OVERVIEW

Atopic dermatitis (AD) is a skin condition with substantial direct and indirect effects on patients. Guidelines for the management of AD were published in 2014, and while many of the tenets of basic AD skin care are well established, patients with AD are still not achieving optimal disease control in real-world practice. In this activity, Dr. Jonathan Silverberg reviews the burden of AD and the unmet needs within AD management today. Components of basic skin care from the 2014 guidelines are reviewed, followed by the most recent data supporting approved therapies and newly emerging oral and topical JAK-STAT inhibitors.

CONTENT AREAS

- AD burden and unmet needs
- Role of moisturizers and bathing
- Role of topical corticosteroids and adjunctive systemic therapies
- Recent post-hoc and real-world analyses supporting crisaborole and dupilumab
- Mechanism of action of JAK-STAT inhibitors
- Phase 3 trial results for JAK-STAT inhibitors as monotherapy and combination therapy
- Emerging monoclonal antibodies

FACULTY

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Target Audience

This activity was developed for a national audience of dermatologists, pediatric dermatologists, allergists, nurse practitioners, physician assistants, and other clinicians involved in the management of patients with atopic dermatitis.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Describe the burden of disease experienced by patients with atopic dermatitis
- Develop and modify, as needed, evidence-based treatment plans that address both symptoms and concerns of patients with atopic dermatitis
- Summarize the latest research developments in the pharmacologic treatment of atopic dermatitis

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The estimated time to complete the activity is .75 hour.

This activity was released on October 29, 2021 and is eligible for credit through October 29, 2022.

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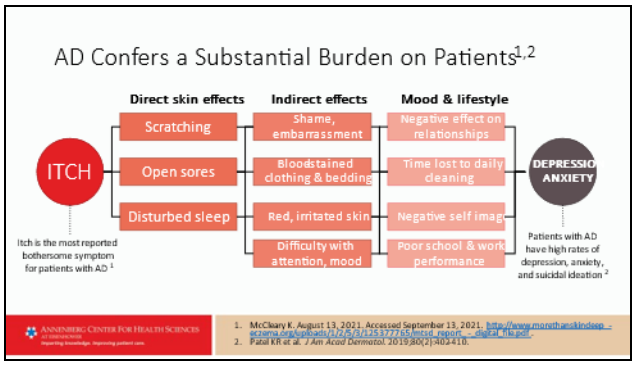
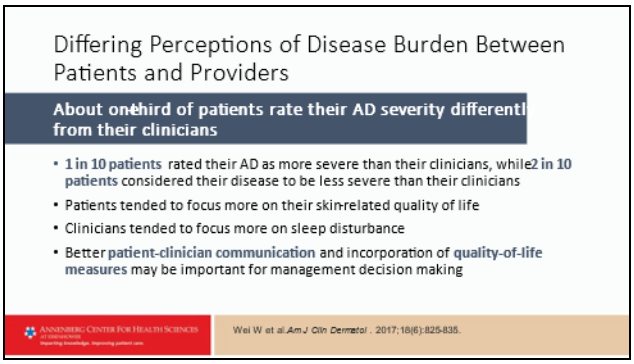
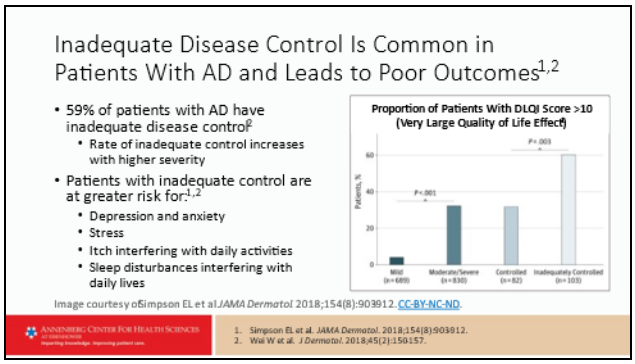
Unmet Needs in AD Care



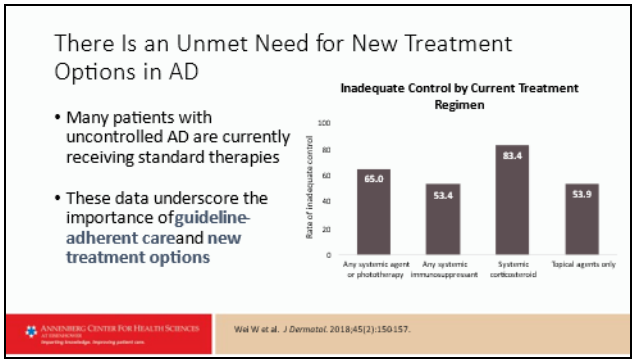
Atopic dermatitis is associated with really a substantial and multidimensional burden of disease and most of the hallmark, you know, the hallmark symptom of the disease, is itch. It is the most common symptom and is also reported to be the most burdensome symptom of the disease and it has a number of direct and indirect effects. It leads, obviously, to scratching as an attempt to alleviate the itch, but that will then lead to breaks in the skin, open sores. There will be impacts on sleep disturbance, impacts on mental health, as you can see here, shame, embarrassment, many other sequelae of disease in terms of like bleeding on the sheets and oozing and weeping. And certainly many issues with respect to trigger avoidance, task avoidance in life, impacts on activities of daily living, poor school and work performance, downstream sequelae of depression, anxiety, cognitive dysfunction, attention deficit disorder, hyperactivity disorder, etc.



There are a number of different perceptions that can come up between patients and providers. And there are several studies that have looked at this now and they all kind of show the same concept that a large subset of patients will rate their disease severity differently than the clinicians rate the disease severity. Not only that, but patients, actually their concerns, what impacts their life more than anything else, what bothers them more about their atopic dermatitis, is quite different than what clinicians will focus on. One in 10 patients in this study rated their atopic dermatitis as being more severe than the clinician and 2 in 10 patients considered their disease to be less severe than their clinicians. So, we don't always see eye to eye. Patients tended to focus more on their skin-related quality of life. Clinicians tended to focus more on sleep disturbances. And better patient-clinician communication and incorporate of quality-of-life measures may be important for management decision-making. I, in my own practice, I have a hybrid research-clinical setting and I incorporate quality of life tools and other measures routinely, and I find them invaluable in terms of elevating clinical practice.

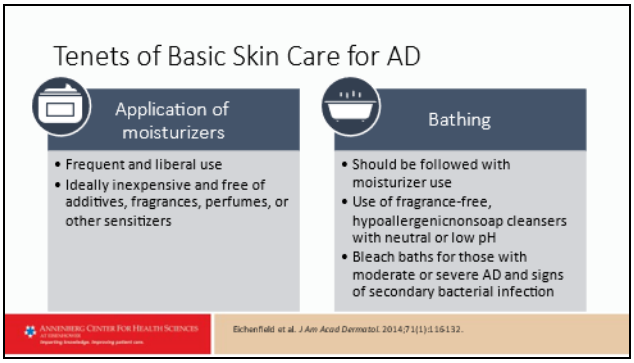


Disease control is quite common in patients. It's quite a common issue that comes up in patients with atopic dermatitis. And when patients have inadequate control, that's going to lead to more, you know, problematic outcomes. So, these are data from a very interesting real-world observational study that looked at patients with moderate-to-severe atopic dermatitis and found that 59% of patients with atopic derm had inadequate disease control and the rate of inadequate control increased with higher severity. I think that's an important point because we often think of control and severity as the same thing. They're not. Severity is a separate construct from control, but they're highly correlated with each other. Patients with inadequate control were at greater risk for depression and anxiety, stress, itch interfering with their daily activities, and sleep disturbances interfering with their daily activities.

