Chronic Spontaneous Urticaria

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Disclosures

Investigator: GSK, Genentech

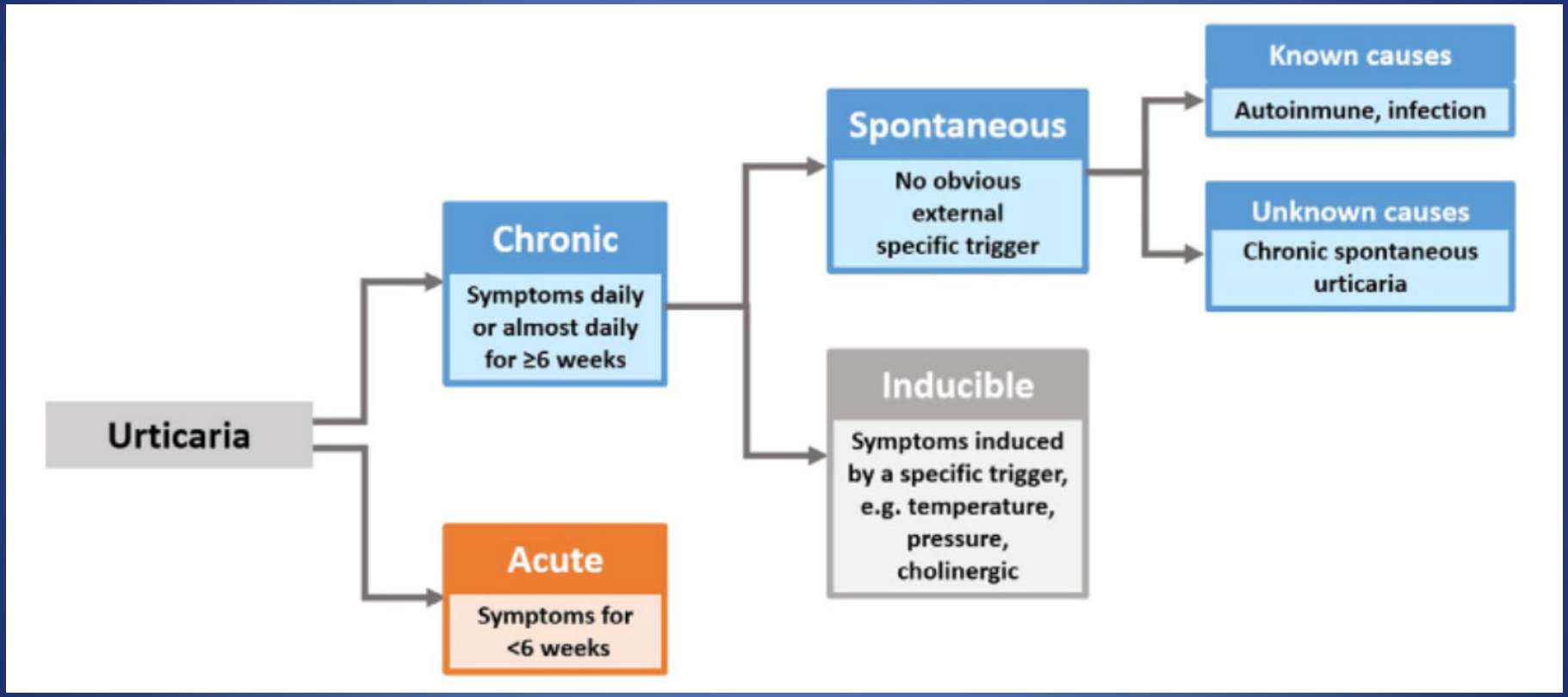
Advisory Board: Astra-Zeneca, GSK, Genentech, Sanofi

Speaker: Astra-Zeneca, Genentech

Learning objectives

- Apply best practices for the evaluation and differential diagnosis of chronic urticaria
- Describe the pathophysiology and inflammatory pathways of chronic urticaria
- Compare different guidelines for management and stepwise treatment of chronic spontaneous urticaria (CSU)
- Review current and emerging biologic therapies for the treatment of chronic urticaria

Classifying urticaria



Sánchez-Borges et al. World Allergy Organization Journal (2021) 14:100533
http://doi.org/10.1016/j.waojou.2021.100533

Subtypes of Inducible Urticaria

	Type of Inducible urticaria	Frequency (Percent of total CIU)
Physical	Dermographism	2-28.5%
	Cold Urticaria	2-13.4%
	Heat Urticaria	Unknown
	Solar Urticaria	<0.4%
	Vibratory Urticaria	Unknown
	Delayed Pressure Urticaria	7.3-37%
Non Physical	Cholinergic Urticaria	5-11%
	Aquagenic Urticaria	0,4%
	Contact Urticaria	Unknown

Table 1. Prevalence of inducible urticarias

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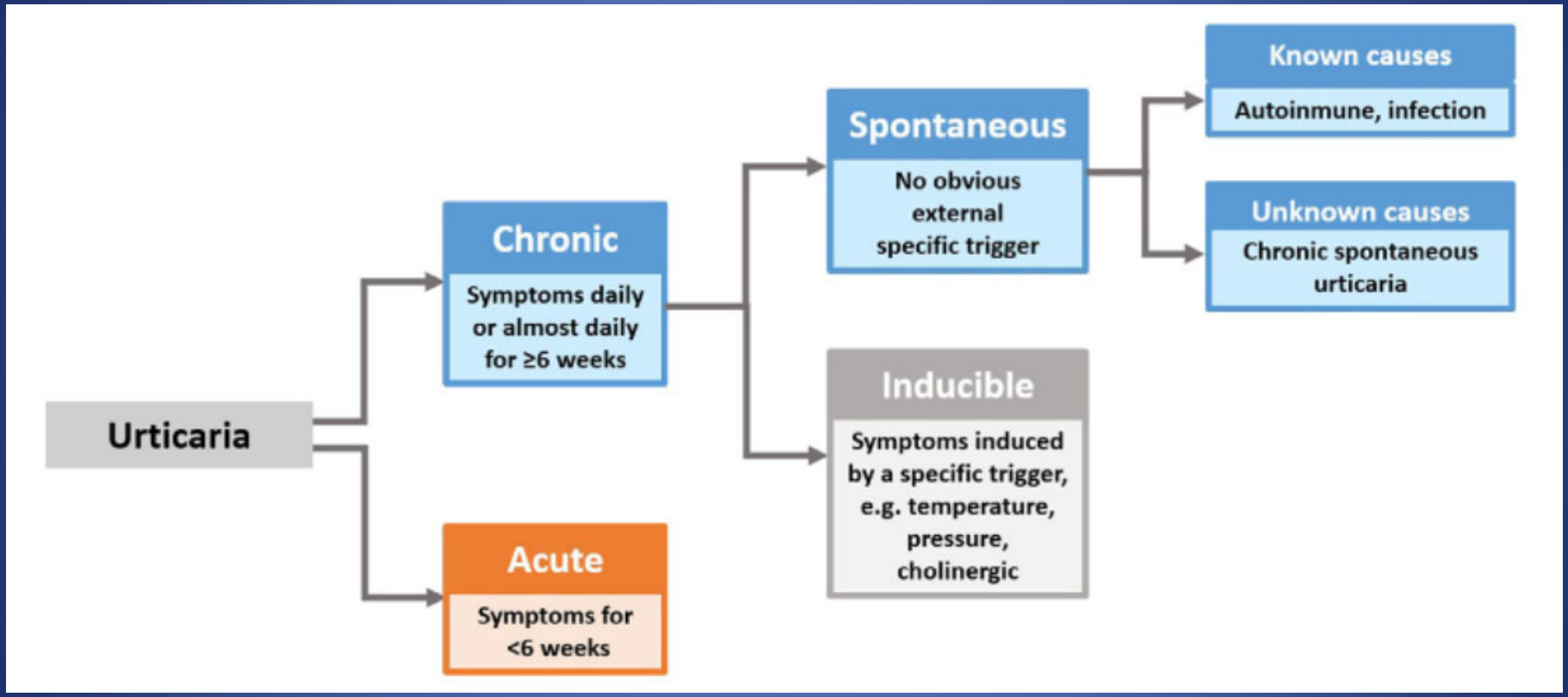

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Urticaria and angioedema often, but not always, co-exist

For patients with CSU:

- 40% of patients have both urticaria and angioedema
- 50% have urticaria alone
- 10% have angioedema alone

Differential diagnosis of chronic urticaria with or without angioedema

Urticaria alone:

- Urticarial vasculitis
- Cryopyrin-associated Periodic Syndrome
  - Muckle-Wells Syndrome
  - Familial Cold Auto-inflammatory Syndrome (FCAS)
  - Neonatal-Onset Multisystem Inflammatory Disease (NOMID)
- Schnitzler syndrome
- Urticaria pigmentosa

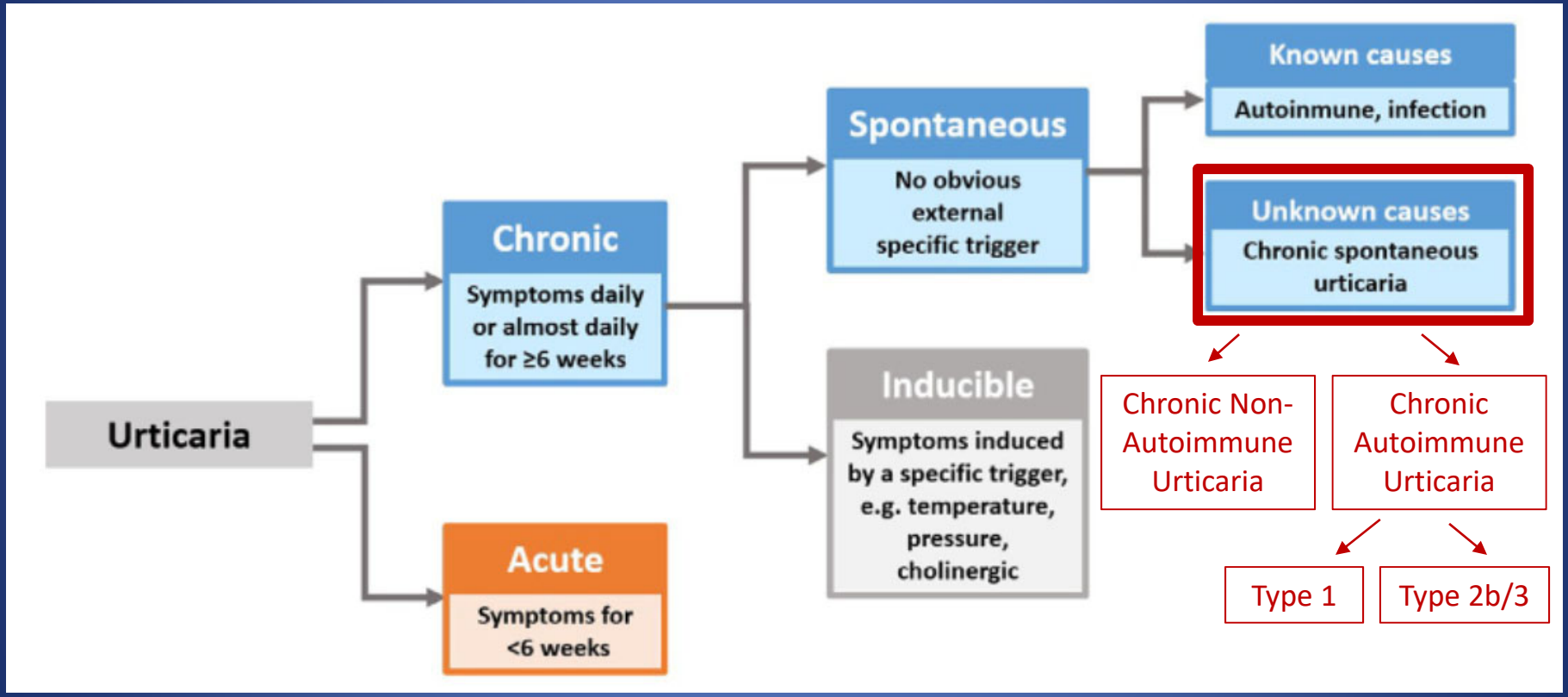
Angioedema alone:

