



8th YEAR

08-10 November 2024

InterContinental Dubai - Festival City
United Arab Emirates



Latest updates in CSU

Prof. Dr. Emek Kocatürk Göncü

Charite University Institute of Allergology, Berlin, Germany



**27th WORLD CONGRESS
OF DERMATOLOGY 2031
DUBAI - CANDIDATE CITY**

Conflict of Interest

- Speaker and consultant for Novartis and Menarini

Common Nettle

Plant ⋮

Overview

Benefits

Taste



Wikipedia

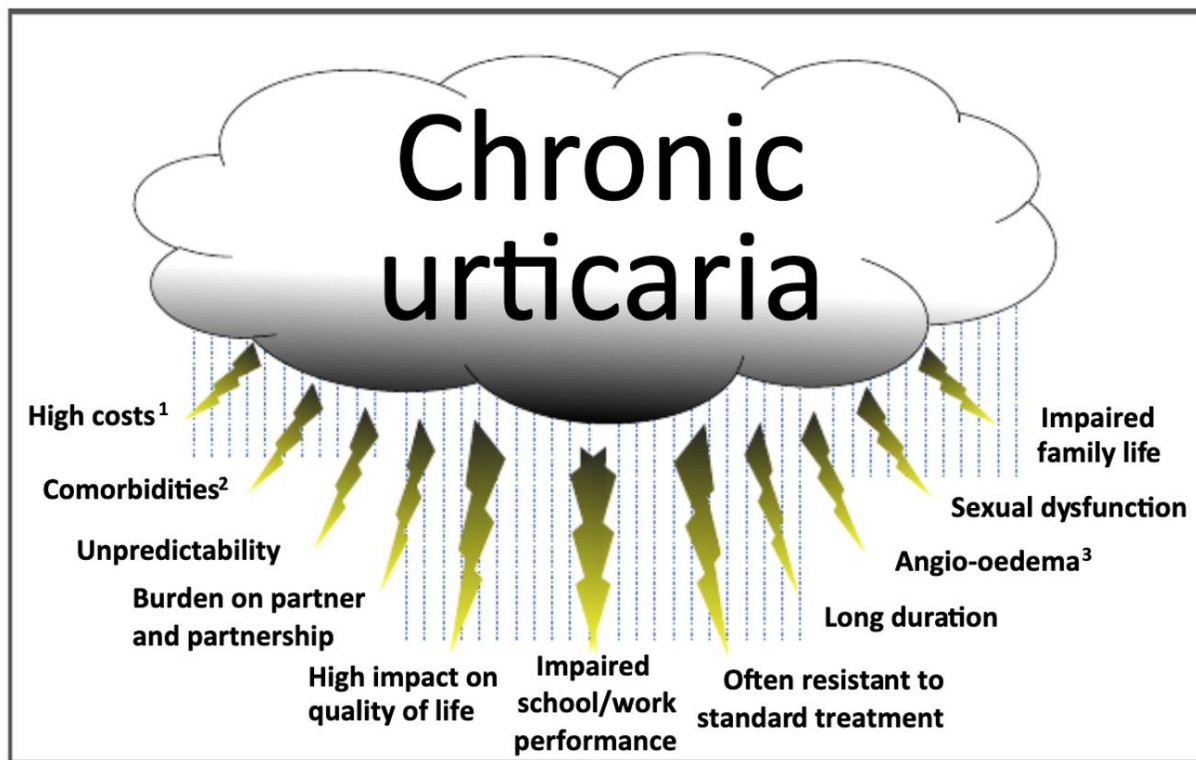
https://en.wikipedia.org/wiki/Urtica_dioica ⋮

Urtica dioica



The global burden of chronic urticaria for the patient and society

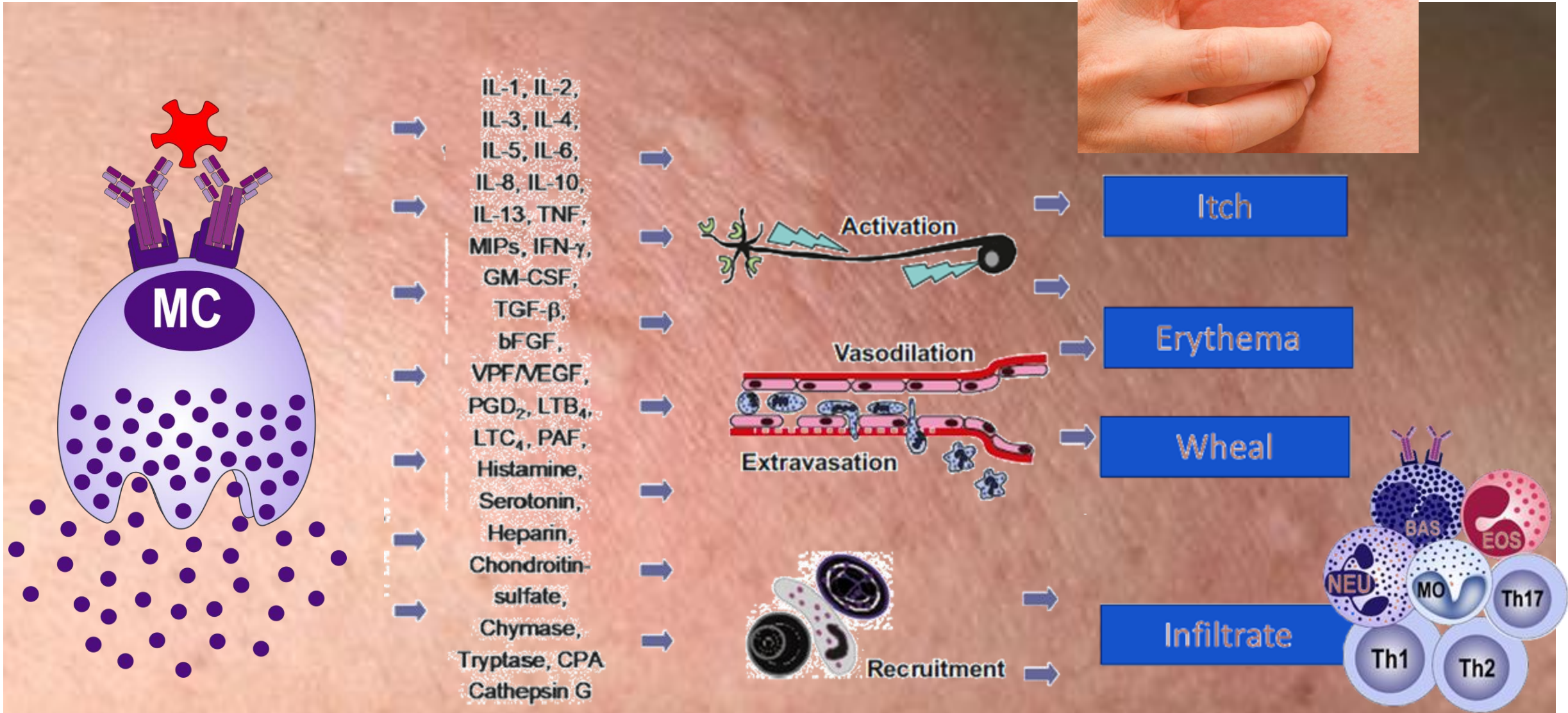
M. Gonçalo ¹, A. Giménez-Arnau, ² M. Al-Ahmad, ³ M. Ben-Shoshan, ⁴ J.A. Bernstein, ⁵ L.F. Ensina, ⁶ D. Fomina, ^{7,8} C.A. Galvan, ⁹ K. Godse, ¹⁰ C. Grattan, ¹¹ M. Hide, ¹² C.H. Katelaris, ¹³ M. Khoshkhui, ¹⁴ E. Kocaturk, ¹⁵ K. Kulthanan, ¹⁶ I. Medina, ¹⁷ I. Nasr, ¹⁸ J. Peter, ¹⁹ P. Staubach, ²⁰ L. Wang, ²¹ K. Weller ²² and M. Maurer ²²