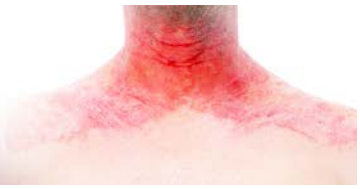


I think it highlights that there are still a number of unmet needs for new treatment options in atopic dermatitis. Many patients with uncontrolled atopic dermatitis are hardly receiving standard of care therapies and not controlled. And they underscore, you know, the importance of more therapies, better therapies and guidelines that really incorporate new options to advance the care of our patients with atopic dermatitis. As you can see illustrated in this figure here, amongst this cohort that I discussed with you already that has poor control, high rates of poor control, we still see that even within those who are getting systemic therapies, systemic immunosuppressants, systemic corticosteroids or just topical therapies, high rates of inadequate control.

Components of Basic AD Care

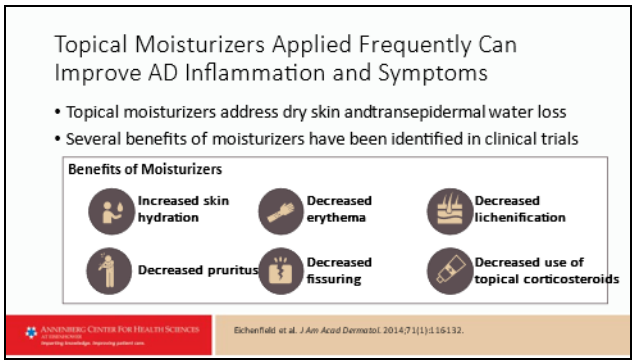


There's an extraordinary amount of talk about, you know, best practices with respect to topical therapy in general in dermatology, in particular in atopic dermatitis, but we're going to focus in on a few key concepts as it pertains to atopic dermatitis. The one, moisturizers, emollients in general, very important aspect of topical therapy for this disease. We recommend early and often use of moisturizers and ideally, we'd like to find moisturizers that are inexpensive, right? We don't want to have something that's going to cause a massive financial burden for patients. We want something that's



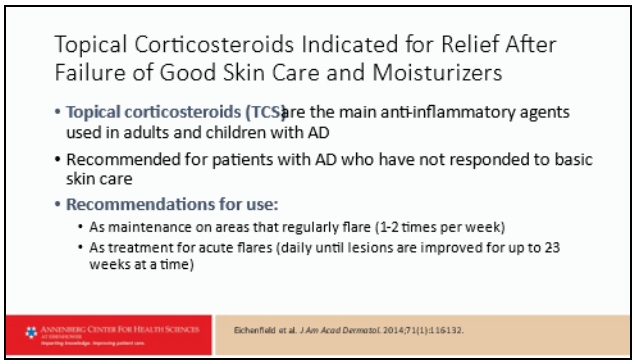
going to be pretty clean, from an ingredients standpoint, and clean doesn't mean all natural. In fact, sometimes it means not all natural. It means going synthetic. Things that don't have additives, fragrances, perfumes or other sensitizers which, I should point out, many of which are often naturally sourced ingredients.

From a bathing perspective, such an important issue to address with our patients with atopic dermatitis, ideally we recommend that patients put on their moisturizer or topical medications after the bath that will help to seal in the moisture that they get during the bath, use of fragrance-free hypoallergenic, preferably nonsoap cleaners, nondetergent cleansers, that will have a neutral or low pH would be all good properties to look for in things that are not going to aggravate the underlying atopic dermatitis. There's some controversy here about bleach baths, which are considered an option for those with moderate or severe atopic dermatitis, particularly amongst those who have signs of secondary bacterial infection, but they don't really work all that well based on the evidence, but they are an option to use in some patients.



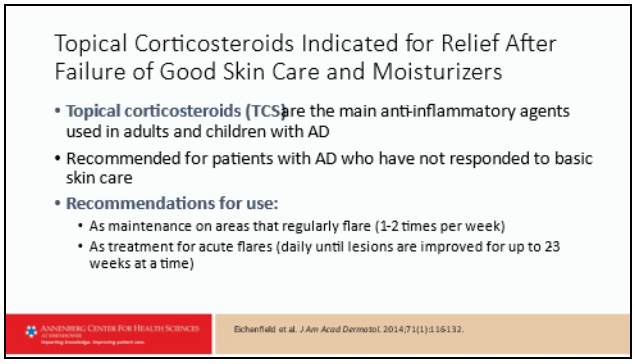
Topical moisturizers, you know, they work, and they have a number of important properties in patients with atopic dermatitis. One, they can increase skin hydration. They actually may have direct antipruritic effects. Certainly that's true for any moisturizer, but now there's so many different moisturizers that will have over-the-counter ingredients that are meant to be antipruritic. They may have the ability to reduce the erythema and other signs of inflammation and decrease fissuring. They're incredibly important in patients who have cracks in the skin and fissures in the skin because they're so painful when they have those open sores and open cracks. Putting on the moisturizer just allows them sometimes to even just move around and not aggravate and split those cracks open and feel more pain. And, of course, also they'll have a steroid-sparing effect that by using these non-medicated approaches more regularly, patients can often decrease the use of topical corticosteroids. So, not only impacts on barrier, but also many improvements with respect to inflammation as well.

Topical corticosteroids are considered to be the mainstay of therapy in terms of medicated approaches that we use, whether it's in adults or children, and when patients have an inadequate response to, you know, over-the-counter therapies alone, we would then step up to topical steroids as the next step. And they're typically recommended for patients who've already tried that basic skin care approach. When we think about this concept of step up to therapy or step-up approach to therapy that's used in the atopic dermatitis yardstick or used in the European guidelines. In truth, we don't necessarily have to step through those, you know, rigidly. We can often start patients concomitantly on moisturizers as well as topical corticosteroids.

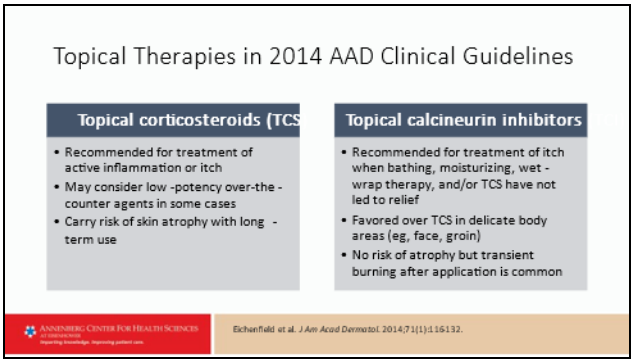


The recommendations for use are typically more for this reactive therapy or treating acute flares and that would be putting on the topical steroids 1 to 2 times a day for treating an active flare, but they can also be used proactively or for maintenance therapy between flares where patients can put it on 1 to 2 times a week, sometimes even up to 3 times a week, between flares, on clear skin to prevent the next round of flares from happening.

Adherence to Evidence-Based Guidelines

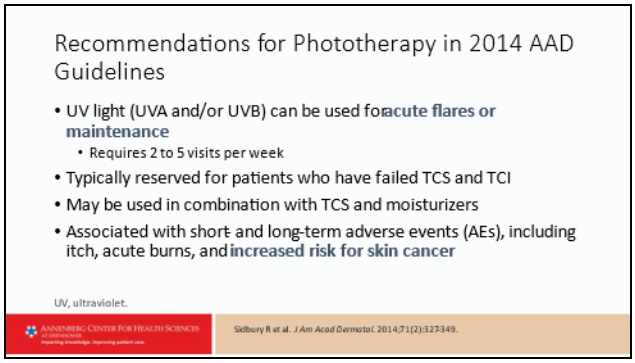


This is a schematic of the 2014 American Academy of Dermatology Guidelines which really just illustrates that there's a range of therapies to address a range of severities of disease. Where we have, for our basic patients, basic management for our milder patients and really for all patients, where we would deal with basics of skin care, antiseptic measures, trigger avoidance, but that might be enough for the mild patient or the very mild patient. That's not going to be enough for the moderate-to-severe patient and for that moderate-to-severe patient, we're going to be adding on the prescription topical anti-inflammatories, topical corticosteroids, calcineurin inhibitors, phosphodiesterase/C4 inhibitors, etc. And then, of course, we have this concept of addressing both acute as well as maintenance management of the disease.



