TÜRKİYE
ULUSAL ALLERJİ
VE KLİNİK İMMÜNOLOJİ DERNEĞİ

BİZ BİZE KAMP

Kronik ürtiker hala poliklinikte en zor hasta mı?

Doç. Dr. Murat Türk

Kayseri Şehir Eğitim ve Araştırma Hastanesi

Erişkin İmmünoloji ve Allerji Hastalıkları Kliniği

Kronik Ürtiker

- Tekrarlayan ürtiker plakları ve/veya anjioödem ataklarının altı haftadan uzun sürmesi ile karakterize hastalıktır

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.

Chronic Urticaria Subtypes	
Chronic Spontaneous Urticaria (CSU)	**Inducible Urticaria**
Spontaneous appearance of wheals, angioedema, or both for >6 weeks due to known[a] or unknown causes.	Symptomatic dermographism[b] Cold urticaria[c] Delayed pressure urticaria[d] Solar urticaria Heat urticaria[e] Vibratory angioedema[f] Cholinergic urticaria Contact urticaria Aquagenic urticaria

Note: Chronic urticaria (CU) is classified as spontaneous (CSU) and inducible (CIndU). CSU comes as CSU with known cause and CSU with unknown cause. CIndU is further subclassified as symptomatic dermographism, cold urticaria, delayed pressure urticaria, solar urticaria, heat urticaria, and vibratory angioedema (collectively referred to as chronic physical urticaria), as well as cholinergic urticaria, contact urticaria, and aquagenic urticaria. CU patients can have more than one form of CU including more than one form of CIndU and they often do.

Table is based on expert consensus and achieved ≥90% agreement in the consensus conference.

[a]For example, type I autoimmunity (autoallergy) and type IIb autoimmunity, with mast cell–activating autoantibodies

[b]Formerly called *urticaria factitia* or dermographic urticaria.

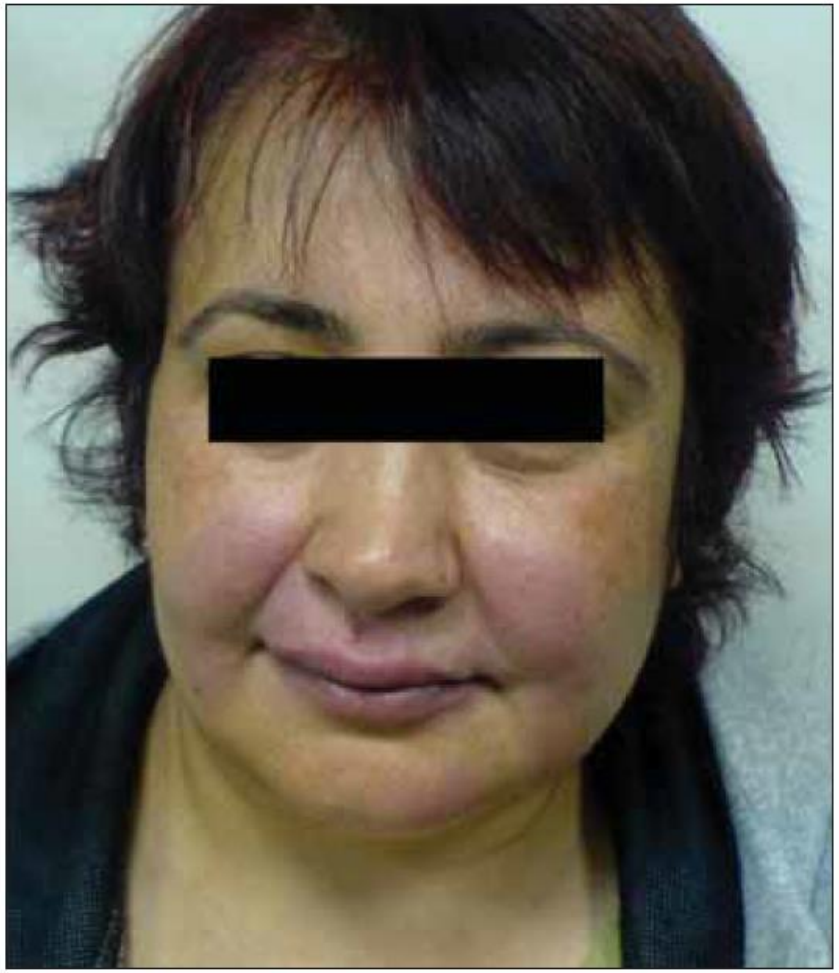
[c]Also called cold contact urticaria.

[d]Also called pressure urticaria.

[e]Also called heat contact urticaria.

[f]Also called Vibratory angioedema/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.



Metronidazol ve Diüretik ile Tedavi Edilen Atipik Yerleşimli Morbus Morbihan Olgusu

Tablo 1. Orofasyal Ödem Nedenleri (4-11)

Konjenital	**İnflamatuvar**
Fasyal hemihipertrofi	Anjioödem
İnfantil kortikal hiperostozis	Rozasea
Mc-Cune Albright sendromu	Akne vulgaris
Hurler sendromu	Melkersson-Rosenthal sendromu
Diğer depo hastalıkları	Sarkoidoz
Sturge-Weber sendromu	Chrohn hastalığı
Lenfanjiom, hemanjiom	Lupus eritematozus
MEN tip III	Pannikülit
	Skleroderma / morfea
	Ascher sendromu
Enfeksiyöz	**Diğer**
Rekürren erizipel	Miksödem
Trişinozis	Tiroid otoimmünitesi
Kronik herpes simpleks labialis	Superior vena kava sendromu
Lepra	Sistemik amiloidoz
Tüberküloz (lupus vulgaris)	Eozinofili ile birlikte fasiyal ödem
Gingivit ve dental enfeksiyonlar	
Malign	
Anjiosarkom	
Lenfoma	
Lenfosarkom	
Mikozis fungoides	
Lösemi (öz. KLL)	

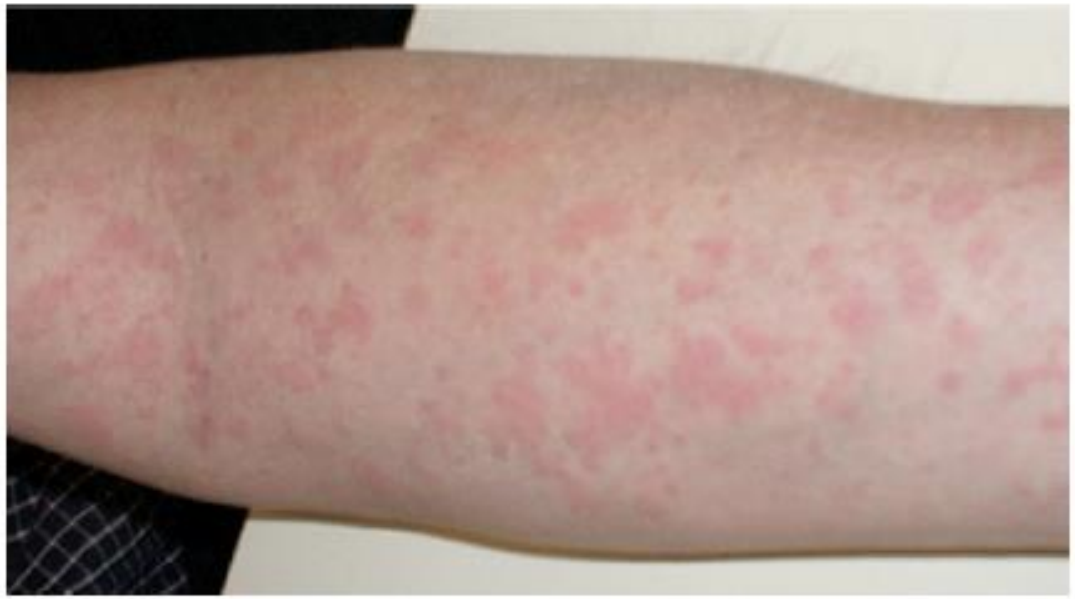


Figure 1 Urticarial rash on the lower arm of a Schnitzler syndrome patient.

TABLE 7 Differential diagnoses of urticaria

Maculopapular cutaneous mastocytosis (urticaria pigmentosa) and indolent systemic mastocytosis with involvement of the skin
Mast cell activation syndrome (MCAS)
Urticarial vasculitis
Bradykinin-mediated angioedema (eg, HAE)
Exercise-induced anaphylaxis
Cryopyrin-associated periodic syndromes (CAPS; urticarial rash, recurrent fever attacks, arthralgia or arthritis, eye inflammation, fatigue, and headaches), that is, Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS), or Neonatal Onset Multisystem Inflammatory Disease (NOMID).
Schnitzler's syndrome (recurrent urticarial rash and monoclonal gammopathy, recurrent fever attacks, bone and muscle pain, arthralgia or arthritis and lymphadenopathy)
Gleich's syndrome (episodic angioedema with eosinophilia)
Well's syndrome (granulomatous dermatitis with eosinophilia/ eosinophilic cellulitis)
Bullous pemphigoid (prebullous stage)
Adult-onset Still's disease (AOSD)

Note: These diseases and syndromes are related to urticaria 1) because they can present with wheals, angioedema, or both and/or 2) because of historical reasons. They are differential diagnoses of urticaria.

Tablo 1. Anjioödem türleri ve ayırıcı tanı (4*)

Anjioödem türleri
Histamin İlişkili - Alerji: Besin, ilaç, arı venomu - Spontan ve/veya idiyopatik ürtiker ve anjioödem
Bradikinin aracılı - C1-İNH HAÖ - Normal C1-İNH HAÖ - Edinilmiş C1 İNH eksikliği - Anjiyotensin dönüştürücü enzim inhibitörü (ACEİ) kullanımı
Lökotrien ilişkili - Non-steroid anti-inflamatuvar ilaç - Aspirin
Anjioödemin ayırıcı tanısında düşünülmesi gereken hastalıklar
Otoimmün hastalıklar Tiroid hastalıkları Hidrostatik ödem Gleich sendromu (Eozinofilinin eşlik ettiği epizodik anjioödem) Clarkson sendromu (Kapiller kaçış sendromu) Protein eksikliği Akut kontakt dermatit DRESS Sendromu (İlaçla ilişkili döküntü, eozinofili ve sistemik semptomlar) Dermatomiyozit Vena kava superior sendromu Morbus Morbihan (Rozaseaya bağlı kronik lenfödem) Hipokomplementemik ürtikeryal vaskülit Orofasiyal granülomatozis Subkutanöz amfizem İdiyopatik ödem

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.
Türkiye Ulusal Alerji ve Klinik İmmünoloji Derneği, Herediter Anjioödem Tanı ve Tedavi Ulusal Rehberi 2022.

Variable	Outline of purported mechanism
Autoimmunity	Female predominance is evident in both systemic and organ-specific autoimmunities and CSU. The positive autologous serum skin test is frequently associated with underlying autoimmunity and altered T cell subsets. Autoreactive IgE and IgG antibodies are common in CSU, and removal of former with anti-IgE therapy suggests direct ability of IgE autoantibodies to activate mast cells.
Pseudoallergens	The mast cell Mas-related G protein–coupled receptor X2 may be directly stimulated by the low molecular weight colourings, preservatives and additives or they lower the threshold for other factors to fully activate the mast cells to release CSU mediators. In predisposed people, salicylates and non-steroidal anti-inflammatory drugs increase overall leukotriene activity by COX-1 inhibition leading to mast cell activation and further CSU activity.
Stress	Stress induces the release of several neuropeptides that can activate mast cells via Mas-related G protein–coupled receptor X2. Stress can also impair T regs function leading to dysregulated T and B cell control with increased tendency to autoimmunity and inflammation.
Infection	Parasites excite humoral autoimmunity especially a polyclonal IgE which may have autoreactive components. Gut infection may also increase epithelial permeability allowing the entry of bacterial components and low molecular weight pseudoallergens.
Atopy	Much of work here is in children but anything which stimulates the immune system worsens CSU. Atopic patients also have raised IgE levels and a proportion of these may be autoreactive.
Iron deficiency	How iron deficiency worsens CSU is unclear, but iron supplementation can be helpful in some such patients.
Hormonal variation	CSU described to be worse with uncontrolled thyroid dysfunction and pre-menstrually in women. In both cases, appropriate hormonal treatment can be helpful. Unclear whether increased stress mediates the worsening of CSU in these conditions.
Dysbiosis of gastrointestinal tract	Altered populations of several types of stool bacteria are evident CSU. These alterations may promote increased gut epithelial permeability and absorption of immune stimulating compounds as well as affecting gastrointestinal tolerance mechanisms.
Vitamin D3	Reduced serum levels evident in CSU. Vitamin D3 reduces Th1 and Th17 cells and increases T regulatory cell function that can diminish autoimmunity and lower inflammation.

değildir

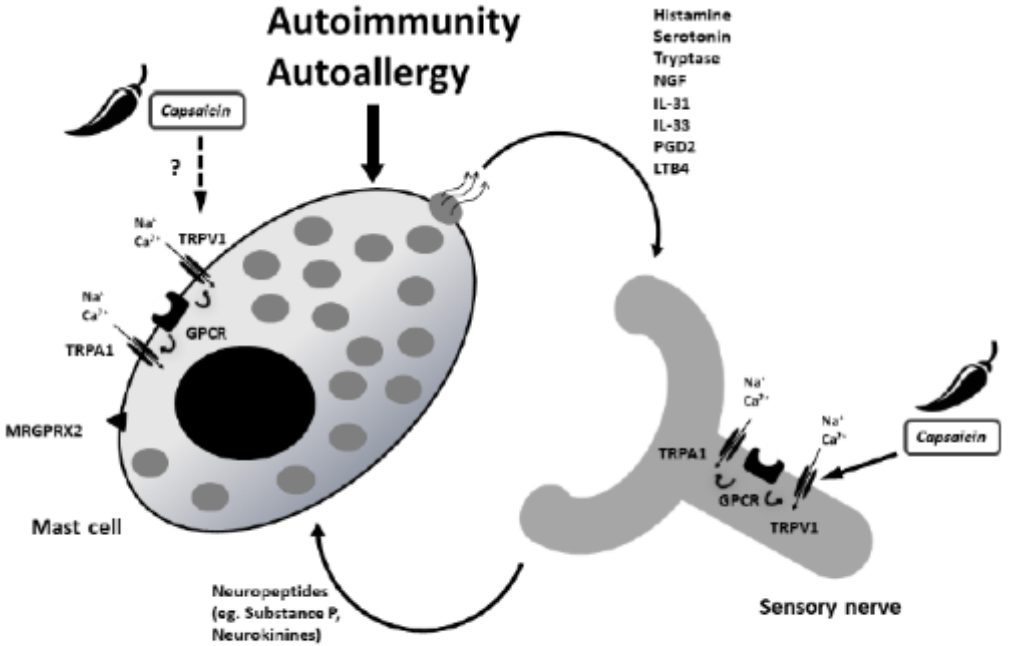
Bansal RA et al. Curr Treat Options Allergy 2020

Worsening of chronic spontaneous urticaria after intake of hot pepper

Murat Türk,[1] İnsu Yılmaz,[1] Tomasz Hawro,[2] Marcus Maurer[2]

Table 1. Patient characteristics

	Overall	With worsening of urticaria after intake of hot pepper	Without worsening of urticaria after intake of hot pepper	p
Patients; n (%)	85	39 (46)	46 (54)	
Age; years ± SD	39.1 ± 11.9	40 ± 13.2	38.4 ± 10.7	0.54
Female gender (%)	62 (73)	31 (80)	31 (67)	0.23
Co-existing diseases (%)				0.34
Atopic	4 (5)	3 (8)	1 (2)	
Autoimmune	6 (7)	4 (10)	2 (4)	
Duration of urticaria; years (IQR)	2 (1-5)	2 (0.95-5)	2.5 (1-5)	0.5
Treatment for CSU (%)	73 (89)	31 (84)	42 (93)	0.17
St-sgAH	31 (38)	17 (46)	14 (31)	0.18
Hi-sgAH	18 (22)	9 (24)	9 (20)	0.79
Omalizumab	24 (29)	5 (14)	19 (42)	0.007
Disease control status at the time of study (%)				0.81
Controlled	55 (67)	24 (65)	31 (69)	
Uncontrolled	27 (33)	13 (35)	14 (31)	