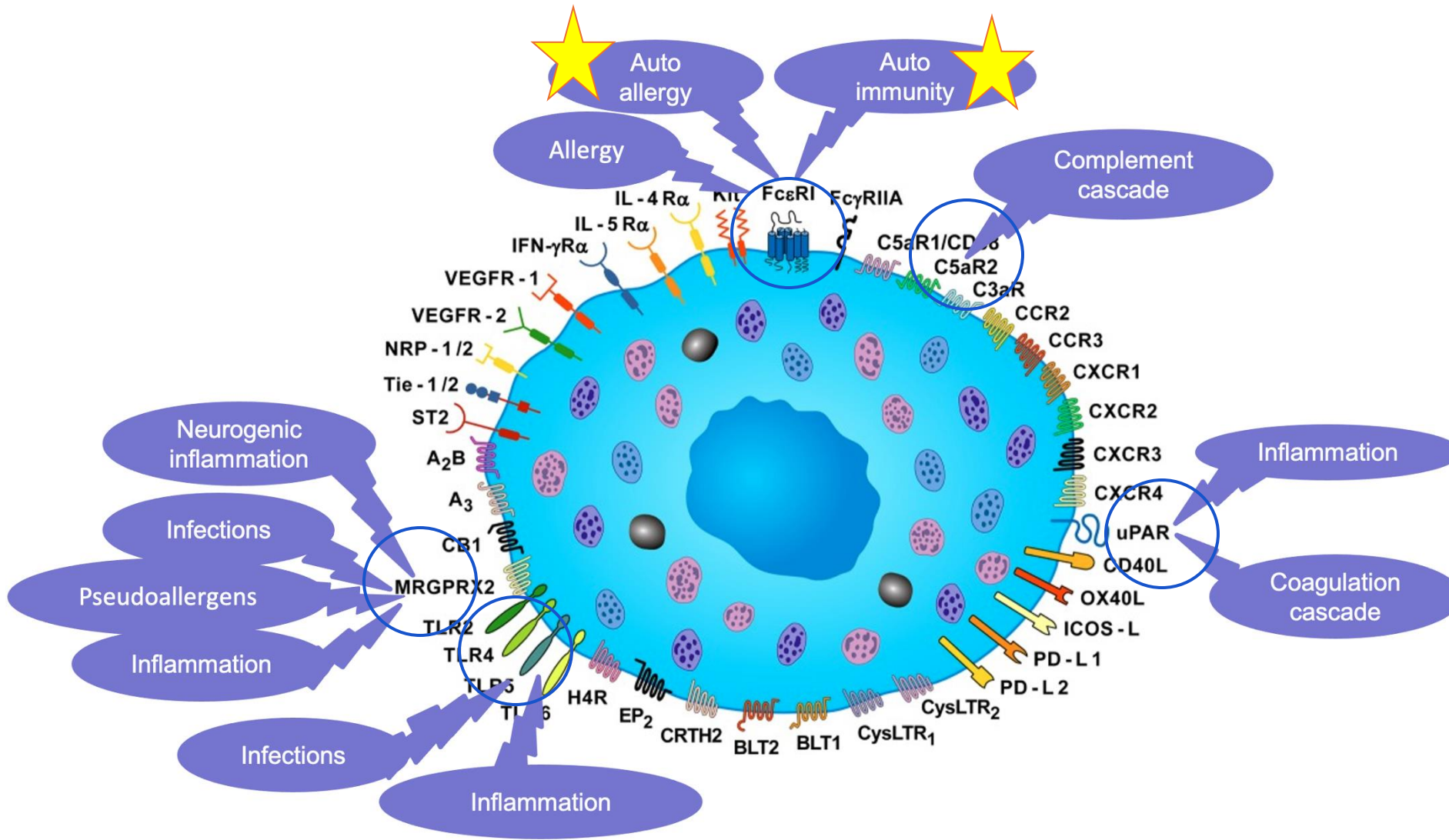
Classification of Chronic Urticaria

Acute urticaria < 6 weeks	Chronic urticaria ≥ 6 weeks	
	Chronic spontaneous urticaria Spontaneous appearance of wheals, angioedema, or both for >6 weeks due to known or unknown causes <div style="border: 1px solid red; padding: 5px; display: inline-block;">75%</div>	Chronic inducible urticaria Symptomatic dermographism Cold urticaria Delayed pressure urticaria Solar urticaria Heat urticaria Vibratory angioedema Cholinergic urticaria Aquagenic urticaria Contact urticaria
		<div style="border: 1px solid black; padding: 5px; display: inline-block;">Physical urticaria</div>
		<div style="border: 1px solid black; padding: 5px; display: inline-block;">Other inducible urticaria</div>

Pathophysiology of urticaria



What activates mast cells in chronic urticaria?



Autoimmune mechanisms in CSU

Type I autoallergic CSU

Auto-allergens

IgE-anti-TPO

IgE-anti-IL-24

IgE-anti-ds-DNA

Histamine, cytokine,
chemokines and other
inflammatory mediators

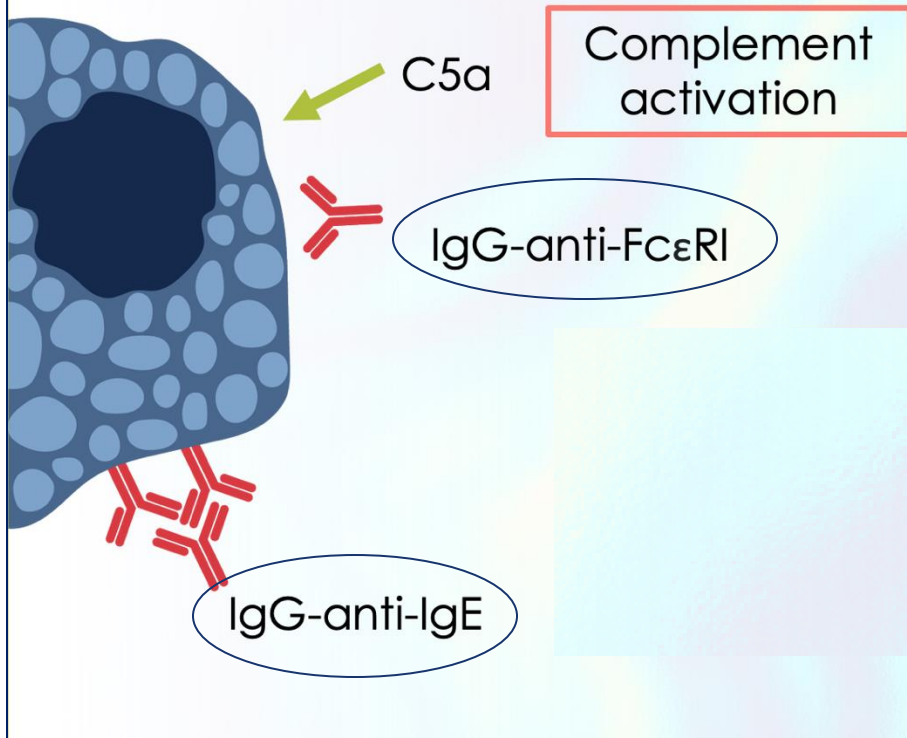
- Characterized by IgE antibodies directed to self-antigens
- IgE to more than 200 autoantigens including:
 - Thyroid peroxidase (TPO)
 - Eosinophil peroxidase (EP)
 - Double-stranded DNA (ds-DNA)
 - IL-24
 - Tissue factor (TF)
 - Eosinophil cationic protein (ECP)
 - FcERI
 - Thyroglobulin (87%)
 - Transglutaminase

~50%

- High comorbid atopic diseases
- High/normal total IgE
- Good response to omalizumab

Autoimmune mechanisms in CSU

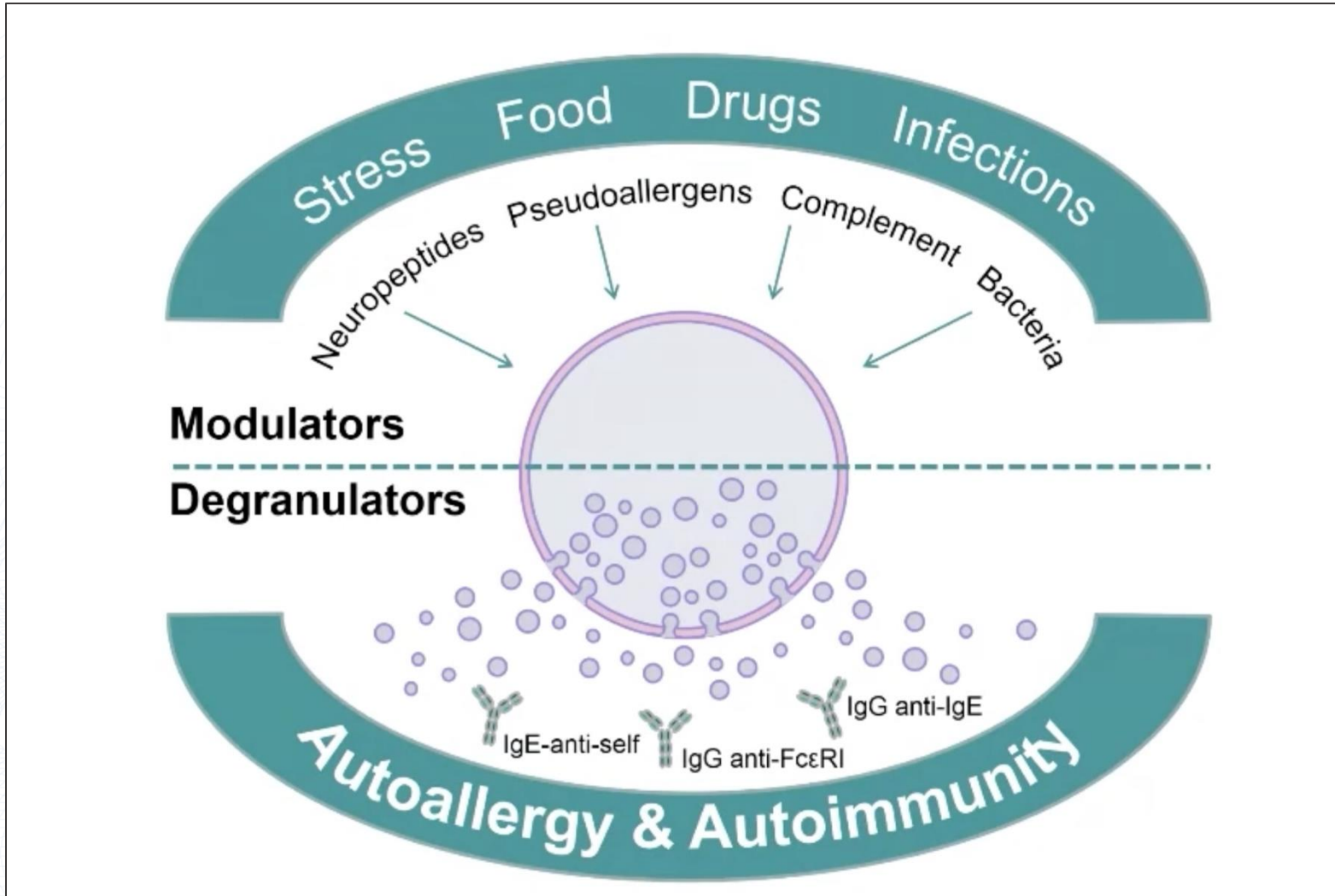
Type IIb autoimmune CSU



- High comorbid autoimmune diseases
- Low total IgE
- Poor response to omalizumab

~8-40%

CSU Pathomechanism Summary



Environmental factors



Genetic tendency



Causative factor

Diagnosis of autoimmune CSU types

Type I autoallergic CSU

Presence of:

