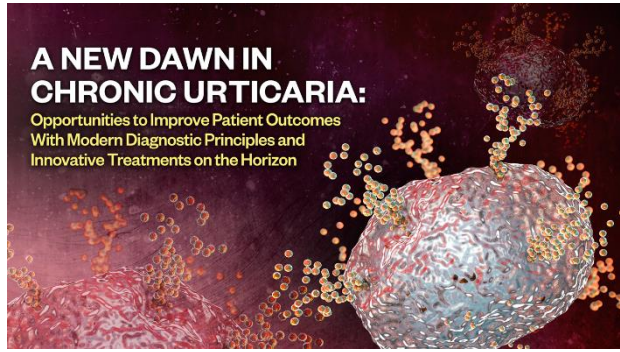
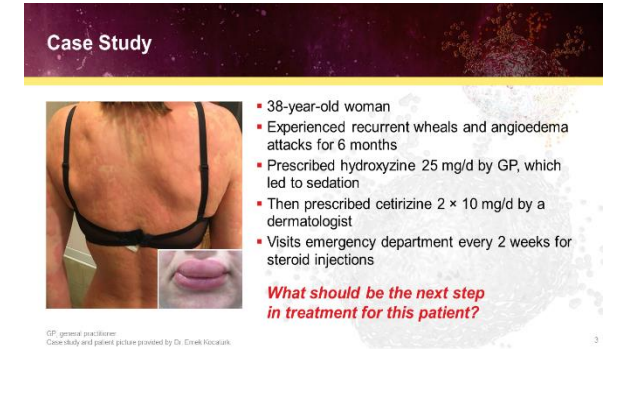
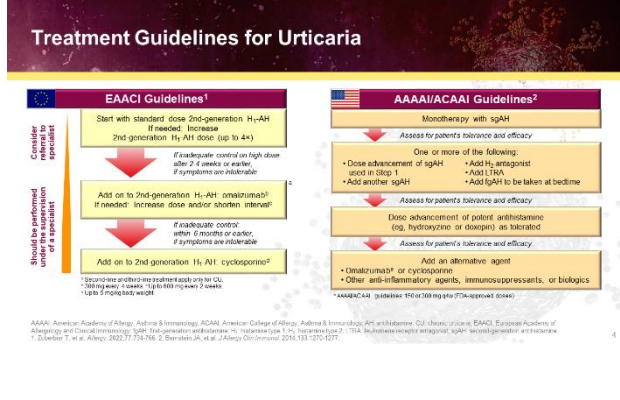


A NEW DAWN IN CHRONIC URTICARIA: Opportunities to Improve Patient Outcomes With Modern Diagnostic Principles and Innovative Treatments on the Horizon

Fulfilling an Unmet Need in Treating CU: How Might New and Emerging Approaches Fit Into the Paradigm?

<p>1</p>		<p>Hello, my name is Emek Kocatürk Göncü. I'm a professor of dermatology in Koç University Medical School, Istanbul, Turkey. I'm also a researcher in Charité University</p>
<p>2</p>		<p>Medical School, Institute of Allergology, Berlin, Germany. So today, I'm going to speak about my favorite disease, chronic urticaria, mainly focusing on current treatment and the future options of treatment that are seen on the horizon. First of all, I'd like to start with a case presentation. The cases we usually see in our common practices and which demonstrate that chronic urticaria sometimes can be very burdensome, both for the patients and also for the treating physician.</p>
<p>3</p>		<p>So, this case is a 38-year-old woman. She was experiencing recurrent wheals and angioedema attacks for 6 months and she was prescribed hydroxyzine 25 mg daily. But she said that treatment led to sedation. And then she went to a dermatologist, and she was prescribed cetirizine two times daily. But she says that she's still visiting emergency department every 2 weeks for getting steroid injections to get relief for her symptoms. So, what should be the next step in treatment for this patient?</p>
<p>4</p>		<p>To get the answers, let's take a look to the treatment guidelines of urticaria. The first guideline I'd like to cover is the European [Academy of] Allergy and Clinical Immunology guidelines. Let's say European guidelines. This guideline is released in 2022, so it's a new guideline. And the first step is to start with standard doses of second-generation H₁ antihistamines and if the patient is refractory to this treatment, then the guideline recommends to updose up to four-fold in standard dose refractory patients. If the patients are</p>

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		<p>not responding to even four-fold of antihistamine treatments, then the guideline recommends to step up to omalizumab treatment and combine second-generation antihistamines with omalizumab treatment and to stay on omalizumab treatment at least 4 months before deciding that omalizumab is not working. And the third option is immunosuppressive treatment with cyclosporine. And the guideline also suggests short-term use of systemic steroids in case of exacerbations, maximum 10 days. And here you see the American Academy of [Allergy, Asthma, and Immunology] guidelines. This guideline was released in 2014. And here I want to make a note that in 2014, omalizumab was new on the market for chronic spontaneous urticaria. So, there were not enough experience for omalizumab treatment when these guidelines were written. So, like the European guidelines, American Academy of Allergy Immunology guideline also recommends to start with second-generation antihistamines, H₁ antihistamines, and then updose to four-fold in the same second-generation antihistamine. But this guideline also has other options in the second step, like adding another second-generation antihistamine, adding H₂-antagonists, adding leukotriene receptor antagonist, and even first-generation antihistamines to be taken at bedtime. Here I want to note that the European guidelines suggest against using first-generation antihistamines because of their sedative and anticholinergic adverse effects. And the third treatment step in the American guideline is those advancements of potent antihistamines. And if no response to these three steps, then the last step includes omalizumab, cyclosporine, other anti-inflammatory agents, and immunosuppressive agents.</p>
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<p>5</p>	<p>Treatment Guidelines for Urticaria</p> <p>British Guidelines</p> <p>2nd-generation H₁-antihistamine (licensed dose) 2nd-generation H₁-antihistamine (up to 4-fold the licensed dose; except mizolastine) Consider switching 2nd-generation H₁-antihistamine Montelukast, in addition to a 2nd-generation H₁-antihistamine <i>Progress through first-line options every 2-4 weeks</i></p> <p>Consider BHR/Abtotal IgE</p> <p>(in addition to a 2nd-generation H₁-antihistamine) Omalizumab or cyclosporine</p> <p>(in addition to a 2nd-generation H₁-antihistamine) 1st-generation H₁-antihistamine, H₂-antihistamine, azelastine, doxepin, doxepin, hydroxychloroquine, IVIg, methotrexate, mycophenolate mofetil, NB-UVB, sulfasalazine, tacrolimus, or tranexamic acid (the latter only for angioedema without weals)</p> <p><small>BHR: basophil histamine release assay; H₁: histamine type 1; H₂: histamine type 2; IgE: immunoglobulin E; IVIg: intravenous immunoglobulin; NB-UVB: narrowband ultraviolet B Saborio RA, et al. Br J Dermatol. 2022;186:388-413</small></p>	<p>So, the next guideline I'd like to mention is the British [Association of Dermatologists] guidelines. This is also a new guideline, which was released in 2022. So, the first step is, again, second-generation H₁-antihistamines and up dosing up to four-fold. Except mizolastine because of its cardiac side effects. And also the British guidelines added some other options like other second-generation H₁-antihistamines and also montelukast to their first step of treatment. And the second step is omalizumab or cyclosporine. But they also added the laboratory workup of basophil histamine release assay or total IgE levels to decide on the endotype of patients or to predict the patient's response to the second step of treatment. Because we already know that patients with basophil histamine release assay positivity may be better responding to cyclosporine treatment and patients with low total IgE levels may respond poorly or slowly to omalizumab treatment. So, it is good to consider the patient profiles before starting treatment. So British guideline also considers this and in patients who are not responding to omalizumab or cyclosporine treatment, they recommend other treatments. These treatments, of note, these treatments were not put in the algorithm box in the European guidelines due to lack of evidence or not enough evidence.</p>
<p>6</p>	<p>EAACI/GA^{LEN}/EuroGuiDerm/APAAACI 2021 Urticaria Guideline¹</p> <p>EAACI Guidelines</p> <p>Start with standard dose 2nd-generation H₁-AH If needed: Increase 2nd-generation H₁-AH dose (up to 4x)</p> <p>If inadequate control on high dose after 2-4 weeks or earlier if symptoms are intolerable</p> <p>Add on to 2nd-generation H₁-AH: omalizumab If needed: Increase dose and/or shorten interval</p> <p>If inadequate control within 5 months or earlier if symptoms are intolerable</p> <p>Add on to 2nd-generation H₁-AH: cyclosporine</p> <p>A short course of glucocorticosteroids may be considered in case of severe exacerbation</p> <p><small>AH: antihistamine; APAAACI: Asia Pacific Association of Allergy, Asthma and Clinical Immunology; CU: chronic urticaria; EAACI: European Academy of Allergy and Clinical Immunology; EuroGuiDerm: European Centre for Urticaria and Angioedema; GA^{LEN}: Global Allergy and Asthma European Network; GALEN: Global Allergy and Asthma European Network; H₁: histamine type 1; IgE: immunoglobulin E; IVIg: intravenous immunoglobulin; NB-UVB: narrowband ultraviolet B ¹ Subecki T, et al. Allergy. 2022;77:734-746</small></p>	<p>So, I'd like to make a note on the European guidelines, that European guidelines recommend staying on omalizumab treatment minimally 6 months before deciding that omalizumab is not working and also managing treatment according to patient needs. For example, if the patient becomes symptomatic at the third week of omalizumab injection, then we can shorten treatment intervals in these patients. Or if the patient is partially responding, partially, to omalizumab treatment, we can</p>