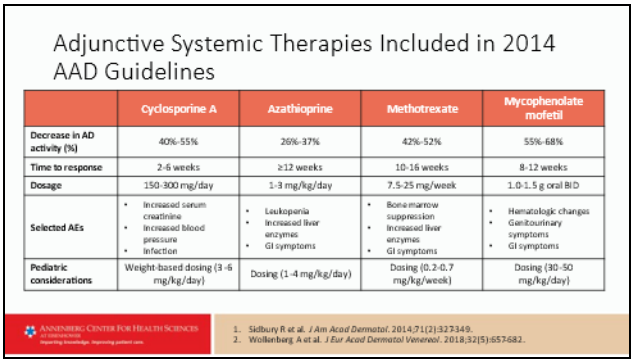
The topical guidelines for the AAD, the guidelines back in 2014 addressed topical therapies and so when they talk about topical corticosteroids, they are recommended for the treatment of active inflammation or itch. You know, we often will try to minimize the amounts used or the potencies used when possible and, you know, so we may consider lower potency, over-the-counter options in some cases. That would really be in the mildest of the mild. They do carry a risk of skin atrophy, particularly with longer-term use, but we also have to be careful not to be too gun-shy and use such sparing amounts or such low potency options that the patient is destined to fail as well. So, we always have, whenever we're thinking about topical therapy, we always have to address giving appropriate potencies and giving appropriate quantities and making sure patients know the right way of putting it on.

This is certainly true for topical calcineurin inhibitors as well. Here, it is recommended for treatment of, you know, itch when bathing, moisturize, wet wrap therapy and/or TCS have not led to relief. Now, in the US, our perspective is a little bit different because of the cost and access around topical calcineurin inhibitors. In Europe, they're used a little bit more regularly because they're a little bit cheaper. And it is generally favored to use TCIs because they're not steroids and we prefer to use nonsteroidal options over topical corticosteroids, particularly in those sensitive skin areas, like the face, the groin, eyelids, etc, where we are more concerned about those steroid side effects. There is no risk of atrophy although, very commonly, patients will experience topical site or application site stinging or burning and that usually is a transient phenomenon, although, every once in a while, it can be a persistent phenomenon as well.



The AAD guidelines also address phototherapy and the recommendations are to use ultraviolet therapy, UVA and/or UVB, as an option for acute flares or maintenance. Now, be careful about how to interpret this because UVB, narrow-band UVB, is a safer therapy as a general rule, but it's much slower. UVA tends to be faster and broadband UVB tends to be faster. So, narrow-band UVB is not a great option for treating flares. It's better for long-term therapy and maintenance. UVA-1, broadband UVB would be better options for the management of acute disease as well, although it is very rare that we find access to UVA-1 or broadband UVB anymore in the United States. This is something that can be challenging for patients to use. It requires in-office treatments a minimum of 2 times a week, sometimes more, and that is something that is just very challenging to access. There's just not enough phototherapy sites around and so this is an option, but it's unfortunately not a universally available option for many patients.

It is typically reserved for patients who have already failed topical therapy, can be used in combination with topical corticosteroids, even calcineurin inhibitors, moisturizers, etc. And it is associated itself with short- and long-term adverse events, including flare-ups of atopic dermatitis, itch, acute burns and potentially, with longer-term use, increased risk for skin cancer.



	Cyclosporine A	Azathioprine	Methotrexate	Mycophenolate mofetil
Decrease in AD activity (%)	40%-55%	26%-37%	42%-52%	55%-68%
Time to response	2-6 weeks	≥12 weeks	10-16 weeks	8-12 weeks
Dosage	150-300 mg/day	1-3 mg/kg/day	7.5-25 mg/week	1.0-1.5 g oral BID
Selected AEs	• Increased serum creatinine • Increased blood pressure • Infection	• Leukopenia • Increased liver enzymes • GI symptoms	• Bone marrow suppression • Increased liver enzymes • GI symptoms	• Hematologic changes • Genitourinary symptoms • GI symptoms
Pediatric considerations	Weight-based dosing (3-6 mg/kg/day)	Dosing (1-4 mg/kg/day)	Dosing (0.2-0.7 mg/kg/week)	Dosing (30-50 mg/kg/day)

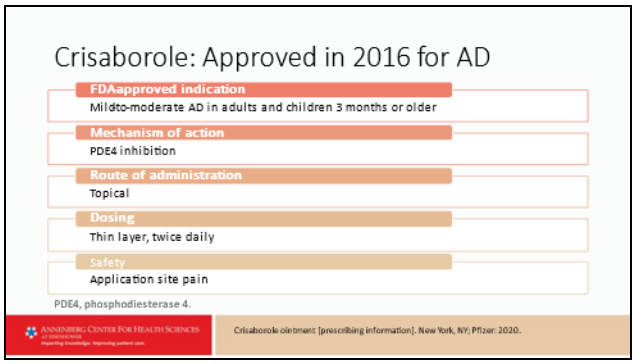
When we think about the different oral systemic therapies, everything on this table are options that are used all off-license, all off-label, in the United States. Cyclosporine A is approved in Europe, but it is not approved in the United States. None of these other options are. They all have shown variable efficacy in this disease and a lot of that is dose-dependent effects in terms of efficacy where lower doses are often better-tolerated, but often don't work. The higher doses often work a little bit better

but come with substantial toxicity issues. There's also, you know, a physician burden of using these with respect to lots of laboratory monitoring at baseline and follow-up. And so, you know, a lot of challenges with these older-fashioned oral immunosuppressing therapies.

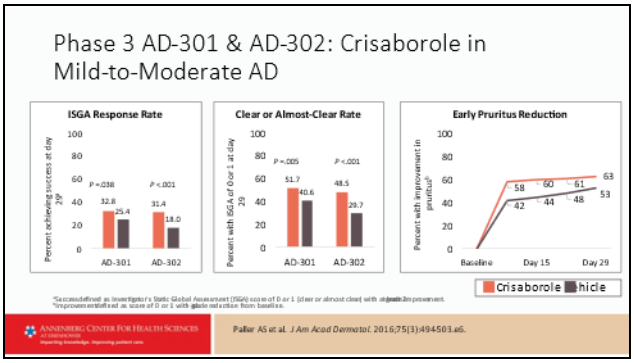
And I should point out, also, that they all come with a lot of potential toxicities. It depends on the drug. There are differences between them. Some with more liver toxicity, cyclosporine has more kidney toxicity, problems with blood pressure, malignancy risk, serious infection risks, major, major challenges and things that we have to navigate when we use these therapies.

AD Therapies Approved After 2014 AAD Guidelines

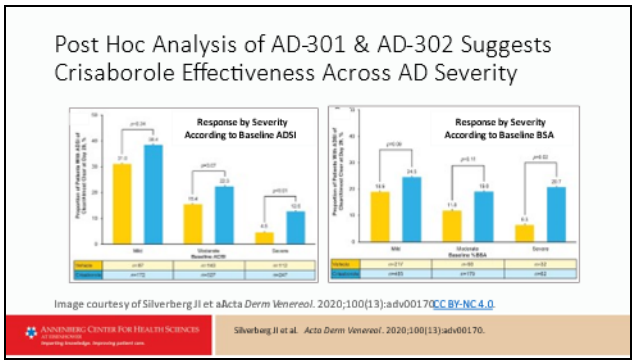
Now, the atopic dermatitis guidelines that were published back in 2014 by the American Academy of Dermatology very quickly became outdated because we had new therapies that were approved subsequently.



We had crisaborale, topical crisaborale, as a topical phosphodiesterase C4 inhibitor approved for mild-to- moderate disease, back in 2017 or 2016 at the end. It was first available to us to use in 2017 and was approved from ages 2 and up. We subsequently got approval for ages three months and up. It is a topical nonsteroidal. The recommendation is to put it on, a thin layer, twice daily, and this has shown a remarkably good safety profile in the trials and post-approval, but the one thing we do see come up is application-site stinging or burning as a fairly common adverse event.

