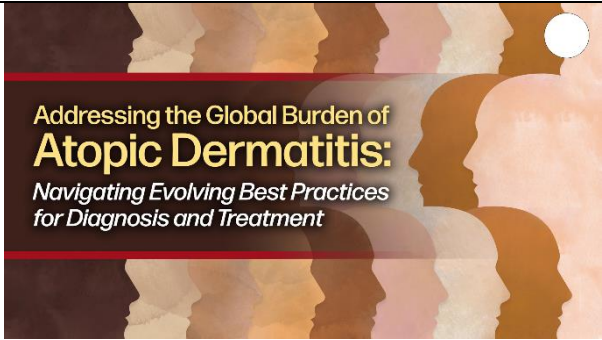
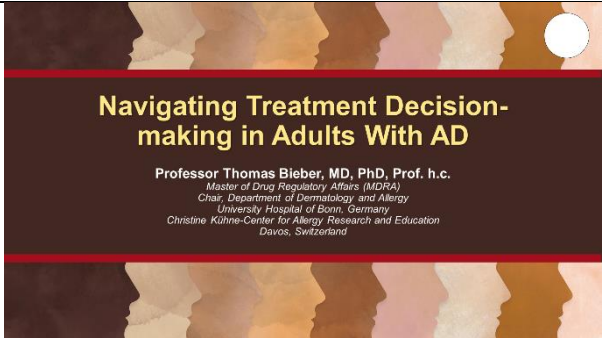
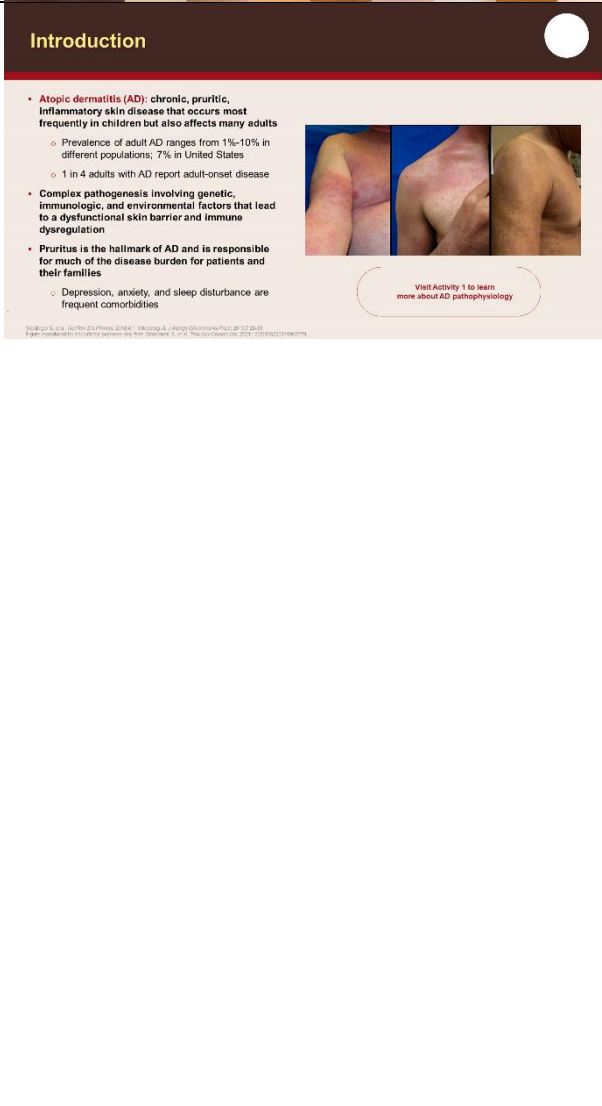



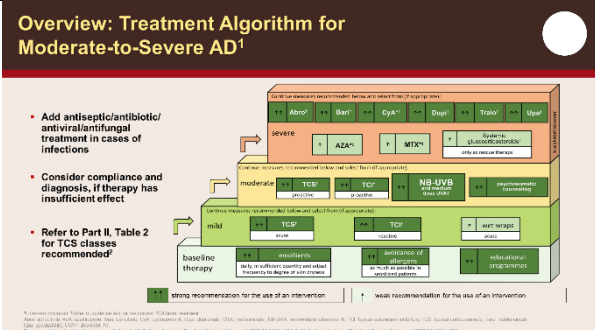
Addressing the Global Burden of Atopic Dermatitis: Navigating Evolving Best Practices for Diagnosis and Treatment

Navigating Treatment Decisionmaking in Adults With AD

1		<p>Hello, my name is Thomas Bieber. I'm a dermatologist and allergist at the University of Bonn in Germany, and I welcome you to this series of presentations, Addressing the Global Burden of Atopic Dermatitis.</p>
2		<p>And today, I would like to address the treatment decision-making in adult patients with this disorder.</p>
3		<p>I think that, for most of you, I don't need to present the clinical pictures of the phenotype of this disorder, but I just would like to remind you the key points, that is, that this is the most important and most common inflammatory skin disorder globally. It affects 1 in 4 adults, particularly in adult-onset disease. It affects many more children, but this will not be the topic of this presentation. And we know that this huge heterogeneity in the clinical phenotype is somehow mirroring what happens in the immune system and in the skin self. So, the complex pathogenesis involves genetics, immunology, and environmental factors, and probably also epigenetic regulation, that are all contributing to that highly itching and particularly complex disorder. The disorder itself has a number</p>

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		<p>of consequences in terms of impacts on the quality of life of these patients, and particularly also in the families and the relatives or caregivers. And I would like to suggest that you also visit Activity 1 to learn a little bit more about the pathophysiology of this disorder. That will guide you a little bit to the pharmacological interpretive options for this particular disorder.</p>
<p>4</p>		<p>And that's exactly what we would like to discuss in the following minutes, that is, the current management and treatment options and recommendations that are currently, at least according to the guidelines, available.</p>
<p>5</p>	 <p>Overview: Treatment Algorithm for Moderate-to-Severe AD¹</p> <ul style="list-style-type: none"> • Add antiseptic/antibiotic/antiviral/antifungal treatment in cases of infections • Consider compliance and diagnosis, if therapy has insufficient effect • Refer to Part II, Table 2 for TCS classes recommended² <p>Legend: strong recommendation for the use of an intervention weak recommendation for the use of an intervention</p> <p><small>¹ Revised algorithm. Refer to guideline and its revision. TCS used instead. Refer to Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ² See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ³ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁴ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁵ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁶ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁷ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁸ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁹ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ¹⁰ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ¹¹ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ¹² See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ¹³ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ¹⁴ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ¹⁵ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ¹⁶ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ¹⁷ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ¹⁸ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ¹⁹ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ²⁰ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ²¹ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ²² See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ²³ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ²⁴ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ²⁵ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ²⁶ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ²⁷ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ²⁸ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ²⁹ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ³⁰ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ³¹ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ³² See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ³³ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ³⁴ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ³⁵ See Part II, Table 2 for details. © 2022 American College of Dermatology. 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All rights reserved. ⁴⁶ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁴⁷ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁴⁸ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁴⁹ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁵⁰ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁵¹ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁵² See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁵³ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁵⁴ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁵⁵ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁵⁶ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁵⁷ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁵⁸ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁵⁹ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁶⁰ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁶¹ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁶² See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁶³ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁶⁴ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁶⁵ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁶⁶ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁶⁷ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁶⁸ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁶⁹ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁷⁰ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁷¹ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁷² See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁷³ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁷⁴ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁷⁵ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁷⁶ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁷⁷ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁷⁸ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁷⁹ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁸⁰ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁸¹ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁸² See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁸³ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁸⁴ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁸⁵ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁸⁶ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁸⁷ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁸⁸ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁸⁹ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁹⁰ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁹¹ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁹² See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁹³ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁹⁴ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁹⁵ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁹⁶ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁹⁷ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁹⁸ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ⁹⁹ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved. ¹⁰⁰ See Part II, Table 2 for details. © 2022 American College of Dermatology. All rights reserved.</small></p>	<p>So this picture just shows you one of the figures of the most recent guidelines. Looking at the stepped-tier plan for adults, in that case, patients with atopic dermatitis. And as you can see here, this is what you see in all or almost all the guidelines worldwide, starting with the kind of baseline or basic therapy, which includes, on one hand, the use of emollients and other preparations aimed to address the barrier dysfunction. Of course, the avoidance of allergens, because we know that in a subpopulation of patients, allergies may play a significant role in the induction of exacerbations. And also, the educational programs should not be forgotten because these</p>

