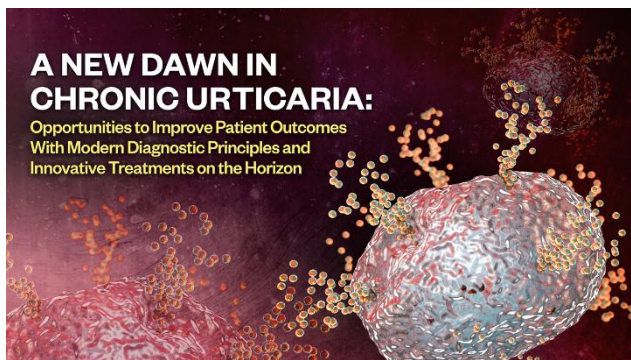
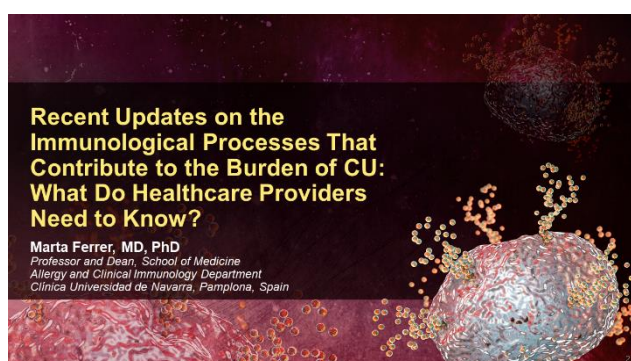
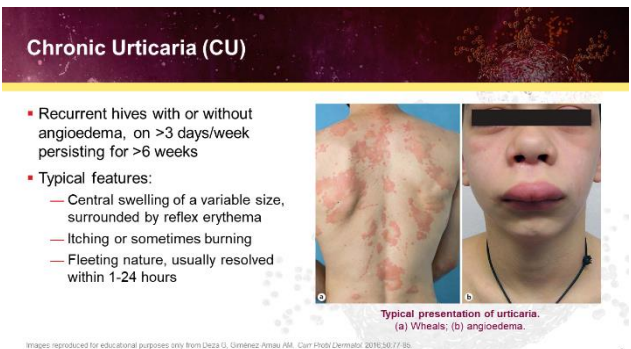


# A NEW DAWN IN CHRONIC URTICARIA: Opportunities to Improve Patient Outcomes With Modern Diagnostic Principles and , Innovative Treatments on the Horizon

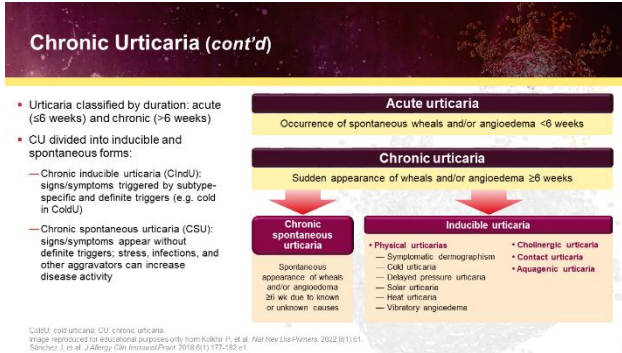
Recent Updates on the Immunological Processes That Contribute to the Burden of CU: What Do Healthcare Providers Need to Know?

<p>1</p>		<p>Welcome to a New Dawn in Chronic Urticaria: Opportunities to Improve Patient Outcomes with Modern Diagnostic Principles and Innovative Treatments on the Horizon.</p>
<p>2</p>		<p>We will cover Recent Updates on the Immunological Processes that Contribute to the Burden of CU: What Do Healthcare Providers Need to Know?</p>
<p>3</p>		<p>Chronic urticaria is not a life-threatening disease; however, it implies a very high impact on quality of life and has important comorbidities. In this activity, we will cover this quality-of-life impact. We will briefly explain the epidemiology of chronic urticaria comorbidities, and then we will focus on new targets for drugs that they are developing and could cover those patients that are not controlled with present treatments that we have at hand.</p>

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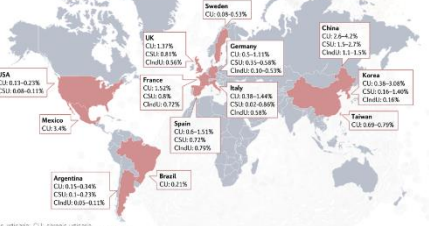
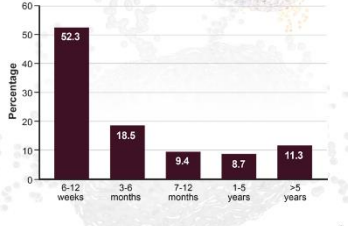
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As you know, and I think, I believe it was explained in the previous activity, urticaria is classified as acute urticaria (when hives last less than 6 weeks) and chronic urticaria. Chronic urticaria is also divided into chronic spontaneous urticaria, which is the focus of my talk. That consists of the appearance of wheals with or without angioedema daily or almost daily with no known [trigger]. Whereas inducible urticaria are different types of urticaria that consist of the appearance of hives in the skin, but where the trigger, where the stimulus, was in contact with the skin. The big difference between chronic spontaneous urticaria and inducible urticaria is that inducible urticarias are mainly mediated by mast cell degranulation and mediated by histamine. So, the hives, they just last for 30 minutes, 1 hour, [at most] 2 hours, and once histamine is metabolized, the urticaria is gone. Yet chronic spontaneous urticaria hives appear and disappear every 24 to 36 hours but the hives stay longer. Depending on the stimulus, inducible urticaria is classified as dermographism, and the stimulus is scratching on the skin; or cold urticaria, contact with cold; solar; delayed pressure urticaria, which is a little different from others, because usually it's in the form of angioedema and the skin lesion appears 6 hours after the stimulus. Solar (heat urticaria) and vibration is the trigger for vibratory angioedema. There are other types of urticaria; one is relatively frequent, which is called cholinergic urticaria, in which the stimulus is the increase of the body core temperature. So that's why these patients when they exercise or when they get in buildings with heat, they break into hives, usually the whole body. But once the body is cooled



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		<p>down, they [rapidly] disappear. So, it's completely different — the picture of inducible urticaria and chronic spontaneous urticaria.</p>