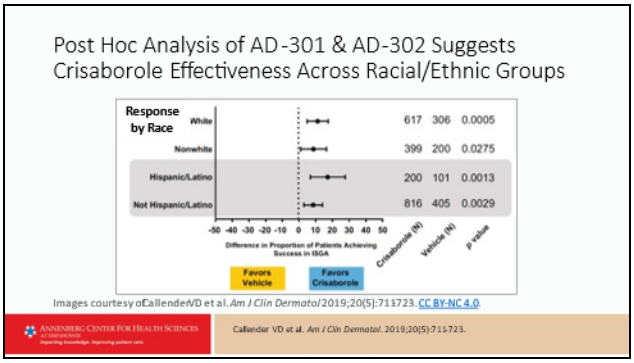


This is just a snapshot of a lot of data that have been presented already from the phase 3 pivotal studies, AD-301, 302. These are identically designed, vehicle-controlled studies looking at topical crisaborale in patients with mild-to-moderate disease, children, adolescents and adults. And we see significant improvements in terms of the proportion of patients who achieve the Investigator's Static Global Assessment scores of clear, almost clear with a 2-grade improvement. This is the FDA's preferred endpoint in the United States for regulatory approval. We see even higher rates of patients who achieve clear or almost clear skin without the 2-grade improvement requirement and we also see significant improvements in terms of proportion, the percent reduction for itch and that shows already by week one substantial reductions, significant reductions compared to vehicle.

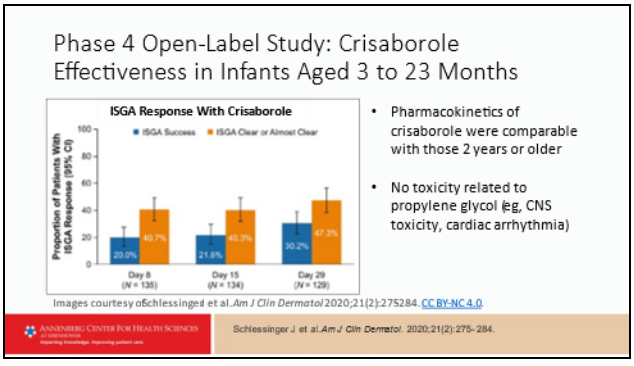


There's some post-hoc, there's actually been many post-hoc studies that have been done looking at the data from the AD-301 and 302 studies. This is one that I had the privilege of taking the lead on and where we looked at different severities. And the background for this is because we know that the approval for crisaborole is for patients with mild-to-moderate disease. But if you actually look at the baseline severity characteristics of patients, you had a body surface area ranging from 5% to 95%. Someone with 95% may have mild lesions, but that's really a more moderate-to-severe patient slipping into the trial. So, we wanted to look at the improvements, the reductions in severity, stratify by other tools, not just the ISGA, but other tools that may reveal the patient actually has more severe disease.

One was body surface area, and you can see on the left that even amongst patients who have very high body surface area that crisaborole showed significant improvements compared to vehicle. And, in fact, the more severe and extensive the disease, the more effective, the greater the vehicle control delta was for crisaborole. And so, similarly when we look at something called the Atopic Dermatitis Severity Index which looks at the individual signs of the disease, added up, as well as itch, we also see that the more severe patients actually had an even greater differential with crisaborole compared to the vehicle, compared to the milder patients.

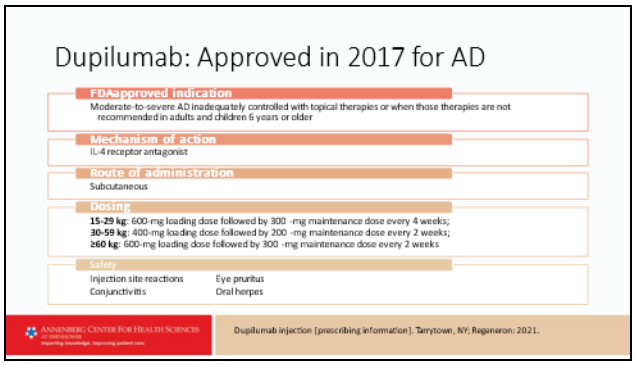


We had another important post-hoc analysis that looked at the efficacy of crisaborole stratified by different races and ethnicities. And this is very important because so many of our studies lack diversity in terms of the patient populations that are recruited and we're often left with all these unanswered questions about how well different drugs might work in diverse patient populations. And here we see, from this post-hoc analysis, that crisaborole worked well in both White and non-White patients and worked as well in Hispanic and non-Hispanic patients. Demonstrating that there is good effectiveness across these different patient populations.



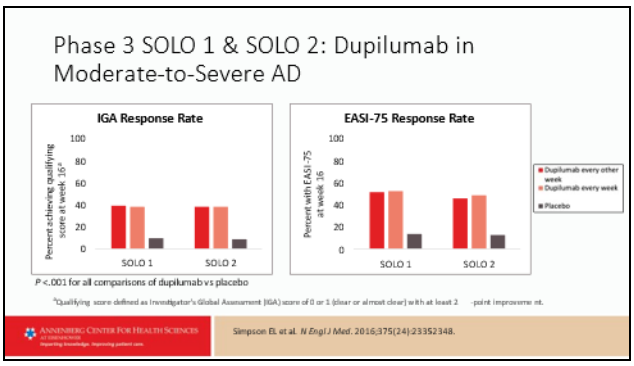
We also have a phase 4, open-label study that was done in children ages 3 months to 23 months and

these are the data that were used to give us the label update that got us the approval from ages 3 and up. And we see, even though it's open-label—which is always a challenge, right, it's not vehicle-controlled, it's open-label—but with this, we see overall similar efficacy rates in this open-label study in terms of ISGA clearance, ISGA success rates compared to what we're seeing in the AD-301 and 302 vehicle-controlled studies. No new toxicity signals that came up and so with this very nice data, we had a label update. Now we have approval for ages 3 months and up.



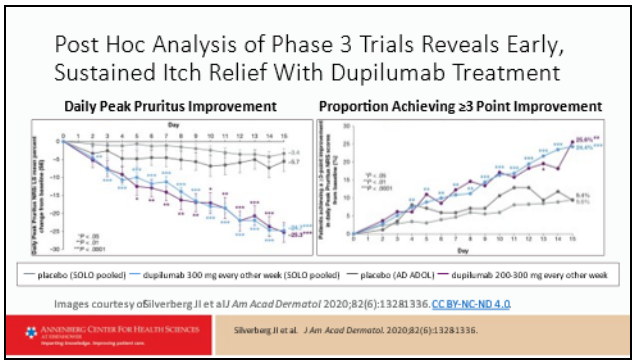
Dupilumab was approved in 2017, March of 2017, for, at that time, adults with moderate-to-severe atopic dermatitis. We got an update for adolescents in March of 2019 and we got an update for children, ages 6 and up, in March, I believe March of this year. And the approved language is moderate-to-severe disease inadequately controlled with topical therapies or topical therapies are contraindicated. Mechanism of action here is it is a biologic, a monoclonal antibody, that targets interleukin-4 receptor alpha subunit, inhibiting the signaling of interleukins 4 and 13. And there are slightly different dosing regimens as listed here for different age groups, recognizing that different age groups often come also with different weight groups.

In terms of safety, overall a good safety profile. The big issues that come up would be injection-site reactions, although this is not a major problem in clinical practice. The eye issues, in terms of conjunctivitis, eye pruritus, etc, which come up a fair amount or most of the time as mild, but something we do have to navigate. There is a slight signal, but it's there for oral herpes that show up as cold sores, not a signal for eczema herpetic or herpes zoster. And then there's also something that has shown up in our anecdotal experience though and now in publications as well, for facial erythema, which often goes together with conjunctivitis that happens with the drug as well.