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		<p>are extremely important, particularly because these patients are always keen to learn more about the disorder. And the issue of compliance is really something that is relevant in the management of these patients. And then as in almost all the diseases that we know, we have to approach these patients depending on the severity. So, the treatment algorithms are different depending on whether you are looking at the mild patients, moderate patients, or more severe patients, as shown on this slide. For the mild patients, you can afford to treat the acute flares with topical steroids in a more reactive way. While for the more mild to moderate forms, I would say the use of topical steroids and topical calcineurin inhibitors in a proactive way is very useful, in order to better control the disease on the long run and to avoid frequent exacerbations. And this has been nicely shown in a number of studies about a decade ago in the context of the line extension of Protopic, for example. As an add-on therapy, and I would really specify that this is not an alternative, this is not something which is in between the topical treatment and the systemic treatment. It's just an add-on, the UVB treatment that is, I think, extremely helpful for a number of patients,</p>
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		<p>particularly those that report that the disorder is improving, typically during the summer time. Psychosomatic counseling is also of importance because it, again, very much contributes to an increased compliance of these patients. And for the more severe patients you have to rely on kind of systemic treatment and currently we have, and we will go to that more in details afterwards, I would say the old-fashioned treatments, like the immunosuppressive treatments, like cyclosporine and methotrexate, azathioprine, and the systemic steroids. While on the other hand, you have the more modern treatment with the biologics (dupilumab, tralokinumab), and the JAK kinase inhibitors (baricitinib, upadacitinib, and abrocitinib).</p>
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6	<div data-bbox="421 1413 1018 1742"> <h3>Limitations of Historic Therapies: TCS</h3> <ul style="list-style-type: none"> ▪ Mainstay of therapy for moderate-to-severe AD, but may not be sufficient for certain patients ▪ Limited by anatomic use restrictions and local AEs <ul style="list-style-type: none"> ◦ Skin atrophy, striae, and/or application site reactions ▪ Systemic AEs: less likely to occur, but may develop with prolonged use of high-potency TCS on thin epidermal regions ▪ Withdrawal reactions: may occur with inappropriate, prolonged, or frequent use, particularly with mid- to high-potency TCS ▪ Steroid addiction: dependence on TCS to manage eczema symptoms, leading to continuous or increasing use ▪ Can occur due to skin tolerance to the effects of steroids, leading to a need for higher doses to achieve the same symptom relief  <p><small>© 2014 American Academy of Dermatology. All rights reserved. Reproduction of this document is prohibited without written permission from the American Academy of Dermatology. For more information, visit www.aad.org. Downloaded from www.aad.org on 08/11/14.</small></p> </div>	<p>Coming back to the limitations of the historic therapies, particularly the TCS as you see here, you probably have seen a number of these patients who have used topical steroids for many, many weeks and months, leading sometimes to this kind of steroid addiction situation as you see on the lower right part of the slide, in this kid that has used TCS for a longer period of time and then experienced this withdrawal with acute</p>
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		exacerbation of the disorder.
7	<p>Limitations of Historic Therapies: TCI Immunomodulators</p> <ul style="list-style-type: none"> ▪ Pimecrolimus: mild-to-moderate AD <ul style="list-style-type: none"> ○ 1% indicated for patients aged ≥6 months depending on country ▪ Tacrolimus: moderate-to-severe AD <ul style="list-style-type: none"> ○ 0.1% indicated for patients aged >15 years ○ 0.03% indicated for children aged ≥2 years ▪ Common AEs: local skin irritation (burning, pruritus, and erythema) at the application site <ul style="list-style-type: none"> ○ May drive some patients to discontinue TCIs prematurely ▪ Black box warning: although a causal relationship has not been established, rare cases of malignancy (eg, skin and lymphoma) have been reported in patients treated with TCIs <p><small>© 2015 American Academy of Dermatology. All rights reserved. See www.aad.org for more information. Reproduction of this document is prohibited without the express written permission of the American Academy of Dermatology. For more information, please contact the American Academy of Dermatology at 301.755.4600 or www.aad.org.</small></p> 	<p>On the other hand, we also have the TCIs. I wouldn't say that these are really immunosuppressive drugs, but immunomodulators topically, but we have two drugs available — pimecrolimus and tacrolimus. Pimecrolimus clearly is not so efficient as tacrolimus. And it's certainly the first choice for the treatment of patients with more mild-to-moderate forms, particularly in the pediatric populations. While the tacrolimus treatment is very effective in moderate and sometimes severe patients that are suffering from this disorder. But for both compounds, you know, and the patients will report this, this typical local irritation is a kind of tingling and burning sensation, particularly during the first few days after the first application. So, you have to explain to the patients this kind of side effect and that the side effect will fade, most probably, once the inflammation has been improved, the barrier function has been restored somehow, and the drug will be much less aggressive, I would say, in terms of side effects. You all are aware about the black box warnings issued in 2005 in the context of these two products. Meanwhile, we know that there is no scientific evidence for this</p>

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		<p>black box warning, and that both drugs are really safe in the management of these disorders.</p>
<p>8</p>	<div data-bbox="421 421 1023 745"> <p>Limitations of Historic Therapies: Systemic Immunosuppressive Agents</p> <ul style="list-style-type: none"> Cyclosporine A <ul style="list-style-type: none"> Discontinued in nearly half of patients due to ineffectiveness or patient-reported or clinician-reported (nephrotoxicity and hypertension) AEs Oral corticosteroids <ul style="list-style-type: none"> Long-term use not recommended due to AE profile and risk of severe rebound flares after discontinuation Off-label drugs (eg, azathioprine, methotrexate, and mycophenolate mofetil) <ul style="list-style-type: none"> Often discontinued due to ineffectiveness or AEs Long-term effectiveness and safety data are scarce <div data-bbox="746 521 895 707"> <p>AEs of Oral Corticosteroids:</p> <ul style="list-style-type: none"> Increased risk of infection Weight gain Osteoporosis Worsening of diabetes or hypertension Cataracts Muscle weakness Fluid retention Peptic ulcers Easy bruising Allered mood or psychosis </div>  </div>	<p>So, with regard to the systemic immunosuppressive agents, like cyclosporine A, topic and oral steroids, and off-label drugs azathioprine and methotrexate particularly, we all know and are aware about the use of this drug. In Europe, cyclosporine A is the only one which is approved by the European Medicines Agency, while azathioprine, methotrexate, and mycophenolate are not approved, and I assume will never be approved for this indication. And you know that the use of oral steroids, according to the last guidelines, is very much restricted to very particular situations. When you have a patient with a very severe flare, maybe you can afford to use oral steroids, but certainly not for mid-term or long-term use as we still unfortunately, we still see in some patients that are referred to us. And the problems related to the oral steroids are nicely shown here on the right side of the slide. You know all about these steroids' side effects and I think, nowadays, we have enough new drugs available as an alternative to this kind of treatment.</p>

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9

Patient Case 1



23-YEAR-OLD WOMAN WITH A 15-YEAR HISTORY OF AD THAT IS WORSENING RECENTLY

- Medical history: asthma, treated with albuterol inhaler
- Current treatment:
 - Pimecrolimus cream on face
 - Clobetasol 0.05% to problem areas involving other body sites
 - Triamcinolone to all non-facial skin, twice weekly for maintenance
- Physical examination: 30% BSA dermatitis, vIGA-AD 4, Pruritus NRS 8
- Reports difficulty with daily activities including decreased work productivity and sleep disturbance


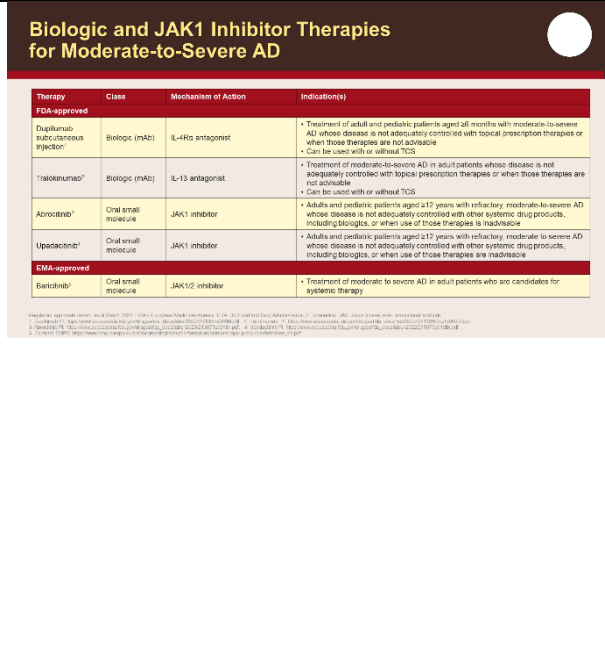
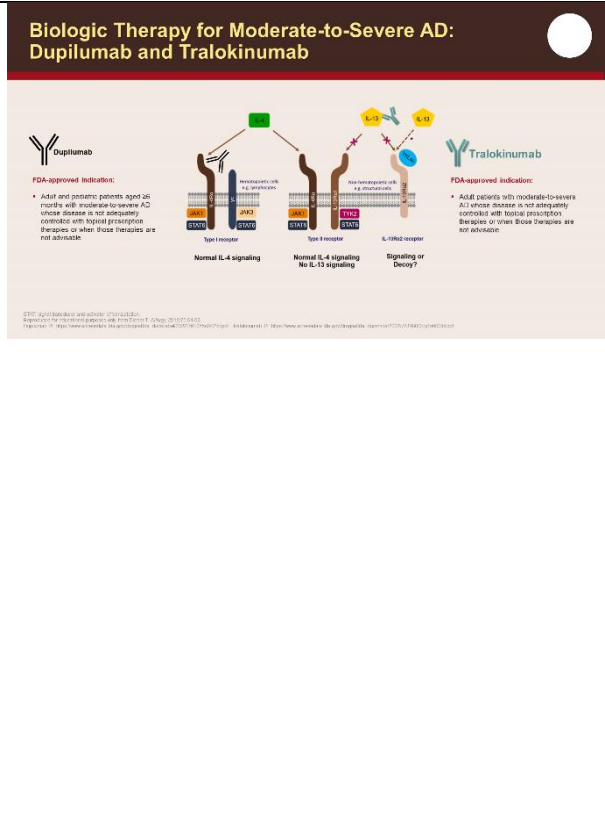
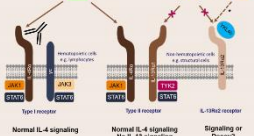


We will revisit this case later, but consider what might be an appropriate next step for this patient.

So, this is a typical patient, I would say, that I would like to briefly present here and we will come back to that patient afterwards. This is a 23-year-old woman that has a 15-year history of atopic dermatitis that worsened recently. Very important in the history is the fact that she's a typical atopic patient, particularly suffering from asthma as another atopic comorbidity, and she is treated with an albuterol inhaler. The current management of the disorder was tried with pimecrolimus on the face, clobetasol on the problem areas, and triamcinolone to nonfacial skin twice weekly for maintenance. What is interesting is the body surface area which is 30%, which is quite a lot and, as you can see here, the vIGA, which is 4, which is in fact implying that this patient is classified as a severe form. Not surprisingly, having a pruritus NRS of 8. And of course, not unexpected, this young lady reports about issues with the daily activities, particularly the impact on the working productivity and the sleep disturbance. So, this is a kind of archetypical patient that we will come back in a moment to.