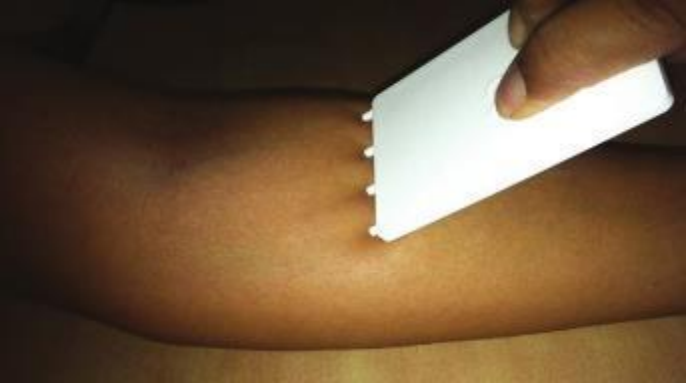


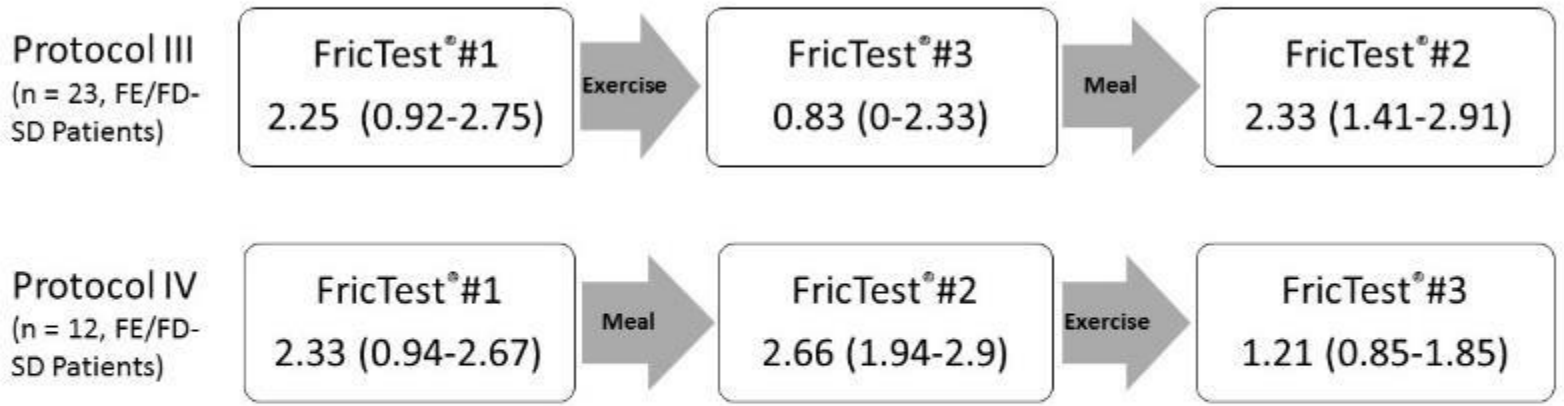
Ligand	Histamine	Bradykinin	LTB-4	IL-31	Serotonin	Substace P
Receptor	H1R, H4R	B2R, MRGPRX2	LTB-4 receptor-2	IL-31RA	5-HT2	MRGPRX2
Channel	TRPV1	TRPV1, ?	TRPV1	TRPV1	TRPA1	?

Türk et al. Worsening of chronic spontaneous urticaria after intake of hot pepper. APJAI 2021.

Tetikleyiciler

- Hastalığın altta yatan nedeni ile ilişkili değildir
- Mast hücreleri doğrudan uyararak ya da uyarılabilirlik potansiyelini düşürerek etki edebilir
- Kontrollü provokasyonlarda her seferinde benzer etki sağlanamayabilir





Ertaş et al. Yayınlanmamış veri.

Kronik Ürtiker

- Her yaş grubunda görülebilir, pik insidans 20-40 yaş
- Hastaların büyük kısmında 1 yıldan uzun sürmekte

Maurer M, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA²LEN task force report. Allergy. 2011 Mar;66(3):317-30.

Prevalans

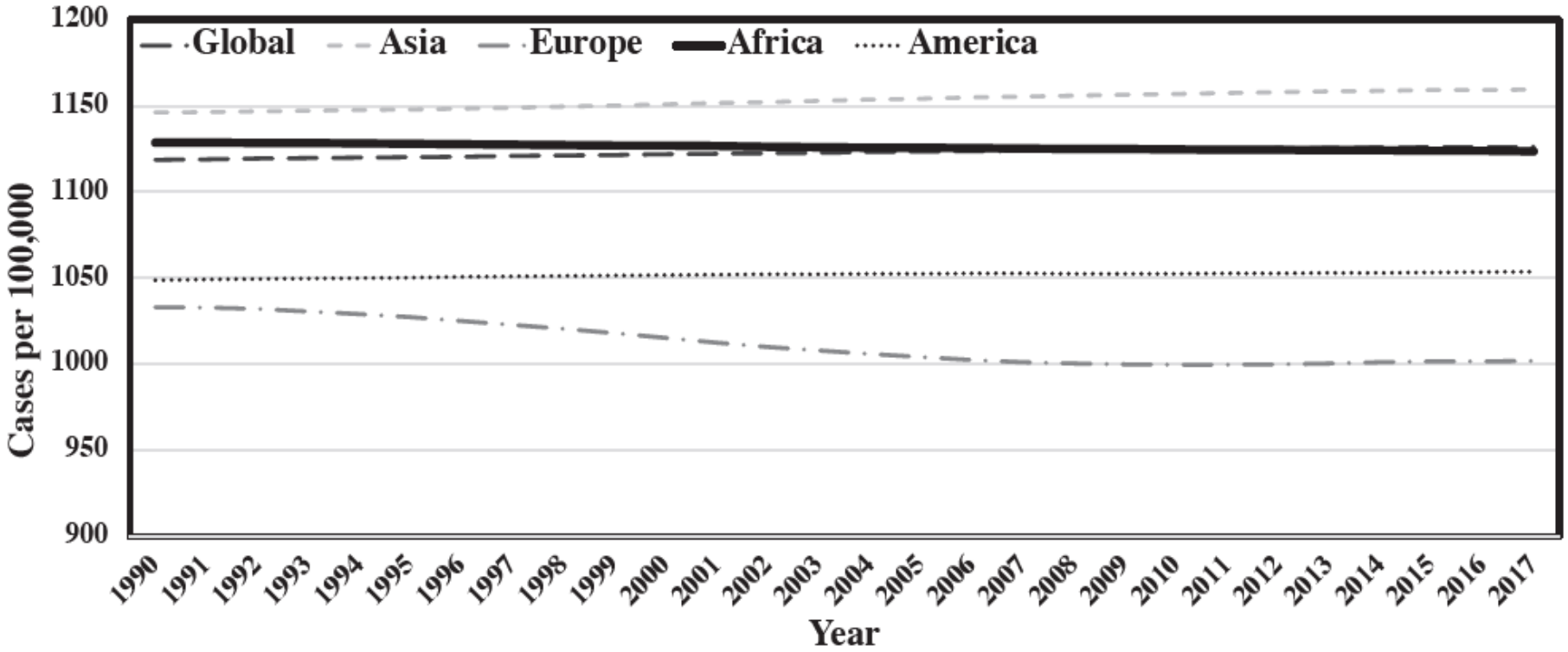


Fig. 3. Trends in prevalence of urticaria from 1990 to 2017.

Peck G, et al. Global Epidemiology of Urticaria: Increasing Burden among Children, Females and Low-income Regions. Acta Derm Venereol. 2021 Apr 22;101(4):adv00433.

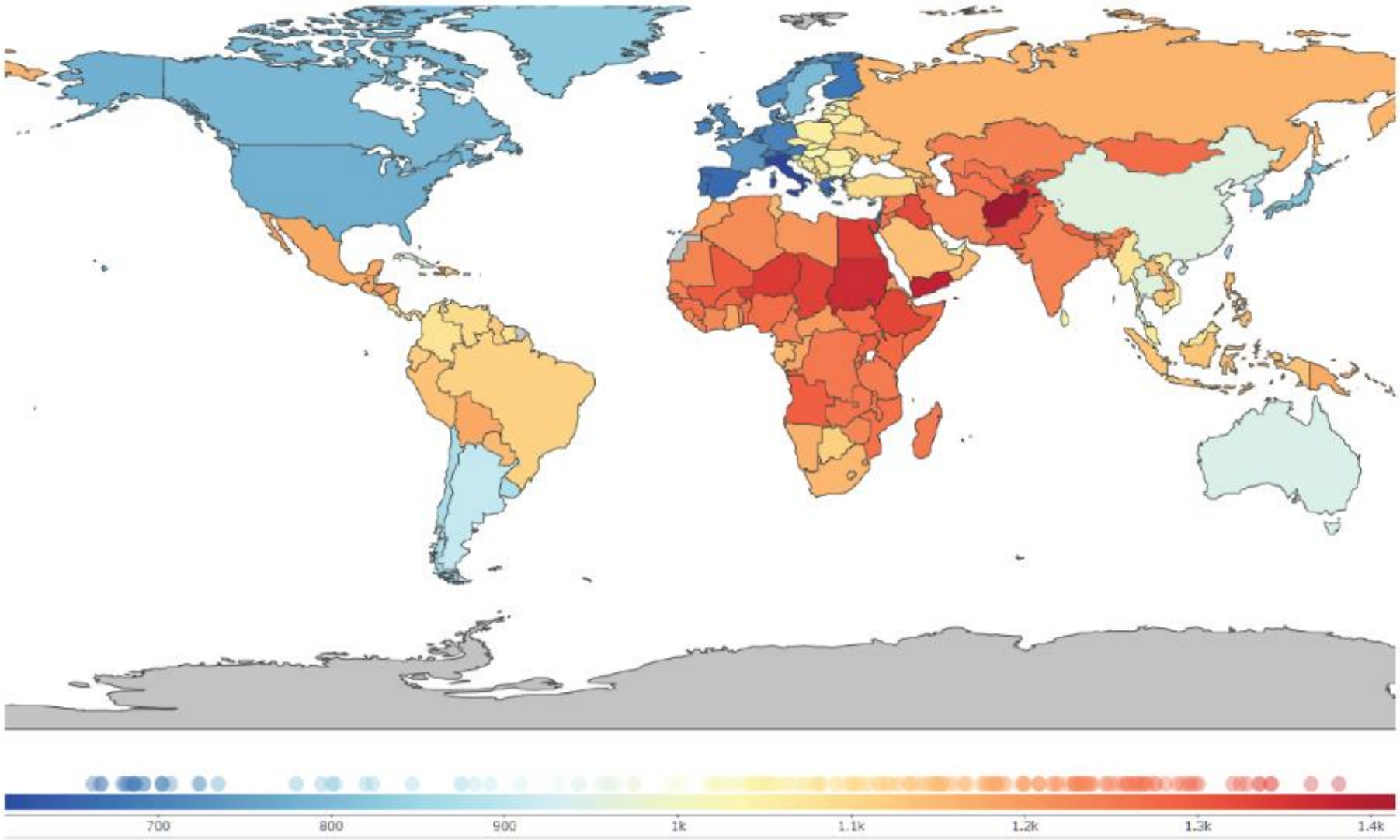
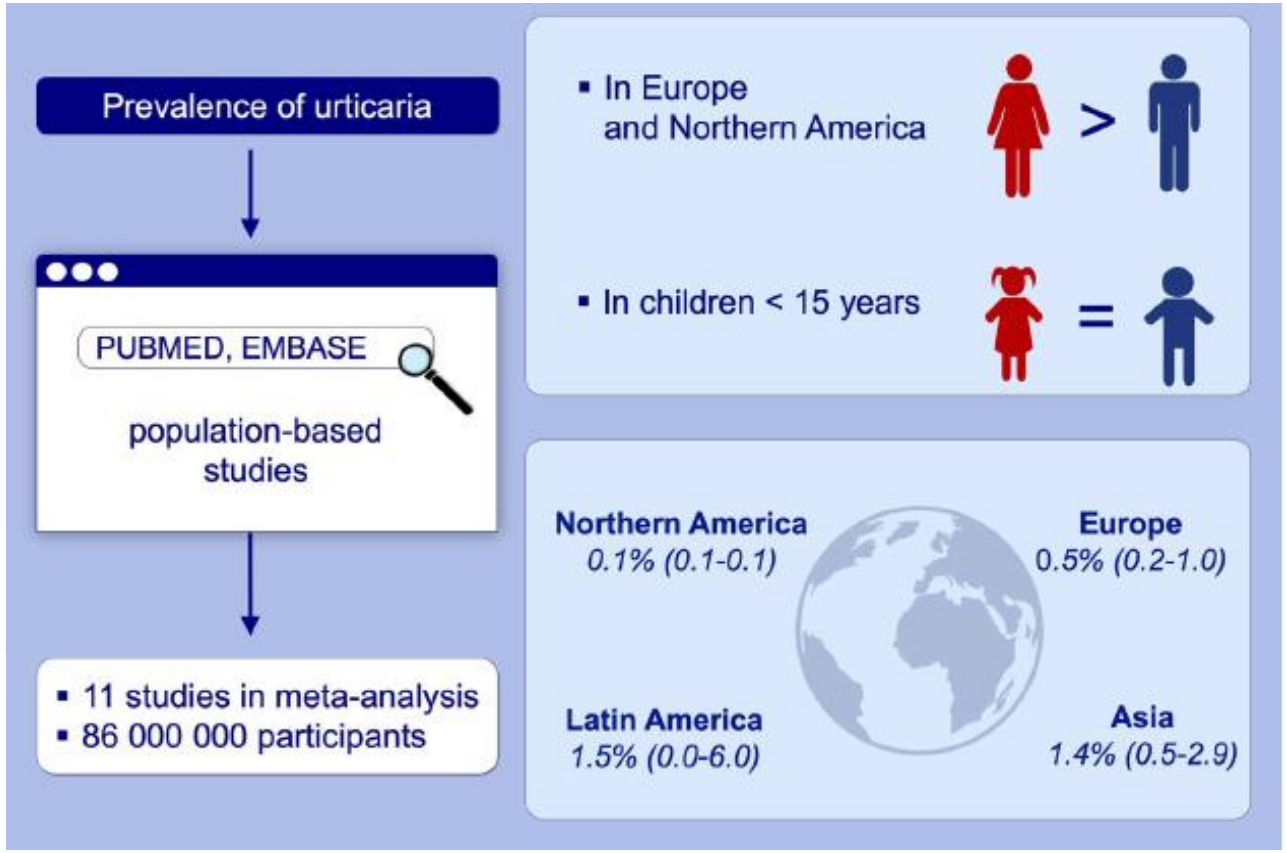


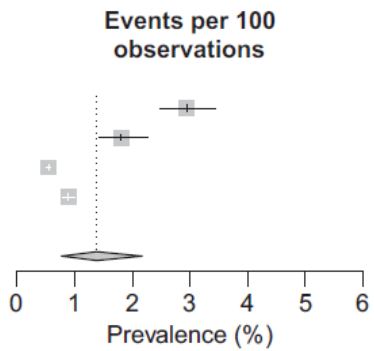
Fig. 2. Global distribution of urticaria. Prevalence of urticaria per 100,000 population in 2017. *Source:* Global Burden of Disease, Institute of Health Metrics and Evaluation (IHME), University of Washington. https://vizhub.healthdata.org/gbd-compare/.

Peck G, et al. Global Epidemiology of Urticaria: Increasing Burden among Children, Females and Low-income Regions. Acta Derm Venereol. 2021 Apr 22;101(4):adv00433.



Study	Cases	Total	Prevalence (%)	95% CI	Weight
Gaig 2004 (>17 y)	147	5003	2.9	[2.5; 3.4]	24.5%
Zuberbier 2010 (80% >19 y)	74	4093	1.8	[1.4; 2.3]	24.2%
Vietri 2015 (>17 y)	1079	197 463	0.5	[0.5; 0.6]	25.8%
Balp 2017 (>17 y)	320	36 000	0.9	[0.8; 1.0]	25.6%
Random effects model		**242 559**	**1.4**	**[0.8; 2.2]**	**100.0%**

Heterogeneity: I^2 = 99%, τ^2 = 0.0009, P < .01



Peck G, et al. Global Epidemiology of Urticaria: Increasing Burden among Children, Females and Low-income Regions. Acta Derm Venereol. 2021 Apr 22;101(4):adv00433.
Fricke J et al. Prevalence of chronic urticaria in children and adults across the globe: Systematic review with meta-analysis. Allergy. 2020 Feb;75(2):423-432.