- anti-TPO-IgE or
- anti-IL-24 or
- both

Type IIb autoimmune CSU

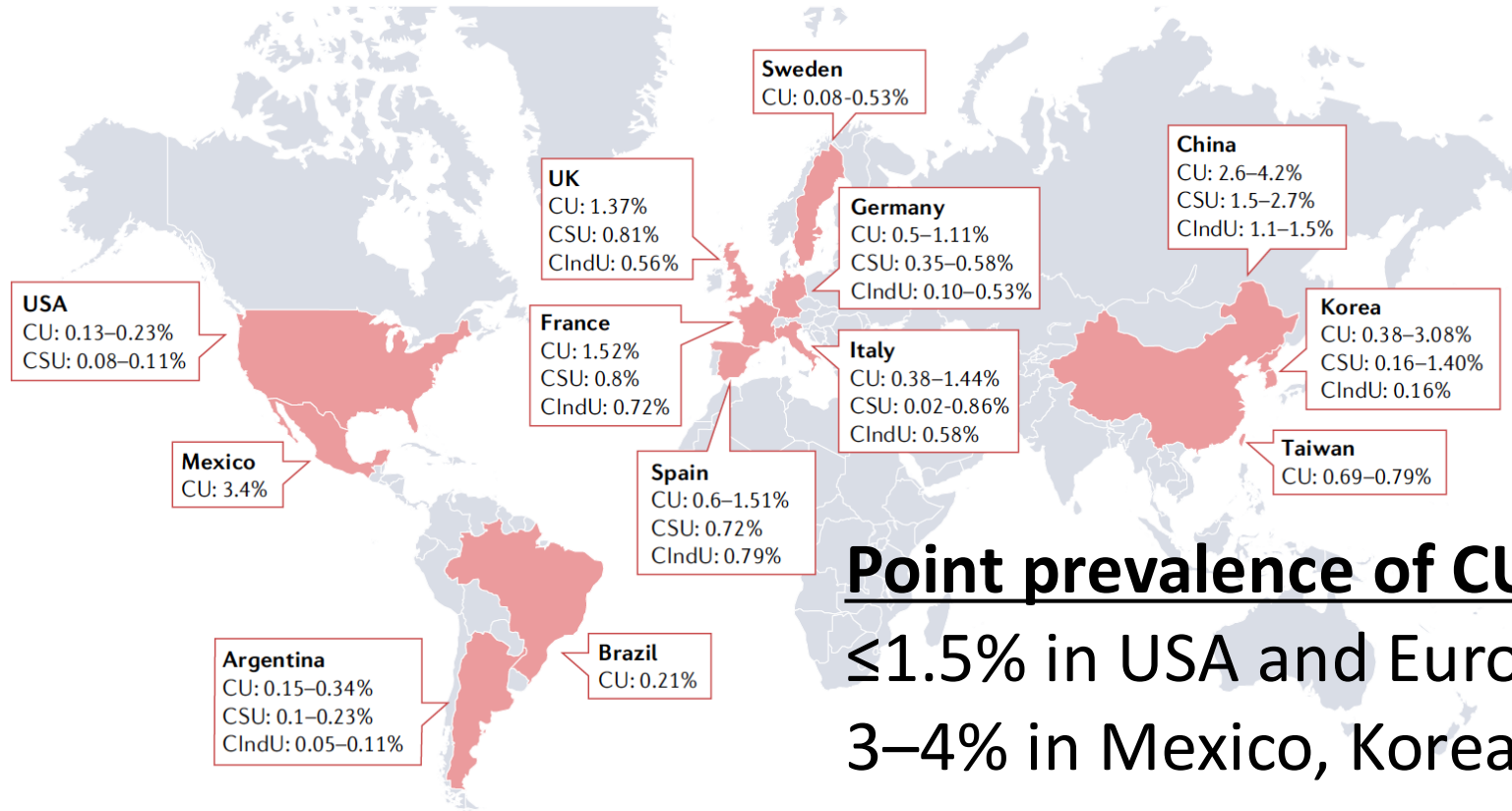
Presence of:

- positive ASST and
- positive BAT and
- positive IgG-anti-FcεRI and
- positive IgG-anti-IgE

Autoimmune type IIb CSU is severe, comes with markers

Clinical		Laboratory	
Female	87-93%	↓ total IgE (<40-43 kU/l)	69-86%
Autoimmune diseases	~60%	↑ IgG-anti-TPO	39-62%
Symptoms >5 d/w	92%	ANA+	9-58%
Nocturnal symptoms	70-79%	Basopenia	30%
Angioedema	62-76%	Eosinopenia	24%

Epidemiology

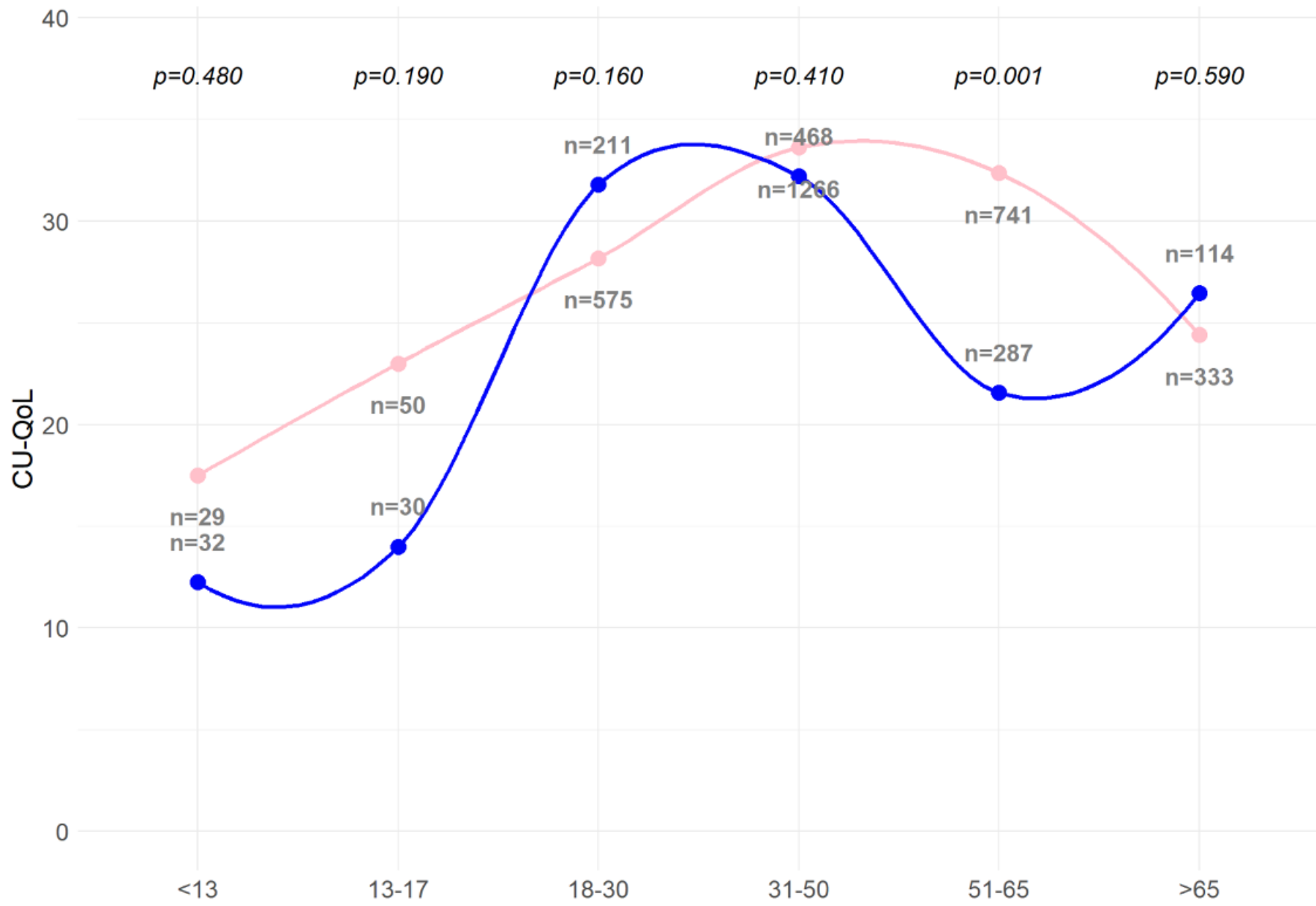


Point prevalence of CU

≤1.5% in USA and Europe

3–4% in Mexico, Korea and China

Females 70%, males 30%



Emek Kocaturk^{1,2,3}, Pavel Kolkhir^{1,2}, Pascale Salameh^{1,2}, Yana Hackler^{1,2}, Riccardo Asero⁴, Mojca Bizjak⁵, Ana Gimenez-Arnau⁶, Clive Grattan⁷, Leonie Shirin Herzog^{1,2}, Thomas Buttgereit^{1,2}, Hanna Bonnekoh^{1,2}, Daria Fomina^{8,9,10}, Elena Kovalkova⁸, Marina Lebedkina⁸, Alija Kasperska-Zajac¹¹, Kanokvalai Kulthanan¹², Maryam Khoukhi¹³, Jonny Peter¹⁴, Aurelie Du-Thanh¹⁵, Raisa Meshkova¹⁶, Mohamed Abuzakouk¹⁷, Michael Makris¹⁸, Laurence Bouillet¹⁹, Stamatios Gregoriou²⁰, Simon Francis Thomsen²¹, Joachim Dissemond²², Petra Staubach²³, Andrea Bauer²⁴, Inna Danilycheva²⁵, Martijn van Doorn^{26,27}, Claudio Parisi²⁸, Karsten Weller^{1,2}, Marcus Maurer^{1,2}

Results

4136 CSU patients, 2994 (72.4%) were female (Table 1) ratio was significantly higher in >18 y vs ≤18 y (2.7 vs 1.4; p=0.01)

- Female patients showed higher rates of:
- wheals with angioedema (59.6% vs 51.7%; p<0.001)
 - systemic symptoms
 - fever [4.1% vs 3.3%; p<0.001]
 - joint/bone/muscle pain [15.7% vs 10.2%; p<0.001]
 - malaise [14.8% vs 11.8%; p<0.001]
 - positive family history for chronic urticaria (8.6% vs 5.2%; p=0.002)
 - concomitant diseases (Table 2)
 - elevated ESR (19.1% vs 10.1%; p<0.001)
 - use of immunosuppressive medications (20.5% vs 16.7%; p=0.006)
 - higher quality of life impairment (CU2QoL score 32 vs 27.7; p<0.001)

Table 2: Comparison between female and male patients with respect to comorbidities

Comorbidity	Female	Male	P
asthma	144 (4.9%)	53 (4.7%)	0.640
dermatitis	554 (18.8%)	236 (20.9%)	0.129
rhinitis	848 (11.8%)	94 (8.3%)	0.004
allergy	125 (4.3%)	48 (4.3%)	1
diabetes mellitus	150 (5.1%)	88 (7.8%)	0.004
hypertension	554 (18.8%)	221 (19.6%)	0.798
epidemiology	308 (10.5%)	144 (12.8%)	0.093
hypothyroidism	416 (14.1%)	127 (11.3%)	0.048
hypertension	74 (2.5%)	19 (1.7%)	0.184
hypertension	198 (6.7%)	68 (6%)	0.612
autoimmune disease	583 (20.9%)	72 (6.7%)	<0.001
autoimmune disease	360 (12.2%)	58 (4.7%)	<0.001
autoimmune disease	8 (0.3%)	2 (0.2%)	0.708
autoimmune disease	6 (0.2%)	3 (0.3%)	0.925
autoimmune disease	609 (20.7%)	172 (15.3%)	<0.001
autoimmune disease	246 (8.4%)	53 (4.7%)	<0.001
autoimmune disease	339 (11.5%)	105 (9.3%)	0.133
autoimmune disease	205 (7%)	138 (12.2%)	<0.001

Conclusions

Female patients appear to have a distinct CSU phenotype, which differs from male patients with more systemic symptoms and comorbidities and lower quality of life highlighting the need for a tailored diagnosis and treatment approach

Diagnostic work up in CSU

Allergy EUROPEAN JOURNAL OF ALLERGY
AND CLINICAL IMMUNOLOGY



GUIDELINES | Open Access | CC BY-NC-ND

The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria

No extensive work up!

