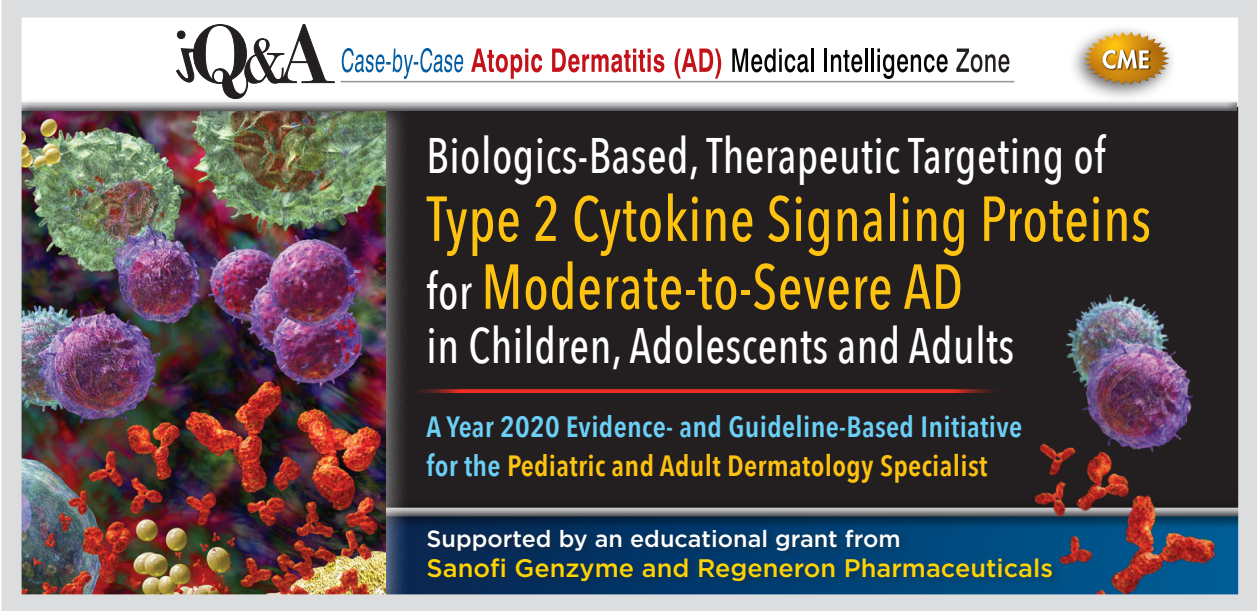
Biologics-Based, Therapeutic Targeting of Type 2 Cytokine Signaling Proteins for Moderate-to-Severe AD in Children, Adolescents and Adults

A Year 2020 Evidence- and Guideline-Based Initiative for the Pediatric and Adult Dermatology Specialist



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QUESTION #1: From a broad, introductory perspective, why is it important to parse out clinical phenotypes among pediatric and adult populations with atopic dermatitis? What is the importance of identifying clinical signatures and how can this impact prognosis and prediction of therapeutic response and tolerability to specific therapies?

QUESTION #2: You have made the important point that the heterogeneity of atopic dermatitis (AD) in pediatric, adolescent, and adult populations is a critical feature of this disease and, through more precise identification of phenotypes and endotypes, can provide more precise roadmaps for therapy. Can you elaborate on why this is clinically important?

QUESTION #3: Given the broad, differentiated spectrum of therapeutic modalities available for moderate-to-severe AD, can you provide your colleagues with an evidence-based—even loosely protocolized—roadmap, a "therapeutic ladder," perhaps, for how this range of treatments, from topical corticosteroids to immunologically-based therapies, including dupilumab, should be sequenced in pediatric and adolescent patients with AD?

QUESTION #4: Can you share with us, using a specific patient example, a case where topical therapies have failed to produce an acceptable clinical response, and in whom consideration of immunotherapy—including systemic treatment with dupilumab—would be indicated? How do you make these decisions on a case-by-case, clinical signature basis on the pediatric-adolescent age group at the front lines of AD care?

QUESTION #5: Can you review, based on clinical trials, the current evidentiary basis for the deployment of dupilumab in pediatric and adolescent age groups, and how clinical outcomes, time to resolution, and dosing consideration compare to results reported for the original landmark trials in adults demonstrating efficacy and safety of dupilumab in moderate-to-severe AD?

QUESTION #6: With respect to dosing regimens and duration of therapy using dupilumab in pediatric and adolescent age groups, what do trials, FDA approval guidance, and your clinical experience suggest as practical roadmaps in this population? Can you provide distinct dosing recommendations for the adolescent, adult, and pediatric age groups?

QUESTION #7: Many dermatologists who observe and report excellent efficacy and tolerability with dupilumab also are asking: "How long should treatment be continued, and are there definitive criteria established for cessation of therapy? And how long is it safe to continue therapy? Is monitoring required?" Can you provide guidance on these commonly asked questions and on the stability of the safety profile?

QUESTION #8: With respect to dupilumab, what is the mechanistic relevance of targeting type 2 cytokine signaling systems—IL-4 and IL-13—and how does this translate into clinical effectiveness observed in clinical trials?

QUESTION #9: In the dupilumab trials, do patients treated with this agent respond predictably in terms of amelioration of specific symptoms—itch, redness, appearance—and how long does it take to see treatment response? What percentage of patients respond and what percentage of patients treated with dupilumab can be categorized as "true treatment failures?"