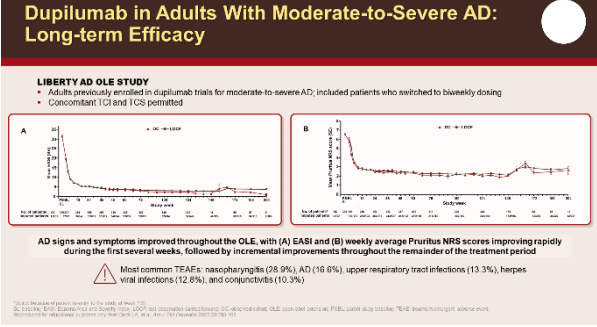
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10	 <p style="text-align: center;">Novel Targeted Therapies for AD</p>	So now let's speak about the new therapies.																																
11	 <p style="text-align: center;">Biologic and JAK1 Inhibitor Therapies for Moderate-to-Severe AD</p> <table border="1" data-bbox="443 658 1002 869"> <thead> <tr> <th>Therapy</th> <th>Class</th> <th>Mechanism of Action</th> <th>Indication(s)</th> </tr> </thead> <tbody> <tr> <td colspan="4">FDA-approved</td> </tr> <tr> <td>Dupilumab Subcutaneous injection¹</td> <td>Biologic (mAb)</td> <td>IL-4/13 antagonist</td> <td> <ul style="list-style-type: none"> Treatment of adult and pediatric patients aged ≥6 months with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable Can be used with or without TCs </td> </tr> <tr> <td>Tralokinumab²</td> <td>Biologic (mAb)</td> <td>IL-13 antagonist</td> <td> <ul style="list-style-type: none"> Treatment of moderate-to-severe AD in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable Can be used with or without TCs </td> </tr> <tr> <td>Abrocitinib³</td> <td>Oral small molecule</td> <td>JAK1 inhibitor</td> <td> <ul style="list-style-type: none"> Adults and pediatric patients aged ≥12 years with refractory moderate-to-severe AD whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable </td> </tr> <tr> <td>Upadacitinib⁴</td> <td>Oral small molecule</td> <td>JAK1 inhibitor</td> <td> <ul style="list-style-type: none"> Adults and pediatric patients aged ≥12 years with refractory moderate-to-severe AD whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable </td> </tr> <tr> <td colspan="4">EMA-approved</td> </tr> <tr> <td>Baricitinib⁵</td> <td>Oral small molecule</td> <td>JAK1/2 inhibitor</td> <td> <ul style="list-style-type: none"> Treatment of moderate to severe AD in adult patients who are candidates for systemic therapy </td> </tr> </tbody> </table> <p><small> ¹ Dupilumab (Dupixent) (IL-4/13 inhibitor) [package insert]. Sanofi, Inc.; 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761040Orig1s001_label.pdf. ² Tralokinumab (Taltz) (IL-13 inhibitor) [package insert]. Novartis Pharmaceuticals Corporation; 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761040Orig1s001_label.pdf. ³ Abrocitinib (Cibulite) (JAK1 inhibitor) [package insert]. AbbVie Inc.; 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761040Orig1s001_label.pdf. ⁴ Upadacitinib (Rinvoq) (JAK1 inhibitor) [package insert]. AbbVie Inc.; 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761040Orig1s001_label.pdf. ⁵ Baricitinib (Tribiod) (JAK1/2 inhibitor) [package insert]. AbbVie Inc.; 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761040Orig1s001_label.pdf. </small></p>	Therapy	Class	Mechanism of Action	Indication(s)	FDA-approved				Dupilumab Subcutaneous injection ¹	Biologic (mAb)	IL-4/13 antagonist	<ul style="list-style-type: none"> Treatment of adult and pediatric patients aged ≥6 months with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable Can be used with or without TCs 	Tralokinumab ²	Biologic (mAb)	IL-13 antagonist	<ul style="list-style-type: none"> Treatment of moderate-to-severe AD in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable Can be used with or without TCs 	Abrocitinib ³	Oral small molecule	JAK1 inhibitor	<ul style="list-style-type: none"> Adults and pediatric patients aged ≥12 years with refractory moderate-to-severe AD whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable 	Upadacitinib ⁴	Oral small molecule	JAK1 inhibitor	<ul style="list-style-type: none"> Adults and pediatric patients aged ≥12 years with refractory moderate-to-severe AD whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable 	EMA-approved				Baricitinib ⁵	Oral small molecule	JAK1/2 inhibitor	<ul style="list-style-type: none"> Treatment of moderate to severe AD in adult patients who are candidates for systemic therapy 	We roughly have in the States these four products, while in Europe we have a fifth one. So, in the US situation we have the two main biologics available, dupilumab and tralokinumab. And in the States, you also have upadacitinib and abrocitinib as the typical JAK kinase inhibitors. In Europe, we also have baricitinib, which is a JAK1 and 2 inhibitor that is available for the treatment of moderate-to-severe patients.
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12	 <p style="text-align: center;">Biologic Therapy for Moderate-to-Severe AD: Dupilumab and Tralokinumab</p> <div style="display: flex; justify-content: space-around;"> <div data-bbox="443 1339 582 1473"> <p>Dupilumab</p> <p>FDA-approved indication:</p> <ul style="list-style-type: none"> Adult and pediatric patients aged ≥6 months with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable </div> <div data-bbox="598 1339 853 1473">  <p>Normal IL-4 signaling</p> <p>Normal IL-4 signaling</p> <p>No IL-13 signaling</p> </div> <div data-bbox="869 1339 1008 1473"> <p>Tralokinumab</p> <p>FDA-approved indication:</p> <ul style="list-style-type: none"> Adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable </div> </div> <p><small> ©2017, Pfizer Inc. and AbbVie Inc. All rights reserved. Dupilumab (Dupixent) (IL-4/13 inhibitor) [package insert]. Sanofi, Inc.; 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761040Orig1s001_label.pdf. Tralokinumab (Taltz) (IL-13 inhibitor) [package insert]. Novartis Pharmaceuticals Corporation; 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761040Orig1s001_label.pdf. </small></p>	Now, with regard to the mode of action, as you know, the biologic therapy for moderate-to-severe atopic dermatitis currently is feasible by two main products. Dupilumab, which has primarily been approved for atopic dermatitis, but meanwhile had a line extension for other indications like asthma, chronic rhinosinusitis, and eosinophilic esophagitis, and most recently also for prurigo nodularis. So the drug itself is now approved for a whole range of patients suffering from this disorder down to patients that are aged 6 months and older. On the other hand,																																

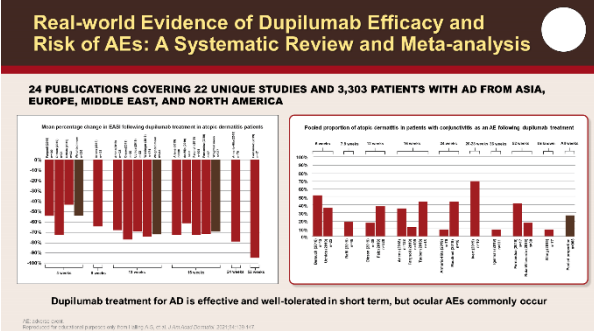
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		<p>we have tralokinumab, which is also FDA-approved for adult patients, but the approval for adolescence is currently ongoing. And the same indication as for dupilumab — moderate-to-severe patients that are not adequately controlled with the topical prescription therapy or for those patients where the therapy is not advisable. So, let's have a look at some data of these different products.</p>
<p>13</p>	 <p>Dupilumab in Adults With Moderate-to-Severe AD: Long-term Efficacy</p> <p>LIBERTY AD OLE STUDY</p> <ul style="list-style-type: none"> Adults previously enrolled in dupilumab trials for moderate-to-severe AD; included patients who switched to biweekly dosing Concomitant TCI and TCS permitted <p>A EASI (0-72) vs Week (0-168)</p> <p>B Fruitus NRS (0-10) vs Week (0-168)</p> <p>AD signs and symptoms improved throughout the OLE, with (A) EASI and (B) weekly average Fruitus NRS scores improving rapidly during the first several weeks, followed by incremental improvements throughout the remainder of the treatment period</p> <p>Most common TEAEs: nasopharyngitis (28.9%), AD (16.6%), upper respiratory tract infections (13.3%), herpes viral infections (12.6%), and conjunctivitis (10.3%)</p>	<p>First with dupilumab, and you are probably aware about the number of studies which have been done. It's really incredible the phase 3 program that Regeneron and Sanofi have started in the context of the clinical development of that particular drug. And this slide just shows you the long-term efficacy of dupilumab in patients that have been exposed, as shown here, for up to 4 years to dupilumab. And you see clearly there is, in fact, nothing that looks like a kind of escape mechanism. So, the patients that are responsive for this drug, they stay responsive for a longer period of time. And I think this is really good news for these patients that have this chronic disorder and that need a long-term management. And the slide shows you, on one hand, improved easy scoring, on the left side, and on the right side you have this really nice response in</p>

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		<p>terms of improvement of the pruritus, starting from a very substantial scale of 7 points typically, going down to 2 points, and very stable response here.</p>
<p>14</p>	 <p>Real-world Evidence of Dupilumab Efficacy and Risk of AEs: A Systematic Review and Meta-analysis</p> <p>24 PUBLICATIONS COVERING 22 UNIQUE STUDIES AND 3,303 PATIENTS WITH AD FROM ASIA, EUROPE, MIDDLE EAST, AND NORTH AMERICA</p> <p>Mean percentage change in IGA1 following dupilumab treatment in atopic dermatitis patients</p> <p>Pooled proportion of atopic comorbidities in patients with conjunctivitis as an AE following dupilumab treatment</p> <p>Dupilumab treatment for AD is effective and well-tolerated in short term, but ocular AEs commonly occur</p>	<p>And these are the data from the phase 3 trial when you now are trying to look at what happens really under real-world conditions. And we are very lucky because we have, really, a high number of publications reporting the experience with dupilumab in many, many different centers worldwide. We have now more than 3,300 patients from different countries, which have been included in these real-world studies. And the bottom line and result of this is that the data that have been generated in the context of the phase 3 trials have been really nicely reproduced in the context of the real world. On the other hand, as you know, I think the single issue that may be related with the use of dupilumab are — or is — the conjunctivitis. And not unexpected, you will see that in the real-world evidence reports across the literature, you will also see that signal of this eye problem that has been reported, and you can see here on the right side. Typically, there is a kind of correlation between the duration of the treatment and the proportion of patients reporting that kind of side effect.</p>

