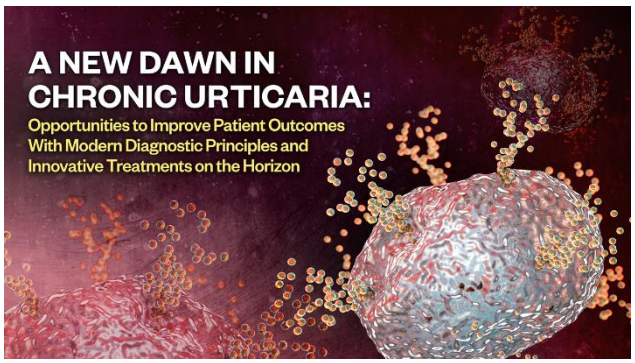
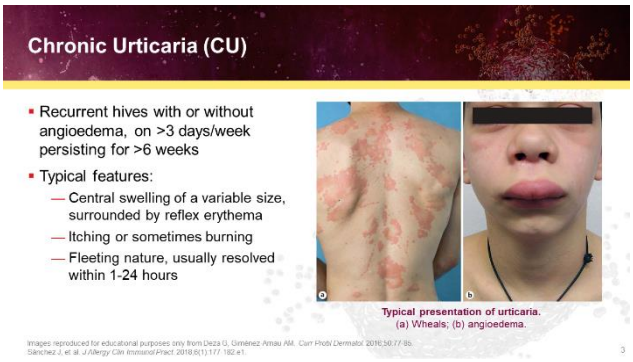
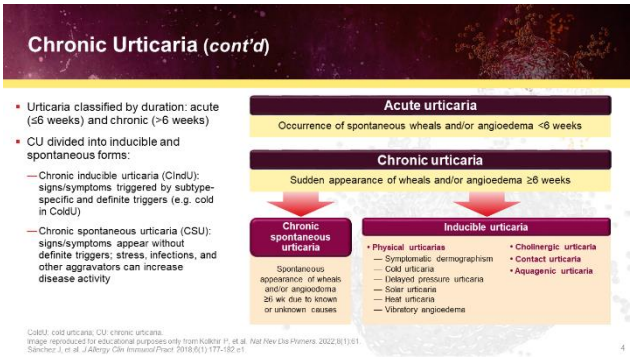
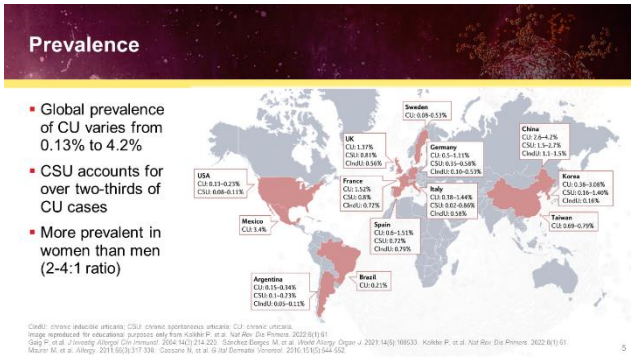
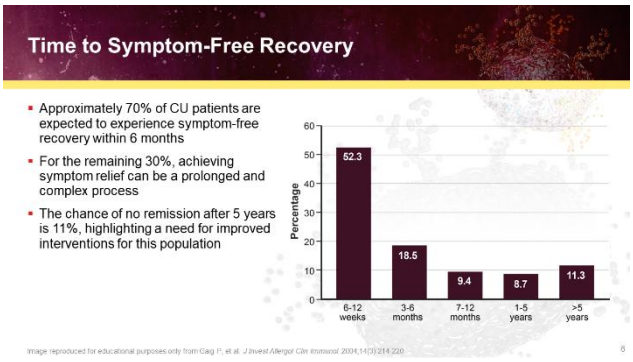
A NEW DAWN IN CHRONIC URTICARIA: Opportunities to Improve Patient Outcomes With Modem Diagnostic Principles and , Innovative Treatments on the Horizon