Basic lab work-up:

CBC
CRP/ESR
Anti-TPO IgG
Total IgE

Should be done in each CSU patient

International Urticaria Guideline introduces a more **PERSONALIZED APPROACH** in patients with CSU

7C

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 ^{aiTIB}		
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		
Course	Monitor CSU activity, impact and control		
Components	Assess potential biomarkers or predictors of treatment response		

Hashimoto, atopic com, mental com

CU-Q2oL

UAS, UCT


Low IgE

Look for and treat comorbid conditions

Comorbidities

- Autoimmune diseases
- Allergic diseases
- Mental disorders
- Infections
- Metabolic syndrome
- Chronic inducible urticaria


Autoimmune diseases in CSU

- Hashimoto's thyroiditis
 - Vitiligo, pernicious anemia
 - Graves' disease
 - DM
 - RA
 - Psoriasis
 - Coeliac disease
- 

Allergic diseases in CSU

- Allergic rhinitis
- Allergic asthma
- Atopic eczema

Mental disorders in CSU

- Depression
 - Anxiety
 - Somatoform disorders
 - Post-traumatic stress disorder
 - Social phobia
- 

Infections in CSU

- H.pylorii
- Intestinal parasites
- Strep-staph
- Hepatitis viruses
- Anisakis

Management of comorbidities may provide benefit for the better management of the disease

Parameters	Mental Health Disorders	Metabolic Syndrome	Autoimmune Diseases	Chronic Inducible Urticaria	Cancer
Patients with chronic spontaneous urticaria who have comorbidity	8.5%-31.6%	5.9%-19.7%	10.5%-28%	>10%	
Appearance in relation to chronic spontaneous urticaria	In many cases, after diagnosis of chronic spontaneous urticaria	Unknown	In about 80% of patients with autoimmune diseases, autoimmune disease is diagnosed after urticaria	Of	
Most common forms	Anxiety (9.6%-30.6%), mood disorders including depression (6.6%-29.4%), sleep-wake disorders (36.7%)	Central obesity (13.9%), dyslipidemia (11.3%), hyperglycemia (5.9%), arterial hypertension (19.7%)	Autoimmune diseases (e.g., due to systemic lupus erythematosus)	Chronic inducible urticaria (7.3%), cold urticaria (13.4%), delayed pressure urticaria (7.3%)	Solid cancers, Helicobacter pylori, allergic rhinitis
Pathogenetic or causal relation to chronic spontaneous urticaria	Due to urticaria symptoms, impairment in quality of life (consequence)		In some cases, can also induce urticaria, e.g., due to systemic lupus erythematosus	Possible pathogenetic association	Causal association is possible but rare
Association with chronic spontaneous urticaria endotype		Any endotype	Autoimmune endotype	Any endotype except IgG-mediated autoimmune endotype	Any endotype
	Probably decrease in quality of life	Probably longer urticaria duration	Possibly longer urticaria duration, more active urticaria, worse response to treatment	Longer duration of urticaria, further decrease in quality of life	Urticaria can improve after successful treatment of underlying cause



Association of Cardiovascular Disease and Chronic Spontaneous Urticaria: A Case–Control Study

Luis F. Andrade¹ · Zaim Haq² · Parsa Abdi³ · Sarah G. Brooks¹ · Veronica Voronina⁴ · Michael J. Diaz⁵ · Gil Yosipovitch^{1,6}

Table 1 Sociodemographic and clinical traits of chronic urticaria case/controls in the All of Us Research Program

Characteristic	Cases, <i>N</i> (%) (<i>n</i> = 254)	Controls, <i>N</i> (%) (<i>n</i> = 1016)	<i>p</i> -value
Age, years			> 0.99
18–39	69 (27.17)	276 (27.17)	
40–59	81 (31.89)	324 (31.89)	
60–74	78 (30.71)	312 (30.71)	
≥ 75	26 (10.24)	104 (10.24)	
Female (%)	217 (85.43)	868 (85.43)	> 0.99
Race/ethnicity			> 0.99
White	160 (62.99)	640 (62.99)	
Black	43 (16.93)	172 (16.93)	
Hispanic	≤ 20 ^a (≤ 7.87)	80 (7.87)	
Associated comorbidity			
Ever smoker	107 (42.13)	496 (48.82)	< 0.001
Alcohol use disorder	22 (8.66)	52 (5.12)	0.036
Disease			
→ Hypertension	124 (48.82)	407 (40.06)	0.013
→ Coronary atherosclerosis	35 (13.78)	93 (9.15)	0.035
→ Congestive heart failure	≤ 20 ^a (≤ 7.87)	36 (3.54)	0.361
→ Cardiac arrhythmia	94 (37.01)	156 (15.35)	< 0.001

^aValues less than 20 are reported as ≤ 20 per the All of Us data use standards

PRO tools to assess disease activity and control in chronic urticaria and angioedema

	CSU	Angioedema	CINDU
Disease activity	UAS	AAS	Critical threshold testing
Quality of life	CU-QoL	AE-QoL	CINDU-QoL
Disease control	UCT	AECT	UCT

PRO	Format (time span)	Domain	Scoring system	Scoring range	Correlating response	MCID
UAS7	Diary (based on the last 7 days)	Pruritus intensity and number of hives	0-3	0-42	0 = Itch and hive free 1-6 = Well-controlled 7-15 = Mild activity 16-27 = Moderate activity 28-42 = Severe activity	9.5-10.5
AAS7	Diary (based on the last 7 days)	Severity of physical discomfort, ability to perform daily activities, cosmetic impact, and global assessment of severity	0-3	0-10	-	8
UCT	4-item questionnaire (based on the last 4 weeks)	Physical symptoms, impact on QoL, treatment effectiveness, symptom control	0-4	0-16	16 = Completely controlled 12-15 = Well-controlled <12 = Uncontrolled	3
AECT	4-item questionnaire (based on the last 4 weeks)	Frequency of angioedema, angioedema-related QoL impairment, the unpredictability of angioedema attacks, and angioedema control by current treatment	0-4	0-16	0-9 = Poorly controlled 10-16 = Controlled disease	-
CU-Q2oL	23-item questionnaire (based on the last 2 weeks)	Pruritus, swelling, daily life activities, sleep, appearance, and limitations	1-5	0-100	Mild = 0-15 Moderate = 16-50 Severe >50	15
AE-QoL	17-item questionnaire (based on the last 4 weeks)	Functioning, fatigue/mood, fear/shame, and food	1-5	0-100	-	6
DLQI	10-item questionnaire (based on the last 7 days)	Symptoms/feelings, daily activities, leisure, work or school, personal relationships, and treatment side effects	0-3	0-30	0-1 = No impact 2-5 = Little impact 6-10 = Moderate impact 11-20 = Very high impact 21-30 = Extremely high impact	4

Urticaria Control Test (UCT)

1. How much have you suffered from the **physical symptoms of the urticaria (itch, hives (welts) and/or swelling)** in the last four weeks?

very much **0** much **1** somewhat **2** a little **3** not at all **4**

2. How much was your **quality of life** affected by the urticaria in the last 4 weeks?

<https://moxie-gmbh.de/>

very often **0** often **1** sometimes **2** seldom **3** not at all **4**

4. **Overall**, how well have you had your urticaria **under control** in the last 4 weeks?

not at all **0** a little **1** somewhat **2** well **3** very well **4**

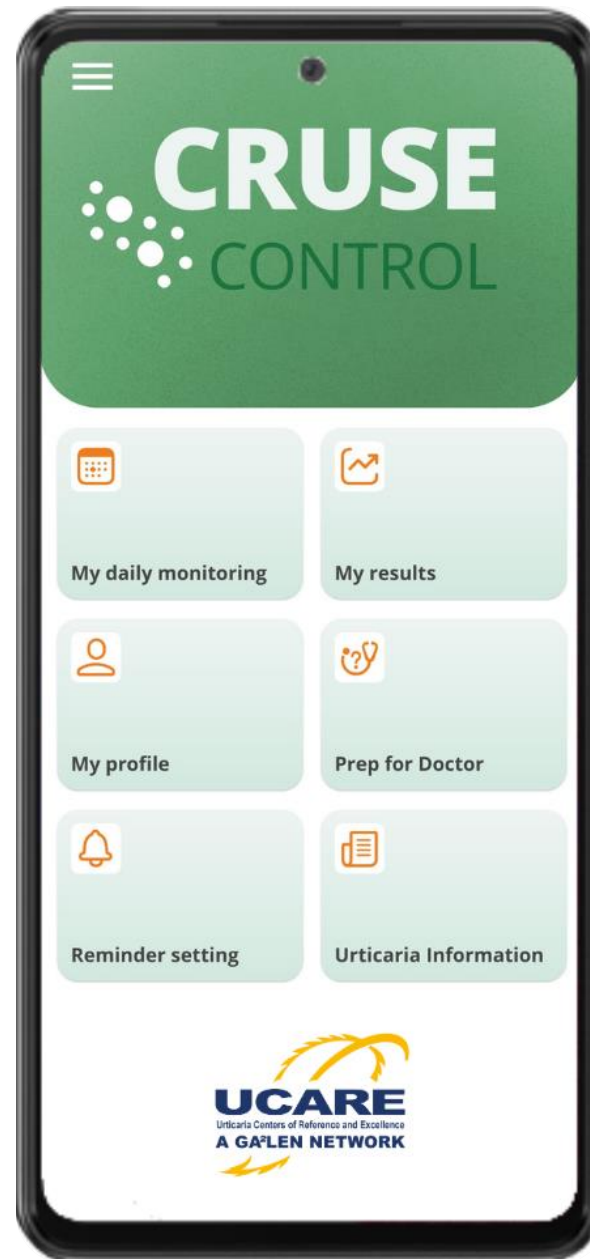
Total score: 0-16

UCT score <12 poorly controlled urticaria
UCT score ≥12 well controlled urticaria

Weller K, et al. J Allergy Clin Immunol 2014;133(5):1365–72.