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<p>17</p>	<h3>Tralokinumab in Adults With Moderate-to-Severe AD: Efficacy—Combination With TCS</h3> <p>ECZTRA 3 (NCT03363854)</p> <ul style="list-style-type: none"> • Aged ≥18 years, diagnosis of AD for ≥1 year, inadequate response to topical medications or systemic treatment for AD in the past year • Overall frequency and severity of AEs were comparable between tralokinumab and placebo, majority nonserious and mild or moderate in severity <p>At week 16, significantly more patients receiving tralokinumab achieved the IGA 0/1 and EASI 75 compared with placebo.</p> <p>Overall frequency and severity of AEs were comparable between tralokinumab and placebo, majority nonserious and mild or moderate in severity.</p>	<p>This efficacy can be improved, typically with the combined use with topical steroids. And this is, by the way, the same situation for dupilumab where, in the so-called CHRONOS study, they have shown that that the combo of dupilumab and TCS indeed provides a plus, I would say, in terms of response, of something like 10% to 15%.</p>																																																																																																												
<p>18</p>	<h3>Oral JAK1 Inhibitors for Moderate to Severe AD</h3> <p>ABROCITINIB</p> <ul style="list-style-type: none"> • Selective JAK1 inhibitor • Approved in the US, EU, and Japan for treatment of adult and pediatric patients aged ≥12 years with refractory, moderate-to-severe AD <p>UPADACITINIB</p> <ul style="list-style-type: none"> • Selective JAK1 inhibitor • Approved in the US, EU, and Japan for treatment of adult and pediatric patients aged ≥12 years with refractory, moderate-to-severe AD <p>BARICITINIB</p> <ul style="list-style-type: none"> • JAK1/2 inhibitor • Approved in many countries, including the EU and Japan, for the treatment of adult patients with moderate-to-severe AD who are candidates for systemic therapy 	<p>So now let's switch to the next class of molecules — the oral JAK kinase inhibitors. The oral JAK kinase inhibitors are of three different drugs: Abrocitinib, which is a selective JAK1 inhibitor; upadacitinib, which is also a selective JAK1 inhibitor; and baricitinib, which is the JAK1 and 2 inhibitor. All these products are approved in the different countries except baricitinib, which is not approved currently in the States for this indication.</p>																																																																																																												
<p>19</p>	<h3>Baricitinib in Adults With Moderate-to-Severe AD: Efficacy at Week 16¹⁻⁵</h3> <table border="1"> <thead> <tr> <th>Treatment (mg) (n/N)</th> <th>Responder rate (% of pts) (OR vs PL; 95% CI)</th> <th>EASI75</th> <th>EAS90</th> <th>SCORAD/75</th> <th>LUM 0, 1 from BL at 16W (mean [SD])</th> </tr> </thead> <tbody> <tr> <td colspan="6">Monotherapy</td> </tr> <tr> <td colspan="6">BREEZE-AD1</td> </tr> <tr> <td>BAR 4 (175)</td> <td>56.9 (1.1; 3.4-7.7)***</td> <td>24.8 (3.7; 30.4-31)***</td> <td>16.0 (4.1; 10.4-16.7)**</td> <td>16.4 (8.7; 23.0)***</td> <td>-50.9** (35)</td> </tr> <tr> <td>PL (126)</td> <td>11.4 (2.6; 1.2-6.6)*</td> <td>18.7 (2.5; 10-4.7)**</td> <td>10.4 (2.5; 1.5-6.7)*</td> <td>7.3 (6.1; 1.8-21.6)**</td> <td>-51.9** (31)</td> </tr> <tr> <td>PL (164)</td> <td>4.8</td> <td>8.8</td> <td>4.8</td> <td>1.2</td> <td>-34.8 (37)</td> </tr> <tr> <td colspan="6">BREEZE-AD2</td> </tr> <tr> <td>BAR 4 (132)</td> <td>13.9 (3.8; 1.8-8.1)**</td> <td>21.1 (4.4; 2.2-8.8)**</td> <td>13.0 (6.2; 2.8-8.9)**</td> <td>11.4 (7.1; 2.8-21.8)**</td> <td>-54.9** (35)</td> </tr> <tr> <td>PL (132)</td> <td>10.0 (2.3; 1.4-5.9)*</td> <td>17.0 (3.5; 1.7-8.6)**</td> <td>8.6 (3.9; 1.4-10.4)*</td> <td>7.3 (6.0; 1.6-16.9)**</td> <td>-54.9** (35)</td> </tr> <tr> <td>PL (164)</td> <td>4.5</td> <td>6.1</td> <td>2.2</td> <td>1.5</td> <td>-29.9 (32)</td> </tr> <tr> <td colspan="6">BREEZE-AD3</td> </tr> <tr> <td>BAR 2 (146)</td> <td>24.3**</td> <td>20.0**</td> <td>30.0***</td> <td>14.4**</td> <td>-54.4** (27)</td> </tr> <tr> <td>PL (141)</td> <td>5.4</td> <td>6.2</td> <td>3.4</td> <td>2.7</td> <td>-54.1 (27)</td> </tr> <tr> <td colspan="6">Combination Therapy</td> </tr> <tr> <td colspan="6">BREEZE-AD4</td> </tr> <tr> <td>BAR 4 + TCS (111)</td> <td>31 (2.8; 1.4-6.6)**</td> <td>48 (3.3; 1.4-6.6)**</td> <td>24 (2.1; 1.0-4.2)*</td> <td>18 (2.1; 2.4-3.7)*</td> <td>-67.2*** (16, 6)</td> </tr> <tr> <td>PL + TCS (139)</td> <td>24 (1.3; 0.9-2.0)</td> <td>43 (2.6; 1.4-4.8)**</td> <td>17 (1.2; 0.6-2.6)</td> <td>11 (1.3; 0.9-2.8)</td> <td>-58.2** (29, 3)</td> </tr> <tr> <td>PL + TCS (139)</td> <td>15</td> <td>20</td> <td>14</td> <td>7</td> <td>-62.1 (29, 5)</td> </tr> </tbody> </table> <p>• Baricitinib 4 mg showed a significant improvement at week 16 compared with placebo in primary and secondary disease severity endpoints</p> <p>• Improvements in patients enrolled in BREEZE-AD1 and BREEZE-AD2 were maintained over up to 68 weeks of treatment⁶</p> <p>• Most common TEAEs were infections, mainly mild to moderate upper respiratory tract infections, and herpes simplex</p> <p>• Most frequent laboratory change was an increase in serum CPK to grade 1-2</p>	Treatment (mg) (n/N)	Responder rate (% of pts) (OR vs PL; 95% CI)	EASI75	EAS90	SCORAD/75	LUM 0, 1 from BL at 16W (mean [SD])	Monotherapy						BREEZE-AD1						BAR 4 (175)	56.9 (1.1; 3.4-7.7)***	24.8 (3.7; 30.4-31)***	16.0 (4.1; 10.4-16.7)**	16.4 (8.7; 23.0)***	-50.9** (35)	PL (126)	11.4 (2.6; 1.2-6.6)*	18.7 (2.5; 10-4.7)**	10.4 (2.5; 1.5-6.7)*	7.3 (6.1; 1.8-21.6)**	-51.9** (31)	PL (164)	4.8	8.8	4.8	1.2	-34.8 (37)	BREEZE-AD2						BAR 4 (132)	13.9 (3.8; 1.8-8.1)**	21.1 (4.4; 2.2-8.8)**	13.0 (6.2; 2.8-8.9)**	11.4 (7.1; 2.8-21.8)**	-54.9** (35)	PL (132)	10.0 (2.3; 1.4-5.9)*	17.0 (3.5; 1.7-8.6)**	8.6 (3.9; 1.4-10.4)*	7.3 (6.0; 1.6-16.9)**	-54.9** (35)	PL (164)	4.5	6.1	2.2	1.5	-29.9 (32)	BREEZE-AD3						BAR 2 (146)	24.3**	20.0**	30.0***	14.4**	-54.4** (27)	PL (141)	5.4	6.2	3.4	2.7	-54.1 (27)	Combination Therapy						BREEZE-AD4						BAR 4 + TCS (111)	31 (2.8; 1.4-6.6)**	48 (3.3; 1.4-6.6)**	24 (2.1; 1.0-4.2)*	18 (2.1; 2.4-3.7)*	-67.2*** (16, 6)	PL + TCS (139)	24 (1.3; 0.9-2.0)	43 (2.6; 1.4-4.8)**	17 (1.2; 0.6-2.6)	11 (1.3; 0.9-2.8)	-58.2** (29, 3)	PL + TCS (139)	15	20	14	7	-62.1 (29, 5)	<p>So, let's start with baricitinib, which was the first drug, or the first class approved for the treatment of moderate-to-severe atopic dermatitis, in Europe at least. And as you can see here, again, based on the vIGA for the studies looking at two different doses, 4 mg and 2 mg. You see here that an average 20% of the patients have reached that particular endpoint, a little bit more of course for EASI-75. This clearly shows you that that</p>
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		<p>drug, at least compared to the others (and if you are doing a kind of network meta-analysis this will be more obvious), baricitinib seems to be less efficacious compared to, I would say, the competitors like abrocitinib and upadacitinib. But again, as I mentioned, the combination therapy with TCS allows you to have a plus of at least 10% to 15% in terms of efficacy. As for most of the JAK kinase inhibitors, you will see a number of potential side effects; we will come to that later. But for baricitinib, particularly the safety profile was, at least in my experience, clinically really acceptable compared to what I have seen with other drugs.</p>
<p>20</p>	<p>Abrocitinib in Patients Aged ≥12 Years With Moderate-to-Severe AD: Pooled Efficacy Analysis</p> <p>PHASE 2B TRIAL (NCT02766167) AND 2 PHASE 3 TRIALS (NCT03349009, JADE MONO-1; NCT03575871, JADE MONO-2):</p> <ul style="list-style-type: none"> • Patients aged 18-75 years (phase 2B) or ≥12 years (phase 3) with moderate-to-severe AD for ≥1 year • Inadequately responsive to topical medications or an inability to receive topical treatment • Phase 2b: randomized 1:1:1 to abrocitinib (200 mg, 100 mg, 50 mg, or 10 mg) or placebo • Phase 3: randomized 2:2:1 to abrocitinib (200 mg or 100 mg) or placebo <p>A substantial proportion of patients with moderate-to-severe AD reaching abrocitinib met high threshold efficacy endpoints</p> <p>Most common AEs were nasopharyngitis, headache, and acne; most patients had AEs that were mild or moderate in severity</p> <p>Proportion of patients who achieved (A) EASI-75 response, (B) EASI-90 response, (C) IGA 0-1 response, and (D) IGA 0-2 response at weeks 2, 4, 8, and 12.</p>	<p>Now, abrocitinib is the JAK1 selective inhibitor which is a really interesting molecule. It is currently approved also for adolescents, which is not yet the case for upadacitinib. And as you can see here again on this slide, when you look at the number of patients who have reached EASI-75 response, which is the upper left panel of the slide, you see here 60% of these patients have reached that endpoint. That's really remarkable. That's really something that could be classified as a really excellent response. And this is also translated in terms of EASI-90 — that is</p>

