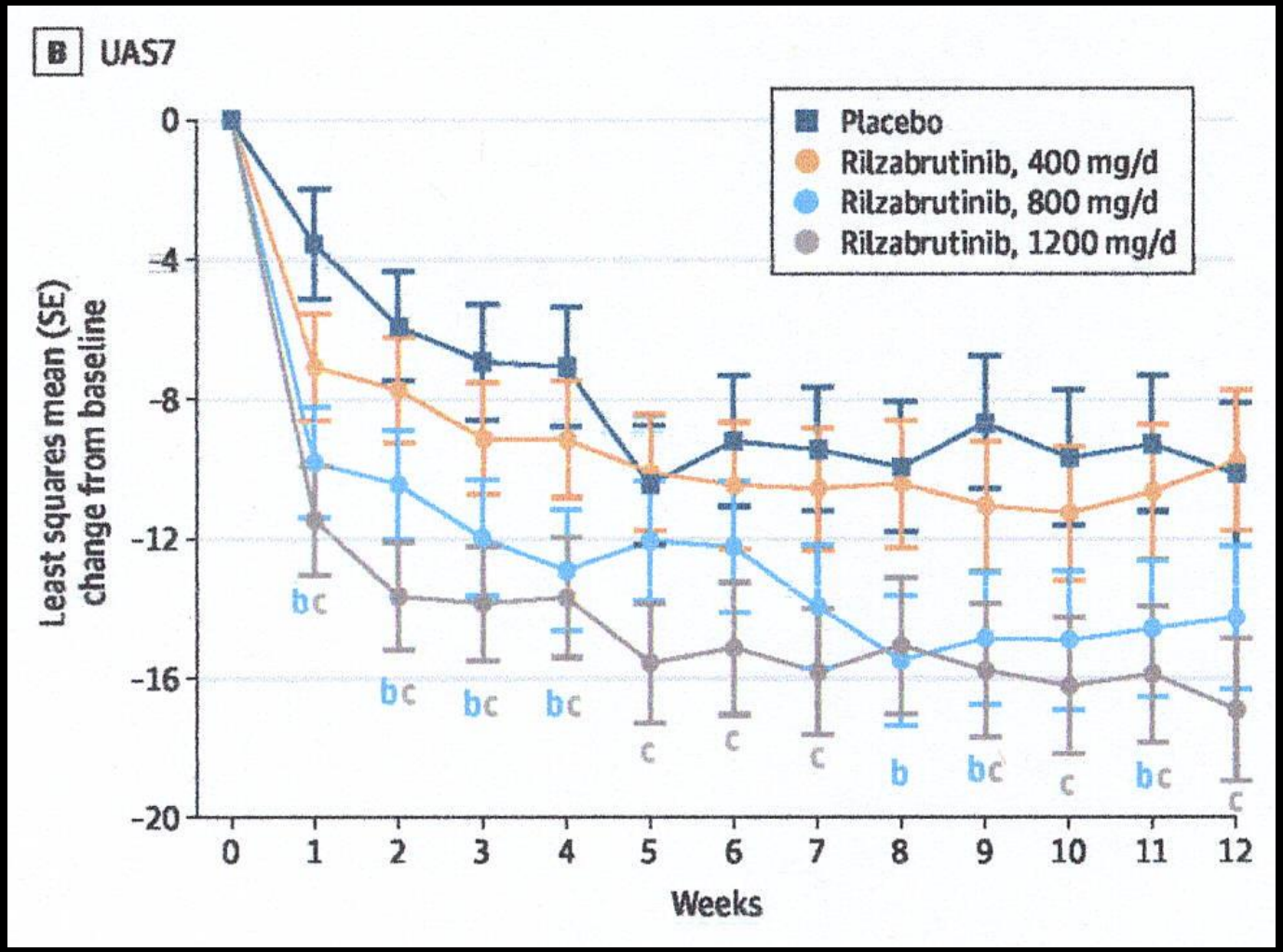




Metz M, et al. ***N Engl J Med 2025; 392: 984-994.***

Therapeutic Role for BTK Inhibition

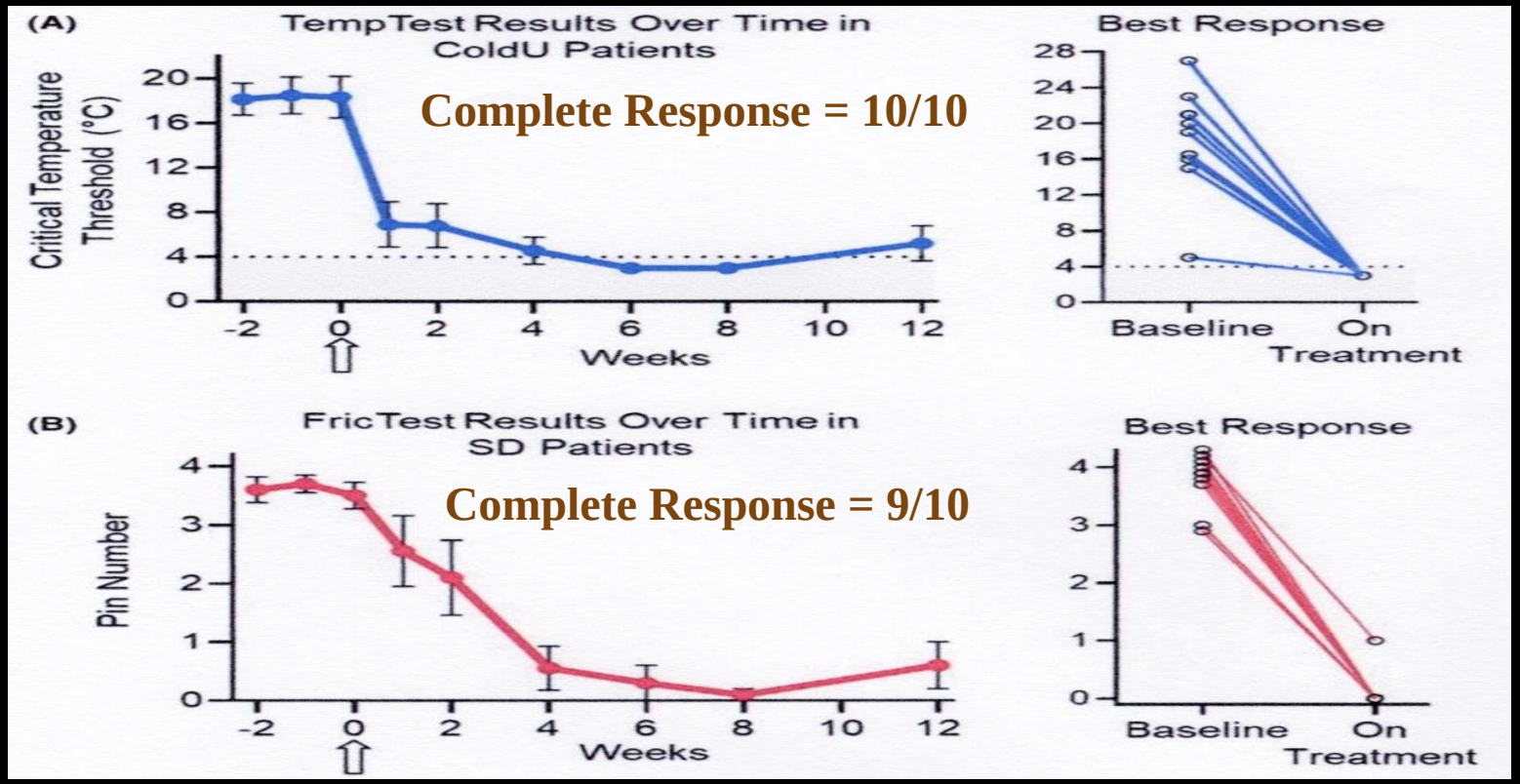
Rilzabrutinib – Phase 2



Gimenez-Arnau, et al. JAMA Dermatol. Published online April 23, 2025. doi:10.1001/

Therapeutic Role for c-KIT Inhibition

- Barzolvolimab (CDX-0159) is IgG1κ mAb binding the extracellular domain of KIT with high specificity and sub-nanomolar affinity.
- Open-label Phase 1b study evaluating safety/tolerability and clinical efficacy of a single dose of barzolvolimab in patients with antihistamine refractory CIndU.