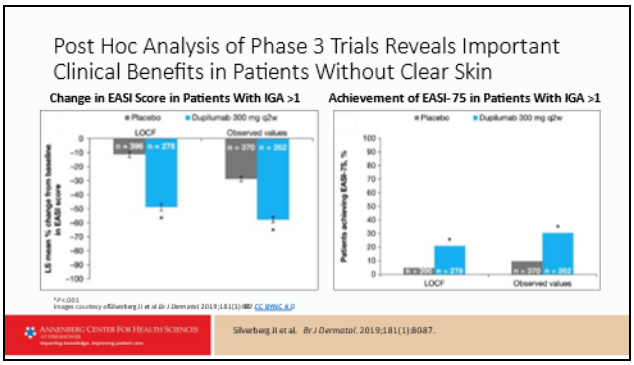
There are just an absolutely extraordinary amount of data available now showing the efficacy and effectiveness of dupilumab in children, in adults. We do not have the time to cover all of that, but I'm going to show you some of the most important pivotal data. On this slide, we see data from the flagship monotherapy study, SOLO 1, SOLO 2. No background topical therapy allowed in these studies and 2 different dosing regimens were tested, dupilumab once weekly or dupilumab every other week at a 300 mg dose, both getting a 600 mg loading dose. Both doses overall showed similar results in terms of their efficacy and both were highly statistically significant compared to the placebo. The FDA gave us the lower dose of every other week dosing. And we see roughly 35% to 40%

of patients being treated with dupilumab who achieve this IGA clear, almost clear with a 2-grade improvement and approximately 50% of patients who achieve an EASI-75 response.

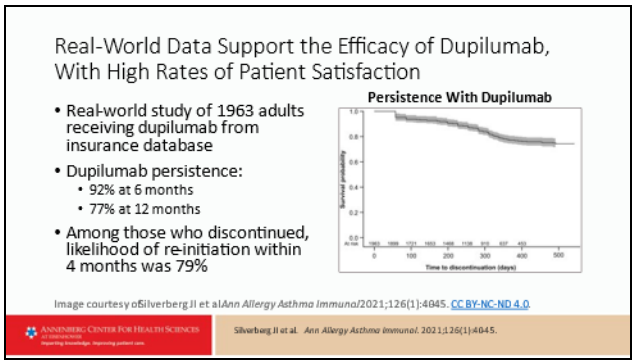


There are many, many, many post-hoc analyses that have been presented with dupilumab data. When we look particularly at itch which, of course, as we talked about already, it's the most common, it's the most burdensome symptom, you don't have to wait 16 weeks, which was the time of their primary efficacy endpoints. Significant reductions in itch were already observed as early as day 2 or day 3. So, that's just after the loading dose and depending on which outcome and which trial is examined, maybe as early as day 2 or day 3 for meaningful improvements. So, it's not everyone who's getting those improvements early on, but it's already significant compared to the vehicle early on. And if you look at the curves, there is no clear indication of a plateau which looks like over time, as we move beyond that 2-week period and certainly even beyond the 16-week period, there's continued improvements in terms of itch.

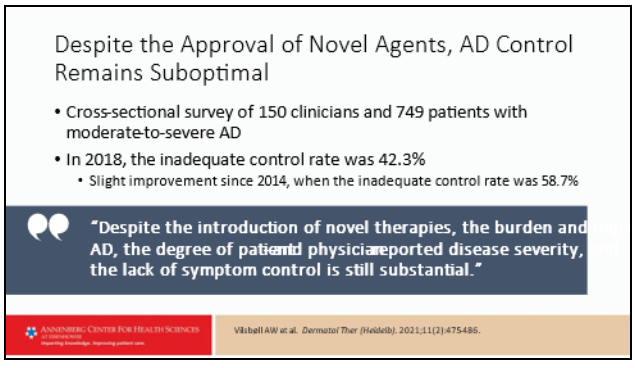
One of the tricky parts about interpreting the IGA success rates, again this is the FDA's preferred efficacy endpoint, now the FDA likes this endpoint because they feel that patients don't understand the nuances of being 75% better or 82% better, some random number. They know am I clear or am I not. So, they like that endpoint as being patient-intuitive. The problem is it's almost too rigorous to tell us what a meaningful improvement is. A patient might be really happy and doing really well, but they still have a couple of lesions left over or some mild itch left over. So, the IGA clear, almost clear may miss what are actually very important clinical improvements.



This is a presentation of data, a post-hoc that I had the privilege of taking the lead on, looking at how did patients do if they were nonresponders, so-called nonresponders by this ISGA score, IGA score clear, almost clear. What we found was that even amongst those who were labeled as nonresponders, high proportions of patients achieved EASI-75 responses, had significant reductions in EASI score, significant improvements in quality of life, significant improvements in terms of itch. So, not everyone, you know, plenty of patients did well even if they were not responders by regulatory definition.



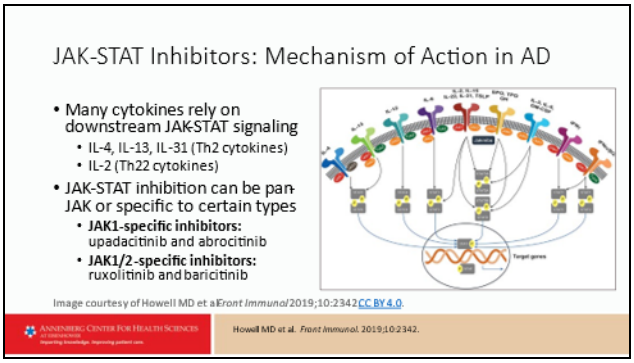
There's some also very important data to think about in terms of real-world effectiveness and disease, you know, drug persistence. Now, there's lots and lots of data from all over the world, but this is a study that I had the privilege of taking the lead on looking at real-world drug persistence in the United States amongst those early adopters in 2017, 2018 post-approval. And what was found was that there was a 92% persistence, continued use of dupilumab at 6 months, about a 77% persistence at 12 months . . . but we certainly need to know more about what happens longer-term. And even amongst those who had initially discontinued, a high proportion, almost 80%, needed to get back onto drug and were back on within 4 months.



Despite the approval of these different novel agents, we still unfortunately see suboptimal control of the disease in many patients. These are data from a cross-sectional survey of 150 clinicians, almost 750 patients with moderate-to-severe disease and this is in 2018, post the approval, shortly after the approval of dupilumab and crisaborale. And the inadequately controlled rate was still 42% and so that was an improvement when compared to data from 2014 that showed an almost 60% inadequate control, so that's great, but it was still 40%. And so, that tells us that there's still more who needed it.

Emerging Therapies: Phase 3 Efficacy & Safety Data

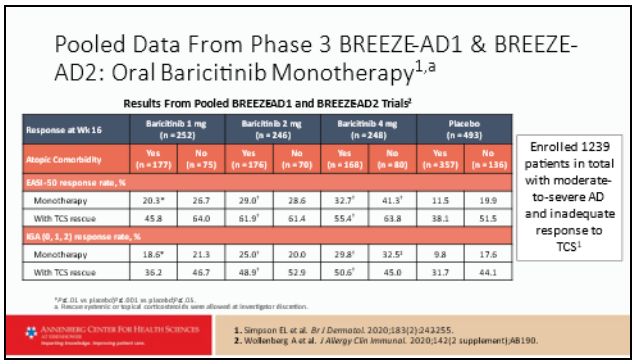
This is one of the most exciting times in atopic dermatitis. There's so much going on in the pipeline, so many new therapeutics, new paradigms, new mechanisms of action. It is amazing to see how rich the data are. But we're going to focus for today's discussion on phase 3 efficacy and safety data.