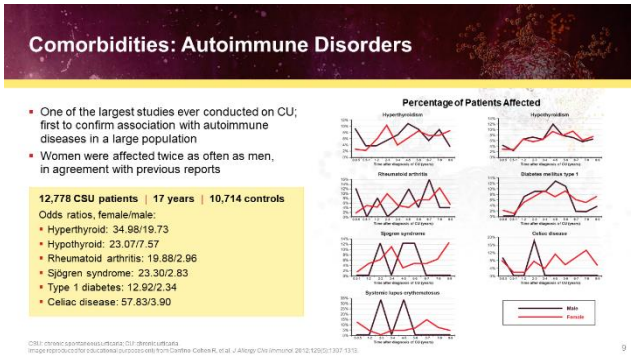
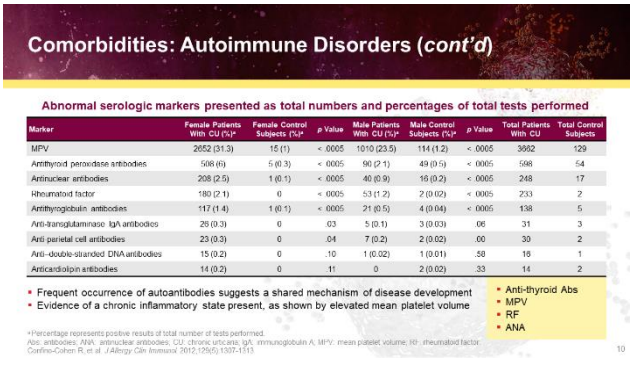
Recent Updates on the Immunological Processes That Contribute to the Burden of CU: What Do Healthcare Providers Need to Know?

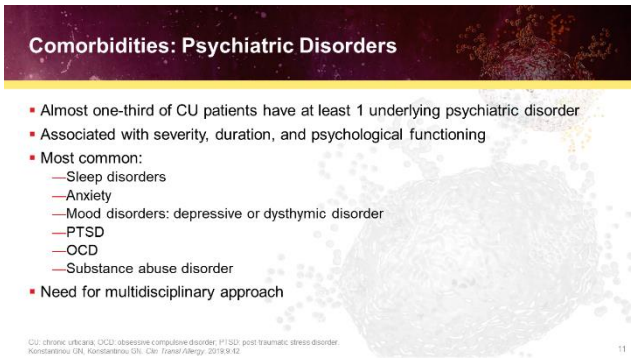
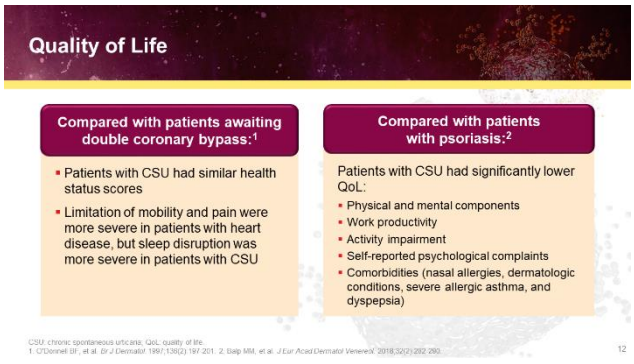
1		Welcome to a New Dawn in Chronic Urticaria: Opportunities to Improve Patient Outcomes with Modern Diagnostic Principles and Innovative Treatments on the Horizon.
2		We will cover Recent Updates on the Immunological Processes that Contribute to the Burden of CU: What Do Healthcare Providers Need to Know?
3		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.