<p>5</p>	<div data-bbox="331 472 965 824"> <h3>Prevalence</h3> <ul style="list-style-type: none"> <li>Global prevalence of CU varies from 0.13% to 4.2%</li> <li>CSU accounts for over two-thirds of CU cases</li> <li>More prevalent in women than men (2-4:1 ratio)</li> </ul>  <p><small>Credit: chronic inducible urticaria; CSU: chronic spontaneous urticaria; CU: chronic urticaria. Image reproduced for educational purposes only from Kikkhri P. et al. Nat Rev Dis Primers. 2022;8(1):1. Gagj P. et al. J Invest Allergol Clin Immunol. 2004;14(3):214-220. Sánchez-Borges M. et al. World Allergy Organ J. 2021;14(5):186033. Kikkhri P. et al. Nat Rev Dis Primers. 2022;8(1):1. Mazure M. et al. Allergy. 2011;66(3):317-336. Ciccarelli N. et al. G Ital Dermatol Venereol. 2016;141(5):544-552.</small></p> </div>	<p>The prevalence is interesting because, globally, all the studies find similar prevalence along different countries, which goes from 0.2% to 4%. But the most interesting thing, and mainly in chronic spontaneous urticaria, is that in all the studies, the prevalence in women is three times higher than in men, and this is in line of the autoimmune basis of this disease that we will cover later.</p>
<p>6</p>	<div data-bbox="331 1037 965 1388"> <h3>Time to Symptom-Free Recovery</h3> <ul style="list-style-type: none"> <li>Approximately 70% of CU patients are expected to experience symptom-free recovery within 6 months</li> <li>For the remaining 30%, achieving symptom relief can be a prolonged and complex process</li> <li>The chance of no remission after 5 years is 11%, highlighting a need for improved interventions for this population</li> </ul>  <p><small>Image reproduced for educational purposes only from Gagj P. et al. J Invest Allergol Clin Immunol. 2004;14(3):214-220.</small></p> </div>	<p>How long does chronic urticaria last? This is a study that we performed in a large population in Spain, and 70% last less than 1 year. But the most important percentages are related to patients whose urticaria lasts for more than 1 year. Specifically, 30% of patients fall under this category, while some cases persist between 1 and 5 years. Of particular importance is the 11% of patients whose urticaria lasts for more than 5 years. Urticaria, also, we should take into account that appears at some point in life and after these years they completely disappear. We don't have any biomarker that could predict when chronic or spontaneous urticaria disappears, but that's a story in the natural course of urticaria. And many times, after 10 to 15 years it comes back, and then again, as spontaneously as it had come, it disappears.</p>

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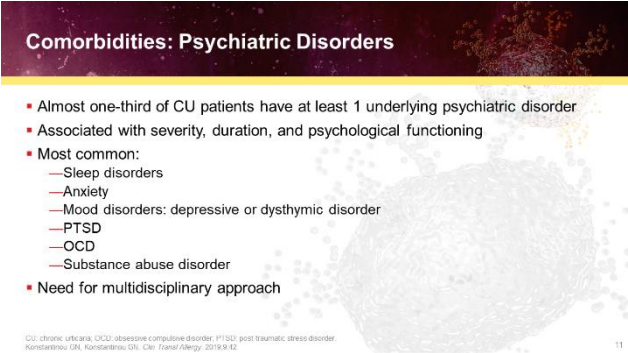
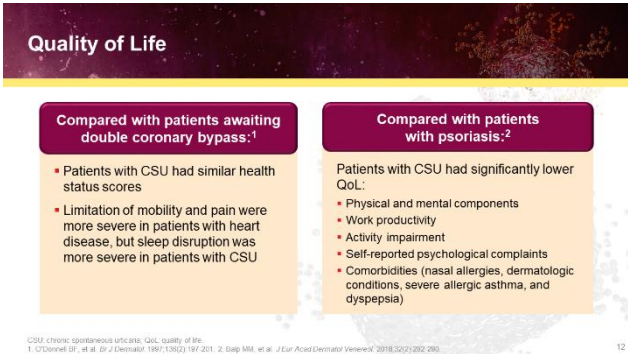
<p>7</p>	<p><b>Physical Burden</b></p> <p>Can vary depending on the severity of the condition and the individual</p> <ul style="list-style-type: none"> <li>Severe itching, hives, and swelling on the skin</li> <li>Pain and discomfort</li> <li>Interference with daily activities</li> <li>Fatigue</li> <li>Loss of sleep</li> </ul>  <p><small>Images obtained from DermNet New Zealand Chewes M. J Allergy Clin Immunol 2003;106(3):684-8702</small></p>	<p>The main burden for patients suffering from chronic spontaneous urticaria is itch. The itch is very severe and interferes especially with night sleep. And that's the reason why many physicians prescribe to patients suffering from chronic spontaneous urticaria sedating antihistamines at bedtime. And I always point out, but what urticaria patients suffer is not insomnia, but they suffer from itch. So it's a much better approach to up those second-generation nonsedating antihistamines at night, increase the dose to control the itch rather than prescribe a sedating antihistamine because on top of the itch, the patient would have on the very next day, somnolence because of the antihistamine.</p>
