So for many years, we've had topical therapy being the mainstay of treatment, and they remain the mainstay of treatment of atopic dermatitis, particularly in mild, localized disease. If someone has extensive disease-- and by extensive, I would say more than 10% body surface area-- it is just impractical to treat those patients topically. If somebody has severe disease, meaning disease that is refractory to topical therapy or disease that is simply too expensive to treat with topical therapy, then they graduate to the next lines of treatment that we have.

For topical therapy, the mainstay of treatment has been corticosteroids, topical corticosteroids. And they are used by virtually every dermatologist, and they are highly effective. But they are associated with some side effects. They thin the skin. They're not supposed to be used, certainly not for prolonged periods of time, on certain parts of the body, like the face and intertriginous or flexural areas, where they cause a variety of side effects.

Around the eyes, they can cause cataracts and glaucoma. On the face, they caused a rash called perioral dermatitis. In the axillae or the groin, the medial thighs, they cause stretch marks, striae. They cause thinning of the skin on the arms and legs which often lead to an entity called steroid purpura, where a patient's skin is so thin that it doesn't cushion the blood vessels of the skin, so patients bleed easily. They also thin the dermis so that you can see telangiectasia through that thinned dermis.

So they are associated with a fair number of mostly local cutaneous side effects. They are indeed, if you use them on large body surface areas or for much too long periods of time, particularly with super potent steroids, they are indeed absorbed and can lead to Cushing's syndrome-- systemic steroid toxicity, if you will. But that rarely happens in a way that is clinically significant. So most dermatologists are not worried about Cushing's syndrome from topical steroids, but they are worried about the other side effects that I mentioned.

There are other topical agents that are effective as well, topical calcineurin inhibitors. In the United States, we still have this foolish black box warning that they may be associated theoretically with cancers. I think that that largely has been disproven, but they still have that warning. And they are modestly effective. The two available are pimecrolimus cream and tacrolimus ointment. There is another class, topical phosphodiesterase inhibitors. Crisaborole is the one that's approved in the United States.

And those are, again, moderately effective and don't carry with them the steroid side effects that we have been taught to worry about. There's a little bit of irritation associated with crisaborole and with calcineurin inhibitors, but that usually is-- it can be dealt with as long as patients are explained that they may be irritating. Once patients are beyond topical therapy, the next options that they're offered are phototherapy. And primarily, that would be narrowband UVB. In the old days, we used to use broadband UVB, and we used to use PUVA, but narrowband has emerged as, I think more, effective and certainly safer than PUVA.

It's not that effective. Patients often flare when phototherapy has started. And often, we'd have to treat patients initially with something like systemic steroids when we started phototherapy, so not that satisfying a treatment. And then more recently, much more recently, we have been introduced to biologic therapies for atopic dermatitis. The first one approved was dupilumab, and it's highly effective, not associated with the side effects of some of the other immunotherapies that we've been using in the past.

Now, I will say in this area, we can go right from topical therapy to dupilumab. But there are other parts of the country, and certainly the world, where because the cost of dupilumab might be prohibitive, insurers will force us to go through immunosuppressive treatments like systemic steroids, which, frankly, have many drawbacks. They are associated with-- even a Medrol dose pack, a six-day tapering dose of steroids, is associated with a marked increase over a 30 to 90-day period of venous thromboembolism, which most of my colleagues are not aware of. They're associated with bone fractures and with infections related to immunosuppression.

They also are associated with poor control of blood sugars, diabetes, hypertension, and a whole host of other immunosuppressive features that we know occur with systemic steroids. I think the surprise there is that even a short course causes some of those side effects. The other immunosuppressive therapies that we are often asked for patients to fill-- and the one that I used the most until dupilumab was available-- was cyclosporine. Very effective, associated with nephrotoxicity.

In fact, in patients who are on cyclosporine for more than two years, at least in adults, there's a study which did kidney biopsies in those patients, and 100% of patients showed evidence of nephrosclerosis after two years. So we're very concerned about nephrotoxicity. Also associated with hypertension, all of the side effects of immunosuppression. And so it's a drug that used to be one of the most effective, and frankly, used to be one of the safer treatments we had for atopic dermatitis. We now have something safer.

Azathioprine is a drug that I have avoided using because the therapeutic dose of azathioprine that's used for atopic dermatitis is very close to the bone marrow toxic dose. So that's a treatment I have not liked. Better tolerated is mycophenolate mofetil, and that's been around for years as a transplant drug. It is also associated with immunosuppression, increased numbers of cases of herpes zoster, and a little bit of bone marrow toxicity, but much less than azathioprine. And lastly, a susceptibility to malignancies that are associated with immunosuppression. So there is an increase in lymphoproliferative diseases in patients treated mycophenolate mofetil, and we've learned about that mostly from transplant patients where that drug is routinely used.

And probably, I shouldn't have left this for last, but a commonly used treatment for atopic dermatitis is methotrexate before we had dupilumab. That drug also is associated with significant bone marrow toxicity, also hepatotoxicity. So it's a drug that is-- these are moderately effective, not as effective as cyclosporine, though, and certainly not as effective as dupilumab. Fortunately, because we now have biologic therapies-- dupilumab is the first. lebrikizumab and tralokinumab are coming. Those are very effective treatments for atopic dermatitis, and they are not associated with many of the side effects that we've been used to seeing.

In fact, the one that is approved, dupilumab, pretty much is associated with one side effect, and that is conjunctivitis, which is usually short-lived, even if you don't treat it, and goes away by itself. But that's the main side effect. So we now finally do have a drug that's safe and effective.