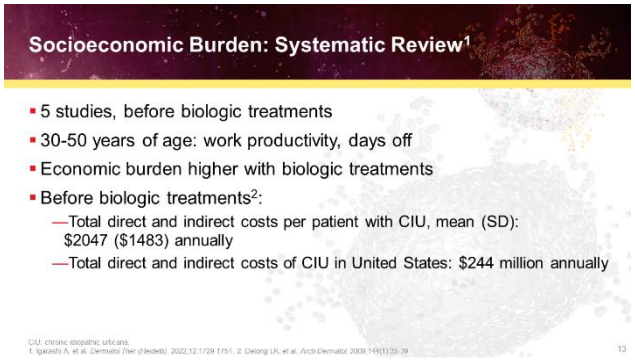
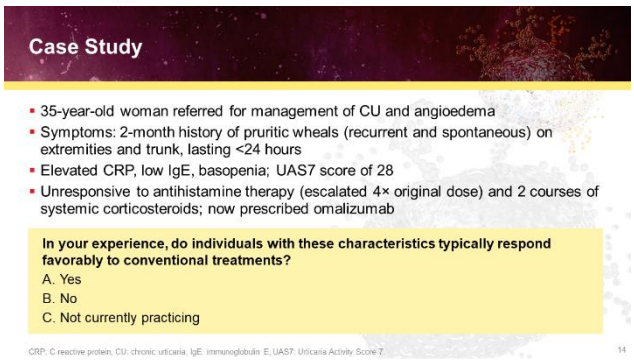
4		As you know, and I think, I believe it was explained in the previous activity, urticaria is classified as acute urticaria (when hives last less than 6 weeks) and chronic urticaria. Chronic urticaria is also divided into chronic spontaneous urticaria, which is the focus of my talk. That consists of 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

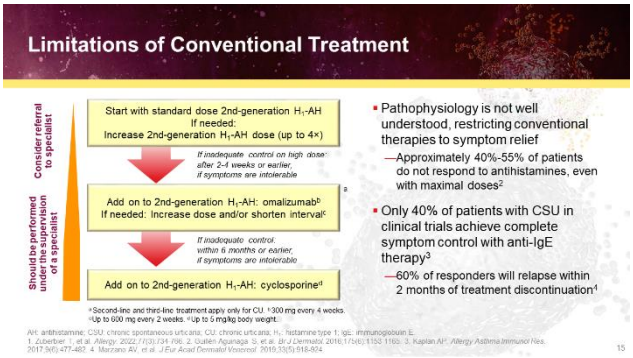
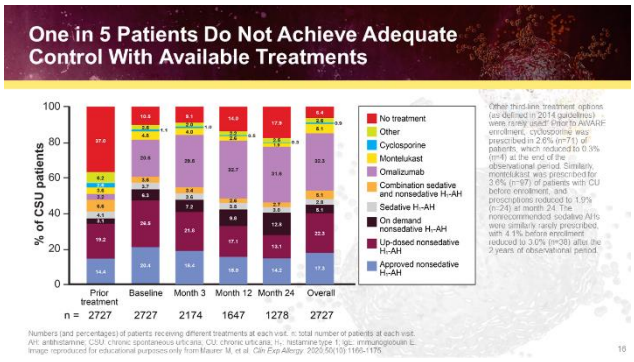
		down, they [rapidly] disappear. So, it's completely different — the picture of inducible urticaria and chronic spontaneous urticaria.
5		The prevalence is interesting because, globally, all the studies find similar prevalence along different countries, which goes from 0.2% to 4%. But the most interesting 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.
6		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.