CRUSE CONTROL

- ChRonic
- Urticaria
- Self-
- Evaluation

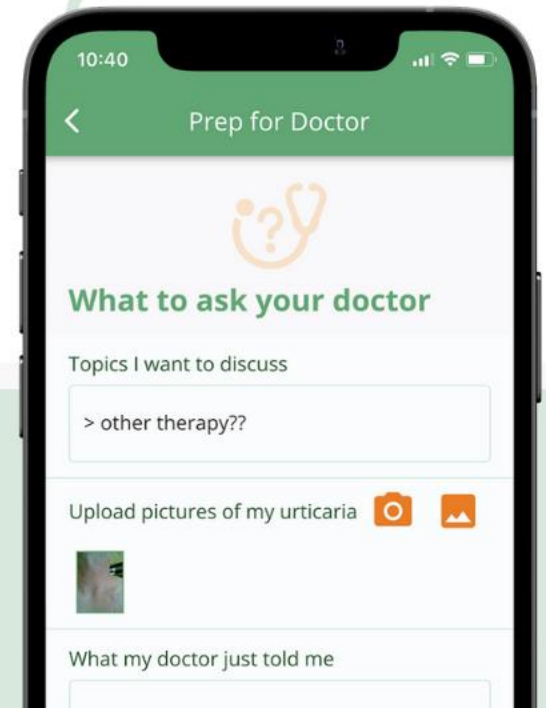
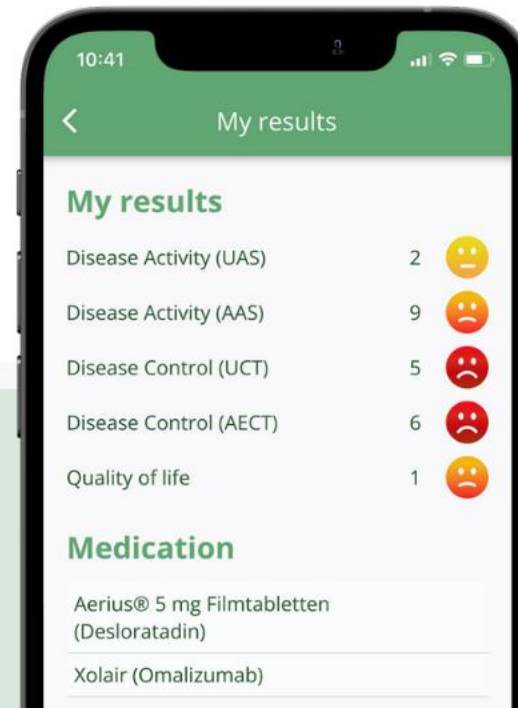
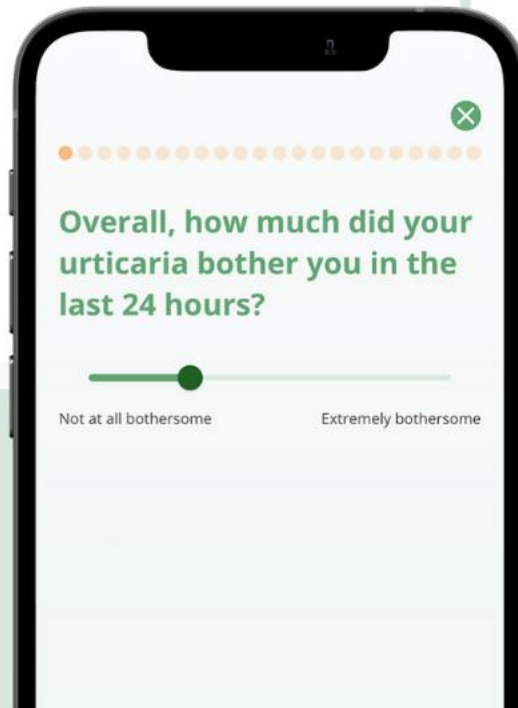


4.5 The CRUSE app

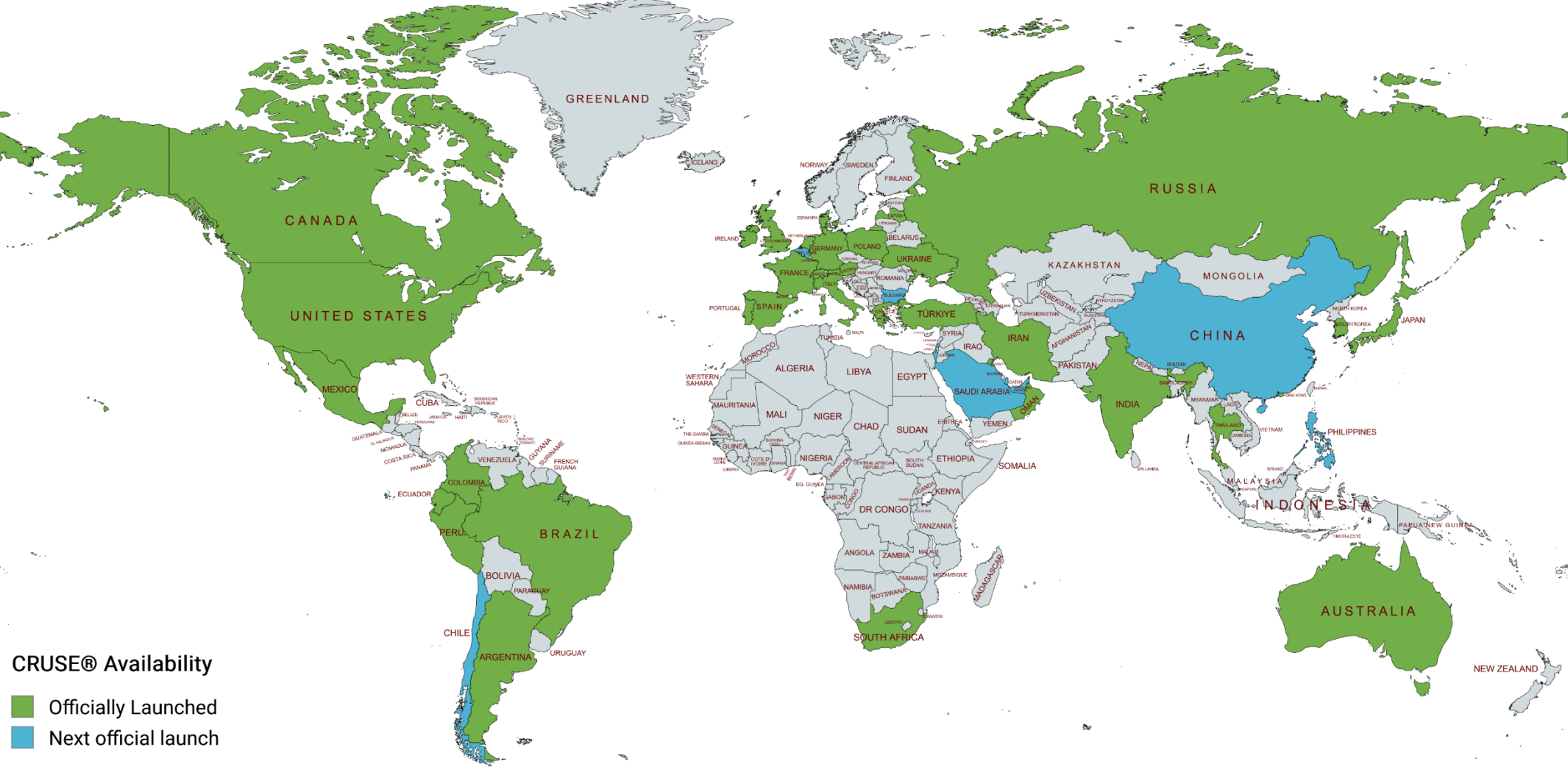
Urticaria Activity Score (UAS)
Angioedema Activity Score (AAS)
Urticaria Control Test (UCT)
Angioedema Control Test (AECT)
VAS – Urticaria
VAS – productivity
VAS – EQ5D

PROM Scores
Current Medication

Prep for Doctor
+Send Report Function



4.5 The CRUSE app – Global availability



Biomarkers for treatment response in CSU

> [J Allergy Clin Immunol Pract.](#) 2021 Nov;9(11):4138-4146.e8. doi: 10.1016/j.jaip.2021.07.043.
Epub 2021 Aug 4.