- ACE-inhibitor-induced angioedema
- Bradykinin-mediated hereditary or acquired angioedema (HAE/AAE)

Both urticaria and angioedema:

- Gleich Syndrome
- Lymphocytic variant of HES

Classifying urticaria



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Epidemiology & natural history of CSU

- Prevalence: affects 1% of the population at any given time
- Typically begins in 3rd-5th decades
- Women 2x as often as men
- Average duration of disease: 2-5 yrs
  - 30-50% have spontaneous remission by 1 year
  - Approximately 20% of cases last longer than 5 yrs
- Dramatic impact on QOL – similar to CHF
- Mean yearly direct and indirect costs of CSU in the US estimated to be $244 million
  - 62.5% medication costs
  - 15.7% work absenteeism

Diagnostic approach

- 80-90% of cases have no identifiable cause
- A good history and physical exam is most important!
- Laboratory testing, if any, should be guided by history & physical

What to do in every CSU patient			
Questions	Physical examination*	Basic tests**	UCT

* Including review of patient photo documentation
** Differential blood count, CRP/Erythrocyte sedimentation rate, IgG-anti-TPO, total IgE

Confirm	Rule out differential diagnoses
Cause	Look for indicators of CSU^{aiTI}, CSU^{aiTIIb}
Cofactors	Identify potential triggers, aggravators
Comorbidities	e.g. check for CIndU, autoimmunity, mental health
Consequences	e.g. identify problems with sleep, distress, sexual health, work and social performance
Components	Assess potential biomarkers or predictors of treatment response
Course	Monitor CSU activity, impact and control

Metz M et al. Journal of Allergy and Clinical Immunology: In Practice, 2021-06-01, Volume 9, Issue 6, Pages 2274-2283,

Diagnostic approach

- Testing to consider, when appropriate:
  - Labs:
    - Draw labs ONLY as indicated by history and physical
    - AAAAI “Choosing Wisely” initiative advises against performing routine diagnostic testing in CSU patients
    - “Autoimmune” testing: autologous serum skin testing (ASST), anti-IgE receptor antibody, histamine release assay (CU index), or basophil CD203c expression

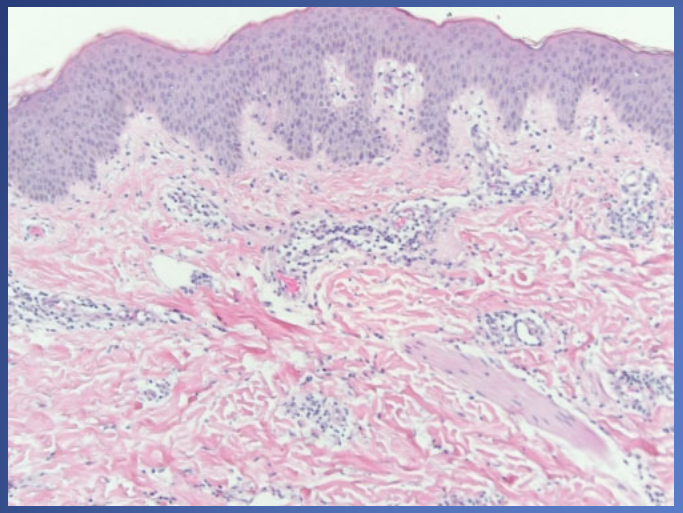
When to consider a skin biopsy: Features of atypical urticaria

- Individual lesions last longer than 24 hours
- Lesions are painful or burning
- Lesions leave residual bruising
- Urticarial vasculitis should be considered if these features are present

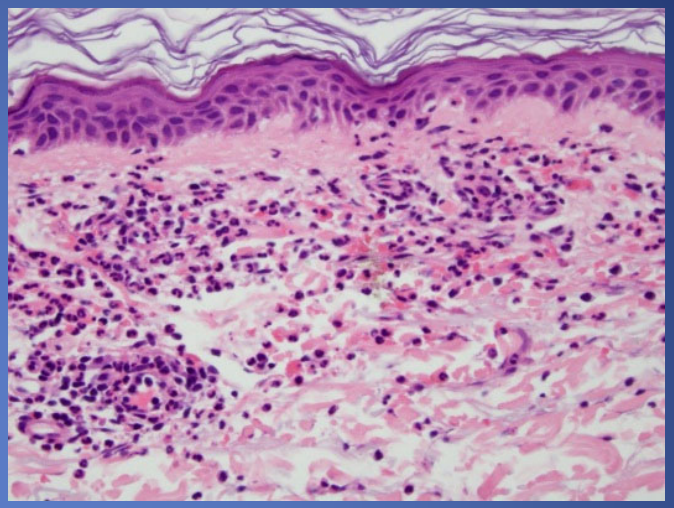
Skin biopsy in urticaria

- Biopsy often shows interstitial edema with perivascular mixed infiltrate (lymphs, eo and some PMNs or basophils)
- Other disorders in the differential will show PMN predominance, atypical mast cells, leukocytoclasis and/or vasculitis

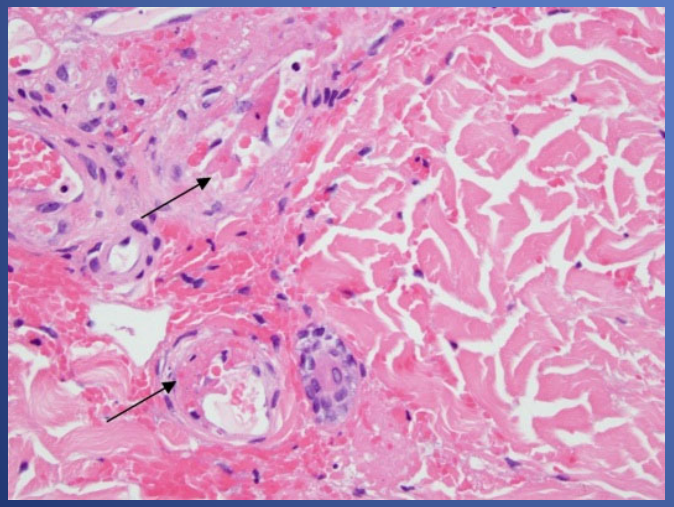
Skin Biopsy



Conventional urticaria

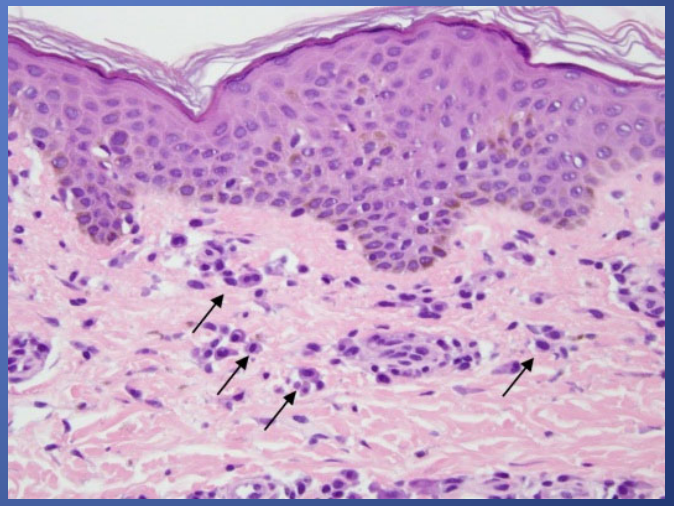


Leukocytoclastic vasculitis



Neutrophil-rich urticaria

http://www.skinpathology.org



Urticaria pigmentosa

http://www.actasdermo.org

TABLE IV. Laboratory tests and CSU features that are linked to long disease, high disease activity and/or response to treatment

Parameter	Measurement	References
Laboratory tests and CSU features linked to long disease duration		
	Elevated IgG anti-TPO	111,112
	High CSU severity/activity	111,113
Parameters or biomarkers linked to higher CSU activity		
	Elevated prothrombin fragment 1+2	114-117
	Elevated D-dimer	116,117
	Elevated CRP	11,22,118,119
	Elevated mean platelet volume	120-122
	Elevated IL-6	123-126
CSU parameters or biomarkers linked to poor response to treatment with sgAHs		
	Presence of concomitant CIndU	64,73
	ASST positivity	73
	High D-dimer	11,127,128
	High UAS	73,129-131
	High CRP	22,73
	Previous corticosteroid treatment	130,131
	Low blood basophil and eosinophil counts	21,73
CSU parameters or biomarkers linked to poor response to omalizumab treatment		
	Low total IgE	29,132-136
	Positive BHRA	137
	History of previous immunosuppressive treatment	134,138-140
	Low basophil FcεRI expression	132,141
CSU parameters or biomarkers linked to good response to cyclosporine treatment		
	Low total IgE	142,143
	Positive BHRA	144-146

Potential biomarkers of severity and/or treatment response

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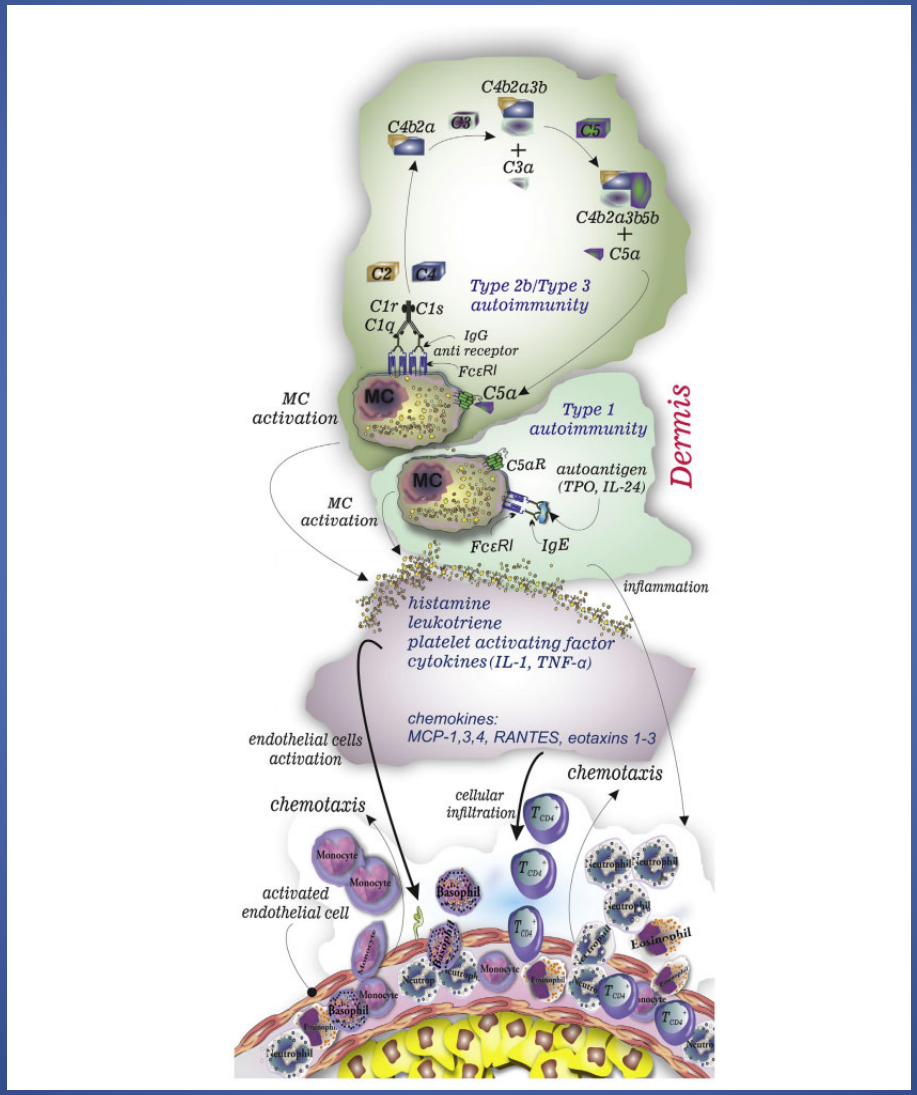
Pathophysiology of CSU