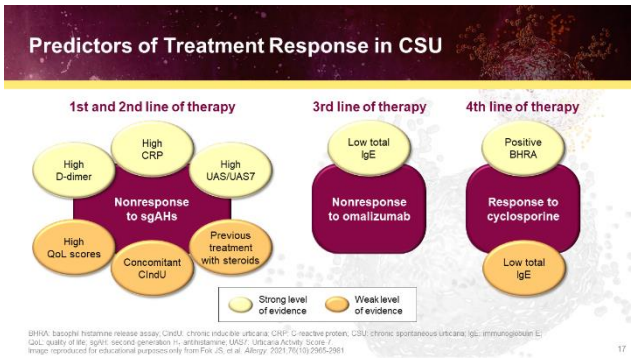
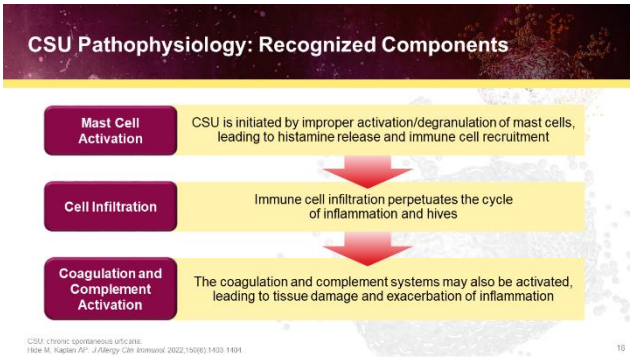
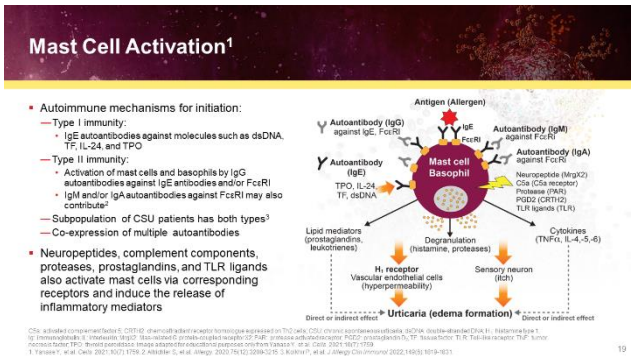
7		The main burden for patients suffering from chronic spontaneous urticaria is itch. The itch is very severe and interferes especially with night sleep. And that's the reason why many physicians prescribe to patients suffering from chronic spontaneous urticaria sedating antihistamines at bedtime. And 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.
8		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.

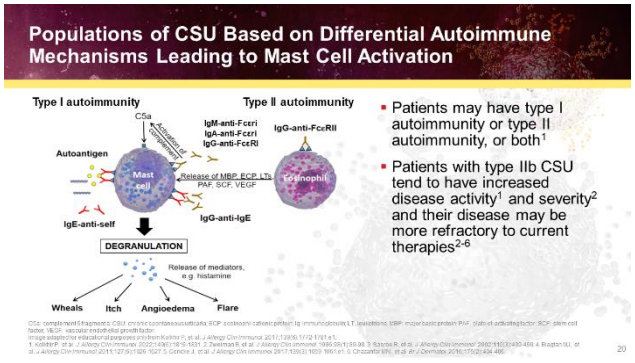
9		The second comorbidities that are found in chronic spontaneous urticaria are autoimmune disorders, as I will tell later. In a significant percentage of patients, 40% of patients, there is an autoimmune physiopathology underneath the urticaria. I bring here this very interesting study. It's very large, with more than 12,000 patients suffering from chronic spontaneous urticaria that were followed along 17 years in an Israel cohort and compared with 10,000 controls without suffering chronic spontaneous urticaria. And as you see here, the odds ratio or the probability to develop an autoimmune disease is very high. Especially here in women than in men. Autoimmune thyroid disease, rheumatoid arthritis, type 1 diabetes, Sjögren's disease, and also autoimmune biomarkers are significantly higher in this sample than controls.
10		The take-home message of this is that chronic spontaneous urticaria patients should be followed a long time for autoimmune disease, especially those who have autoimmunity biomarkers.