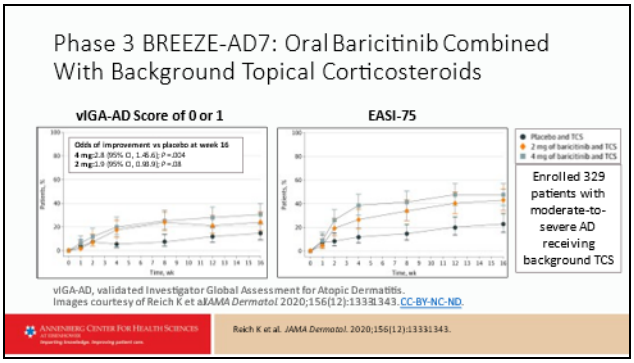
We'll get started by talking about the JAK-STAT inhibitors. The JAK, or Janus kinase inhibitors, are a very important new class of medications in dermatology, really across all immune-mediated diseases, and the reason why is because there's a lot of complex cytokines that are implicated in atopic dermatitis. Interleukins 4 and 13 are sort of the hallmark ones that we think about now because dupilumab targets those, the signaling of those, but there are other ones that have been implicated as

well. Interleukin-22, potentially even IL-17 in a subset of patients, interleukin-31 particularly for itch and certain other inflammatory effects and many others. And the way those extracellular cytokines signal intracellularly is they have to bind to a receptor and then that receptor has to transduce a signal intracellularly. And the way all of those different cytokines that I mentioned, signal, is through the JAK-STAT pathway, but particularly they share the JAK1 subunit as a common pathway for how they are signaling intracellularly.

This is something that, you know, we see now several different JAK inhibitors that have been developed for, and studied for, atopic dermatitis. We have ones that are selective for JAK1 in particular, and that is upadacitinib and abrocitinib. And then we have ones that target JAK1 and JAK2 more selectively and those are ruxolitinib and baricitinib. Now, upadacitinib and abrocitinib are studied as oral agents, baricitinib is being studied as an oral agent, ruxolitinib is already approved as an oral agent for other diseases in the myelodysplastic family, etc, but it was recently approved for topical application in atopic dermatitis.



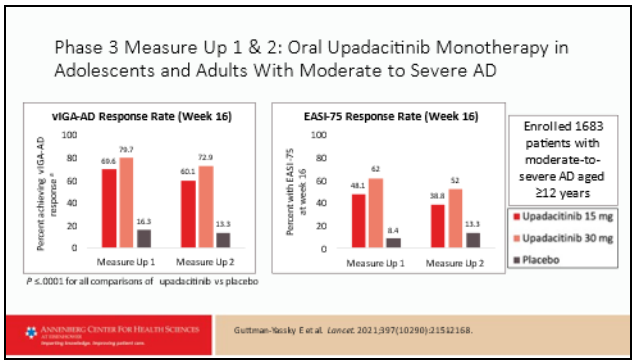
Let's talk about some of these data because there's so much to talk about here. And we can't talk about all the trials because cumulatively there's about 40 trials between these drugs. We're just going to talk about some of the high-level key data to know about. So, first we'll start off with baricitinib. All of the phase 3 studies have the same acronym of BREEZE in front of them, so BREEZE-AD1, -AD2 are the flagship monotherapy studies, very similar in a sense to the SOLO-1, SOLO-2 for dupilumab. And here we see that there were 3 different doses that were tested of baricitinib, 1 mg, 2 mg and 4 mg, all compared to placebo. There were significantly higher proportions of patients who achieved EASI-50 responses and IAG clear, almost clear, responses when compared to the placebo, particularly in those higher doses for baricitinib. And we see even better results when we combined with topical therapy, if they were using it. These were monotherapy studies, but some had to be rescued, and so you see that there's additional value to be gained when adding on topical therapy there.



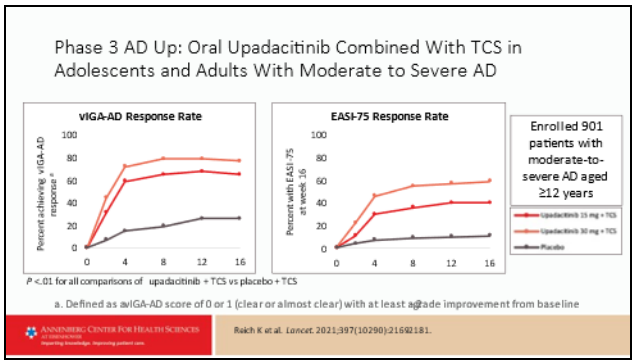
When we look at the BREEZE-AD7 study, this is the combination therapy study that looked at baricitinib plus topical corticosteroids and here we see also significant improvements with respect to the proportion of patients who achieve the IGA score of clear, almost clear, with a 2-grade improvement or the EASI-75 responses as well. And in these studies, consistently there's a dose-dependent, dose response observed where 2 mg appears to be better than placebo in the studies that had a 1 [mg], certainly placebo, but 2 mg is even better than the 1 mg dose in those studies that had a 1 mg dose. And

in most of the studies, the 4 mg dose being better than the 2 mg dose.

The, baricitinib is currently approved in some countries and it's still under investigation and awaiting approval in others.

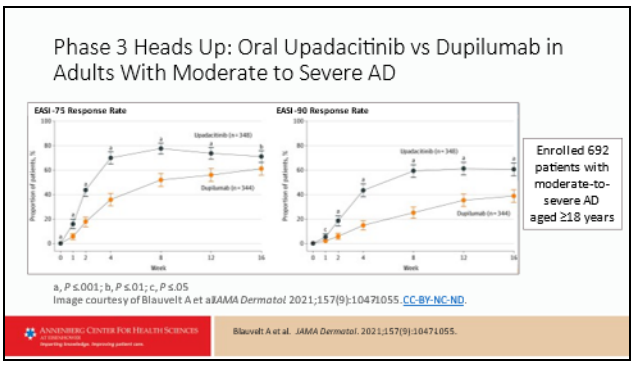


We also have oral upadacitinib as a more preferential or selective JAK1 inhibitor and these are data from the phase 3 Measure Up, Measure Up 2 studies, also flagship monotherapy studies, and here we see also dose-dependent increases for upadacitinib 15 mg compared to placebo, the 30 mg dose even better than the 15 mg dose in terms of achieving validated IGA scores of clear, almost clear with a 2-grade improvement or EASI-75 response rates. And major, major differences compared to the placebo control groups and, you know, arguably has set the bar in terms of efficacy in terms of just some of these endpoints.



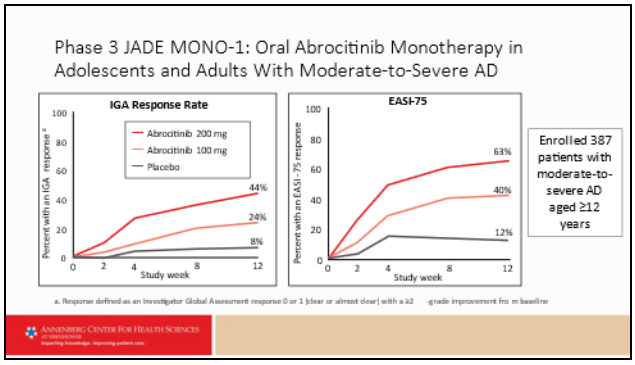
When we look at the use of upadacitinib in combination with topical therapy, here we see that there's some very rapid responses, already by what looks like week 1 or week 2, significant improvements compared to placebo for both of these drugs and, for both of these doses, and for both of these endpoints of the IGA clear, almost clear or EASI-75 responses.

What's really exciting is not only do we have placebo-controlled data, but now we actually have head-to-head data, active comparators against dupilumab as the therapy, only approved therapy in the United States up until this point.