Maurer et al. J Allergy Clin Immunol Pract 2021;9:1067-78)

Inflammatory pathways in CSU: role of autoimmunity

- Mast cell activation is thought to initiate the process, most likely through autoimmune mechanisms (Type 1 or Type 2b/3)
  - Type 1 autoimmunity = IgE to autoallergens (IL-24 or TPO, for example, although not always clearly identified)
  - Type 2 autoimmunity = IgG autoantibodies to IgE (5-10%) or its receptor (30-45%)
- Once activated, mast cells release mediators

Gimenez-Arnau et al. J Allergy Clin Immunol Pract 2021;9:2195-208)

Inflammatory pathways in CSU: role of complement

- In type 3 autoimmunity, two IgG antibodies in close proximity fix complement via the classical pathway
- C5a is liberated, which binds to C5aR on mast cell surface
- This leads to further mast cell activation and mediator release

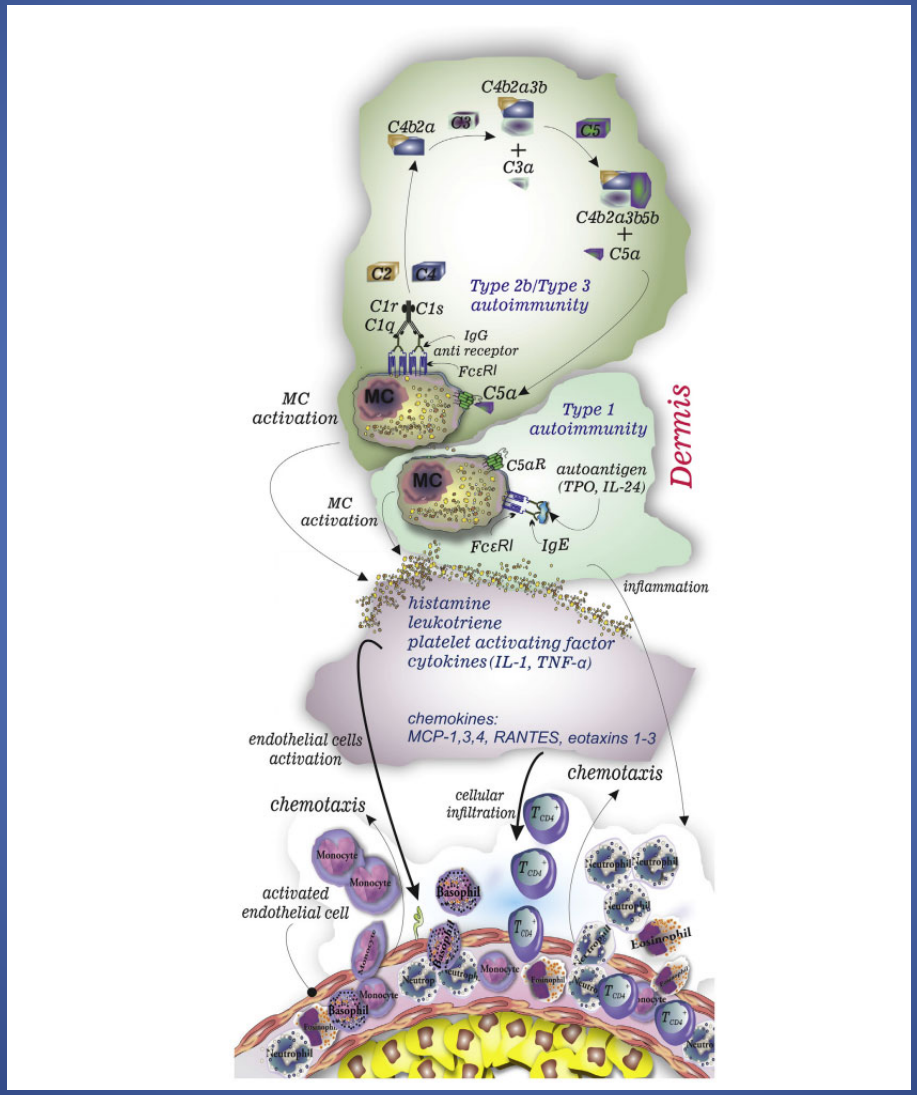
Gimenez-Arnau et al. J Allergy Clin Immunol Pract 2021;9:2195-208)

Inflammatory pathways in CSU: role of the cellular infiltrate

- Chemokines initially released by mast cells attract inflammatory cells to the tissue
- Cellular infiltrate contains:
  - T lymphocytes (Th2 > Th1)
  - Monocytes
  - Eosinophils
  - Basophils
  - Neutrophils (variable)
  - Other lymphoid subsets
- These cells interact with activated endothelial cells

Gimenez-Arnau et al. J Allergy Clin Immunol Pract 2021;9:2195-208)

Pathophysiology of CSU



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Before moving to pharmacotherapy: Educate the CSU patient

- Discuss epidemiology and natural history to set realistic expectations.
- Encourage avoidance of non-specific mast cell triggers:
  - Physical factors
  - NSAIDs/narcotics
  - Stress (physical or psychological)
  - Alcohol

AAAAI/ACAAI Urticaria Guidelines

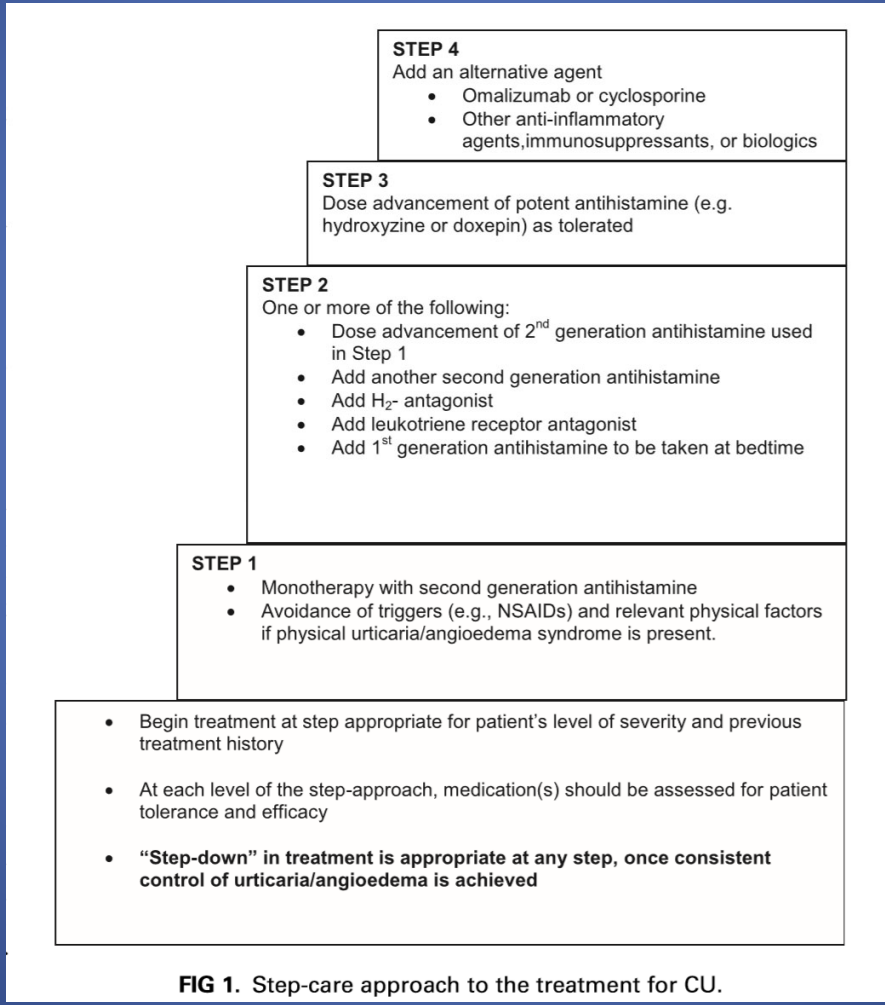
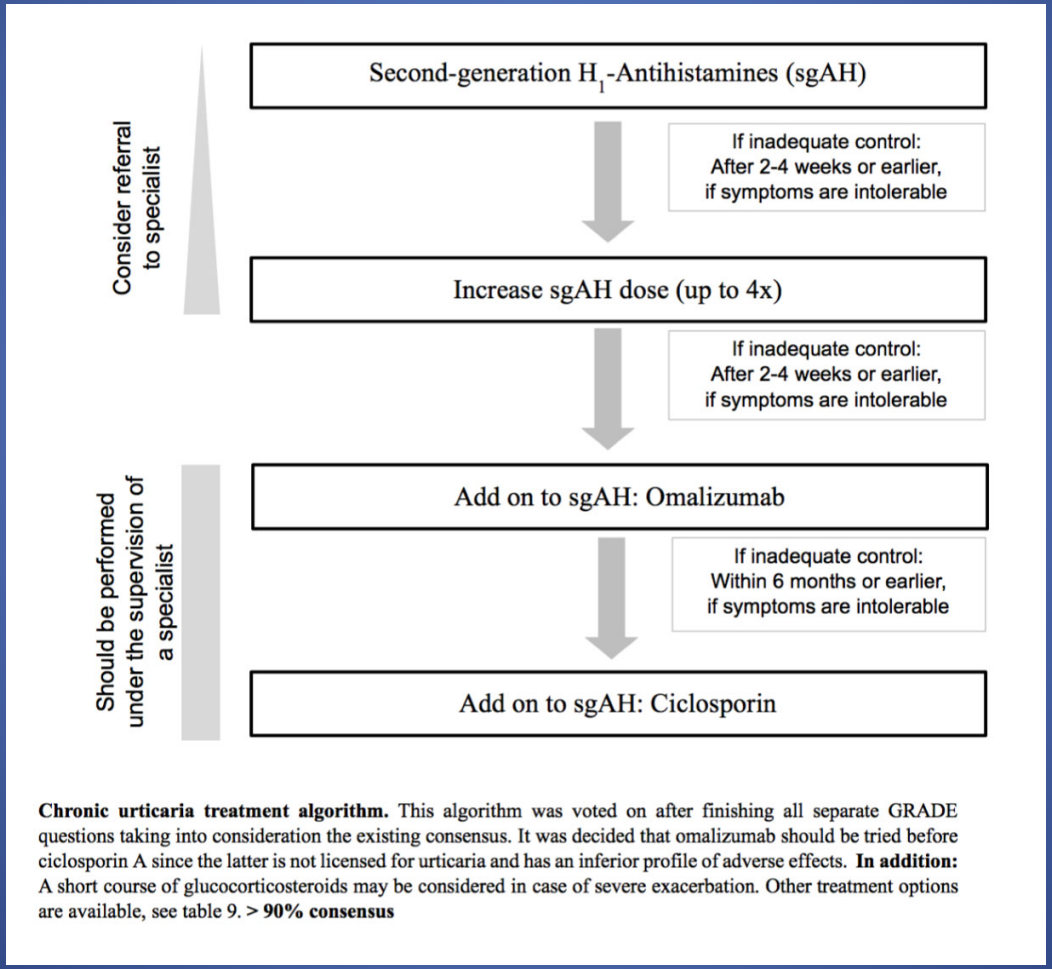


FIG 1. Step-care approach to the treatment for CU.