Autoimmune Chronic Spontaneous Urticaria Detection with IgG Anti-TPO and Total IgE

Pavel Kolkhir ¹, Elena Kovalkova ², Anton Chernov ², Inna Danilycheva ³, Karoline Krause ⁴,
Merle Sauer ⁴, Andrey Shulzhenko ³, Daria Fomina ⁵, Marcus Maurer ⁶

Strong level
of evidence

Weak level
of evidence

Main aim of treatment in CSU

Allergy EUROPEAN JOURNAL OF ALLERGY
AND CLINICAL IMMUNOLOGY



GUIDELINES |  Open Access |   

The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria

**TREAT THE DISEASE
UNTIL IT IS GONE!**



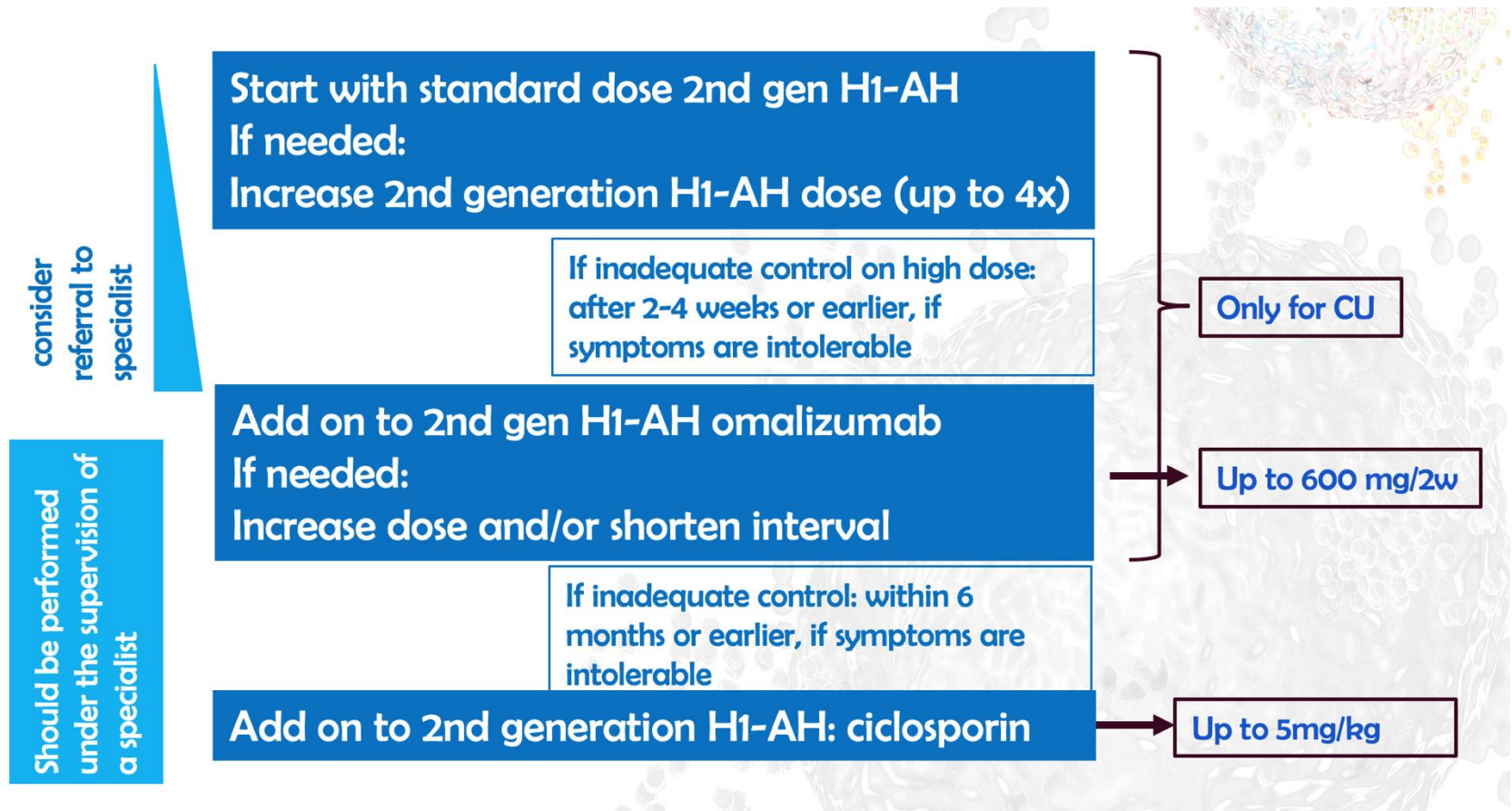
1. Aim for complete disease control



2. To continue treatment and maintain complete response until spontaneous remission occurs

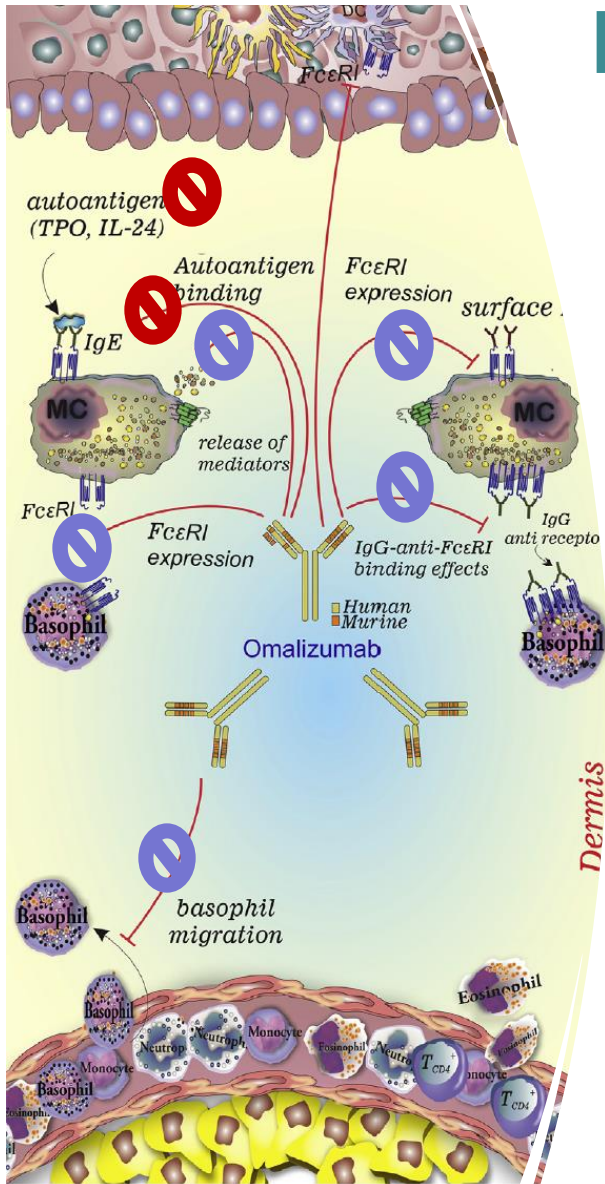
Zuberbier T, Aberer W, Asero R, et al. Allergy. 2021;73(7):1393-414

Step wise treatment approach in Chronic Urticaria



Zuberbier T, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022 Mar;77(3):734-766.

Mechanism of action of omalizumab in CSU



Rapid:

Free IgE ↓ therefore mast cell and basophil degranulation does not happen (within 3 days)

Can bind free allergens and autoallergens



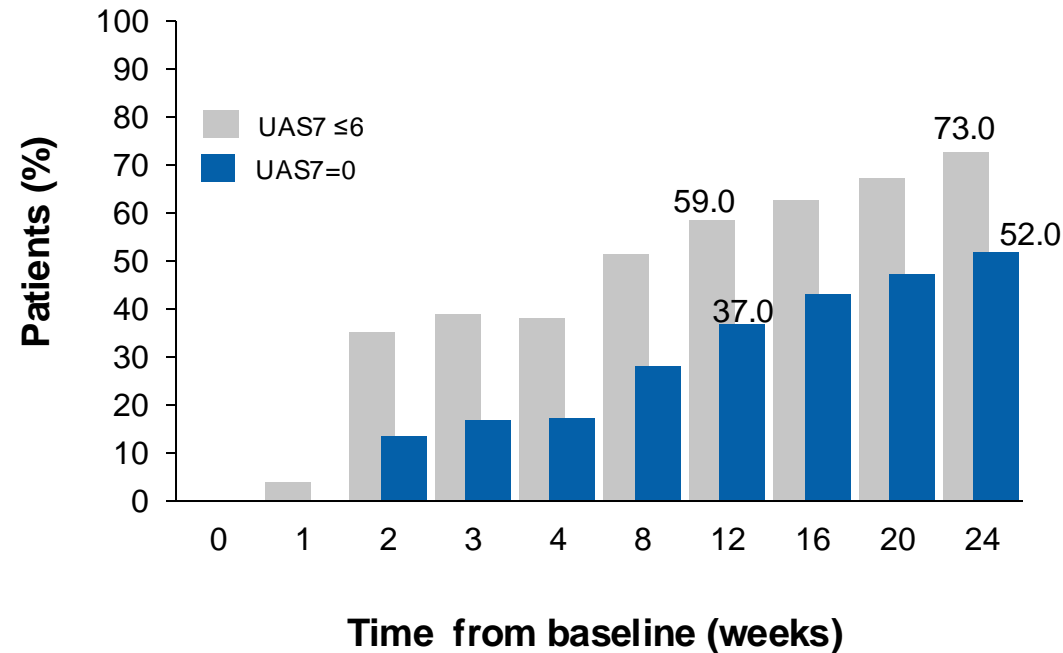
Slow/late:

Down-regulation of FcεRI on mast cell (weeks) and basophil (within 4 weeks)

Inflammatory mediator and cytokine release ↓ = anti-inflammatory effect

Slow responders to omalizumab treatment can still reach complete control

Omalizumab responder rates increase over a 24-week period^{1,2}



Some patients may have a slow response to omalizumab

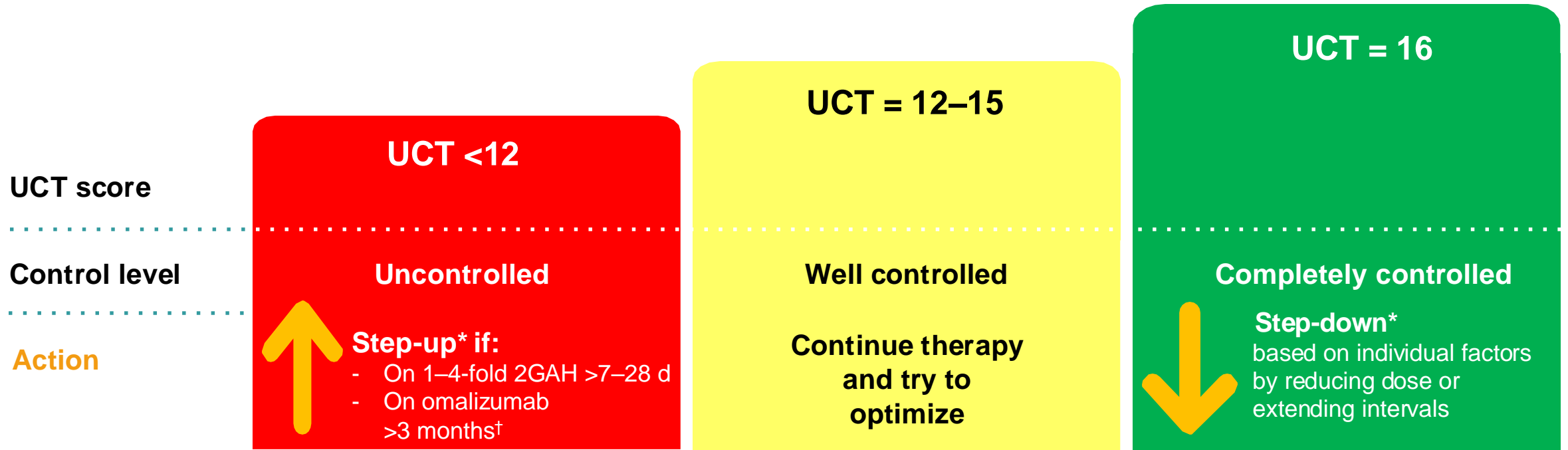


Many patients with CSU discontinue biologic treatment before it begins to have an effect