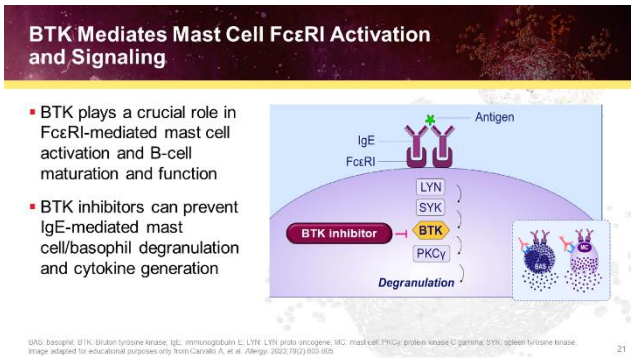
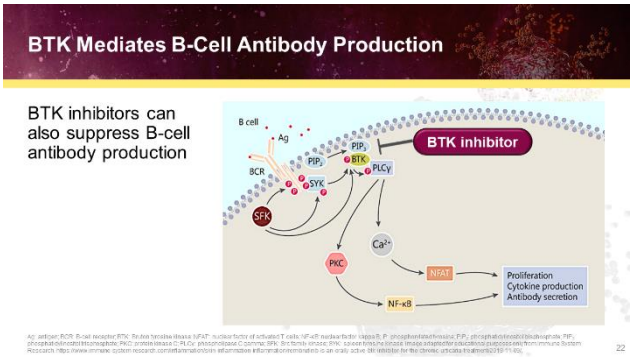
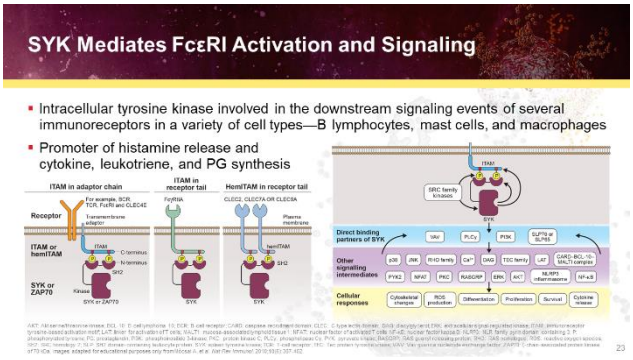
11		And the third group of disorders that are associated with chronic spontaneous urticaria are psychiatric disorders, because the emotional impact of this disease is very high. In the previous activity, the professor explained the pathway of these patients, that they visit several specialists and they 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.
12		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

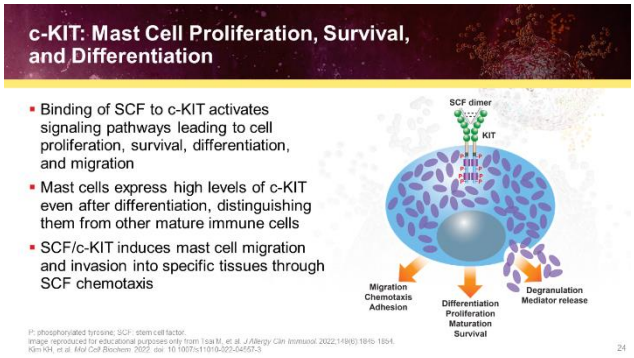
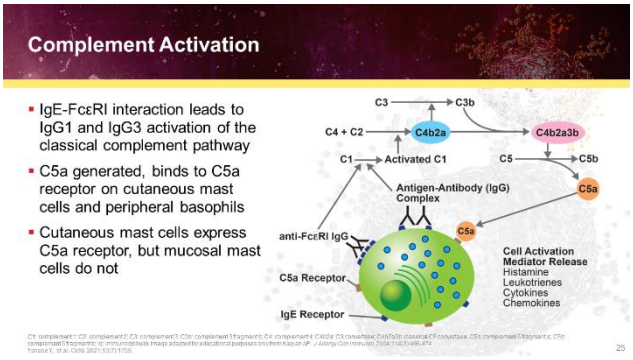
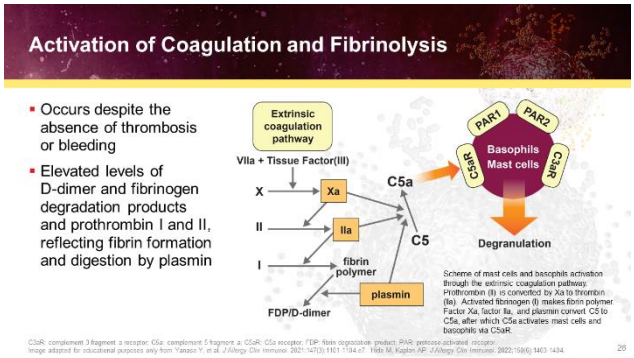
		of life is lower in chronic spontaneous urticaria [in] all these dimensions than psoriasis. I think this data is very strong and is very graphic for us.
13		Finally, there is also a health cost impact of this disease. There are these data that I explain here, are the last studies. However, both of them, 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.
14		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?