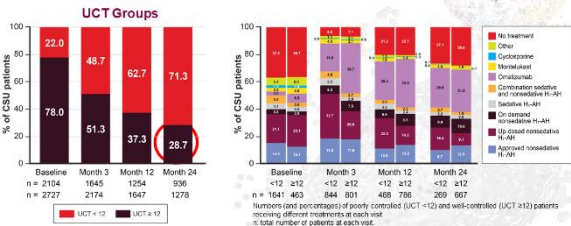
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		<p>increase the dose of omalizumab up to 1200 mg per month, but it is important to note that this is off-label treatment.</p>												
<p>7</p>	<p>Case Study</p> <p>After referral to our clinic, her cetirizine dose was increased to 4 x 10 mg/d</p> <ul style="list-style-type: none"> CBC and routine chemistry tests in normal ranges (no basopenia nor eosinophilia) Anti-TPO IgG: 112 IU/mL (>34) TSH, FT4 levels in normal ranges Total IgE: 340 IU/mL (>100) CRP: 30 mg/dL Helicobacter pylori(-) Urine analysis: normal No chronic infections No psychiatric comorbidity Thyroid USG: normal UCT score: 4 <p>She was started on omalizumab 300 mg SC every 4 weeks. UCT score:</p> <ul style="list-style-type: none"> After 4 weeks: 4 After 8 weeks: 5 After 12 weeks: 4 <p>What should be done next to treat this patient?</p> <p><small>CBC: complete blood count; CRP: C-reactive protein; FT4: free T₄; Ig: immunoglobulin; SC: subcutaneously; TPO: thyroid peroxidase; TSH: thyroid-stimulating hormone; UCT: Urticaria Control Test; USG: ultrasonography.</small></p> <p><small>Case study and patient picture provided by Dr. Emek Kocatürk.</small></p>	<p>So, let's come back to our case study. So this patient referred to our clinic again and her cetirizine dose was increased up to four-fold and a laboratory workup was performed. The laboratory workup showed that the patient had higher anti-TPO levels, and a bit higher total IgE levels. CRP was elevated, but she didn't have any infections, any psychiatric comorbidities, her thyroid ultrasound was normal, and we did a urticaria control test and the urticaria control test score was 4. That means that the patient's disease is not controlled at time of referral. So, this patient was started on omalizumab treatment 300 mg every 4 weeks. And we were expecting to have higher scores of urticaria control tests because the urticaria control test, when it is higher than 12, then that means that urticaria is under control. But for this patient after, even after three injections of omalizumab, we still have the urticaria control test score of 4. So, what should be done next to treat this patient?</p>												
<p>8</p>	<p>Modification of Treatment</p> <table border="1"> <thead> <tr> <th>UCT score</th> <th>UCT < 12</th> <th>UCT = 12-15</th> <th>UCT = 16</th> </tr> </thead> <tbody> <tr> <td>Control level</td> <td>Uncontrolled</td> <td>Well controlled</td> <td>Completely controlled</td> </tr> <tr> <td>Action</td> <td> <p>Step-up* if:</p> <ul style="list-style-type: none"> On 1- to 4-fold 20mg > 7-28 days On OMA > 3 mo </td> <td>Continue therapy and try to optimize</td> <td> <p>Step-down:</p> <p>Based on individual factors by reducing dose or extending intervals</p> </td> </tr> </tbody> </table> <p><small>*For Omalizumab. Individual decisions are based on estimated trigger exposure (eg, cold/allergens in winter).</small></p> <p><small>20mg: 20mg prednisone 14, azelastine; Omalizumab: Omalizumab; chronic inducible urticaria; OMA, omalizumab; UCT: Urticaria Control Test.</small></p> <p><small>Quintero T, et al. Allergy. 2022;77:734-766.</small></p>	UCT score	UCT < 12	UCT = 12-15	UCT = 16	Control level	Uncontrolled	Well controlled	Completely controlled	Action	<p>Step-up* if:</p> <ul style="list-style-type: none"> On 1- to 4-fold 20mg > 7-28 days On OMA > 3 mo 	Continue therapy and try to optimize	<p>Step-down:</p> <p>Based on individual factors by reducing dose or extending intervals</p>	<p>So, the European guidelines recommends the physicians to maintain treatments based on UCT scores. When UCT score is under 12, then that means that the disease is uncontrolled, so we need to step up treatment. So, if the patient is on standard dose of antihistamines, we need to upfold antihistamine treatment or if the patient is on omalizumab treatment, we need to updose omalizumab treatment. If UCT scores are between 12 and 15, then the patient is well controlled and we can continue treatment and try to optimize our treatment. And if UCT is 16, then that means that the urticaria is completely controlled and we can start stepping down the treatment. So, if it's four-fold antihistamines, we can decrease to two-fold antihistamines or</p>
UCT score	UCT < 12	UCT = 12-15	UCT = 16											
Control level	Uncontrolled	Well controlled	Completely controlled											
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		<p>we can start decreasing omalizumab doses or opening omalizumab intervals.</p>																														
<p>9</p>	<p>Case Study</p>  <ul style="list-style-type: none"> • Omalizumab dose was increased to 450 mg for 1 month and afterwards to 600 mg/month^a <ul style="list-style-type: none"> —UCT score after 6 monthly injections: 8 • Continued systemic steroid injections on demand • Omalizumab was stopped and cyclosporine 4 mg/kg (220 mg) was started <ul style="list-style-type: none"> —UCT score after 2 weeks: 11 • Wants to stop because of adverse effects <p><small>^aDose per EAACI guidelines. ^bEPH recommended FDA-approved doses of 150 to 300 mg. ^cEAACI: European Academy of Allergy and Clinical Immunology; FDA: US Food and Drug Administration; EPHF: Expert Task Force on Technical Parameters; UCT: Urticaria Control Test. 1. Gombosi L, et al. Allergy. 2022;77(2):86. 2. Gombosi L, et al. Allergy Clin Immunol. 2018;103(3):307.</small></p>	<p>So, in this patient, we increased omalizumab dose, first up to 450 mg per month, then to 600 mg. And we continued injection 6 months, and she had a total of nine injections of omalizumab, but her UCT score was still 8 and she told that she was continuing systemic steroid injections on demand. So, in this case, omalizumab was stopped and cyclosporine 220 mg was started. She was starting to get relief of her symptoms, because UCT score went up to 11 at 2 weeks. But the patient complained of having some adverse effects and wanted to stop treatment because of fear of having serious side effects. So, this is the point where the guidelines fail, because we don't have any other evidence-based treatment options to give for this patient. So now</p>																														
<p>10</p>	<p>Question</p> <p>What percentage of patients with chronic urticaria are unable to achieve satisfactory symptom relief with current treatments?</p> <p>A. 15% B. 30% C. 50% D. Uncertain</p>	<p>what we are going to do? At this point, I want to ask you a question. What do you think is the percentage of patients with chronic urticaria that are unable to achieve satisfactory symptom relief with current treatments? A. 15% B. 30% C. 50% D. Uncertain. So, the answer is 30%.</p>																														
<p>11</p>	<p>One in 3 Patients Still Are Not Under Control With Available Treatments</p>  <p>UCT Groups</p> <table border="1"> <thead> <tr> <th>Time Point</th> <th>UCT < 12 (%)</th> <th>UCT ≥ 12 (%)</th> </tr> </thead> <tbody> <tr> <td>Baseline</td> <td>78.0</td> <td>22.0</td> </tr> <tr> <td>Month 3</td> <td>51.3</td> <td>48.7</td> </tr> <tr> <td>Month 12</td> <td>37.3</td> <td>62.7</td> </tr> <tr> <td>Month 24</td> <td>28.7</td> <td>71.3</td> </tr> </tbody> </table> <p>% of CSU patients receiving different treatments at each visit</p> <table border="1"> <thead> <tr> <th>Time Point</th> <th>UCT < 12 (%)</th> <th>UCT ≥ 12 (%)</th> </tr> </thead> <tbody> <tr> <td>Baseline</td> <td>1641</td> <td>1641</td> </tr> <tr> <td>Month 3</td> <td>844</td> <td>844</td> </tr> <tr> <td>Month 12</td> <td>468</td> <td>468</td> </tr> <tr> <td>Month 24</td> <td>269</td> <td>269</td> </tr> </tbody> </table> <p><small>Abb: aralkidamide; CSU: chronic spontaneous urticaria; H₂: histamine type 1; UCT: Urticaria Control Test. Maurer M, et al. Clin Exp Allergy. 2020;50:1186-1175.</small></p>	Time Point	UCT < 12 (%)	UCT ≥ 12 (%)	Baseline	78.0	22.0	Month 3	51.3	48.7	Month 12	37.3	62.7	Month 24	28.7	71.3	Time Point	UCT < 12 (%)	UCT ≥ 12 (%)	Baseline	1641	1641	Month 3	844	844	Month 12	468	468	Month 24	269	269	<p>And this result is from AWARE study, which was published in Clinical and Experimental Allergy in 2020. In this AWARE study, the patients were given guideline treatment options, but at the end of 24 months, 28.7% of the patients were still not controlled. They had a UCT score of below 12.</p>
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When Guideline Options Fail...