Bernstein et al. J Allergy Clin Immunol 2014;133:1270-7.

EAACI/GA(2)LEN/EDF/WAO International Urticaria Guidelines



Chronic urticaria treatment algorithm. This algorithm was voted on after finishing all separate GRADE questions taking into consideration the existing consensus. It was decided that omalizumab should be tried before ciclosporin A since the latter is not licensed for urticaria and has an inferior profile of adverse effects. **In addition:** A short course of glucocorticosteroids may be considered in case of severe exacerbation. Other treatment options are available, see table 9. **> 90% consensus**

Zuberbier et al. Allergy 2018; 73(7):1393-1414.

Comparing the International and US guidelines

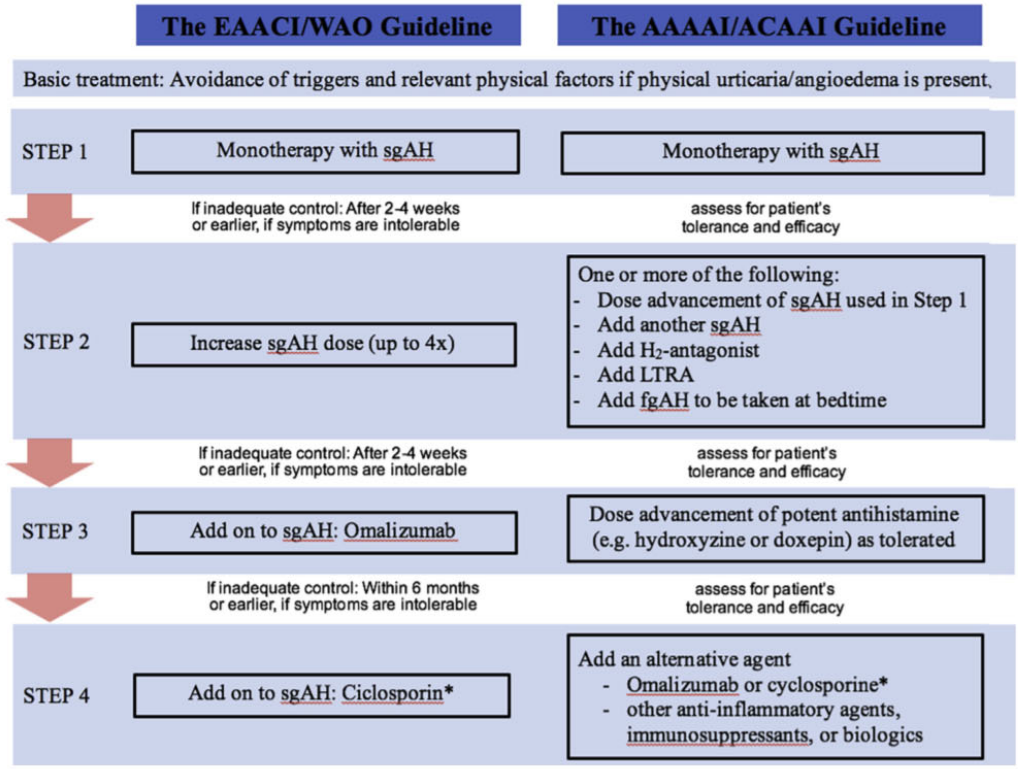


FIGURE 2. Comparison of treatment algorithms of the international and US guidelines. EAACI, European Academy of Allergology and Clinical Immunology; fgAH, first-generation antihistamine; LTRA, leukotriene receptor antagonist; sgAH, second-generation antihistamine; WAO, World Allergy Organization. *Different spellings as used in the respective guideline.Additional comments: EAACI/WAO: A short course of corticosteroids may be considered in case of severe exacerbation. AAAAI/ACAAI: Begin treatment at step appropriate for patient's level of severity and treatment history; "step-down" treatment is appropriate at any step, once consistent control of urticaria/angioedema is achieved.

Zuberbier and Bernstein. JACI Pract 2018; 6(4): 1144-51.

Antihistamines in CSU

- STEP 1 (US) – Use a second generation antihistamine (sgAH) daily
  - loratadine, desloratadine, fexofenadine, cetirizine, levocetirizine (available OTC)
- STEP 2 (US) - Increase the amount of sgAH or add another form of AH (or LTRA)
  - Increase sgAH up to four-fold (either using a single sgAH or several sgAHs)
  - Add a first generation antihistamine (fgAH) at bedtime -- diphenhydramine, hydroxyzine, chlorphenhiramine
  - Add an H2 blocker or LTRA
- STEP 3 (US) - Increase the amount of "potent" AH (hydroxyzine or doxepin)

Antihistamines in CSU

- STEP 1 (international) – Use a second generation antihistamine (sgAH) daily
  - loratadine, desloratadine, fexofenadine, cetirizine, levocetirizine (available OTC)
- STEP 2 (international) - Increase the amount of sgAH
  - Increase sgAH up to four-fold (either using a single sgAH or several sgAHs)

No mention of H2 blocker, LTRA, or “potent” AH

When antihistamines are insufficient

- STEP 4 (US):

Omalizumab

Cyclosporine A

Other immunomodulators

- STEP 3 (International):

Omalizumab

- STEP 4 (International):

Cyclosporine A

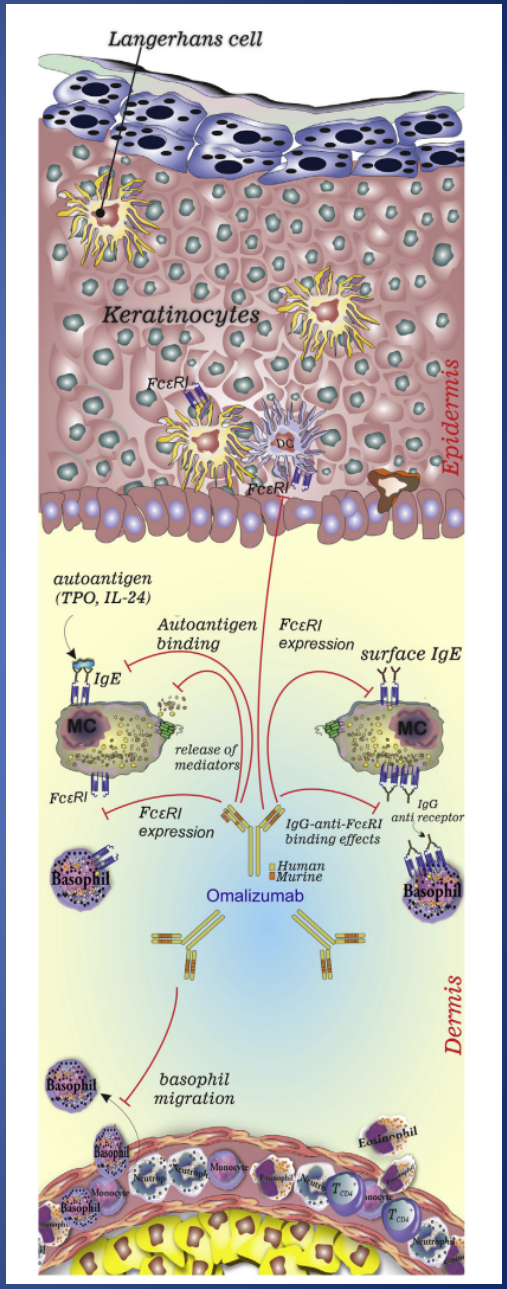
No mention of other immunomodulators

When antihistamines are insufficient: omalizumab

- Two doses approved for CSU in 2014: 150mg and 300mg every 4 weeks
- Available for both office and home administration
- Dosing does NOT depend on IgE level/weight
- No lab monitoring needed
- Generally very well-tolerated (anaphylaxis 0.2%, local rxns 40%)
- Optimal duration of therapy unknown

Omalizumab mechanism of action

- Humanized recombinant monoclonal anti-IgE antibody
- Binds to circulating IgE, thereby decreasing cell-bound IgE
  - Decreases autoantigen binding (impacts type 1 autoimmunity)
- Decreases expression of FcεR1 (high-affinity IgE receptor)
  - Decreases effect of IgG-anti-FcER1 binding effect (impacts type 2b/3 autoimmunity)
- Decreased mediator release
- Decreased cellular infiltration



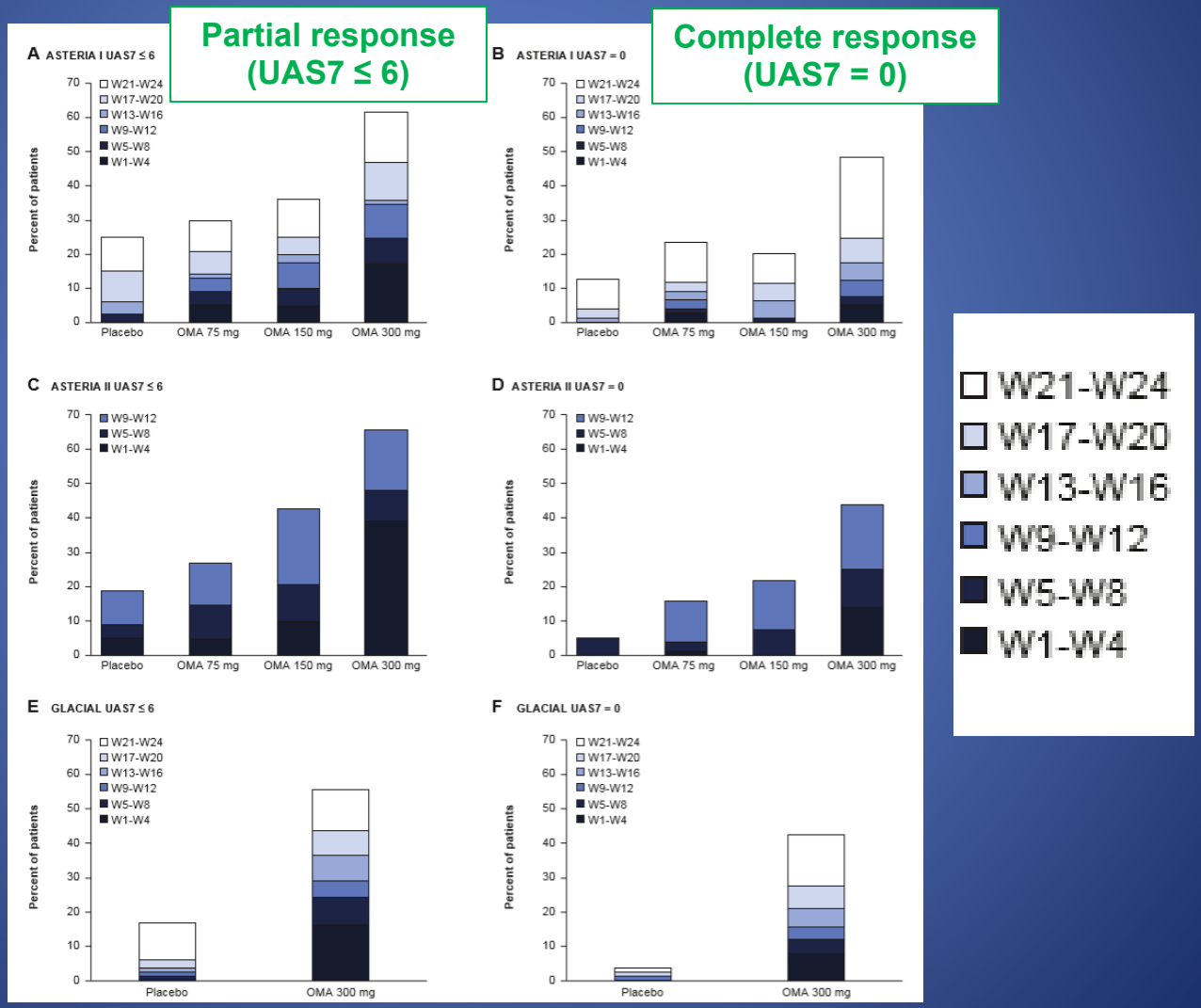
Maurer et al. J Allergy Clin Immunol Pract 2021;9:1067-78)

Omalizumab in practice: key points

- Omalizumab shows dose-dependent effectiveness in CSU with an excellent safety profile.
- Omalizumab works fast in many patients, although some patients do take more time to start responding.
- Omalizumab up-dosing can lead to response in initial non-responders.
- Omalizumab is not thought to be disease modifying.
- Re-treatment with omalizumab following discontinuation and relapse is effective.