<p>8</p>	<p><b>Comorbidities: Skin Disorders</b></p> <ul style="list-style-type: none"> <li>DPU — Up to 36% of patients with CIndU</li> <li>Dermatographism — Up to 35% of patients with CIndU</li> </ul>  <p><small>CIndU: chronic inducible urticaria, DPU: delayed pressure urticaria. Images obtained from DermNet New Zealand. Kulkarni P, et al. Nat Rev Dis Primers 2022;8(1):61</small></p>	<p>There are three types of comorbidities we should take into account in chronic spontaneous urticaria. And the first one is that many times chronic spontaneous urticaria coexists with an inducible urticaria, especially with delayed pressure urticaria and dermatographism. And it's frequent to see that patients that are controlled with omalizumab, the spontaneous urticaria is gone. But the physical urticaria there — in the past, physical urticaria was known as inducible urticaria. So, the inducible urticaria stays and is not very well controlled as chronic spontaneous urticaria. The fact that a patient has two types of chronic spontaneous urticaria plus an inducible urticaria is a clinical marker of severity and a bad response to, especially to antihistamines.</p>





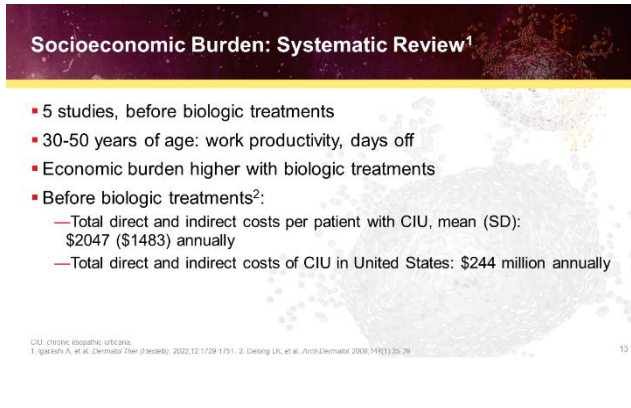
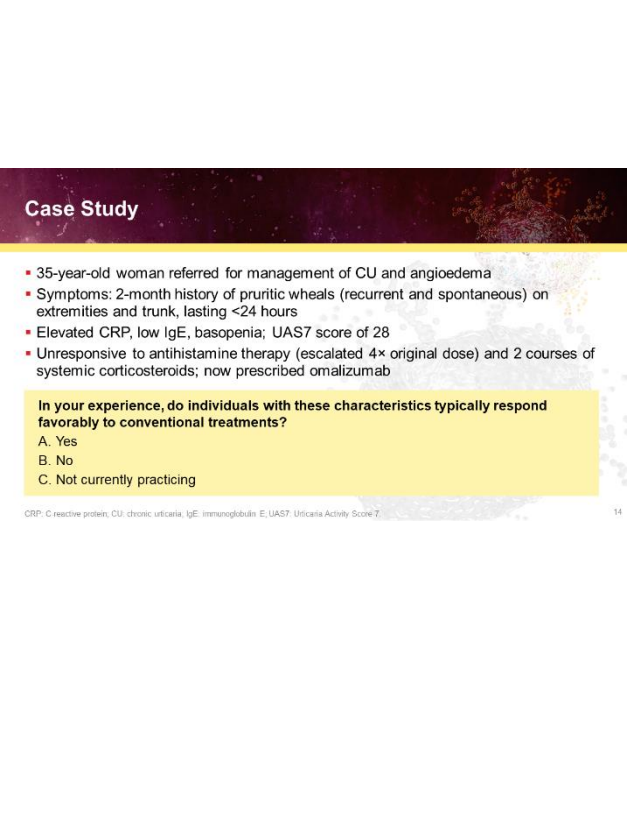
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<p>11</p>	 <p><b>Comorbidities: Psychiatric Disorders</b></p> <ul style="list-style-type: none"> <li>▪ Almost one-third of CU patients have at least 1 underlying psychiatric disorder</li> <li>▪ Associated with severity, duration, and psychological functioning</li> <li>▪ Most common:             <ul style="list-style-type: none"> <li>— Sleep disorders</li> <li>— Anxiety</li> <li>— Mood disorders: depressive or dysthymic disorder</li> <li>— PTSD</li> <li>— OCD</li> <li>— Substance abuse disorder</li> </ul> </li> <li>▪ Need for multidisciplinary approach</li> </ul> <p><small>CU: chronic urticaria; OCD: obsessive compulsive disorder; PTSD: post-traumatic stress disorder; Konstantinou GN, Konstantinou GN. Clin Transl Allergy. 2019;9:42.</small></p>	<p>And the third group of disorders that are associated with chronic spontaneous urticaria are psychiatric disorders, because the emotional impact of this disease is very high. In the previous activity, the professor explained the pathway of these patients, that they visit several specialists and they look for a cause of this daily break hives and the itch, the angioedema. They sometimes perceive that the treatment is not working, and this causes a high anxiety. Plus this patient, they have a bad sleep, rest. So, there is the perfect storm for them to be with high index of psychiatric disorders. We performed a study in Spain with a large population of patients with chronic spontaneous urticaria compared with other allergic diseases and found that patients suffering from chronic spontaneous urticaria were the ones who had the highest impact in psychiatric quality of life, even more than asthma or atopic dermatitis. Don't forget that those patients also they have many visits to here and the story of long spontaneous urticaria is tough for them.</p>
<p>12</p>	 <p><b>Quality of Life</b></p> <div style="display: flex; justify-content: space-around;"> <div style="border: 1px solid black; padding: 5px; width: 45%;"> <p><b>Compared with patients awaiting double coronary bypass:<sup>1</sup></b></p> <ul style="list-style-type: none"> <li>▪ Patients with CSU had similar health status scores</li> <li>▪ Limitation of mobility and pain were more severe in patients with heart disease, but sleep disruption was more severe in patients with CSU</li> </ul> </div> <div style="border: 1px solid black; padding: 5px; width: 45%;"> <p><b>Compared with patients with psoriasis:<sup>2</sup></b></p> <p>Patients with CSU had significantly lower QoL:</p> <ul style="list-style-type: none"> <li>▪ Physical and mental components</li> <li>▪ Work productivity</li> <li>▪ Activity impairment</li> <li>▪ Self-reported psychological complaints</li> <li>▪ Comorbidities (nasal allergies, dermatologic conditions, severe allergic asthma, and dyspepsia)</li> </ul> </div> </div> <p><small>CSU: chronic spontaneous urticaria; QoL: quality of life. 1. O'Donnell JF, et al. Br J Dermatol. 