Terhorst-Molawi et al. Allergy. 2023;78:1269-1279

Barzolvolimab – Adverse Reactions

Adverse Event (AE)	Cold Urticaria	Dermatographism	Total (N = 21)
Any AE (%)	11 (100)	10 (100)	21 (100)
Hair Color Changes	8 (73)	8 (80)	16 (76)
Taste Change	3 (27)	5 (50)	8 (38)
Nasopharyngitis	2 (18)	3 (30)	5 (24)
Malaise	4 (36)	1 (10)	5 (24)
Headache	3 (27)	1 (10)	4 (19)

Terhorst-Molawi et al. Allergy. 2023;78:1269-1279

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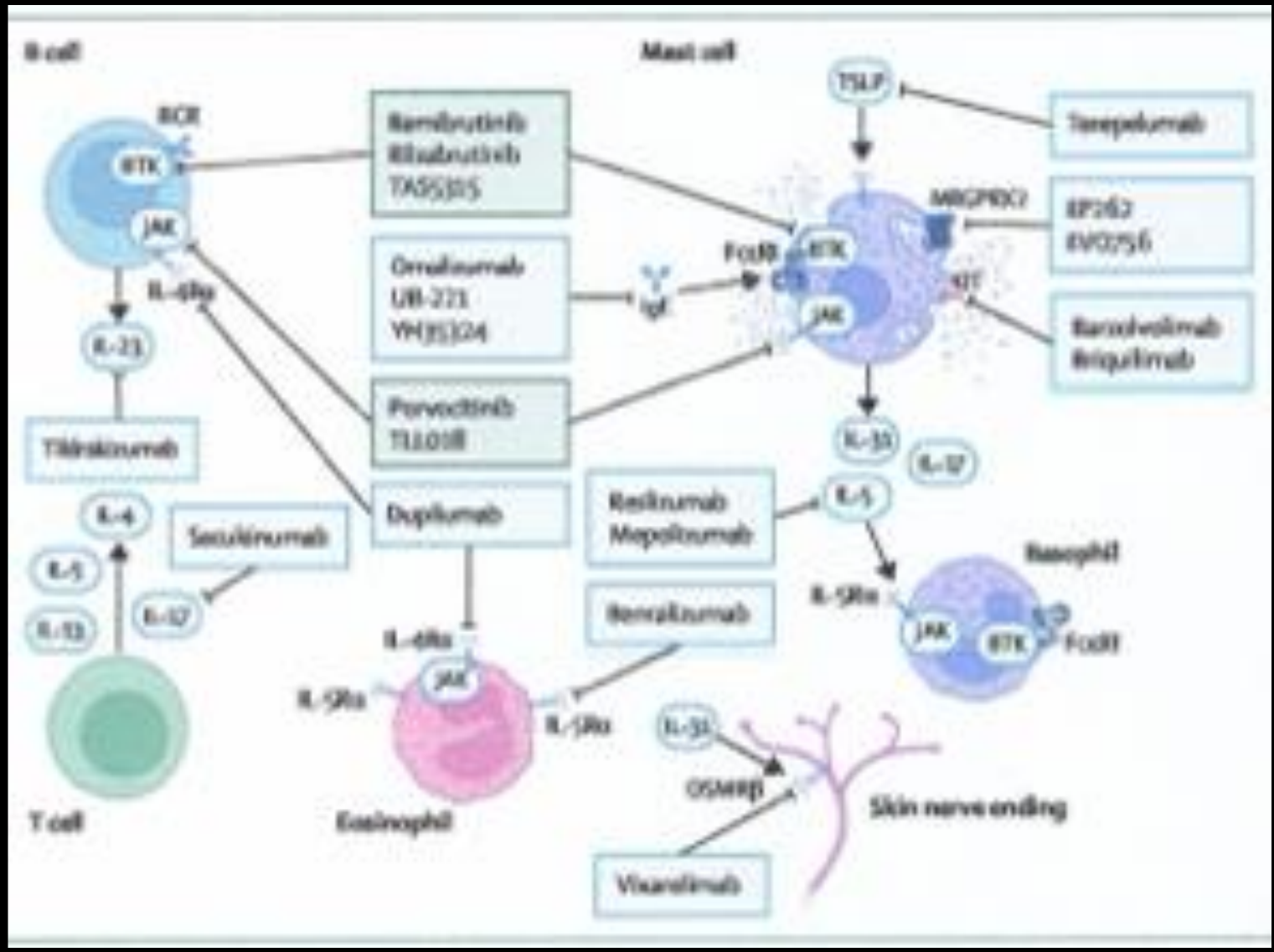
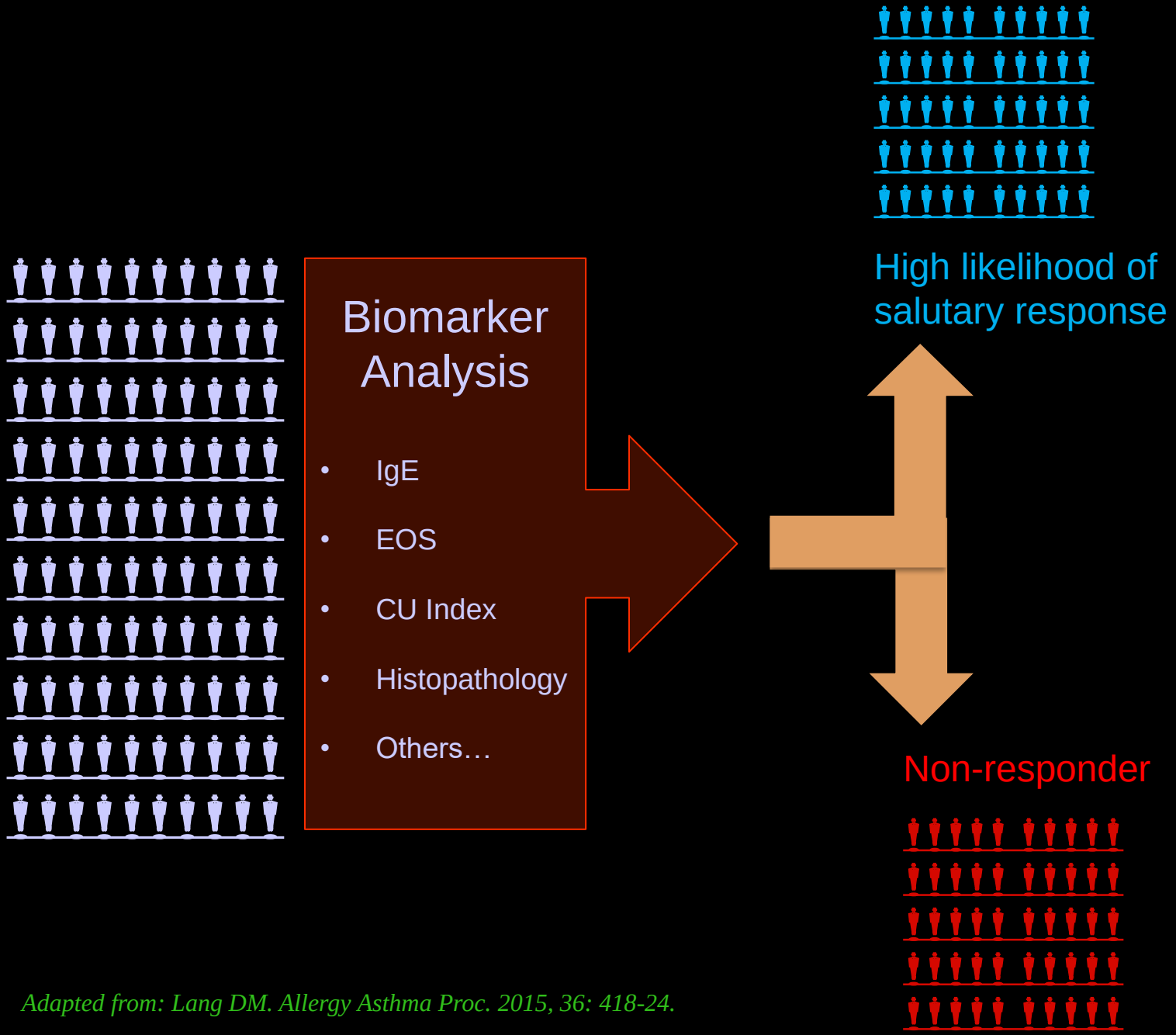
Lang DM. N Engl J Med 2022; 387: 824-31