1. Zhao et al. JACI 2016; 137: 1742-50.
2. Kaplan et al. JACI 2016; 137:474-81.
3. Metz et al. Clinical Reviews in Allergy & Immunology (2020) 59:38–45
4. Maurer et al. JACI 2018; 141(3): 1138–1139.e7

Omalizumab responders by week and by dose in the pivotal phase 3 studies



Kaplan et al. JACI 2016; 137:474-81.

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Omalizumab updosing can lead to response in non-responders

Table 2 Proportion of patients with chronic spontaneous urticaria achieving complete or partial response on updosing omalizumab from 300 to 450 or 600 mg every 4 weeks

Study	Updosed to 450 mg	Updosed to 600 mg	Efficacy parameter (UAS7/UCT)	Complete/partial response, %
Asher et al.	9		UAS7 ≤ 6	66.7 ($n = 6$)/22.2 ($n = 2$)
Kocatürk et al.	17	11	UCT ≥ 12 and UAS7 ≤ 6	64.3 ($n = 18$)
Barcelona Istanbul		11	UCT ≥ 12	72.7 ($n = 8$)
Vadasz et al.	78			64.1 ($n = 50$)
Curto-Barredo et al.	79		UAS7 ≤ 6	75.0 ($n = 59$)/25.0 ($n = 20$)
Salman et al.	13		UCT ≥ 12 and UAS7 ≤ 6	46.2 ($n = 6$)/23.1 ($n = 3$)
Aghdam et al.	11	33	UCT ≥ 12 and UAS7 ≤ 6	32.0 ($n = 14$)/30.0 ($n = 13$)

UAS7 Urticaria Activity Score over 7 days; UCT, Urticaria Control Test

Metz et al. Clinical Reviews in Allergy & Immunology (2020) 59:38–45

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XTEND-CIU study: study design

- Xolair Treatment Efficacy of loNger Duration in CIU
- Age 12-75; UAS7 ≥ 16 for 7 consecutive days
- Randomized controlled trial with 3 phases:
  - Phase 1: N = 205; 24 wk open-label, omalizumab 300mg Q4wks
  - Phase 2: N = 134 pts (those with UAS7 ≤ 6 for last 2 wks of phase 1); randomized to omalizumab or placebo for 24 wks
  - Investigator assessed clinical worsening during phase 2 → transition to open-label omalizumab
  - Phase 3: d/c omalizumab and observe x 12 weeks

Maurer et al. JACI 2018; 141(3): 1138–1139.e7

XTEND-CIU study: CSU often flares after omalizumab discontinuation

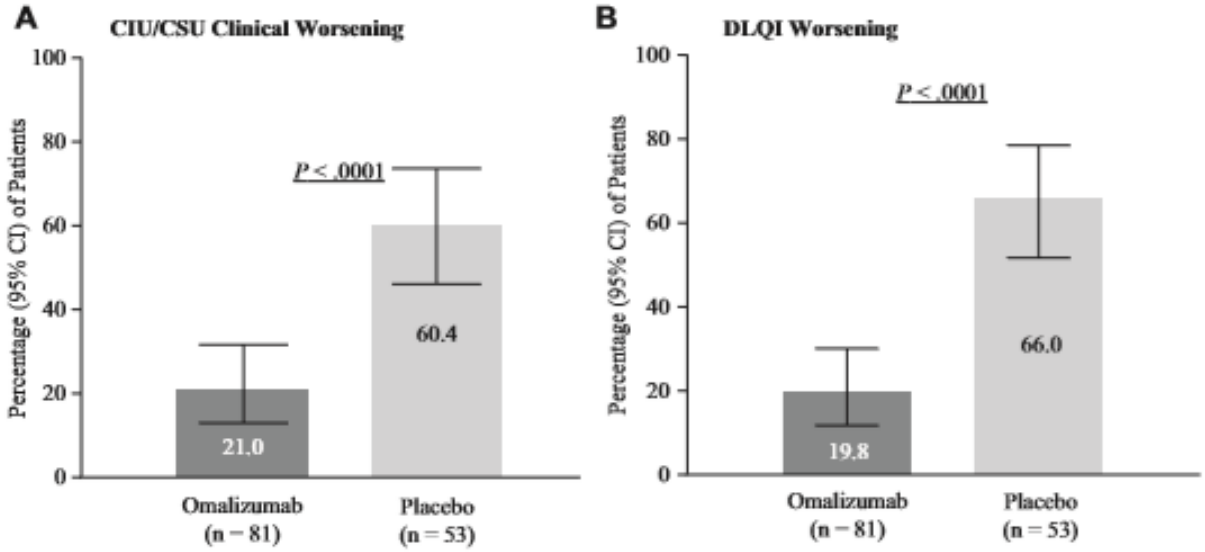


FIG 1. Percentages of patients experiencing **(A)** CIU/CSU clinical worsening defined by UAS7,* and **(B)** Dermatology Life Quality Index (DLQI) worsening† were significantly lower in omalizumab- vs placebo-treated patients. *UAS7 of at least 12 for 2 consecutive weeks. †At least 3-point increase in the DLQI score.

Maurer et al. JACI 2018; 141(3): 1138–1139.e7

XTEND-CIU study: Omalizumab is effective for re-treatment

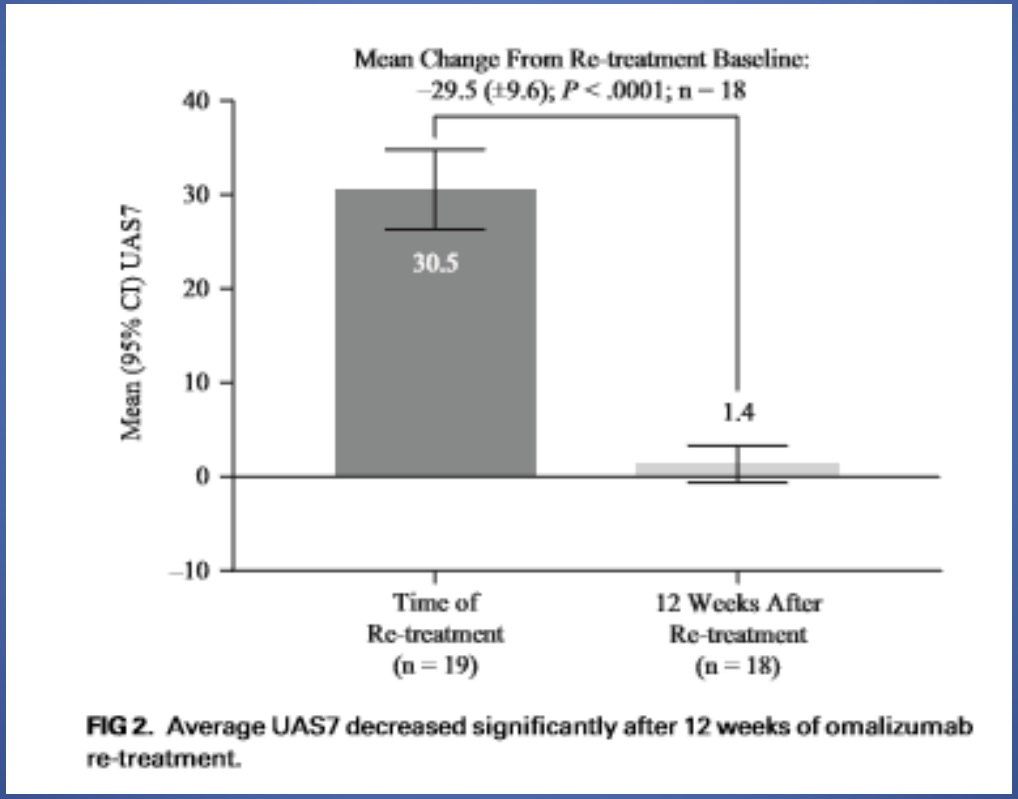


FIG 2. Average UAS7 decreased significantly after 12 weeks of omalizumab re-treatment.

Maurer et al. JACI 2018; 141(3): 1138–1139.e7

When antihistamines are insufficient: Cyclosporine A and other immunomodulators

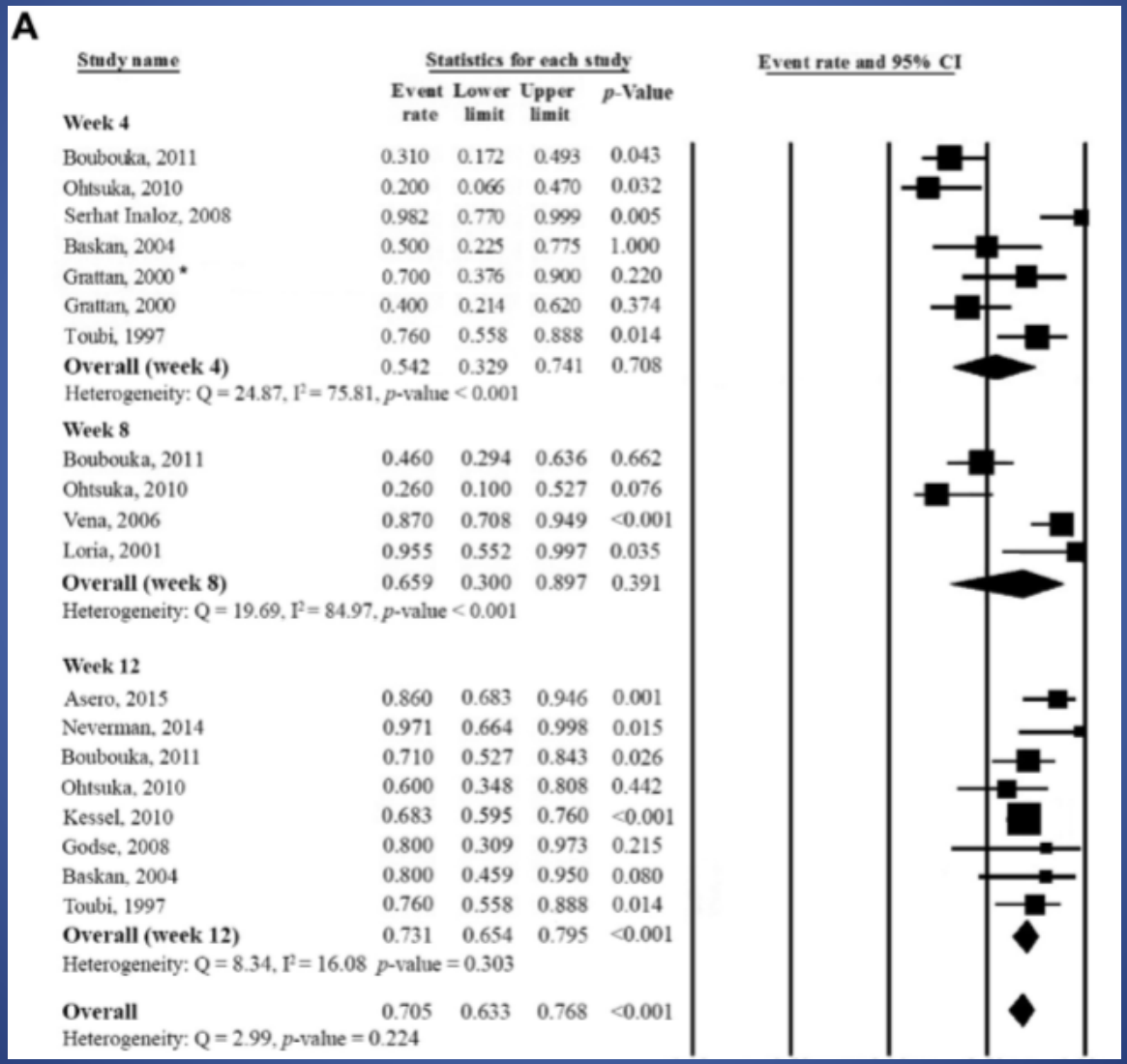
- Cyclosporine A
- Mycofenolate mofetil
- Sulfasalazine
- Dapsone
- Hydroxychloroquine
- Prednisone

Cyclosporine A (CSA)

- Mechanism: suppresses T cell activation, causes cytokine release, inhibits IgE receptor-mediated release of histamine, lipid mediators and cytokines by basophils and MCs
- Several case reports, retrospective studies, and open-label prospective studies have shown efficacy of cyclosporine in CSU
- Side effects include: GI sxs, headache, parasthesias (>10%), infections, ??malignancy
- Monitor: BP and renal function regularly, plasma levels

1. Grattan et al. Br J Derm 2000; 143(2):365-72.
2. Vena et al. . J of Am Acad Derm 2006; 55(4):705-9.
3. Kessel and Toubi. Allergy 2010; 65(11):1478-82.