LETTER

Prevalence and risk factors of chronic urticaria in China: A nationwide cross-sectional study

Xiao Zhang, Xiaoting Song, Mei Zhang, Chun Li, Zhengjing Huang, Bo Liu, Miao Yu, Shuanglu Liao, Tingting Luan, Torsten Zuberbier, Marcus Maurer, Zuotao Zhao ✉, Limin Wang ✉

First published: 24 March 2022 | https://doi.org/10.1111/all.15287

- China Chronic Diseases and Risk Factors Surveillance
- 184.326 katılımcı
- Kronik ürtiker tahmini prevalansı %2.6

Table S1 Characteristics of Chinese adult participants, 2018-2019

	Overall	Prevalence of chronic urticaria
Total	184326	2.6 (2.4, 2.8)
Age (years)		
18-29	9915 (5.4)	2.1 (1.5, 2.7)
30-39	18470 (10.0)	1.9 (1.6, 2.1)
40-49	33374 (18.1)	2.6 (2.4, 2.9)
50-59	48209 (26.2)	3.1 (2.9, 3.4)
60-69	49835 (27.0)	3.7 (3.4, 4.0)
70+	24523 (13.3)	3.5 (3.0, 4.0)
Sex		
Men	81828 (44.4)	2.3 (2.0, 2.6)
Women	102498 (55.6)	2.9 (2.6, 3.1)
Residence		
Urban	75117 (40.8)	2.3 (2.0, 2.6)
Rural	109209 (59.2)	2.9 (2.6, 3.2)
Latitude (degree)		
18.3-29.9	65099 (35.3)	2.3 (1.8, 2.7)
30.0-39.9	88430 (48.0)	2.6 (2.3, 3.0)
40.0-49.3	30797 (16.7)	3.1 (2.7, 3.6)
Education		
Less than high school	147399 (80.0)	2.9 (2.6, 3.2)
High school	23989 (13.0)	2.2 (1.8, 2.5)
College or above	12938 (7.0)	1.8 (1.4, 2.2)
Cigarette Smoking		
Never	127752 (69.3)	2.6 (2.4, 2.9)
Ever	56574 (30.7)	2.5 (2.1, 2.8)
Excessive alcohol drinking		
No	168172 (91.2)	2.6 (2.3, 2.8)
Yes	16137 (8.8)	2.7 (2.3, 3.1)
Physical inactivity		
No	27835 (15.1)	2.9 (2.4, 3.4)
Yes	156474 (84.9)	2.5 (2.3, 2.8)
Sleep duration (hours)		
<5	8372 (4.5)	5.2 (4.3, 6.0)
5-6.9	41225 (22.4)	3.4 (2.9, 3.9)
7-10	130168 (70.6)	2.2 (2.0, 2.5)
>10	4560 (2.5)	5.0 (2.2, 7.7)
Family size		
<4	112961 (61.3)	2.8 (2.5, 3.1)
≥4	71365 (38.7)	2.3 (2.0, 2.6)
Annual household income per capita (CNY)		
<7000	47322 (25.7)	3.5 (3.0, 4.1)
7000-17499	46824 (25.4)	2.4 (2.0, 2.8)
≥17500	47479 (25.7)	2.4 (2.1, 2.6)
Don't know/refuse to answer	42701 (23.2)	2.2 (1.8, 2.5)
Household fuel use		
No	119827 (66.1)	2.4 (2.1, 2.7)
Yes	61353 (33.9)	3.2 (2.8, 3.5)
BMI (kg/m^2)		
<24	83464 (46.6)	2.5 (2.2, 2.9)
≥24	95537 (53.4)	2.7 (2.5, 2.9)
Abdominal obesity		
No	107710 (60.1)	2.5 (2.3, 2.8)
Yes	71436 (39.9)	2.8 (2.5, 3.0)
Diabetes		
No	144244 (82.8)	2.5 (2.3, 2.7)
Yes	29997 (17.2)	3.4 (3.0, 3.8)
Dyslipidemia		
No	104921 (58.7)	2.5 (2.2, 2.7)
Yes	73895 (41.3)	2.8 (2.5, 3.2)
Cardiovascular disease		
No	172710 (93.7)	2.5 (2.3, 2.7)
Yes	11598 (6.3)	5.2 (4.5, 5.9)
Atopy		
No	176034 (95.5)	2.3 (2.1, 2.5)
Yes	8292 (4.5)	8.1 (7.2, 9.0)

Zhang X,et al. Prevalence and risk factors of chronic urticaria in China: A nationwide cross-sectional study

KRONİK ÜRTİKER Hastalık Yükü

- Ağrı
- Uyku bozukluğu
- Yorgunluk
- Psikolojik etkiler
- Anksiyete
- Depresyon
- Cinsel işlev bozukluğu
- İş gücü kaybı

Original Article

Sexual Functioning Is Frequently and Markedly Impaired in Female Patients with Chronic Spontaneous Urticaria

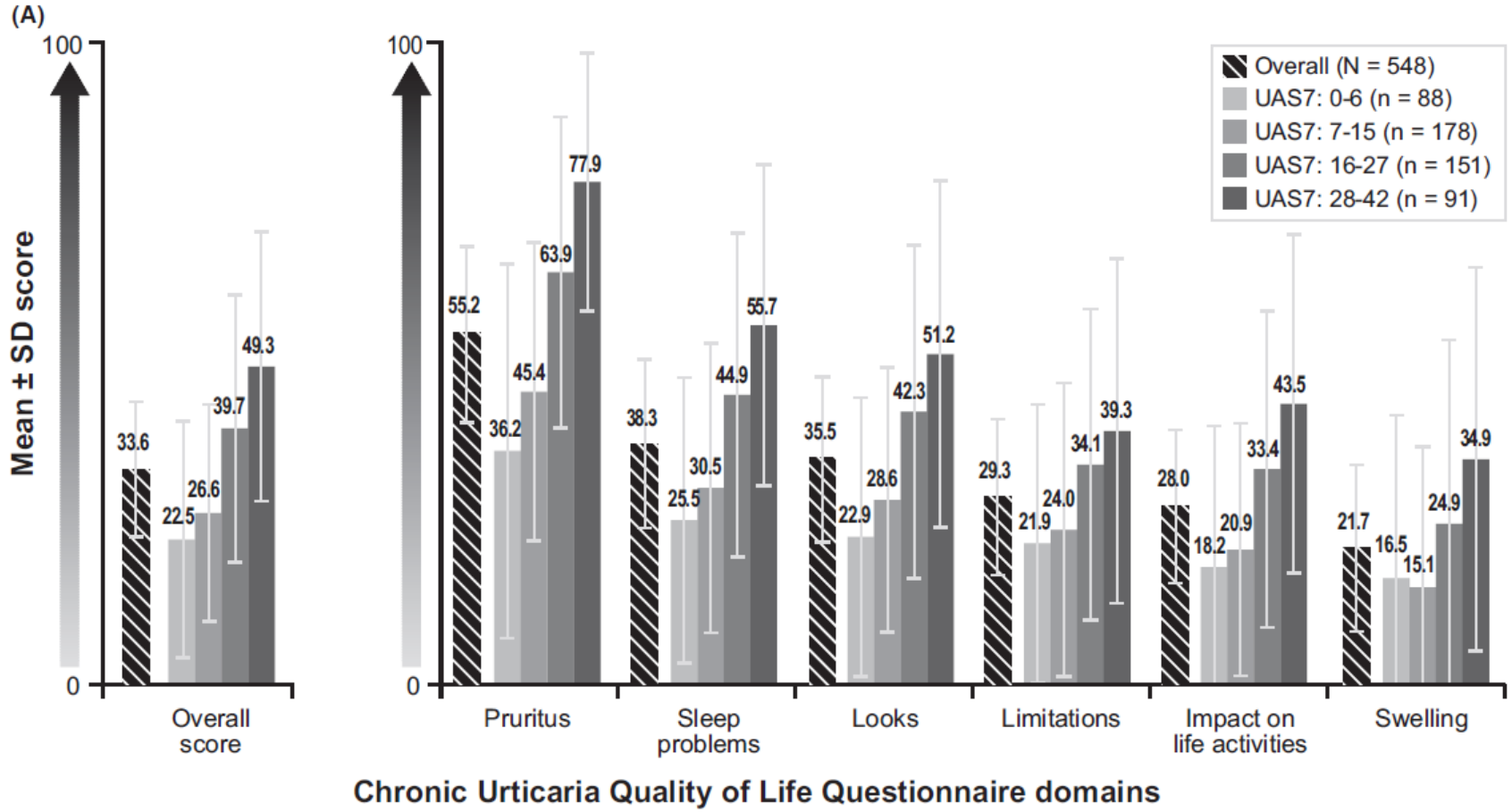
Ragıp Ertaş, MD[a], Kemal Erol, MD[b], Tomasz Hawro, MD[c], Halim Yılmaz, MD[d], and Marcus Maurer, MD[c] *Kayseri and Konya, Turkey; and Berlin, Germany*

Original Article

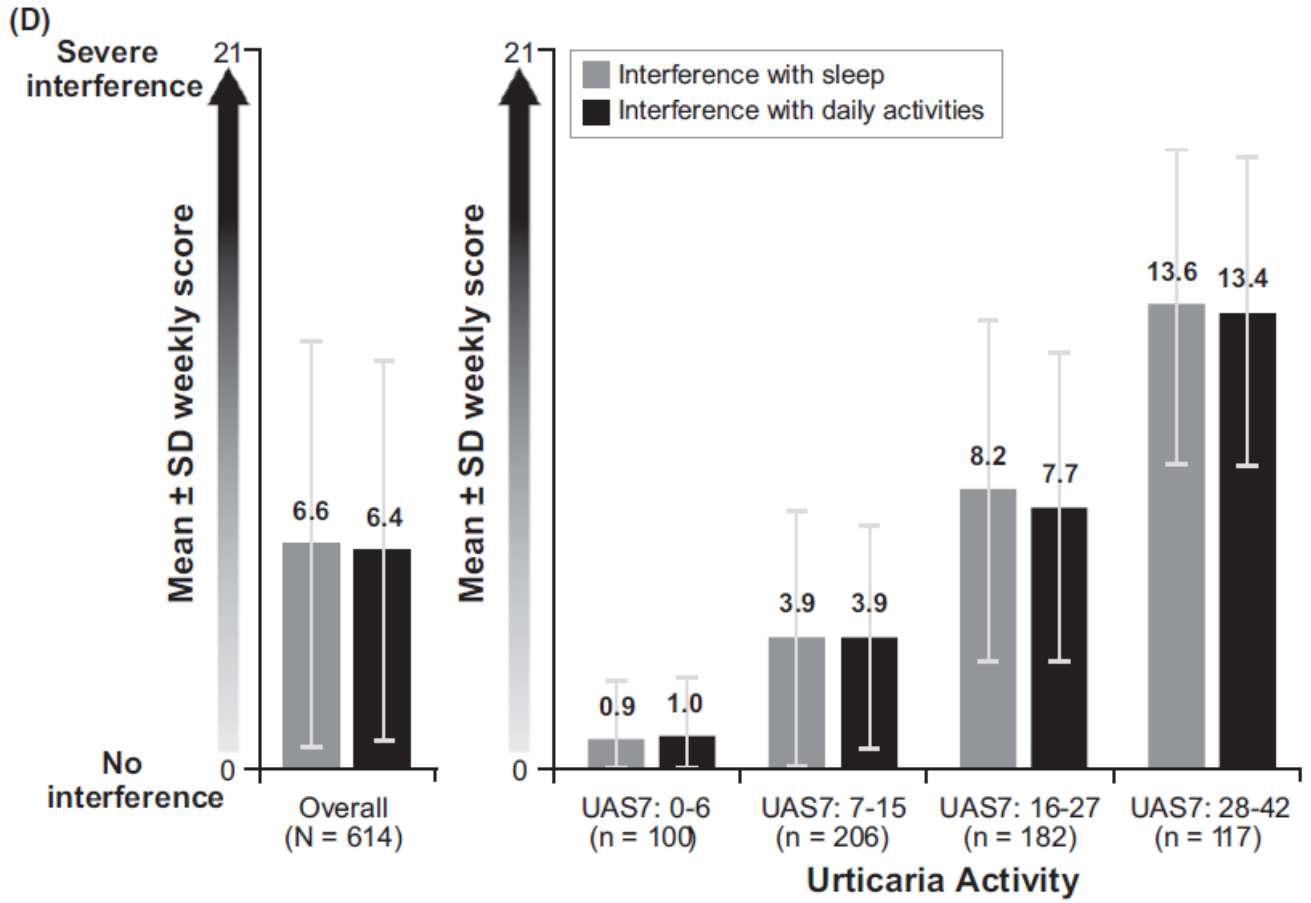
Fatigue Is Common and Predicted by Female Gender and Sleep Disturbance in Patients with Chronic Spontaneous Urticaria

Kemal Erol, MD[a], Şule Ketenci Ertaş, MD[a], and Ragıp Ertaş, MD[b] *Kayseri, Turkey*

The Frequency of Chronic Widespread Pain and Its Impact on Quality of Life in Patients with Chronic Spontaneous Urticaria



Maurer M, et al. The burden of chronic spontaneous urticaria is substantial: Real-world evidence from ASSURE-CSU. Allergy. 2017 Dec;72(12):2005-2016.



Maurer M, et al. The burden of chronic spontaneous urticaria is substantial: Real-world evidence from ASSURE-CSU. Allergy. 2017 Dec;72(12):2005-2016.

ÜRTİKER- Hastalık Yükü

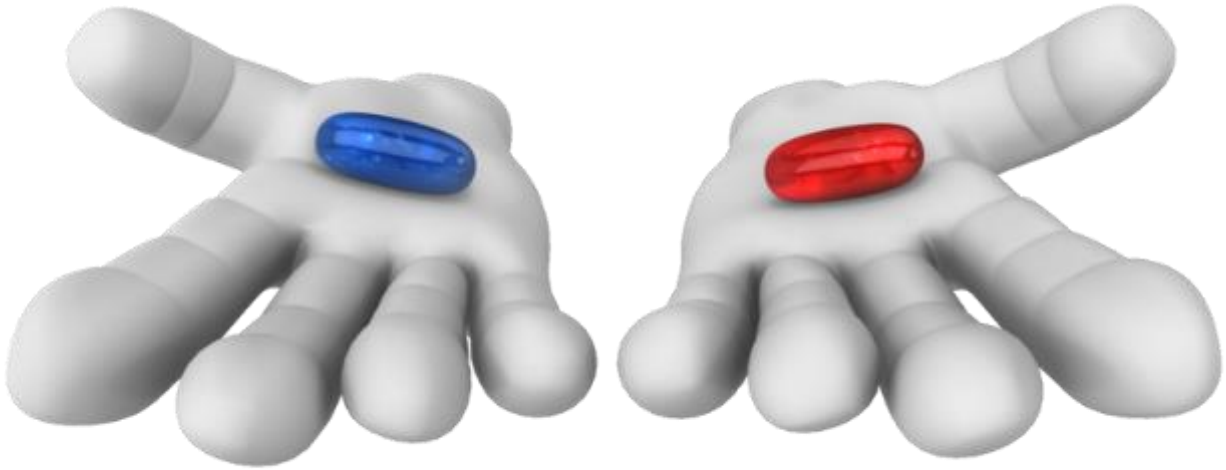
Çalışmalar KSÜ'nün yaşam kalitesine etkisinin

- Psoriasis, atopik egzema, bazal hücreli karsinom ve lepra gibi diğer dermatolojik hastalıklardan daha fazla olduğunu

- Bypass cerrahisi ihtiyacı olan koroner arter hastalarındakine benzer olduğunu göstermektedir

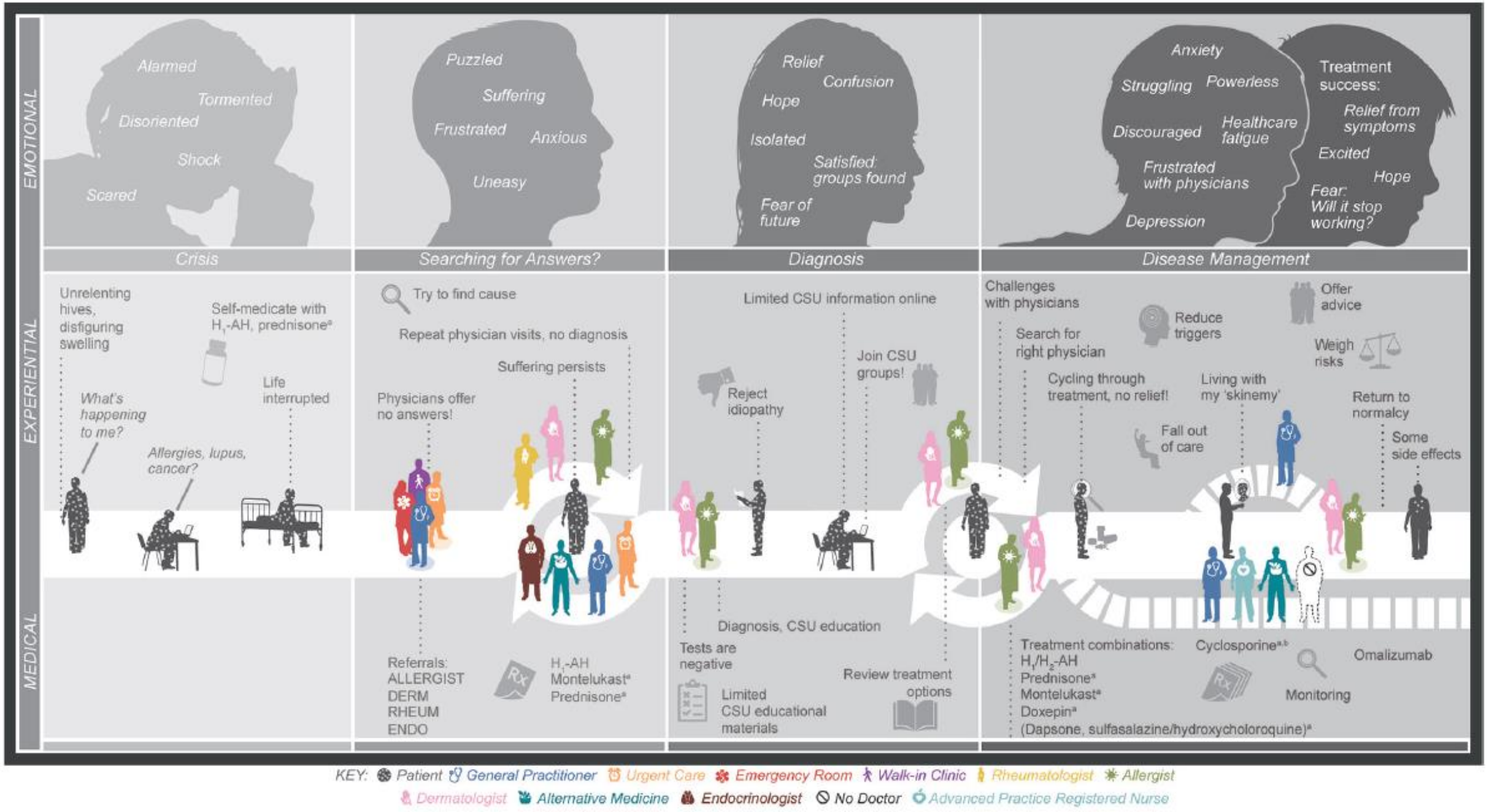
Silvares MRC, et al. Rev Assoc Med Bras 2011;57:577−82.
O'Donnell BF, et al. Br J Dermatol 1997;136:197–201.