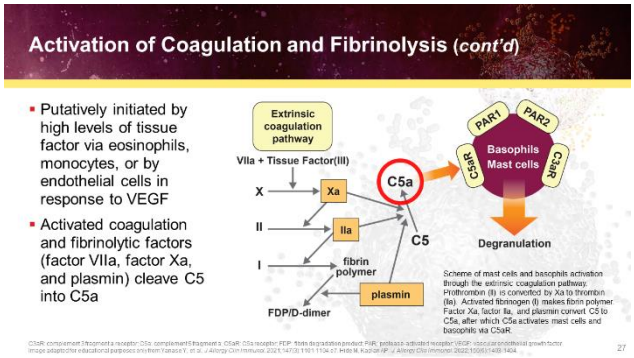
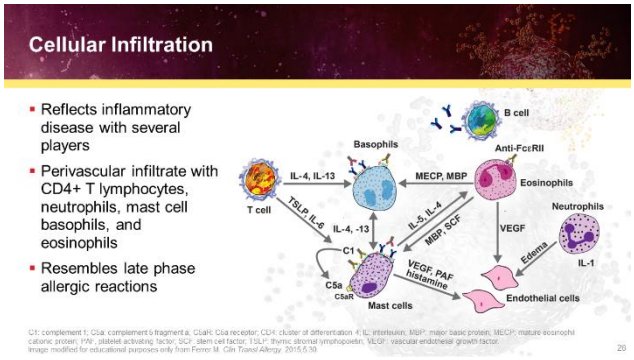
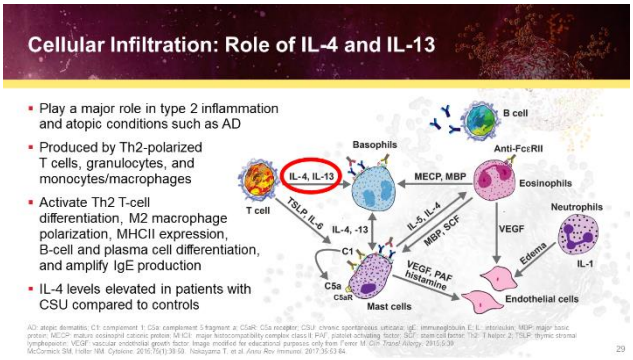
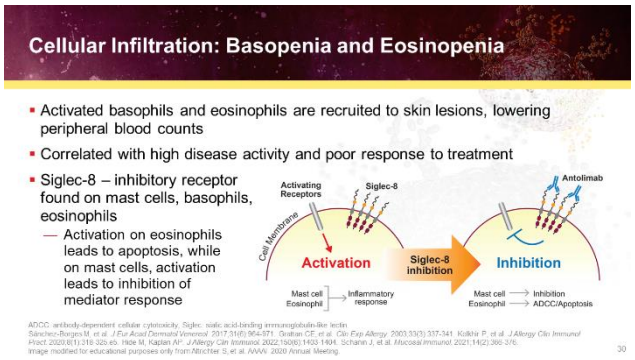
15		These are the pretty straightforward treatment guidelines, which is stepwise. Going from standard dose of antihistamine; if no response, up dose up to four times; no response, go to omalizumab; and then if no response is found, the next step is cyclosporine. We should say that it's very, as I say, 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
16		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.