QUESTION #10: In light of the significant unmet need for AD treatment in children between the ages of 2 and 12, and even younger, what do the most recent clinical trials show about the safety and efficacy of dupilumab in young age groups?

QUESTION #11: What is your current view of the "therapeutic ladder" for AD in the pediatric and adolescent age group, and in this heterogeneous disease, what is the specific trigger for systemic immunotherapy; and where does dupilumab-mediated, type 2 cytokine-targeting fit into your sequential approach to AD in the younger population?

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QUESTION #12: What is the prevalence of AD in various age groups and what is the range of clinical phenotypes in pediatric and adolescent age groups? What is the impact on the individual patient with AD, and how do co-morbidities make management especially challenging?

QUESTION #13 : What is the rationale and evidence that supports prompt, intensive, severity-of-disease-appropriate management of moderate-to-severe AD in the pediatric and adolescent age group?

QUESTION #14: Can you align the heterogeneous range of clinical phenotypes seen in children and adolescents with AD to the appropriate severity-of-disease metrics that would trigger specific therapies, from topical agents to systemic immunotherapy, including those that are type 2 cytokine-targeting?

QUESTION #15: In general, what are the triggers and clinical phenotypes in the pediatric age group that expert consensus, guidelines, and trial evidence suggest should be treated with topical therapies, and what symptomatic, historical, or skin-based findings suggest the need to intensify therapy?

QUESTION #16: How do you select among systemic agents for moderate-to-severe disease, including the use of systemic immunotherapy with dupilumab, which targets type 2 cytokine signaling? Where does this IL-4/IL-13 inhibitor fit into the sequencing of systemic therapy in pediatric and adolescent patients?

QUESTION #17: What is the mechanistic rationale for deploying a biologic agent such as dupilumab that inhibits type 2 cytokine signaling? And what range of symptoms—itch, redness, and systemic burden—in pediatric and adolescent patients are ameliorated by targeted inhibition of IL-4 and IL-13?

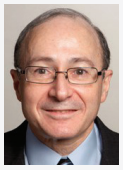
QUESTION #18: In light of the recent approval (May 2020) of dupilumab for AD in pediatric patients between the ages of 6 and 11 years of age, can you review the evidentiary basis for this approval based on clinical trials, and the practical implications?

QUESTION #19: Since systemic immunotherapy targeting type 2 cytokine signaling will likely be started in younger pediatric populations, for what duration of therapy do you recommend with cytokine-inhibiting biologics such as dupilumab? And how often is monotherapy vs. combination therapy advisable in the pediatric and adolescent age groups? Is 12 months of therapy a minimum duration in your opinion?

QUESTION #20: Can you share a specific patient case of a pediatric patient with severe AD in whom you intensified therapy with dupilumab, and what the outcome was? How did the discussion evolve with the family and what specific end points were affected and after how many months of therapy?

QUESTION #21: Can you describe another specific patient with AD who has more moderate but persistent disease, who is doing fairly well, control-wise, with topical treatments, but in whom you felt intensification with a systemic type 2 cytokine-signaling inhibitor was appropriate?

QUESTION #22 : How would you summarize the status of the current arsenal for AD and, in particular, the degree to which new systemic therapies are addressing the unmet for long-term disease management in the pediatric and adolescent population?



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QUESTION #23: Can you give us a sense of the disease burden—physiological, symptomatic, and psychological—associated with atopic dermatitis (AD) in children and adolescent patients; and to what degree is it, or can it be, truly debilitating? And to what degree have biologics altered the risk-benefit equation for treating pediatric patients?

QUESTION #24: From a protocol perspective, what is the canonical approach to sequencing therapy for patients with moderate-to-severe AD, what are the risks for established agents, and how has the introduction of type 2 cytokine-signaling inhibitors such as dupilumab changed our approach to sequencing agents for this disease in the younger population?

QUESTION #25: Are there specific clinical phenotypes that are uniquely responsive to inhibition of type 2 cytokine-signaling proteins, or do patients across the moderate-to-severe spectrum of AD seem to respond with predictable success?

QUESTION #26: Can you identify and share with your colleagues a specific case of a pediatric patient with AD who required intensification of therapy with a systemic, immunotherapeutic agent? And what were the specific triggers for deploying a type 2 cytokine-signaling protein inhibitor such a dupilumab?

QUESTION #27: After what length of treatment with dupilumab do you expect to see a clinical response in pediatric patients, how long do you expect the response to last, and what is your recommendation as far as duration of therapy with dupilumab?

QUESTION #28: Many dermatologists—and patients—are asking whether, during the Covid-19 pandemic, biologics such as dupilumab should be stopped in patients with AD? What are your recommendations?

QUESTION #29: How do you transition pediatric or adult patients who may already be on other systemic agents such as cyclosporine or methotrexate to dupilumab? Can you provide practical guidance that is applicable to the front lines of AD care?

QUESTION #29: Now that dupilumab has received formal FDA approval for use in the 6-11 age group, can you share what your clinical experience has been using this biologic in the pre-adolescent, pediatric age group?

QUESTION #30: What is the take home lesson about biologic therapy for AD and what does the future hold? What are the continuing unmet needs?