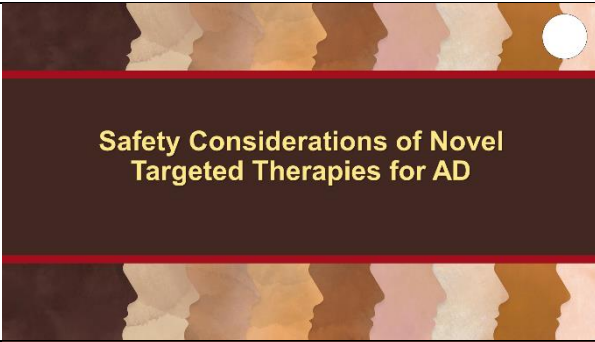

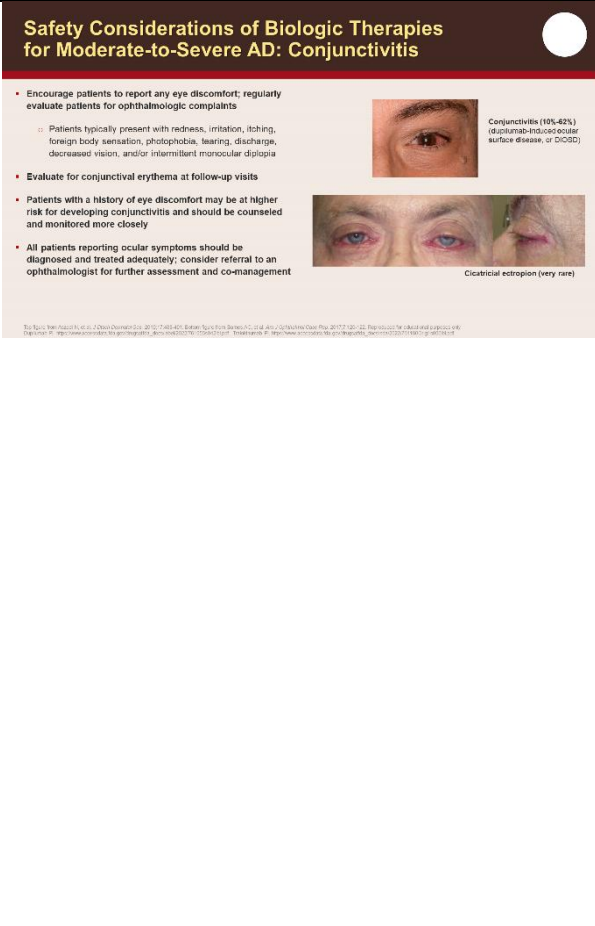
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		<p>in the panel C just below that, with something that's 30% of the patients. That's really a remarkable response.</p>
<p>21</p>	<p>Upadacitinib in Adults With Moderate-to-Severe AD: Efficacy at Week 52</p> <p>ANALYSIS OF FOLLOW-UP DATA FROM THE LARGE, GLOBAL, REPLICATE PHASE 3 MEASURE UP 1 AND MEASURE UP 2 RANDOMIZED CLINICAL TRIALS (N=1,609)</p> <p>Efficacy over time for (A) EASI-75 and (B) vIGA-AD 0/1.</p> <ul style="list-style-type: none"> Once-daily use of upadacitinib (15 mg or 30 mg) resulted in long-lasting efficacy with consistent responses observed through 52 weeks, both in patients who received upadacitinib from the start of treatment and in placebo treated patients who were rerandomized to upadacitinib at week 16 <p><small>FIG 1. U.S. LPTI-10002015. Reproduced from: ClinicalTrials.gov, from Chimenti CL, et al. JAMA Dermatol. 2022;158(8):810.</small></p>	<p>Similarly, upadacitinib seems to have the same kind of efficacy, maybe a little bit better in some clinical trials, particularly for the highest dose, which is 30 mg here. But as you can see here, and in contrast to the biologics, you have quite a rapid mode of action here. You've reached a plateau in terms of efficacy already after 8 to 12 weeks, which is really in sharp contrast to what we know from dupilumab and particularly tralokinumab. And this is true, of course, again for EASI-75 on the left side and IGA 0/1 on the right side. One important point, which is not mentioned on this slide, is the dramatic difference between dupilumab, tralokinumab on one hand and the JAK kinase inhibitors with regards to their efficacy in terms of controlling the pruritus. So, the kinetics, in terms of response for the pruritus as a symptom, is really very, it's really amazing to see how fast the JAK kinase inhibitors are inducing a substantial relief of the pruritus and pain sensation of most of these patients. This is, in my opinion, one of the most important differences between these small molecules on one hand,</p>


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		<p>and the biologics on the other hand.</p>		
<p>22</p>		<p>So, let's look about the safety considerations that I already have mentioned a little bit before.</p>		
<p>23</p>	 <ul style="list-style-type: none"> Like all biologics administered subcutaneously, dupilumab and tralokinumab may be associated with injection site reactions Can include, but are not limited to, injection site swelling, pain, and bruising 	<p>So of course, for the biologics, we are all aware about the side effects, particularly related to the injection site. And this is something that you can see in almost all the products that are injected; whether these are biologics or something else, this doesn't make any difference.</p>		
<p>24</p>	 <ul style="list-style-type: none"> Encourage patients to report any eye discomfort; regularly evaluate patients for ophthalmologic complaints <ul style="list-style-type: none"> Patients typically present with redness, irritation, itching, foreign body sensation, photophobia, tearing, discharge, decreased vision, and/or intermittent monocular diplopia Evaluate for conjunctival erythema at follow-up visits Patients with a history of eye discomfort may be at higher risk for developing conjunctivitis and should be counseled and monitored more closely All patients reporting ocular symptoms should be diagnosed and treated adequately; consider referral to an ophthalmologist for further assessment and co-management <table border="1" data-bbox="901 1220 1005 1254"> <tr> <td>Conjunctivitis (10%-42%)</td> <td>(dupilumab-induced ocular surface disease, or C/OOD)</td> </tr> </table> <p>Cicatricial ectropion (very rare)</p>	Conjunctivitis (10%-42%)	(dupilumab-induced ocular surface disease, or C/OOD)	<p>The difference is made by the side effect that I mentioned already, which is the conjunctivitis. So, the conjunctivitis is reported in 10% to 11% in the first phase 3 trial with dupilumab and the highest rate was reported in one particular real-world evidence report, where this high frequency has been quite uniquely reported in that publication. So, I think it's important also to mention that typically in, at least in our experience clinically, if a patient already had conjunctivitis, which is quite frequent in atopic dermatitis, before you start with dupilumab, there is a substantial risk that this symptom will be even exacerbating during the treatment with</p>
Conjunctivitis (10%-42%)	(dupilumab-induced ocular surface disease, or C/OOD)			