Kronik ürtiker hala poliklinikte en zor hasta mı?



You take the blue pill, the story ends, you wake up in your bed and believe whatever you want to believe

You take the red pill, you stay in Wonderland, and I show you how deep the rabbit hole goes



Goldstein S, et al. Perspectives on Living with Chronic Spontaneous Urticaria: From Onset through Diagnosis and Disease Management in the US. Acta Derm Venereol. 2019 Nov 1;99(12):1091-1098.

Table I. Key themes associated with living with chronic spontaneous urticaria

Themes	Patients' perspectives
"What the heck is going on?"	I had swelling around my eyes. I couldn't go to work that day. I called my boss and sent him a picture of my face. I said, "I'm not feeling well. I can't go out."
	I thought that I was allergic to something – drinking, something in the air. I couldn't think of anything. I was wracking my brain.
	I had done all that research, and everything kept pointing to all these autoimmune disorders, like lupus, rheumatoid arthritis and Sjogren's. I thought, oh my God, I have some, like, fatal disease that eventually is going to kill me.
"Living with my 'skinemy'"	You feel very helpless. You don't feel like anybody understands what you're feeling. You feel like you're going mad/crazy.
	I remember one of my co-workers telling me to get away from her, because she thought I was going to give her something. She said, "Don't touch me! I don't want what you have." I said, "You can't catch this." She replied, "Well, I don't know what you have, and I don't want you anywhere [near me]. I don't want you to touch me because that looks really bad."
	I feel like I am a burden to my family. Even though they see what I go through on a daily basis, they really just don't get it. [My husband] thinks that it is all in my head.
Relief and confusion at diagnosis	I didn't go to the doctor until after it had been happening for probably 5 or 6 days, and then I went to my general primary care physician and got bloodwork done from there. And she was baffled. She's never seen anything like this before and she was so confused, which didn't make me feel comfortable.
	The general practitioner said, "Well, I would say you probably need to go and see an allergist. It's probably something you're eating and you're not even realizing, like a gluten allergy or things like that."
	I don't like the word idiopathic. It means that they're not sure what the cause is, and they're not sure how to help you. To me, there's got to be a cause.
"My own personal hell"	There's no relief in sight. It takes you into a very dark place because there's no escape from it and it feels like it's never going to end. It's like your body is torturing you.
	There were many days where I would just stay in bed because I was very uncomfortable. It's very hard to get housework done when you have hives and they're itching and they're really flaring up.
	It's kind of akin to having the 'flu. You feel really awful and you just want to be left the hell alone in those terms, but along with feeling sick, you're itching and you're burning and you're stinging.
"I feel like an experiment"	I often had to educate my doctors on the condition because many did not understand it. I finally started printing out information about chronic idiopathic urticaria and handing it over to them because some just didn't take me seriously. Maybe they would take an article from a peer-reviewed medical journal seriously?
	I have been to one doctor after another since developing chronic idiopathic urticaria. Most doctors will not listen to what I have to say.
	I had a nurse once who reacted very intensely to how I looked. She kept saying, "I can't believe you look like that." It was humiliating. Some bedside manner.
	I wanted somebody to pretend like they were trying to figure it out. I wanted a doctor to be really interested in what was going on, instead of labeling me.
	There was one drug that worked super great [*sic*] but it then stopped working. The symptoms came back. We tried to increase the dose and it didn't work. Your hives figure out what you're trying to do. My body had adapted.

Goldstein S, et al. Perspectives on Living with Chronic Spontaneous Urticaria: From Onset through Diagnosis and Disease Management in the US. Acta Derm Venereol. 2019 Nov 1;99(12):1091-1098.

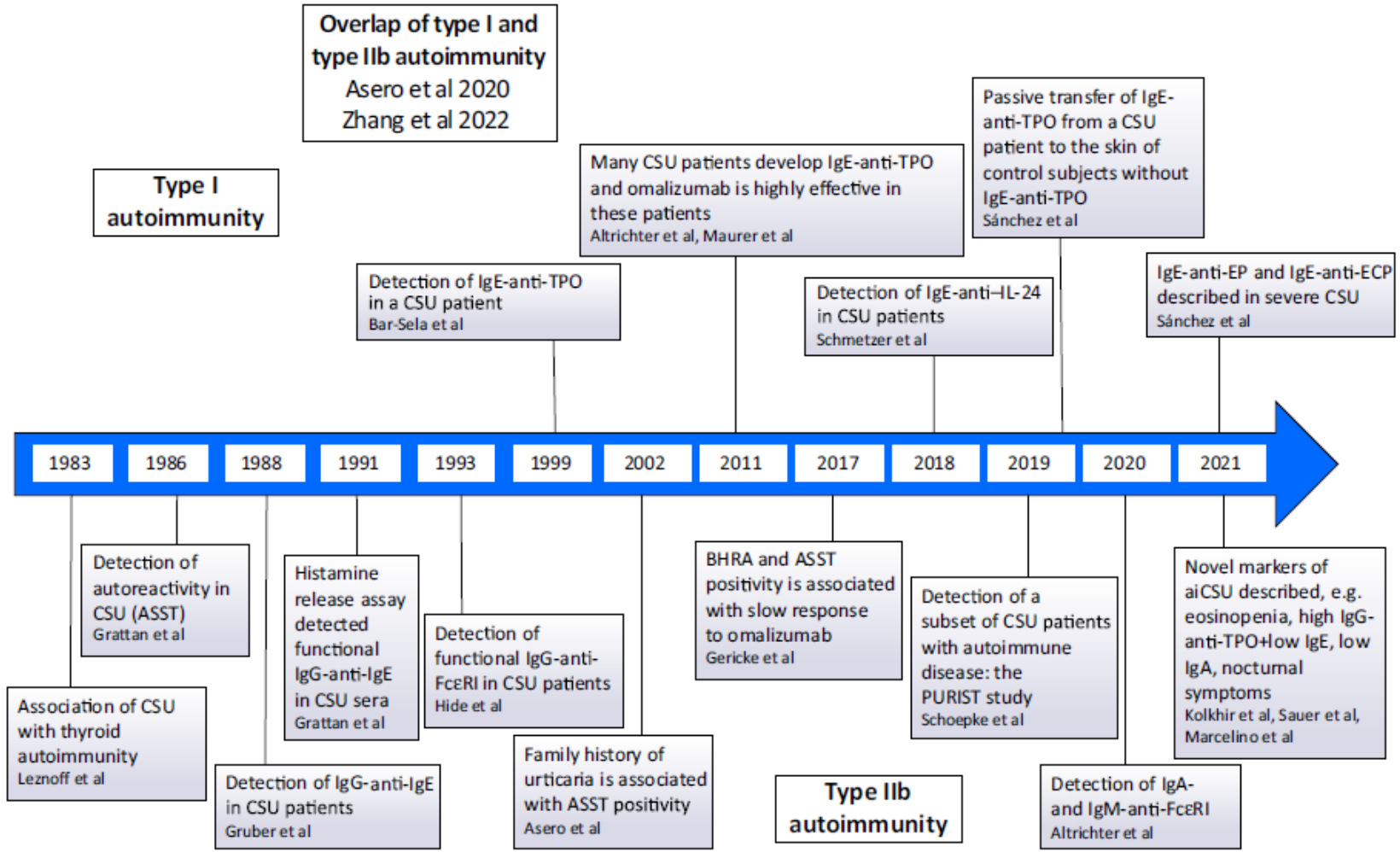
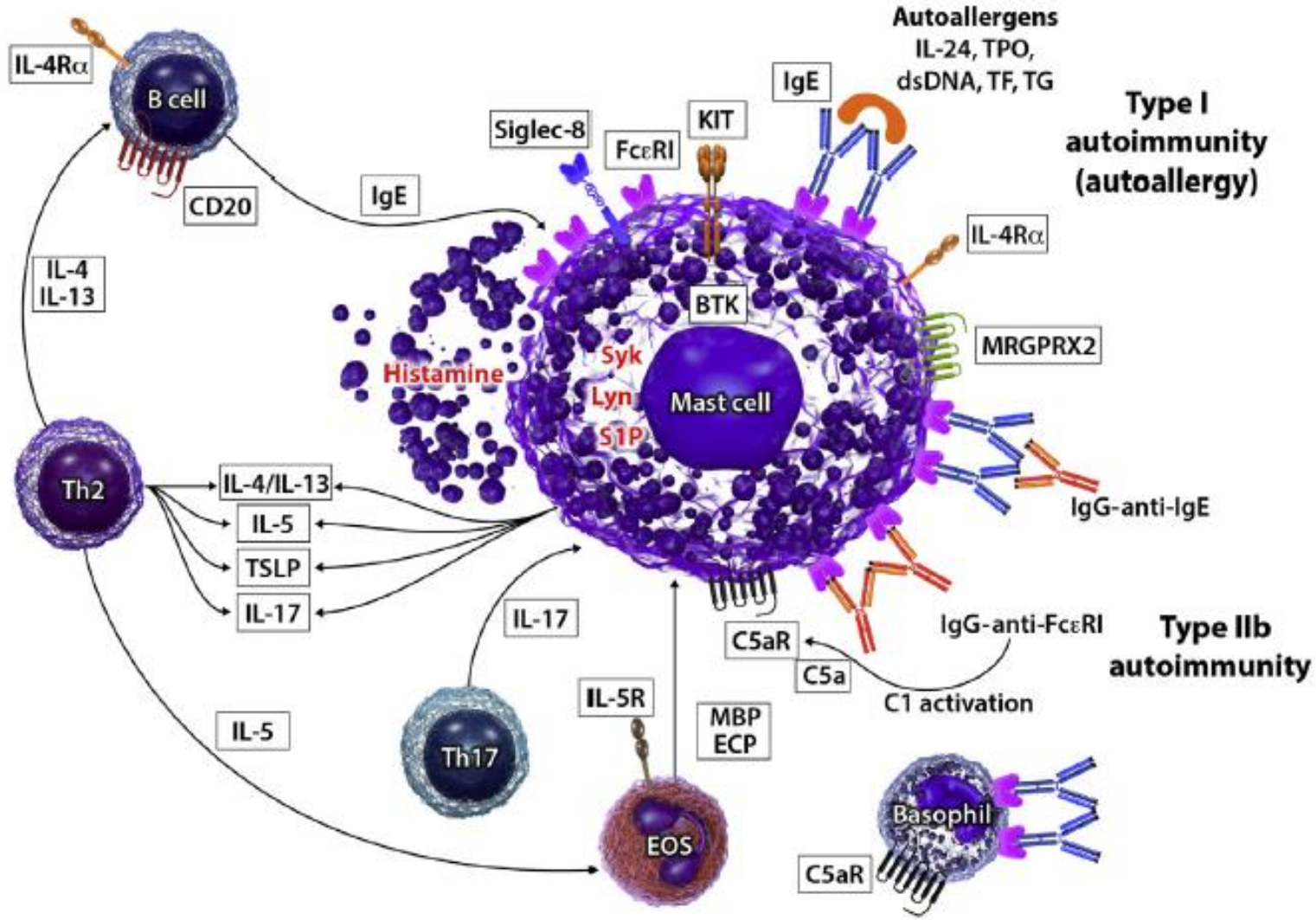
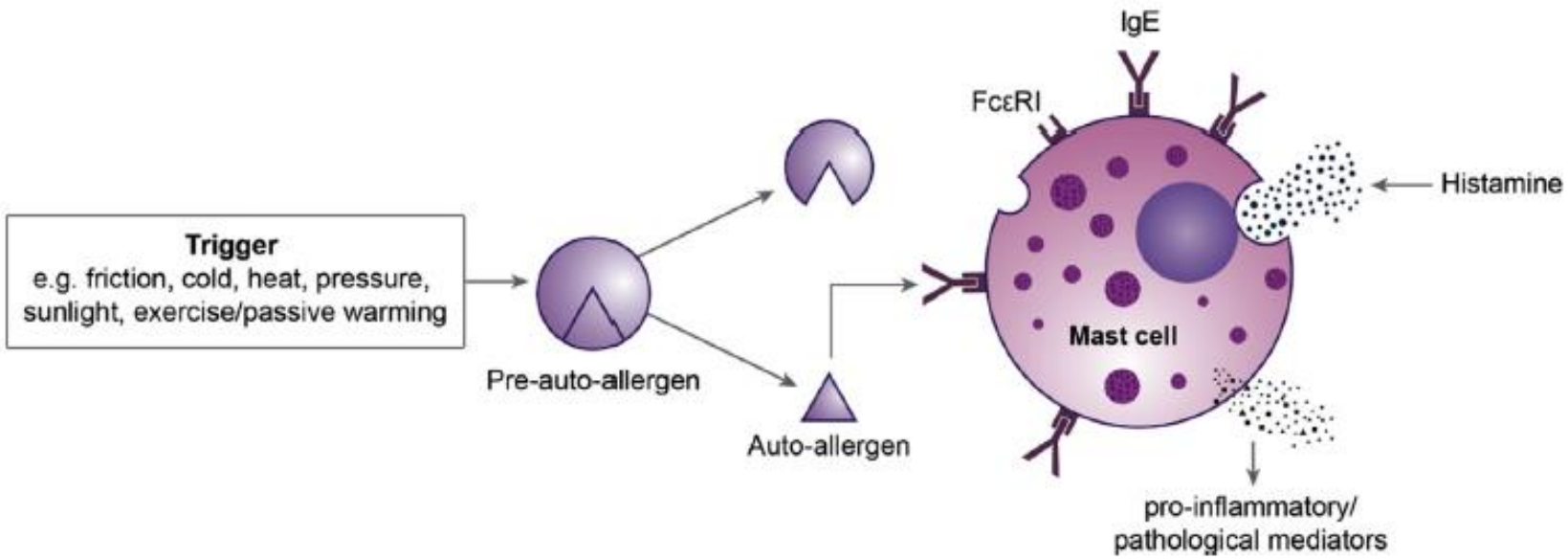


FIG 1. Timeline of advances in the research on aiCSU (data from references 13, 14, 16, 18-21, 25, 26, 38-42, 45-49, 51, 57, 59, and 138). *EC*, Eosinophil cationic protein; *EP*, eosinophil peroxidase.

Kolkhir P, et al. Autoimmune chronic spontaneous urticaria. J Allergy Clin Immunol 2022;149:1819-31.



Kolkhir P, et al. Autoimmune chronic spontaneous urticaria. J Allergy Clin Immunol 2022;149:1819-31.



Maurer M, et al. Omalizumab treatment in patients with chronic inducible urticaria: A systematic review of published evidence. J Allergy Clin Immunol. 2018 Feb;141(2):638-649.