1997;136(2):197-201. 2. Saap MM, et al. J Eur Acad Dermatol Venereol. 2018;32(2):282-290.</small></p>	<p>There are two studies that depict quality of life comparing other diseases and because sometimes physicians, we perceive that it's not a life-threatening disease or could respond to histamine, antihistamines, we could overlook the lack of quality of life of these patients. The first study is pretty old, performed in the UK by O'Donnell, but they found very interesting and very striking data, which is that quality of life is similar to patients that have suffered a double coronary bypass. But I like even more this recent study from the Zuberbier team that compares chronic spontaneous urticaria quality of life with psoriasis, and found that quality</p>

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		<p>of life is lower in chronic spontaneous urticaria [in] all these dimensions than psoriasis. I think this data is very strong and is very graphic for us.</p>
<p>13</p>	 <p><b>Socioeconomic Burden: Systematic Review<sup>1</sup></b></p> <ul style="list-style-type: none"> <li>5 studies, before biologic treatments</li> <li>30-50 years of age: work productivity, days off</li> <li>Economic burden higher with biologic treatments</li> <li>Before biologic treatments<sup>2</sup>:             <ul style="list-style-type: none"> <li>Total direct and indirect costs per patient with CIU, mean (SD): \$2047 (\$1483) annually</li> <li>Total direct and indirect costs of CIU in United States: \$244 million annually</li> </ul> </li> </ul> <p><small>CU, chronic idiopathic urticaria. 1. Igarashi A, et al. Dermatol Ther (Hershey). 2022;12:1729-1751. 2. DeLong LN, et al. Arch Dermatol. 2008;144(1):35-39.</small></p>	<p>Finally, there is also a health cost impact of this disease. There are these data that I explain here, are the last studies. However, both of them, they are performed before we had biologicals for chronic spontaneous urticaria or BTK inhibitors that are also expensive. So, I think this economical burden if we recalculate this now, it should be much, much higher.</p>
<p>14</p>	 <p><b>Case Study</b></p> <ul style="list-style-type: none"> <li>35-year-old woman referred for management of CU and angioedema</li> <li>Symptoms: 2-month history of pruritic wheals (recurrent and spontaneous) on extremities and trunk, lasting &lt;24 hours</li> <li>Elevated CRP, low IgE, basopenia; UAS7 score of 28</li> <li>Unresponsive to antihistamine therapy (escalated 4x original dose) and 2 courses of systemic corticosteroids; now prescribed omalizumab</li> </ul> <p><b>In your experience, do individuals with these characteristics typically respond favorably to conventional treatments?</b></p> <p>A. Yes B. No C. Not currently practicing</p> <p><small>CRP: C reactive protein; CU: chronic urticaria; IgE: immunoglobulin E; UAS7: Urticaria Activity Score 7.</small></p>	<p>I want to read a case study. It's a 35-year-old woman that is referred to our clinic and complains of chronic urticaria and angioedema. She refers a 2-month history of pruritic wheals. They are recurrent and spontaneous on extremities, trunk, lasting — every single hive — less than 24 hours. She has in the blood test elevated CR protein, has a low IgE value with basopenia, UAS score of 28, and is unresponsive to antihistamine therapy that has been already escalated up to four-fold from the standard dose and two courses of systemic corticosteroids. And now she's prescribed, she's being prescribed omalizumab. In your experience, do individuals with these characteristics typically respond favorably to conventional treatment? Yes, no, or not currently practicing?</p>