Conventional Medications	Biologics	Drugs Under Investigation
Dapsone	Mepolizumab	BTK inhibitors
Hydroxychloroquine	Reslizumab	Barzolvolimab (c-KIT inhibitor)
Sulfasalazine	Secukinumab	Tezepelumab (anti-TSLP)
Colchicine	Rituximab	Benralizumab (IL-5R α blocker)
Phototherapy (UVA, PUVA, NB-UVB)	IVig	Dupilumab (anti-IL-4/13)
Azathioprine	TNF-alpha antagonists	Lirentelimab (Siglec-8)
Methotrexate		Mepolizumab (anti-IL-5)
Mycophenolate mofetil		

BTK: Bruton tyrosine kinase; IL: Interleukin; IVig: intravenous immunoglobulin; HSA/HR: nonreducing ultrafiltrate; PUVA: psoralen ultraviolet A; R: receptor; Siglec: sialic acid-binding immunoglobulin-like lectin; TNF: tumor necrosis factor; TSLP: thymic stromal lymphopoietin; UVA: ultraviolet A.
Kocaturk E, et al. J Allergy Clin Immunol Pract. 2022;10:3696-3191.

So, what can we do when guideline options fail? We seem to have a lot of options, but when we look at the conventional part of this table, we have a lot of anti-inflammatory and immunosuppressive treatments, which have serious side effects and also which need close laboratory monitoring, which are difficult to monitor. So, we have dapsone, hydroxychloroquine, phototherapy, azathioprine, methotrexate, and mycophenolate mofetil. And we have some biologics, which have shown effects in case series, and we have biologics that are under investigation.

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Emerging Treatments for CU

Btko, bcr-abl1, BTK, Bruton tyrosine kinase; C5a, complement 5 fragment; CD, cluster of differentiation; CU, chronic urticaria; Fc ϵ R1, high-affinity IgE receptor; HSA/HR, nonreducing ultrafiltrate; IL-4, interleukin 4; IL-5, interleukin 5; IL-13, interleukin 13; IL-17, interleukin 17; IL-17R, interleukin 17 receptor; I α , interleukin 13 receptor; IVig, intravenous immunoglobulin; HSA/HR, nonreducing ultrafiltrate; PUVA, psoralen ultraviolet A; R, receptor; Siglec, sialic acid-binding immunoglobulin-like lectin; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin; UVA, ultraviolet A.
Medford from Kocaturk E, et al. Clin Toxicol Allergy. 2017;1:1.