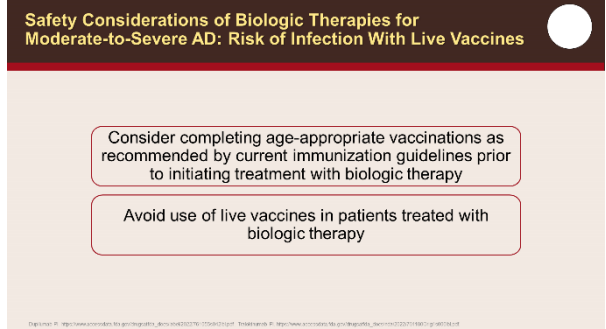
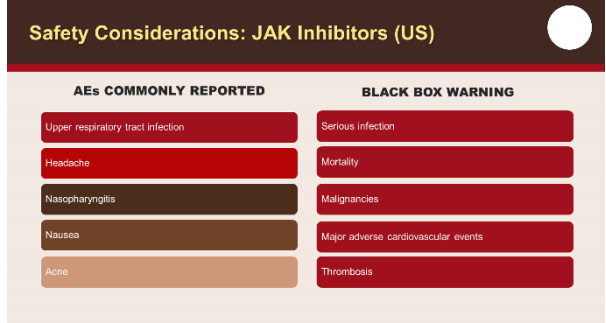
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		<p>dupilumab. It must not be, but there is a risk for exacerbation of that particular symptom. Very rarely, you will see cicatricial ectropion as shown on the right side of the slide — a very rare complication of the use of dupilumab in these patients.</p>												
<p>25</p>	<div data-bbox="422 667 1018 996"> <h3>Safety Considerations of Biologic Therapies for Moderate-to-Severe AD: Conjunctivitis (cont)</h3> <ul style="list-style-type: none"> Topical treatment options for biologic-associated conjunctivitis include tear substitutes and several pharmacologically active agents: <ul style="list-style-type: none"> Fluorometholone 0.1% eye drops are approved for the treatment of inflammatory disorders of the anterior surface of the eye Eye drops containing cyclosporine are suitable for treatment of severe conjunctivitis Another option for treating conjunctivitis is tacrolimus 0.03% eye ointment (off label) <div data-bbox="750 772 997 952"> <h4>Formulation of Oily Cyclosporine 1% Eye Drops</h4> <table border="1"> <tr> <td colspan="2">Rx (NRF 12.21)</td> </tr> <tr> <td>Cyclosporine</td> <td>1.0 g</td> </tr> <tr> <td>Retined castor oil</td> <td>9.9 g</td> </tr> <tr> <td>Medium chain triglycerides</td> <td>to 100.0 g</td> </tr> <tr> <td colspan="2">Shelf life: 1 week</td> </tr> <tr> <td colspan="2">Note: maximum 5 g or 5 ml per bottle</td> </tr> </table> </div> </div>	Rx (NRF 12.21)		Cyclosporine	1.0 g	Retined castor oil	9.9 g	Medium chain triglycerides	to 100.0 g	Shelf life: 1 week		Note: maximum 5 g or 5 ml per bottle		<p>So, this is something that we know from the daily practice. However, at least in my routine and experience empirically, I have only a limited number of patients that require stopping the treatment because of that side effect. In most of the cases it remains mild-to-moderate, and most importantly it can be treated by either topical or eye drops containing steroids, or by eye drops containing cyclosporine A, and the formulation is shown on the right side of the slide. And there are also some options for treating this with an eye ointment which contains tacrolimus, but this is an off-label use, of course.</p>
Rx (NRF 12.21)														
Cyclosporine	1.0 g													
Retined castor oil	9.9 g													
Medium chain triglycerides	to 100.0 g													
Shelf life: 1 week														
Note: maximum 5 g or 5 ml per bottle														
<p>26</p>	<div data-bbox="422 1563 1018 1892"> <h3>Safety Considerations of Biologic Therapies for Moderate-to-Severe AD: Helminth Infections</h3> <ul style="list-style-type: none"> Helminth infections can co-occur with AD and should be treated before initiating biologic therapy Can be common in tropical and subtropical regions and disproportionately affect resource-limited areas If patients become infected while receiving biologic therapy and do not respond to anti-helminth treatment, discontinue biologic therapy until the infestation resolves <div data-bbox="829 1680 973 1803">  <p>Cutaneous Larva Migrans</p> </div> </div>	<p>As you know, dupilumab also blocks IL-13, which makes sense to control the inflammation in the skin, as I mentioned, but also blocks IL-4. And IL-4 is well known also to be important for the fight against parasites. So, if you see patients that have a helminth infection that occurs during the treatment with AD, you</p>												

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		<p>should think about this and also maybe transiently stop the treatment, focus on the treatment of the helminth infection, and then you can restart the treatment. I know from colleagues in South America, that not seldomly when they are starting the treatment with dupilumab they are even giving some systemic anthelmintic treatment in order to avoid any kind of complication related to the initiation of the treatment with dupilumab.</p>												
27	 <p>Safety Considerations of Biologic Therapies for Moderate-to-Severe AD: Risk of Infection With Live Vaccines</p> <ul style="list-style-type: none"> Consider completing age-appropriate vaccinations as recommended by current immunization guidelines prior to initiating treatment with biologic therapy Avoid use of live vaccines in patients treated with biologic therapy 	<p>So, with regard to further considerations of the biological treatment, something that is frequently asked by the patients, particularly in the context of the COVID infection and vaccination strategies, I think it is wise before you start the treatment to recommend the vaccinations to be done. Because you never really know what the potential interference could be, and particularly avoid the use of live vaccinations during the treatment with biological therapy. But this is also the case, by the way, for the JAK kinase inhibitors.</p>												
28	 <p>Safety Considerations: JAK Inhibitors (US)</p> <table border="1"> <thead> <tr> <th>AEs COMMONLY REPORTED</th> <th>BLACK BOX WARNING</th> </tr> </thead> <tbody> <tr> <td>Upper respiratory tract infection</td> <td>Serious infection</td> </tr> <tr> <td>Headache</td> <td>Mortality</td> </tr> <tr> <td>Nasopharyngitis</td> <td>Malignancies</td> </tr> <tr> <td>Nausea</td> <td>Major adverse cardiovascular events</td> </tr> <tr> <td>Acne</td> <td>Thrombosis</td> </tr> </tbody> </table>	AEs COMMONLY REPORTED	BLACK BOX WARNING	Upper respiratory tract infection	Serious infection	Headache	Mortality	Nasopharyngitis	Malignancies	Nausea	Major adverse cardiovascular events	Acne	Thrombosis	<p>Now, in terms of safety profile for the JAK kinase inhibitors, we know, and this is the situation for the US, that there is a black box warning that has been issued by the FDA based on the safety profile. And this black box issue mentions</p>
AEs COMMONLY REPORTED	BLACK BOX WARNING													
Upper respiratory tract infection	Serious infection													
Headache	Mortality													
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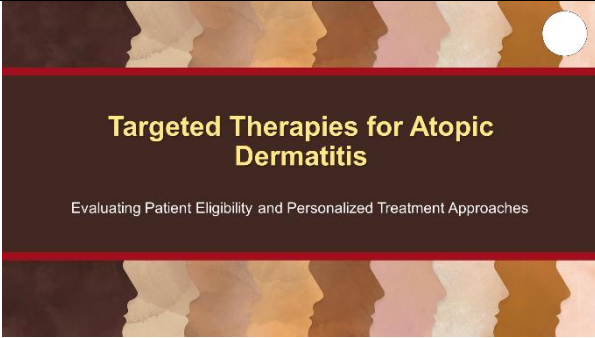
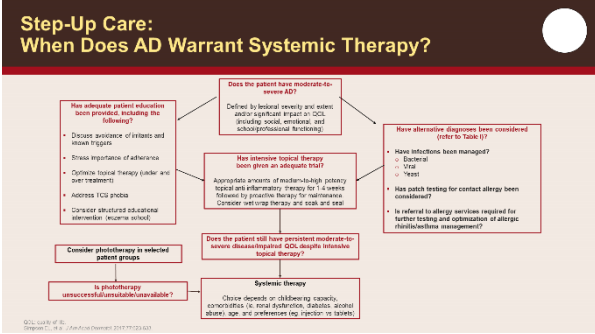
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		<p>increased risk or history of cancer are those patients at high risk. And you should reconsider the treatment of these patients, if you think about starting with JAK kinase inhibitors; the same also, by the way, for patients who have particular risk to develop thrombosis and preliminary embolism.</p>										
30	<div data-bbox="421 696 1018 1032"> <p>Monitoring and Routine Care of Patients Taking JAK Inhibitors</p> <table border="1"> <thead> <tr> <th>Time Point</th> <th>Labs</th> </tr> </thead> <tbody> <tr> <td>Prior to starting JAK inhibitor treatment</td> <td>HBV, HCV, and HIV TB (PPD, Quantiferon, TB-Gold) Fasting lipids, CMP, CBC with differential</td> </tr> <tr> <td>At 4 weeks</td> <td>LFTs, CBC with differential</td> </tr> <tr> <td>At 12 weeks</td> <td>Fasting lipids</td> </tr> <tr> <td>Every 3-6 months (or sooner after dose increases)</td> <td>LFTs, CBC with differential</td> </tr> </tbody> </table> <p>OTHER CARE:</p> <ul style="list-style-type: none"> • Vaccinations per guidelines (eg, herpes zoster vaccination); avoid use of live vaccines • Skin checks annually, examining for non-melanoma and other skin cancers • Age-appropriate cancer screening </div>	Time Point	Labs	Prior to starting JAK inhibitor treatment	HBV, HCV, and HIV TB (PPD, Quantiferon, TB-Gold) Fasting lipids, CMP, CBC with differential	At 4 weeks	LFTs, CBC with differential	At 12 weeks	Fasting lipids	Every 3-6 months (or sooner after dose increases)	LFTs, CBC with differential	<p>So, what kind of routine work should be done before treating patients with JAK kinase inhibitors? Prior to starting the treatment, you have a little bit of lab work. You have to look at virus infections like HIV, hepatitis. Of course, you have to exclude tuberculosis and you have to look at lipids and to do a CBC in order to be sure that these patients do not have any kind of underlying disorder. After 4 weeks, minimal work to be done with the CBC, and looking at the lipids again after 12 weeks, and then every 3 to 6 months a little lab work in order just to control that everything is OK. As I mentioned, the vaccinations per guidelines, very important, and to avoid the live vaccinations. Skin checks should be done for nonmelanoma skin cancer. And of course, for all patients, always advisable: the age-appropriate cancer screening.</p>
Time Point	Labs											
Prior to starting JAK inhibitor treatment	HBV, HCV, and HIV TB (PPD, Quantiferon, TB-Gold) Fasting lipids, CMP, CBC with differential											
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<p>31</p>	 <p>Targeted Therapies for Atopic Dermatitis Evaluating Patient Eligibility and Personalized Treatment Approaches</p>	<p>So now, with all these drugs available and the multiple options and the multiple kind of disease situations and the heterogeneous phenotype backgrounds of all these patients and not only the kids, but particularly in the adults, let's discuss a little bit the option of the target therapy and the so-called shared decision-making process that is involved here in a modern management of these patients.</p>
<p>32</p>	 <p>Step-Up Care: When Does AD Warrant Systemic Therapy?</p> <p>Flowchart steps:</p> <ul style="list-style-type: none"> Does the patient have moderate-to-severe AD? (Defined by clinical events and/or areas of significant impact on QoL, including social, emotional, and school/professional functioning.) <ul style="list-style-type: none"> Yes: <ul style="list-style-type: none"> Has adequate patient education been provided, including the following? <ul style="list-style-type: none"> • Disease avoidance of irritants and skin triggers • Stress importance of adherence • Optimize topical therapy (order and skin treatment) • Address ICS abuse • Consider structured educational intervention (e.g., nurse school) Has intensive topical therapy been given as adequate trial? <ul style="list-style-type: none"> • Appropriate amount of medium-to-high potency topical anti-inflammatory therapy for 14 weeks followed by proactive therapy for maintenance. Consider wet-wrap therapy and seal and seal. Has alternative diagnoses been considered (refer to Table 1)? <ul style="list-style-type: none"> • Have infections been managed? <ul style="list-style-type: none"> o Bacterial o Viral o Fungal • Has patch testing for contact allergy been considered? • Is referral to allergy services required for further testing and optimization of allergic rhinitis/asthma management? No: <ul style="list-style-type: none"> Consider phototherapy in selected patient groups. <ul style="list-style-type: none"> • Is phototherapy contraindicated/unavailable/unavailable? Does the patient still have persistent moderate-to-severe disease after 14 weeks of intensive topical therapy? <ul style="list-style-type: none"> • Systemic therapy. (Choice depends on childbearing capacity, comorbidities, or renal/hepatic, systemic organ abuse), age, and preferences (eg, injection vs tablet). <p><small>© 2017, published by Elsevier. For personal use only. All rights reserved. https://doi.org/10.1016/j.jad.2017.07.001</small></p>	<p>So, the first question of course, is: Among all these patients that you are taking care of with this particular disorder, when do you advise or when do you discuss with the patient that he warrants a systemic therapy? And I would urge you to look at this paper by my colleague Eric Simpson, published in 2017, where we tried to collect all, let's say, the evidence, the pros and cons, and suggesting this kind of, let's say, decision tree that would guide you to the decision of deciding a systemic therapy for a particular patient. And again, I would like to highlight here that the phototherapy is not an alternative, in my opinion, for any kind of treatment. It can only be considered as an alternate, as an add-on option, either for topical or for systemic therapy.</p>