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<p>15</p>	<p><b>Limitations of Conventional Treatment</b></p> <p>Start with standard dose 2nd-generation H<sub>1</sub>-AH. If needed: Increase 2nd-generation H<sub>1</sub>-AH dose (up to 4x)<sup>1</sup></p> <p>If inadequate control on high dose<sup>2</sup> after 2-4 weeks or earlier, if symptoms are intolerable</p> <p>Add on to 2nd-generation H<sub>1</sub>-AH: omalizumab<sup>3</sup>. If needed: Increase dose and/or shorten interval<sup>4</sup></p> <p>If inadequate control within 6 months or earlier, if symptoms are intolerable</p> <p>Add on to 2nd-generation H<sub>1</sub>-AH: cyclosporine<sup>5</sup></p> <p>*Second-line and third-line treatment apply only for CU. *300 mg every 4 weeks. †Up to 600 mg every 2 weeks. ‡Up to 5 mg/kg body weight.</p> <p>AV: antihistamine; CSU: chronic spontaneous urticaria; CU: chronic urticaria; H<sub>1</sub>: histamine type 1; IgE: immunoglobulin E. 1. Zuberbier T, et al. <i>Allergy</i>. 2022;77(3):591-600. 2. Quillen Aguirre S, et al. <i>Br J Dermatol</i>. 2016;175(5):1162-1163. 3. Kaplan AP. <i>Allergy Asthma Immunol Res</i>. 2017;9(6):e177-182. 4. Marcano AV, et al. <i>J Clin Invest Dermatol</i>. 2019;3(3):156-164.</p>	<p>These are the pretty straightforward treatment guidelines, which is stepwise. Going from standard dose of antihistamine; if no response, up dose up to four times; no response, go to omalizumab; and then if no response is found, the next step is cyclosporine. We should say that it's very, as I say, straightforward, simple; however, the real rate response with this treatment is not 100%. First of all, with standard antihistamine dose, the rate response is around 30%. Updosing the antihistamine could increase the response up to 60%, and then omalizumab of course has also a very high response. However, there is this</p>
<p>16</p>	<p><b>One in 5 Patients Do Not Achieve Adequate Control With Available Treatments</b></p> <p>% of CSU patients</p> <p>Legend: No treatment, Other, Cyclosporine, Mometasone, Omalizumab, Combination sedative and non-sedative H<sub>1</sub>-AH, Sedative H<sub>1</sub>-AH, On-demand non-sedative H<sub>1</sub>-AH, Up-dosed non-sedative H<sub>1</sub>-AH, Approved non-sedative H<sub>1</sub>-AH</p> <p>Other third-line treatment options (as defined in 2014 guidelines) were rarely used: Other 5-AHTs, emollients, cyclosporine was prescribed in 2.0% (n=71) of patients, which reduced to 0.3% (n=4) at the end of the observational period. Similarly, mometasone was prescribed for 3.0% (n=97) of patients with CU before enrollment, and prescriptions reduced to 1.0% (n=24) at month 24. The non-sedative, evidence AHTs were similarly rarely prescribed, with 4.1% before enrollment, reduced to 3.0% (n=93) after the 2 years of observational period.</p> <p>n = 2727 2727 2174 1647 1278 2727</p> <p>Numbers (and percentages) of patients receiving different treatments at each visit. n = total number of patients of each visit. AV: antihistamine; CSU: chronic spontaneous urticaria; CU: chronic urticaria; H<sub>1</sub>: histamine type 1; IgE: immunoglobulin E. Image reproduced for educational purposes only from Mason M, et al. <i>Clin Exp Allergy</i>. 2022;52(10):1165-1175.