A 2017 meta-analysis suggests that cyclosporine is effective at low-moderate doses



A

Study name	Event rate	Lower limit	Upper limit	p-Value
Week 4				
Boubouka, 2011	0.310	0.172	0.493	0.043
Ohtsuka, 2010	0.200	0.066	0.470	0.032
Serhat Inaloz, 2008	0.982	0.770	0.999	0.005
Baskan, 2004	0.500	0.225	0.775	1.000
Grattan, 2000 *	0.700	0.376	0.900	0.220
Grattan, 2000	0.400	0.214	0.620	0.374
Toubi, 1997	0.760	0.558	0.888	0.014
Overall (week 4)	0.542	0.329	0.741	0.708
Heterogeneity: Q = 24.87, I^2 = 75.81, *p*-value < 0.001				
Week 8				
Boubouka, 2011	0.460	0.294	0.636	0.662
Ohtsuka, 2010	0.260	0.100	0.527	0.076
Vena, 2006	0.870	0.708	0.949	<0.001
Loria, 2001	0.955	0.552	0.997	0.035
Overall (week 8)	0.659	0.300	0.897	0.391
Heterogeneity: Q = 19.69, I^2 = 84.97, *p*-value < 0.001				
Week 12				
Asero, 2015	0.860	0.683	0.946	0.001
Neverman, 2014	0.971	0.664	0.998	0.015
Boubouka, 2011	0.710	0.527	0.843	0.026
Ohtsuka, 2010	0.600	0.348	0.808	0.442
Kessel, 2010	0.683	0.595	0.760	<0.001
Godse, 2008	0.800	0.309	0.973	0.215
Baskan, 2004	0.800	0.459	0.950	0.080
Toubi, 1997	0.760	0.558	0.888	0.014
Overall (week 12)	0.731	0.654	0.795	<0.001
Heterogeneity: Q = 8.34, I^2 = 16.08 *p*-value = 0.303				
Overall	0.705	0.633	0.768	<0.001
Heterogeneity: Q = 2.99, *p*-value = 0.224				

Statistics for each study

Event rate and 95% CI

Kulthanan G et al. JACI Pract 2017

Alternative agents can be effective for CIU

TABLE V. Efficacy of alternative agents

Alternative agent	Insufficient duration	Failed	Partial	Partial control	Complete control	Remission
Dapsone	2	11	7	3	13	8
Sulfasalazine	10	19	14	2	3	2
Hydroxychloroquine	7	21	9	2	6	6
Tacrolimus	2	11	7	3	13	8
Mycophenolate	4	9	5	1	6	4
Omalizumab	0	6	5	2	13	0
Cyclosporine	0	1	3	1	1	5

Seth et al. JACI Pract 2017; 5: 165-70.

Alternative agents for CIU are relatively well tolerated

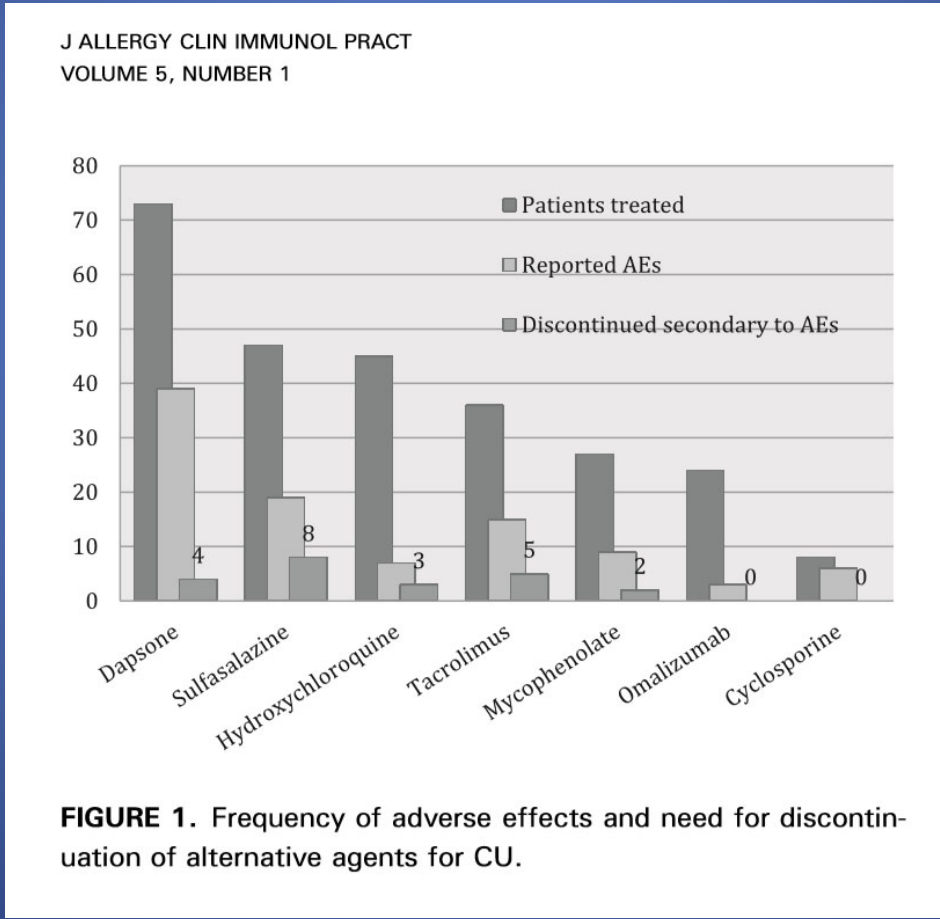


FIGURE 1. Frequency of adverse effects and need for discontinuation of alternative agents for CU.

Seth et al. JACI Pract 2017; 5: 165-70.

Other options are mostly based on case reports and case series

- Methotrexate
- Tacrolimus
- Sirolimus
- IVIG
- Rituximab

Learning objectives

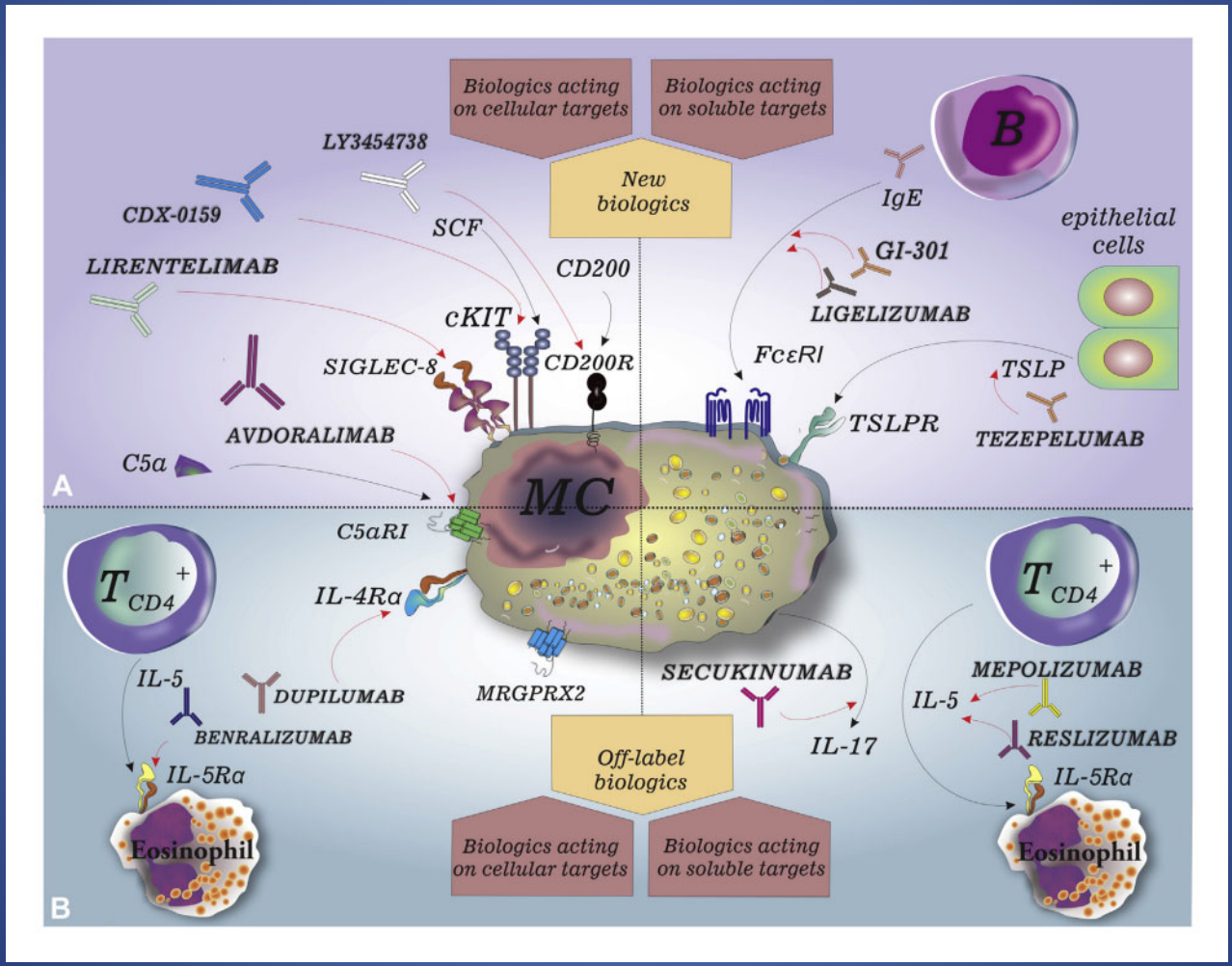
- Apply best practices for the evaluation and differential diagnosis of chronic urticaria
- Describe the pathophysiology and inflammatory pathways of chronic urticaria
- Compare different guidelines for management and stepwise treatment of chronic spontaneous urticaria (CSU)
- Review current and emerging biologic therapies for the treatment of chronic urticaria