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AD: Goals of Treatment



Relieve symptoms: reduce itching, dermatitis, and inflammation to provide relief and improve QoL for the patient



Prevent exacerbations: implement measures to prevent flare-ups, including avoiding triggers, maintaining skin hydration, and using topical treatments as prescribed



Restore skin barrier function: repair and protect the skin barrier to reduce transepidermal water loss and minimize the risk of skin infections



Minimize treatment risks: ensure that treatments used to manage AD are safe and effective, while minimizing the risk of AEs

So, what are the goals of the treatment when you see this kind of patient and you discuss with him clearly what you would like to reach together with him in the context of this treatment? First, of course, to relieve the symptoms, particularly itching. But you also would like to prevent exacerbation. Which is an issue which is, in many patients, really relevant and sometimes also related to some kind of provocations, but not only sometimes related to skin care which is not appropriately done, and many other things. And this brings me to the issue of the restoration of the skin barrier function, which is absolutely mandatory. So the baseline treatment, the basic therapy using emollients, is absolutely mandatory in the management of this disorder. And last, but not least, you always have to minimize the treatment risk, and here I come back to the issue we just discussed before, when it comes to discuss with the patients the pros and cons of each kind of treatment, biologics and particularly JAK kinase inhibitors. And that's what we would like to do now in the next exercise, in the next couple of minutes.

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Patient Case 1, Revisited

23-YEAR-OLD WOMAN WITH A 16-YEAR HISTORY OF AD THAT IS WORSENING RECENTLY

- Medical history: asthma, treated with albuterol inhaler
- Current treatment:
 - Fluticasone cream on face
 - Clobetasol 0.05% to problem areas involving other body sites
 - Triamcinolone to all non-facial skin, twice weekly for maintenance
- Physical examination: 30% BSA dermatitis, vIGA-AD 4, Pruritus NRS 8
- Reports difficulty with daily activities including decreased work productivity and sleep disturbance



Which of the following would be the most appropriate next step for this patient?

Ruxolitinib cream 1.5%

Biologic therapy (dupilumab)

Biologic therapy (tralokinumab)

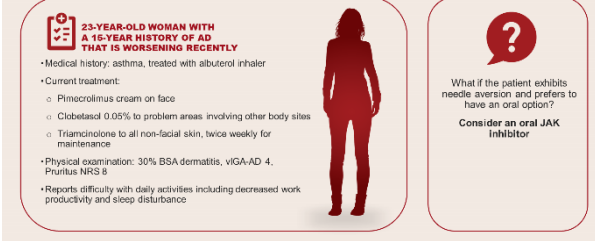
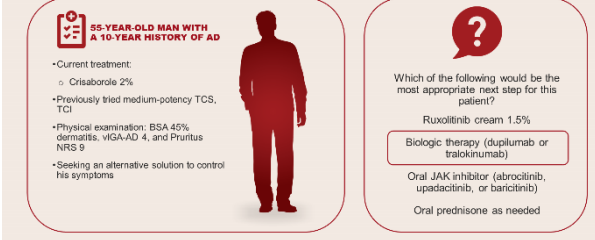
Oral JAK inhibitor (abrociclib, upadacitinib, or baricitinib)

Oral prednisone as needed

I come back to that lady that I have presented before. And as you remember, this lady has a more severe form of the disorder, with a quite substantial body surface area which is affected, 30%. But obviously, and most importantly, she has asthma, which is important in this history to be collected, because this will guide you first in the treatment option. So, if you ask the question, "Which of the following would be the most appropriate next step for the patient?" Either, just starting to treat with ruxolitinib topically, JAK kinase 1/2 inhibitor. By the way, only available at least in the US, not so far available in Europe, unfortunately. Or you provide, or you advise the patient to use a biologic like "dupi" or "tralok," or an oral JAK kinase inhibitor, or potentially the use of oral prednisone. And here, obviously, I think the choice is quite easy. I would advise to prescribe or to initiate a treatment with dupilumab, not so much with tralokinumab, because this patient has asthma, and as you know, asthma is another indication for dupilumab. So, dupilumab would be my first choice, not tralokinumab. With dupilumab you would have, for this particular patient, I'd say, according to the motto, "buy one, get two indications treated," and this would be the optimal

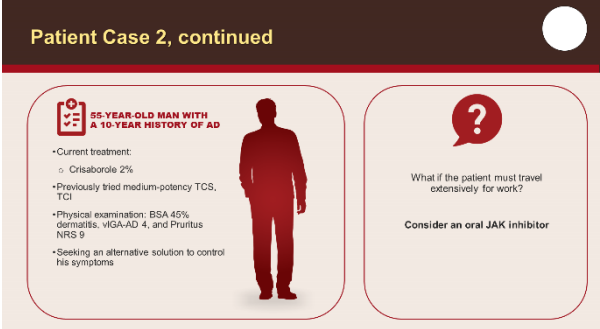
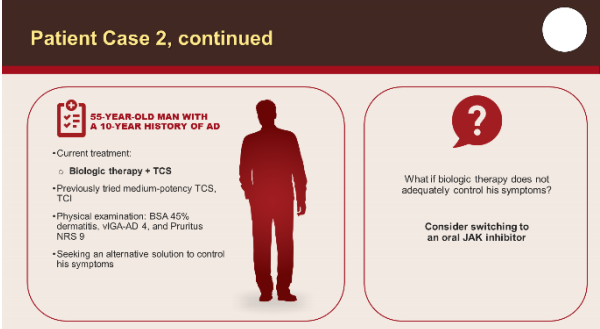
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		situation for this particular patient.
35	<p>Patient Case 1, Revisited</p>  <p>23-YEAR-OLD WOMAN WITH A 16-YEAR HISTORY OF AD THAT IS WORSENING RECENTLY</p> <ul style="list-style-type: none"> • Medical history: asthma, treated with albuterol inhaler • Current treatment: <ul style="list-style-type: none"> ○ Pimecrolimus cream on face ○ Clobetasol 0.05% to problem areas involving other body sites ○ Triamcinolone to all non-facial skin, twice weekly for maintenance • Physical examination: 30% BSA dermatitis, vIGA-AD 4, Pruritus NRS 8 • Reports difficulty with daily activities including decreased work productivity and sleep disturbance <p>What if the patient exhibits needle aversion and prefers to have an oral option? Consider an oral JAK inhibitor</p>	<p>However, if the patient exhibits needle aversions and prefers to have an oral option, what would be the option that you would choose? She's a young lady. She has severe atopic dermatitis, obviously not really controlled by the topical treatment. So, she is, in that case, a candidate for an oral JAK kinase inhibitor, clearly. And you have the choice between, in Europe, baricitinib, abrocitinib, and upadacitinib or just “abro” and “upa” in the States.</p>
36	<p>Patient Case 2</p>  <p>55-YEAR-OLD MAN WITH A 10-YEAR HISTORY OF AD</p> <ul style="list-style-type: none"> • Current treatment: <ul style="list-style-type: none"> ○ Crisaborole 2% • Previously tried medium-potency TCS, TCI • Physical examination: BSA 45% dermatitis, vIGA-AD 4, and Pruritus NRS 9 • Seeking an alternative solution to control his symptoms <p>Which of the following would be the most appropriate next step for this patient?</p> <ul style="list-style-type: none"> <input type="checkbox"/> Ruxolitinib cream 1.5% <input type="checkbox"/> Biologic therapy (dupilumab or tralokinumab) <input type="checkbox"/> Oral JAK inhibitor (abrocitinib, upadacitinib, or baricitinib) <input type="checkbox"/> Oral prednisone as needed 	<p>Another patient, 55 years old, a man with a 10-year history of atopic dermatitis. The current treatment crisaborole 2%, which I think is nonsense, to be honest, with regards to the severity of this patient. A body surface area of 45%, a vIGA of 4, so clearly a severe patient with a high pruritus score of NRS 9. So, it doesn't make sense at all to try crisaborole in that particular patient. So, which of the following would be the most appropriate next step for this patient? Trying another topical treatment with “ruxo.” Or switch to a biological therapy with “dupi” or “tralo.” Or an oral JAK kinase inhibitor like “abro,” “upa,” or baricitinib. Or again trying to control the disease, but only at the short term, with</p>