</p>	<p>AWARE study that with a very large sample gathered all response rate; there is still 15% of patients that do not respond to available treatment and those patients are the ones who are important. Moreover, we are talking about partial response or complete response. Patients suffering from chronic spontaneous urticaria should get a complete response. We cannot be happy with a partial response, partial itch, hives in some parts of the body, some days with angioedema, this is considered partial response. Yet this, for the quality of life of patients, is really bad. So, we still have room for improvement. We still have new molecules in order to offer to our patients suffering from current spontaneous urticaria complete control of the disease.</p>



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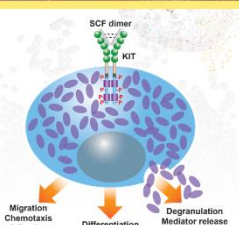
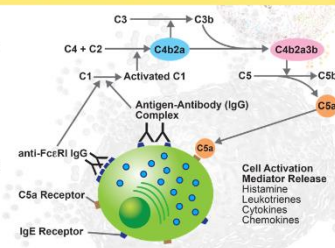
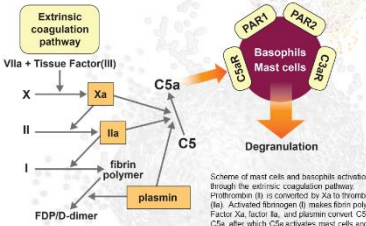
<p>17</p>	<p><b>Predictors of Treatment Response in CSU</b></p> <p><b>1st and 2nd line of therapy</b></p> <ul style="list-style-type: none"> <li>High D-dimer</li> <li>High CRP</li> <li>High UAS/UAS7</li> <li>High QoL-scores</li> <li>Concomitant CINDU</li> <li>Previous treatment with steroids</li> </ul> <p>Nonresponse to sgAHs</p> <p><b>3rd line of therapy</b></p> <ul style="list-style-type: none"> <li>Low total IgE</li> </ul> <p>Nonresponse to omalizumab</p> <p><b>4th line of therapy</b></p> <ul style="list-style-type: none"> <li>Positive BHRA</li> <li>Low total IgE</li> </ul> <p>Response to cyclosporine</p> <p>Legend: Yellow circle = Strong level of evidence, Orange circle = Weak level of evidence</p> <p><small>BHRA: basophil histamine release assay; CINDU: chronic inducible urticaria; CRP: C-reactive protein; CSU: chronic spontaneous urticaria; IgE: immunoglobulin E; QoL: quality of life; sgAHs: second generation H<sub>1</sub> antihistamine; UAS7: Urticaria Activity Score 7. Image reproduced for educational purposes only from Fink JS, et al. Allergy. 2021;76(10):2945-2961.</small></p>	<p>Do we have biomarkers to predict the response to the treatments that we have now on hand? We do know that patients with very severe disease with high UAS score, CR protein, D-dimer very high, they don't respond to antihistamine. But, which is more important now, there have been a number of studies that demonstrate that low levels of IgE, of basal IgE, are good, it's a good predictor of a nonresponse to omalizumab and even to cyclosporine.</p>
<p>18</p>	<p><b>CSU Pathophysiology: Recognized Components</b></p> <ul style="list-style-type: none"> <li><b>Mast Cell Activation</b>: CSU is initiated by improper activation/degranulation of mast cells, leading to histamine release and immune cell recruitment</li> <li><b>Cell Infiltration</b>: Immune cell infiltration perpetuates the cycle of inflammation and hives</li> <li><b>Coagulation and Complement Activation</b>: The coagulation and complement systems may also be activated, leading to tissue damage and exacerbation of inflammation</li> </ul> <p><small>CSU: chronic spontaneous urticaria. Hsieh M, Kaplan AP. J Allergy Clin Immunol. 2022;150(6):1430-1441.</small></p>	<p>So, and this is the last part of this activity, thinking on the pathophysiology of chronic urticaria, which could be the new targets to control this group of patients that are not controlled with the present treatments? And everything in chronic urticaria starts with mast cell activation. Mast cell activation leads to cell infiltration, and cell infiltration also causes coagulation and complement activation. So, from this pathway that is also so-called because this also stimulates mast cells that attracts more cells. There are many possible targets that we could think of.</p>