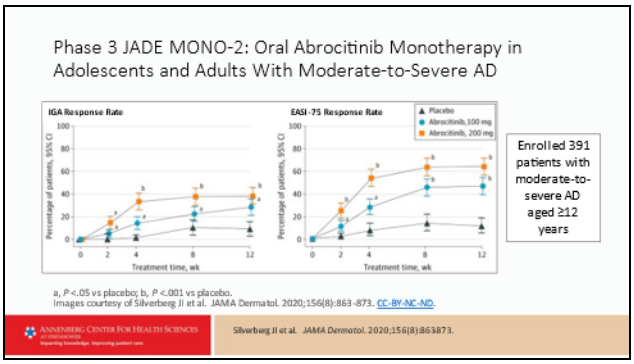


Here we see that, at all time points up until week 16, that upadacitinib was more effective than dupilumab and this is true when looking at the EASI-75 responses and also looking at the EASI-90 responses. Now, it's tricky here in terms of the interpretation because when you look at the EASI-75 responses, what you see is that, for upadacitinib, it may dip down a little bit towards the end of the study whereas for dupilumab there isn't a clear indication of a plateau so they look like they start to catch up a bit for the EASI-75 response which would be a moderate, clinically-important difference or moderate clinical improvement of the disease. But when you look on the right at the EASI-90 responses, the kinetics are quite different. And here we see a much broader differential in efficacy

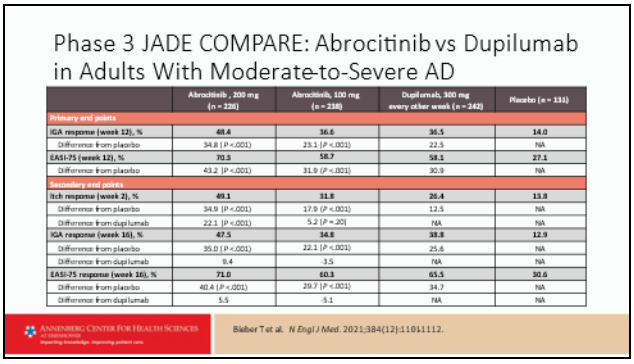
where upadacitinib has an even better likelihood of showing these deeper response compared to dupilumab. And while dupilumab also here doesn't look like there's a clear plateau for EASI-90 responses, we see a much larger differential and we don't see that drop-off in efficacy for EASI-90 responses. So, really where you see upadacitinib shine compared to dupilumab is in those deeper endpoints, EASI-90s, and there's also now post-hocs that have looked at EASI-100s and much deeper responses with respect to itch as well.



Abrocitinib, another preferential JAK1 inhibitor. These are data from the JADE MONO-1 study. This is very similar to the SOLO-1 study and to the other studies that I showed you in terms of BREEZE-AD1, -AD2. Very similar inclusion/exclusion criteria, monotherapy. The key difference in the abrocitinib development program is the studies used 12 weeks as their primary efficacy endpoint whereas in dupilumab and abrocit, and upadacitinib and baricitinib, those all used 16 weeks as their primary efficacy time points. And here we see also dose-dependent improvements in terms of IGA response rates, EASI-75s. The abrocitinib 200 mg dose being more effective than the 100 mg dose and both being more effective than placebo for both of these endpoints.



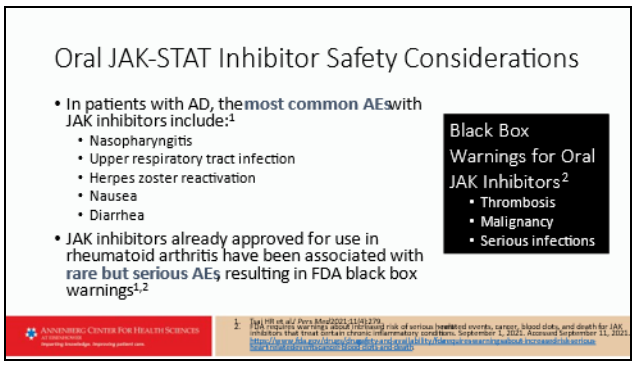
We see similar results observed as well for the JADE MONO-2 study. Identically designed, slightly different numbers, but pretty much the same endpoints, same results. And here we also have very important head-to-head data of abrocitinib vs dupilumab in adults with moderate-to-severe disease.



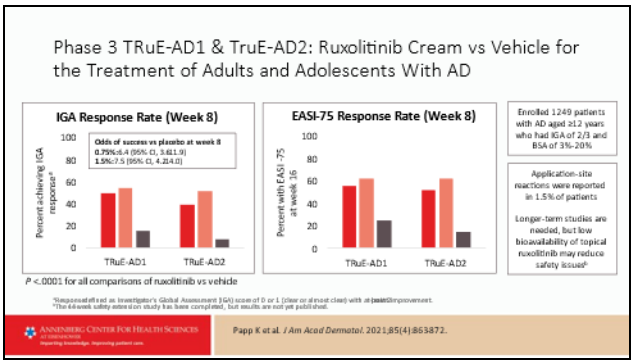
	Abrocitinib, 200 mg (n = 226)	Abrocitinib, 100 mg (n = 238)	Dupilumab, 300 mg every other week (n = 242)	Placebo (n = 131)
Primary end points				
IGA response (week 12), %	48.4	36.6	36.5	14.0
Difference from placebo	34.8 (P <.001)	23.1 (P <.001)	22.5	NA
EASI-75 (week 12), %	70.3	58.7	58.1	27.1
Difference from placebo	43.2 (P <.001)	31.9 (P <.001)	30.9	NA
Secondary end points				
Itch response (week 2), %	49.1	31.8	26.4	13.8
Difference from placebo	34.9 (P <.001)	17.9 (P <.001)	12.5	NA
Difference from dupilumab	22.1 (P <.001)	5.2 (P =.20)	NA	NA
IGA response (week 16), %	47.5	34.8	38.8	12.9
Difference from placebo	35.0 (P <.001)	22.1 (P <.001)	25.6	NA
Difference from dupilumab	9.4	-3.5	NA	NA
EASI-75 response (week 16), %	71.0	60.3	65.5	30.6
Difference from placebo	40.4 (P <.001)	29.7 (P <.001)	34.7	NA
Difference from dupilumab	5.5	-5.1	NA	NA

Here we see, as one might have expected or interpreted based on looking at the network meta-analysis exercise of comparing between studies, we see that abrocitinib, at the 200 mg dose, was more effective than dupilumab and then the 100 mg dose is pretty much neck-and-neck with dupilumab for various endpoints. And this is true whether you look at IGA response points, EASI-75s, etc, out at week 12 and even if you're looking at around week 16.

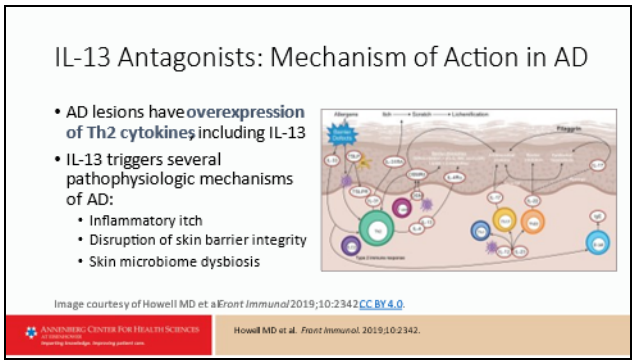
What's interesting is there's some differences in the kinetics, though, because early on, at week 2, abrocitinib is markedly faster and more potent than dupilumab, whereas when you start pushing out to week 16, remember I showed you in the kinetics curves in the head-to-head studies with upadacitinib, that dupilumab sort of keeps climbing a little. Well, when you look out at week 16, what we see is that dupilumab just overtakes the abrocitinib 100 mg dose and is slightly more effective. So, I think the way we would interpret that then is the efficacy of dupilumab is sandwiched right in between the efficacy of the abrocitinib 100 and the 200 mg dose.