Table 1. Features of type I and type IIb autoimmune CSU

Features	Type I versus type IIb autoimmunity
Autoantibodies	auto-IgE (e.g., against TPO, TG, TF, IL-24, dsDNA) in type I [12, 13, 15, 111], auto-IgG (against IgE, FcεRI) in type IIb [112–114]
Diagnosis	total auto-IgE and specific IgE to autoallergens[1] in type I [115], triple positivity: BHRA/BAT+ASST+WB/ELISA+ in type IIb [24, 25]
Disease activity/severity	tends to be higher in type IIb [12, 14, 25, 111][2]
Disease duration	tends to be longer in type IIb as shown in some [116, 117] but not all [25] studies
Rates of concomitant autoimmune diseases	tend to be higher in type IIb [25, 118–121]
Rates of concomitant allergic diseases	might be higher in type I [119]
Total IgE levels	low in type IIb and normal or high in type I [14, 25]
Basopenia rates	might be higher in type IIb [24, 111][2]
Eosinopenia rates	tend to be higher in type IIb [122]
C-reactive protein levels	may be higher in type IIb [25, 123]
ANA positivity rates	may be higher in type IIb [124]
Responder rates to sgAHs	may be lower in type IIb [122–125]
Responder rates to omalizumab	high in type I [28] and low in type IIb [62, 122, 126]
Speed of response to omalizumab	slow in type IIb [127]
Immunosuppressive therapy	can be effective in type IIb [128–134][3]

TABLE 1 Cluster analyses with machine learning-based algorithms identify fo

	All patients $n = 337$ (100%)	Cluster 1 $n = 25$ (7.4%)	Cluster 2 (42.1%)
CSU; *n* (%)	312 (93)	0 (0)[a]	142 (100)[b]
CIndU; *n* (%)	172 (51)	25 (100)[a]	69 (49)[b]
Angioedema; *n* (%)	198 (59)	12 (48)[a,b]	56 (39)[b]
Median age in years (IQR)	39 (28–49)	42 (28–51)[a]	3 (29–48)[a]
Female gender; *n* (%)	237 (70)	16 (64)[a,b]	71 (50)[b]
CU duration; months (IQR)	24 (9–76)	12 (5–96)[a,b]	36 (12–96
Family history; *n* (%)	72 (21)	6 (24)[a,b]	20 (14)[b]
Triggering factor(s); *n* (%)	262 (78)	18 (72)[a]	115 (81)[a]
IgE; IU/ml (IQR)	102 (38–226)	75 (35–189)[a,b]	132 (56–2
IgG-anti-TPO positivity; *n* (%)	68 (20)	4 (16)[a,b,c]	6 (4.2)[c]
ANA positivity; *n* (%)	82 (24)	2 (8)[a,b]	2 (1.4)[b]
Hypertension; *n* (%)	37 (11)	5 (20)[a]	0 (0)[b]
Diabetes mellitus; *n* (%)	45 (14)	3 (12)[a]	12 (9)[a]
Hypothyroidism; *n* (%)	64 (19)	6 (24)[a,b]	19 (13)[b]
Psychiatric disease; *n* (%)	115 (34)	10 (40)[a,b]	57 (40)[b]
Rheum. disease; *n* (%)	57 (17)	5 (20)[a]	28 (20)[a]
Atopic dermatitis; *n* (%)	12 (4)	0 (0)[a,b]	11 (8)[b]
Asthma; *n* (%)	57 (17)	5 (20)[a]	22 (16)[a]

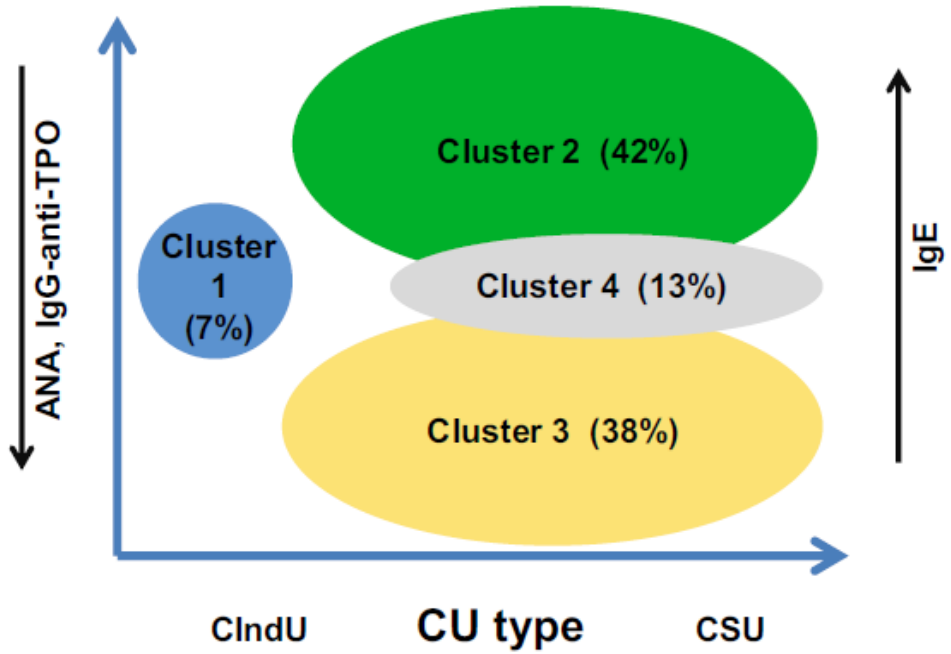


FIGURE 1 The four chronic urticaria clusters. The clusters are plotted according to the characteristics of how chronic urticaria (CU) is classified in real life as having chronic inducible urticaria (CIndU) or chronic spontaneous urticaria (CSU), and, for the latter, as having autoimmune or autoallergic CSU. Cluster 1 is the "CIndU cluster," cluster 2 is the "high IgE cluster," cluster 3 is the "autoimmune cluster," and cluster 4 is the "high comorbidity" cluster. Surface areas represent the size of the population distributed to each cluster (ANA, antinuclear antibodies; IgE, serum total IgE level; and TPO, thyroid peroxidase)

Türk M, et al. Identification of chronic urticaria subtypes using machine learning algorithms. Allergy. 2022 Jan;77(1):323-326.

TABLE 6 Recommended diagnostic tests in frequent urticaria subtypes

Types	Subtypes	Routine diagnostic tests (recommended)	Extended diagnostic programme[a] (based on history) For identification of underlying causes or eliciting factors and for ruling out possible differential diagnoses if indicated
Spontaneous urticaria	Acute spontaneous urticaria	None	None[b]
	CSU	Differential blood count. ESR and/or CRP	Avoidance of suspected triggers (eg, drugs); Conduction of diagnostic tests for (in no preferred order): (i) infectious diseases (eg, *Helicobacter pylori*); (ii) functional auto-antibodies (eg, autologous skin serum test); (iii) thyroid gland disorders (thyroid hormones and auto-antibodies); (iv) allergy (skin tests and/or allergen avoidance test, eg, avoidance diet); (v) concomitant CIndU, see below[69]; (vi) severe systemic diseases (eg, tryptase); (vii) other (eg, lesional skin biopsy)

Tablo 4. Kronik ürtikerde tanısal testler

	Rutin tanısal tetkik	Öyküye dayalı ileri tanısal tetkikler
Kronik ürtiker	Tam kan, ESH, CRP Şüpheli ilaçların kesilmesi	- Enfeksiyon hastalıkları (*H. pilori* vs.) - Tiroid hormon ve otoantikorları - Uyarılabilir ürtikerler için deri testleri - Üç hafta süre ile psödoallerjensiz diyet - Otolog serum deri testi - Lezyonel deri biyopsisi

ESH: Eritrosit sedimentasyon hızı, CRP: C-reaktif protein, *H. pilori: Helikobakter pilori*

İleri merkezlerde total IgE, IgG-anti-TPO ve diğer biyomarkerlar istenebilir

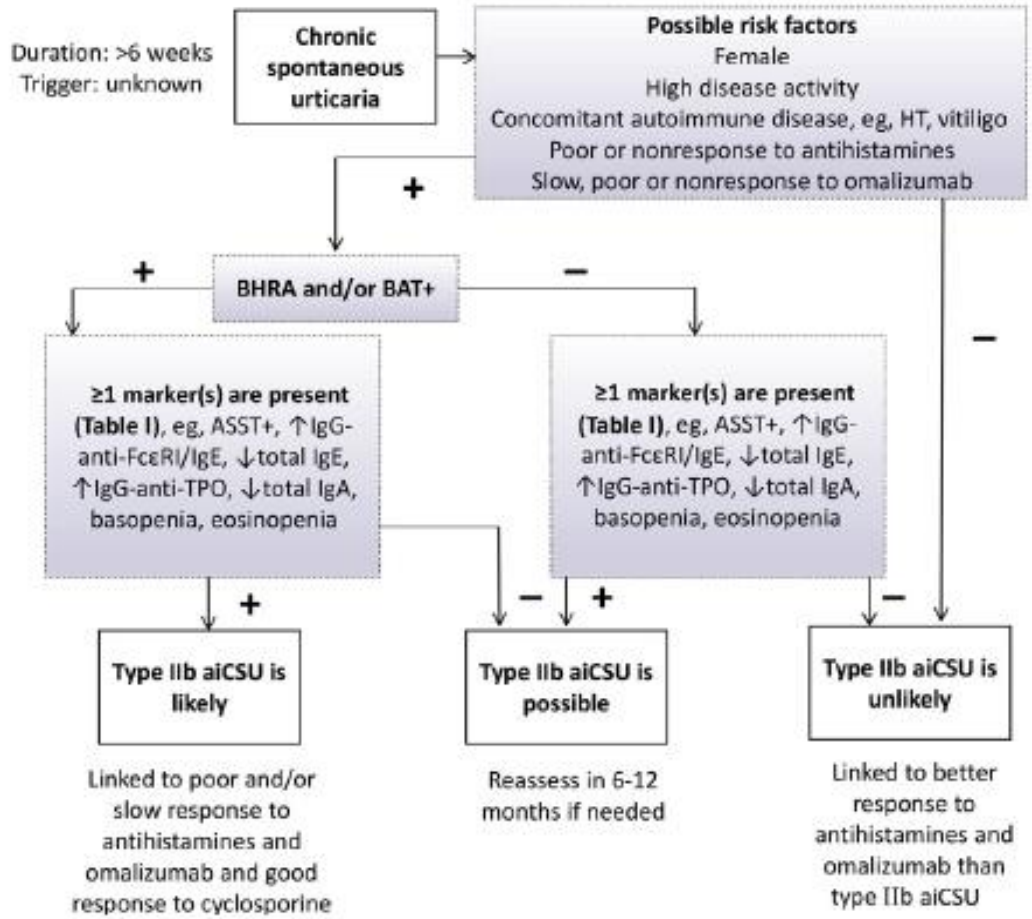
Kocatürk Göncü et al. Turkderm - Arch Turk Dermatol Venerology 2016
Zuberbier T et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022 Mar;77(3):734-766.

TABLE I. Emerging demographic, clinical, and laboratory markers of type IIb aiCSU

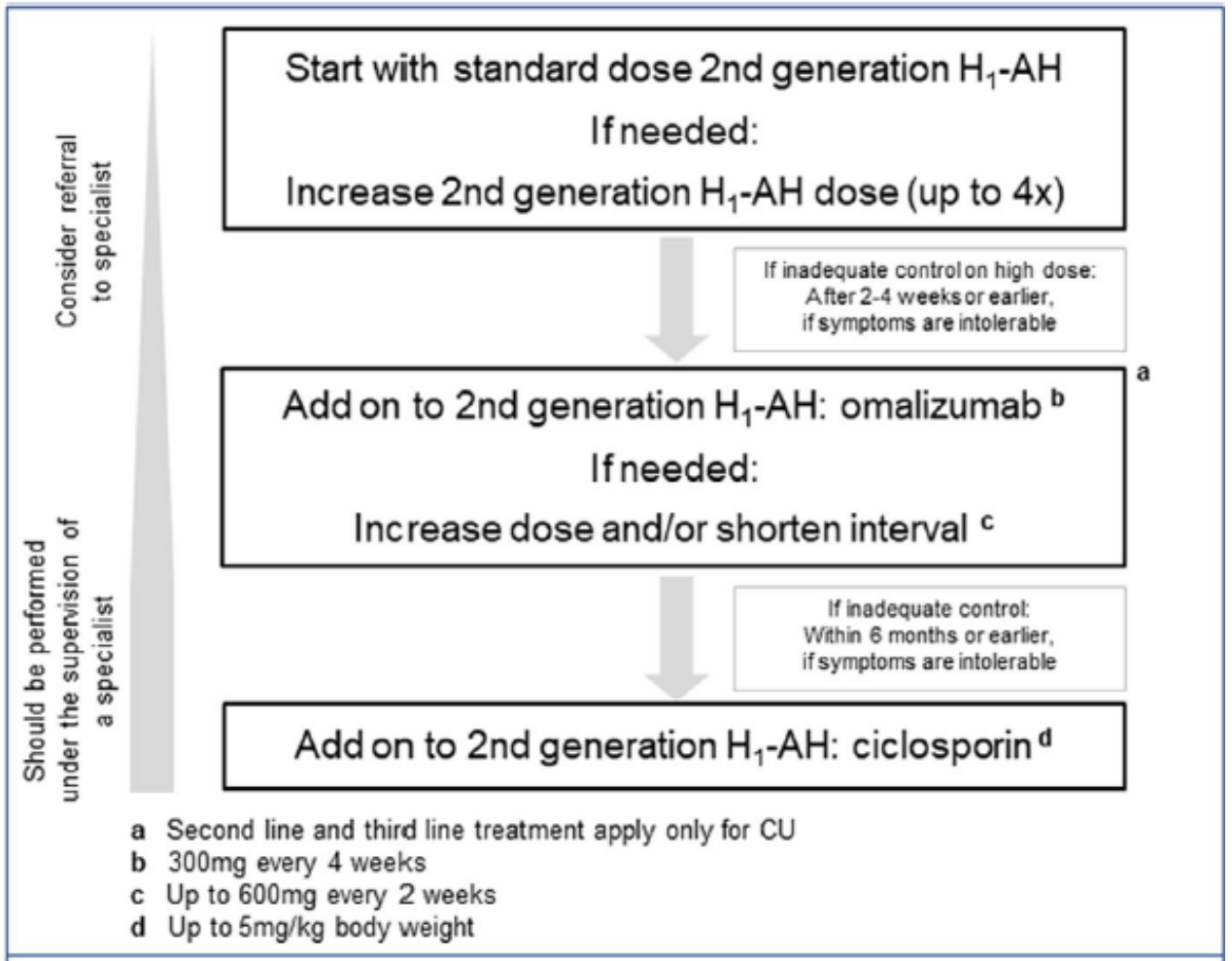
Markers	Results	% of patients with type IIb aiCSU	How type IIb aiCSU was diagnosed	First author [reference]
Sex	High female rates	87%-93%	Triple positivity* or high IgG-anti-TPO plus low IgE	Kolkhir,[51] Schoepke[18]
Autoimmune diseases	Present, higher risk	Mostly HT (60%) and vitiligo (7%)	Triple positivity	Kolkhir,[57] Schoepke[18]
Angioedema	Present	62%-76%	High IgG-anti-TPO plus low IgE or BAT/BHRA positivity	Kolkhir,[51] Marcelino[46]
Nocturnal symptoms	Present	70%-79%	BAT/BHRA positivity	Marcelino[46]
Symptoms for >5 d/wk	Present	92%	BAT/BHRA positivity	Marcelino[46]
Disease activity (UAS7)	High (median, 21)	—	Triple positivity or BAT/BHRA positivity	Schoepke,[18] Ye,[124] Curto-Barredo,[125] Marcelino[46]
Quality of life (DLQI)	Low (mean, 9-10)	—	BAT/BHRA positivity	Marcelino[46]
Total IgE	Low (<40 IU/mL or <30 IU/mL)	69%-86% or 38%-41%	Triple positivity or BAT/BHRA positivity	Kolkhir,[51] Schoepke,[18] Sauer,[48] Marcelino[46]
IgG-anti-TPO	High (≥34 kU/L)	39%-62%	Triple positivity or BAT/BHRA positivity	Kolkhir,[51] Schoepke,[18] Marcelino[46]
IgA	Low (<1.84 g/L or <0.7 g/L)	73.5% or 9.6%	BAT positivity	Sauer[48]
Blood basophil counts	Low (<0.01 × 10^9/L)	30%	Triple positivity or BHRA positivity	Kolkhir,[47] Schoepke[18]
Blood eosinophil counts	Low (<0.05 × 10^9/L)	24%	BHRA positivity	Kolkhir[47]
Disease control (UCT)	Low (mean, 7.7-7.8)	—	BAT/BHRA positivity	Marcelino[46]
Response to sgAHs	Poor response	87%	BAT positivity	Irinyi[126]
Response to omalizumab	Slow, poor, and/or nonresponse	50%	BHRA or BAT positivity	Gericke,[49] Palacios,[127] Ghazanfar,[128] Endo[129]

DLQI, Dermatology Life Quality Index; *HT*, Hashimoto's thyroiditis; *UAS7*, Urticaria Activity Score over 7 days; *UCT*, Urticaria Control Test.
*Positive result as of ASST + BAT/BHRA + immunoassay for IgG-anti-FcεRI/IgE.