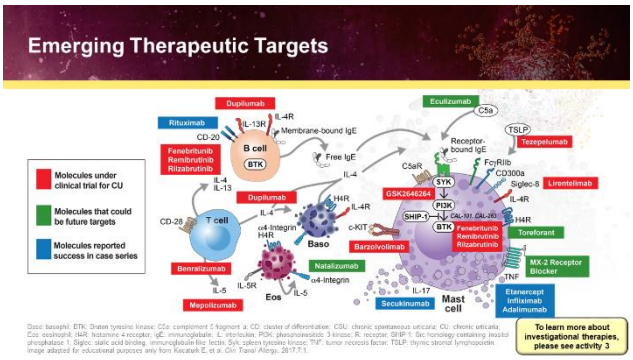
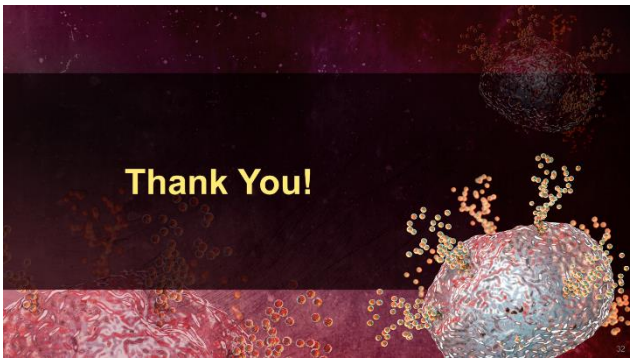
17		Do we have biomarkers to predict the response to the treatments that we have now on hand? We do know that patients with very severe disease with high UAS score, CR protein, D-dimer very high, they don't respond to antihistamine. But, which is more important now, there have been a number of studies 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.
18		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.
19		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).

		But the problem of this is that autoimmunity [is only] demonstrated in 40% of cases. There is still 60% of patients who are having the same disease with the same response to treatment, [in whom] we could not demonstrate autoimmunity. But the important thing is that once the mast cell, I think basophils also play a role, is activated, it produces histamine and histamine is the responsible of the itch — stimulating the histamine receptor in the neurons and also the vasodilation and increase of permeability in the vessels, in the skin vessels. But the important thing here is that mast cells not only produce proteases or histamine, but plenty of different cytokines, chemokines, that would be responsible [for] the cell infiltrate. So [the] IgE receptor would be one of the targets that we could develop new drugs.
20		And the next thing we should consider is that we could design new molecules that act on all of these mediators. Is there any difference between this type of autoimmunity and this one [type I and type IIb]? Could these patients be clinically distinguished? And they are different. Patients suffering from type IIb from IgG autoantibodies, they really have more basopenia, lower levels of IgE, and the urticaria is more severe and is more resistant to treatment.

21		The next step we could target in new drugs is that once the mast cell is activated through the IgE receptor, this would be our third target. Several signaling molecules, which usually are kinases, they activate. It's a signaling cascade, they active in a chain and this is responsible of the mast cell degranulation. It is of special interest the Bruton tyrosine kinase and blocking these kinases, as now there are several BTK inhibitors that are being trialed in urticaria could block the mast cell degranulation.
22		But the importance of BTK inhibitors are not only blocking mast cell degranulation, but also they are, if we block the BTKs, we could also block the antibody synthesis by the lymphocytes. So, these drugs could touch two important mechanisms in urticaria.
23		The next target is another signaling molecule, which is SYK, which is responsible for many, many other signaling cascade and signaling signs, both in B cells and mast cells. So, this is another target that is higher, as you see here, than BTK. So, IgE receptor, Bruton tyrosine kinase, and then SYK also; these three are possible targets.

24		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.
25		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
26		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.

27		So, if we blocked C5a, we could have this double action.
28		And then, there is the cellular infiltration. There are several cells that could be blocked, and this is a cartoon I made for a review on the immunological changes in chronic spontaneous urticaria.
29		But here I want to point out that there is a role for IL-4, IL-13 as well that activates both mast cells and basophils; that targeting could be also interesting.
30		And finally another molecule, thinking on the mechanism of chronic urticaria, could be this Siglec-8 inhibitory receptor. So far, we've talked about blocking activating receptors, Ig receptors, signaling molecules, but what about activating inhibitors? And that's a case of Siglec-8 that also could lead to eosinophil apoptosis. And what we found in chronic spontaneous urticaria biopsies are eosinophils, so targeting Siglec-8 that causes

		eosinophil apoptosis could be also another target.
31		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.
32		So, thank you very much for your attention and this is the second activity of chronic spontaneous urticaria.