Emerging Biologic Therapies for CSU

- Phase 3 trials:
  - Dupilumab, remibrutinib
- Phase 2 trials:
  - Avdoralimab (targets C5aR1), CDX-0159 (c-kit inhibitor), lirentelimab (binds to siglec-8, an inhibitory receptor), LY345473 (binds to C200R, another inhibitory receptor)
- Phase 1 trials:
  - GI-301 (reduces free IgE), Tezepelumab (targets TSLP)
- Proof of concept completed:
  - Benralizumab (targets IL-5Rα), secukinumab (targets IL-17)

Maurer et al. J Allergy Clin Immunol Pract 2021;9:1067-78)

Emerging Biologic Therapies for CSU



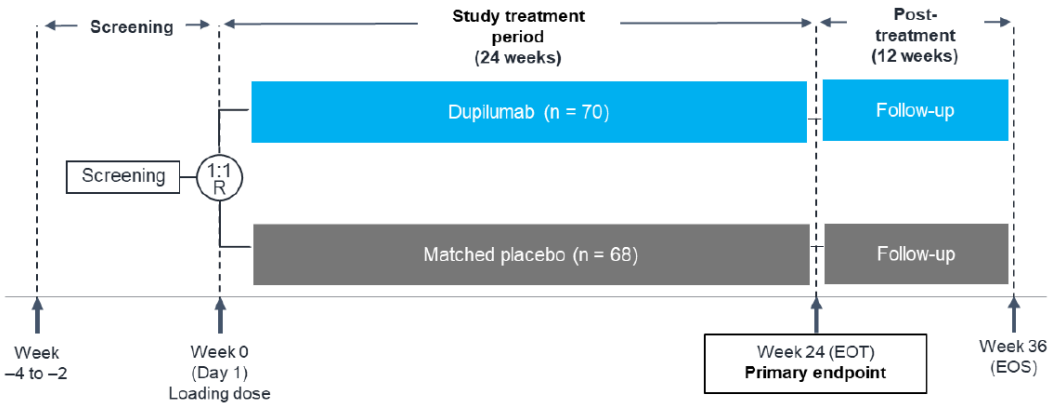
Maurer et al. J Allergy Clin Immunol Pract 2021;9:1067-78)

Dupilumab in CIU

- CUPID A – oma naïve, non-EU; data currently being presented to FDA
- CUPID B – oma failures; prematurely stopped due to futility
- CUPID C – oma naïve, EU, ongoing

Methods

Study design



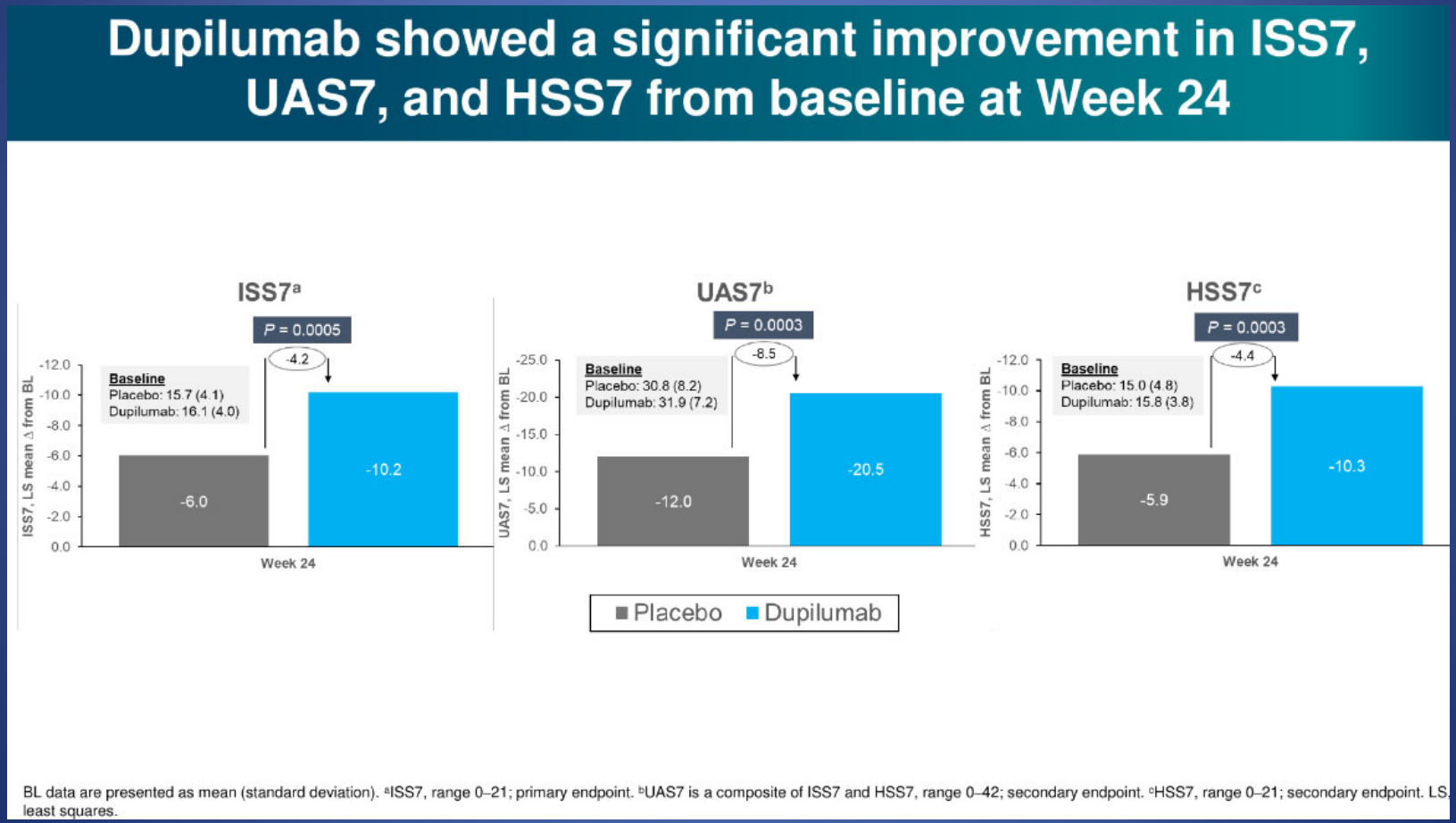
- **Patient population:** Aged ≥ 6 years; diagnosis of CSU > 6 months prior to screening visit; presence of itch and hives for > 6 consecutive weeks despite H1-AH use; UAS7 ≥ 16 and ISS7 ≥ 8; and omalizumab-naive
- **Background therapy:** Study-defined H1-AH (up to 4-fold recommended dose)
- **Efficacy endpoints**
  - Primary endpoint: change in ISS7 from baseline (BL) at Week 24
  - Secondary endpoints: change in UAS7 from BL at Week 24; change in HSS7 from BL at Week 24
- **Safety endpoints:** TEAEs, serious adverse events

- **Study assessment instruments**
  - Itch Severity Score over 7 days (**ISS7**, range 0–21): sum of daily ISS (ranging from 0 = none to 3 = intense) over 7 days
  - Hive Severity Score over 7 days (**HSS7**, range 0–21): sum of daily HSS (ranging from 0 = 0 hives to 3 = > 50 hives) over 7 days
  - Urticaria Activity Score over 7 days (**UAS7**, range 0–42): sum of the daily HSS7 and ISS7 scores over 7 days

Maurer et al. *Presented at the 2022 Annual Meeting of the American Academy of Dermatology (AAD 2022); Boston, MA, USA; March 25–29, 2022; Boston, MA, USA.*

Dupilumab in CIU

- CUPID A study results: EFFECT ON ITCH & HIVES



Maurer et al. *Presented at the 2022 Annual Meeting of the American Academy of Dermatology (AAD 2022); Boston, MA, USA; March 25–29, 2022; Boston, MA, USA.*

Dupilumab in CIU

- CUPID A study results: SAFETY

Safety summary and conclusions

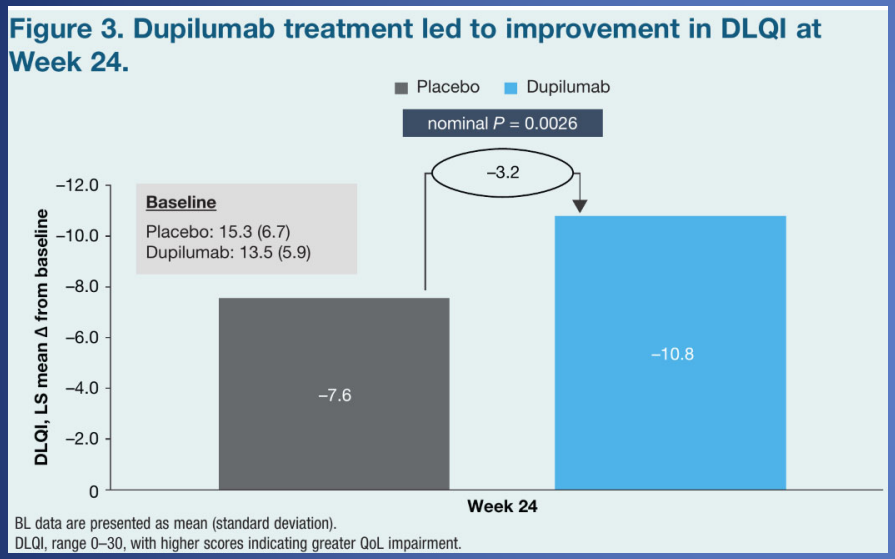
Overall TEAEs reported in ≥ 5% of patients in any treatment group were comparable for placebo and dupilumab

n (%)	Placebo (n = 68)	Dupilumab (n = 70)
Any event	40 (58.8)	35 (50.0)
Skin and subcutaneous tissue disorders	18 (26.5)	9 (12.9)
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 reaction[a]	2 (2.9)	4 (5.7)
Injection-site erythema	4 (5.9)	3 (4.3)

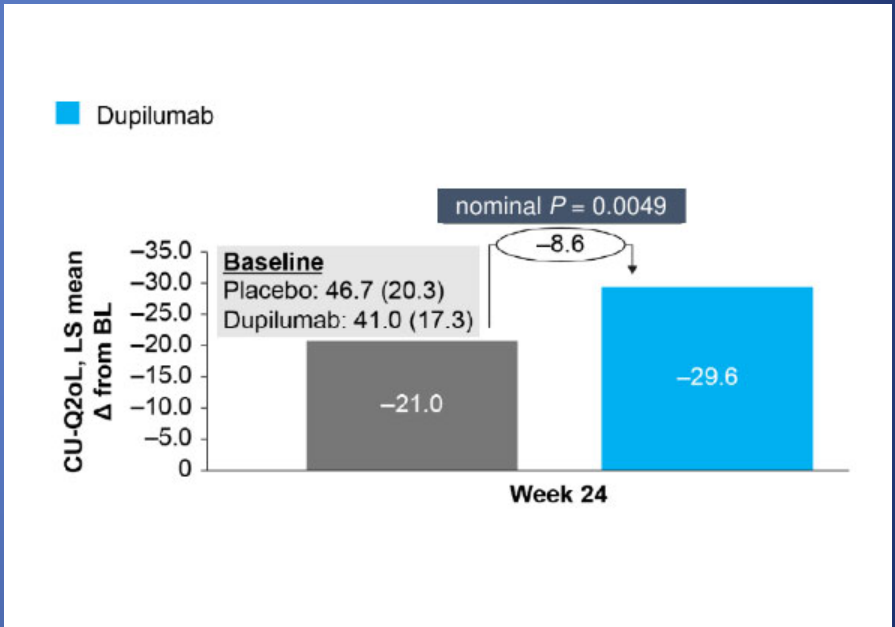
Maurer et al. *Presented at the 2022 Annual Meeting of the American Academy of Dermatology (AAD 2022); Boston, MA, USA; March 25–29, 2022; Boston, MA, USA.*

Dupilumab in CIU

- CUPID A study results: EFFECT ON QOL



Maurer et al. Presented at the 2023 American Academy of Allergy Asthma and Immunology Annual Meeting (AAAAI 2023); San Antonio, TX, USA; February 24–27, 2023.