So here we see the options in the pathomechanism slide of urticaria. The red ones are the molecules that are under clinical trial for chronic urticaria. We see dupilumab here, BTK inhibitors here, anti-IL-5s here, c-KIT inhibitor here, and Siglec-8 here, and TSLP monoclonal antibody here. And also we have some other molecules that have been shown to be effective in case series, such as TNF-alpha blockers, secukinumab, IL-17 blocker, and a CD20 monoclonal antibody rituximab has been shown to be effective in case series. And also we can have in the future some other targets such as H4 receptor blocker, C5a blockers, natalizumab, alpha 4 integrin monoclonal antibody, or MX2 receptor blockers can be options in the future. So, let's dive into treatments that are

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Dupilumab as a Novel Therapy for Difficult-to-Treat Chronic Spontaneous Urticaria

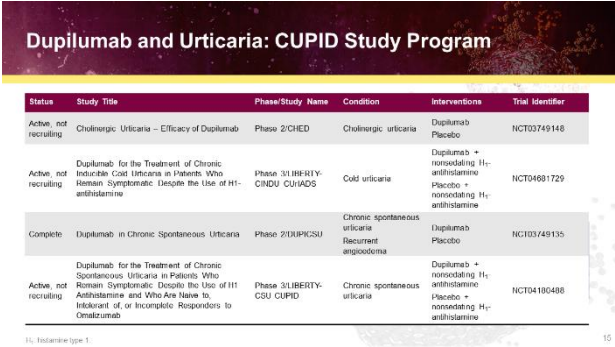
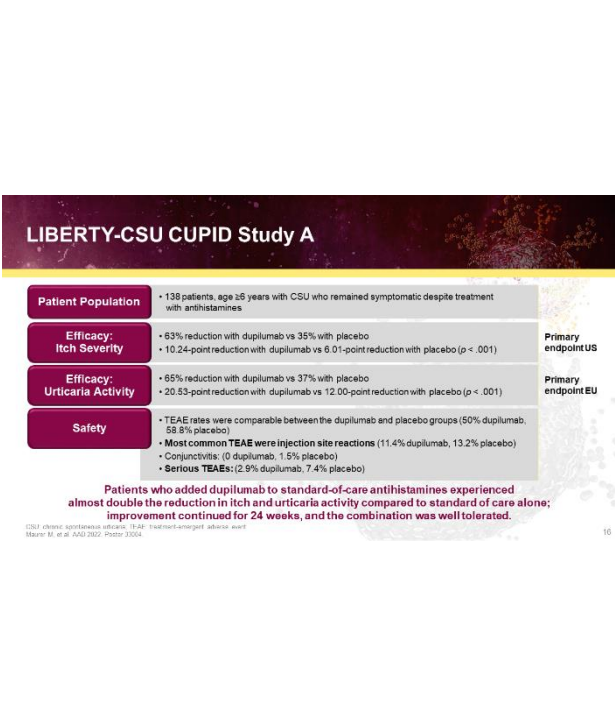
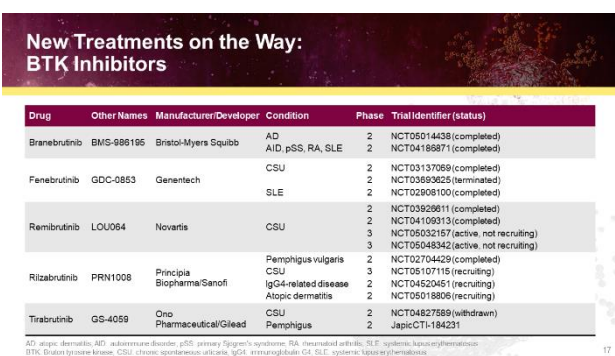
Characteristics of all 6 patients who responded favorably to dupilumab for refractory CSU*

Patient No.	Age (y)	Sex	Duration of illness (y)	Medical history	Concomitant Medications	Dupilumab, 300 mg monthly (no. of months)	Dupilumab, 150 mg monthly (no. of months)	Baseline IAS	IAS at 3 mo post-dupilumab	IAS at 6 mo post-dupilumab	IAS at 12 mo post-dupilumab	UAS Present	UAS at 6 mo	UAS at 12 mo
1	18	Male	2	JA, AD	Ketotifen 2 mg po BID, gabapentin 300 mg po TID, mepolizumab 10 mg po daily, prednisone 150 mg po BID, budesonide 80 mg po daily	6	4	31	Not done	1	5			
2	40	Female	4	AD, autoimmune hypothyroid	Ketotifen 2 mg po BID, dapsone 100 mg po daily, prednisone 40 mg po daily, protopic 0.1% ointment BID	6	3	30-42	Not done	Not done	3	30		
3	50	Female	12	AD	Cetirizine 40 mg po daily, protopic ointment 0.1% BID	4	2	37	0	4	73			
4	28	Male	3	AD	Cetirizine 40 mg po daily, protopic ointment 0.1% BID	6	6	42	2	2	30			
5	31	Female	6	AD, severe asthma	Rhusadine 40 mg po daily, protopic ointment 0.1% BID	38	0	Not done	Not done	Not done	3	29		
6	50	Male	7	AD, severe asthma	Rhusadine 40 mg po daily, protopic ointment 0.1% BID, dapsone ointment BID	12	0	30	3	2	20			

*Follow-up period was 12 months.
*Treatment is data case presented.
AD, atopic dermatitis; BID, twice daily; BSA, body surface area; CSU, chronic spontaneous urticaria; IAS, investigator global assessment; JA, juvenile idiopathic arthritis; po, per os (by mouth); TID, 3 times daily; UAS, Urticaria Activity Score.
Lee JK, Simpson RS. J Allergy Clin Immunol Pract. 2016;7:1698-1691.e1.

under investigation for chronic urticaria. So, the dupilumab is an IL-4 blocker, and there have been increasing reports of chronic urticaria patients, many subtypes of chronic urticaria that responded well to dupilumab treatment and one of these reports is here, was presented by Lee JK in JACI Practice Journal. And they presented six cases of patients who had both atopic dermatitis and chronic spontaneous urticaria. These patients did not respond to