<p>19</p>	<p><b>Mast Cell Activation<sup>1</sup></b></p> <ul style="list-style-type: none"> <li><b>Autoimmune mechanisms for initiation:</b> <ul style="list-style-type: none"> <li>Type I immunity: <ul style="list-style-type: none"> <li>IgE autoantibodies against molecules such as dsDNA, TF, IL-24, and TPO</li> </ul> </li> <li>Type II immunity: <ul style="list-style-type: none"> <li>Activation of mast cells and basophils by IgG autoantibodies against IgE antibodies and/or FcεRI</li> <li>IgM and/or IgA autoantibodies against FcεRI may also contribute<sup>2</sup></li> </ul> </li> <li>Subpopulation of CSU patients has both types<sup>3</sup></li> <li>Co-expression of multiple autoantibodies</li> </ul> </li> <li><b>Neuropeptides, complement components, proteases, prostaglandins, and TLR ligands also activate mast cells via corresponding receptors and induce the release of inflammatory mediators</b></li> </ul> <p><small>CSU: chronic spontaneous urticaria; CCR10: chemokine receptor 10; dsDNA: double-stranded DNA; FcεRI: Fcε receptor 1; IgE: immunoglobulin E; IL-24: interleukin 24; IgG: immunoglobulin G; IgM: immunoglobulin M; IgA: immunoglobulin A; IL-24: interleukin 24; TPO: thyroperoxidase; TF: tissue factor; TLR: Toll-like receptor; TLR ligands: TLR ligands; Urticaria (edema formation): Urticaria (edema formation).  <sup>1</sup> Tarsa P, et al. Cells. 2021;10(12):2094-2105. <sup>2</sup> Kishimoto A, et al. J Allergy Clin Immunol. 2022;149(5):1079-1091.</small></p>	<p>And how are mast cells activated? As I mentioned before, autoimmunity is an important fact in chronic urticaria. Many years ago in the 50s, Lesnoff reported a high number of patients suffering from chronic urticaria; they also have autoimmune thyroiditis. That led to the group of Malcom Greaves in the UK, and then other groups, to demonstrate that patients suffering from urticaria had IgG antibodies against the IgE receptor or even against IgE (type IIb immune reaction). And now, in more recent years, a second hypothesis has emerged, which is that those patients will have IgE against self-proteins (type I immune reaction).</p>







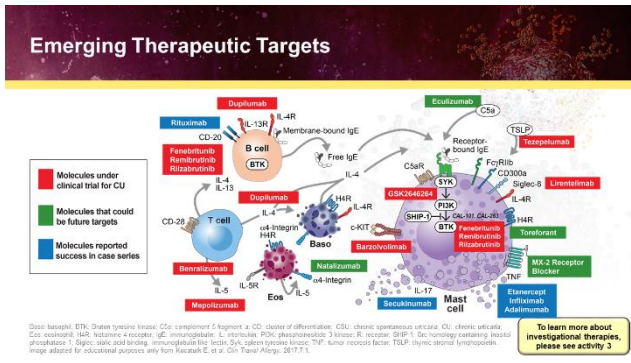
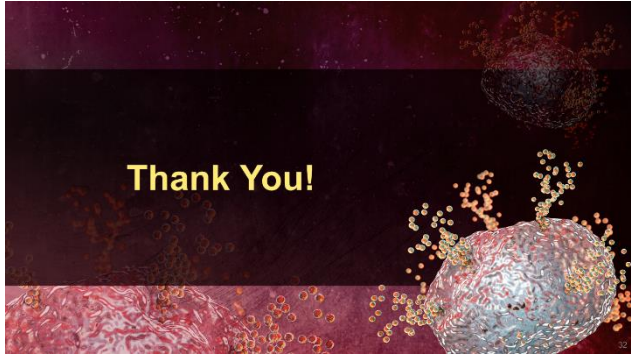
**A NEW DAWN IN CHRONIC URTICARIA: Opportunities to Improve Patient Outcomes With Modern Diagnostic Principles and , Innovative Treatments on the Horizon**  
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<p>24</p>	<p><b>c-KIT: Mast Cell Proliferation, Survival, and Differentiation</b></p> <ul style="list-style-type: none"> <li>Binding of SCF to c-KIT activates signaling pathways leading to cell proliferation, survival, differentiation, and migration</li> <li>Mast cells express high levels of c-KIT even after differentiation, distinguishing them from other mature immune cells</li> <li>SCF/c-KIT induces mast cell migration and invasion into specific tissues through SCF chemotaxis</li> </ul>  <p><small>P: phosphorylated tyrosine; SCF, stem cell factor. Image reproduced for educational purposes only from [56]M. et al. J Allergy Clin Immunol. 2022;149(6):1816-1824. Kim KH, et al. Mol Cell Biochem. 2022. doi: 10.1007/s11010-022-04567-3</small></p>	<p>But mast cells as you know, they have many different receptors. And one of the most important receptors of mast cells are the stem cell factor ligand receptor, which is c-KIT. Because c-KIT not only activates signaling pathway, but also, it's responsible [for] mast cell proliferation, survival, differentiation. The levels of c-KIT correlate with many mast cell actions and also causes mast cell migration, so blocking this receptor is the fourth possible target to treat urticaria.</p>