It is recommended that patients with CSU are treated with omalizumab for at least 6 months, in order to achieve disease control

Guidelines recommend stepping up/stepping down in the treatment algorithm according to the course of disease



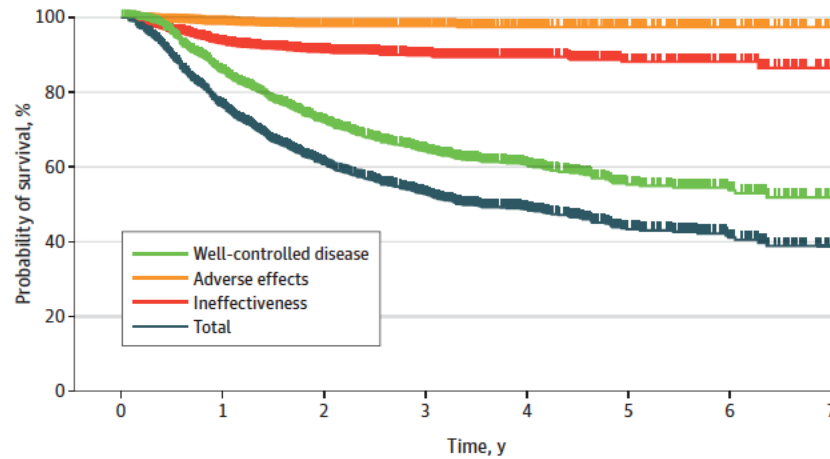
Multinational Drug Survival Study of Omalizumab in Patients With Chronic Urticaria and Potential Predictors for Discontinuation

Reineke Soegiharto, MD; Mehran Alizadeh Aghdam, MD, PhD; Jennifer Astrup Sørensen, MD; Esmee van Lindonk, BSc; Ferhan Bulut Demir, MD; Nasser Mohammad Porras, MD; Yoshimi Matsuo, MD; Lea Kiefer, MD, PhD; André C. Knulst, MD, PhD; Marcus Maurer, MD, PhD; Carla Ritchie, MD; Michael Rudenko, MD, PhD; Emek Kocatürk, MD, PhD; Roberta F. J. Criado, MD, PhD; Stamatis Gregoriou, MD, PhD; Tatjana Bobylev, MD; Andreas Kleinheinz, MD, PhD; Shunsuke Takahagi, MD, PhD; Michihiro Hide, MD, PhD; Ana M. Giménez-Arnau, MD, PhD; Andaç Salman, MD, PhD; Rabia O. Kara, MD, PhD; Bahar Sevimli Dikicier, MD, PhD; Martijn B. A. van Doorn, MD, PhD; Simon F. Thomsen, MD, PhD; Juul M. P. A. van den Reek, MD, PhD; Heike Röckmann, MD, PhD

N=2325

Figure 1. Drug Survival of Omalizumab in Chronic Urticaria Patients

A Drug survival differentiated by reason for discontinuation



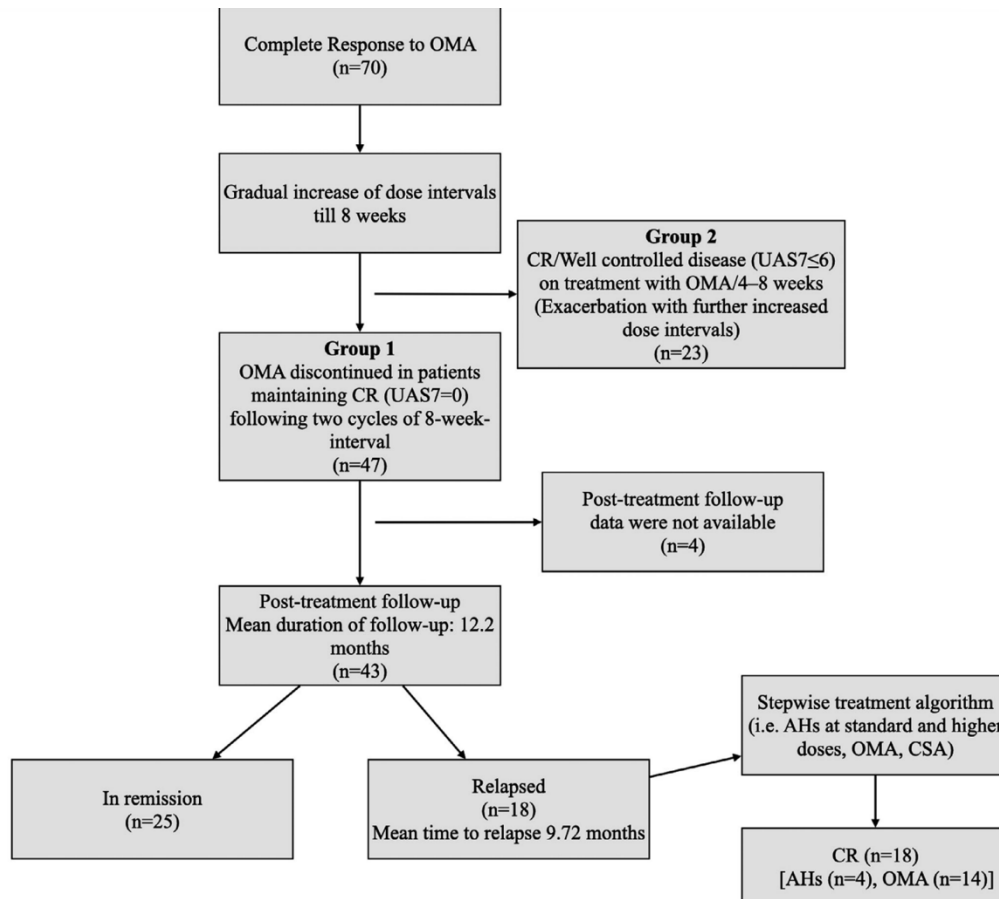
- Average duration of omalizumab treatment=3.3 years
- Predictors of longer treatment
 - Longer disease duration >2 years
 - Presence of CIndU

Extending dosing intervals have higher remission rates than fixed dosing

> Australas J Dermatol. 2021 Aug;62(3):398-402. doi: 10.1111/ajd.13656. Epub 2021 Jun 22.

Remission of chronic spontaneous urticaria following omalizumab with gradually extended dosing intervals: Real-life data

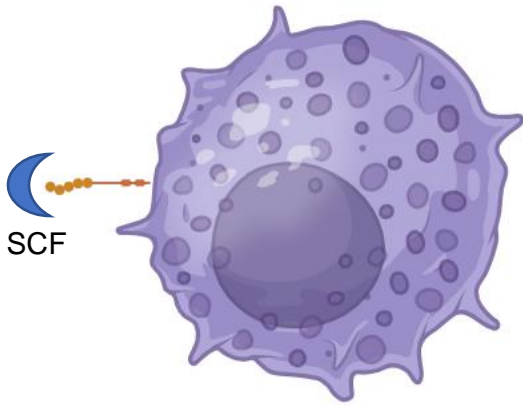
Andac Salman ¹, Meryem Aktas ¹, Ozlem Apti Sengun ¹



- with gradually **extending dosing intervals** following a complete response, **58.1% maintained remission for 14.9 months**
- studies with fixed dosing intervals has reported lower remission rates (39–39.8%)