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<p>15</p>	 <p>Dupilumab and Urticaria: CUPID Study Program</p> <table border="1"> <thead> <tr> <th>Status</th> <th>Study Title</th> <th>Phase/Study Name</th> <th>Condition</th> <th>Interventions</th> <th>Trial Identifier</th> </tr> </thead> <tbody> <tr> <td>Active, not recruiting</td> <td>Cholinergic Urticaria – Efficacy of Dupilumab</td> <td>Phase 2/CHED</td> <td>Cholinergic urticaria</td> <td>Dupilumab Placebo</td> <td>NCT03749148</td> </tr> <tr> <td>Active, not recruiting</td> <td>Dupilumab for the Treatment of Chronic Inducible Cold Urticaria in Patients Who Remain Symptomatic Despite the Use of H1-antihistamine</td> <td>Phase 3/LIBERTY-CINDU CU/ADS</td> <td>Cold urticaria</td> <td>Dupilumab + non-sedating H₁ antihistamine Placebo + non-sedating H₁ antihistamine</td> <td>NCT04691729</td> </tr> <tr> <td>Complete</td> <td>Dupilumab in Chronic Spontaneous Urticaria</td> <td>Phase 2/URPCSU</td> <td>Chronic spontaneous urticaria Recurrent angioedema</td> <td>Dupilumab Placebo</td> <td>NCT03749135</td> </tr> <tr> <td>Active, not recruiting</td> <td>Dupilumab for the Treatment of Chronic Spontaneous Urticaria in Patients Who Remain Symptomatic Despite the Use of H1 Antihistamine and Who Are Naïve to, Inadequate of, or Incomplete Responders to Omalizumab</td> <td>Phase 3/LIBERTY-CSU CUPID</td> <td>Chronic spontaneous urticaria</td> <td>Dupilumab + non-sedating H₁ antihistamine Placebo + non-sedating H₁ antihistamine</td> <td>NCT04180488</td> </tr> </tbody> </table> <p><small>15. H1: histamine type 1.</small></p>	Status	Study Title	Phase/Study Name	Condition	Interventions	Trial Identifier	Active, not recruiting	Cholinergic Urticaria – Efficacy of Dupilumab	Phase 2/CHED	Cholinergic urticaria	Dupilumab Placebo	NCT03749148	Active, not recruiting	Dupilumab for the Treatment of Chronic Inducible Cold Urticaria in Patients Who Remain Symptomatic Despite the Use of H1-antihistamine	Phase 3/LIBERTY-CINDU CU/ADS	Cold urticaria	Dupilumab + non-sedating H ₁ antihistamine Placebo + non-sedating H ₁ antihistamine	NCT04691729	Complete	Dupilumab in Chronic Spontaneous Urticaria	Phase 2/URPCSU	Chronic spontaneous urticaria Recurrent angioedema	Dupilumab Placebo	NCT03749135	Active, not recruiting	Dupilumab for the Treatment of Chronic Spontaneous Urticaria in Patients Who Remain Symptomatic Despite the Use of H1 Antihistamine and Who Are Naïve to, Inadequate of, or Incomplete Responders to Omalizumab	Phase 3/LIBERTY-CSU CUPID	Chronic spontaneous urticaria	Dupilumab + non-sedating H ₁ antihistamine Placebo + non-sedating H ₁ antihistamine	NCT04180488	<p>So, dupilumab is under investigation for chronic urticaria, both for chronic spontaneous urticaria and also cold urticaria and cholinergic urticaria.</p>																														
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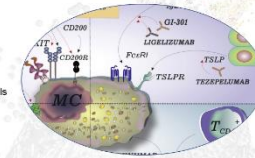
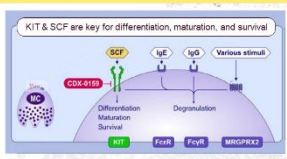
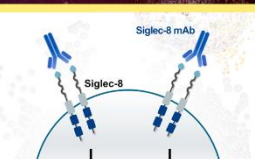
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<p>18</p>	<p>New Treatments on the Way: BTK Inhibitors</p> <ul style="list-style-type: none"> Work in CSU through decreased signaling of FcεRI in MCs and basophils Potential for efficacy in CSU due to <ul style="list-style-type: none"> Inhibition of BTK-mediated degranulation in MCs Autoantibody production in B cells <p><small>BCR: B-cell receptor; BTK: Bruton tyrosine kinase; CSU: chronic spontaneous urticaria; Ig: immunoglobulin; MC: mast cell; FcεRI: FcεRI; histamine: histamine; S-IgE: spleen tyrosine kinase; Medvedev-Davletov F, et al. Allergy. 2022;77:2558-2568.</small></p>	<p>studies ongoing with BTK inhibitors. So, what do BTK inhibitors do? BTK is a signaling molecule that is found in mast cells, basophils, and B cells. And they help in transducing the signal. And then by this way, with the signal link, this leads to degranulation of mast cells and basophils. And, also, when BTK works then B cells are able to produce immunoglobulins. And when they are blocked, mast cells and basophils do not activate or release mediators and B cells do not produce immunoglobulins. So this shows the dual effect mechanism for chronic spontaneous urticaria. So, you can both inhibit production of immunoglobulins and also inhibit mast cell and basophil degranulation.</p>																														
<p>19</p>	<p>New Treatments on the Way: BTK Inhibitors—Fenebrutinib</p> <p><small>Arora V. Open Access J. Published 24 November 2022. Fenebrutinib in H1-antihistamine-refractory chronic spontaneous urticaria: a randomized phase 2 trial. Allergology International. 2023;72(1):1-10. doi:10.1016/j.allint.2022.11.001. Liu, N.H., et al. Chronic Urticaria. Lancet. 2020;395(10249):1024-1034. doi:10.1016/S0140-6736(20)30545-9. Jones-McLellan, L.M., et al. J. Allergy Clin. Immunol. 2021;147(1):1-10. doi:10.1016/j.jaci.2020.09.047.</small></p> <ul style="list-style-type: none"> Demonstrated improvement in weekly hive, itching, and UAS7 scores Was found highly effective especially in pts with IgG autoantibodies (greater reductions in IgG-anti-FcεRI were associated with greater decreases in UAS7 at week 8) Significant increases in transaminases, especially with 200-mg dose <p><small>BTK: Bruton tyrosine kinase; IgG: immunoglobulin G; UAS7: Urticaria Activity Score. Metz M, et al. N Engl J Med. 2021;377:1981-1995.</small></p>	<p>So, the first BTK inhibitor which was tested in chronic spontaneous urticaria was fenebrutinib. And fenebrutinib demonstrated improvement in weekly hive itching and UAS7 scores in the phase 2 trial, and it was also found highly effective especially in patients with IgG autoantibodies. These patients has the autoimmune 2B type chronic spontaneous urticaria. Because there were greater reductions in IgG-anti-Fc-epsilon receptor 1 associated with great decreases in UAS7 scores. But, unfortunately, there were significant increases in transaminases, especially with the 200-mg dose. Fenebrutinib did not continue the studies in chronic spontaneous urticaria, so it's not under development now.</p>																														
<p>20</p>	<p>New Treatments on the Way: BTK Inhibitors—Remibrutinib</p> <p>Shown efficacy and safety in phase 2 studies of CSU:</p> <ul style="list-style-type: none"> Rapid improvement in UAS7 scores as early as at week 1 60% reached UAS7 = 0 Most common adverse events were headache, nasopharyngitis, infections, and skin/subcutaneous tissue reactions <table border="1"> <thead> <tr> <th>Status</th> <th>Study Title</th> <th>Intervention(s)</th> <th>Phase</th> <th>Trial Identifier</th> </tr> </thead> <tbody> <tr> <td>Available</td> <td>Global Managed Access Program Cohort for Remibrutinib in Adult Patients With Chronic Spontaneous Urticaria</td> <td>Remibrutinib</td> <td>1b/1a</td> <td>NCT05175724</td> </tr> <tr> <td>Not yet recruiting</td> <td>An Extension Study of Long-term Efficacy, Safety and Tolerability of Remibrutinib in Chronic Spontaneous Urticaria Patients Who Completed Preceding Studies With Remibrutinib</td> <td>Remibrutinib (blinded) Placebo Remibrutinib (open label)</td> <td>3</td> <td>NCT05613001</td> </tr> <tr> <td>Active, not recruiting</td> <td>A Safety and Efficacy Study of Remibrutinib in the Treatment of CSU in Japanese Adults Inadequately Controlled by H1-antihistamines (JSCURT)</td> <td>Remibrutinib</td> <td>3</td> <td>NCT05048342</td> </tr> <tr> <td>Active, not recruiting</td> <td>A Phase 3 Study of Efficacy and Safety of Remibrutinib in the Treatment of CSU in Adults Inadequately Controlled by H1-Antihistamines (RELIMX 1)</td> <td>Remibrutinib (blinded) Placebo Remibrutinib (open label)</td> <td>3</td> <td>NCT05020311</td> </tr> <tr> <td>Active, not recruiting</td> <td>A Phase 3 Study of Efficacy and Safety of Remibrutinib in the Treatment of CSU in Adults Inadequately Controlled by H1-Antihistamines (RELIMX 2)</td> <td>Remibrutinib (blinded) Placebo Remibrutinib (open label)</td> <td>3</td> <td>NCT05022157</td> </tr> </tbody> </table> <p><small>BTK: Bruton tyrosine kinase; CSU: chronic spontaneous urticaria; H1: histamine type 1; UAS7: Urticaria Activity Score. Arora V. UACI 2022. Oral presentation. Maier M. GALEN UGARE 2021. Oral presentation.</small></p>	Status	Study Title	Intervention(s)	Phase	Trial Identifier	Available	Global Managed Access Program Cohort for Remibrutinib in Adult Patients With Chronic Spontaneous Urticaria	Remibrutinib	1b/1a	NCT05175724	Not yet recruiting	An Extension Study of Long-term Efficacy, Safety and Tolerability of Remibrutinib in Chronic Spontaneous Urticaria Patients Who Completed Preceding Studies With Remibrutinib	Remibrutinib (blinded) Placebo Remibrutinib (open label)	3	NCT05613001	Active, not recruiting	A Safety and Efficacy Study of Remibrutinib in the Treatment of CSU in Japanese Adults Inadequately Controlled by H1-antihistamines (JSCURT)	Remibrutinib	3	NCT05048342	Active, not recruiting	A Phase 3 Study of Efficacy and Safety of Remibrutinib in the Treatment of CSU in Adults Inadequately Controlled by H1-Antihistamines (RELIMX 1)	Remibrutinib (blinded) Placebo Remibrutinib (open label)	3	NCT05020311	Active, not recruiting	A Phase 3 Study of Efficacy and Safety of Remibrutinib in the Treatment of CSU in Adults Inadequately Controlled by H1-Antihistamines (RELIMX 2)	Remibrutinib (blinded) Placebo Remibrutinib (open label)	3	NCT05022157	<p>But what is under development is the remibrutinib and it has late-stage trials ongoing at the moment for chronic spontaneous urticaria. In the phase 2 studies, there was rapid improvement in UAS7 scores as early as at week 1. And 60% of the patients reached UAS7 zero, which is a really good achievement. And most common adverse events were headache, nasopharyngitis, infections, and skin subcutaneous tissue reactions. And not very serious adverse events occurred.</p>
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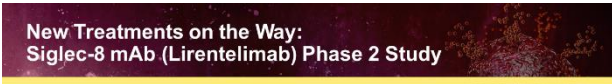