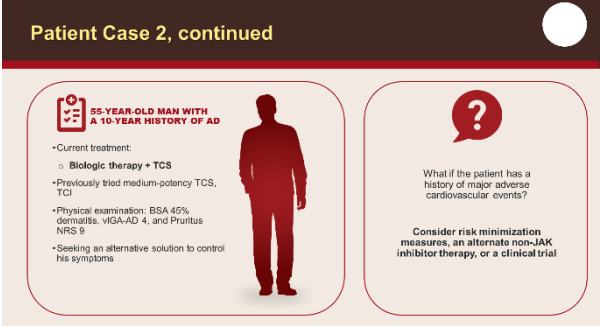
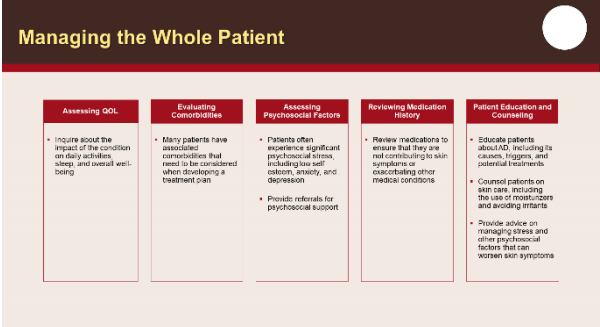
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		<p>a shot of oral prednisolone. I think again in these patients you should first start with the biologic treatment. And in that case, I think you can have the choice between dupilumab and tralokinumab, because the patient is not suffering from asthma, so you can have the option of using tralokinumab, but you have to explain to the patient that this takes a little bit longer in order to fully control the disorder.</p>
37	 <p>Patient Case 2, continued</p> <p>55-YEAR-OLD MAN WITH A 10-YEAR HISTORY OF AD</p> <ul style="list-style-type: none"> • Current treatment: <ul style="list-style-type: none"> ◦ Crisaborole 2% • Previously tried medium-potency TCS, TCI • Physical examination: BSA 45% dermatitis, vIGA-AD 4, and Pruritus NRS 9 • Seeking an alternative solution to control his symptoms <p>What if the patient must travel extensively for work?</p> <p>Consider an oral JAK inhibitor</p>	<p>The problem is that biologics have to be kept in the fridge, and if you have a patient that due to his work is extensively traveling, you have a problem, because the patient will ask you, say, “I’m sorry I cannot use. I cannot bring with me all this stuff. You know the syringes and the biologic because this is too cumbersome to be put in my luggage and to keep it cool” and all these kind of things. So, what could be the other option? And clearly here this would be a candidate for an oral JAK kinase inhibitor, provided that he is not a patient at risk.</p>
38	 <p>Patient Case 2, continued</p> <p>55-YEAR-OLD MAN WITH A 10-YEAR HISTORY OF AD</p> <ul style="list-style-type: none"> • Current treatment: <ul style="list-style-type: none"> ◦ Biologic therapy + TCS • Previously tried medium-potency TCS, TCI • Physical examination: BSA 45% dermatitis, vIGA-AD 4, and Pruritus NRS 9 • Seeking an alternative solution to control his symptoms <p>What if biologic therapy does not adequately control his symptoms?</p> <p>Consider switching to an oral JAK inhibitor</p>	<p>And the question of course is, here, if nothing works with the biologics? Or something else? So, you have to consider to switch from the biologic to the JAK kinase inhibitor. So, imagine you have a patient who was on the biologics or under an off-label</p>

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		<p>treatment, and it is not fully controlled. You may be considering switching to an oral JAK kinase inhibitor.</p>
<p>39</p>		<p>But now comes the situation: He is 55 years old; he may have a risk for cardiovascular disorder because he potentially already had, let's say, a stroke or a heart attack; so he's certainly not the best candidate for JAK kinase inhibitor. But you have to consider this, you have to discuss this intensely with the patient and try to find something else. Maybe coming back to an off-label use. Maybe to an intense treatment with UVB plus topical treatment or even include him in a clinical trial. But again, with the clinical trial, you will potentially face the issue of the compliance if he is traveling very often; so this is really a very difficult case to manage.</p>
<p>40</p>		<p>So now comes the point, what I mentioned before already, that is you need to discuss all these issues with your patients. So shared decision-making now is, I think, in my experience, the most powerful way to find out what is the optimal treatment option for a given patient. You have to assess not only the severity, to be honest, you have to look at other dimensions. You have to look at the impact on the quality of life, for example. You have to ask about the</p>

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		<p>comorbidity. Think about asthma. Recently, I had a patient who had asthma and EOE and chronic rhinosinusitis, and he came with atopic dermatitis, so he was the ideal candidate for dupilumab, because this drug is approved for all these different kinds of atopic comorbidities. Psychosocial factors — important to be considered in the management. The medication history, as I mentioned before, you know, you have to know what are these patients taking. Please also think about the drug–drug interaction issues, particularly when you are using small molecules like the JAK kinase inhibitors that may potentially interact with other drugs, particularly in older patients. And do not forget the patient education and counseling. This is so important to increase the compliance of these patients, that's absolutely mandatory, and I think we need to spend some time. I know that in daily practice, time is probably the thing that is lacking for most dermatologists. But in the context of the care of patients with atopic dermatitis, you need to spend some time to explain to the patients what it is about and what is the best therapeutic option for this patient.</p>
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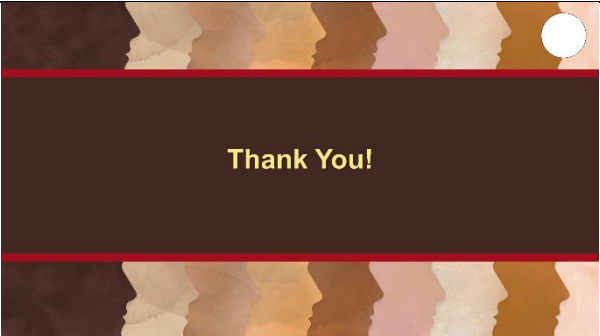
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<p>41</p>	<p>Importance of Patient-Clinician Partnership¹</p> <p>The flowchart outlines a six-step process:</p> <ol style="list-style-type: none"> Describe problem → Listen carefully (nonverbal attentiveness, interactive conversation) Attend to recommendations → Assess and suggest alternatives (inquire about day-to-day management at home and offer a long-term treatment plan options) Choose among options → Write down advice (tailor regimen to daily routine) Try out clinical recommendations → Educate (review short-term goals of therapy, provide criteria for making decisions at home) Inform doctor of results → Refine therapeutic plan Revise practice as needed and proceed <p>A callout box states: "Many adult patients with AD prefer to have a large amount of control in decision-making for their care²".</p> <p><small>1. Lee Coker, MD, et al. JAMA Dermatology. 2016;152(10):1107-1112. 2. Bieber, et al. JAMA Dermatol. 2012;158(9):1101.</small></p>	<p>So, this is a little bit, you know, the kind of process that you should go within your brain in order to find out what is the optimal treatment for a given patient that you are taking care of. You have to describe the problem, to look at the recommendations, to choose among the options that are available. Maybe to try out some clinical recommendations and to refine the therapeutic plan. That's something that is part of your daily practice. You have to look at all these points when it comes to finding the optimal treatment for a given patient.</p>
<p>42</p>	<p>Engaging Patients in Care and Shared Decision-making</p> <p>The diagram lists five pillars:</p> <ul style="list-style-type: none"> Empowering Patients: Provide patients with information about their condition, including the risks and benefits of different treatment options, and encourage them to ask questions and assess their preferences. Inviting Active Participation: Encourage patients to participate in the decision-making process by asking for their opinions, listening to their concerns, and valuing their input. Using Decision Aids: Decision aids, such as brochures, videos, and online tools, can help patients better understand their options and make informed decisions. Addressing Values and Preferences: Ask patients about their values and preferences regarding treatment, including their priorities for symptom relief, potential side effects, and quality of life impact. Encouraging Collaboration: Work together with patients to weigh the benefits and risks of different options and reach a mutually agreed upon plan. 	<p>And the shared decision-making with the patient is based on these five pillars: Empowering the patients. Inviting for active participation, and here again the compliance is extremely important. Using decision aids: There are currently a number of documentations and brochures, videos, and online tools that are available for this kind of decision aids. Addressing values and preferences, that's a very individual issue, whether the patients have particular kinds of concerns. And finally, encouraging the collaboration. You can only reach that final goal of having the optimal treatment option when, in fact, the patients are</p>

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		<p>working with you, understands to weigh the benefit and risk of the different options that you have discussed with this patient. I was, I hope I was able to give you a little bit an insight on the current therapeutic options available for the treatment of moderate-to-severe atopic patients, adult patients by the way. The management of kids with atopic dermatitis has been addressed in another presentation.</p>
43		<p>Again, thank you very much for your attention.</p>