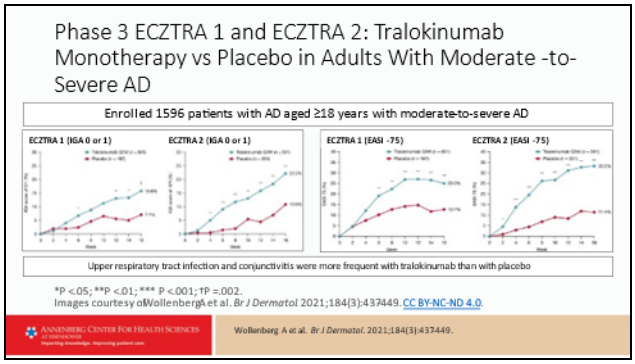
There are a number of safety considerations when thinking about this class. We're not going to be able to talk about everything safety-wise because there's so many different nuances and there's still things that we're learning. But, in patients with atopic dermatitis, the most common adverse events with the JAK inhibitors were nasopharyngitis, upper respiratory tract infections, herpes zoster reactivation, nausea and diarrhea. We also do see acne come up as a signal as well. And there again, there are slight differences between the different drugs. There are also black box warnings for the JAK inhibitors as a class now for venous thrombosis and malignancy, serious infections, major cardio, adverse cardiovascular events and fortunately these are all quite rare, but there's now class-wide labeling for all of these drugs, regardless of the numbers actually observed in the atopic dermatitis studies. And the JAK inhibitors are already approved for use in rheumatoid arthritis and we look forward to their approval imminently for atopic dermatitis in many countries around the world.



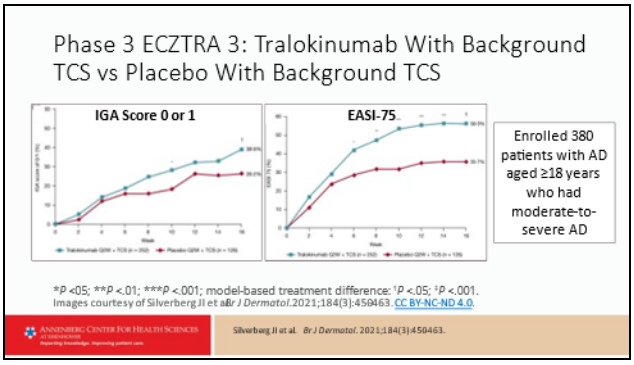
Let's talk about topical JAK inhibition and we now have an approved topical JAK inhibitor in the United States, which is ruxolitinib cream, and we have data from the phase 3 TRuE-AD1, TRuE-AD2 studies. These are monotherapy in the sense that it's just ruxolitinib vs a vehicle control for treatment of adolescents and adults with mild-to-moderate atopic dermatitis. Now, what we see are highly significant improvements in terms of the proportion of the patients who achieve an IGA response or an EASI-75 response compared to vehicle. And the primary efficacy endpoint here is at week 8, although we see significant improvements far earlier than week 8.



We also have other mechanisms of actions now that are being investigated. So, dupilumab inhibits the signaling of interleukin-4 and -13. Now we're seeing investigation of interleukin-13 selective inhibition and interleukin-13 is actually thought to be the more dominant, more important cytokine in the pathogenesis of atopic dermatitis, both in terms of its proinflammatory effects and impact on skin barrier.

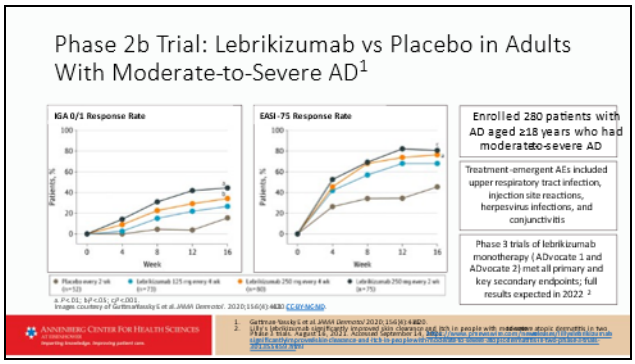


Here we see data for the tralokinumab monotherapy studies. These are data from the ECZTRA 1 and ECZTRA 2 studies. Very similar design and inclusion/exclusion criteria to what I showed you previously for dupilumab and for the JAK inhibitors. Primary efficacy endpoint assessed at week 16. This study focused particularly on adults with moderate-to-severe disease. And what we see is, by week 16, significant reductions or improvements to the proportion of patients who have IGA clear, almost clear, with a 2-grade improvement and EASI-75 responses. Relatively similar results across the 2 different studies. And what is notable, though, when you look at the kinetics of the improvement is that there really is no indication of a plateau, that it looks like, with more time and continued therapy, there would be even higher rates of response for, to tralokinumab for moderate-to-severe atopic dermatitis. Upper respiratory tract infection and conjunctivitis were frequent with tralokinumab compared to placebo.

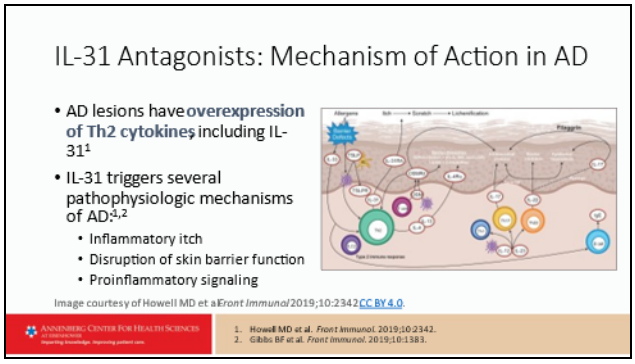


When we look at the ECZTRA 3 study which looked in combination with TCS use, here we also see significant reductions in terms of skin clearance and significantly higher proportions of patients who achieve IGA clear, almost clear with a 2-grade improvement and EASI-75 responses and a boost in the efficacy levels with the addition of TCS. And so this really argues that, in the real world, when using these therapies, there is value of adding on topical therapy to get that synergistic benefit.

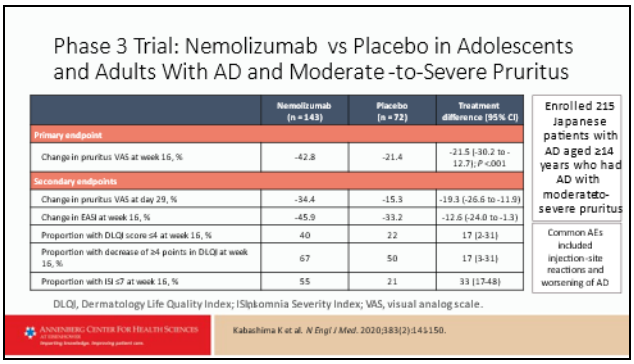
EASING THE DISEASE BURDEN OF PATIENTS WITH ATOPIC DERMATITIS



We also have phase 2b data for lebrikizumab which is another preferential IL-13 inhibitor and here we see dose-dependent increases in terms of IGA clear, almost clear, response rates and EASI-75 response rates in adults with moderate-to-severe disease. And we have phase 3 studies that are underway now for this drug, as well, in atopic dermatitis.



There's also interleukin-31 antagonists. Now, interleukin-31 is a very important cytokine from the perspective of itch, as well as other pro-inflammatory effects, and may even have direct effects on keratinocytes and skin barrier.



And so we have data now for phase 3 readouts from a study done in Japan that looked at nemolizumab at a 60 mg dose compared to placebo, and there were significant reductions with respect to itch, significant reductions, and this statistical analysis in this study is a little bit atypical in terms of it didn't look at the superiority of certain endpoints, but numerical differences in terms of EASI and quality of life and a number of other endpoints.

And this is a separate development happening in Japan with different doses and different regulatory pathway, but we also have now development in the United States and the rest of the world, particularly of the 30 mg dose, which is now being studied in phase 3 and in phase 2b showed very promising results.

Key takeaways, moderate-to-severe atopic dermatitis is a debilitating disease with itch as the most common and most bothersome symptom. There's an unmet need for novel emerging therapies for atopic dermatitis to improve the rates of symptom control. Oral and topical JAK inhibitors have been shown to improve outcomes for patients with moderate-to-severe atopic dermatitis. And then, novel injectable antagonists of IL-13 and IL-31 have also been shown to improve outcomes in patients with moderate-to-severe disease.