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<p>21</p>	<p>New Treatments on the Way: Tezepelumab—Anti-TSLP Human mAb</p> <ul style="list-style-type: none"> • MCs express TSLP receptors • TSLP is markedly upregulated in the wheals of patients with CSU • Tezepelumab is efficacious for the treatment of patients with asthma <ul style="list-style-type: none"> —Decreases blood eosinophil counts and total serum IgE levels —Most common AEs associated with tezepelumab in asthma studies were pharyngitis, arthralgia, and back pain  <table border="1"> <thead> <tr> <th>Status</th> <th>Study Title</th> <th>Condition</th> <th>Interventions</th> </tr> </thead> <tbody> <tr> <td>Active (not recruiting)</td> <td>Study to Evaluate Tezepelumab in Adults With Chronic Spontaneous Urticaria (IMPACT)</td> <td>Chronic spontaneous urticaria</td> <td>Tezepelumab: Dose 1 Tezepelumab: Dose 2 Omalizumab Placebo</td> </tr> </tbody> </table> <p><small>AEs, adverse events; CSU, chronic spontaneous urticaria; IgE, immunoglobulin E; mAb, monoclonal antibody; MC, mast cell; TSLP, thymic stromal lymphopoietin. Meurer M, et al. J Allergy Clin Immunol Pract. 2021;9:1007-1016.</small></p>	Status	Study Title	Condition	Interventions	Active (not recruiting)	Study to Evaluate Tezepelumab in Adults With Chronic Spontaneous Urticaria (IMPACT)	Chronic spontaneous urticaria	Tezepelumab: Dose 1 Tezepelumab: Dose 2 Omalizumab Placebo	<p>So, another treatment that is under development is the tezepelumab, which is an anti-TSLP human monoclonal antibody. TSLP is markedly upregulated in the wheals of patients with CSU, and so this is the originating mechanism of action that will be identified if it will be effective in patients with CSU or not. So, it's under clinical trial, but no results have been posted yet.</p>							
Status	Study Title	Condition	Interventions														
Active (not recruiting)	Study to Evaluate Tezepelumab in Adults With Chronic Spontaneous Urticaria (IMPACT)	Chronic spontaneous urticaria	Tezepelumab: Dose 1 Tezepelumab: Dose 2 Omalizumab Placebo														
<p>22</p>	<p>New Treatments on the Way: C-KIT Inhibitor (CDX-1059, Barzolvolimab)</p> <ul style="list-style-type: none"> • 21 ColdU, 10 SD patients • Single IV infusion 3 mg/kg • Complete response by provocation testing: <ul style="list-style-type: none"> —100% of ColdU patients —90% of SD patients • Response sustained 77 days in ColdU, 57 days in SD • Marked depletion of skin mast cells and serum tryptase • Well tolerated: <ul style="list-style-type: none"> —Reversible hair color changes and taste disorders due to inhibition of KIT signaling in other cells  <table border="1"> <thead> <tr> <th>Status</th> <th>Study Title</th> <th>Interventions</th> <th>Phase</th> <th>Trial Identifier</th> </tr> </thead> <tbody> <tr> <td>Recruiting</td> <td>A Phase 2 Study of CDX-1059 in Patients With Chronic Spontaneous Urticaria</td> <td>Barzolvolimab Placebo</td> <td>2</td> <td>NCT03362365</td> </tr> <tr> <td>Recruiting</td> <td>A Study of CDX-1059 in Patients With Chronic Inducible Urticaria</td> <td>Barzolvolimab Placebo</td> <td>2</td> <td>NCT19-405660</td> </tr> </tbody> </table> <p><small>CDX-1059, cold inducible urticaria; SD, symptomatic dermographism; SDF-1, stromal cell derived factor-1; SDF-1R, stromal cell derived factor-1 receptor; TcR, T cell receptor; FcγR, Fc gamma receptor; MHCPIR2, mast cell protease 2 receptor. Aizawa D, et al. Allergy. 2022;77:2383-2400. Terhune-Milawa D, GALEN USCAR. 2021. Oral presentation.</small></p>	Status	Study Title	Interventions	Phase	Trial Identifier	Recruiting	A Phase 2 Study of CDX-1059 in Patients With Chronic Spontaneous Urticaria	Barzolvolimab Placebo	2	NCT03362365	Recruiting	A Study of CDX-1059 in Patients With Chronic Inducible Urticaria	Barzolvolimab Placebo	2	NCT19-405660	<p>And the other option is the really dramatic treatment of c-KIT inhibitor barzolvolimab, which led to dramatic achievements in patients with inducible urticarias in the phase 1b study. So, this treatment leads to mast cell depletion. So, and it's associated with very good results. The study included 21 cold urticaria patients and 10 symptomatic dermographism patients. These patients were given single IV infusions. And complete response by provocation testing was reported by 100% of cold urticaria patients and 90% of symptomatic dermographism patients. And the response sustained 77 days in cold urticaria and 57 days in symptomatic dermographism patients. And there were marked depletion of skin mast cells and serum tryptase in these patients. It was well tolerated. However, there were reversible hair color changes and taste disorders due to inhibition of KIT signaling in other cells. So, the phase 2 program is ongoing with barzolvolimab with chronic spontaneous urticaria and also chronic inducible</p>
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Recruiting	A Study of CDX-1059 in Patients With Chronic Inducible Urticaria	Barzolvolimab Placebo	2	NCT19-405660													
<p>23</p>	<p>New Treatments on the Way: Siglec-8 mAb (Lirentelimab)</p> <ul style="list-style-type: none"> • Siglec-8 is an inhibitory receptor selectively expressed on MCs and eosinophils and, to a lesser degree, basophils • Siglec-8 engagement by antibodies has been shown to inhibit MC activation and induce apoptosis in eosinophils • Lirentelimab (AK002), is humanized, nonfucosylated IgG1 mAb against Siglec-8  <p><small>ADCC, antibody-dependent cellular cytotoxicity; IgG1, immunoglobulin G1; mAb, monoclonal antibody; MC, mast cell; Siglec, sialic acid-binding immunoglobulin-like lectin. Youngblood DA, et al. Cells. 2020;10:19.</small></p>	<p>urticaria. The other option is the mast cell silencing lirentelimab, which is a Siglec-8 monoclonal antibody. Siblec-8 is an inhibitory receptor which is found on mast cells and also on eosinophils. So, when a monoclonal antibody targets Siglec-8, then mast cells and eosinophils get silenced and do not activate. So, there was</p>															