Kolkhir P, et al. Autoimmune chronic spontaneous urticaria. J Allergy Clin Immunol 2022;149:1819-31.

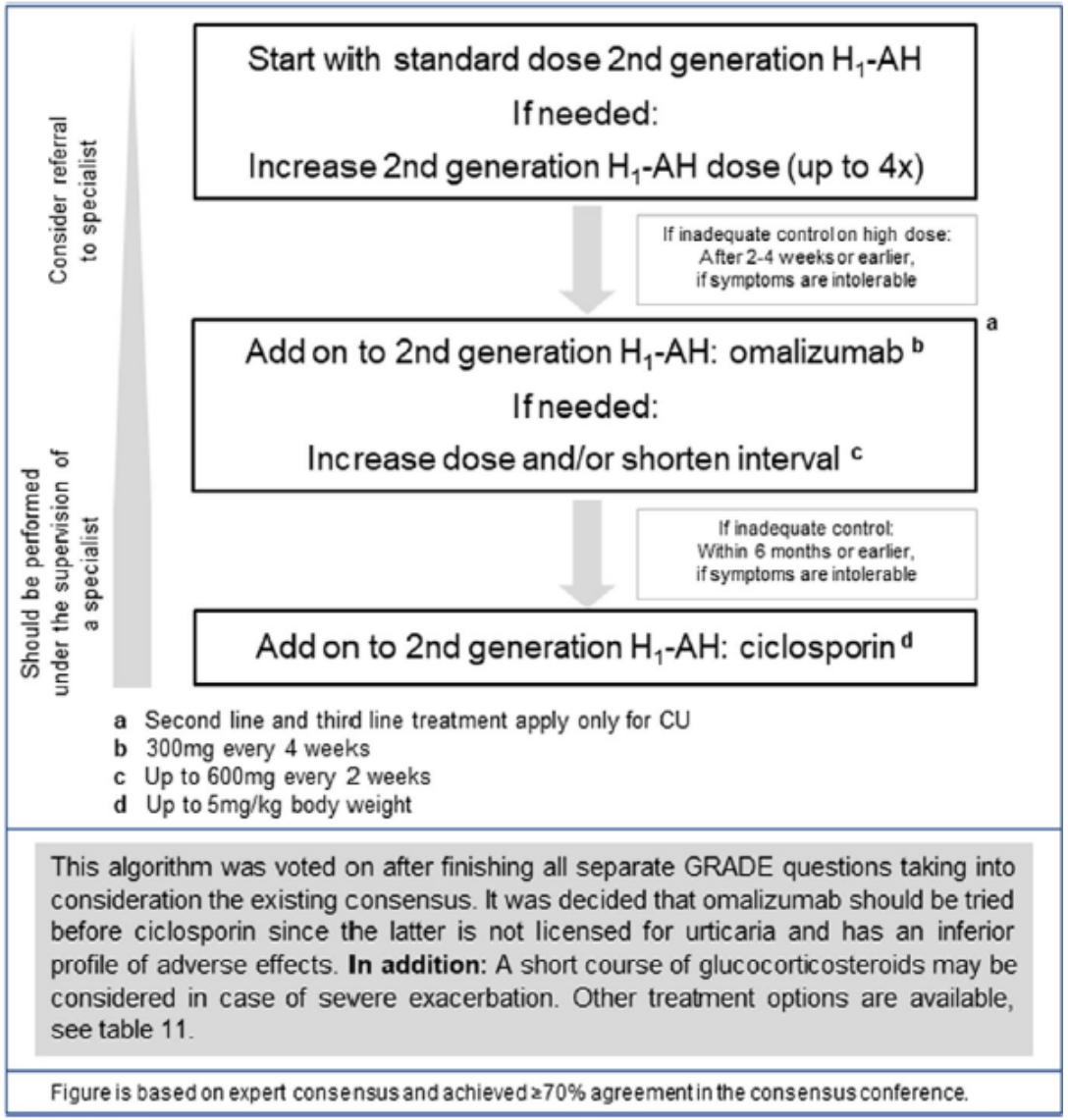


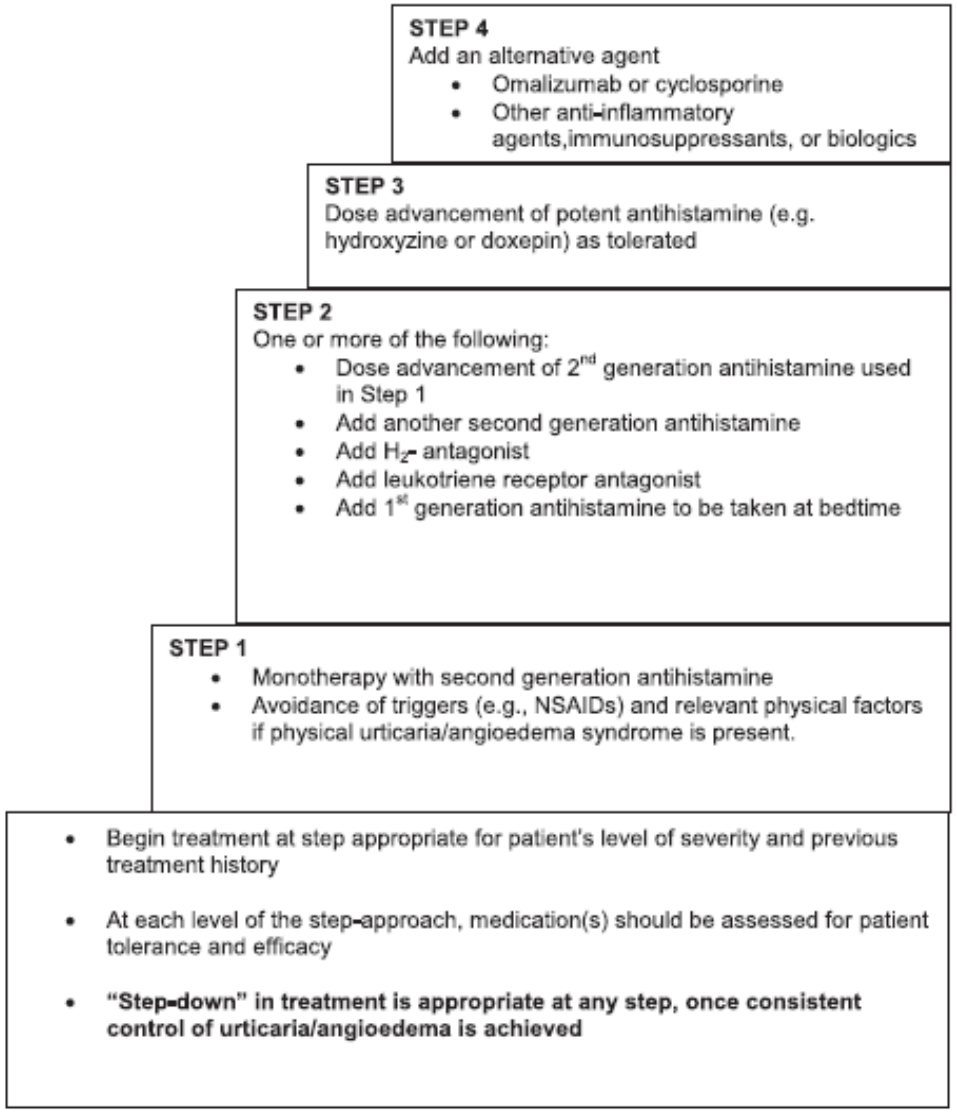
Kolkhir P, et al. Autoimmune chronic spontaneous urticaria. J Allergy Clin Immunol 2022;149:1819-31.



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 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 11.

Figure is based on expert consensus and achieved ≥70% agreement in the consensus conference.

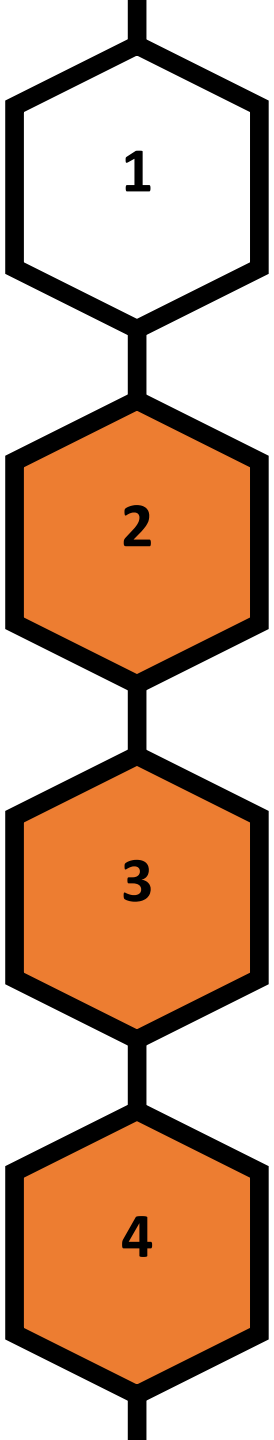




Zuberbier T et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022 Mar;77(3):734-766.
Bernstein JA et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol. 2014 May;133(5):1270-7.

KSÜ Standart Tedavi 1. Basamak

Uzmana refere etmeyi akılda tut



İkinci-kuşak H1-AH

%10 ila %20 hasta standart doz AH'ye yanıt verecektir.

İkinci-kuşak H1-AH'yi standart dozun 4 katına kadar arttır

Yetersiz kontrol: 2 - 4 hf yada daha erken, tedaviye yanıt yoksa

Doz artırımı yaklaşık %50'den fazla hastada yanıtsızlıkla sonuçlanıyor.

KSÜ Standart Tedavi
2. Basamak

Tedavide amaç: hastalık gidene kadar tedavi et!

İkinci-kuşak H1-AH'ye Omalizumab ekle

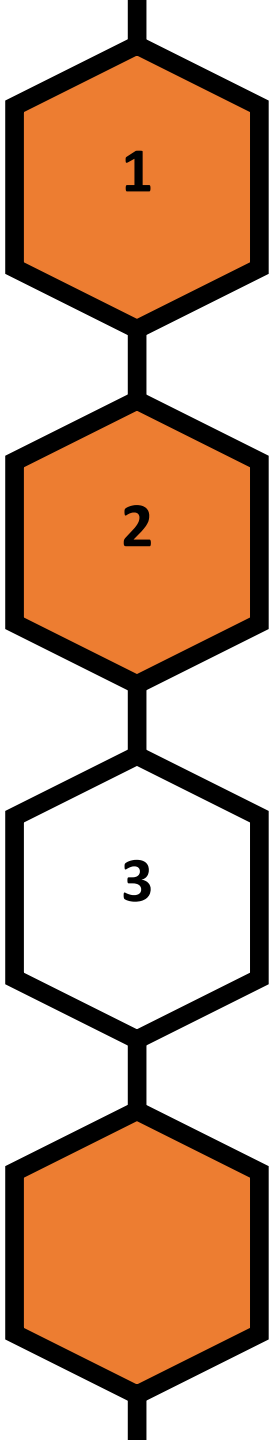
Gerekirse dozu yükselt ve/veya aralığı kısalt
(600mg 2hf'da 1 e kadar)

Yetersiz kontrol: 6 ay içerisinde, tedaviye yanıt yoksa…

Omalizumab kullanım sonuçları (300 mg / ay)
% 30 - 40 tam kontrol (UAS7 = 0)
%50 – 60 iyi kontrol (UAS7 < 7)

KSÜ Standart Tedavi
3. Basamak

Uzman denetiminde yönetilmeli

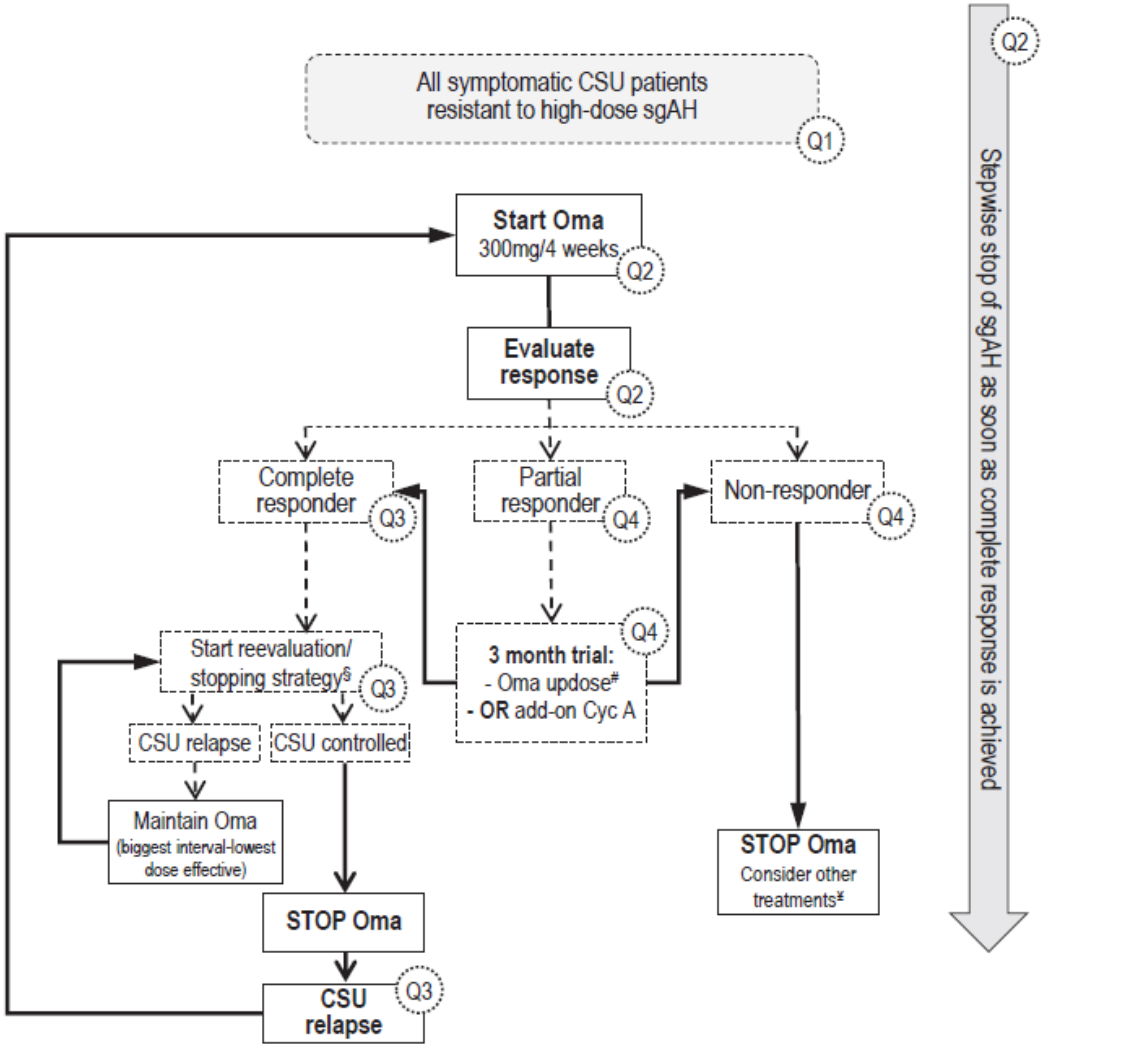


AH ve Omalizumab tedavilerine rağmen, halen %20 hasta SİKLOSPORİNE ihtiyaç duyuyor.

Siklosporin için önemli uyarılar var:
Hipertansiyon
Böbrek yetmezliği
Tedavi süresi kısıtlılığı <1 yıl
Dikkatli hasta takibi
Yanıt ??

İkinci-kuşak H1-AH'ye Siklosporin ekle

Doz 5mg/kg'a kadar



Special populations:
- Pregnancy: Not approved in pregnancy but suggested to be safe. Category B risk status from FDA.
- Children: Omalizumab is approved for children over 12 years-old. Data suggest it can be considered in younger ages.

Q1

§ Can be achieved by extending treatment intervals or by reducing omalizumab dose to 150mg.
# Can be achieved by using higher omalizumab doses, shortening treatment intervals or by combining both strategies.
¥ Cyclosporine should be preferred, in accordance to current guidelines. Other options can also be considered.