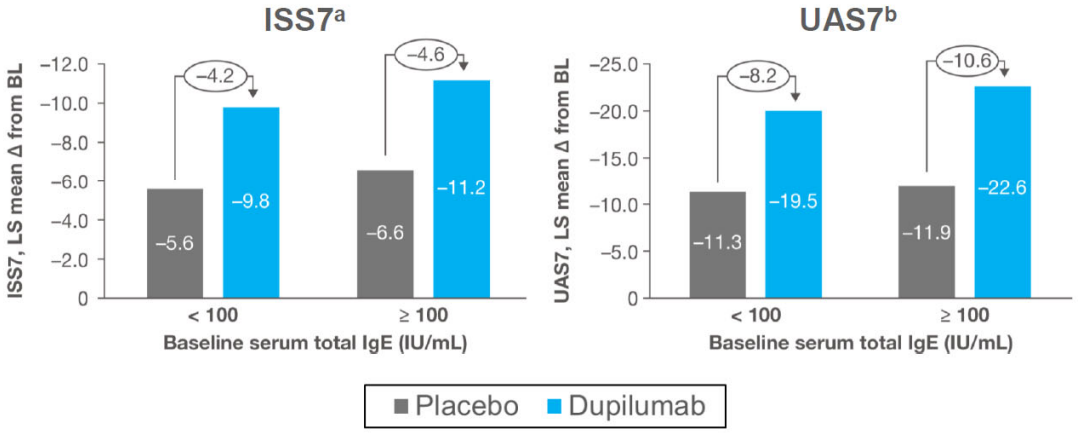


Maurer et al. Presented at the 81st Annual Meeting of the American Academy of Dermatology (AAD2023); New Orleans, LA, USA; March 17–21, 2023.

Dupilumab in CIU

- CUPID A study results: EFFECT OF BL IgE LEVEL

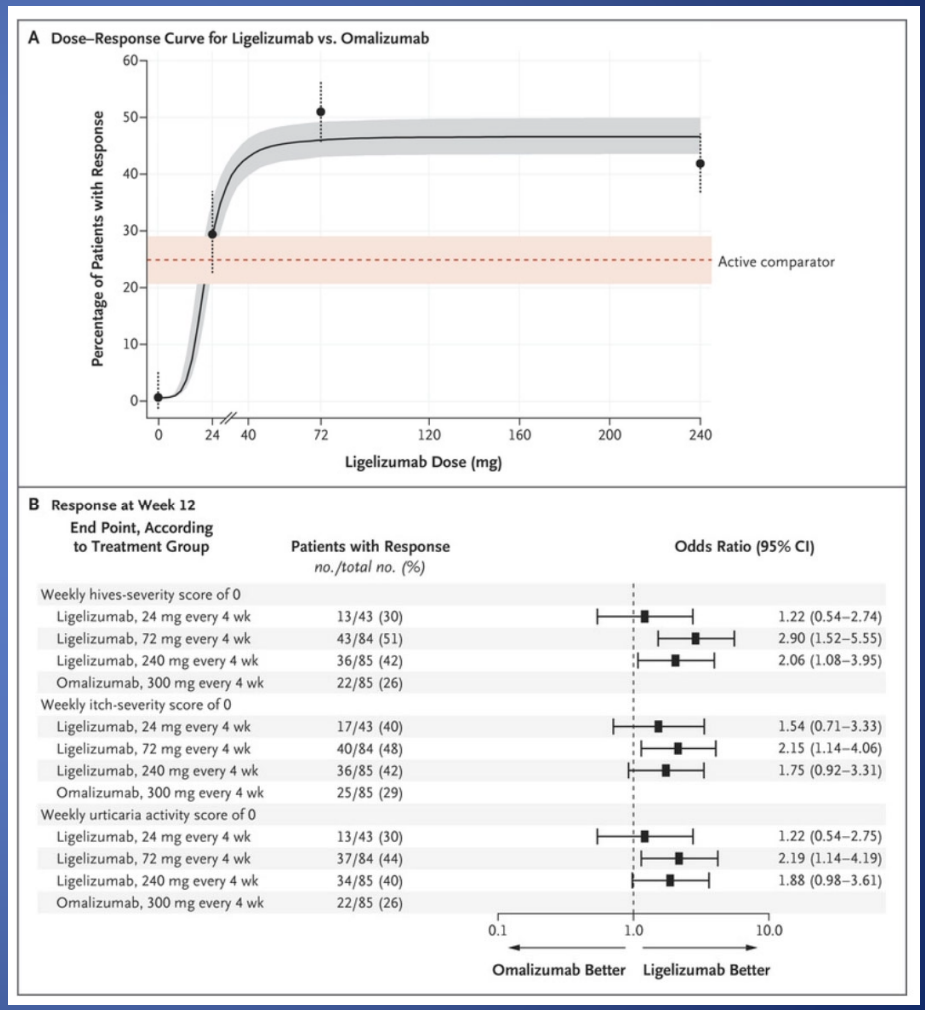
Similar improvements in ISS7 and UAS7 were seen in patients with CSU with normal and elevated IgE levels



Presented at the 31st Congress of the European Academy of Dermatology and Venereology (EADV 2022); Milan, Italy; September 7–10, 2022.
LS, least squares.

Ligelizumab (QGE031)

- High-affinity anti-IgE antibody
- Not yet FDA approved for any other indication
- Ligelizumab 72mg and to a certain extent 240mg outperformed placebo and omalizumab in phase 2b trials



B Response at Week 12

End Point, According to Treatment Group	Patients with Response *no./total no. (%)*	Odds Ratio (95% CI)
Weekly hives-severity score of 0		
Ligelizumab, 24 mg every 4 wk	13/43 (30)	1.22 (0.54–2.74)
Ligelizumab, 72 mg every 4 wk	43/84 (51)	2.90 (1.52–5.55)
Ligelizumab, 240 mg every 4 wk	36/85 (42)	2.06 (1.08–3.95)
Omalizumab, 300 mg every 4 wk	22/85 (26)	
Weekly itch-severity score of 0		
Ligelizumab, 24 mg every 4 wk	17/43 (40)	1.54 (0.71–3.33)
Ligelizumab, 72 mg every 4 wk	40/84 (48)	2.15 (1.14–4.06)
Ligelizumab, 240 mg every 4 wk	36/85 (42)	1.75 (0.92–3.31)
Omalizumab, 300 mg every 4 wk	25/85 (29)	
Weekly urticaria activity score of 0		
Ligelizumab, 24 mg every 4 wk	13/43 (30)	1.22 (0.54–2.75)
Ligelizumab, 72 mg every 4 wk	37/84 (44)	2.19 (1.14–4.19)
Ligelizumab, 240 mg every 4 wk	34/85 (40)	1.88 (0.98–3.61)
Omalizumab, 300 mg every 4 wk	22/85 (26)	

Maurer et al. N Engl J Med. 2019 Oct 3;381(14):1321-1332.

Ligelizumab (QGE031)

- Early data from current phase 3 trials in CSU are promising, per recent press release:

Novartis provides an update on Phase III ligelizumab (QGE031) studies in chronic spontaneous urticaria (CSU)

Dec 20, 2021

Ad hoc announcement pursuant to Art. 53 LR

- *Ligelizumab, a high-affinity anti-IgE antibody, demonstrated superiority compared with placebo at Week 12 in Phase III PEARL 1 and PEARL 2 trials, but not versus omalizumab*[1]
- *Novartis is continuing to evaluate the PEARL data and will provide an update in due course as well as next steps for the program*

Basel, December 20, 2021 – Novartis today announced top-line results from PEARL 1 and PEARL 2 Phase III studies in chronic spontaneous urticaria (CSU), which showed that the studies met their primary endpoints of superiority for ligelizumab versus placebo at Week 12, but not versus omalizumab[1].

https://www.novartis.com/news/media-releases/novartis-provides-update-phase-iii-ligelizumab-qge031-studies-chronic-spontaneous-urticaria-csu

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Dupilumab

- Anti-IL-4Rα
- Blocks IL-4 and IL-13 mediated inflammation
- FDA approved for multiple conditions:
  - atopic dermatitis
  - eosinophilic asthma
  - steroid-dependent asthma
  - chronic rhinosinusitis with nasal polyposis
- Promising phase 3 data in eosinophilic esophagitis

Dupilumab

- Early data from current phase 3 trials in CSU are promising, per recent press release:

Dupixent® (dupilumab) significantly improved itch and hives in patients with chronic spontaneous urticaria, a step forward in demonstrating the role of type 2 inflammation in these patients

- Fifth disease that Dupixent has demonstrated positive pivotal results
- Phase 3 trial met its primary endpoints and all key secondary endpoints at 24 weeks, showing Dupixent nearly doubled reduction in itch and urticaria activity scores
- CSU results further demonstrate the potential of targeting IL-4 and IL-13 via IL-4Ra blockade in improving diseases with components of type 2 inflammation
- Approximately 300,000 people in the U.S. have moderate to severe CSU that does not respond adequately to antihistamines alone
- Data continue to support well-established safety profile of Dupixent

PARIS and TARRYTOWN, N.Y. – July 29, 2021 - A pivotal Phase 3 trial evaluating Dupixent® (dupilumab) in patients with moderate-to-severe chronic spontaneous urticaria (CSU), an inflammatory skin disease, met its primary endpoints and all key secondary endpoints at 24 weeks. Adding Dupixent to standard-of-care antihistamines significantly reduced itch and hives for biologic-naïve patients, compared to those treated with antihistamines alone (placebo) in Study A (the first of two trials) of the LIBERTY CUPID clinical program.

https://www.sanofi.com/en/media-room/press-releases/2021/2021-07-29-07-00-00-2270858

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Remibrutinib (LOU064)

- Highly selective, potent BTK antagonist
- Not yet FDA approved for any other indication
- Currently in phase 3 trials for CSU
- Phase 2b data for CSU are promising, per a recent press release:

Novartis data show rapid and effective disease activity control with remibrutinib (LOU064) in patients with chronic spontaneous urticaria

Sep 30, 2021

- *Results from a Phase IIb study show all remibrutinib doses provided significant improvements in UAS7 change from baseline at week 4 and week 12 compared to placebo, and a favorable safety profile across the entire dose range tested*
- *All doses provided clinically meaningful improvements with respect to the proportion of patients achieving UAS7=0 (complete absence of hives and itch) and UAS7≤6 (well-controlled disease activity) vs. placebo over the treatment period, starting as early as Week 1*
- *Remibrutinib is a highly selective, potent oral BTK inhibitor with a potential best-in-class profile, under investigation for a number of immune-mediated conditions; Phase III studies in CSU are expected to begin enrolling patients by the end of 2021*
- *Novartis datasets at EADV 2021 demonstrate our continued commitment to innovation in immuno-dermatology, aiming to ease the burden of these life-limiting diseases*
- *CSU is a distressing and unpredictable disease that remains inadequately controlled for many, highlighting the importance of pursuing new modes of action*

https://www.novartis.com/news/media-releases/novartis-data-show-rapid-and-effective-disease-activity-control-remibrutinib-lou064-patients-chronic-spontaneous-urticaria#:~:text=Basel%2C%20September%2030%2C%202021%20%E2%80%94,chronic%20spontaneous%20urticaria%20(CSU).

Take-home points

- CU is a common condition with significant morbidity
- Published guidelines, which start with the use of antihistamines, can help guide therapy for CSU
- Omalizumab, the only FDA approved biologic therapy for CSU, is effective and safe, although it is not disease modifying
- Various other immunomodulators exist for those pts resistant to initial therapeutic interventions
- There are several emerging biologic therapies, especially dupilumab, with promise in the treatment of CSU

Questions?