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<p>24</p>	 <p>New Treatments on the Way: Siglec-8 mAb (Lirentelimab) Phase 2 Study</p> <p>CR at Week 22:</p> <ul style="list-style-type: none"> Omaliuzumab-naive, 92% (95% CI, 64%-100%) Omaliuzumab-refractory, 36% (95% CI, 11%-69%) ChoiU, 82% (95% CI, 48%-98%) SDerm, 40% (95% CI, 12%-74%) Most common adverse events were infusion-related reactions (43%), nasopharyngitis (21%), and headache (19%) <p>An open-label, proof-of-concept study of lirentelimab for antihistamine-resistant chronic spontaneous and inducible urticaria</p> <p>Sabine Altmeyer, MD,^{1,2,3,4} Peter Staibach, MD,⁵ Malika Pasha, MBA,⁶ Rupinder Singh, MD,⁷ Alan T. Cheng, BS,⁸ Jonathan A. Bernstein, MD,^{9,10,11} Heidi S. Bernstein, MD, PhD,¹² Frank Steinhilber, MD,¹³ and Bruce Hanau, MD¹⁴ <small>Berlin and Mainz, Germany; Salzburg, Austria; Cleveland, Ohio</small></p> <table border="1"> <thead> <tr> <th rowspan="2">Parameter</th> <th colspan="3">CSU</th> <th colspan="2">CindU</th> </tr> <tr> <th>Omaliuzumab-naive</th> <th>Omaliuzumab-refractory</th> <th>Omaliuzumab-naive and -refractory</th> <th>CU</th> <th>SDerm</th> </tr> </thead> <tbody> <tr> <td>UCT score change from baseline, n</td> <td>13</td> <td>11</td> <td>24</td> <td>11</td> <td>10</td> </tr> </tbody> </table> <p><small>ChoiU, cholinergic urticaria; CindU, chronic inducible urticaria; CR, complete response; CSU, chronic spontaneous urticaria; CU, chronic urticaria; mAb, monoclonal antibody; SDerm, symptomatic dermographism; Siglec, sialic acid-binding immunoglobulin-like lectin; UCT, Urticaria Control Test. Altmeyer S, et al. J Allergy Clin Immunol. 2022;149:1038-1050.e7.</small></p>	Parameter	CSU			CindU		Omaliuzumab-naive	Omaliuzumab-refractory	Omaliuzumab-naive and -refractory	CU	SDerm	UCT score change from baseline, n	13	11	24	11	10	<p>a phase 2 study on lirentelimab which included omalizumab-naive and also omalizumab-refractory patients and which showed nice improvement in both with more refractory patients, and also cholinergic urticaria and symptomatic dermographism patients. And most common adverse events were infusion-related reactions, nasopharyngitis, and headaches. So, it is also a promising</p>																			
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<p>25</p>	 <p>Promising Treatments for CU: Summary</p> <table border="1"> <thead> <tr> <th></th> <th>Dupilumab</th> <th>Remibrutinib</th> <th>Barzolvolimab</th> <th>Benralizumab</th> <th>Lirentelimab</th> </tr> </thead> <tbody> <tr> <td>Target</td> <td>IL-4 and IL-13</td> <td>BTK</td> <td>KIT</td> <td>IL-5Rα</td> <td>Siglec-8</td> </tr> <tr> <td>Mechanism of action</td> <td>Anti-IL-4Rα monoclonal antibody</td> <td>Oral selective covalent BTK inhibitor</td> <td>Anti-KIT monoclonal antibody</td> <td>Anti-IL-5 receptor antibody</td> <td>Anti-Siglec-8 monoclonal antibody</td> </tr> <tr> <td>Phase</td> <td>3</td> <td>3</td> <td>2</td> <td>2</td> <td>2</td> </tr> <tr> <td>Trial Identifiers</td> <td>NCT05526621, NCT03749148, NCT04681729, NCT03749135, NCT04100408</td> <td>NCT05170724, NCT05513001, NCT05048342, NCT05032157, NCT05030311, NCT05677451</td> <td>NCT05368285, NCT05403660</td> <td>NCT03183024, NCT04812725</td> <td>NCT05528861</td> </tr> <tr> <td>Study results</td> <td>In a phase 3 trial in patients refractory to omalizumab, did not reach statistical significance in an interim analysis. Results from a phase 3 trial in biologic-naïve patients showed significantly reduced itch and hives compared to standard of care¹</td> <td>A rapid improvement in UAS7 was observed as early as at week 1 in phase 2b trial²</td> <td>Sustained and high efficacy in inducible urticarias in phase 1b study³</td> <td>Improvement in UAS7 and CUGQL scores in phase 4 study⁴</td> <td>Showed efficacy in all 3 forms of antihistamine-resistant CU in phase 2a trial⁵</td> </tr> </tbody> </table> <p><small>BTK, Bruton tyrosine kinase; CSU, chronic spontaneous urticaria; CU, chronic urticaria; CUGQL, Chronic Urticaria Quality-of-Life; IL, interleukin; R, receptor; Siglec, sialic acid-binding immunoglobulin-like lectin; UAS7, Urticaria Activity Score-7. 1. Sandhu P, et al. N Engl J Med. 2022;386:1471-1481. doi:10.1056/NEJMoa2113779. 2. Hanau B, et al. J Allergy Clin Immunol. 2022;149:1038-1050.e7. 3. Tachibana M, et al. J Allergy Clin Immunol. 2022;149:1038-1050.e7. 4. Tachibana M, et al. J Allergy Clin Immunol. 2022;149:1038-1050.e7. 5. Bernstein JA, et al. N Engl J Med. 2020;383(14):1395-1397. 6. Altmeyer S, et al. J Allergy Clin Immunol. 2022;149:1038-1050.e7.</small></p>		Dupilumab	Remibrutinib	Barzolvolimab	Benralizumab	Lirentelimab	Target	IL-4 and IL-13	BTK	KIT	IL-5R α	Siglec-8	Mechanism of action	Anti-IL-4R α monoclonal antibody	Oral selective covalent BTK inhibitor	Anti-KIT monoclonal antibody	Anti-IL-5 receptor antibody	Anti-Siglec-8 monoclonal antibody	Phase	3	3	2	2	2	Trial Identifiers	NCT05526621, NCT03749148, NCT04681729, NCT03749135, NCT04100408	NCT05170724, NCT05513001, NCT05048342, NCT05032157, NCT05030311, NCT05677451	NCT05368285, NCT05403660	NCT03183024, NCT04812725	NCT05528861	Study results	In a phase 3 trial in patients refractory to omalizumab, did not reach statistical significance in an interim analysis. Results from a phase 3 trial in biologic-naïve patients showed significantly reduced itch and hives compared to standard of care ¹	A rapid improvement in UAS7 was observed as early as at week 1 in phase 2b trial ²	Sustained and high efficacy in inducible urticarias in phase 1b study ³	Improvement in UAS7 and CUGQL scores in phase 4 study ⁴	Showed efficacy in all 3 forms of antihistamine-resistant CU in phase 2a trial ⁵	<p>treatment option. So as a summary, the most important upcoming treatments are shown in this table and the first one is dupilumab. Which is on phase 3 development. In the phase 3 trial in patients refractory to omalizumab, it did not reach its clinical significance. In an interim analysis, but the results from the phase 3 trial in biologic-naïve patients showed significantly reduced itch and hives compared to standard dose of antihistamines. And remember, remibrutinib is a BTK Bruton kinase inhibitor, and it's an oral selective and covalent oral drug in phase 3 clinical trials. And it showed repeat improvement in UAS7 as early as at week 1 in phase 2B trials. Barzolvolimab is an anti-KIT monoclonal antibody which is in phase 2 trials. It showed sustained and high efficacy in inducible urticarias in phase 1B study. Benralizumab is an anti-IL-5 receptor antibody which is on phase 2 clinical trials; it showed improvement in UAS7 and chronic urticaria quality-of-life scores in phase 4 studies. Lirentelimab is an anti-Siglec-8 monoclonal antibody, which is under development phase 2; it showed efficacy in all three forms of antihistamine-resistant chronic urticaria in phase 2a trial.</p>
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Comprehensive Care in Context of Emerging Treatments