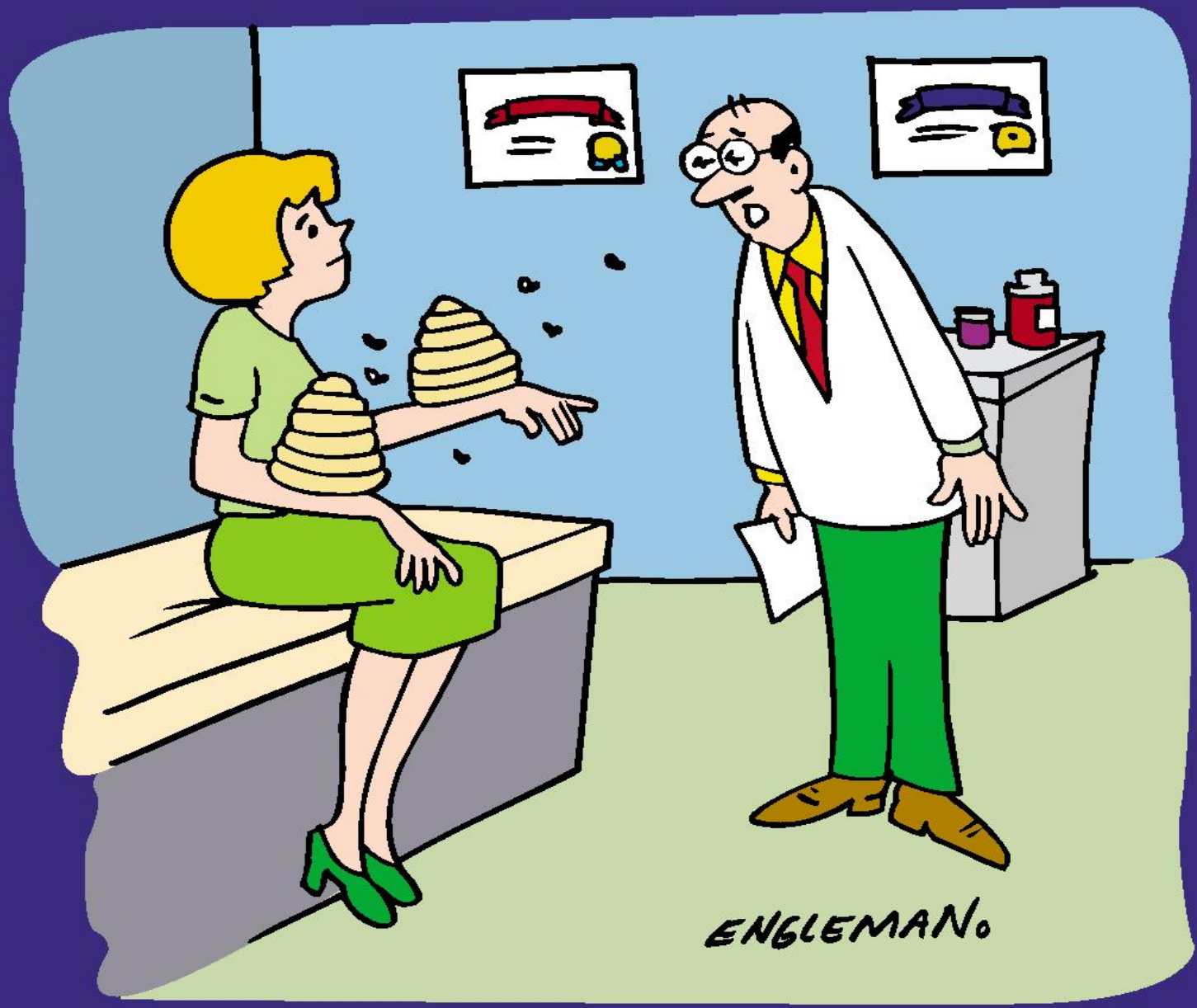
Step 3 – The Future



Zuberbier T, et al. Lancet 2024; 404: 393–404



Adapted from: Lang DM. Allergy Asthma Proc. 2015, 36: 418-24.



"Nothing serious . . .just a case of hives."