<p>25</p>	<p><b>Complement Activation</b></p> <ul style="list-style-type: none"> <li>IgE-FcεRI interaction leads to IgG1 and IgG3 activation of the classical complement pathway</li> <li>C5a generated, binds to C5a receptor on cutaneous mast cells and peripheral basophils</li> <li>Cutaneous mast cells express C5a receptor, but mucosal mast cells do not</li> </ul>  <p><small>C1: complement 1; C2: complement 2; C3: complement 3; C3b: complement 3 fragment; C4: complement 4; C4b2a: C3 convertase; C4b2a3b: classical C3 convertase; C5: complement 5; C5a: C5 complement 5 fragment; C5b: complement 5 fragment. Image adapted for educational purposes only from [56]M. et al. J Allergy Clin Immunol. 2022;149(6):1816-1824.</small></p>	<p>What about complement? In the third layer, we talk about complement and here we are in a paper that we published with Kaplan, we portrayed how this IgG autoantibodies are from the subtype IgG1. And when binding in a close distance, they activate complement, and then by activating complement, they form C5a that activates mast cells. So C5A is another</p>
<p>26</p>	<p><b>Activation of Coagulation and Fibrinolysis</b></p> <ul style="list-style-type: none"> <li>Occurs despite the absence of thrombosis or bleeding</li> <li>Elevated levels of D-dimer and fibrinogen degradation products and prothrombin I and II, reflecting fibrin formation and digestion by plasmin</li> </ul>  <p><small>C3aR: complement 3 fragment a receptor; C5a: complement 5 fragment a; C5aR: C5a receptor; FDP: fibrin degradation product; PAR: protease activated receptor. Image adapted for educational purposes only from [56]M. et al. J Allergy Clin Immunol. 2022;149(6):1816-1824.</small></p>	<p>possible target. As you know, endothelial cells and eosinophils, through the tissue factor, are responsible to activate extrinsic coagulation pathway, and this is the one which is responsible for the higher levels of the dimer. And, interestingly enough, it's not contained by thrombosis or bleeding. And also here it's formed C5a. So, if we blocked C5a, we could have this double action.</p>





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		<p>eosinophil apoptosis could be also another target.</p>
<p>31</p>	 <p><b>Emerging Therapeutic Targets</b></p> <p>Legend:  <span style="color: red;">■</span> Molecules under clinical trial for CU  <span style="color: green;">■</span> Molecules that could be future targets  <span style="color: blue;">■</span> Molecules reported success in case series</p> <p><small>Baso: basophil; BTK: B-tyrosine kinase; C5a: complement 5 fragment; CD: cluster of differentiation; CSU: chronic spontaneous urticaria; CU: chronic urticaria; Eos: eosinophil; HHR: histamine H4 receptor; IgE: immunoglobulin E; IL: interleukin; PDK: phosphoinositide 3-kinase; R: receptor; SHP-2: Src homology containing inositol phosphatase 2; Siglec: sialic acid binding, immunoglobulin-like lectin; SYK: spleen tyrosine kinase; TNF: tumor necrosis factor; TSLP: thymic stromal lymphopoietin. Image adapted for educational purposes only from Kocarak E, et al. Clin Transl Allergy. 2017;7:1.</small></p> <p><b>To learn more about investigational therapies, please see activity 3</b></p>	<p>In the next activity, all these molecules will be covered, so here I just display the summary and all the things we've explained so far: targeting the IgE receptor, C5a, c-KIT, Siglec-8, IL-4, IL-13, and of course all the BTK, SYK, tyrosine kinase signaling molecules.</p>
<p>32</p>	 <p><b>Thank You!</b></p>	<p>So, thank you very much for your attention and this is the second activity of chronic spontaneous urticaria.</p>