Türk et al. How to Treat Patients with Chronic Spontaneous Urticaria with Omalizumab: Questions and Answers. J Allergy Clin Immunol Pract. 2020 Jan;8(1):113-124. JACI In Practice 2020

Tedavi direncini belirleyen biyobelirteçler

Tablo 2. Tedavi etkinliğinde kullanılabilecek potansiyel biyobelirteçler[2,4-12,15]

Biyobelirteç	Antihistaminikler	Omalizumab	Siklosporin
Direnç			
Klinik	Hispanik etnisite Atopik astım varlığı Rinosinüzit varlığı Hipertansiyon varlığı Tiroid hastalıkları Yüksek UAS7 Uzun süren ürtikeryal lezyonlar (wheals) Yüksek hastalık aktivitesi	–	–
Moleküler	↑C5a ↑IL-6 ↑D-dimer OSDT + ↑CRP	BHRA + OSDT + BAT+ ANA+ Düşük IgE seviyeleri CD203c ekspresyon artışı görülen (upregülasyon) bazofiller D-dimer	D-dimer
Yanıt			
Klinik	–	–	Kısa süreli KSÜ Başlangıçta yüksek hastalık şiddeti
Moleküler	↑LCN2 ↑Clusterin	BHRA – OSDT – BAT– CD203c bazofil yok Yüksek IgE seviyeleri Yüksek FcεRI ↓D-dimer ↓IL-31 ↓CRP ↑Bazofil sayısı	BHRA + BAT + OSDT + Düşük IgE seviyeleri D-dimer seviyelerinde düşüş CRP seviyelerinde düşüş
Relaps artışı			
Klinik	–	Başlangıçta yüksek UAS7 Düşük UAS AAC	–
Moleküler	–	Yüksek IgE düzeyi	–

LCN2, serum lipocalin-2; BAT, bazofil aktivasyon testi; BHRA, bazofil histamin release assay; OSDT, otolog serum deri testi; AAC, eğri üzerindeki alan.

Predictors of treatment response in chronic spontaneous urticaria

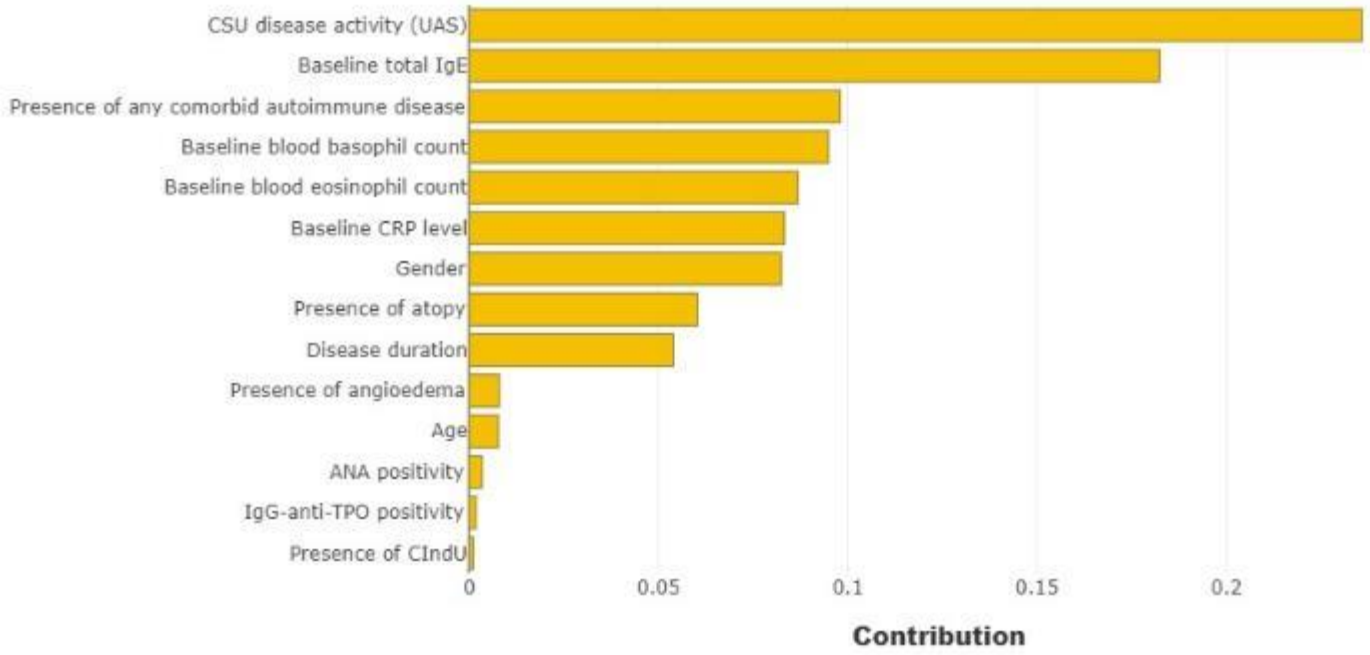
Jie Shen Fok[1,2,3] | Pavel Kolkhir[1,4] | Martin K. Church[1] | Marcus Maurer[1]

- sgAH yanıtsızlığı için kuvvetli markerler
  - Yüksek UAS7/UCT
  - Yüksek D-Dimer
  - Yüksek CRP
- Omalizumab yanıtsızlığı için kuvvetli markerler
  - Düşük total IgE
- Siklosporin yanıtı için kuvvetli markerler
  - Pozitif BHRA
  - Düşük total IgE???

Fok JS, Kolkhir P, Church MK, Maurer M. Allergy. 2021

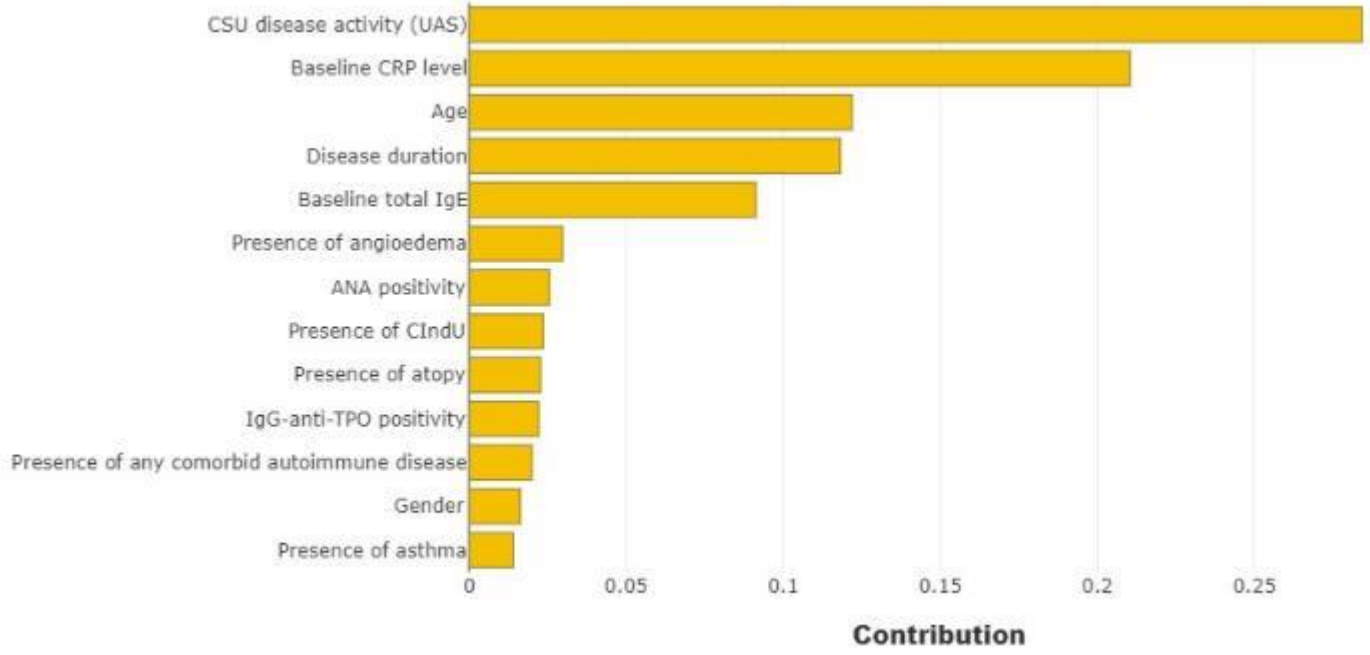
St doz AH yanıtının prediksiyonu

Düşük hastalık şiddeti
(p=0.001; OR: 1.477; 95% CI: 1.171-1.863)



Yüksek doz AH yanıtının prediksiyonu

Düşük hastalık şiddeti
(p<0.001; OR: 2.101; 95% CI: 1.793-2.462)



Türk et al. Yayımlanmamış veri.

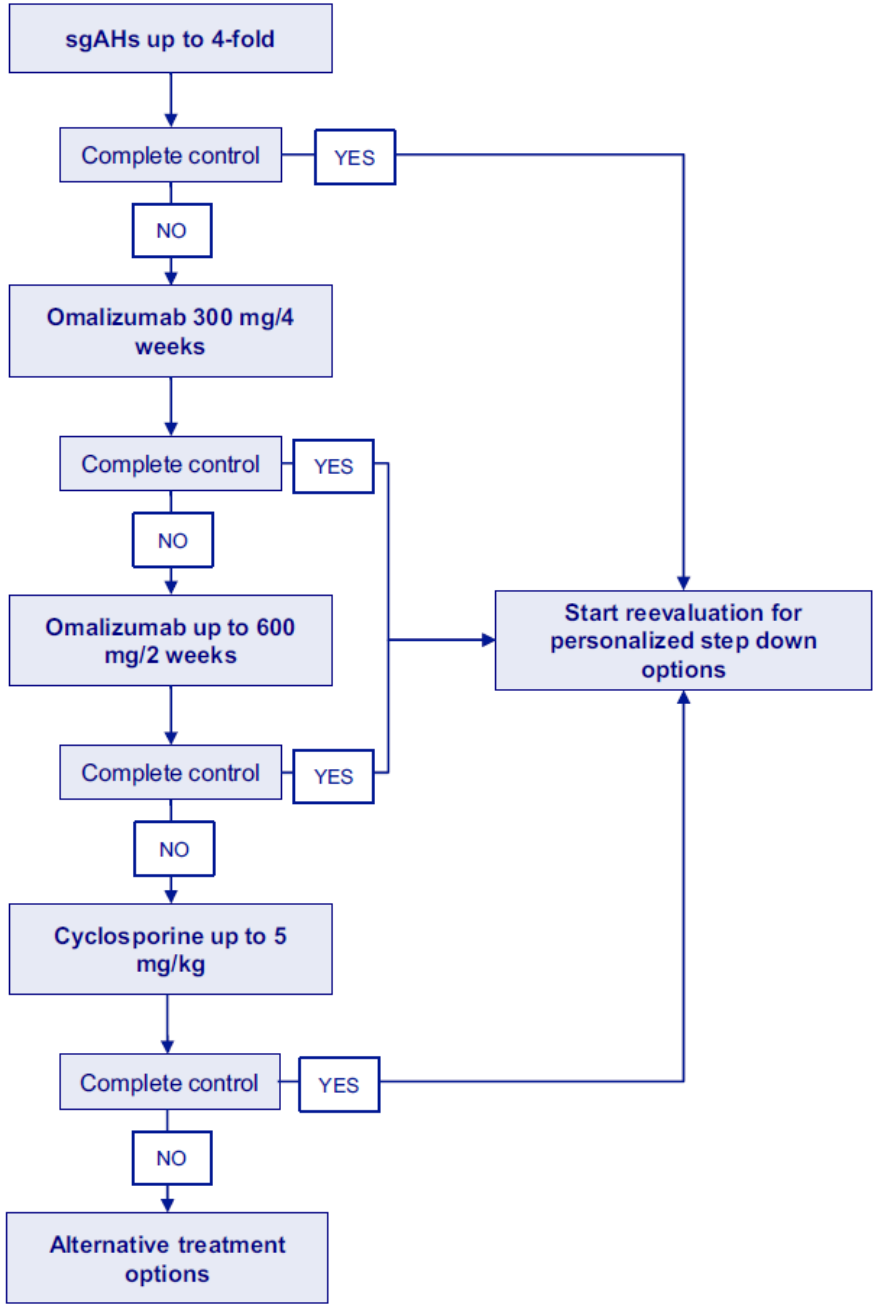


FIGURE 1 Personalized step-up therapeutic management plan of chronic spontaneous urticaria. The use of second-generation antihistamines (sgAH) starting from the standard dose up to fourfold is the recommended first-line treatment in all patients with CSU. If complete disease control cannot be achieved with this treatment, the second-line treatment option is omalizumab added-on to sgAHs, which should be started at the standard dose of 300 mg every 4 weeks, with updosing, in patients with inadequate response, until complete controlled disease is achieved. If complete disease control cannot be obtained within 3 months of omalizumab updosing, treatment with cyclosporine added-on to sgAHs should be started. In case of unresponsiveness to all these treatments, alternatives include several treatment options like doxepine, H2 antihistamines, leukotriene receptor antagonists, immunosuppressives, danazol, warfarin, tranexamic acid, IVIG, hydroxychloroquine, rituximab, anti-TNF-Alpha, colchicine, and more. Due to the low level of evidence in support of these treatments, the current international urticaria guideline recommends considering alternative treatment options only in special cases, those antihistamine treatment, omalizumab, and cyclosporine have failed. All treatment steps and recommendations in this figure are in line with the current international guideline[3]

Türk M, et al. Experience-based advice on stepping up and stepping down the therapeutic management of chronic spontaneous urticaria: Where is the guidance? Allergy. 2022 May;77(5):1626-1630.

Kronik Ürtiker Yönetimi

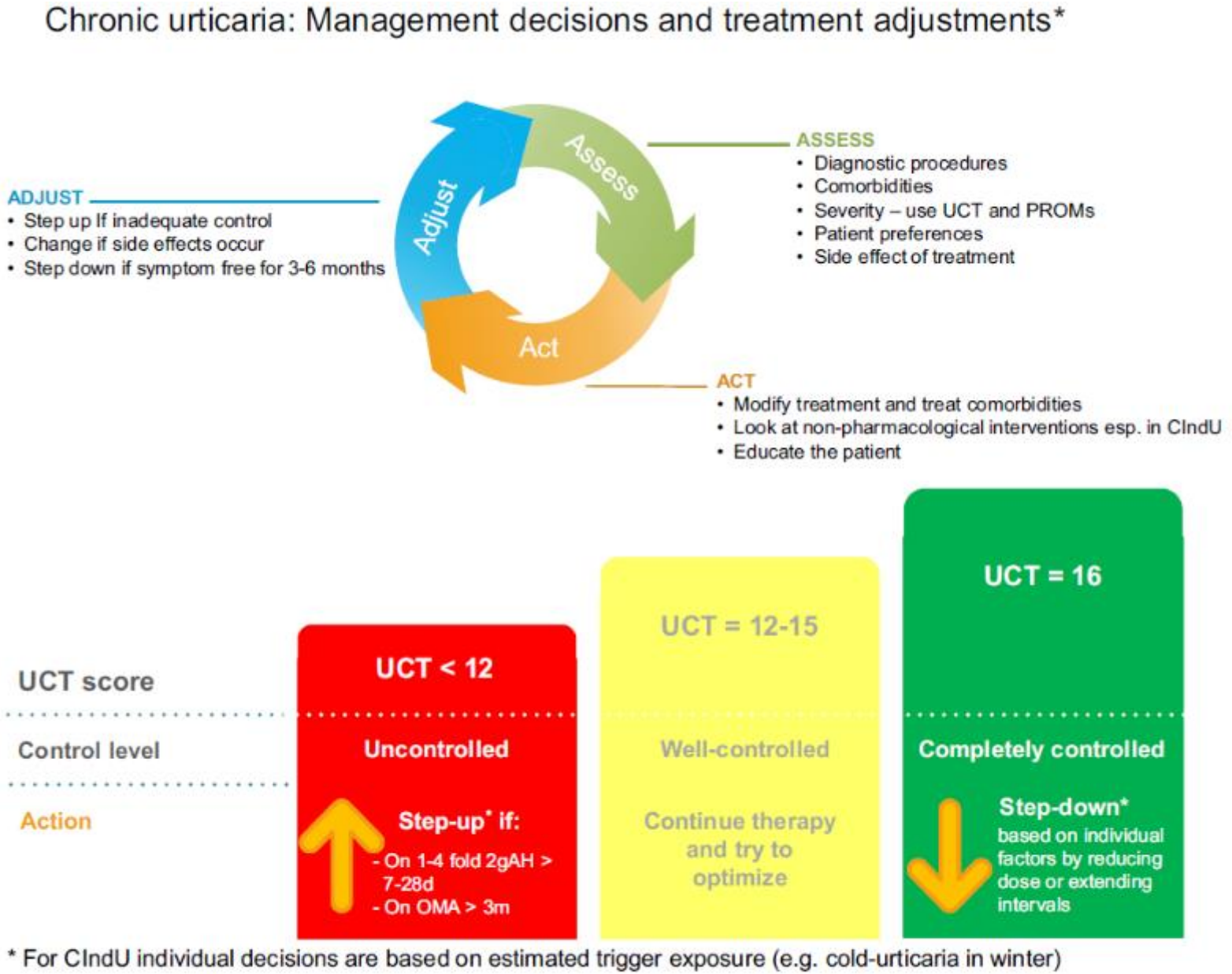
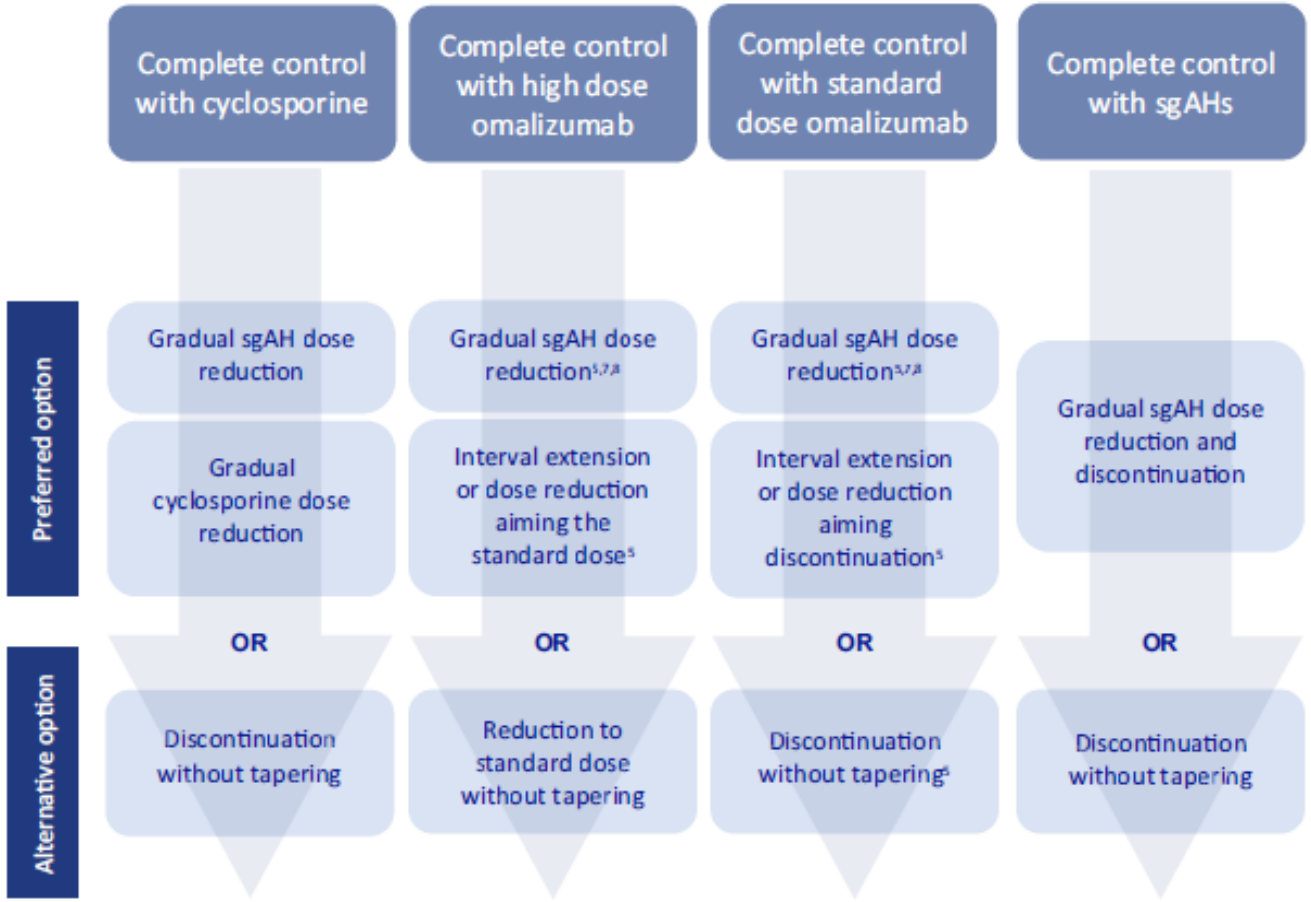


