Now we have a set of traditional systemic agents that aren't approved for use in the US. That includes methotrexate. That includes cyclosporine, azathioprine, mycophenolate, and a few others.

Methotrexate works but it doesn't work that well. The percentage of people who'll get 50% better. Maybe it's, depending on who you ask, 30% to 50%. It requires, as well as an oral agent, it requires blood monitoring because of its impact on, potentially, liver function and blood counts as well.

It can be used long term. Relative efficacy isn't that great. We don't have that big a literature, and it's not approved. Cyclosporine, it's quick, highly effective. Essentially a miserable drug in terms of its side effect profile. We don't use it longer than a year. We have serious concerns about secondary malignancy associated with it.

We've had a lot of experience, my colleague Wynnis Tom in San Diego and myself, with other systemic therapies, such as mycophenolate and azathioprine. Dr. Tom has written a whole book on systemic therapies. But the side effect profile is pretty tough with these drugs.

So then we really look to the first systemic approved agent designed for atopic dermatitis in the US, which is dupilumab, an IL-4, 13 blocker. And this is an evolving part of atopic dermatitis because that drug was first approved in adults. Now approved 12 to 18. About or approved, depending upon when you're listening to this, probably for 6 to 12-year-olds. Already being studied down into the 2 to 6 years of age, and then younger after that.

So very, very interesting drug. Highly effective being approved for atopic dermatitis at different ages, as well as for refractory asthma, 12 plus, as well as for nasal polyposis. And it's really effective in the TH2 blockade. Obviously, the TH4, 13 are important because you can see the clinical impact of these drugs.

And the choice of whether one uses a traditional systemic agent like methotrexate or cyclosporine versus dupilumab has a lot to do with access and approval and insurance coverage. I think that most of us would love to go to first line systemic agent with dupilumab right now, and potentially other biologic agents in development as well. Because the efficacy and safety combination seems quite good.

The blood monitoring for dupilumab at baseline and over every few months is none. There's no recommended blood monitoring because it appears to be selectively impacting the immune system enough that we can say it's sort of not immunosuppressive. At least, the companies will have to say that from an FDA perspective.

And so it's relatively safe. You have to monitor for conjunctivitis and make sure that the patient's appropriately using their medicine and cheer them on to make sure that they adhere to their regimens. But clinical response is generally quite good over time. And the safety doesn't require a lot of monitoring.

So we're in this evolution in therapy as we look to more of our biologic agents. And then potentially in the future, JAK inhibitors, which will have a different risk benefit profile than our biologic agents, that's something that I think has really sort of changed our perspective. And it will probably change the percentage of patients who we bring into systemic therapy, as compared to historically, meaning that our traditional systemic agents be restricted to much more severe patients.

Now we have new orations that are approved moderate to severe in severity and probably, as we realize the impact of the disease, even on moderate patients, remain more liberally used these products going forward.

So thinking about the pathophysiology of atopic dermatitis, we've had different perspectives over time as we emphasized different aspects of our disease understanding and also discovery. But there's a little bit more unification of it over time. And that very much relates to some of our newer systemic medicines, specifically biologic agents that are TH2 skewed in terms of their impact on the disease.

So what do I mean by sort of a change in perspective? Well, for a while, we were really recognizing some of the intrinsic problems with barrier dysfunction and atopic dermatitis. Th is erratic skin-- the ability in clinical studies for someone to do transepidermal water loss studies on a baby and predict the development of atopic dermatitis because that might be associated with skin that both has a tendency to be drier and maybe potentially sensitize.

So we have barrier dysfunction. And then with this open skin and presentations of antigens potentially, that skin gets sensitized, which goes along with probably other aspects of the immune system that makes someone have more of a tendency to develop inflammation in the skin, which manifests as atopic dermatitis.

So we know that if we minimize barrier dysfunction with moisturizers, we may improve skin barrier, and in some cases, even treat low levels of inflammation. But we also know that anti-inflammatory agents, whether they're topical or now systemic, can improve the inflammation in the skin, but also a barrier dysfunction.

So our insight into this is very much affected by the studies that have been done specifically on IL-4, IL-13 blockade. We know that the TH2 cytokine profile was important in atopic dermatitis. At least, we thought it was. And then it was proven that it was in that when you used dupilumab, a specific TH2 blocker, via IL-4 and IL-13 cytokines, that we influenced atopic dermatitis.

So just visualize that if I have someone who's got very inflamed skin and they had the cubital fossa on their face and neck, for instance, and I give them a systemic agent that blocks IL-4 and IL-13, and I look a few months later, and if they're in that clear, almost clear group, they're clear or almost clear. And it's worked essentially through the bloodstream in terms of impacting on the influence of IL-4 and IL-13 cytokine.

By blocking that down through the systemic aspects of the disease, we also block the clinical manifestations in the skin. Now we know that also improves skin barrier function. It actually regularizes the microbiome, so we have less staph aureus and more of other bacterial agents or other microbes on the skin that are more normally there. So there's an improvement of different aspects of the pathogenesis by giving a systemic cytokine blocker.

So this is fascinating. We've learned this. As I said, it's sort of unification of barrier dysfunction to some of the genetic elements that contribute to that, and inflammation, showing that effective anti-inflammatory therapy improves both the inflammation in the skin, as well as the barrier dysfunction, and, of course, some of the symptoms as compared to signs, because we can have markedly decreased itch with systemic dupilumab use as well.