Current treatment for CSU

Trigger avoidance



IgE type autoantibodies

Omalizumab: Binding IgE

%50-70

Omalizumab: downregulating FcER1

IgG type autoantibodies

Ciclosporine: inhibiting ab production

%50

Antihistamines

Histamine

IL-4
IL-13
IL-5

IL-31
IL-17
TNF

Ciclosporine: inhibiting T cell function

%40-100

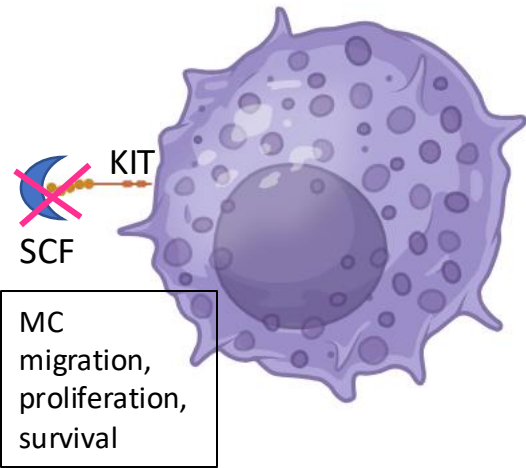
Created by Biorender

15-30% of CU patients will still need further treatment options



Drugs under clinical trials for CU

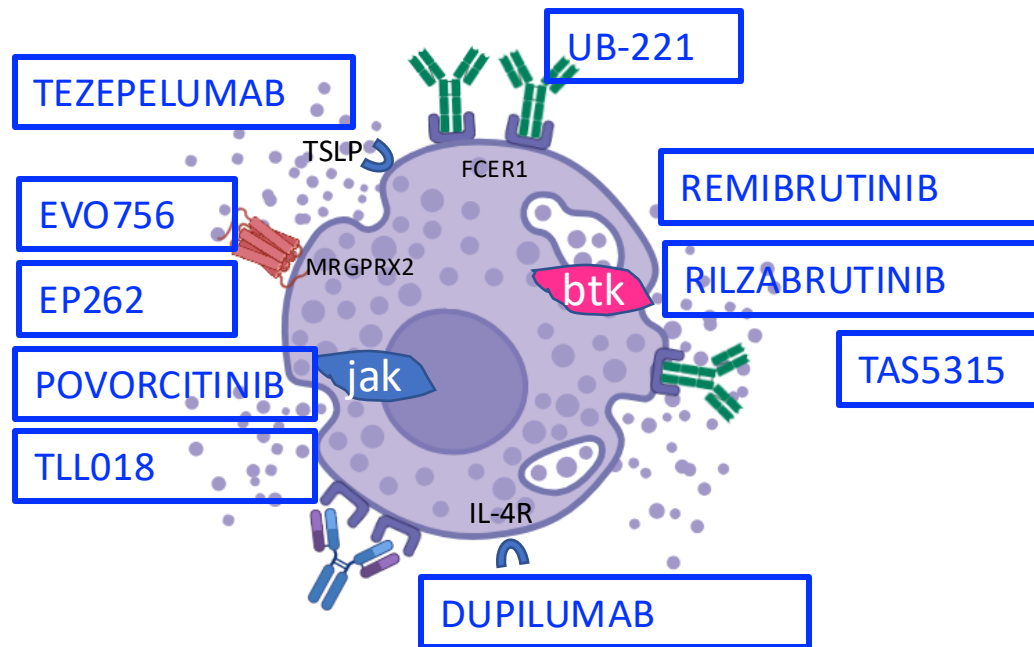
Mast cell depletion



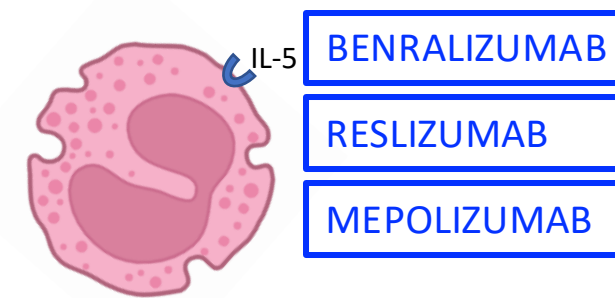
BARZOLVOLIMAB

BRIQUILIMAB

Antagonism of mast cell activation



Targeting recruiting cells

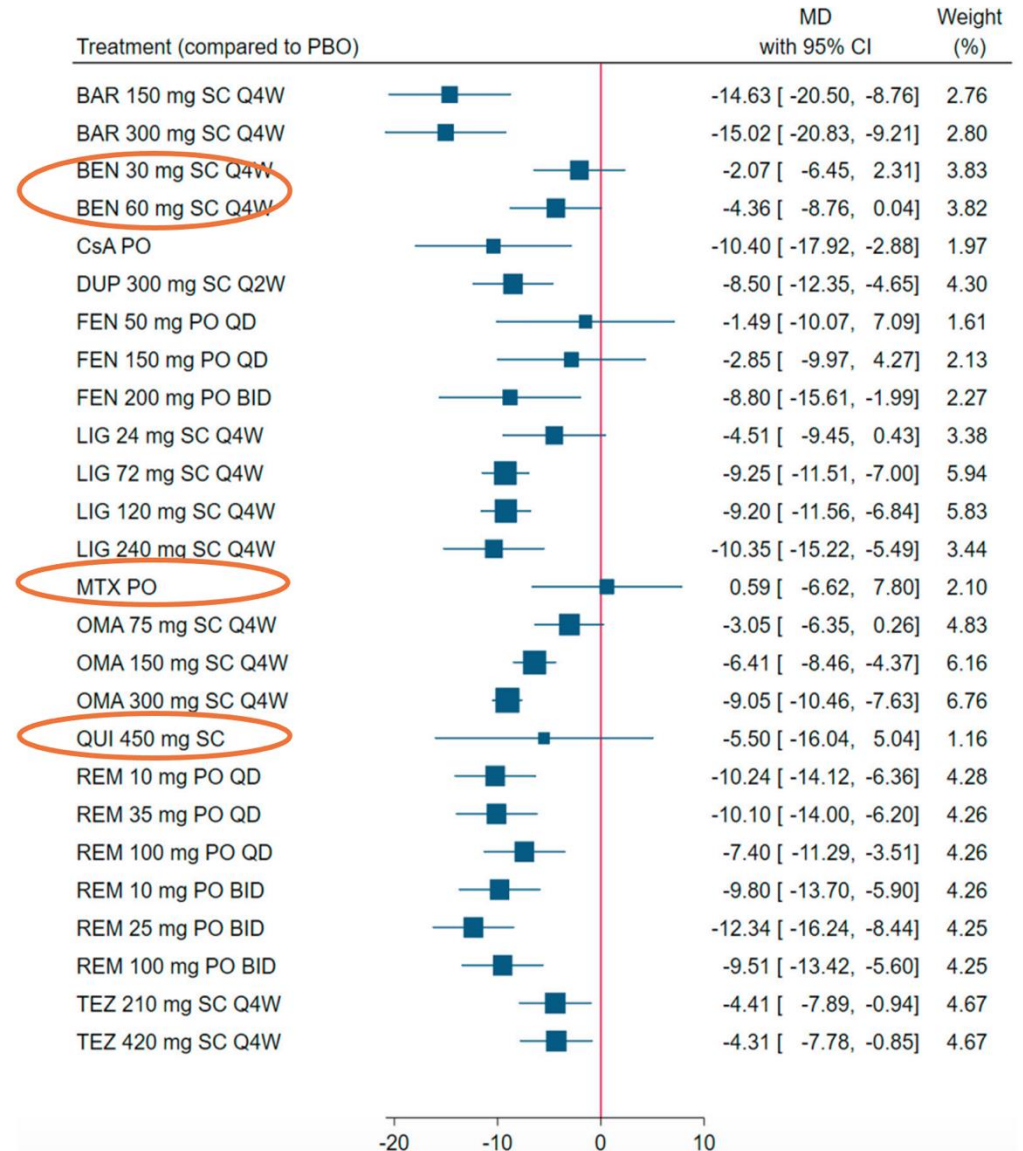


Created by Biorender

Evaluating the efficacy and safety of biologic and oral drugs for refractory chronic spontaneous urticaria: systematic review and network meta-analysis

Yaxuan Zheng¹, Min Luo¹, Jiahao Huang¹, Marcus Maurer², Huichun Su³

- **Efficacy:**
- **Barzolvolumab was the most effective** drug for UAS7/HSS7/ISS7
- **Remibrutinib** may be considered ranking **first** when choosing an **oral** agent
- **Efficacy and safety:**
- **Omalizumab, dupilumab, ligelizumab, remibrutinib, and fenebrutinib are superior** to barzolvolumab, methotrexate, hydroxychloroquine, cyclosporine, quilizumab, benralizumab, and placebo



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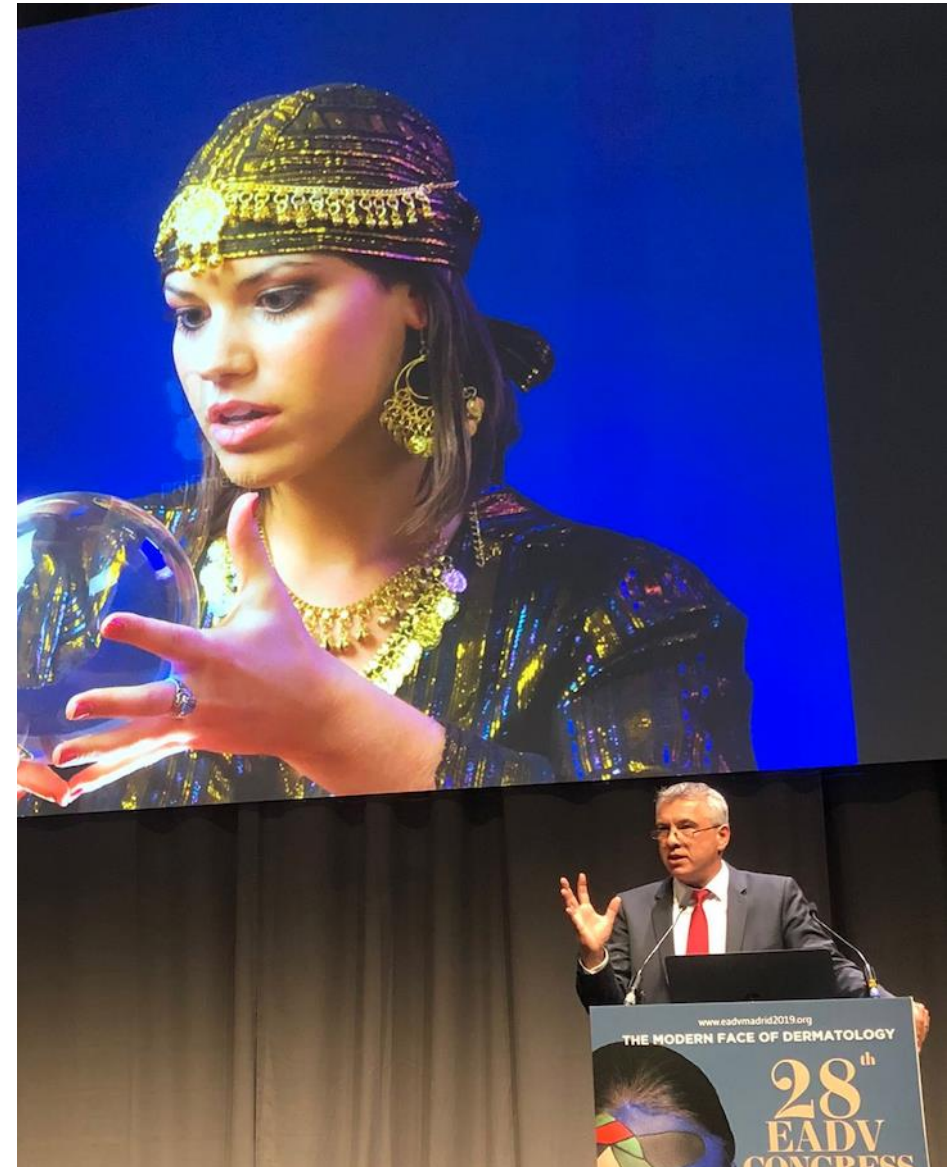
REVIEW ARTICLE



Disease modification in chronic spontaneous urticaria

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We need long remission of the
disease...



Patient-Centered Care and Quality of Life

Good communication skills and having enough time for the patients



4.5 UCARE Meetings/Conferences: 7th GA²LEN Global Urticaria Forum (GUF 2024)

Date: 4th and 5th December 2024

Langenbeck-Virchow-Haus, Lecture Hall
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>> UCARE GUIDELINE Consensus Meeting on 6th December