FIGURE 3 Chronic urticaria: Management decisions and treatment adjustments. CIndU: chronic inducible urticaria; d: days; m: months; PROMs: patient-reported outcome measures; OMA: omalizumab ; 2gAH: 2nd generation H_1-antihistamine; UCT: Urticaria Control Test

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



Türk M, et al. Experience-based advice on stepping up and stepping down the therapeutic management of chronic spontaneous urticaria: Where is the guidance? Allergy. 2022 May;77(5):1626-1630.

H_1-Antihistamines May No Longer Be Necessary for Patients With Refractory Chronic Spontaneous Urticaria After Initiation of Omalizumab

Ensina LF[1,2], Arruda LK[3], Campos RA[3], Criado RF[5], Rodrigues Valle S[5], Melo JML[3], Oliveira JCS[4], Dortas Jr SD[6], Cusato-Ensina AP[1], Camelo-Nunes IC[2], Agondi RC[7]
[1]*CPAlpha Clinical Research Center, Barueri, Brazil*
[2]*Federal University of São Paulo, São Paulo, Brazil*
[3]*Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil*
[4]*Federal University of Bahia, Salvador, Brazil*
[5]*Faculdade de Medicina do ABC, Santo André, Brazil*
[6]*Federal University of Rio de Janeiro, Rio de Janeiro, Brazil*
[7]*Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil*

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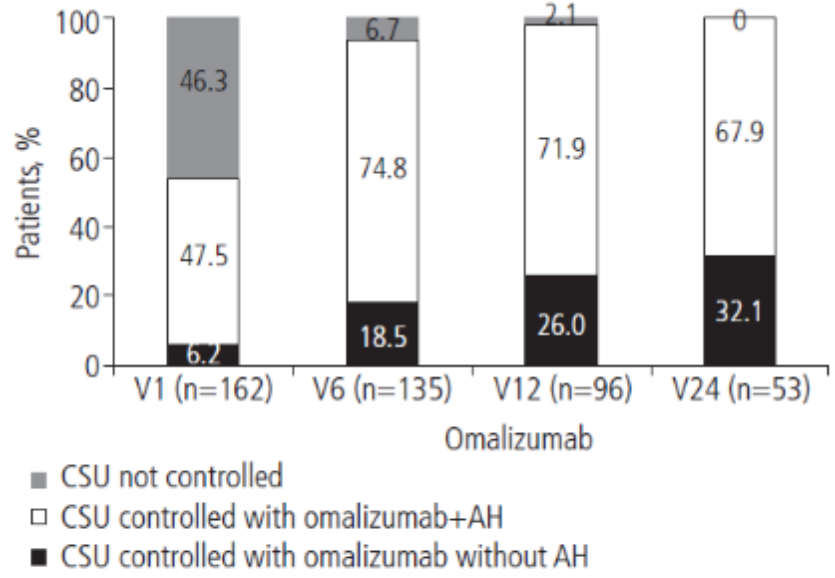


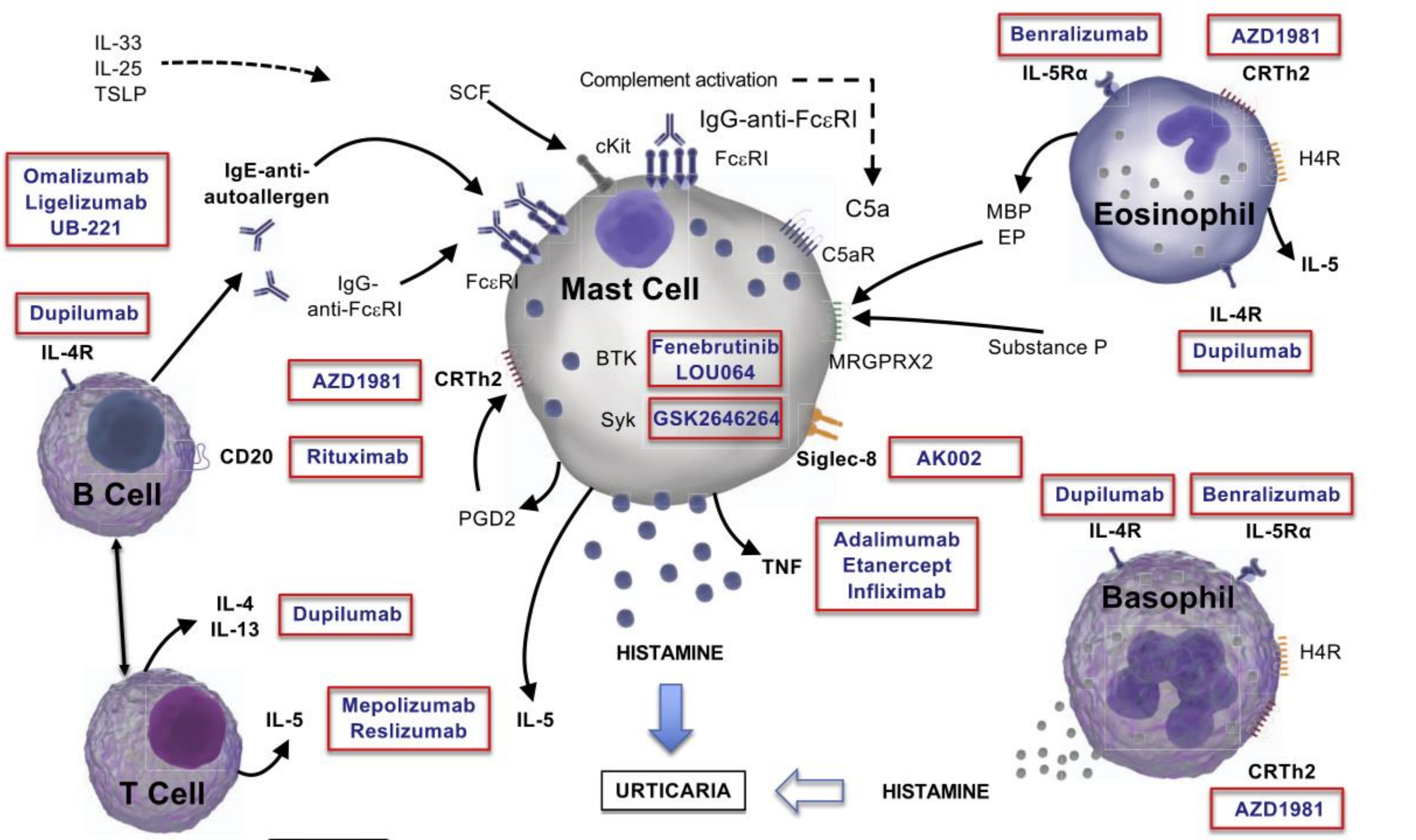
Figure. Patients taking omalizumab at the different monthly visits (1, 6, 12, and 24 months). CSU indicates chronic spontaneous urticaria; AH, antihistamines.

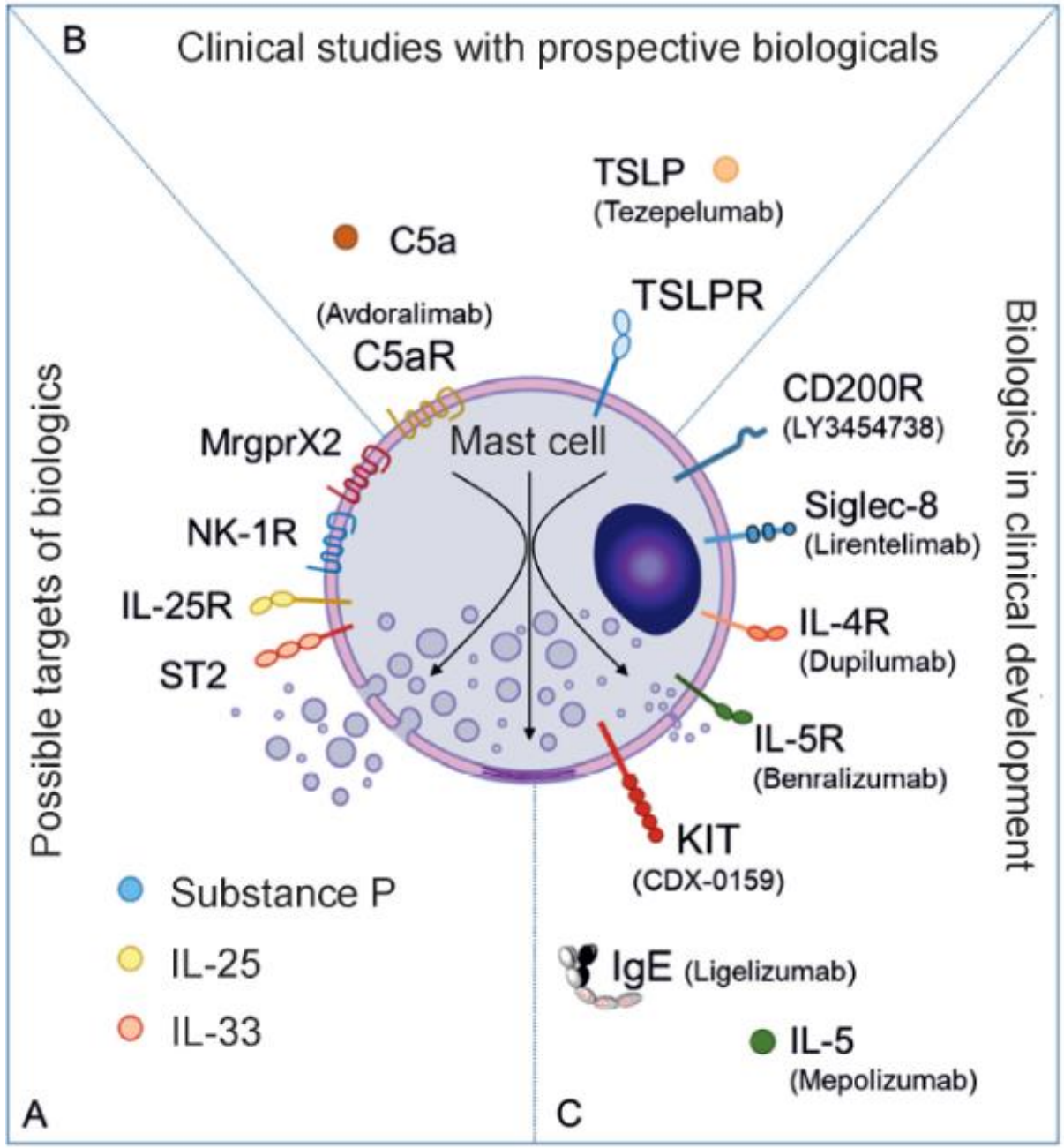
- 298 hastalık Katalan (XUrCB) serisi benzer şekilde hastaların %23.5'i omalizumab tedavisi altında AH almayı bırakmış
- İzole CSU olanlar ve omalizumab tedavi yanıtı iyi olanlarda AH bırakma oranları daha yüksek

Ensina et al. J Investig Allergol Clin Immunol 2020

Yüksek tam remisyon oranlarına rağmen, halen hastalıkta tam kür sağlayan tedavi yoktur

Tedaviye rağmen yaklaşık %50 hastada KSÜ 5 yıl süreyle semptomatik kalıyor


IL-33
IL-25
TSLP
SCF
Complement activation
IgG-anti-FcεRI
cKit
FcεRI
C5a
C5aR
IgE-anti-autoallergen
IgG-anti-FcεRI
FcεRI
Mast Cell
BTK
Syk
Fenebrutinib
LOU064
GSK2646264
MRGPRX2
Substance P
Siglec-8
AK002
CRTh2
AZD1981
PGD2
TNF
Adalimumab
Etanercept
Infliximab
HISTAMINE
IL-5
Mepolizumab
Reslizumab
IL-4
IL-13
Dupilumab
Omalizumab
Ligelizumab
UB-221
Dupilumab
IL-4R
B Cell
CD20
Rituximab
T Cell
URTICARIA
HISTAMINE
Benralizumab
AZD1981
IL-5Rα
CRTh2
Eosinophil
H4R
MBP
EP
IL-5
IL-4R
Dupilumab
Dupilumab
Benralizumab
IL-4R
IL-5Rα
Basophil
H4R
CRTh2
AZD1981



Gelecekte Hedef Olabilecek Tedaviler

The Mas-Related G Protein Coupled Receptor X2 (MRGPRX2)

Histamin 4 reseptörü

NK-1R

C5a ve reseptörü CD88 (Avdoralimab)*

Kök hücre faktörü (SCF)

Diğer inhibitör Mast hücre resptörleri

Tip 2 İmmuniteyi tetikleyen sitokinler:
IL-33, IL-25 ve TSLP (Tezepelumab)*

Substance P

Metz M, Maurer M. Use of biologics in chronic spontaneous urticaria - beyond omalizumab therapy?. *Allergol Select*. 2021;5:89-95.

*Prospektif klinik çalışması devam edenler

Ürtiker Yönetiminde Sık Yapılan Yanlışlar

1. Gereksiz testler (yiyecek alerjisi vb.)

2. Uygun olmayan birinci nesil sedate edici AH

3. Anafilaksi riski hakkında yanlış bilgilendirme

4. Yalnızca isteğe bağlı ve gerektiğinde tedavi

5. Sistemik OKS uzun süreli kullanımı

6. Hastanın üst merkeze geç refere edilmesi