- Avoidance of triggering factors
- Offering clinical trial enrollment when appropriate
- Treatment of comorbidities*
- Good communication skills and having enough time for patients!


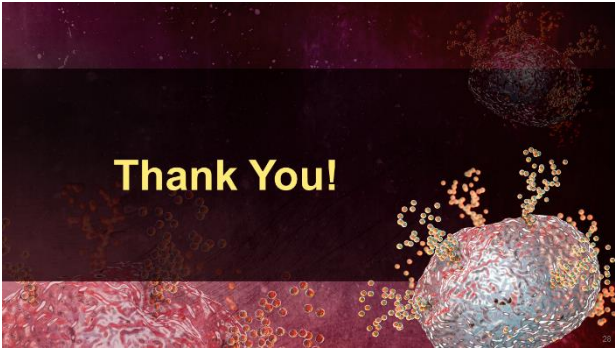
* Includes treatment of concomitant infections, inflammatory and autoimmune disease and management of psychiatric comorbidities. UCARE Network 2022. <https://go2em.ucare.com/>

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So, it is nice to see that we have these new treatment options on the horizon coming and we are excited to be able to use these options. But there are some other factors that we should not forget to consider, while managing our chronic urticaria patients. We need to make some discussions and talks with these patients and ask about the triggering factors, such as some forms of inducible urticarias. We need to ask about cold or hot weather or sports or pressure, or symptomatic dermographism, like stroking the skin. So, we need to ask about inducible urticarias and also about nonsteroid anti-inflammatory medications — if they lead to angioedema exacerbations or urticaria exacerbations. And also stress, infections, and also vaccinations can cause exacerbations in our patients. So, we need to give information to our patients on these topics. And also we need to find out comorbidities, especially Hashimoto thyroiditis is very common in chronic spontaneous urticaria patients, so we need to be aware of this. We can check anti-TPO levels and also they may have other autoimmune disorders and also psychiatric comorbidities. In one-third of the patients we find depression, anxiety, panic attack, so it's important to consider. And also sometimes chronic infections or chronic inflammation such as gastritis or tooth infections. So, we need to be aware of them and ask about the symptoms of these conditions and give available appropriate treatments for these patients. And of course, while we have that many options under development, so we need to also invite patients to enroll in clinical trials if appropriate. So, good communication skills and having enough time for patients is also important, because when we speak and give time for these patients, then these patients become more connected to us and continue our treatment and that

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		<p>really makes importance, that really makes some sense for these patients to follow the treatment you give.</p>
<p>27</p>	 <p>Key Take-Aways</p> <ul style="list-style-type: none"> Despite the prevalence and impact of CU, there remain unmet clinical needs for effective management of the disease Advances in our understanding of the pathogenesis of CU have led to the development of more effective and targeted treatments for CU Promising treatments include mAbs targeting IL-4Rα, IL-5 or IL-5Rα, KIT, or Siglec-8, as well as small molecule oral BTK inhibitors Ensuring comprehensive and multidisciplinary care is crucial for achieving best possible patient outcomes <p><small>BTK: Brutin tyrosine kinase; CU: chronic urticaria; E: itraiedekin; mAb: monoclonal antibody; R: receptor; Siglec: sialic acid binding immunoglobulin-like lectin</small></p>	<p>So, what are the key takeaways from my presentation? So, we saw that still there are patients that do not respond to available treatment. So, it's evident that we need some new treatments and by advances in the treatment of urticaria, then we have new pathogenesis pathways. So, we are discovering more about chronic urticaria. The promising treatments include monoclonal antibodies targeting IL-4, IL-5, c-KIT, Siglec-8, as well as small molecule oral BTK inhibitors. But however, ensuring comprehensive and multidisciplinary care is crucial for achieving best possible patient outcomes in chronic urticaria treatments.</p>
<p>28</p>	 <p>Thank You!</p>	<p>Thank you for your attention.</p>